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Editorial

Has the time come for cyanoacrylate injection to become the standard-of-care for gastric varices?

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The prevalence of gastric varices varies between 5% and 33% among patients with portal hypertension with a reported incidence of bleeding of about 25% in 2 years and with a higher bleeding incidence for fundal varices.[1] Risk factors for gastric variceal hemorrhage include the size of fundal varices [more with large varices (as >10 mm)], Child class (C>B>A), and endoscopic presence of variceal red spots (defined as localized reddish mucosal area or spots on the mucosal surface of a varix).[2] Gastric varices bleed less commonly as compared to esophageal varices (25% versus 64%, respectively) but they bleed more severely, require more blood transfusions and are associated with increased mortality.[3,4] The approach to optimal treatment for gastric varices remains controversial due to a lack of large, randomized, controlled trials and no clear clinical consensus. The endoscopic treatment modalities depend to a large extent on an accurate categorization of gastric varices. This classification categorizes gastric varices on the basis of their location in the stomach and their relationship with esophageal varices.[1,5] Gastroesophageal varices are associated with varices along the lesser curve (type 1), or along the cardia (type 2); isolated gastric varices are present in the fundus (type 1) or at ectopic sites in the stomach or the first part of the duodenum (type 2).[1,5]

Although, endoscopic variceal band ligation is the undisputed gold standard therapy for bleeding esophageal varices, this approach has been less successful for the treatment of bleeding gastric varices.[6] Treatment options for gastric varices includes the radiological insertion of a transjugular intrahepatic portosystemic stent shunt (TIPSS) and the endoscopic injection of sclerosing agents, such as absolute alcohol, ethanol oleate, sodium tetradecyl sulfate, tissue adhesives and thrombin.[7] N-butyl-2-cyanoacrylate (NBC) is the most commonly used tissue adhesive for the treatment of gastric varices in clinical practice and is superior to intravariceal injections using ethanol oleate or absolute alcohol.[7] American Association for the Study of Liver Diseases guidelines[1] and the Baveno V consensus[5] recommend endoscopic therapy with NBC as first-line treatment for bleeding isolated gastric varices and gastroesophageal varices type 2. Endoscopic variceal ligation or sclerosing agents can be used in bleeding from gastroesophageal varices type 1. A transjugular intrahepatic portosystemic stent shunt (TIPSS) should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy or where endoscopic therapy is not available.

NBC is a liquid with a consistency similar to water and therefore it can be given by intravariceal injection. When added to a physiologic medium such as blood, NBC rapidly polymerizes, forming a hard substance. Hence, after injection into a varix, NBC plugs the lumen resulting in rapid hemostasis in cases of active bleeding and eradication of gastric varices. NBC is commonly used in Europe and Asia for the treatment of gastric varices but is not approved by FDA in the United States.

In this issue of Tropical Gastroenterology, Choudhuri et al[8] from India report impressive results using NBC, Nectacryl, for the treatment of bleeding fundal gastric varices (mostly isolated gastric varices and gastroesophageal varices type 2) as an emergency procedure for active bleeding in 62 patients and as an elective procedure for prevention of rebleeding in 108 patients. The overall hemostasis rate at 48hours was 82.3 % in actively bleeding group. Overall bleeding recurred in 14.5% of the patients. Definitive success was achieved in 89.9% of patients with a complete follow up who had been followed. No significant complications were noticed except for injection site ulceration in 32 patients. The major limitations of this study were a retrospective nature, 9% of patients were lost to follow-up and there was only one intervention group.

In another study from India, recently published in Gastrointestinal Endoscopy, Kumar et al[9] reported a success rate of initial hemostasis in 84.8% among 46 patients with actively bleeding gastric varices. Rebleeding was seen in 23.4% patients over a mean follow-up of 16 months. Large gastric variceal size, fundal location, and large esophageal variceal size were predictive of gastric variceal bleed. The mortality was 8.8% for all varices and Child-Pugh status was the only predictor of mortality. The only limitation of this study was that it had only one intervention group.

The technique of NBC injection was important in these 2 studies.[8,9] While former has used minimally diluted NBC with lipiodol in 4:1 ratio, the later used undiluted glue. Further, to prevent embolization, Kumar et al[9] limited maximum amount of cyanoacrylate per injection to 1 to 2 mL per varix and per session to 4 mL. Similarly, Choudhuri et al[8] have used 0.5 to 4ml of cyanoacrylate glue per aliquot that was primarily decided by the size of varix. These approaches have been taken in an attempt to reduce the embolic complications of cyanoacrylate glue. The rationale for diluting cyanoacrylate glue with lipiodol is to delay the otherwise early polymerization reaction in order to complete the injection and remove the needle. Previous studies have used varied dilution with lipiodol (0.5:1.5 to 2:1).[10,11] There are several case reports of severe complications related to embolization including cerebral stroke,[12] pulmonary embolism,[13] portal vein embolism,[14] splenic infarction,[15] retro-gastric abscess[16] and septicemia[17] which have raised concern about its safety. When embolic phenomena occur, fatalities have also been reported.[18-20]These two studies are important for eliminating the risk of embolization by using undiluted or minimally diluted NBC. In another study, the endoscopists switched from diluted NBC to undiluted NBC midway through the study, after noticing embolic complications with diluted NBC, and thereafter reported absence of embolic complications with undiluted NBC.[21]

Most evidence for the use of cyanoacrylate in gastric variceal bleeding comes from series based in India, Japan, Europe, and the United States, which report good initial hemostasis rates of over 93% (range, 71-100), rebleeding rates of 23% (range, 7.6-52) and mortality of 28% (range, 3.7-82.5) in 24 trials.[7] Both studies have shown efficacy of NBC on above-mentioned parameters according to the literature. Case series have also highlighted the utility of cyanoacrylate treatment in specific clinical situations such as pregnancy,[22] in children[22,23] and in infants.[24] Repeated injections are required to obliterate the varices and secondary bleeding. In a recent study, b-blocker were compared with NBC injection for the prevention of secondary bleed. Patients with gastroesophageal varices type 2 with eradicated esophageal varices or isolated gastric varices type 1 who had bled from gastric varices were randomised to NBC injection (n=33) or b-blocker treatment (n=34). The probability of gastric variceal rebleeding rate in the NBC group was significantly lower than in the b-blocker group (15% vs 55%, p=0.004) and the mortality rate was lower (3% vs 25%, p=0.026) during a median follow-up of 26 months. This study further confirms the findings reported earlier that gastric variceal eradication should be the aim with NBC injections on a regular follow-up.[25] Weeks to months after the injection, the mucosa overlying the glue cast sloughs off and the plug is extruded into the stomach; this may be followed by bleed in a rare patient due to ulcer formation at the extrusion site. We minimize the chances of ulcer bleed of this kind by giving proton pump inhibitors in a single dose; however the efficacy of this approach needs to be confirmed with a prospective randomized controlled trial.

Three studies have compared endoscopic NBC injection with TIPPS placement for the management of gastric variceal bleeding.[26-28] Lo et[27] found that TIPSS was more effective than NBC injection in preventing rebleeding from gastric varices, with similar survival and frequency of complications. Mahadeva and colleagues[26] retrospectively analyzed that NBC injection was more cost effective than TIPSS in the management of acute gastric variceal bleeding. A major limitation of this study was the short follow-up of just 6 months with cyanoacrylate and 12 months with TIPSS, which must be taken into account when interpreting the findings. Procaccini et al[28] compares TIPSS

insertion versus NBC injection with TIPSS insertion as a rescue treatment and concluded that in patients with similar characteristics, therapy with NBC performed as well as a TIPSS in controlling and preventing gastric variceal hemorrhage with no significant differences in survival. Patients receiving cyanoacrylate therapy experienced significantly less long-term morbidity related to therapy than patients who received a TIPSS and was primarily attributable to the development of hepatic encephalopathy. However there was no information whether the hepatic encephalopathy occurred *de novo* or it resulted from deterioration of preexisting encephalopathy after TIPSS insertion. In view of the heterogeneous results of above-mentioned 3 studies, a prospective, multicenter, randomized trial would be required to confirm the role of TIPSS in the management of gastric variceal bleeding. Until such a study is performed and the results are available, the recommendations of current guidelines as mentioned-above should be followed.[1,5]

While the role of NBC injection in the management of the treatment of bleeding fundal gastric varices has been clearly established, there is limited data on its role for the primary prophylaxis. In a study, 11 (37.9%) patients with large fundal varices with red color signs, especially cherry red spots, underwent prophylactic sclerotherapy for gastric varices with NBC. The results were the same as for the secondary prophylaxis for the gastric variceal bleeding.[21] Subsequently, Chang et al[29] evaluated safety and long-term outcomes of prophylactic NBC injection for non-bleeding gastric varices with a high risk of bleeding in 33 patients [large tumorous (n=27), red color sign (n=14) or rapidly growing in size (n=1)]. Obliteration of gastric varices was achieved in all of the treated patients. The mean duration of follow-up was 12.2 months and eradication of gastric varices was achieved in 21 (95%) of 22 patients who were followed-up more than 3 months. Index gastric varices recurred in three of 21 patients (14%) and re-bleeding in index gastric varices after NBC injection occurred in two of 26 patients (8%). This study shows that prophylactic NBC injection can be a promising procedure for eradication of non-bleeding gastric varices in case with a high risk of bleeding. In another study by Mishra et al,[30] cyanoacrylate injection was more effective than b-blocker therapy in preventing gastric variceal bleed and improving mortality. Size of gastric varix >20mm, a MELD score of >17, presence of portal hypertensive gastropathy and the treatment method predicted 'high risk' of first bleed from gastric varices. These preliminary investigations favor endoscopic intervention with NBC injections for the primary prophylaxis of gastric variceal bleed.

Has the time come for cyanoacrylate injection to become the standard treatment for gastric varices? The answer is 'Yes'. However, issues related to the role of NBC in the primary prophylaxis and the place of TIPSS in the management of gastric varices need further large multicenter randomized trials.

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Quarterly Review

Esophageal function tests in clinical practice: A review

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ABSTRACT

Diseases of esophagus are common in gastroenterology practice. Improvement in diagnosis and better understanding in pathophysiology of these diseases have been possible recently due to advancement in technology. Advancement made in the field of computer softwares is another key development aiding further improvement in these instruments. In this article, we review techniques, interpretation and clinical utility of various tests of esophageal function with special reference to manometry, ambulatory pH and impedance monitoring. Esophageal manometry is simple to perform. Recent, availability of commercial user-friendly software has made analysis of recorded data easy. High resolution spatio-temporal manometry is advancement over conventional manometry. Manometry is a useful tool for diagnosis, follow-up and research in esophageal motility disorders. Ambulatory 24-h pH metry and impedance monitoring are also easily analyzed by commercially available software. 24-h impedance combined with pH-metry is currently considered as the gold standard for diagnosis of gastroesophageal reflux disease (GERD). All patients with GERD may not require these investigations, but those with atypical symptoms, those refractory to medical treatment and requiring surgery do. Esophageal transit study is useful in understanding functional correlates of abnormalities in manometry and is particularly useful during follow up studies and in research.

KEYWORDS: Esophageal manometry, esophgeal pH monitoring, reflux esophagitis, esophageal motility disorders, esophageal function.

Introduction

The human esophagus is a 25 to 35 cm long muscular tube.[1] The contractions of the esophagus propel food into the stomach and also help to clear refluxed acid back to the stomach. The lower esophageal sphincter (LES) remains tonically contracted preventing reflux of acid from stomach to the esophagus. LES relaxes during swallowing, vomiting and belching to allow foods and gastric contents to pass into and out of the stomach. Tests of esophageal function evaluate contraction of its muscle and the movement of the food bolus and refluxate resulting from it. It also evaluates exposure of the esophagus to acid. These tests include (a) contrast radiography, (b) manometry, (c) 24-h ambulatory pH-metry and impedance monitoring, (d) radionuclide esophageal transit studies. The latter three methods will be reviewed in this article.

Esophageal manometry equipment

Esophageal manometry is performed either with water perfusion or with solid state system.[2] The solid state system, though more sensitive to pressure changes, is expensive and fragile. Therefore, water perfusion system is preferred in most centers. Water perfusion system consists of several capillary tubes connected to a multilumen perfusion catheter (usually 6-8 lumen) and external transducers. These tubes are continuously perfused with deaerated water at a constant rate (approximately 0.5 ml/min) by a low compliance pneumohydraulic pump powered by compressed nitrogen.[3] Each lumen of the catheter terminates in a side hole and senses intraluminal pressure of esophagus by relative obstruction to flow of perfused water. Currently, we are using a water perfusion system with a catheter having 8 side-holes. The proximal four side holes, which are 5

cm apart, are positioned in the esophageal body while the distal four, placed circumferentially, are in the lower esophageal sphincter (LES) zone. Intra-gastric pressure is used as baseline for any pressure measurement. Each capillary tube, opening at a side-hole at one end is connected to an external transducer at the other end in such a way that the tracing from the most proximal port is displayed at the top of the computer screen and that from the most distal port appears at its bottom. Esophageal manometery records contractions of circular muscles and not that of longitudinal muscles.

Technique

Patient preparation: Esophageal manometry is performed after overnight fast. All the drugs that may interfere with esophageal motility and LES pressure (prokinetics, calcium channel blockers, anticholinergics etc.) should be discontinued at least 48-h prior to the study. Patients are not sedated, as their cooperation is essential for the study. The procedure is explained to the patient.

Intubation and placement of the catheter: Manometry catheter is passed through one nostril into the stomach. An extra length of the catheter is initially inserted so as to have all the 8 ports inside the stomach. The location of catheter ports can be confirmed by noting the effect of inspiration on pressure tracing or by noting a rise in pressure in all ports by pressure over the epigastrium. Inspiration causes an upward deflection in pressure recording if the opening of the catheter is in the stomach whereas a downward deflection is produced if the same is in the esophagus.

Study of LES pressure: LES pressure can be assessed either by station pull-through (SPT) or by rapid pull-through (RPT) techniques.[3] During SPT, the manometry catheter is gently and gradually pulled out, through a small length (1-cm) at a time, and pressure is recorded at each site. Each port reaches a point where it shows a rise in pressure that passes through the high-pressure zone and, finally, reaches a point where pressure becomes low again. The length of high-pressure zone is determined taking the mean of values obtained from each port. When the manometry catheter port is in LES, inspiration causes an exaggerated rise in pressure; when the port crosses LES and lies in esophageal body, inspiration causes lowering of pressure tracing due to negative intrathoracic pressure generated during inspiration. This point where pressure tracing changes is known as pressure inversion point or point of respiratory reversal.[3]

Study of body motility: We study esophageal body motility with 4 distal circumferential ports at LES and 4 proximal ports at esophageal body. Body motility may be studied in response to dry and wet swallows. However, non-specific abnormalities in body motility in response to dry swallows may be found even in normal subjects. Therefore, we study body motility and LES relaxation in response to 10 wet swallows. For study of body motility, patient is instructed to swallow only on command. 5-ml water is given in each swallow. One must wait for 30 seconds between two swallows to avoid the phenomenon of deglutitive inhibition.[4] The timing of the swallow is marked on the screen using appropriate keyboard command to allow subsequent analysis of the record.

Study of LES pressure by rapid pull through: On completion of SPT, the catheter is pushed back into stomach again. After waiting for 1-2 minutes, the patient is asked to hold his breath in quiet expiration and refrain from swallowing. The catheter is then gently but steadily pulled out across LES.

Interpretation

Currently, most laboratories use computer-based programs for acquisition and analysis of the recorded data. The parameters analyzed include, (a) LES parameters (resting pressure, length of the high pressure zone, relaxation in response to wet swallows and three-dimensional pressure profile), (b) body motility (amplitude, duration and abnormalities of each contraction wave e.g. double or multiple peaks, whether spontaneous contractions are present, whether contraction are propagated or simultaneous and if propagated, velocity of propagation).[5] We prefer using SPT technique for assessment of most of the above parameters of LES function.[6] The average value of several measurements from different ports obtained in mid-expiratory phase is taken as basal LES pressure. RPT has several disadvantages.[5] It may show spuriously low LES pressure if the patient took an inadvertent dry swallow at the time of RPT. LES relaxation is determined as the minimum pressure observed during a swallow. Relaxation should be considered normal if LES pressure drops greater than 90% from mean resting LES pressure.[7] Normal values of different parameters of esophageal manometry and criteria for diagnosis of various esophageal motility disorders are given in **Table 1** and **Table 2**, respectively.[8, 9] **Figure 1** shows manometry tracings in various motility disorders. Studies describing normal values of esophageal manometry in Indians are awaited.

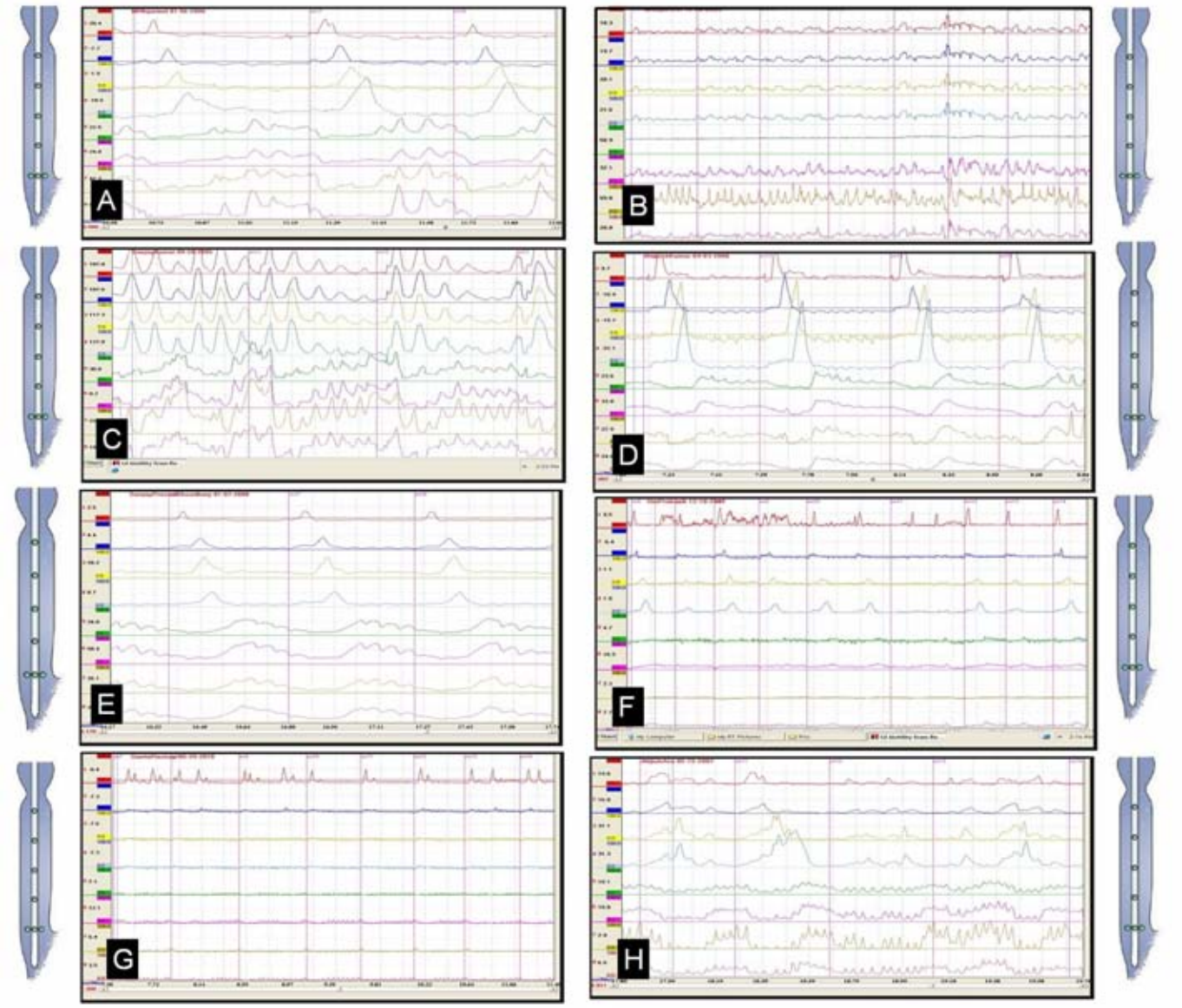

Figure 1: Shows some of the typical normal and abnormal conventional manometry tracings recorded in our laboratory. A line diagram of esophagus with manometry catheter having distal 4 circumferential ports and proximal 4 radial ports are shown for better understanding. (A) Normal peristaltic contractions; note progressive increase in contraction amplitude as it travels down the esophagus. Note that LES started relaxing the moment contraction occurred in uppermost port and remained relaxed till it reached the lower esophagus, (B) classic achalasia; note simultaneous low amplitude contractions (average amplitude in esophagus of <40-mm Hg) and incomplete relaxation of LES, (C) vigorous achalasia: repetitive high amplitude contraction in body (average amplitude in esophagus of >40-mm Hg) and incomplete relaxation of LES, (D) Nut cracker: high amplitude contraction (>180 mm Hg) in distal esophagus. Note complete relaxation of LES, (E) hypertensive LES: high LES pressure (>40 mm Hg) with normal body motility, (F) hypotensive LES: low LES pressure (<10 mm Hg), (G) progressive systemic sclerosis (PSS): very low amplitude contractions in distal esophagus with low LES pressure, (H) diffuse esophageal spasm (DES): some simultaneous (>20%) and some peristaltic contractions.

Clinical utility

Esophageal manometry is useful in diagnosis of several diseases like achalasia cardia, diffuse esophageal spasm and nutcracker esophagus .[9-12] In fact, manometry is the gold standard for the diagnosis of these conditions. Manometry may also be useful in evaluating the effect of treatment in achalasia cardia.[13] In some diseases like gastroesophageal reflux disease (GERD), manometry may be useful in prognosis. Several studies showed that patients with GERD and very low LES pressure (<10 mm Hg) often have severe disease.[14] Some studies suggested partial fundoplication in patients with GERD and low amplitude contractions (<30 mm Hg) in distal esophagus,[15] though this has been debated.[16] In systemic diseases such as

Table 1: Normal values of various parameters of esophageal manometry as obtained from 10 wet swallows.[8]

Parameters	Mean values	Standard deviations
LES pressure (mm Hg)		
• Rapid pull through	29.0	12.1
• Station pull through	24.4	10.1
Amplitude of contractions (mm Hg)		
• Proximal body	62	29
• Mid body	70	32
• Distal body	109	45
Duration of contraction waves (sec)		
• Proximal body	2.8	0.8
• Mid body	3.5	0.7
• Distal body	4.0	1.1
Velocity of propagation (cm/sec)		
• Proximal	3.0	0.6
• Distal	3.5	0.9

progressive systemic sclerosis, involvement of esophagus as diagnosed by manometry[17] and may be associated with severe GERD and reduced quality of life. Patients treated with endoscopic sclerotherapy for esophageal varices in the past, may have non-specific changes in esophageal manometry[18] that should be remembered while interpreting manometry tracing.

High Resolution Manometry (HRM)

HRM is a relatively new technology, foundation of which was laid in the early 1990s by Clouse and Staiano. Pressure profile was assessed during several swallows using catheter having multiple ports at closely spaced positions in the oesophagus. Time, catheter position and average pressure were then reconstructed into pseudo-3D ''topographic plots'' that demonstrated the functional anatomy of the oesophagus and that of the gastro-oesophageal junction. There are several advantages of HRM over conventional manometry most important of which are ease of performance and better ability to diagnose and classify esophageal motility disorders.

Equipment

Most of the HRM systems use solid state instead of water perfusion catheters. However, we use water perfusion catheter in our HRM system as solid state catheters are costlier. The number of ports in catheters of HRM may vary from 16 to 64. We use a catheter with 16 ports, of which upper 8 ports (3 cm apart) record body motility and lower 8 (1 cm apart) evaluate LES.

Table 2: Criteria for diagnosis of esophageal motility disorders.[9-12] Also refer to figure 1 for better understanding.

Disease	Essential feature(s)	Other features
Achalasia criteria	Absence of any peristaltic contraction	High LES pressure Incomplete LES relaxation Higher intraesophageal pressure than intragastric
Diffuse esophageal spasm	>10% simultaneous contractions Intermittent normal peristalsis	Contraction wave abnormalities (Triple peaks, long duration, >6 s, spontaneous) LES abnormalities (high resting pressure, incomplete relaxation)
Nutcracker esophagus	Average distal esophageal amplitude (>180 mm Hg)	Long duration contractions
Hypertensive LES	Isolated high LES pressure (>45 mm Hg)	
Non-specific esophageal motility disorders	Any one or more of followings >20% non-transmitted contractions Triple peak contractions Retrograde contractions Low amplitude contractions (<30 mm Hg) Isolated LES relaxation Long duration peristaltic contraction	

Technique

Patient preparation and catheter introduction for HRM are same as in conventional manometry.

Study of the body motility and LES: In contrast to conventional manometry, SPT need not be done to assess LES during HRM as location of LES is seen through isobaric pressure in colored scale. This reduces patient's discomfort. As in conventional manometry, esophageal body motility is evaluated by 10 or more water swallows (5 ml each) every 30 sec. It is displayed in time, duration and pressure either through color plot, contour plot, line tracing or 3-dimensional plot.

Interpretation

Appearance of HRM signals is appreciable easily due to color plots. In addition to normal features, one can pick up the segmental nature of the esophageal peristalsis, abnormal bolus

transport due to poor contraction, long transition zone and focal spasm in the mid esophagus.[19,20] **Figure 2** shows tracings of HRM in various esophageal motility disorders recorded in our laboratory. It is very useful to differentiate vigorous achalasia, diffuse esophageal spasm (DES) and prolonged or repetitive nutcracker which may be difficult sometimes in conventional manometry.[21] Hiatus hernia may also be seen in patients with GERD in HRM by movement and interaction of intrinsic LES and diaphragm.[22-23] Using conventional manometry, esophageal motor disorders can be classified into five groups (**Table 2**). Due to advanced technique of HRM the diagnostic criteria for esophageal motility disorders has been improved and classification into several sub-groups has been possible (**Figure 3**).[24]

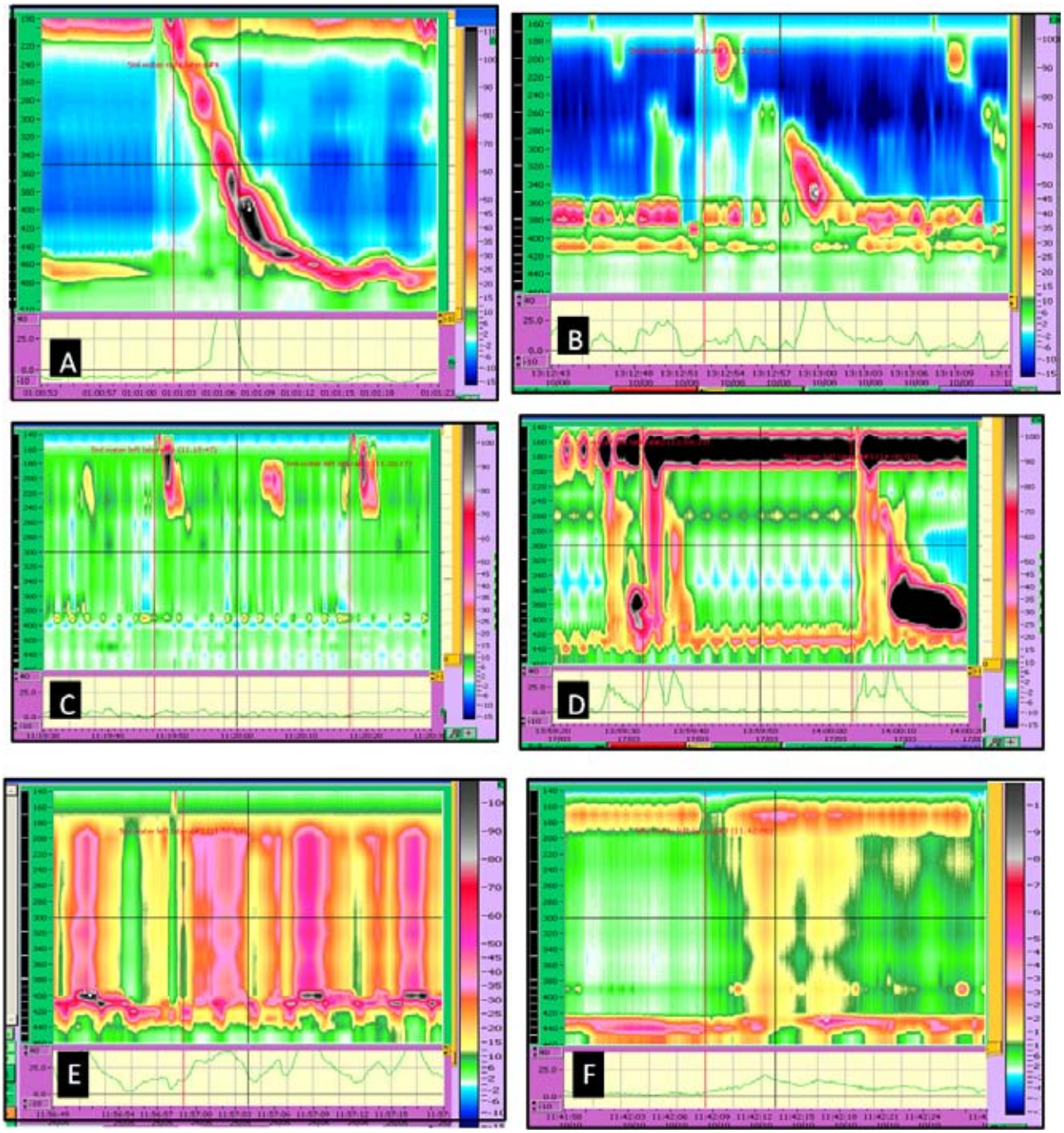

Figure 2: High resolution manometry tracings of: (A) healthy subject: shows peristaltic contractions in body with complete LES relaxation. (B) long transition zone. This tracing also shows hiatus hernia, (C) progressive systemic sclerosis (PSS): there is absence of progression of contraction from proximal to distal part of esophagus with low LES pressure, (D) diffuse esophageal spasm (DES): simultaneous, prolonged, high amplitude contractions some of which are peristaltic, (E) vigorous achalasia: high amplitude (average amplitude in esophagus of >40-mm Hg), simultaneous contractions in body with high LES pressure and incomplete relaxation. (F) classic achalasia: simultaneous low amplitude contractions (average amplitude in esophagus of <40-mm Hg) and incomplete LES relaxation.

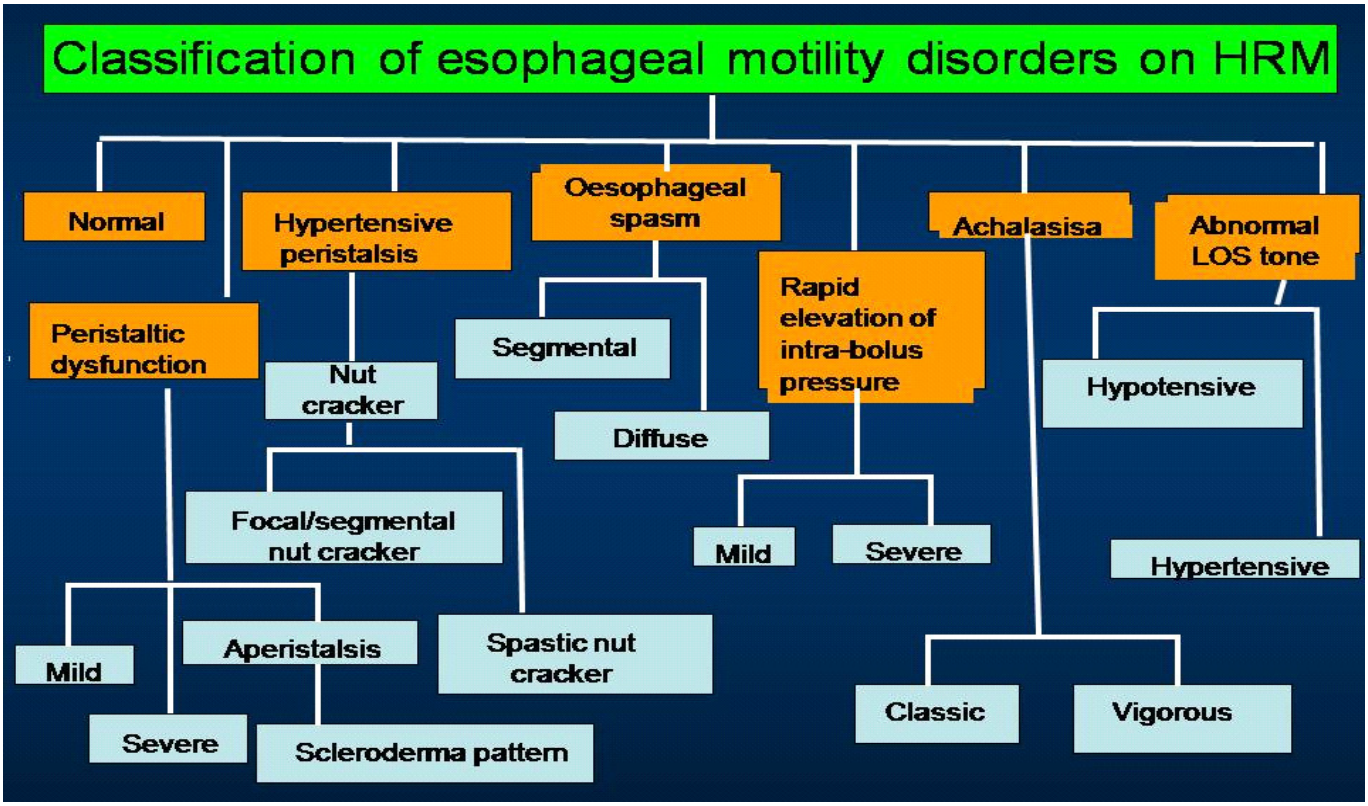

Figure 3: Classification of esophageal motility disorder on high resolution manometry (Chicago classification)

Clinical utility

In conventional manometry, abnormal motility patterns present in a short segment of the esophagus, may be missed. HRM is likely to pick-up such abnormalities as the ports are very closely placed. HRM technique is less time consuming and easier to perform than conventional manometry.

Ambulatory esophageal pH monitoring equipment

The equipment for pH monitoring includes pH electrode, data logger and computer with software. Electrodes available for ambulatory esophageal pH monitoring include monocrystalline antimony electrodes, glass electrodes and ion-sensitive field effect transistor electrode. Glass electrodes, despite being costlier than antimony electrodes, are popular in India due to their long life. Both monopolar (requires an external cutaneous reference electrode) and combination glass electrodes (with built-in reference) are available commercially. Most laboratories, including ours, prefer combination electrode, as monopolar electrode may be inaccurate due to loose contact and changes in pH around the reference electrode due to sweating. The glass has a high electrical conductivity. Ratio of hydrogen ion concentration on the two sides of the glass is proportional to the generation of electrical potential at the liquid glass interface; measurement of pH is dependent on this potential difference. Portable solid-state data recorder store data that is converted into digital signal, transferred to the personal computer and is analyzed with software. Several commercially available software programs are available for this purpose and each has its relative merits and demerits. Technique, interpretation and indications of ambulatory esophageal pH monitoring has been reviewed recently.[25]

Technique

24-h ambulatory pH monitoring is done after overnight fast. All drugs that affect esophageal motility and LES pressure must be discontinued at least 72-h before the study. Proton pump inhibitors must be withdrawn for at least one month before the study. Procedure must be adequately explained to the patients.

Electrode calibration: pH electrode must be calibrated before and at the end of each study as failure to do so may lead to gross inaccuracy. Calibration is performed with both acidic and neutral buffer of known pH (usually pH 4 and 7).

Positioning of pH electrode: The proximal pH electrode needs to be placed 5-cm above the upper border of LES, determined by manometry. The distal pH electrode is kept in the stomach to record gastric acidity. Therefore, manometry should be done before pH monitoring. Some authors suggest positioning of pH probe by noting pH change while withdrawing the electrode from stomach, by fluoroscopy and, in reference to gastroesophageal mucosal junction noted endoscopically;[26-27] however, these methods may not be accurate.

24-h monitoring: Data logger is hanged from patient's shoulder. He/she is asked to remain ambulatory. A diary is given to the patients with instructions to record the time of meal, symptoms and body posture. Advice to avoid acidic drinks during the study should be given to the patients. The patient should eat and drink the usual foods during the study. We do not perform pH monitoring as an outpatient procedure as we do not want to let the patients go home with the costly equipment. However, outpatient pH monitoring is more physiological than inpatient study. Once the study is completed, the electrode is removed and the signal files are downloaded and analyzed with software provided with the system.

Interpretation

The parameters that are evaluated during analysis of 24-h pH record include (a) percentage of time lower esophageal pH<4, (b) percent of reflux time in supine posture, (c) percent of reflux time in upright posture, (d) total number of reflux episodes, (e) reflux episodes of more than 5 minutes duration, (f) duration of longest reflux episode. Of these, percentage of time lower esophageal pH <4 is the most important parameter. Upper limits of normal of percentage of time lower esophageal pH <4 are 5 (total), 6 (in upright posture) and 2.5 (in supine period) in our laboratory.[25] Accordingly, gastroesophageal reflux may be erect, supine or combined. A 24-h pH record showing combined gastroesophageal reflux is shown in **Figure 3** (D).

Clinical utility

Gastroesophageal reflux disease (GERD) is diagnosed by symptoms, response to proton pump inhibitors[28] and if esophagogastroduodenoscopy has already been done, by typical endoscopic findings, if present.[29,30] 24-pH monitoring is not essential in all patients with GERD. However, it is essential in patients with atypical symptoms including reflux-induced asthma; patients refractory to medical treatment and before undertaking surgery.

Combined Multichannel Intraluminal Impedance & pH Monitoring (MII-pH)

Equipment

The equipment consists of impedance electrode, data logger with flash card and computer with software. We commonly use catheters with 6 impedance electrodes (impedance measuring segments) and a pair of pH electrodes (**Figure 4**). Electrical impedance (expressed in ohms) around the catheter in the area between the two pair of electrodes is inversely proportional to the electrical conductivity in the area between the two electrodes. [31] In the absence of swallow or reflux within the esophagus, the impedance is identified by the electrical conductivity of the inner wall of the esophagus itself and it is relatively stable, and is known as impedance baseline value. Impedance increases if gas refluxes into esophagus (belching) whereas liquid reduces it. Bolus movement recorded by impedance monitoring are either retrograde and ante-grade.[32] Retrograde bolus movements denote reflux. If refluxate is liquid, impedance drops by 50% in two consecutive or more recording sites. Antegrade bolus movement is due to swallow. The pH sensor during impedance monitoring classifies reflux episodes are categorized as acid (<4) and non acid (>4).[33]

Technique

Preparation for the test, electrode calibration and 24-hours monitoring technique are similar to the ambulatory pH-metry.

Interpretation

Parameters recorded during MII-pH monitoring include: (a) total reflux (liquid and gaseous) percent time and those in upright and recumbent posture. (b) acidic and non-acidic reflux in upright, recumbent and both posture. (c) duration of esophageal pH<4 in upright and recumbent and both the periods, (d) acid exposure percent time in upright, recumbent and both the postures, (e) mean acid clearance time, and (f) symptom correlation to reflux (acidic and non acidic).

Clinical utility

In contrast to pH-metry alone, impedance-pH metry can detect non-acid and gas reflux in addition to acidic reflux[32,33,34]. Therefore, it may be used to diagnose reflux even on treatment with acid lowering drugs.[35] Impedance-pH monitoring is more

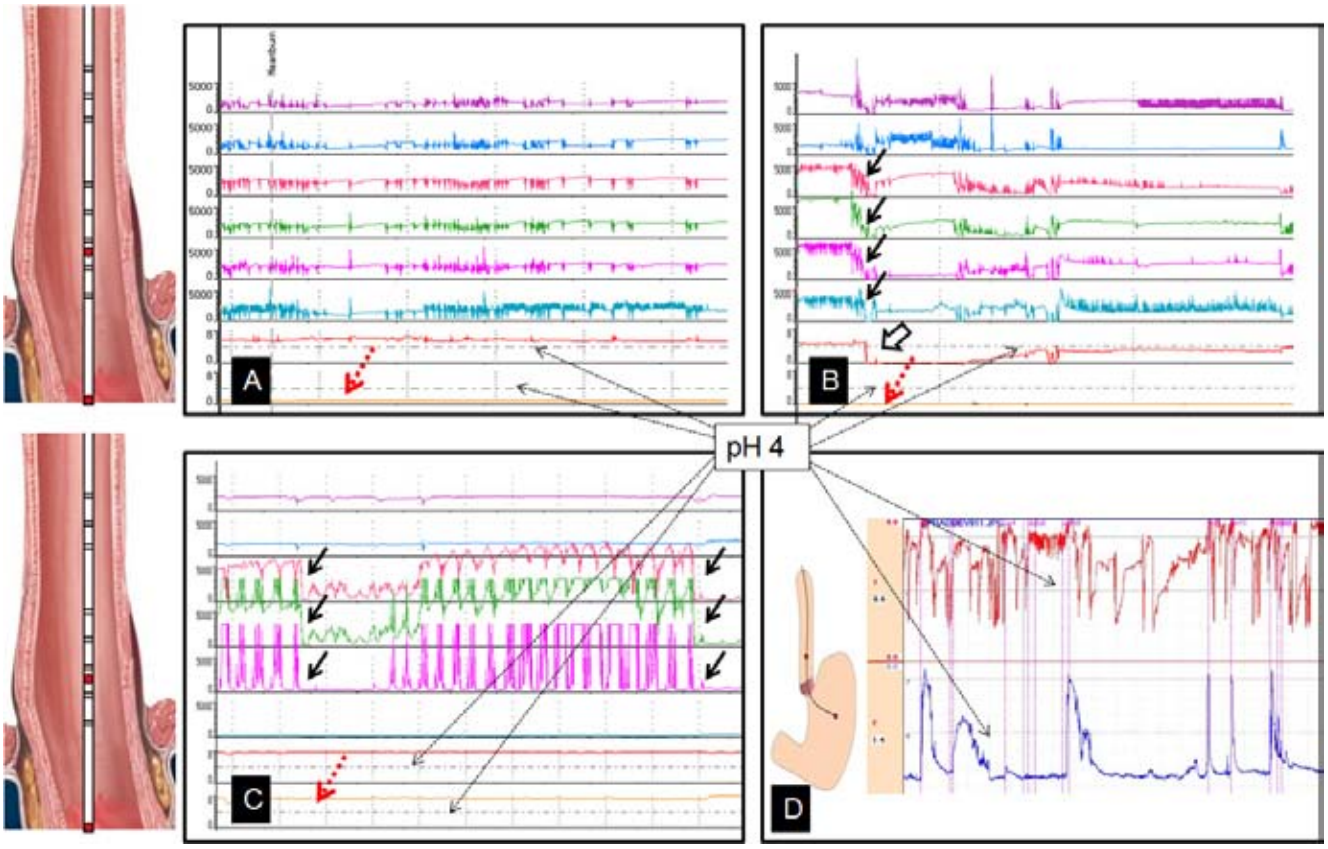

Figure 4: Shows some of the impedance-pH monitoring signals recorded from our laboratory using eight impedance sensors and two pH sensors. (A) No reflux is identified by the impedance sensors or pH sensor. Dotted red arrow shows the gastric pH which is below 4. The lines indicating pH4 are shown using dotted black arrows. (B) Acidic liquid reflux: Black solid arrows show the drop of impedance in the esophagus and broad open arrow indicates fall in esophageal pH below 4. (C) Non-acidic liquid reflux: Fall in impedance in the distal esophagus (indicated by black solid arrows) without fall in pH below 4. Note that the gastric pH is above 4 (indicated by dotted red arrows) as the patient was on proton pump inhibitor. (D) The schematic diagram shows the pH probe with two pH sensor, one is placed in the esophagus and other in the stomach. In the tracing, red line shows the esophageal pH and blue one gastric. 24-h ambulatory pH-metry record shows abnormal gastro-esophageal reflux.

sensitive to diagnose GERD. It is useful to investigate patients with atypical symptom of GERD.[36,37,38] **Figure 4** shows some of the impedance-pH metry signals of patients investigated in our laboratory.

Esophageal transit scintigraphy

Scintigraphic technique using radioactive liquid or solid bolus to study the aboral and retrograde movement of the esophageal luminal contents is fairly simple to perform. It non-invasively quantifies the time, extent and pattern of the bolus clearance from the esophagus.[39] Radionuclide transit scintigraphy has many variations regarding radionuclide used, bolus content, patient position, method of image acquisition and analysis.

Technique

Patients fast overnight before the study and remain off all the drugs that can alter esophageal motility for 3-5 days. A general protocol includes image acquisition in supine position; practice swallows of bolus followed by bolus of 99mTechnitium Sulfur colloid in 10-15ml water. Dynamic images are acquired every 0.1-0.8 frame/sec by computer and gamma camera while the patient is asked to swallow. Individual and dynamic cine images are reviewed. Quantification may be performed to calculate the transit time from individual segments of the esophagus and percentage clearance of bolus. Functional condensed dynamic images give a good visual evaluation of the pattern of clearance of the bolus.

Interpretation and clinical utility

Qualitative cine images may be adequate to diagnose severe abnormalities. Some form of quantification is commonly used to diagnose less severe abnormalities and is particularly helpful in follow up of the patients after therapy. Various quantification methods have been compared. Normal mean liquid esophageal

transit time varies depending on technique used and is usually within a range between 6-15 sec. Computer generated curves or functional images help in evaluating the clearance pattern. Clearance curves from the proximal, middle and distal thirds of the esophagus normally show smooth progression of the tracer activity into stomach. This pattern may be lacking in disease states. Functional images condense the dynamic image data into a single image with one spatial dimension (vertical) and one temporal dimension (horizontal).

In achalasia the esophageal segmental pattern is typically flat in all the segments with little evidence of the bolus progression. Transit studies may show normal progression of the bolus through the upper and mid esophagus but prolonged retention of the activity in distal esophagus. Scleroderma patients typically demonstrate greater than 50% retention of the activity in distal esophagus even after 10 min of multiple swallows. In diffuse esophageal spasm there are multiple uncoordinated peaks representing disorganized transit of bolus through all the segments of esophagus.

Esophageal transit studies are also being used to elucidate the patho-physiological details of the disease like gastro-esophageal reflux in which, contribution of delayed lower esophageal transit is hypothesized. Though manometry often scores over esophageal transit studies in diagnosis of esophageal motility disorders, transit studies may be recommended, (a) when esophageal manometry is not available or is not tolerated by the patient; (b) when manometry is equivocal or negative but reasonable suspicion of disease remains; (c) when serial changes and response to therapy need to be monitored; (d) to evaluate functional correlates of manometric abnormalities particularly for research.

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Original Article

Long term efficacy and safety of N-butyl-cyanoacrylate in endoscopic treatment of gastric varices

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ABSTRACT

Introduction: Endoscopic glue (N-butyl-2-cyanoacrylate) injection has emerged as promising therapy for bleeding gastric varices (GV). We evaluated safety and long term efficacy of this technique in patients with portal hypertension and large bleeding GV.

Patient and Methods: 170 patients (mean age 40.9±14y; 132 male; 142 had cirrhosis, 40 Child A, 62 Child B, 40 Child C) underwent glue injection into GV (F3 140, F2 30; fundal 114) as emergency procedure for active bleeding in 62 and electively for prevention of rebleeding in 108. Glue was injected intra-variceally under endoscopic vision, 0.5-4ml/aliquot, repeated at 3 weeks till varices were eradicated/solidified. The efficacy was assessed by hemostasis at 48 h, primary, secondary, definitive success and treatment failure.

Results: The overall hemostasis rate at 48h was 82.3% (51/62). Follow up was available in 158 patients for mean of 30.7 ± 17.2 months. Repeat injections were performed in 76. The mean number of injections were 1.9±1.0 (1-4); total volume was 2.5±1.7 ml / patient. The status of GVs at last follow up was : disappeared in 32 (22.6%); F1 solidified in 46 (32.3%); F2 solidified in 64 (45.0%). Bleeding recurred in 14.5% (23/158); 60% within 2 weeks of injection. The primary, secondary and definitive success rates were 85.4% (135/158), 4.4% (7/158) and 89.9% (142/158) respectively and treatment failure rate was 10% (16/158). No significant complications were noticed except for injection site ulceration in 32. Twenty patients died on follow up (9 died of uncontrolled bleeding, 11 died of liver failure)

Conclusion: Endoscopic glue injection into bleeding GVs was effective in achieving hemostasis in 82% with a definitive success rate of 90% and had a good safety profile on long term follow up.

KEYWORDS : N-butyl cyanoacrylate , gastric varices, variceal bleed, glue

Introduction

Gastric varices develop in about 20 to 30% of patients with portal hypertension.[1-3] The cumulative risk of bleeding from gastric varices has been reported to be 16%, 36% and 44% at 1, 3 and 5 years follow up in patients with cirrhosis.[4] Bleeding from gastric varices (GV) although less common than from esophageal varices, is more severe.[5] Treatment is difficult and the options include surgery (porto-systemic shunts[6] and non-shunt surgeries),[5,7,8] transjugular intrahepatic portosystemic

shunt (TIPS)[9] and endoscopic methods.[10-13] Both surgical and radiological intervention carries significant risk of mortality and morbidity.[14-18] Endoscopic sclerotherapy using various agents like hypertonic glucose solution, sodiumtetradecylsulfate, ethanolamine oleate and absolute alcohol have been tried in the treatment of gastric variceal bleeding but the results have not been satisfactory.[19-22]

Tissue adhesive agents (glue) have been used as an alternative to sclerosing agents in the management of bleeding esophageal varices by Gotlib and Zimmerman[23] in 1984 and for gastric varices by Soehendra et al in 1986.[11] N-butyl-cyanoacrylate polymerizes instantaneously and solidifies on contact with blood[24] and is presently used for endoscopic management of gastric variceal bleeding worldwide except in United States. The control of active variceal bleeding has been reported to be 93% to 100% but up to 30% of patients may have recurrence of bleeding on follow up.[25] This procedure has been reported to be safe in small series, but carries a small risk of systemic embolization and is technically demanding.[26]

The aim of the present study is to evaluate the short and long-term efficacy and safety of endoscopic variceal injection of N-butyl-cyanoacrylate (Nectacryl / Histoacryl) in the management of bleeding gastric varices.

Study Design

Patients

We retrospectively analyzed our endoscopic data of more than 2000 patient who underwent endoscopic treatment for variceal bleeding from 1996 to October 2005. Of these 170 patients underwent endoscopic gastric variceal injection with N-butyl-2-cyanoacrylate for acute hemostasis or prevention of re-bleeding. The mean age was 40.9 + 14.0 (range 13- 69) years; 132 were male. The etiology of portal hypertension was cirrhosis of liver in 142 and extra hepatic portal venous obstruction in 28 patients (**Table 1**). Most of the patients of cirrhosis had compensated liver function (Child- A 40; B 62; C 40). The etiology of cirrhosis was alcohol in 34, hepatitis B in 20, hepatitis C in 10, Budd-Chiari syndrome in 2 and autoimmune liver disease in 3 each and the remaining 73 did not have any marker positive. As these 73 patients did not undergo anthropometric measurement or liver biopsy or assessment for risk factors for nonalcoholic fatty liver disease, we could not comment whether majority had NAFLD as cause of liver disease. These patients were not investigated with IgG antiHBc or HBV DNA test to rule out occult viral infection. In a study published from our center occult HBV constituted about 10% of cases of cirrhosis.[27] Doppler US was done to evaluate for portal vein thrombosis in all patients. 6 of 142 (4.2%) cirrhosis patients had portal vein thrombosis at initial evaluation. Four patients had recurrence of gastric variceal bleeding due to blocked surgical shunts (interposition porto-caval shunt- 2 and lieno-renal shunt- 2). The gastric varices at endoscopy were classified according to system proposed by Hashizume et al, in respect to the form (F), location(L) and presence of red color signs as this classification includes location and form of gastric varices independent of esophageal varices.[28]Esophageal varices if present were classified grade 1 to 4 according to Conn's classification[29] and presence of RCS was noted. Most of the varices were large (F_3 140 and F_2 30), located in the fundus (fundus in 114, lesser curve in 9, cardia in 9, fundus along with lesser curve in 9 and all the three sites in 13) and 135 had RCS. One hundred and thirty four patients were on endoscopic treatment for esophageal varices (grade I-II in 91; 3 in 26 and 4 in 18 patients) at the time of first session of N-butyl-cyanoacrylate injection. One hundred sixteen patients received endoscopic variceal ligation, rest 18 received sclerotherapy using 1% polidoconol initially followed by combined endoscopic treatment (variceal ligation till variceal size decreases to II followed by sclerotherapy) as per our department policy.[30] Majority had grade I-II esophageal varices at the time of first glue injection. Six patients had recurrence of bleed from esophageal varices which was treated with endoscopic sclerotherapy and in these patients rebleeding was presumed to be from esophageal as gastric varix was completely obliterated and stigmata of bleeding was present on esophageal varices.

The bleeding was classified as recent if a) there was active spurt, b) ongoing ooze, or c) fibrin clot seen on the GV or if blood was seen in the stomach in the presence of large gastric varices and no other cause for bleeding could be found. The patients were classified as past bleeder if there was history of upper gastrointestinal bleed in presence of large gastric varices (F_2 and F_3) with red color signs without any other cause (< grade 2 esophageal varices without stigmata of recent bleed). According to the bleeding pattern the patients were divided in two groups; A. first presentation as gastric variceal bleeding, B. bleeding from gastric varices after successful eradication/ control of esophageal varices by endoscopic band ligation or sclerotherpy. We had 36 and 134 patients in group A and B respectively.

Table 1: Characteristics of patients with gastric varices (n=170)

Features	Number
Age (Mean± SD) Years	40.9± 14.0
Gender(M/F)	132/38
Causes of PHT	
• Cirrhosis	142
• EHPVO	28
Etiology of cirrhosis	
• Alcohol	34
• Hepatitis B	20
• Hepatitis C	10
• Budd Chiari Syndrome	2
• Autoimmune	3
• Cryptogenic	73
Child Status	
• A/B/C	40/62/40
Gastric Varices	
• Form - F1/F2/F3	0/30/140
• Location - Fundus/Cardia/Lesser Curve	114/9/9
• Combination	38
• Red color sign	135
Bleeding status	
• Recent bleed	62
• Past bleed	108
Bleeding Pattern	
• *De novo gastric* variceal bleed	34
• Post esophageal variceal sclerotherapy	134

Methods

Standard commercial 21-gauge flexible sclerotherapy needle of 8 mm length was used to inject N-butyl-2-cyanoacrylate (Nectacryl; Dr. Reddy's Laboratories Ltd. Hyderabad, India/ Histoacryl; B.Braun Melsungen AG, Germany) into the gastric varices. A standard forward-viewing video endoscope (EG 2940; Pentax) was used. The tip of the endoscope and the accessory channel were primed with silicone oil before injection to prevent clogging of endoscope during the procedure. The sclerotherapy needle was primed with lipiodol before injection. Glue was mixed with lipiodol in 4:1 ratio and used for injection. The largest of the varices with red color sign was chosen first (**Figure 1 &2**). After targeting, the needle was taken out from the sheath, a deep puncture of the gastric varix made, and the glue quickly injected followed by flushing of the needle with lipiodol. The volume used was 0.5 to 4ml per aliquot. The amount per injection was decided by size of varix (~0.5ml for F1, 1-2ml for F2 and 2-4ml for F3 varix).[31] Routine upper abdomen radiograph were done after each session to check the presence and contour of glue cast and satisfactory obliteration of feeding vessel (**Figure 3**). In presence of active bleed from a gastric varix the bleeding point or a site near it was chosen.

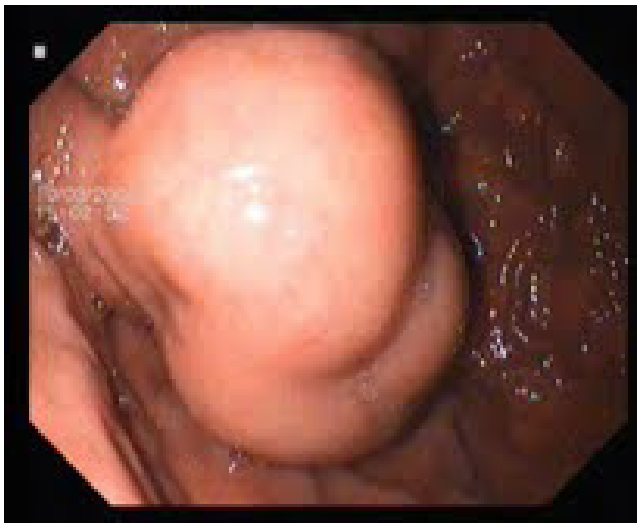

Figure 1: Endoscopic picture showing F3 gastric varix

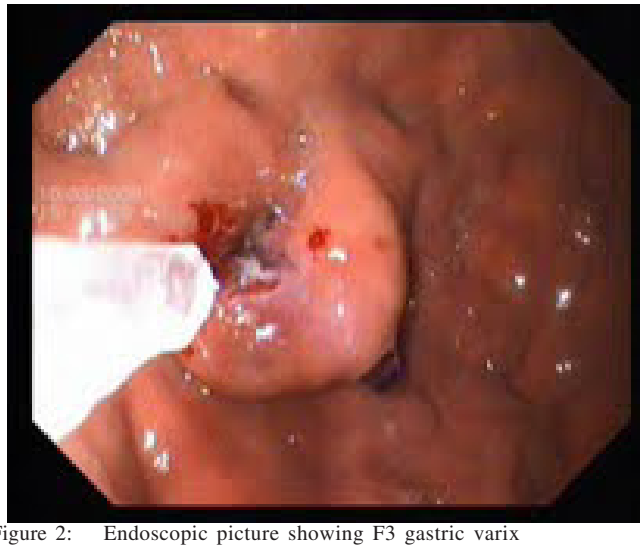

Figure 2: Endoscopic picture showing F3 gastric varix

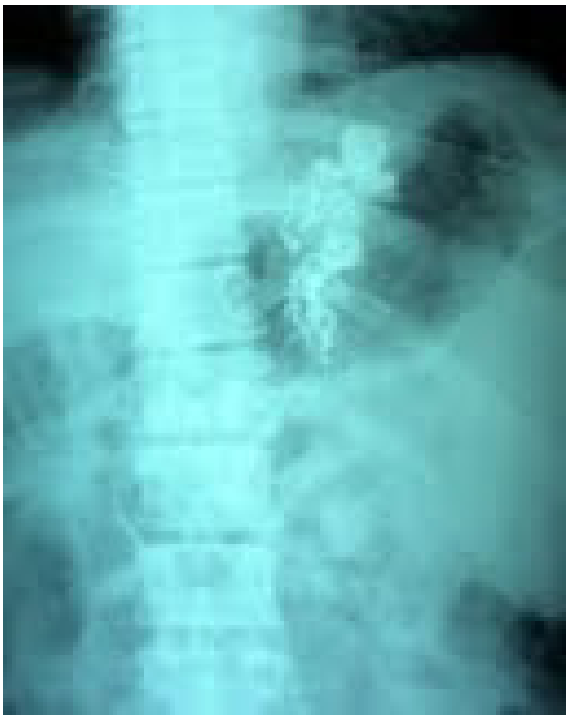

Figure 3: Abdomen X-ray showing glue cast filling gastric varix and feeding vessel

Patients underwent repeat endoscopic evaluation after 3 weeks for 3 months then every 3 months up to 1 year then 6 monthly or any time if the patients had recurrence of bleed. Gastric varices were classified as obliterated if they felt to be hard on blunt probing with the needle sheath, and non-obliterated if they appeared compressible and indented on pressure. N-butyl-cyanoacrylate injection was repeated if the patients had recurrence of bleed or had unobliterated varices with or without red color signs. After one recurrence of bleeding the patients were also given the choice of surgical treatment. If the patients had esophageal varices, endoscopic variceal sclerotherapy or ligation was also done at 3 weekly interval till the varices were eradicated.

The outcome assessment included hemostasis for active bleeding which was defined as control of bleeding at 48 hours. The recurrence of bleeding was defined as bleeding arising from the injected or nearby gastric varices after 48 hours. The use of alternative treatment (balloon tamponade or surgery or TIPS) and mortality were recorded. The gastric variceal status at the time of last follow up was recorded. Primary success was defined as absence of recurrent bleeding following N-butyl-cyanoacrylate injection during the entire period of follow up. Secondary success was defined as absence of recurrent bleeding following reinjection of N-butyl-cyanoacrylate for first recurrence of bleeding during the entire period of follow up. Definitive hemostasis included both primary and secondary success. Treatment failure was defined as failure to achieve definitive hemostasis by endoscopic N-butyl-cyanoacrylate injection. "The authors affirm that all research related to this study was carried out in accordance with the Helsinki Declaration as revised in 1989".

Statistics

The results are expressed as mean ± standard deviation. Statistical software SPSS 10.0 was used for data analysis. The risk factors for recurrent bleeding including Child Pugh class, age, gastric varix location, number of sessions and volume of glue injection were analyzed by Spearman's correlation coefficient and Chi Square test. p value <0.05 was taken as significant. Logistic regression analysis was done to analyze the predictive value of Child-Pugh status, initial gastric variceal form and location, volume and number of sessions of N-butyl-cyanoacrylate injection for recurrence of bleeding from gastric varices in the follow up period. Event curve (recurrence of bleeding) was constructed by Kaplan Meier method for etiology of portal hypertension, Child-Pugh class, bleeding pattern and the difference was assessed by Log rank test.

Results

170 patients received N-butyl-cyanoacrylate injection for gastric varices. Of them, 62 underwent glue injection as an emergency procedure to achieve hemostasis from actively bleeding GV and in 108 patients it was done as an elective procedure for prevention of re-bleeding. The 48-hours hemostasis in recent bleeders was 82.3%, (51 out of 62). Among eleven patients who could not achieve 48 hours hemostasis, 1 was taken for emergency TIPS, 10 were managed with pharmacological treatment as they were unfit for surgery. Bleeding was controlled in all of them. Six of the ten who were managed with pharmacological treatment underwent a repeat glue injection electively. Four of the six were lost to follow up (**Figure 4**). The mean volume of N-butyl-2-cyanoacrylate injected at first injection was 1.4 ± 0.6 (range 0.5 to 4) ml.

Among 108 patients who underwent elective glue injection, the initial bleeding was managed with pharmacological treatment in 78 patients at secondary care hospital and later referred to our center. Remaining 30 patients were managed at our hospital with pharmacological treatment as these patients were unfit for endoscopy due to hepatic encephalopathy. The mean time interval between first episode and glue injection was 10.5± 4.2 days (4-30 days).

Of the 170 patients, 12 were lost to follow up after initial endoscopic treatment. The remaining 158 patients had mean period of follow up of 30.7 ± 17.2 months (12 to 66 months); 80 patients had follow up for more than 20 months. Total volume injected per varix was 1.6 ± 0.6ml (range 0.5-4 ml) and per patient was 2.5 ± 1.7 ml per patient and mean sessions required for eradication were 1.9±1.0. On follow up, 76 patients underwent repeat sessions of N-butyl-2-cyanoacrylate injection (mean 2.3 ± 0.6); the mean cumulative volume of N-butyl-cyanoacrylate injected per patient was 2.8 ± 1.6 (0.5 to 8 ml). Before 2004, we used to prepare aliquots of 1ml each and during glue injection there used to be considerable time delay due to exchange of syringes. Now we prepare aliquot according to predefined volume (volume drawn in a single syringe). We used to encounter problems of clogging of needle during injection frequently before 2004. For last 2 years with the above modification needle clogging is rare. During subsequent 2 years we have been able to salvage most needles by immediate flushing with lipiodol after injection.

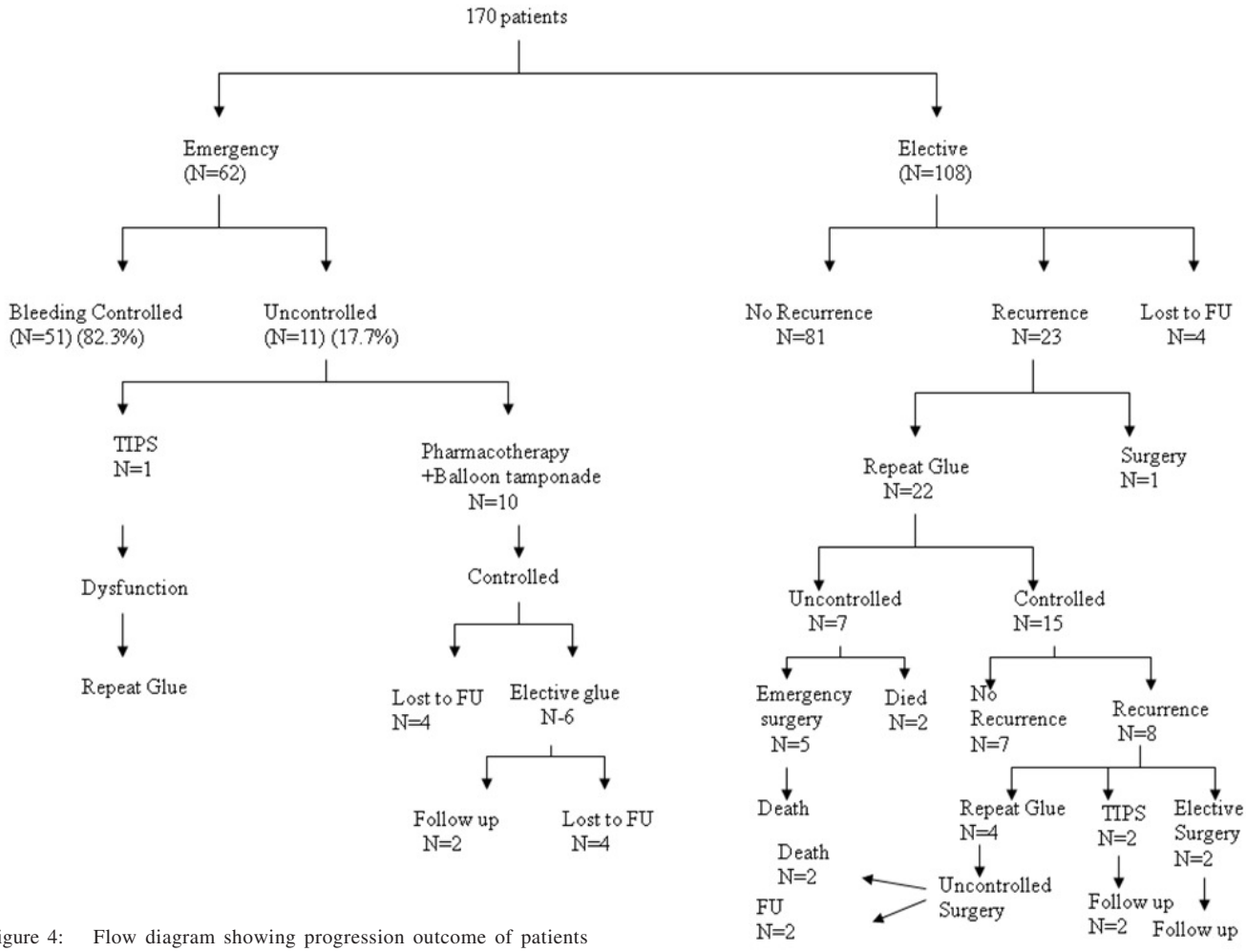

Figure 4: Flow diagram showing progression outcome of patients

At the time of last follow up, the gastric variceal status was completely obliterated in 32 (22.6%), F1 and solidified in 46 (32.6%) and F_2 and solidified in 64 (45.0%; **Table 2**). After initial regression 16 (11 %) patients had shown increase in size of gastric varices on follow up.

Bleeding from gastric varices recurred in 23 (14.5%) of 158 patients, 8 of whom had a 2nd recurrence of bleed. The first recurrence occurred after a mean duration of 2.5 (range 1 week to 24) months. Majority of them 69.5% (16 out of 23) had recurrence within 6 months. In ten (45.4%) of the patients the rebleed was due to sloughing of the glue cast and formation of ulcer at the injection site and in the remaining 13 patients it was due to recurrence of large gastric varices as these patients had completely obliterated or solidified varices on follow up and bleeding occurred from varices which were not there at initial evaluation and appeared at different site compared to initial varices.

On logistic regression analysis, number of sessions of N-butyl-cyanoacrylate injection (p =0.04) and Child status (p=0.01) showed statistical significance for recurrence of bleeding. There was significant difference between recurrence of bleed and non-recurrence group of number of sessions of N-butyl-cyanoacrylate injection (p=0.04), total volume of N-butyl-cyanoacrylate injected (p= 0.01) and gastric variceal location (p 0.043) (**Table 3**). The Kaplan-Meier event curve (**Figure 5 & 6**) comparing Child status showed significant overall difference (Log rank test).

We assessed feasibility of TIPS only in those patients in whom initial control of bleeding with glue had failed. Four of 23 patients who had failed endoscopic treatment had portal vein thrombosis and were not candidates for TIPS while in remaining patients TIPS was feasible. Of these 23 patients, 22 underwent repeat N-butyl-cyanoacrylate injection; one was taken up for gastroesophageal devascularization. The 48 hours bleed control following repeat N-butyl-cyanoacrylate injection was 68.1% (15 of 22). Two patients died (8.6%) due to uncontrolled bleeding. Remaining five were taken for emergency devascularization, all five died due to liver failure during postoperative period. Eight patients out of 15 (53.3%) had 2nd recurrence of bleeding within 2 to 12 months following N-butyl-

cyanoacrylate injection for first recurrence. The sloughing of glue cast and ulcer formation was the cause of recurrence in 4 patients. Four of them underwent another session of N-butyl-cyanoacrylate injection and in all four patients it failed to control the bleeding and they were taken up for shunt surgery. In two pateints, distal splenorenal shunt and in the remaining two patients interposition portocaval shunt was done. Two of them died during postoperative period due to liver failure, remaining two are on follow up. Two patients underwent TIPS as both had poor liver function and unfit for surgery. Both the patients are on follow up with patent TIPS. The remaining two patients after initial bleed control by medical treatment underwent shunt surgery and are on follow up.

Table 2: Results of Glue injection (n=158).

Features	Number of patients (%)
Forty eight hours hemostasis	51/62 (90.3)
Success	
• Primary success	135/158 (85.4)
• Secondary success	7/158 (4.4)
• Definitive success	142/158(89.9)
Recurrence of bleed	
• First recurrence	23/158 (13.9)
• Secondary recurrence	8/158 (5.0)
Total number of sessions (mean± SD)	1.9±1.0
Total number of glue injected (ml)(mean±SD)	2.5±1.7
Gastric varices status at last follow up (142)	
• F1/F2/F3	64/46/0
• Disappeared	32(22.5)
Total follow up (months)(mean± SD)	30.7±17.2
Deaths	20

Table 3: Comparison between group with no recurrence and recurrence bleed

Features	No recurrence group (n=135)	Recurrence group (n=23)	p value*
Age (mean+ SD) yrs	38.6+ 14.7	41.2±14.0	NS
Sex male/female	104/31	18/5	
Etiology			
• Cirrhosis	113	19	NS
• EHPVO	22	4	NS
Child status			
• A	33	4	p=0.01
• B and C	80	15	p=0.01
Bleeding status			
• Recent bleeder	54	0	
• Past bleeder	81	23	NS
Bleeding pattern			
• First gastric variceal bleed	25	11	NS
• Post esophageal variceal Scerotherapy	110	12	NS
Gastric variceal status			
• Form F3	115	22	
• Location fundus	31	22	p=0.04
Total volume of nectacryl injected (Mean + SD)	2.4± 1.4	2.8±1.6	p=0.01

Abberivation: EGPVO-Extra hepatic portal venous obstruction

Table 4: Predictive factors for recurrence of bleeding

Factors	Odd ratio (95% CI)	p value
Child C	5.88 (1.52-22.6)	p=0.01
No of Session	1.91 (0.89-4.11)	p=0.04
GVx (Location)	0.95 (0.68-1.32)	p=0.7
Volume of injection	1.07 (0.80-1.43)	p=0.06
Age	1.01 (0.95-1.04)	p=0.4

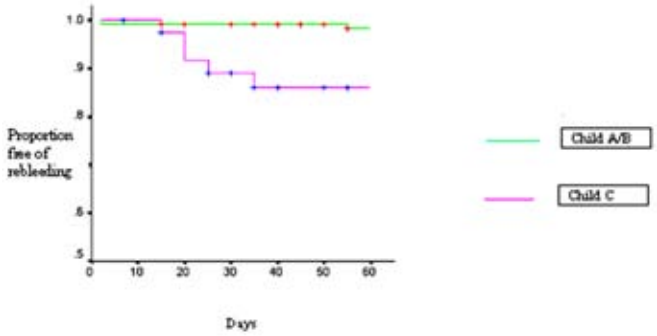

Figure 5: Cumulative proportion (Kaplan-Meier plot) of patients of child status (Child A/B vs. Child C) free of bleeding (p=0.0004)

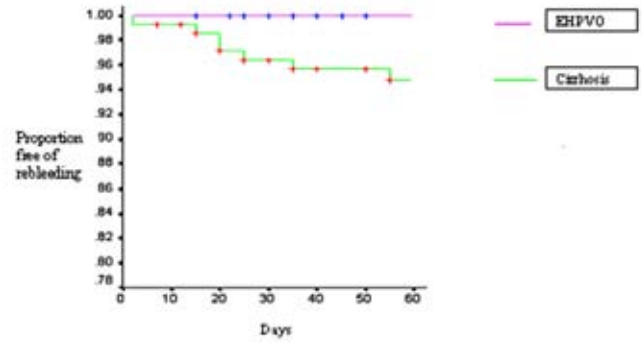

Figure 6: Cumulative proportion (Kaplan-Meier plot) of patients with EHPVO vs. Cirrhosis free of bleeding (p=ns)

The primary and secondary success was 85.4% (135 out of 158) and 4.4% (7 out of 158) respectively. The definitive success was 89.9% and the treatment failure was 10%.

None of the patients had significant complications related to the procedure except for injection site ulceration in 32 patients. One of the patients with cirrhosis of liver had one successful pregnancy following one session of N-butyl-cyanoacrylate injection without any effect in the fetus. During glue injection, few patients complained of chest pain and cough but none of them showed any evidence of glue embolization on chest and abdomen radiographs or additional hospital stay or intervention due to procedure. Total of 20 patients died

{uncontrolled gastric variceal bleed-9 (postendoscopic treatment-2, post surgery-7), Liver failure-11}.(**Table 4**)

Discussion

N-butyl-cyanoacrylate is very effective in controlling active bleeding from gastric varices. The reported success for hemostasis in active gastric variceal bleeding is 90% to 100%.[3,31] The other sclerosants used in previous studies for treatment of gastric varices had poor control and high recurrence of bleed.[19,20,32]Sarin et al have reported use of absolute alcohol as sclerosant for treatment of gastro esophageal varices.[20]They have reported acute hemostasis only in two thirds of the patients and high rebleeding rate of 53% from isolated gastric varices. We have found good efficacy of N-butyl-cyanoacrylate injection for bleeding gastric varices. The 48-hours hemostasis for recently bleeding gastric varices was 82.3% for the first injection, which is comparable to the published reports.[31,33]We had to reinject the gastric varices for second and third recurrence of bleeding as relatives of the patients were not willing for major surgery. The efficacy of N-butyl-cyanoacrylate for active bleeding was low in recurrent gastric variceal bleeding. Huang et al reported the success of repeat superglue injection for first recurrence of gastric variceal bleed to be 71.4% (15 out of 21).[31]We achieved 68% (15/22) hemostasis at 48 hours repeat injection of N- butyl-cyanoacrylate for the first recurrence and 0% for second recurrence. Secondary success rate in our study was 4.4 %(7/158), as defined by absence of recurrent bleeding following reinjection of N-butyl-2-cyanoacrylate for first recurrence of bleeding during the entire period of follow up. This may be due to longer follow up and due poor liver function (as most of them were Child- Pugh stage C).

It is not clear whether the patients with recurrence of bleeding following N-butyl-cyanoacrylate injection should be reinjected. TIPS followed by liver transplant could be a better option if the facilities are available.

The primary, secondary and definitive success in our series was 85.4%, 4.4% and 89.9% respectively. Huang et al have reported primary, secondary and definitive success of 76.6%, 16.7% and 93.3% in a recently published study using superglue for the treatment of gastric varices. The mean follow up period in their study was 13.2 $\pm$ 2.0 months.[31]We had a much longer follow up period of 30.7 $\pm$ 17.2 months compared to study by Huang et al . This probably explains the lower secondary success rates in our study, because it is known that the rate of rebleeding from varices increases with the length of follow up.[4]

Although N-butyl-cyanoacrylate has a high success rate in hemostasis of actively bleeding varices, the recurrence of bleeding continues to be a problem. In most of the studies the recurrence of bleeding is reported to be around 30%.[31,34]In our series the recurrence of bleeding was 13.9 % (22 out of 158). The first recurrence of bleeding occurred in most patients 77.2% (17 out of 22) within 6 months after the initial N-butyl-cyanoacrylate injection. N-butyl-cyanoacrylate forms a cast in the varices and blocks it. It can ulcerate and slough out leading to recurrence of bleeding. About 45.5% (10 out of 22) our patients had rebleeding due to ulceration and extrusion of the cast. All our patients were on proton pump inhibitors. We encountered ulcer at injection site commonly, but in these 10 patients with recurrence of bleeding, there was ulcer at injection site with stigmata of recent bleed and no other source of bleeding. We could not find any explanation to more catastrophic bleed in our study as compared to self limited bleed due ulceration as reported by Huang et al.[31]

Huang et al reported post cyanoacrylate injection cast extrusion in 26.6% of patients within a mean period of 6 months.[31] It is not clear whether the volume and site of injection has any influence on formation of ulcers and cast extrusion. Binmoeller and Soehendra suggested that paravariceal injection leads to more ulceration, so the injection should be strictly intravariceal.[24] Majority of the recurrence of bleeding occurred in cirrhosis patients. Various factors like size of varices, underlying disease, portal vein thrombosis and liver function status have been reported as risk factors for recurrence of bleeding.[4] When we tried to compare the patients who had recurrent bleeds from gastric varices with those who did not, poor liver function and fundal location seemed to be associated with a higher risk of rebleed.

The schedule of gastric variceal N-butyl-cyanoacrylate injection varies as there are no definite guidelines in the literature. There can be two approaches following first injection; either re-inject only if the patient rebleeds on demand basis,[34]or re-inject the varices repeatedly on follow up till they are completely obliterated or disappeared.[24,31]There are no randomized studies to show that one approach is better than the other. In a comparative study, Lee et al reported repetitive injection group had significantly reduced rate of late recurrence of bleeding compared to the 'on demand' injection group.[34]But, this study was nonrandomized and the two groups were not receiving injection at the same period of time. They have used

endoscopic ultrasound guidance for repetitive injections. Palpation of varices with blunt sheath of the sclerotherapy needle has been used to assess the obliteration of gastric varices.[24,31]We followed a policy of repetitive injection depending on the size of the varices on follow up endoscopy. The obliteration of varices was assessed by blunt palpation with sheath of sclerotherapy needle.

The dilution of glue and volume injected per session varies in different reported series. We have used sufficient volume of N-butyl-cyanoacrylate to cause hardness of the targeted varix. In different studies authors have also used this agent varying from undiluted to 1:1 to 2:1 dilution with lipiodol.[29,35]The dilution is made to delay the polymerization so that the injector does not get stuck in the solidified varix. Traditional dilution (1:1 or 2:1) of glue with lipiodol has been reported to cause systemic and pulmonary embolization (depends on speed and volume of injection). On the other hand use of undiluted glue frequently causes needle clogging and does not permit radiological visualization of the glue cast to ensure blockage of feeder vessel.[36,37]Our experience with limited dilution of glue (4:1) provided benefit on both these issues. We have not encountered any problem related to quick solidification of N-butyl-cyanoacrylate or pulmonary embolism with this small amount of lipiodol.

The accompanying esophageal varices require band ligation or sclerotherapy because they also carry the risk of bleeding.[26]We treated the esophageal varices with endoscopic variceal ligation or injection of sclerosant initially followed by combined endoscopic treatment as per our department policy.

There have been no reports in literature of use of N-butyl-cyanoacrylate for prophylaxis of bleeding from large gastric varices. Some of the patients on esophageal variceal sclerotherapy, who develop large gastric varices with RCS on follow up, pose a problem. Whether prophylactic injection of glue into their gastric varices would help is not clear. Some authors have advocated routine injection of glue into large gastric varices detected at the time of esophageal variceal sclerotherapy.[24]We feel this is an unsettled issue which needs to be addressed in prospective trials. There was reduction in the size of gastric varices on follow up after glue injection. Large F3 varices were present in 82.8% at the initiation of treatment. At the last visit, majority of varices had decreased in size {F2 solidified in (45.0%), F_1 solidified in (32.3%)} or had completely disappeared in (22.5%). Most of reported series mention about obliteration (solidification on palpation with blunt sheath of sclerotherapy needle) and not about eradication of gastric varix.[24,31]After initial regression, 11 % of patients showed increase in size of gastric varices during follow up. The decrease in size of gastric varices depends on the policy of N-butyl-2-cyanoacrylate injection. The repeated injection group aims at total obliteration of varices. Lee et al reported > 90% obliteration of isolated gastric varices after 2.2 $\pm$ 1.7 sessions.

Except for the post injection local ulceration, we have not found any major complications of cyanoacrylate injection. One of our patients had a successful pregnancy without any adverse effect to the fetuses. Safety of cyanoacrylate in control of acute bleeding from gastric varices during pregnancy has been reported.[38] The overall mortality in this study was 12.6% (20 of 158), most of them (11 out of 20) were related to liver failure due end stage liver disease.

In conclusion, the first N-butyl-cyanoacrylate injection is very effective in controlling bleeding from gastric varices. This agent is not so effective for the recurrence of bleeding from gastric varices. Repeated injections are required to obliterate the varices. In long term follow up, N-butyl-cyanoacrylate has a good safety profile. The issues like therapeutic modalities for recurrence of bleed following N-butyl-cyanoacrylate injection and prophylactic endoscopic treatment of large unbled gastric varices with RCS who are already on sclerotherapy program for esophageal varices needs further study.

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Original Article

Manometric spectrum of fecal incontinence in a tertiary care center in northern India

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ABSTRACT

Background: Since, there is scanty data on manometric spectrum of fecal incontinence (FI) from India, ano-rectal manometry (ARM) parameters of patients with FI attending a tertiary care hospital were analyzed retrospectively.

Methods: Data on 140 consecutive patients with FI (age 44.8 ± 17.4 y, 89 male) referred for ARM were analyzed and interpreted according to standard criteria.

Results: Low resting pressure (mainly due to internal sphincter; <40mmHg) and squeeze pressure (mainly due to external sphincter; <60 mmHg) were found in 88/140 (63%) and 44/140 (31.4%) patients, respectively. Low squeeze pressure indicating external sphincter defect was more commonly found in female than male [23/51 (45.1%) vs. 21/89 (23.6%), p=0.013] though other parameters on ARM were comparable among the two genders.

Conclusion: Parameters of ano-rectal functions were abnormal in varying combinations on ARM in a large proportion of patients with FI attending a tertiary care center and females more often had low squeeze pressure indicating external sphincter defect than males though anal resting pressure, length of the high pressure zone and tolerability to intra-rectal balloon distension were comparable.

KEYWORDS: Ano-rectal manometry, fecal evacuation disorder, ano-rectal function, obstetric trauma, anal sphincter

Introduction

Fecal incontinence (FI) is a common problem with estimated prevalence ranging from 0.4 to 18 percent of adult community subjects in developed countries.[1] Fecal incontinence profoundly reduces patient's quality of life with significant psychosocial implications.[2] It is more prevalent and severe in older people with reported frequency as high as 50% among elderly residents of nursing homes in the West.[3]

Fecal incontinence is not caused by a combination of multiple abnormalities in most patients such as defects in internal, external anal sphincters and rectal sensory abnormalities.[4] Ano-rectal manometry (ARM) along with imaging studies provides morphological and physiological assessment of the internal and external anal sphincters, rectal sensory function, compliance, and recto-anal reflexes. Detailed pathophysiological information on mechanisms of FI may help guide further treatment of these patients.[5] Defects in the external or the internal sphincters can be differentiated by ARM. Resting anal sphincter pressure is a reflection of internal anal sphincter function and low squeeze pressure or the voluntary anal contraction abnormality is noted when the external anal sphincter is defective.[6,7] ARM with biofeedback training improves objective and subjective parameters of ano-rectal function in patients with FI.[8] There is no study, however, on spectrum of ano-rectal sphincter function in patients with FI in

India. We therefore, retrospectively analyzed the spectrum of abnormalities on ARM in patients with FI in a tertiary referral center in northern India.

Methods

Data from 140 patients with FI referred for ARM to the Gastrointestinal Pathophysiology and Motility Laboratory of the Department of Gastroenterology in a tertiary care center during eight-year period (June 2001 to June 2009) were analyzed in this study retrospectively. The authors affirm that all research related to this study was carried out in accordance with the Helsinki Declaration as revised in 1989.

Each patient underwent ARM after informed consent using a water perfusion manometry system (RedTech, Calabasas, Los Angeles, USA) using a standard technique. Two eight-lumen manometry catheters, one with radial ports placed 0.5 cm apart with a balloon at its tip to test for recto-anal inhibitory reflex (RAIR) and the other with all 8 ports placed circumferentially were used. The manometry catheter with circumferential ports was inserted deep inside the rectum with the patient in the left lateral position. The catheter was subsequently pulled 1 cm at a time (station pull-through, SPT) till the high pressure zone of the sphincter was reached and then, it was pulled 0.5 cm at a time till it came out of the high pressure zone. SPT was repeated twice. The length of the sphincter zone and resting sphincter pressure were estimated from an average of length and pressure data obtained from the SPT done twice. For measuring the squeeze sphincter pressure, the manometry catheter was pushed back into the rectum, sphincter was again localized using SPT, the patient was asked to squeeze the anal sphincter, and the catheter was pulled rapidly at a constant rate (rapid pull-through, RPT). This was repeated twice and an average of the values obtained on two recordings was used to measure the squeeze sphincter pressure. After removing the catheter with circumferential ports, the catheter with radial ports with balloon was inserted deep inside the rectum; 2–3 ports were positioned in the high pressure zone of the sphincter using the SPT technique. Subsequently, the balloon, which had been positioned inside the rectum, was inflated with an incremental volume of air (20 ml, 40 ml, 60 ml and so on) and deflated after inflation each time. During the inflation, RAIR was observed, the rectal sensations and maximum tolerable volume (feeling of distension, urge to pass stool and pain) were also assessed.

Criteria: The ARM signal was analyzed using GIPC software from RedTech. The data so obtained were interpreted based on the standard criteria described previously.[9-11] A resting pressure <40 mmHg, squeeze pressure < 60mmHg, length of anal high pressure zone <2.5 cm in females and <3 cm in males were considered as abnormal. Maximum tolerable volume <200ml on intra-rectal balloon distension was considered as abnormal.[9-11]

Statistical analysis: The data were checked for distribution using Shapiro-Wilk test. Parametric continuous data were expressed as mean and standard deviation. Non-parametric continuous data were expressed as median and inter-quartile range. Parametric and non-parametric continuous unpaired data were analyzed by unpaired t test and Wilcoxon ranksum test, respectively. Categorical data were analyzed by Chi-squared test and Fisher's exact test as applicable. P values less than 0.05 were considered significant.

Results

Demographic Parameters: Demographic and clinical parameters are shown in **Table 1**. All the patients had clinically significant FI.

ARM parameters: Most patients with abnormal ARM parameter had multiple abnormalities (**Figure 1**). The internal sphincter defect as evidenced by low resting pressure (<40mmHg) was noted in 88/140 (63%) with median pressure of 34 mmHg (range 7 to 133 mmHg). External sphincter defect as evidenced by low squeeze pressure (<60mmHg) was found in 44/140 (31.4%) with median squeeze pressure of 76.5-mmHg (range 14 to 312 mmHg). **Table 2** shows ARM parameters of female patients as compared to those of males. Female patients more often had low squeeze pressure suggesting external sphincter defect though other ARM parameters were comparable among the two genders.

Of 128/140 patients in whom data on tolerability to intra-rectal balloon distension was available, 93 (72.7%) had low maximum tolerable volume (abnormal < 200 ml). Median value of maximum tolerable volume was 140 ml (range 40 to 300 ml). The maximum tolerable volume among female and male patients was comparable (**Table 2**).

RAIR data was available in 108/140 patients. Most patients 87/108 (80.5%) had normal RAIR. 18/108 (16.6%, 12 males) patients had too low basal sphincter pressure to appreciate RAIR. Incomplete RAIR was observed in 3/108 patients (all diabetic).

Anal high pressure zone was short (<2.5 cm in females and <3 cm in males) in 47/149 (33.6%) patients. The frequency of finding a short anal high pressure zone was comparable among females and male s[15/51 (29.4%) vs. 34/89 (38.2%), p =ns).

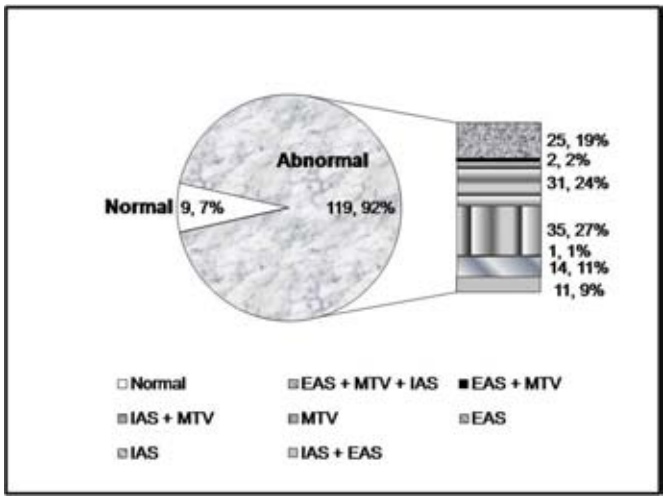

Figure 1: The chart shows frequency of abnormal findings on ano-rectal manometry in patients with fecal incontinence (n=128 in whom all the parameters of ano-rectal manometry were available for analysis). Abbreviation used: IAS: internal anal sphincter, MTV: maximum tolerable volume, EAS: external anal sphincter. Each of these abbreviations denotes that this particular parameter was below the cut-off limit as defined in the text.

Table 1: Demographic and clinical parameters in patients with fecal incontinence

	N=140
Gender (male/female)	89/51
Age (y, mean + SD)	44.8 ± 17.4
Clinical Data	
Diabetes	20 (14.3%)
Inflammatory bowel disease	8 (6%)
Neurological diseases	13* (9.3%)
History of rectal/peri-anal surgeries	8 (6%)

*Note: * Neurological diseases included 11 patients with spinal cord diseases, one with mental retardation and one with stroke with hemi-paresis*

Discussion

In the current retrospective analysis, we found that parameters of ano-rectal functions were abnormal in varying combination on ARM in a large proportion of patients with FI attending a tertiary care center and female patients more often had external sphincter defect than male patients though anal resting pressure, length of the high pressure zone and tolerability to intra-rectal balloon distension were comparable.

Maintenance of continence involves the proper functioning of the sphincters, the rectal sensation and compliance and the rectoanal angle. The internal anal sphincter contributes approximately 70% to 85% of the resting sphincter pressure and is chiefly responsible for maintaining anal continence at rest.[12,13] The external anal sphincter is under voluntary control through the pudendal nerve and squeeze pressure on ARM is the reflection of external anal sphincter function.

In our study, the majority of patients had a combination of defects as previously described by others.[4] A large proportion of patients (35/128) had abnormally low maximum tolerable volume on intra-rectal balloon distension with normal sphincter pressures highlighting the importance of rectal compliance and sensitivity in maintenance of continence. Our result, however, was contradictory to two studies from Sun et al and Holmberg et al who found that all the patients with reduced tolerance to intra-rectal balloon distension had low sphincter pressure.[4,14] FI in patients without anal sphincter weakness might result from, (1) failure to maintain anal pressure during rectal distension, and (2) a blunted sensation or lack of adaptation of the bowel wall to rectal filling. Siproudhis et al in a series of patients with normal anal sphincter pressure suggested a

Table 2: Anorectal manometry parameters in male and female patients with fecal incontinence

	Female (n=51)	Male (n=89)	p- value
Age (years)	45.6 (16.3)	44.4 (18.1)	0.709
Length of high pressure zone (cm)	2.7 (2.4,3.1)	3 (2.5,3.5)	0.142
Maximum resting pressure (mmHg)	62 (38,96.5)	60 (36.5,84.5)	0.374
Effective resting pressure (mmHg)	31 (21.5,54)	35 (21,44)	0.706
Low resting pressure (internal sphincter defect)*	31/51 (60.8%)	57/89 (64%)	0.84
Maximum squeeze pressure (mmHg)	60 (42,102.5)	85 (60,119)	0.021
Average squeeze pressure (mmHg)	34 (21,62)	48 (35.5,70.2)	0.045
Low squeeze pressure (external sphincter defect)**	23/51 (45.1%)	21/89 (23.6%)	0.013
Increment on squeeze pressure (mmHg)	24 (12.5,65)	54 (30,77)	0.006
Volume of balloon for rectal sensation (ml)	20 (20,40)	30 (20,40)	0.154
Volume of balloon for urge	60 (40,80)	60 (40,100)	0.177
Maximum tolerable volume of balloon	140 (100,185)	130 (100,200)	0.592
Reduced rectal compliance	33/44 (75%)	60/84 (71.4%)	0.82

*Note: All the continuous variables with data that are not normally distributed are expressed as median and interquartile range. Categorical and continuous data were analyzed using Chi-squared test and Wilcoxon ranks sum test, respectively. *Low resting sphincter pressure was defined as average resting pressure <40 mmHg and **low squeeze pressure was defined as average squeeze pressure <60 mmHg.*

reduced rectal adaptation could be involved in fecal leakage in patients without anal sphincter weakness.[15]

In our study, a defective external anal sphincter was significantly more common in female subjects. Obstetric injury is a contributing factor for FI. Obstetric trauma tends to be either a combination of injury to both sphincters or to the external sphincter alone and more severe injury is more likely to cause FI.[16,17] In the Indian subcontinent home deliveries are common with risk of perineal injury and subsequent development of FI.[18,19] In a series by Enck et al, both internal and external sphincter pressures were lower in female subjects; however, in our study population external sphincter defect was more common in female subjects.[20] This difference might be attributed to the obstetric practices in India. Since it is a retrospectively study, information on obstetric injury was not available in all the female patients. A prospective study is needed on this issue.

In conclusion, we found that FI in most patients is of multifactorial etiology with varying combinations of internal, external sphincter or rectal compliance defects. External sphincter defect was more common in females as compared to males.

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Original Article

Malnutrition is not an etiological factor in the development of tropical pancreatitis – A case-control study of Southern Indian patients

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ABSTRACT

Background and Aim: Malnutrition is implicated as an etiological factor in tropical pancreatitis (TP). The aim of the present study was to elucidate whether malnutrition is the cause or the result of TP.

Methods: Consecutive recently diagnosed patients with TP were evaluated for their nutritional status and dietary patterns before and after the onset of TP. The nutritional status of patients before the onset of TP was compared with that of healthy controls to demonstrate the role of malnutrition as an etiological factor for TP.

Results: Of 256 consecutive patients with chronic pancreatitis, 89 were diagnosed as TP patients with disease duration of less than 1 year (mean age 32.14 ± 14 years; 60 % males) and comprised the study group. The nutritional status before the onset of TP was comparable with that of controls (n=101) with 15% of patients and 12% of the controls being malnourished (BMI <18.5kg/m^2). However, after the onset of TP, 52% (n=46) of patients lost weight and the percentage of malnourished patients increased from 15% to 38% (p=<0.001) indicating that there was significant weight loss after the disease onset. When the causes of weight loss were evaluated, it was found that low calorie intake significantly contributed to weight loss (p=0.001).

Conclusion: Malnutrition is not an etiological factor of TP and weight loss occurred as a result of low calorie intake after the onset of TP.

KEYWORDS: malnutrition, tropical pancreatitis, chronic pancreatitis, calorie intake

Introduction

Chronic pancreatitis (CP) is a condition characterized by irreversible destruction and fibrosis of the exocrine parenchyma leading to exocrine pancreatic insufficiency and progressive endocrine failure leading to diabetes.[1] CP is a common problem with a prevalence varying from 10-125/100,000 population.[2-4] Chronic alcoholic pancreatitis is the commonest type of CP seen in the western population, while in the tropics there is a distinct non-alcoholic type of CP of uncertain etiology which is far more prevalent and is known as tropical pancreatitis (TP).[1] TP can be defined as a juvenile form of chronic calcific non-alcoholic pancreatitis prevalent almost exclusively in the developing countries of the tropical world. Some of its distinctive features are younger age of onset, presence of large intraductal calculi, an accelerated course of the disease leading to the end points of diabetes and/or steatorrhea and a high susceptibility of pancreatic cancer.[5-7] Recent work has focused on the role of genetic mutations in the etiopathogenesis of TP, but other factors such as nutritional, environmental and

autoimmune have also been suggested[8,9] Since poverty and malnutrition were common in the countries from where the disease had been reported,[10-11] malnutrition was suspected as a causative factor in the development of TP.[12] The earlier reports on TP were from Southern India describing that most patients with TP were undernourished, implicating malnutrition as a cause of TP.[13-15] However, malnutrition could be the result rather than the cause of the disease since CP with consequent malabsorption could itself lead to malnutrition. We, therefore, conducted a case-control study to elucidate whether malnutrition was the causative factor of TP in patients belonging to Southern India.

Methods

Patients

All consecutive patients with CP attending Asian Institute of Gastroenterology, a single specialty large referral centre, between May 2007 and December 2008 were enrolled and diagnosis of CP was made based on the following criteria:[16] Pancreatic calcification on plain x-ray of the abdomen, Ultrasonography (USG) or computed tomography (CT) scans showing pancreatic calcification and/or pancreatic ductal dilation and Endoscopic retrograde pancreatography (ERP) showing irregularity and/or dilation of the main pancreatic duct and/or pancreatic duct side branches, and/or presence of pancreatic stones/strictures. The etiology of chronic pancreatitis was determined as: Alcoholic CP- if a patients has been drinking more than 80g alcohol per day for greater than 5 years,[17] Tropical pancreatitis: if no definite cause was identified and miscellaneous CP: Other causes of CP such as hyperparathyroidism, obstruction and trauma were grouped under miscellaneous etiologies.

Patients were included in the study based on the following criteria: Etiology of chronic pancreatitis identified as TP and patients with disease duration of less than 1 year. Patients were excluded from the study for the following reasons: patients with acute exacerbation of CP, patients with CP of other etiologies (alcoholic CP and miscellaneous CP), patients with co-existing diseases such as alcoholic liver disease, renal failure, pancreatic cancer, tuberculosis, HIV/AIDS and pregnant women. Healthy individuals (n=101) who were age, sex and socio-economic status matched were included as controls from among those who came to the institute for routine health check up.

Nutritional Assessment

All patients and controls underwent detailed nutritional assessment which comprised of the following:

Anthropometric measurements

Anthropometric measurements included height, body weight and body mass index (BMI). Body weight and BMI included the previous body weight (body weight before onset of CP), present body weight (body weight after disease onset) and the weight loss. BMI was calculated by using the formula weight (kg)/height $(m)^2$. BMI was classified as: Low BMI (<18.5 $kg/m^{2)}$ – indicating malnourished participants; Normal BMI (18.5-24.9 kg/m^2) – indicating well nourished participants; High BMI (>25 kg/m^2) – indicating overweight and obese participants

Dietary Assessment

All the participants were interviewed by the clinical nutritionist regarding their dietary intake before and after the disease onset. The educational and socio-demographic profile was also recorded. A semi-quantitative food frequency questionnaire was used to collect nutrient and dietary information on the food groups and miscellaneous food items.

The questionnaire included the following:

1. Foods consumed during the day, before and after the disease onset.
2. Food items consumed weekly or monthly
3. Alcohol intake, if consumed
4. Types and amounts of oils used
5. Reasons for avoiding food intake after the disease onset

Daily intake of nutrients and foods were estimated by summing up all the raw foods consumed. Nutrient calculation (calories, percentage of carbohydrates, proteins and fats) from raw foods was done using standard nutrient values of Indian foods.[18]

Weight Loss and its possible causes

Patients were considered to have lost weight after the onset of TP if their weight decreased by 10% or more of the previous

body weight. The following potential causes of weight loss were analyzed:

1. Dietary Restriction: This was assessed by analyzing the dietary restrictions following the onset of TP with regard to calorie and nutrient intake.
2. Diabetes: The presence and duration of diabetes were noted. The diagnosis of diabetes was made using WHO guidelines; fasting plasma glucose of > 126 mg/dl and 2hr postprandial plasma glucose of >200 mg/dl was taken as indicative of diabetes mellitus.[7]
3. Abdominal pain and other gastrointestinal (GI) symptoms: As pain, nausea, vomiting and early satiety may result in restriction of food consumption by the patients, these were recorded as a possible causes of reduced dietary intake leading to weight loss.

Outcome Measures

The relationship between malnutrition and cause of TP was assessed by taking into consideration the previous (before TP) and the present body weights of the patient, weight loss after the onset of TP, the dietary intake before and after the diagnosis of disease, and comparison of previous body weight and BMI of patients with that of controls. Malnutrition was considered as an etiological factor to the development of TP if the previous weight and BMI of patients before the disease onset were significantly less than that of healthy controls.

Ethics

An informed consent was obtained from the patients and controls and the study protocol was approved by the institutional review board.

Statistical analysis

Mean and standard deviation (SD) were calculated for all the anthropometric and dietary parameters. Student t-test and chi-square tests were used to assess the quantitative and qualitative data respectively. SPSS program, version 14.0 (SPSS Inc., Chicago; IL, USA) was used for statistical analysis and a p value less than 0.05 was considered significant in all the analysis.

Results

A total of 256 consecutive patients with CP were included in the study from May 2007 to December 2008. Their mean age was 34.84 ± 14 years. There were 192 (75%) males. Of 256 patients with CP, 77% (n=197) had TP and 45% (n=89) had TP with less than 1 year of disease duration. The mean age of study participants was 32.14 ± 14 years and 60 of them were male (T**able1**). Presence of diabetes and clinical steatorrhea was observed in 13.5% and 11.6% of TP patients.

Comparison of previous nutritional status of TP patients with controls

On the basis of the previous BMI (BMI before TP) of the patients, the nutritional status of the patients was comparable with that of controls (**Table 2**). There was no significant difference between the BMI of healthy controls and TP patients before the disease onset suggesting that malnutrition could not be the causative factor for the development of TP. The average calorie intake of the controls was 1376 ± 123 kcal per day which was similar to the calorie intake of TP patients before disease onset (p = 0.067).

Comparison of nutrition status of TP patients before and after the disease onset

Most patients with TP had a BMI either in the normal range (n= 57, 64%) or in the high BMI category (n= 19, 21%) and only a minority of patients (15%) were underweight before the disease onset (**Table 2**). However, after the onset of TP, of the

Table 1: Baseline characteristics of patients with CP

Characteristics of patients with chronic pancreatitis	
Number	256
Mean age, years (SD)	34.84 (14)
Male, n (%)	192 (75)
Etiology of chronic pancreatitis	
Alcoholic chronic pancreatitis (n)	59
Tropical pancreatitis(n)	197
Characteristics of study participants with TP of less than 1 year duration (n=89)	
Mean age, years (SD)	32.14 (14)
Diabetes, n (%)	12 (13.5)
Clinical Steatorrhea, n (%)	10 (11.6)

n, number; SD, standard deviation; %, percent

Table 2: Comparison of the previous BMI (BMI before disease onset) of TP patients with that of controls

Nutritional Status	**Patients with TP (n=89)**	**Controls (n=101)**	**p value**
Low BMI <18.5, n (%)	13 (15)	12 (12)	NS
Normal BMI 18.5–25, n (%)	57 (64)	66 (65)	
High BMI >25, n (%)	19 (21)	23 (23)	

n, number; %, percent; NS, not statistically significant

57 patients with the normal BMI, 60% (34/57) became malnourished with BMI <18.5 and of the 19 overweight patients, BMI decreased to <25 kg/m^2 in 53% (10/19) due to weight loss. Thus, the percentage of malnourished patients increased from 15% to 38% and that of overweight patients decreased from 21% to 11% (p <0.001) indicating that there was significant weight loss after the disease onset (**Table 3**).

Comparison of dietary intake of patients with TP before and after the disease onset

There was a significant reduction in the calorie, protein, fat and carbohydrate intake in patients with TP after the disease onset (**Table 3**). The percentage distribution of calories into nutrients showed significantly lowered percentage of calories from carbohydrates and fats (p <0.05). Patients were asked about their dietary restrictions and it was observed that 63% were restricting oil and other forms of fats (clarified butter, cheese, high fat milk, non-vegetarian foods and margarine). On questioning them for the reasons for restricting their dietary intake, it was observed that 62% restricted calorie and nutrient intake for the fear of abdominal pain and 38% restricted their dietary intake for abdominal pain, nausea, early satiety and other GI symptoms.

Table 3: Comparison of nutritional status and dietary intake in patients with TP before and after disease onset

	Before disease onset	After disease onset	P-value
Mean weight, kg (SD)	61.2 (12)	56.3 (12)	<0.001*
Mean BMI, kg/m^2 (SD)	22 (4)	19.3 (4)	<0.001*
Calories, kcal (SD)	1300 (308)	1093 (257)	<0.001*
Proteins, g (SD)	37 (13)	31 (10)	<0.001*
Fats, g (SD)	26.5 (9)	19 (7)	<0.001*
Carbohydrates, g (SD)	221 (63)	195 (56)	<0.001*
Calories from proteins, % (SD)	11 (2)	12 (3)	0.244
Calories from fats, % (SD)	18 (4)	16 (5)	<0.001*
Calories from carbohydrates, % (SD)	70 (7)	73 (14)	0.020*

*kg, kilograms; SD, standard deviation; kg/m^2, kilograms per meter square; kcal, kilocalorie; g, grams; %, percent; *, statistical significance of <0.05*

Table 4: Comparison of TP patients with weight loss and no weight loss

	No Weight loss (n=43)	Weight loss (n = 46)	p-value
Age, years (SD)	35.75 (11)	36.95 (12)	0.73
Calories, kcal (SD)	1233 (162)	1019 (256)	0.0016*
Calories from carbohydrates, % (SD)	73 (7)	70 (6)	0.133
Calories from proteins, % (SD)	11 (3)	12 (2)	0.194
Calories from fats, % (SD)	16 (6)	17 (7)	0.513
Diabetes, n (%)	6 (14)	6 (13)	0.975
GI symptoms, n (%)	12 (28)	11 (24)	0.526

*kcal, kilocalorie; SD, standard deviation; %, percent; n, number of patients; *, statistical significance of <0.05*

Weight loss and causes of weight loss in patients with TP

52% (46/89) of patients lost weight after the onset of TP. Patients who lost weight were compared with those who did not. The causes of weight loss that were evaluated were consumption of lower calories, presence of diabetes, GI symptoms such as pain which could contribute to decreased dietary intake. It was seen that patients who lost weight consumed significantly lower calories than those who did not (p = 0.0016, 95% CI, 86.81-343.19). However, there was no statistical significance in presence of diabetes and GI symptoms in patients who lost weight and in those who did not lose weight (**Table 4**), indicating that diabetes and GI symptoms were not independently related to weight loss in this study.

Discussion

There is a paucity of data on the nutritional profile and etiopathogenesis of TP. TP is a variant of CP of unknown etiology, occurring mostly in developing countries of tropical regions and TP is suggested to be the result of environmental gene interaction.[19-20] Clinical and epidemiological evidence have suggested malnutrition as a cause of TP,[17] though there are no reports so far to prove that malnutrition is the causative factor of TP. In the present study, we observed that 76% of patients were normally nourished (normal BMI) or overweight (high BMI) before the onset of TP, and their nutrition status was comparable to that of the controls. We also observed that most patients (52%) lost weight after the onset of TP and the nutrition status significantly declined when compared to that before disease onset. This suggests that malnutrition could be the result and not a cause of TP. Malnutrition could be due to abdominal pain, sitophobia, nausea, vomiting, post prandial satiety and gastric dysmotility which contribute to decreased nutrient intake.[21] One potential limitation of the study, however, could be that determining the disease onset based on the actual

diagnosis is inaccurate as the symptoms could have been persisting even before the precise diagnosis of TP.

Earlier reports on role of malnutrition in the etiology of TP was based on the observations that TP affects the poor population of developing nations and it is indeed true that protein-calorie malnutrition (kwashiorkor) was present in many TP patients.[1,8,22] However, it has been seen that kwashiorkor seldom leads to permanent pancreatic damage and pancreatic stones are absent even in advanced stages of kwashiorkor,[1] suggesting that protein-calorie malnutrition cannot be considered as an etiological factor of TP. There is also a possibility of deficiency of certain micronutrients that might be responsible for onset of TP,[23] which has not been analyzed in this study.

It has been reported that the clinical presentation of TP has changed over the past decade probably due to socio-economic, dietary and lifestyle modifications with older age of disease onset, prevalence in normally nourished individuals, milder pain and diabetes and increased longevity.[19,23] Similar to these findings, we also observed that the mean age of onset was ~32years and most of the patients (76%) were well nourished with BMI >19.5 kg/m^2 before the disease onset, indicating that malnutrition is not a cause of TP.

More than half of the patients lost weight after the onset of TP (52%) and hence we analyzed the contributing factors of weight loss in TP patients. Low calorie consumption was an independent factor contributing to weight loss in these patients. However, when the percent of calories from carbohydrates, proteins and fats was analyzed between patients who lost weight and those who did not, there was no significant difference in percent of macronutrient intake. This explains that all patients with TP decreased the carbohydrate, protein and fat consumption leading to decreased calorie intake which contributed to weight loss in those patients who consumed significantly lesser calories than others. Although, diabetes has been shown to be an independent risk factor for weight loss in patients with TP,[23] our study did not reveal presence of diabetes in TP patients as a risk factor for weight loss. Exocrine pancreatic insufficiency as evidenced by clinical steatorrhea was observed only in 11.6% of our TP patients and the presence of maldigestion due to exocrine pancreatic insufficiency was not shown to be an independent risk factor for weight loss in our study.

In conclusion, this study suggests that malnutrition is not an etiological factor for tropical pancreatitis and malnutrition as observed in patients with tropical pancreatitis was a consequence of low calorie intake.

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Original Article

Helicobacter pylori eradication and histopathological esophagitis in dyspeptic patients

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ABSTRACT

Background: The association of *Helicobacter pylori* with peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, MALT (mucosa associated lymphoid tissue) lymphoma is well recognized.

Aim: This study was conducted to see whether there was any relation between *H pylori* eradication and reflux esophagitis in Iran.

Methods: Eligible dyspeptic patients referred to Gastroenterology clinic in Baqiyatollah hospital were endoscopied and evaluated for endoscopic and pathologic esophagitis and the *H. pylori* infection status was determined by rapid urease test. *H. pylori* infection was treated by an anti *H. pylori* drug regimen and successfully eradicated patients according to negative C^{14} urea breath test were followed and re-endoscopy was performed 6-9 months after the end of treatment.

Results: From175 eligible patients,54% were *H. pylori* positive, 68 of them (72%) had successful H.P. eradication and 64 patients completed the follow-up. The rate of histopathologic inflammatory esophagitis was higher in second endoscopy, compared with that of first endoscopy, i.e., before *H. pylori* eradication (75% vs 40.6%) ($p<0.05$). Progression of pathological esophagitis was seen in 56.3% of patients between the two endoscopic evaluations in spite of no change in clinical and endoscopic findings. There were no significant differences in dietary and smoking habits and body weights on re-endoscopy session compared with that of the first endoscopy visit ($p>0.05$).

Conclusion: This study suggests that *H.pylori* eradication in dyspeptic patients may lead to increased frequency of histopathological esophagitis Hence, In patients presenting with symptoms of dyspepsia , a cautious approach should be exercised if *H.pylori* eradication is being contemplated.

KEYWORDS: Helicobacter pylori, eradication, esophagitis, dyspepsia

Introduction

The association of *H. pylori* with peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, MALT lymphoma is well recognized,[1] but its relationship with functional dyspepsia and GERD is unclear.[2,3] A "test and treat" approach based on non-invasive screening of adult patients less than 45 years (the age cut-off may vary locally) presenting to primary care clinic with persistent dyspepsia has been suggested after exclusion of those with alarm symptoms.[4]

Assuming a high prevalence of functional dyspepsia and *H.pylori* in general population, many patients would need to be treated by this approach, while their long-term outcome is unknown. In 1997 the hypothesis of relationship between *H.pylori* and GERD was suggested, although no correlation was noted between *H.pylori* and severity of esophagitis.[5-7] Recently many new epidemiologic studies have been conducted in this regard.[8,9] Along with decrease of *H. pylori* colonization

in the stomach in western countries, the prevalence of peptic ulcer disease and distal gastric cancer has also decreased.[10] On the other hand, the prevalence of GERD, Barrett's esophagus and esophageal adenocarcinoma (EAC) have increased in recent years, so that EAC have become more common than SCC (squamous cell carcinoma) in western countries.[8,11-13]

GERD is the main risk factor for Barrett's esophagus, which is the only known precursor lesion of EAC. Thus, the essential question that needs to be answered is the protective effect of *H.pylori* colonization in stomach on GERD and its complications. Up to now there are some debates about the protective function of *H.pylori* on GERD. Association is higher in Asian studies than among North American and European ones. Some meta-analyses show significant association between absence of *H.pylori* infection and GERD symptoms, and a positive association between anti *H.pylori* therapy and occurrence of both de novo and rebound/exacerbated GERD. The significance of these associations appears to have been inflated by the effect of single trials and by geographical variations.[14] Considering controversies regarding *H.pylori* association with GERD in different studies in different countries,[15-20] this study was performed to clarify the association between HP infection and GERD in Iran.

Methods

All eligible dyspeptic patients referred to gastro-intestinal endoscopy ward of Baqiyatollah referral hospital and who agreed for follow up upto 1 year were enrolled in the study. Patients with systemic disease, present or past history of malignancy, history of gastric outlet obstruction, recent antibiotic usage, NSAID usage and gastric surgery were excluded from the study. The study protocol was approved by research ethics committee of Baqiyatollah University of Medical Sciences. Informed consent was obtained from the patients before enrollment.

All the participants underwent upper gastrointestinal endoscopy with Olympus GIF 200 after local anesthesia of the pharynx by 10% lidocaine spray. Endoscopy was done by one of the two gastroenterologists and the appearance of the esophagus was recorded according to the Los Angeles criteria. *H.pylori* status was evaluated with rapid urease test (RUT) kit made by Chemenzyme Company (Tehran, Iran) which has been approved by the Reference laboratory of the Health and Education ministry of Iran.

Two biopsy samples were also obtained from about 2.5 cm above esophagogastric junction (EGJ) and oriented on a special filter paper and immersed in 10% formalin solution and sent to the histopathology department of the hospital, which were then processed and evaluated and reported by one pathologist who was blinded to the endoscopic and clinical findings of the patients. All biopsy specimens were obtained by the Jumbo biopsy forceps.

Histopathologic grading of esophagitis was done by a pathologist as non-inflammatory or inflammatory changes (acute or chronic), epithelial necrosis and epithelial repair(**Table 1**). Endoscopic classification of GERD was done according to "Los Angeles"' classification. [21] In addition to demographic, endoscopic and pathologic findings, other data regarding weight changes, food habits, appetite, bowel habits, smoking and ethanol or caffeine consumption were collected and recorded in questionnaires. In patients who were positive for *H. pylori* test, anti *H. pylori* drug regimens was administrated for two weeks. Eradication was done using the traditional quadruple treatment regimen for *H. pylori* including bismuth 240 mg BID, omeprazole 20 mg BID, amoxicillin 1gr, metronidazole 500 mg twice a day for two weeks.

Four to six weeks after the end of treatment, urea breath test (UBT) with C14 was performed in an outside radioisotope laboratory whose staffs were blind to the study design and the intervention administered to the patients. Patients had regular visits for follow up every 1-2 months . The follow up was done by two gastroenterologists. H2 blockers were administered to all the patients for 2 months after triple therapy and as needed thereafter. Six to nine months after successful eradication, re-endoscopy was performed in UBT negative patients (for long term result and detection of histopathological changes) by one of the same two gastroenterologists who was blinded to the first endoscopy report.

On re-endoscopy, biopsy specimens from about 2.5 cm above EGJ were obtained and after orientation of specimens on a special filter paper and immersion in 10% formalin solution sent to the same histopathology department to be examined by the same pathologist who was again blinded to the clinical and endoscopic status of the patients. The specimens were evaluated for histopathologic esophagitis. The patients were recommended not to take any prescription for at least 4 weeks before their re-endoscopy session. A questionnaire similar to the first one was also filled by a general practitioner who was working with the team. The frequencies of continuous variables were expressed as mean and standard deviation. Groups were

compared using unpaired Student t test and categorical variables were compared using chi square test. p values < 0.05 were considered significant. The data was analyzed by SPSS software version 11.0.

Table 1: Histopathological characteristics of esophagitis

1. Normal
2. Nonspecific
   a) Nuclear enlargement
   b) Spongiosis
   c) Acanthosis
3. Non inflammatory
   a) Basal cell hyperplasia
   b) Increased papillary height
4. Acute inflammatory changes
   a) Vascular congestion or stasis
   b) Mucosal edema
   c) Polymorphonuclear infiltration (neutrophils and eosinophils)
5. Chronic inflammatory changes
   a) Mononuclear leukocyte infiltration (macrophages)
   b) Increased macrophage activity
   c) Proliferation of fibroblasts
   d) Ingrowth of vascular endothelium
6. Epithelial Necrosis
   a) Erosion
   b) Ulceration
7. Epithelial repair
   a) Granulation tissue
   b) Fibrosis(stricture formation)
   c) Epithelial regenerationa
   d) Squamous replication
   e) Columnar metaplasia (Barrette esophagus)
   f) Dysplasia

Results

Of 175 consecutive eligible dyspeptic patients, 94 of them were positive for *H.pylori* infection (54%) and H.pylori was successfully eradicated by the 2 weeks anti *H.pylori* drug regimen in about 72% of these cases (68 cases). Mean time of follow-up was 7.6 months. Four patients didn't complete the study or refused to be re-endoscopied on follow-up. Thus 64 patients (44 male, 20 female) completed the study. The demographic characteristics of patients have been shown in **Table 2**.

Clinically, 52 patients (82%) had pyrosis or retrosternal burn. Endoscopically, according to Los-Angeles classification, there were normal distal esophageal mucosa, grade A and B esophagitis in 56.7%, 36.7% and 6.6% patients, respectively. Esophagitis grade C and D and Barrett's epithelium were not seen. Active duodenal ulcer was reported in 30% of patients. Histopathologically, inflammatory esophagitis was reported in (40.6% of the cases. The remaining cases had normal lower esophageal mucosa, non-specific inflammation and non-inflammatory changes (**Table 3**).

Follow-up endoscopy and lower esophageal mucosa biopsy, similar to the first endoscopy was performed in 64 UBT negative patients 6-9 months after the end of 2 weeks *anti-H.pylori* therapy and demographic and clinical characteristics of the patients were gathered again. Endoscopic appearance of lower esophageal mucosa did not change in 34 (53%) cases, but in 13 (20%) patients grade of esophagitis increased. Histopathologically, inflammatory lower esophagitis was reported in 48 cases (75%), while the remaining 16 (25%) had normal esophageal mucosa, non-inflammatory or non-specific esophagitis. Although no grading changes were noted in 21 patients (32.8%), increased grading of pathologic esophagitis was observed in 36 patients (56.3%) ($p<0.05$). Clinically, reflux symptoms did not change in 40 patients (62.5%), but increased in 2 patients (3.1%) and decreased in 22 cases (34.4%). There were no significant differences in dietary and smoking habits in re-endoscopy session compared with those of the first endoscopy visit ($p>0.05$). Forty three patients (74%) had no change in their weight despite of increased appetite in 23 cases (36%). No significant correlation was noted between increased grading of pathologic esophagitis and variables such as sex, age, dietary habit, hiatus hernia and duodenal ulcer.

Table 2: Demographic characteristics of patients who completed the study

Parameters	Male	Female	Total
n (%)	44 (68.8%)	20 (31.3%)	64
Age (Mean±SD)(yrs)	36.39±10.3	41.85±15.8	38.09±12.4
Weight (Mean±SD)(kg)	71.16±10.5	63±10	68.6±11
Height (Mean±SD)(cm)	171.67±7.9	159.67±7.4	168.33±9.4
BMI (body mass index) (Mean± SD) (kg/m2)	21.06±1.7	20.37±0.9	20.8±1.5

Table 3: Clinical, endoscopic and pathologic findings before and after eradication

Variables	Before eradication (%)	After eradication (%)	p-value
Reflux symptomse≥one time/day	22.6	10.9	NS
Normal esophagus (endoscopic)	56.7	64	NS
Grade A esophagitis (endoscopic)	36.7	25	NS
Grade B esophagitis (endoscopic)	6.6	9.4	NS
Grade C esophagitis (endoscopic)	—	1.6	NS
Inflammatory esophagitis(pathologic)	40.6	75	< 0.05*

**p<0.05 significant*

NS: non significant

Discussion

Six to nine months after successful eradication of *H.pylori*, clinical and enodoscopic findings of reflux esophagitis did not change, but the pathologic grading of reflux esophagitis increased; a difference that was not related to the patients age, sex, endoscopic view, change in body weight or dietary habits. Although increased reflux esophagitis have been shown in several studies, the mechanism of injury has not been clearly defined. Some proposed hypotheses are as follow: Inflammatory infiltration secondary to gastric *H.pylori* colonization can cause serious damage to parietal cells and decrease in acid secretion.[20,22,23] After successful *H.pylori* eradication, parietal cell acid secretion returns to normal and thus may facilitate gastro-esophageal acid reflux.[24-26]

Supporting evidences are provided by studies showing independent protective role of cag A+ *H.pylori* and 1L 1b and 1L RN allele polymorphism against GERD [27] and very low prevalence of GERD in some areas like China and Japan (<5%), where there is high prevalence of Cag+ *H.pylori* (80%).[13,28] However, this theory has not been accepted because almost all duodenal ulcer patients have antral gastritis and high acid secretion.

Another hypothesis is urease effect of *H.pylori* leading to ammonium production in stomach that can potentially neutralize acid load in esophago-gastric junction. This process should stop after *H.pylori* eradication.[29,30] Some studies provide evidences that *H.pylori* eradication cause decrease in gastric pH in omeprazole recipients. It seems that *H.pylori* aggravates inhibitory effect of omeprazole on acid secretion so that the presence of *H.pylori* can accelerate improvement of esophagitis.[31-33]

The issue of correlation between *H.pylori* colonization and gastric motility is another controversial theory. While many studies have shown no correlation between *H.pylori* and gastric motility,[34-36] other authors emphasize on the effect of gastrin on LES (lower esophageal spincter) pressure increase. It is postulated that a decrease in serum gastrin level after *H.pylori* eradication may decrease LES pressure and hence facilitate reflux esophagitis. Epidemiologically, some studies have shown significantly lower prevalence of *H.pylori* colonization in GERD patients in comparison with general population (23-31% vs 51-61%). [37,38] However, decreased prevalence of H.pylori in caucasian population of developed countries parallels the increased prevalence of EAC as a final complication of GERD.[39,40] The major limitation of our study was the absence of control group and short follow-up time.

In conclusion, this study suggests that *H.pylori* eradication in dyspeptic patients may lead to increased frequency of histopathological esophagitis Hence, in patients presenting with symptoms of dyspepsia , a cautious approach should be exercised if *H.pylori* eradication is being contemplated.

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Original Article

Attitudes towards maternal screening for hepatitis B virus infection in Iran

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ABSTRACT

Objectives: To evaluate the attitudes of pregnant women towards prenatal screening for hepatitis B.

Methods: A total of 498 pregnant women attending obstetricians' private practices or unversity clinics for routine prenatal check-ups were enrolled. They were given an informative sheet regarding the epidemiology, diagnostic assays, preventive and treatment modalities and prognosis of hepatitis B. Then, we evaluated the attitudes of enrolled population towards antenatal screening for hepatitis B through a self-administered questionnaire.

Results: A total of 486 individuals returned the questionnaire (response rate: 97.6%). 393 participants (82.0%) agreed to HBV testing. Higher level of education was associated with more positive attitudes toward HBV testing. 461 subjects (95.4%) accepted medication or vaccine, if necessary, to spare their child from disease. In the case of positive HBV test, 18.2% of mothers decided to review their prior decision for another pregnancy in future.

Conclusion: Acceptability for prenatal HBV screening and following preventive modalities is good in Iranian population, but more consultation and training sessions for pregnant women should be provided with respect to their socio-demographic characteristics such as age, level of education and willingness to have another child

KEYWORDS: Hepatitis B, prenatal screening, HBV, pregnant women.

Introduction

Despite new recommendations for screening and treatment of HBV (hepatitis B virus) infection, the prevalence of hepatitis B is still dramatically high, accounting for about 350 milion chronic carriers worldwide.[1] According to Iranian studies, about 22% to 37% of general population in Iran are HBcAb positive[2,3] (i.e. previous exposure to HBV) and about 1.3% to 8.69% of the population are chronic HBV carriers; most cases(over 80 percent) were HBeAg negative.[2-6] The newborns from HBsAg-positive mothers are at high risk of becoming carriers of hepatitis B and for the development of hepatocellular carcinoma and chronic liver disease. Thus, preventing perinatal transmission would be an in important part of any national strategy for controlling hepatitis B infection.

In Iran, universal neonatal vaccination against HBV started in 1993 according to WHO recommendations, but our previous study showed that vaccination alone is not effective for prevention of hepatitis B in infants born to HBsAg-positive (and especially HBeAg positive) mothers.[7] Thus, identifying

these 'at risk' infants through prenatal screening of mothers seems crucial to add effect of passive immunization.

Although HBV screening and immunization programs should be clinically effective,but similar to any other community-based plan social, economic and emotional cofactors affect the acceptance of the target population and consequently the efficacy and success of the prevention. Especially, this statement should be considered for infectious diseases in which positive cases found after screening may be susceptible to social ostracism. For instance, a concept map was designed and conducted for spouse to spouse HBV transmission that showed these effects. [8-9]

The present study was conducted to evaluate the acceptability of pregnant women for HBV screening and following prevention and treatment modalities. In our knowledge, such a study was not previously done for HBV. The findings would help the policy makers to assess the overall acceptability of target population and socio-demographic concerns which should be considered in conducting screening and prevention protocols.

Methods

In October 2005, a total of 498 pregnant women (mean age, 26±5 years) attending obstetricians' private practices or unversity clinics for routine prenatal check-ups were enrolled. Participants who had been tested for hepatitis B, or had history of vaccination for HBV were excluded. The sampling method was nonprobability convenience time-base sequential. Participation in the study was not obligatory and only those who gave consent after briefing by the researchers were included in the study.They were given an information sheet regarding modes of transmission of HBV, the infection attack rates, preventive methods and their efficacy, treatment modalities and prognosis of hepatitis B. Afterwards, attitude of participants towards prenatal HBV screening was assessed through a self-administered anonymous questionnaire. Participants were also assured about secrecy of their responses.

The questionnaire included 6 questions denoting the attitudes of participants towards HBV testing and their acceptability for prevention and treatment modalities in the case of positive test results. Age, level of education, trimester of pregnancy, the number of previous labors and willingness to have another child were also recorded. The attitude questions were close-ended offering a choice among "yes", "no", or "I don't know" answers.

Face validity of questionnaire was approved before study by analyzing the responses of preliminary 20 pregnant women from the same population.

Split Halfspearman method was used for evaluating the internal reliability of questionnaire. Content validity was certified by four colleagues specialized in research methodology and social sciences. The questions were as follows (the original text was in fluent Farsi and this is the translation by the authors):

- I agree to be tested for hepatitis B in next few days.
- If my tests were positive, I prefer my husband to know it.
- If my tests were positive, I prefer my family to know it.
- I want to deliver another baby in future.
- If my tests were positive, I would not deliver another baby in future.
- If my tests were positive, I would accept medication and/or vaccine to spare my child from disease.

Results

A total of 486 individuals returned the questionnaire (response rate: 97.6%). Of included cases, 168 subjects (34.6%) were nulliparous. 393 participants (82.0%) agreed to HBV testing. Higher levels of education was associated with more positive attitudes toward HBV testing. (**Table 1**) High percentages of participants preferred to notify their partner and families in case of positive test result (92.8% and 70.8%, respectively). 461 subjects (95.4%) accepted medication or vaccine, if necessary, to spare their child from disease.

181 women showed willingness for another chilld bearing in future. Among these, 18.2% changed their previous decision in case of positive HBV test, and an additional 18.8% of individuals were uncertain about their prior decision.

Discussion

The attitude and acceptability of target population plays an essential role in establishment of any screening program. In our series less than 4% of participants disagreed with HBV testing and most of them agreed with administration of medication to spare their child from disease. 18% of participants changed their plan for another pregnancy in case of positive HBV result. Although the proportion of study subjects

Table 1. Attitude towards maternal HBV screening by demographic characteristics

	Agree (%)	Uncertain (%)	Disagree (%)	Total
Age (yr)				
• ≤25	153 (86.4)	19 (10.7)	5 (2.8)	177
• 26-30	108 (81.2)	20 (15.0)	5 (3.8)	133
• >30	50 (76.9)	11 (16.9)	4 (6.2)	65
Education				
• Elementary	79 (77.5)	19 (18.6)	4 (3.9)	102
• High school	161 (82.6)	29 (14.9)	5 (2.6)	195
• Academic	152 (91.0)	11 (6.6)	13 (2.8)	167
Parity				
• First	222 (84.1)	37 (14.0)	5 (1.9)	264
• Multi	169 (79.7)	31 (14.6)	12 (5.7)	212
Trimester				
• First	76 (81.7)	12 (12.9)	5 (5.4)	93
• Second	120 (80.5)	25 (16.8)	4 (2.7)	149
• Third	175 (82.5)	32 (15.1)	4 (2.4)	212

opposing the concept of screening and further immunization of neonates was very low, it remindes the need for more consultation and training sessions for Iranian mothers.

Most of participants preferred to inform their family and specially their partner of their test result, which is crucial for further immunization and prevention of horizontal transmission of HBV. Although not statistically significant, age negatively correlated with acceptability for HBV testing. This could be due to more concerns of women about positive test result in higher ages. However, it demonstrates that consultation and training sessions for pregnant women should be provided with respect to their socio-demographic characteristics such as age, level of education and willingness to have another child.

The probable reasons for unwillingness for HBV testing included fear of stigmatization and abandonment,economical concerns and lack of self-perceived risk for HBV infection due to unawareness about different possible routes of exposure. The association of acceptability of HBV testing and level of education may indirectly reflect the role of awareness about several possible modes of transmission and possibility of effective treatment in more educated individuals.

Another explanation for the positive role of education might be its association with socioeconomic status and thereby less fear of treatment expenses and social ostracism in case of a positive test. However, making people aware about different possible ways of HBV transmission other than only sexual contact and assuring them about possibility of effective prevention for their child may sensitize them about their HBV status and motivate them for screening.

Various case finding strategies may be proposed including universal screening, selective screening based on a risk assessment and finally voluntary screening.[10] Universal screening has several advantages over selective screening. Searching for certain predicting factors such as history of intravenous drug use and sexually transmitted disease may yield unreliable results due to cultural concerns especially in countries with social backgrounds like Iran. In addition, the costs associated with the time it takes to assess risk exposure may be more than for universal testing.[11]

Voluntary screening for infectious diseases has also yielded disappointing results. A study in United Kingdom reported that the prevalence of HBV infection was twice as high in those who had refused an HIV test compared with those who had accepted the test.[12] This finding clearly demonstrates that at-risk population have less willingness to accept screening tests and greatly supports the idea of universal screening. However, in June 1988, the Center for Disease Control (CDC) recommended prenatal HBsAg screening of all women or, for women who do not have a history of prenatal care, screening at the time of delivery.[13]

Currently, although there is a policy for prenatal screening of hepatitis B in Iran, pregnant women are not routinely tested for hepatitis B in some centers and tests might be limited to women with a history of 'risk behaviour'. In rural areas prenatal care is provided by trained health staff. Unexpectedly, provision of prenatal care in these areas is more systematic and documented than in private or even academic centres. It should be noted that effective control of hepatitis B depends on universal screening based on a clear and unavoidable protocol. This strategy would make HBIG more available for at risk neonates, and would reduce the time spent locating and obtaining this agent. Thus, systematic approach makes HBIG supply to at risk babies easier, more economical and with lower rate of missed cases.

Our study showed that acceptability for prenatal HBV screening and following preventive modalities is good in Iranian population.There may be some limitations in the present study. First, the sample would not be representative for all pregnant women in all communities and there are bound to be many differences in culture, education level and social behaviours with other communities but a similar study may be done in any other area for the same purpose. Second, we used a short questionnare (although it was easy to apply) and statistical methods for calculating validity of our data collection tool (Spearman-Half) that may cause minor methodologic

problems. And finally the study was based on numerical quantitative data and this method does not provide in depth comprehensive view of the subject similar to qualitative designs. More over, it has been suggested that the introduction by law of compulsory screening for infectious diseases greatly improves the compliance with it.[14]

In conclusion, creating awareness about HBV in all sections of the society irrespective of caste, sex, education and financial status is first step towards effective prevention. High acceptability of target population accompanied by meticulous design and supervision of prevention protocol by health system policy makers would be the cornerstone for successful control of hepatitis B. Operational research is required to identify barriers in implementing universal hepatitis B screening. Further studies to disclose any concerns of obstetricians and other involved health care providers surrounding routine antenatal HBV testing would facilitate this way.

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Surgical outcome in relation to duct size at the porta hepatis and the use of cholagogues in patients with biliary atresia

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ABSTRACT

Background : Small ductules communicating with the bile ducts have been described at the porta hepatis in extrahepatic biliary atresia (EHBA) and these form the basis for hepatic porto-enterostomy. The use of cholagogues like dehydrocholic acid (DHC) and ursodeoxycholic acid (UDCA) to enhance bile flow postoperatively has been reported.
Aims : This communication describes our experience with the use of cholagogues following surgery in EHBA and attempts to correlate the outcomes with the diameter of the ductules.
Material and methods : Fifty five EHBA patients treated by the Kasai procedure form the basis of this study; 35 patients treated during 1979-1986 and administered DHC (3-5mg/kg) postoperatively and 20 patients treated during 1999-2002 and administered UDCA (15mg/kg) postoperatively. The diameter of ductules was measured using an optical micrometer on 5μm serial sections; the ducts were classified as type I (no demonstrable ducts, n=14), type II (<50μm, n=22) and type III (>50μm, n=19). The clinical outcome was categorized as 1 (jaundice free survival at 5 years follow-up, n=7), 2 (initial good response but deteriorated after one year, n=27) and 3 (expired within one year following surgery, n=21). The response to surgery was monitored using biochemical liver function tests (LFT), hepatobiliary scintigraphy (HIDA scan) and occurrence of cholangitis.
Results : Age did not affect the size of ducts in both DHC and UDCA groups but patients in the DHC group were older than those treated with UDCA (mean age DHC: 105.22±33.53 days, UDCA: 74.68±23.73 days; p=0.009). There was no statistically significant difference between duct size and postoperative LFT in both groups (DHC p=0.1, UDCA p=0.5). Bile excretion on HIDA scan was significantly better with larger ducts (DHC p=0.003, UDCA p=0.025); overall UDCA showed significantly better bile excretion (p=0.003) but this was not reflected in the surgical outcome. There was no significant difference in the surgical outcome of those treated with DHC or UDCA but a significantly higher incidence of cholangitis was seen with smaller ducts in the UDCA group (p=0.02).
Conclusions : There was no correlation between duct diameter and postoperative LFT but type III ducts were associated with better bile flow on HIDA scan. Cholangitis was seen more often with type I and II ducts in both DHC and UDCA groups. UDCA administration seemed to be beneficial in patients with type III ducts in increasing bile flow and reducing cholangitis.

KEYWORDS: Biliary atresia, dehydrocholic acid, ursodeoxycholic acid

Introduction

In extra hepatic biliary atresia (EHBA), Kasai described the presence of small channels, which varied in size up to 300μm in diameter, in the porta hepatis and with three dimensional reconstruction studies these ducts were shown to communicate

with intrahepatic ducts.[1,2] This has been the basis for anastomosis of a Roux-en-Y loop of jejunum to the porta hepatis, now known as the Kasai's portoenterostomy procedure.[3] Although, the prognosis of biliary atresia has dramatically improved with the introduction of liver transplantation, the Kasai's operation is still the first line of surgical treatment.

The use of steroids and cholagogues, such as phenobarbitol and cholestyramine, to enhance bile flow in cholestatic patients has been described.[4,5] Dehydrocholic acid (DHC), in the past, and ursodeoxycholic acid (UDCA), more recently, have been used with the intention of enhancing success in relief of symptoms, reducing intrahepatic fibrosis and improving the outcome of infantile cholestasis states.[6] This communication describes our experience with the use of DHC and UDCA, although at different time periods, in the management of EHBA and attempts to correlate the outcomes with the diameter of ductules at the porta hepatic in these patients.

Material and methods

Patients

Fifty five patients of EHBA who underwent the Kasai's portoenterostomy formed the basis of this study. They were divided into two groups : retrospective group (patients treated from 1979-1986 and postoperatively administered DHC) and prospective group (patients treated from 1999-2002 and postoperatively administered UDCA). Patients treated between 1987-1998 were excluded from this study because data regarding the duct size at the porta hepatis was not available. Data regarding age, sex, clinical history, pre and postoperative biochemical liver function tests (LFT), hepatobiliary scintigraphy (HIDA scan) and histopathological assessment of ductal size of patients operated between 1979-1986 were collected from case records.

Management protocol

All preoperative HIDA scans were done after 5 days of priming with phenobarbitone (5mg/kg). The uptake by liver and excretion into the gut was noted. All patients with no gut excretion for more than 24 hours were subjected to mini-laparotomy under general anesthesia; peroperative cholangiogram (POC) was performed if a patent gall bladder was present. Cases proven to be EHBA on POC or those with atretic gall bladder and extrahepatic ducts were subjected to Kasai's portoenterostomy.

Tissue processing

The excised specimen of gall bladder, extra hepatic ducts and tissue from porta hepatis was subjected to light microscopic histopathological examination (HPE); all specimens were examined by the same senior pathologist (SDG). The tissue was fixed immediately in 10% neutral formalin, then embedded in paraffin for 5µm serial sections in a transverse plane. These sections were stained with Mayer's hematoxylin and eosin, Masson's trichrome and Van Geison's stains. An optical micrometer was used to measure the internal diameter of the ducts at the porta hepatis. The ducts were classified as: Type I : no demonstrable ducts; Type II : <50µm; and Type III : >50µm in accordance with a previously published report.[7]

Postoperative management and assessment

In the retrospective group (n=35) DHC (3-5 mg/kg) and betamethasone (10 drops/day) were administered for 3 months, where all patients in the prospective group (n=20) were administered UDCA (15mg/kg), phenobarbitone (5mg/kg) for one year, and betamethasone (10 drops/day) for 3 months as soon as oral feeds were instituted.

Patients were monitored for clinical outcome, LFT and biliary excretion by HIDA scan in the first six months; biliary excretion was graded as either excretory or non- excretory. Any episode of cholangitis occurring in the first six months postoperatively was recorded.The outcome of patients as measured by LFT and status of biliary excretion was correlated with the ductal size (types I,II,III). The clinical outcome was broadly categorized as follows :

1. Jaundice free survival at 5 years of follow up
2. Initial good response but deteriorated after one year
3. Expired within one year following surgery

Statistical analysis was done by Microsoft SPSS software for Windows. Comparison of ductal size and outcome (LFT, HIDA) in individual groups were done by student 't' test. Comparison of parameters between the groups were done by Mann-Whitney test. Values of $p<0.05$ were considered significant.

Results

There were 26 male and 9 female patients (M: F – 2.8:1) who were treated post-operatively with DHC and there were 13 male and 7 female patients (M:F = 1.8:1) who were treated post-operatively with UDCA. In the DHC treated sub-set of patients,

there were 13 (37.2%) patients with no demonstrable ducts at the porta hepatic whereas in the UDCA treated subset of patients there was only one (5%) patient with no demonstrable ducts. Type II ducts (<50 μm) were seen in 18 (51.4%) patients in the DHC treated sub-set and 4 (20%) patients in the UDCA treated sub-set of patients. Type III ducts (>50 μm) were seen in 4 (11.4%) patients in the DHC treated sub-set and 15 (75%) patients in the UDCA treated sub-set of patients.

The details of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes between the types of ducts at the porta hepatis in patients treated postoperatively with DHC and UDCA have been summarized in **Tables 1 and 2**. In both the sub-sets the age of the patients had no significant effect on the duct diameter at the porta hepatis (p=0.19 DHC sub-set; p=0.5 UDCA sub-set). Although the post-operative biochemical liver function tests appeared to be better in patients with larger ducts in both sub-sets, the differences were not statistically significant. However, biliary excretion as assessed by hepatobiliary scintigraphy was significantly better in patients with larger ducts in both sub-sets (p=0.003 DHC sub-set; p=0.025 UDCA sub-set) but this was not reflected in the clinical outcomes of surgery.

The mean age at operation, means of post-operative biochemical liver function tests, biliary excretion on hepatobiliary scintigraphy and clinical outcomes of surgery between the patients treated post-operatively with DHC and UDCA have been compared in **Table 3**. The mean age of patients treated with DHC (105.22±33.53 days) was significantly higher than that of the patients treated with UDCA (74.68±23.73) (p=0.009). In the post-operative biochemical liver function tests,

Table 1: **Comparison of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes between the types of ducts at the porta hepatis in patients treated postoperatively with DHC.**

	Type of ducts			p-value
	I	II	III	
N	13	18	4	
Age (days)				
Mean±SD	118.2±35.4	96.2±30.4	103.5±33.4	0.199*
Min. age	75	55	72	
Max. age	180	150	150	
LFT				
Bilirubin–mg% (total)	10.7±5.3	7.1±4.9	5.4±4.0	0.57
Bilirubin–mg% (direct)	6.5±3.7	4.7±3.7	3.4±2.2	0.20
Bilirubin–mg% (indirect)	4.2±0.5	2.4±1.4	2.7±2.1	0.80
Alkaline phosphatase(IU/l)	26.4±2.4	47.2±38.0	18.5±12.7	0.50
SGOT (IU/l)	76.9±49.4	50.1±38.4	18.5±17.7	0.09
SGPT (IU/l)	68.4±48.2	47.2±38.4	18.5±17.7	0.09
HIDA				
Excretion	9	4	4	0.003#
No excretion	4	14	0	
Clinical outcome				
1	0	2	0	0.698^
2	8	9	2	
3	5	7	2	

** between groups; #cross table 2x2; ^cross table 2x3*

Table 2: **Comparison of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes between the types of ducts at the porta hepatis in patients treated postoperatively with UDCA.**

	Type of ducts			p-value
	I	II	III	
N	1	4	15	
Age (days)				
Mean±SD	060.0±00.0	064.0±14.2	077.5±25.3	0.500*
Min. age	-	41	64	
Max. age	-	87	92	
LFT				
Bilirubin – mg% (total)	11.1±0.0	7.8±2.0	6.5±3.8	0.42
Bilirubin – mg% (direct)	6.0±0.0	4.7±2.7	4.8±2.7	0.90
Bilirubin – mg% (indirect)	5.1±0.0	3.1±1.9	2.4±1.4	0.20
Alkaline phosphatase (IU/l)	112±00.0	114.5±57.4	200.8±80.6	0.20
SGOT (IU/l)	112±00.0	114.5±57.4	94.9±60.5	0.83
SGPT (IU/l)	160±00.0	132.0±85.8	58.8±62.5	0.33
HIDA				
Excretion	0	2	11	0.025#
No excretion	1	2	4	
Clinical outcome				
1	0	0	5	0.420^
2	0	2	6	
3	1	2	4	

** between groups; #cross table 2x2; ^cross table 2x3*

Table 3: **Comparison of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes in patients treated postoperatively with DHC and UDCA.**

	DHC (N=35)	UDCA (N=20)	p-value
Age (days)			
Mean±SD	105.22+33.53	74.68+23.73	0.009
LFT			
Bilirubin – mg% (total)	8.99+4.58	6.81+3.49	0.174
Bilirubin – mg% (direct)	5.79+3.29	4.80+2.68	0.294
Bilirubin – mg% (indirect)	3.31+1.90	2.81+1.98	0.974
Alkaline phosphatase (IU/l)	408.54+338.78	243.78+123.30	0.704
SGOT (IU/l)	61.48+40.50	99.25+58.92	0.056
SGPT (IU/l)	64.68+41.05	101.42+84.77	0.008
HIDA			
Excretion	17	13	0.038#
No excretion	18	7	
Clinical outcome			
1	2	5	0.115^
2	19	8	
3	14	7	

 # cross table 2x2; ^cross table 2x3

the levels of serum bilirubin and serum alkaline phosphatase appeared to be lower in patients treated with UDCA but the differences were not statistically significant. However, in patients treated post-operatively with DHC, the post-operative levels of serum glutamic-oxalacetic transaminase (SGOT) were nearly significantly lower (p=0.056) and those of serum glutamic-pyruvic transaminase (SGPT) were significantly lower (p=0.008). Hepatobiliary scintigraphy showed significantly better biliary excretion in patients treated with UDCA (p=0.003) but this had no effect on the surgical outcome.

The various parameters i.e. age, liver function tests, biliary excretion on hepatobiliary scintigraphy and surgical outcomes were also compared separately for the type of ducts within the patients treated post-operatively with DHC and UDCA. Since there was only one patient with type I ducts in the sub-set of patients treated with UDCA this comparison was not done for type I ducts. The details for type II and III ducts are summarized in **Tables 4 and 5** respectively.

In patients with type II ducts (**Table 4**), the differences in age, SGOT and SGPT were similar to those described in table 3; the patients were younger in the UDCA sub-set (p=0.044) and the transaminases were lower in the DHC sub-set (p=0.003, SGOT; p=0.02, SGPT). There was no significant difference in the hepatobiliary excretion and surgical outcomes in this sub-set of patients treated with either DHC or UDCA.

In patients with type III ducts there were no significant differences in age, liver function tests, heptobiliary excretion or surgical outcome (**Table 5**) between patients treated with either DHC or UDCA.

The occurrence and incidence of cholangitis was also studied in these patients (**Table 6**). In the sub-set of patients treated post-operatively with DHC (n=35), 9 patients died in the early post operative period mainly due to sepsis related complications and hence cholangitis was not documented. In the remaining 26 patients, 10 had documented cholangitis (38.4%) in the first six months after surgery. In the sub-set of patients treated post-operatively with UDCA (n=20), there were no early post-operative deaths and 9/20 (45%) patients had documented cholangitis in the first six months postoperatively. There was no significant difference in the incidence of cholangitis in the two sub-sets of patients (p=0.88). In the sub-set of patients treated with DHC the type of ducts did not affect the occurrence of cholangitis but in those treated with UDCA cholangitis was more often seen in patients with no or smaller ducts (p=0.02).

Jaundice free survival was seen in only 2/35 (5.7%) in the DHC sub-set at 5 year follow up; in both these patients the ducts were less than 50µm. In the UDCA subset 5/20 (25%) are alive and jaundice free at 5 years and in all of them the duct size was more than 50µm.

Table 4: Comparison of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes in patients with type II ducts treated postoperatively with DHC and UDCA.

	DHC (N=18)	UDCA (N=4)	p-value
Age* (days)	13.68 (232.5)	7.25 (43.5)	0.044
LFT*			
Bilirubin – mg% (total)	12.29 (209.0)	11.17 (67.0)	0.759
Bilirubin – mg% (direct)	12.03 (220.5)	11.92 (17.2)	0.973
Bilirubin – mg% (indirect)	9.69 (164.5)	18.58 (117.5)	0.812
Alkaline phosphatase (IU/l)	60.06 (154.6)	20.33 (122.2)	1.810
SGOT (IU/l)	10.66 (171.0)	17.50 (105.0)	0.003
SGPT (IU/l)	11.79 (200.5)	12.58 (75.5)	0.020
HIDA			
Excretion	4	2	0.610#
No excretion	14	2	
Clinical outcome			
1	2	0	0.760^
2	9	2	
3	7	2	

Figures indicate rank (mean) and those in parantheses indicate sum of rank; #cross table 2x2; ^cross table 2x3

Table 5: Comparison of age, liver function tests (LFT), hepatobiliary scintigraphy (HIDA) and clinical outcomes in patients with type III ducts treated postoperatively with DHC and UDCA.

	DHC (N=4)	UDCA (N=15)	p-value
Age* (days)	12.30 (61.5)	8.42 (109.5)	1.73
LFT*			
Bilirubin – mg% (total)	9.90 (49.5)	9.75 (121.5)	0.849
Bilirubin – mg% (direct)	8.90 (44.5)	9.73 (126.8)	0.775
Bilirubin – mg% (indirect)	12.00 (60.0)	8.54 (111.0)	0.750
Alkaline phosphatase (IU/l)	21.00 (105.0)	12.00 (156.0)	0.819
SGOT (IU/l)	5.80 (29.0)	10.92 (142.0)	0.387
SGPT (IU/l)	7.60 (38.0)	10.23 (133.0)	0.246
HIDA			
Excretion	4	11	0.630#
No excretion	0	4	
Clinical outcome			
1	0	5	0.370^
2	2	6	
3	2	4	

** Figures indicate rank (mean) and those in parantheses indicate sum of rank; Mann-Whitney test*

#cross table 2x2; ^cross table 2x3

Table 6: The incidence of cholangitis in the DHC and UDCA groups in relation to the types of ducts in the respective groups.

	DHC (N=26)			UDCA (N=20)		
Type of ducts	I	II	III	I	II	III
Cholangitis	4	4	2	1	4	4
No cholangitis	6	8	2	0	0	11
p	0.83^			0.02^		
Incidence of cholangitis*	10/26 (38.5%)			9/20 (45.0%)		

*^cross table 2x3; *p=0.88*

Discussion

The major consideration after hepatic portoenterostomy for EHBA is to maintain a steady flow of bile across the anastomosis. Standard texts of pediatric surgery mention a number of drugs, including bile salts and steroids, that have been tried with variable effects; DHC was administered as part of the post-operative protocol earlier and currently, UDCA has taken the place of DHC.[8,9] Both DHC and UDCA have been shown to have a hepatoprotective and choleretic action and this forms the basis of their use in the post-operative management of EHBA.[10,11]

This study looks at data from two time periods. In the earlier time period (1979-1986) patients with EHBA were administered DHC following the portoenterostomy while in the later period (1999-2002) UDCA was administered. Although these two sub-sets of patients are not strictly comparable, a look at the differences between the two was found to be sufficiently interesting to form the basis of this study, particularly because there is scant data on this aspect.

There was no statistically significant difference in the age at surgery among the three types, categorised according to the duct size, in both DHC and UDCA treated sub-sets, although the patients in the UDCA group were significantly younger as compared to patients in the DHC group. This suggests that in recent times the diagnosis and operation has been done at a younger age as compared to the earlier period.

It has been suggested that age at surgery is inversely related to the outcome.[12,13] In the present study, the difference in age of the patients at surgery with the three types of ducts within each sub-set surgery was statistically not significant and hence it was possible to compare the outcome and postoperative LFT results with duct size without the confounding effect of age in each subset. In an earlier study also, although larger ducts were seen in younger patients, we did not find an inverse relationship between age and surgical outcome.[7]

There was no significant difference among the types of ducts within the DHC as well as UDCA sub-sets independently with post-operative biochemical liver function tests. However, when the DHC sub-set was compared with the UDCA sub-set, both the transaminases, SGOT and SGPT, were significantly lower in the DHC sub-set. This difference was not observed with type III ducts but was seen clearly with type II ducts. This may indicate a better hepatoprotective role for DHC as compared with UDCA and this may assume greater importance if the duct size at the porta hepatis is small.

Thirteen of 20 patients in the UDCA sub-set showed excretion into the gut in the postoperative HIDA scan; in these patients the ducts were significantly larger (p=0.025). In the DHC sub-set, 17 of 35 patients had good excretion into the gut and this was also statistically significant (p=0.003). In the present study more patients with ducts larger than 50µm had shown good excretion. These results are in agreement with other series in the literature.[14] However, patients with ducts smaller than 50µm have also shown biliary excretion into the gut and this has also been reported before.[7] In view of the persistently elevated serum bilirubin in the post-operative period, this suggests that although ductal size may have a definite bearing on postoperative bile flow it may still not have any effect on the LFT following Kasai's portoenterostomy. A search for other factors is required to explain this phenomenon.

Comparing the biliary excretion between the patients in the DHC and UDCA sub-sets, this was seen in a significantly higher number of patients in the UDCA sub-set (p=0.038). Even taking the other factors into consideration, this may suggest that UDCA acts as a better choleretic than DHC to enhance post-operative bile flow. In both the UDCA and DHC sub-sets, cholangitis was seen more often in patients with smaller ducts. Since all the patients had received choleretics, either in the form of DHC or UDCA, it is possible that increase in bile production and flow in the presence of residual obstruction may result in a clinical picture of cholangitis.

Jaundice free survival was seen in only 2/35 (5.7%) in the DHC sub-set at 5 year follow up; in both these patients the ducts were less than 50µm. In the UDCA subset 5/20 (25%) are alive and jaundice free at 5 years and in all of them the duct size was more than 50µm. Thus, factors other than duct size achieve great importance in determining the outcome of surgery e.g. degree of hepatic damage. And, it is obvious that if choleretics have to be of any use then there must be ducts to facilitate the flow of bile. Although bile flow on HIDA is documented in

patients without ducts at the porta, long-term survival may be possible with the use of choleretics only if ducts are present.

In conclusion, following Kasai's portoenterostomy, there was no correlation between the duct size at the porta hepatis with the results of biochemical LFT in patients with EHBA. Patients having larger ducts (>50μm) were associated with good biliary excretion in the postoperative period. This suggests that duct size may have a bearing on postoperative bile flow although this may not be reflected on postoperative LFT. This highlights that LFT may also be dependent on other factors e.g. hepatic parenchymal damage. Cholangitis was seen more often in patients with smaller ducts in both DHC and UDCA sub-sets. This suggests that residual obstruction may be a factor in the causation of clinical cholangitis. The post-operative administration of UDCA seems to be of benefit in patients with ducts larger than 50μm in increasing bile flow and reducing the incidence of cholangitis.

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Surgical Gastroenterology

Evaluating the efficacy of tumor markers CA 19-9 and CEA to predict operability and survival in pancreatic malignancies

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ABSTRACT

Aim: Using CA 19-9 and CEA (elevated >2times of normal) as predictors in determining operability and survival in pancreatic tumors.

Methods: Levels of CA 19-9 and CEA were measured (pre and post operatively) in 49 patients of pancreatic malignancy. CECT was performed for diagnosis and staging. An experienced surgeon determined the operability. The levels of tumor markers were correlated with the operability and the survival based on CECT and intra-operative findings.

Results: 16/24 (67%) patients with CA 19-9 levels (<2times) and 19/24 (79%) patients with CEA levels (<2times) were found to be resectable. 22/25 (88%) patients having elevated CA 19-9 levels (p=0.0002-t) and 17/25(70%) patients having elevated CEA levels (p =0.003) were found to be non-resectable. Of the 27 patients, found resectable on CECT, 5 were non-resectable intra-operatively. All of these had elevated levels of CA 19-9 and 4/5 (80%) had elevated levels of CEA. Only 5/21 (23%) non-resectable patients, with elevated levels of CA 19-9 reported at 1 year follow up. None of the non-resectable patients with CA 19-9 levels >1000U/ml reported at 6 month follow-up. None of the resectable patients pre-operatively showed evidence of recurrence. All achieved normal values post surgery.

Conclusion: Elevated levels of CA 19-9 and CEA (>2 times) predict increased chances of inoperability and poor survival in pancreatic tumors. Levels >3times had increased risk of inoperability even in patients deemed resectable on CT-Scan. Diagnostic laparoscopy would be beneficial in these patients. Levels of CA 19-9 (>1000U/ml) indicate a dismal survival in non-resectable group of patients.

KEYWORDS: pancreatic cancer, CA 19-9, CEA, tumor markers.

Introduction

Pancreatic cancer is a leading cause of death in the developed countries. In India the incidence of pancreatic cancer is low (0.5-2.4 per 100,000 men and 0.2-1.8 per 100,000 women).[1] TGF, CA 19-9, CEA, VEGF are amongst of the several tumor markers available for diagnosis and prognosis of the mass lesions of the head of pancreas.[2] When combined (CA-19.9 and CEA),they have a specificity of 95% in detecting pancreatic cancer.[3] A CT-Scan examination is used to find out the extent, local and distant spread of the disease and is used for preoperative staging of the disease. However, sensitivity and specificity of CT imaging in detecting involvement of lymph nodes and peritoneal disease is low.[4]

Apart from diagnosing the tumor, the tumor markers CA 19-9 and CEA are also useful for (i) indication of prognosis, (ii) assessment of therapeutic efficacy, and (iii) detection of residual or recurrent cancer. According to the American Cancer Society,

for all stages of pancreatic cancer combined, the one-year relative survival rate is 20%, and the five-year rate is 4%. After Whipple's surgery and in the absence of nodal involvement the 5-year survival of the patients is 48%.[5] It becomes important to identify patients with advanced disease at the time of diagnosis, as these patients are unlikely to benefit from major surgical intervention and will benefit from palliative treatments like the neo-adjuvant therapy and endoscopic surgeries.[6] This study was conducted to evaluate the role of these tumor markers beyond their routine use of diagnosis, in predicting the operability, survival and recurrence in cases of pancreatic tumors.

Materials and Methods

This study included 49 patients with pancreatic cancer who were admitted in the Department of Surgical Gastroenterology, Seth G.S Medical College and KEM Hospital, Mumbai, a tertiary care centre with a high patient load. The study lasted for 2 years and also included the patients who have been operated as early as 2007-08 and have been followed up. Patients with obstructive jaundice diagnosed to have exocrine pancreatic cancers and patients diagnosed with a pancreatic malignancy due to any other presenting complaints were included in the study.

Levels of CA-19-9 and CEA were obtained as a part of the investigations carried out in the patients pre-operatively during their hospital stay. CECT-Scan examination to find out the location, boundaries, extent of the tumor and to determine operability was done as a part of the pre-surgical investigations in all patients. The staging of the cancer was then done on the basis of the CECT-scan findings by a senior radiologist. Criteria for non-resectability on CT-Scan[4] included:

- Peritoneal metastases
- Liver metastases with/or ascites
- Extra-pancreatic invasion of adjacent tissues and organs other than the duodenum or bile duct
- Occlusion or stenosis or thrombosis of the major pancreatic vessels
- Encasement of the portal vein was not considered a deterrent to attempted curative surgery, provided that less than half of the vessel circumference and less than 1 cm of its length were affected.

A senior experienced surgeon decided the resectability of the tumors during surgery. Pancreatico-duodenectomy with reconstruction surgery for resection of the tumor was done in resectable cases. A palliative surgery as required or endoscopic stenting was done in non-resectable patients. Postoperatively tumor markers were repeated at every 3 monthly follow up.Levels of tumor markers (pre and post operatively) in both cases- resectable and non-resectable according to the CT-Scan were recorded. CA 19-9 and CEA levels were done for all the patients preoperatively and then at every 3 monthly follow-up. The normal levels of CA-19-9 were 0-37 U/ml and CEA were 0-2.5ng/ml. The levels of CA-19-9 and CEA were more than twice are considered to be significant for the prediction of inoperability.[7]

The primary objectives were :to evaluate the predictive value of CA19-9 and CEA (two times normal) in determining the inoperability of pancreatic malignancy and to evaluate the predictive value of Ca19-9 and CEA (three times normal) in determining inoperability in radiologically resectable pancreatic malignancy. The secondary objective was to evaluate the survival in patients based on the levels of the tumor markers

The data was analyzed with the help of Microsoft excel and Graph pad for statistical analysis. Fischer's exact test was used for statistical analysis.

Results

A total of 49 patients were analyzed in the study of which 25 patients were non-resectable and 24 were resectable, (Male : female ratio being 3:1, age range:38-70 years) with mean age being 55 years and mean survival of resectable patients was 2.6years. (range:1 – 3.7years).

In non-resectable patients, levels of tumor markers CA-19-9 and CEA were increased in 22/25 (88%) and only 3/25 (12%) patients had normal levels. The markers were elevated in 12/24

Table 1: Predictive value of tumor markers for Resectibilty

	CA 19-9		CEA		CA 19-9 + CEA	
	Resectable	**Non-resectable**	**Resectable**	**Non-resectable**	**Resectable**	**Non-resectable**
Levels Increased (>2 times)	8/24 (33%)	22/25 (88%)	5/24 (18%)	18/25 (71%)	12 (50%)	22 (88%)
Normal level (≤2 times)	16/24 (67%)	3/25 (12%)	19/24 (82%)	7/25 (29%)	12 (50%)	3 (12%)
	p = 0.0002		p = 0.0031		p = 0.0096	

(50%) patients who were resectable whereas the other 12 patients had normal levels. This was statistically significant with p-value being 0.0096. This suggests that CA-19-9 and CEA levels predict the inoperability in pancreatic cancers (**Table 1**).

22/25(88%) non-resectable patients had elevated CA 19-9 levels (>2 times) and 20 out of these 22 patients had CA 19-9 levels(>3 times). 8/24(32%) resectable patients had elevated CA 19-9 levels (>2 times).7 of them had the levels ranging from (106- 350 U/ml) and 1 patient had the value above 1000 U/ml. 16/24(67%) resectable patients reported levels of CA-19-9 (<2 times). This result was also statistically significant (p= 0.0002) establishing the predictive value of elevated levels of CA 19-9 in determining inoperability (**Table 1**).

18/25 (71%) non-resectable patients and 5/24 (18%) resectable patients had an elevated level of CEA (>2 times) as compared to 19/24 (82%) resectable patients reported a normal level of CEA. Elevated levels of CEA are predictive in determining the inoperability as this result was also found to be statistically significant (p= 0.0031) (**Table 1**).

Out of the 29 patients who were predicted to be resectable on CT-Scan findings, 24 of them were resectable surgically. 5 patients were non-resectable on exploration. 5/5(100%) had elevated CA 19-9 levels (>3 times). 4/5(80%) patients had a CEA levels (>3 times). The patients were found to be non-resectable due to micro-metastasis in the liver which were <1mm and were not detected on CT-Scan. Some patients also had sub-diaphragmatic seedlings (**Table 2**).

22 patients who underwent curative were followed up at 3, 6, 9months, 1 year and more than 1 year period. 21/22 (95.5%) of the patients reported a CA-19-9 level less than the significant limits in a period of 3 months and 100% patients reported CA-19-9 levels below the significant limits at a 9 month period. 1/22 had CA 19-9 level of 297U/ml at 3 months. The level was showing a declining trend (pre-operative – 505U/ml) and reached normal levels at 6 month follow-up. 20/22 (91%) of the patients reported a CEA level less than the significant limits in a period of 3 months and 100% at 9 month period. None of them reported any evidence of an increase in the level of the tumor markers on follow up. 1 patient did not report for follow up at 6 months and 6 patients did not report at 1 year (**Table 3**).

Table 2: Prediction of Non resectability in comparison with CT- findings

	CA-19-9 (>2 times)	CA-19-9 (>3 times)	CEA (>2 times)	CEA (>3 times)
Non-resectable as on surgery ignoring CT-Scan findings	22/25(88%)	20/25(79%)	18/25(71%)	14/25(58%)
Non-resectable as on surgery as well as on CT-Scan findings	16/20(80%)	15/20(75%)	13/20(65%)	11/20(55%)
Non-resectable on surgery but CT-Scan findings show operability	5/5(100%)	5/5(100%)	5/5(100%)	4/5(80%)

Table 3: Follow up in Resectable patients

	Post-Operative CEA levels		Post-Operative CA-19-9 levels	
	Elevated (>2 times)	Non elevated	Elevated (> 2 times)	Non elevated
3-month follow up	2 (9%)	20 (91%)	1 (4.5%)	21 (95.5%)
6-month follow up	1 (4.5%)	20 (95%)	1 (5%)	20 (95%)
9-month follow up	0 (0%)	19 (100%)	0 (0%)	19 (100%)
1 yearfollow up	0 (0%)	16 (100%)	0 (0%)	16 (100%)
Follow up of more than 1 year	0 (0%)	13 (100%)	0 (0%)	13 (100%)

Table 4: Comparison of Follow-up in Non-resectable Patients and CA-19-9 Levels

	No of Patients who came for Follow-up (Total number= 24 patients)					
	Diagnosis	3-mo	6-mo	9-mo	1-yr	>1-yr
CA 19-9 (>2 times)	21	13	12	6	5	1
CA 19-9 (>3 times)	19	11	7	5	3	1
CA 19-9 (>1000U/ml)	12	5	2	1	0	0
CEA (>2 times)	17	14	9	6	3	0
CEA (>3 times)	14	13	9	5	3	0

24 non-resectable patients were followed up at 3, 6, 9 months, 1 year. 23% (5/21) patients with CA 19-9 levels >2 times reported at 1 year follow up. 14% (3/21) patients with CA 19-9 levels >3 times reported at 1 year follow up. All 12 patients with CA-19-9 levels >1000U/ml failed to report at 1 year follow up. Out of them 7/12 (58%) patients failed to report at 6 month follow up and 8/12 (84%) patients did not report at the 9 month follow up. Patients with elevated tumor marker CA-19-9 seem to have a dismal survival as only 1/21 (4.9%) survived for more than a year (**Table 4**). 14/24 of these had CEA levels >3 times. 3/17 patients (17.6%) with CEA levels >2 times and 3/14 (21.1%) with CEA levels >3 times reported at 1 year follow up.

Discussion

Pancreatic malignancies present a significant challenge in both diagnosis as well as the treatment. The tumor markers are

effective in clinical monitoring post-surgery or during chemotherapy. Sensitivity of CA 19-9 for the detection of pancreatic cancer ranges in various studies from 67 to 92% with specificities ranging from 68 to 92%.[8,9] In our study, 24 patients were found to be non-resectable. 21/24 patients (88%) had elevated levels of CA19-9 (p= 0.0002). 17/24 (71%) had elevated levels of CEA (p =0.003). This suggested that elevated levels of CA 19-9 and CEA (>2 times) predicted inoperability in patients of pancreatic cancer.

Some other studies have similarly shown if high levels of CA 19-9 are taken, the specificity of this tumor marker rises over 90% indicating extended disease. CA 19-9 has been reported to be able to predict resectability of pancreatic cancer. According to these studies however, marked elevation of serum CA 19-9, but not CEA, was seen to be associated with advanced and unresectable periampullary cancers. [10]

MDR-CT is the most widely available and best validated tool for pancreatic imaging. CT criteria for nodal involvement include increased size, abnormal shape, loss of fat within the lymph node hilum, and central low attenuation. However, sensitivity and specificity of CT imaging in detecting involvement of lymph nodes is low.[5] CT scan has high sensitivities of detecting invasion of local vessels and metastatic spread. However it is not the best modality for the detection of peritoneal disease.

In our study, of the 49 patients analyzed, 25 patients were found to be non-resectable on surgery.20/25 patients were non-resectable on the basis of CT scan findings also. However, 5/25 patients were resectable as per CT scan findings. 5/5 (100%) had CA 19-9 levels (>3times) and 5/5 (100%) had CEA levels (>3 times). 5/5 (100%) had CA 19-9 levels (>2times) and 4/5 (80%) had CEA levels (>2 times). In our study, we observed that CA 19-9 and CEA levels >2 times and >3 times predicted inoperability even in patients which were deemed resectable on CT scan.

It showed that in such patients, a diagnostic laparoscopy would be of benefit to pick up evidence of metastasis which may have not been picked up on the CT-scan. Then if the patient is concluded to be non-resectable a palliative endoscopic surgery can be performed and an exploratory laparotomy avoided.

When compared with staging at exploratory laparotomy, laparoscopic staging with palliative endotherapy offers reduced surgical morbidity, decreased hospital stay, shorter recovery time, and less time to administration of adjuvant therapy. There have been some other studies which have showed that laparoscopy identifies intra-abdominal disease unappreciated by other staging. [11] They have similarly suggested that the patients with resectable disease on CT scan with elevated CA19-9 level may be used as a selection criterion for diagnostic laparoscopy. Experts from Fox Chase Cancer Center recommend laparoscopy for patients who are being considered for resection if the CA19-9 level is greater or equal to 100 U/ml. [12] However studies have not shown elevated CEA levels as a predictor of inoperability in such cases.

In our study, out of 24 resectable patients, 7/22 had levels of CA19-9 (>2 times). 1/7 patients reported elevated CA-19-9 levels at 3 months follow up. However the levels of CA 19-9 in that patient was showing a declining trend and with normal levels at 9 month follow up. All the other patients reported normal levels of CA-19-9 at 9 month follow up. Out of the 24 resectable patients, 4/24 patients had levels of CEA (>2 times). Of these 2/4 patients had elevated levels at 3 month follow up. Both these patients were showing a declining trend in the CEA levels. However all of them had normal levels at the 9 month follow up. There was no evidence of recurrence in any of the patients despite having elevated levels of tumor markers pre-operatively.

Of the 25 patients who were non-resectable in our study, 22/25 had levels of CA 19-9 (>2 times), 20/25 had CA 19-9 levels >3 times and 12/25 of them had CA 19-9 levels >1000U/ml. Only 5/21(23%) patients with levels of CA 19-9 > 2 times followed up at the end of one year, compared to 3/19(14%) patients with levels >3 times. None of the 12 patients with CA 19-9 levels more than 1000U/ml survived for a year.

Similarly, 17/24 non-resectable had elevated levels of CEA (>2times) and 14/24 had levels >3 times. Of these each group of patients, 3/17(17.6%) and 3/14(21%) patients followed up at the end of one year. None of the patients followed up after that. This shows that elevated levels of CEA indicated a poorer survival in non-resectable patients of pancreatic cancer.

In conclusion, elevated levels of CA 19-9 and CEA (>2 times) predict increased chances of inoperability and poor survival in pancreatic tumors. Levels greater than 3 times had increased inoperability even if the patients were deemed resectable on CT-Scan. Diagnostic laparoscopy would be beneficial in these patients. Levels of CA 19-9 (>1000U/ml) indicate a dismal survival in non-resectable group of patients.

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Short Report

Prevalence of gastroesophageal reflux disease among patients with bronchial asthma

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Introduction

Bronchial asthma (BA) is a chronic inflammatory condition of the airways characterised by bronchial hyper-responsiveness and narrowing of the airways, which is reversible either spontaneously or with treatment. It affects about 300 million people worldwide including 10% of the Nigerian population.[1] Gastroesophageal reflux disease (GERD) however is a chronic gastrointestinal condition characterised by abnormal exposure of the mucosa of the lower oesophagus to acid due to dysfunction of the lower oesophageal sphincter. About 10-30% of adult population in the Western world are affected.[2]

GERD can aggravate asthma in several ways; and these include vagally mediated reflex triggered by acid in oesophagus as well as micro aspiration of gastric acid resulting in bronchoconstriction.[3] Also some asthma drugs cause lower esophageal sphincter relaxation making acid escape easy. Hyperinflation of the chest in asthma with flattening of the diaphragm is thought to contribute to weakness of the crura muscles and dysfunction of the lower esophageal sphincter and amplification of the thoraco-abdominal pressure gradient during an attack helps to promote GERD.[4]

Reflux symptoms are reported in up to 77% of asthmatics while 32-82% of asthmatics have abnormal pH studies. Silent reflux may be as common as symptomatic reflux with reports suggesting that 25-50% asthmatics have no reflux symptoms but abnormal pH studies[5]. On the other hand, GERD has been known to have extra-oesophageal manifestation including hoarseness of voice, cough and wheezing.[6] Endoscopic studies equally could be normal in up to 50% (non-erosive GERD).[7]

There appears to be a diagnostic dilemma, which is further intrigued by cases of silent GERD. 24-hour oesophageal pH measurement and sometimes manometry has remained the cornerstone of GERD diagnosis, however, this is often not widely available in daily practice because of their cost and invasive nature. Hence, guidelines for their use[8] have been published. Symptom analysis however has been documented as a practical and inexpensive method of diagnosing GERD, but this obviously may not detect cases of silent GERD or with atypical symptoms. A number of validated questionnaires including QUEST, REQUEST™ and FSSG[9] exist with differing sensitivity and predictability.

Reports of relationship between BA and GERD exist in Western literature with sometimes conflicting findings to improper definition of BA and/or GERD.[10-12] There is limited information about this association among asthma sufferers in Nigeria. We aim to study this relationship among our patients to bridge the existing gap with objectives as: to determine the frequency of symptomatic GERD among previously diagnosed asthmatics attending an Asthma clinic by means of a validated questionnaire (frequency scale for symptoms of GERD (FSSG or F-scale)[9] as well as 24 hour nasopharyngeal DX PH detector, to compare GERD prevalence between the asthmatics and a control population matched for age and sex and to document the upper gastrointestinal tract endoscopic findings in the subgroup of subjects found to have GERD.

Methods

This was a descriptive study carried out at the Asthma clinic of Lagos state university teaching hospital (LASUTH) Ikeja for a period of three months. Ethical approval was obtained from the Institution's Research and Ethics committee in August 2007 before commencement of the study in September 2007. BA diagnosis was based on the National Asthma Education and Prevention Program Expert Panel Report.[10]

Other Inclusion criteria included adult patients above 15 years of age, with absence of co-morbidities like diabetes, hypertension, heart failure, significant tobacco use and chronic obstructive airway disease. The control group was recruited from the hospital workforce and medical trainees that had no history of asthma and were free from the aforelisted co-morbidities. All recruited subjects gave a written informed consent before participation. An interviewer administered questionnaire collected information on socio demographic characteristics, asthma symptoms and duration of diagnosis as well as scoring for GERD symptoms using the F-scale.[9.] This is a 12-item questionnaire which utilises both symptom description and its frequency, developed from a cohort of endoscopy proven GERD patients and revalidated in another group of GERD and non-GERD patients. Anthropometrics indices as well as spirometry were done using the digital spirometer, which measures forced expiratory volume in one second (FEV1) as well as peak expiratory rate (PEFR) (for asthmatics).

Subjects with F-Scale >7 were classified as having GERD and were invited to undergo a 24 hour pH study using a new nasopharngeal pH probe[13] (DX-PH) from RESTECH California, USA as well as an upper gastrointestinal endoscopy examination. The new pH probe utilised in this study is minimally invasive and measures both the pH of aerosolised, humidified refluxate and traditional liquid events. Unlike traditional probes it does not require immersion in liquid for accurate reading and can be easily inserted transnasally in the office. The 1.5m thick probe shaft is attached to a small transmitter, which communicates wirelessly with a recorder worn at the patient's waist. Upper gastrointestinal endoscopy was performed after an overnight fasting using an Olympus videoscope (model CLV 140 processor). Local xylocaine spray was used as topical anaesthetic while atropine and diazepam were premedication. Consent was sought and obtained before these procedures.

All data were collated and subjected to analysis using Microsoft SPSS software. Comparison was done using chi-square and expression of qualitative and quantitative data as means, proportion and percentages.

Results

Ninety-eight asthmatics (mean age (SD) 39.8years (17) and male: female ratio of 1:1.5) were studied. There were 78 controls with a mean age of 34±12 and male to female ratio of 1:1.8.

The prevalence of GERD using the F-scale in the asthma group was 36% and 30% in the control (P=0.4). This did not show any statistical difference in the prevalence of GERD in the two groups studied (**Table 1**). The prevalence of GERD appears not to be related to duration of asthma but to asthma severity as measured by PEFR (p=0.001, Cor. Coef. -1.6) (**Table 2**).

Table 1: Prevalence of GERD in asthmatic and control subjects using F-scale questionnaire, 24 hours pH study (Restech) and Upper GI Endoscopic features.

Variable	Asthmatic subjects n (%)	Control subjects n (%)	p-value
Total no of Respondents (F-scale)	98	71	
No with F-scale value > 7	35(36%)	21 (30%)	0.4
No. undergoing 24 hour pH study	5	7	
No. showing acid reflux events	4	7	
No. that consented to upper GI endoscopy	6	2	
No. with endoscopic features* of GERD	6 (100%)	2 (100%)	

**The endoscopic features of GERD ranged from varying degrees of oesophagitis, patulous cardia with visible reflux to Barret's oesophagus.*

Table 2: Relationship between F-scale score and asthma duration & severity using PEFR (peak expiratory flow rate)

Abnormal F-scale score vs Asthma duration				
Variable	**F scale score**		**Total**	**P-value**
	<7	**>7**		
Asthma duration				
• Long (>10yrs.)	28	18(51%)	35	
• Short (<10yrs.)	35	17(33%)	52	0.5

Abnormal F-scale scores vs Asthma severity (PEFR)					
Variable	**F- scale score**		**Total**	**P-value**	**Cor**
	<7	**>7**			**Corf®**
PEFR					
Normal*	16	10	26	0.001	-1.6 (p=0.1)
Abnormal	47	25	27		

**(Predicted normal PEFR for males was >500L/min and above 350L/min for females; Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters)*

Five asthmatics and 7 control subjects with F scale of >7 underwent a 24-hour PH study. Four of the asthmatics and all 7-control subjects showed abnormal acid reflux events in the study (**Table 1**). Only 8 (72.7%) of the subjects with GERD having Fscale >7 (6 asthmatics and 2 controls) agreed to upper gastrointestinal endoscopic examination; and they all showed evidence of GERD ranging from varying degrees of oesophagitis, patulous cardia with visible reflux to barrets oesophagus (**Table 1**).

Discussion

The relation between GERD and BA continues to be subject of research and discourse. Our study has not shown any significant difference in the prevalence of symptomatic GERD among a population of previously diagnosed asthmatics (36%) and another control population of non-asthmatics (30%). The prevalence rate of symptomatic GERD in this study is in keeping with previous reports.[11,12] The asthmatics were already diagnosed based on typical history of recurrent symptoms and reversible obstructive pattern on lung function test while GERD was diagnosed using a validated questionnaire (FSSG) with sensitivity of 62% and specificity of 59% using a cut-off of 8 as was used in the present study. The diagnosis of GERD was further corroborated by the findings of abnormal acid exposure on the 24-hour PH study in 92% of those positive on questionnaire that volunteered to undergo the pH study. One of the subjects was positive on the symptom scale, however, the subject had a normal acid study. The findings of the DX-pH probe used in this study had been found comparable to conventional pH recorders in previous studies.[13]

Previous reports[11,12] had indicated a higher prevalence of GERD among asthmatics than a control population. In the study by Chopra et al,[11] the sample size of the study subjects and control (80 versus 10 respectively) were not matched and scintiscan method used for GERD detection had a low specificity. The longitudinal study by Ruigomez et al[12] showed a small but significant increase in relative risk of incident diagnosis of GERD among patients with new diagnosis of asthma. The diagnosis of GERD and asthma relied on the records of the general practitioners (GP) as the study-entailed extraction of data from UK general practice research database. The diagnostic criteria of these conditions by the various GP are not standardized.

Among the asthmatics, the prevalence of GERD appears not to be related to duration of asthma but to asthma severity as measured by PEFR (p=0.001, Cor. Coef. -1.6). The explanation for this observation is possibly related to the previously reported[4] mechanisms of micro aspiration and vagally mediated bronchoconstriction due to presence of acid in the oesophagus in GERD.

All eight subjects that underwent upper gastrointestinal endoscopy had endoscopic evidence of reflux which is in keeping with earlier reports[14] that combination of symptoms and endoscopic changes are highly specific (97%) for GERD (confirmed with pH testing). One shortcoming of this present study was the relatively fewer number of subjects consenting to do the pH study despite its availability and minimally invasive nature of this device.[13] This may relate to cultural beliefs and attitude toward research. These subjects (except one) had evidence of acid reflux on ambulatory pH, which further confirms the findings on symptom questionnaire. Equally PEFR (peak expiratory flow rate) has a lot of limitations in assessing asthma severity; as readings of up to 100 L/min lower than predicted in men and 85L/min in women are within normal limits.[15]

In conclusion, a higher prevalence of GERD among BA subjects than a control population is noted, but this difference was not significant. Further studies involving a larger sample size are required to validate this finding.

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Footnote
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G.I Technique

Percutaneous liver biopsy

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ABSTRACT

Percutaneous liver biopsy has been performed for more than 120 years, and remains an important diagnostic procedure for the management of hepatobiliary disorders. Modern biochemical, immunologic, and radiographic techniques have facilitated the diagnosis and management of liver diseases but have not made liver biopsy obsolete. This comprehensive review article will discuss the history of development of percutaneous liver biopsy, its indications, contraindications, complications and the various aspects of the biopsy procedure in detail.

KEYWORDS : liver biopsy, indications, contraindications, technique

History

Percutaneous liver biopsy has been performed for more than 120 years. Although, there are reports of liver puncture carried out as early as 1825 by Recamier and by Stanley in 1833 to aid in diagnosis of purulent ecchinococcus, the first liver core biopsy was not performed until 1880 by Paul Ehrlich in Germany for the determination of glycogen in the livers of diabetic patients.[1] In 1895, L.Luatello reported on liver biopsy as a method of diagnosis, the cytomaterial examined as smear or teased-out preparation. F. Schupfer, in 1907, developed thicker needle for liver biopsy, allowing histological assessment of the tissue obtained.

Even after the first large series were reported in the 1930s by Huard and colleagues[2] in France and Baron[3] in the United States, the procedure was still regarded with apprehension. In 1938, I.Silverman further refined the technique of liver biopsy with the introduction of a new aspiration method using a modified biopsy needle, the 'Vim-Silverman needle'. The concept of aspiration cytology was developed by Martin and Ellis in 1920s at the Memorial-Sloan Kettering Cancer center at New York.

Percutaneous liver biopsy was not widely adopted until 1957 when G. Menghini reported a new biopsy method, "One-second needle biopsy": aspiration technique[4] using a thin walled, small caliber needle with sharply slanting bevel and without a trocar, which shortened the duration of the intrahepatic phase of the biopsy to a split second. This new technique marked the birth of histological liver diagnostics and since then, percutaneous trans-thoracic needle biopsy has been the standard method for obtaining liver tissue. It significantly expanded the use of liver biopsy, because of its safety and ease of performance and because of the sufficient quality and quantity of the tissue provided for various studies.

Indications

Percutaneous liver biopsy remains an important diagnostic procedure for the management of hepatobiliary disorders. Modern biochemical, immunologic, and radiographic techniques have facilitated the diagnosis of liver disease but have not made biopsy obsolete.

In each individual case the indication for liver biopsy depends on assessment of the risks relative to the potential benefits of the procedure. The benefit of liver biopsy is

dependent on recognition of the pathognomonic lesion within the tissue sample obtained. Size and distribution of the different histological features and the size of the biopsy cylinder are, therefore, important determinants for the success of the examination. Whether or not a histological diagnosis may be useful for optimal management of a patient can best be judged if the clinical question has been well defined before the biopsy is performed. In a study liver biopsy confirmed the clinical diagnosis in 62.4% of the cases reviewed and fundamentally modified the diagnosis in 20.2%, concluding that liver biopsy remains an indispensable diagnostic procedure in the field of hepatology, since it can result in modification of the clinician's diagnosis in one out of five cases.[5]

Even with modern advances in laboratory and imaging diagnostic technology, percutaneous liver biopsy ranks highly as a diagnostic method and is still performed when the clinical presentation or diagnostic test results are atypical or equivocal. In addition to being "gold" standard in establishing and confirming the diagnosis, the liver biopsy and the histology obtained is important in identifying the etiology, staging and determining the progression of disease and response to therapy.

Indications

1. Granulomatous hepatitis

Caused by infections like tuberculosis, schistosomiasis, drugs including allopurinol, isoniazid, systemic diseases like sarcoidosis, foreign body granulomas or post-transplantation granulomas. Many of these conditions present with unexplained elevation of serum alkaline phosphatase and/or aminotransferases and liver biopsy plays an important role in diagnosing this form of hepatitis and might help in establishing the etiology in most of these cases.

2. Drug-related hepatotoxicity

Hepatotoxicity accounts for approximately 3.5% of all adverse drug effects. Drug induced liver injury can range from mild acute hepatitis to chronic hepatitis, lobular to fulminant hepatitis, destructive cholangitis, hepato-cellular proliferation, veno-occlusive and neoplasms including angiosarcoma, hepatoma and hepatocellular carcinoma. Anabolic steroids, oral contraceptives, phenytoin, isoniazid, amiodarone, and alternative medicines such as herbal teas (eg, bush tea) are common offending agents. Liver biopsy is rarely indicated if a patient develops abnormal liver function tests while using a drug with well-described hepatotoxicity. However, biopsy should be considered in the following clinical situations:

1. The patient is undergoing treatment with a drug not previously associated with liver disease.
2. The patient has clinical evidence of underlying liver disease and develops symptoms that could be attributed to either the disease or the drug.
3. Various drugs are implicated and the pattern of histologic injury will help identify a specific drug, eg, Ito cell (stellate cell) hyperplasia in vitamin A toxicity.
4. It is necessary to differentiate autoimmune hepatitis from drug-induced injury.
5. If there is concern that fulminant liver disease may develop and disease severity must be determined.

3. Methotrexate Therapy

Biopsy is also used as a screening test to identify the development of drug-induced fibrosis. Patients receiving methotrexate for psoriasis, rheumatoid arthritis or inflammatory bowel disease are required to undergo a pretreatment liver biopsy and then repeat biopsies after each accumulated dose of 1.5 grams. However, the utility of liver biopsy for surveillance of methotrexate-induced fibrosis is controversial. Some studies indicate that methotrexate use results in little hepatotoxicity and that surveillance biopsies are not necessary or cost-effective.

4. Fever of unknown origin

Liver biopsy still remains part of the investigation of fever of unknown origin and may establish the cause of fever. The liver can be affected by the spread of infectious organisms from outside the liver; by primary infection by bacterial, viral, spirochetal, protozoal, helminthic, or fungal organisms; and by the systemic effects of granulomatous or lymphoproliferative disorders. The yield from liver biopsy in diagnosing infectious disease is variable. In a small study of 25 patients undergoing percutaneous liver biopsy for fever of unknown origin, the histologic examination provided useful diagnostic information in 9 cases (36 %) [6]. The liver biopsy had no diagnostic utility in the remaining 16 patients, half of whom had spontaneous resolution of the fever without a diagnosis being established.[6] Biopsy is most useful in evaluating patients with altered liver function tests especially elevated alkaline phosphatase levels, with hepatomegaly or with a mass in the

liver. Special staining, immunohistochemistry, and culture techniques must be used as appropriate for identification of common and unusual organisms. Lymphoproliferative and granulomatous diseases (sarcoidosis, tuberculosis, lymphoma, metastatic carcinoma) that cause hepatic infiltration and fever may be diagnosed only by biopsy. Culture of biopsy material can help in the diagnosis of infections such as tuberculosis, *Mycobacterium hominis tuberculosis*, *Mycobacterium avium-intracellulare*, CMV, Histoplasmosis, Candidiasis

5. Metabolic and Genetic Disorders

Liver biopsy is an important method for studying and diagnosing familial diseases or diseases that involve a metabolic or storage disorder. It also helps to ascertain the extent of liver damage

Hemochromatosis

Liver biopsy is diagnostic and provides quantitative measurement of iron load within the liver parenchyma. Laboratory tests that indicate iron overload (iron, total iron-binding capacity, and serum ferritin tests) are helpful for screening patients. Diagnosis in suspected patients has been largely replaced with the genetic analysis (C282Y-H63D) to differentiate Hereditary Hemochromatosis from secondary hemochromatosis and other causes of systemic iron overload. The HFE gene test will identify the 80% of hemochromatosis patients who carry the mutation. Liver biopsy determines the degree and location of stainable iron and the extent of hepatic fibrosis and allows measurement of total iron content and calculation of the hepatic iron index (hepatic iron concentration/ age).

Wilson's disease

A decade earlier, liver biopsy was the only test to confirm the diagnosis and also for estimation of intra-hepatic copper deposition in liver. Although, still considered to be the gold standard test, is seldom performed due to the easy availability of less-invasive serum test and genetic analysis Diagnosis is generally made on the basis of clinical findings, slit-lamp examination of the cornea for Kayser-Fleisher rings, decreased levels of serum ceruloplasmin, and elevated 24-hour urinary excretion of copper. Liver biopsy is important for diagnosis, as the results of histologic examination alone may be misleading. Special histologic staining techniques used to measure copper levels may produce normal results, despite high levels of copper in the liver. A hepatic copper concentration >250 pg per gram of dry weight is diagnostic of Wilson's disease.

a-1 antitrypsin deficiency

Deficiency of a-1-antitrypsin is the most common metabolic disease affecting the liver. Diagnosis of a-1-antitrypsin deficiency is suggested by decreased a-1-antitrypsin levels and is usually confirmed by genotypic analysis. Liver biopsy rarely done for diagnosis, may be helpful if the characteristic periodic acid-Schiff-positive, diastase-resistant globules are present, but the absence of such globules does not exclude the diagnosis.

6. Unexplained Cholestasis

Extrahepatic biliary obstruction

The advent of ultrasonography, computed tomography (CT) scanning, and endoscopic retrograde cholangiography have made liver biopsy unnecessary in most cases. However, 5% of extrahepatic cholestasis cases are diagnosed by biopsy because of the inability to visualize obstructed ducts or the failure to perform imaging studies before biopsy.

Intrahepatic causes of cholestasis

Damage or destruction of hepatocytes alters canalicular transport of bilirubin. Biopsy is needed to diagnose any of the many causes of intrahepatic cholestasis, which include viral hepatitis, alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis (PSC), infiltrative diseases, infections, idiopathic recurrent cholestasis and drug-related hepatotoxicity. The need for liver biopsy in patients with intrahepatic cholestasis from primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) is more controversial. In chronic obstructive biliary tract disease, biopsy may be performed to show irrevocable damage and stage for liver transplantation.

Primary biliary cirrhosis

It is frequently diagnosed by the presence of laboratory abnormalities alone (positive antimitochondrial antibody tests usually associated with an isolated alkaline phosphatase level that is out of proportion to levels of other liver enzymes). Biopsy confirms the serological diagnosis and permits histologic staging and determination of prognosis.

Primary sclerosing cholangitis

The diagnosis of PSC rests almost entirely on cholangiographic findings, and the radiologic image of a diffusely strictured biliary system has supplanted histopathologic criteria for diagnosis. Liver biopsy is diagnostic in only one third of patients with PSC and may show the characteristic "peri-ductal" pattern of fibrosis. Two third times nonspecific histologic abnormalities are typically found. Nevertheless, by demonstrating the degree of biliary fibrosis, biopsy may help to determine optimal timing for liver transplantation.

Infiltrative diseases

An increase in bilirubin or other liver test abnormalities may result from primary hepatic or metastatic tumors. By the time jaundice occurs, much of the liver has been replaced by tumor, and prognosis is poor. Jaundice can occur early when malignancies obstruct the bile duct (eg, cholangiocarcinoma, metastatic adenopathy). Hodgkin's and non-Hodgkin's lymphoma can manifest as diffuse hepatic infiltration with cholestasis. Liver biopsy is generally diagnostic.

Infections

Infections can cause jaundice directly through obstruction of ducts (eg, ascaris), cholestasis (eg, tuberculosis), or hyperbilirubinemia associated with sepsis and endotoxemia (cholestasis lente). In the septic patient, liver biopsy will reveal cholestasis with minimal inflammation, but biopsy should be deferred in very ill patients.

7. Transplantation

Biopsy of donor liver may be indicated to evaluate conditions which might effect graft-survival like excessive steatosis. The use of liver biopsy after liver transplantation is increasing, and policies on histological monitoring vary between liver transplant units. Some units perform routine biopsies on day 7 after transplant to assess acute rejection, whereas others do annual review biopsies at which abnormalities are frequently seen.[7] Liver biopsy is also useful in the diagnosis of invasive cytomegalovirus infection and in assessing recurrent disease.[8,9]

8. Hepatic Neoplasms and Other Focal Lesions

Diagnosis of space-occupying lesion is one of the traditional application of liver biopsy and even remains useful today, as more and more SOL are being identified as incidental findings or during routine screening for cancer or other conditions. FNA might be able to provide tissue diagnosis in most of these cases. Core liver biopsy may be necessary to provide sufficient tissue for immunohistochemistry for identifying unknown primary. Biopsy of focal lesions should be done only after clinical and imaging data have confirmed a solid mass. Biopsies must not be performed on cysts, abscesses, or hemangiomas. If biopsy of a focal lesion is necessary for diagnosis, it is best obtained by ultrasound- or CT-guided fine-needle aspiration. A solid tumor in a cirrhotic liver or an alpha fetoprotein level >400 ng/mL in the presence of a solid tumor is diagnostic of hepatocellular carcinoma, and biopsy rarely adds to management. However, increased a-fetoprotein levels in the setting of active liver disease without a focal lesion may reflect a diffuse tumor and in such cases biopsy may be helpful.

The role of percutaneous liver biopsy in the diagnosis of focal liver lesions depends largely upon the clinical picture. In most patients with malignant hepatocellular carcinoma ultrasound scanning, CT, and measurement of serum a-fetoprotein will allow a diagnosis to be made (in the context of a space-occupying lesion in a cirrhotic patient). Similarly, a patient with a history of colonic resection for neoplasia who presents with a solitary lesion in the liver associated with raised serum carcinoembryonic antigen, may not require a biopsy of the lesion to make the diagnosis of a potentially resectable metastasis. Liver biopsy also carries a documented risk of seeding tumors down the biopsy track.[10] The magnitude of this risk is currently unknown. Modern imaging techniques can also help to define other types of focal hepatic lesions such as hemangiomata and focal nodular hyperplasia. In these situations, some experts believe that the risk of bleeding after biopsy of a malignant tumor is greatest when the tumor is superficial and so recommend traversing normal liver before sampling tumor tissue. Fine needle aspiration biopsy may be a safer option if material for histological examination is required in the case of a suspected angioma.[11]

9. Unexplained Hepatomegaly

The liver may enlarge as a result of various insults, including amyloid disease, Cushing's syndrome, genetic metabolic disorders, alcoholic liver disease, cryptogenic cirrhosis, and neoplasms. Biopsy can often identify the cause of hepatomegaly and perhaps exclude an incorrect clinical diagnosis.

10. Unexplained Abnormalities on Liver Test Results

Liver biopsy is often used in the investigation of persistent abnormal liver enzymes but this must be taken in context, tempered by the results of other routine investigations along with the clinical picture. Liver biopsy provides an accurate diagnosis in >90% of patients with unexplained abnormalities on liver test results. The most common findings on liver biopsy in such cases include non-specific steatosis, NASH or congestion.

Some authors have questioned the utility of liver biopsy in the etiologic diagnosis of biochemical liver abnormalities of unknown cause. In one study, liver biopsy modified the therapeutic approach only in the three patients with hepatic tuberculosis.[12] Liver biopsy confirmed ultrasonographic findings of steatosis and differentiated bland steatosis from NASH, but did not influence the therapeutic approach.[12] Most patients with normal findings on ultrasonography had normal or near-normal biopsies.[12] The indication for liver biopsy should be individualized.

11. Research

Using liver biopsy in the context of research is controversial but has undoubtedly given invaluable information in the past in areas such as chronic hepatitis C and hepatitis B disease progression, studying the response to treatment and the development of new drugs. Liver biopsies should be performed in the context of a clinical trial and where approval has been given by the local research ethics committee. In circumstances where the patient will derive no potential benefit from the procedure, and will thus only accrue the risks of that procedure, the patient should be fully aware of this and give written and informed consent.

12. Non alcoholic fatty liver disease (NAFLD)

The initial clinical and laboratory assessment of a patient with suspected NAFLD should be determined by ASA, ALA, ALP (biochemical markers of liver injury and cholestasis) and liver functions (serum bilirubin, albumin, and prothrombin time). The next steps include presence of hepatitis C or any alternative clinical condition and estimate alcohol consumption. In absence of cirrhosis this is often sufficient for diagnosis. However diagnosis of steatohepatitis as apposed to fatty live alone, and its grade and stage can only be made precisely by a liver biopsy. The cost and risks of the biopsy are generally weighed against the value of the information obtained from the biopsy in estimating prognosis and guiding future management decisions.

13. Chronic viral hepatitis

The usefulness of liver biopsy in management of chronic viral hepatitis was questionable but with the emergence of new antiviral therapies there is no doubt of the value of histology in assessing patients that will be candidates for therapy and will likely benefit from treatment and assessing their response to it.

Chronic hepatitis C patients (with positive serum PCR), should undergo liver biopsy to be considered for antiviral therapy. Up to 50% of patients with active disease have a normal serum ALT, and performing a liver biopsy in these patients will allow an assessment of the grading of disease activity and staging of fibrosis and calculation of the Hepatitis Activity Index (a necroinflammatory-fibrosis scoring system). Unfortunately, histology of a single liver biopsy sample and the monitoring of aminotransferases are poor predictors of disease progression. Serial histology with biopsies taken every two or three years may be needed to assess disease progression and prognosis, especially in refractory cases.

<u>Chronic hepatitis</u>

Liver biopsy is indicated in hepatitis C virus (HCV) or hepatitis B when persistent, i.e., >6 months; when intermittent abnormalities in transaminase levels are observed; or when an alternative diagnosis (eg, alcoholic liver disease, nonalcoholic steatohepatitis [NASH], or hemochromatosis) is possible. Studies have demonstrated that >20% of HCV patients with normal serum alanine aminotransferase levels have advanced liver disease. Follow-up biopsies may be helpful in assessing response to therapy and progression of disease. In HCV, liver biopsy impacts physician judgment with regard to antiviral therapy in several ways:

1. Likelihood of response to interferon: A decreased viral response is observed when diffuse fibrosis or cirrhosis is present.
2. Severity of infection: When the date of infection is relatively certain, the degree of fibrosis allows estimation of the rate of progression. Rapid progression increases the urgency

for therapy, whereas with slower progression, therapy may be deferred.

3. Alternative diagnosis: Another cause of liver disease may be diagnosed in 4% of HCV patients.
4. Posttreatment biopsy: In settings other than clinical trials, posttreatment biopsy does not result in information sufficient to warrant the discomfort, risk, and cost.

Role of Liver Biopsy in Chronic Hepatitis C:

The main reasons for performing a liver biopsy includes current status of the liver injury and identifies features to start therapy. It also reveals advanced fibrosis or cirrhosis that necessitates screening for hepatocellular carcinoma. Though biopsy is used for the grade and stage of liver injury, it can also used for knowing histological progression regarding a disease.

According to the recommendations given by AASLD, a liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prognostic purpose or to make a decision regarding treatment(Class IIa, Level B) Although available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis I persons with chronic hepatitis C infection , but it should not replace the liver biopsy in routine clinical picture(Class IIb, Level C)

Acute hepatitis: The majority of cases of acute icteric hepatitis are diagnosed using viral serology. Liver biopsy in this setting is generally not indicated; however, autoimmune hepatitis may have an acute presentation, and early biopsy to establish the diagnosis may improve outcome.

Autoimmune hepatitis: Autoimmune hepatitis is a self-perpetuating hepatocellular inflammation characterized histologically by the presence of periportal hepatitis. Diagnosis requires the absence of viral markers, alcohol consumption, use of hepatotoxic medications, and biliary lesions. Liver biopsy is essential to establish the diagnosis and determine patient prognosis. The presence of cirrhosis in a liver biopsy specimen indicates a poor prognosis. Biopsy may also be useful in evaluating therapeutic response to steroids or immunosuppressive agents.

Ischemic hepatitis: Ischemic hepatitis with very high aminotransferase values is usually preceded by hypotension, hypoxemia, or both. This may be a manifestation of multiorgan failure and portends a poor prognosis. If the patient survives, aminotransferase levels normalize rapidly, generally within a few days. Liver biopsy is usually not necessary to establish the diagnosis.

Alcoholic liver disease : - If the patient history includes excessive ethanol consumption, biopsy is unnecessary. If biopsy is performed, the most common histologic features are steatosis, ballooning degeneration of hepatocytes, hyaline (apoptotic) bodies, neutrophil inflammation, and pericellular fibrosis.

Contraindications

Liver biopsy is a safe procedure when performed by experienced operators. Froehlich et al[13] noted a lower complication rate for physicians who performed more than 50 biopsies a year. Prior ultrasonographic localization of the biopsy site may decrease the rate of complications for physicians who perform infrequent liver biopsies. “Blind” liver biopsies should be performed by experienced gastroenterologists, hepatologists, or transplantation surgeons.[14] Contraindications to percutaneous liver biopsy are relatively few, but identifying contraindications is important to avoid the major complications associated with the procedure. Contraindications to liver biopsy include the following:

Absolute [15]

Uncooperative patient
History of unexplained bleeding
Bleeding tendency*
Prothrombin time >4 seconds more than control, (INR) greater than 1.6
Thrombocytopenia, Platelets <60,000/mm^3
Prolonged bleeding time (10 min)
NSAID use within last 7 to 10 days
Unavailability of blood transfusion support
Suspected hemangioma or other vascular tumor
Inability to identify an adequate biopsy site by percussion and/or ultrasound
Suspected echinococcal cysts in the liver

Relative[15]

Morbid obesity (transjugular route preferred)
Ascites (transjugular route preferred)
Hemophilia
Infection in right pleural cavity
Infection below right hemidiaphragm

Suspected hemangioma
Suspected echinococcal infection

(* Although these criteria are considered absolute contra-indications by most hepatologists, they can be corrected by transfusions of platelets or fresh-frozen plasma and are therefore not truly absolute.)
† Use of aspirin within 7-10 days is an absolute contraindication to liver biopsy. Use of other NSAIDS within the previous 3 days is generally an absolute contraindication.

1. Uncooperative patient

At the time of biopsy, it is essential for the patients to be cooperative and must be able to hold their breath and remain still during the procedure. An untoward movement when the biopsy needle is in the hepatic parenchyma can result in laceration of the liver and/or capsule which can lead to intra-hepatic and/or intra-peritoneal hemorrhage. Sedation should be considered for such patients, and short-acting benzodiazepianes like lorazepam, midazolam can be used to allay anxiety and fear, with no increased risk.[16] When absolutely necessary, the biopsy may be performed under general anesthesia in uncooperative patients in whom the benefit of obtaining liver histology outweighs the risks of the procedure

2. Extrahepatic cholestasis and cholangitis

Cholestasis due to extrahepatic biliary obstruction is usually stated as a contraindication to liver biopsy due to the risk of bile leakage with subsequent biliary peritonitis, septic shock, and death.[17] With the availability of current hepato-biliary imaging techniques (ERCP, MRCP), the indication for liver biopsy and its benefits in biliary obstruction have decreased significantly and it should only be performed in these cases when there is doubt about the diagnosis and the benefit of knowing liver histology outweighs the risk. The transjugular approach is preferred under these circumstances to minimize the risk biliary peritonitis.[18]

3. Impaired coagulation.

There are widely divergent opinions about the values at which abnormal coagulation indexes become contraindications to percutaneous liver biopsy. There are number of studies that show that the degree of bleeding from the liver puncture site bears no correlation to peripheral blood coagulation parameters, when these parameters are modestly increased.[19,20] Some of these investigators have postulated that this discrepancy in liver bleeding time may be due to the inherent elasticity of the biopsy track collapsing down after the core has been taken, together with the high local concentrations of clotting factors within the hepatic parenchyma.[21] It should, however, be borne in mind that during a blind percutaneous liver biopsy, the liver is not the only structure to be punctured and the skin and subcutaneous tissues (and occasionally other organs) can bleed. Thus, peripheral indexes of clotting must still be taken into consideration. In the absence of factor concentrate inhibitors, liver biopsy is safe if the clotting abnormalities are corrected before and for 24 hours after biopsy.[22,23]

a. Prothrombin time

Several large studies have failed to show an increased risk of bleeding associated with a prolongation of the prothrombin time of four seconds above control values.[19,21,24] The largest retrospective study of percutaneous liver biopsy to date failed to show any correlation between a prolongation of prothrombin time by seven seconds over control values and the occurrence of hemorrhagic complications.[25] By contrast, a number of other studies, however, have corroborated the widely held belief that a coagulopathy predisposes the patient to hemorrhage after percutaneous liver biopsy.[26] A study in UK showed that bleeding was commoner if the international normalized ratio (INR) was raised, with 3.3% of the bleeds occurring when the INR was between 1.3 and 1.5, and 7.1% occurring when the INR was >1.5.[27] This suggests that about 90% of the bleeds occurred in patients with an INR<1.3 and reinforces the fact that having a normal INR or prothrombin time is no reassurance that the patient will not bleed after the procedure.

b. Thrombocytopenia

The level at which thrombocytopenia becomes a contraindication to percutaneous liver biopsy is uncertain from published data. One authority[28] proposes a platelet count above 100,000/mm^3, whereas other groups such as the Mayo Clinic regard counts as low as 56,000/mm^3 to be safe[24] Most recognized UK texts require that the platelet count be above 80,000/cubic mm[29] whereas a survey of most US centers showed a preference for platelet counts above 50,000/cubic mm[30] One study of 87 patients found that those patients with a platelet count below 60,000/mm^3 were significantly more likely to bleed after percutaneous liver biopsy than those with platelet counts above this value.[31] The evidence for a cut off value remains scanty and takes no account of the function of the platelets.

The effect on bleeding of thrombocytopenia due to hypersplenism compared with thrombocytopenia resulting from bone marrow failure has, to our knowledge, not been studied in detail. The absolute value of the platelet count may not be crucial in determining the risk of bleeding as it is well recognized that even those patients with normal prothrombin times and platelet counts can have severely deranged bleeding times. Nevertheless, for a percutaneous liver biopsy the minimum platelet count felt to be safe without the need for support is 60,000/mm^3.

c. Platelet function/bleeding time

The practice of measuring bleeding time (BT) before liver biopsy is much more common in Asia compared with the USA (73 v 36%).[30] BT is seldom if ever measured in UK centers prior to liver biopsy even though the ingestion of aspirin and other non-steroidal anti-inflammatory drugs in the week prior to invasive intervention is a recognized contraindication by several authorities. There are to our knowledge, however, no convincing data to support this as a contraindication to percutaneous liver biopsy.

Patients with renal impairment usually have abnormalities of platelet function. According to one small study, patients with end stage renal failure on hemodialysis are at high risk (up to 50%) of hemorrhagic complications after percutaneous liver biopsy, independent of the BT.[32] This same study suggested that liver transplant recipients with a BT above 10 minutes (upper limit of normal) had a higher incidence of bleeding complications compared with those with a BT below 10 minutes. The sample size, however, is too small to allow any firm conclusions to be drawn.

Several other factors are likely to affect platelet function with or without affecting the BT. This fact, together with the considerable variation in results obtained between different operators, makes the use of BT as a measure of risk for hemorrhage difficult to interpret. One study was able to show that within a group of cirrhotic patients, those with abnormal BT (42%) were more likely to have significantly lower platelet counts, longer prothrombin times and higher blood urea and serum bilirubin than those with normal BT (58%). It also demonstrated that the bilirubin concentration as well as the platelet count were independently correlated with the BT (although the correlation for the latter was weak, and the raised serum bilirubin may well be just a surrogate marker for the severity of liver disease).[33]

4. Ascites

The presence of tense ascites is considered a contraindication to percutaneous liver biopsy, because of the increased difficulty of obtaining a satisfactory specimen due the distance between the abdominal wall and the liver, and also because of the possibility of lacerating the liver with risk of uncontrollable hemorrhage into the ascites. Despite the lack of evidence to support these logical reasoning, most authorities suggest other alternatives for obtaining a liver biopsy in a patient with tense ascites. This includes performing a total paracentesis prior to performing the percutaneous biopsy or performing an image guided biopsy, a transjugular liver biopsy, or a laparoscopic biopsy. There is some evidence to support the fact USG or CT guided liver biopsy in the presence of ascites does not increase the complication rate.[34,35]

5. Cystic lesions

Modern imaging techniques can often identify benign cystic lesions of the liver, thereby eliminating the need for biopsy in many cases. Cystic lesions within the liver may communicate with several structures including the biliary tree and therefore pose a risk of biliary peritonitis after biopsy. The cystic lesion quoted most often as a contraindication to percutaneous liver biopsy was the echinococcal cyst because of the risk of dissemination of the hydatid cysts throughout the abdomen, and the risk of anaphylaxis. Recent advances in the treatment of hydatid disease of the liver mean that this may no longer be so.[36] Aspiration of hydatid cysts with 19-22 gauge needles under ultrasound guidance has been shown to be safe and can be used both diagnostically[37] and therapeutically[38] for the injection of hypertonic saline or 95% ethanol under albendazole cover.

6. Vascular lesions

Biopsies should not be performed on suspected liver hemangiomas. In addition, adenomas, hepatocellular carcinoma, and amyloidosis are also prone to bleeding.

7. Amyloidosis

The use of liver biopsy in the diagnosis of amyloid liver disease was first reported in 1928. Volwiler and Jones reported the first death from hemorrhage after amyloid liver biopsy.[39] which along with other reports of hemorrhage after liver biopsy in patients

with amyloid have lead to the inclusion of amyloid liver disease in the list of contraindications to percutaneous liver biopsy.[39] One intraperitoneal bleed was reported in a small series of liver biopsies in amyloid liver disease in 18 patients, which was managed conservatively.[40] However, there are no large controlled trials to show an increased risk of hemorrhage after liver biopsy in amyloid liver disease. Stauffer and colleagues[40] decided that liver biopsy was a useful method in the establishment of the diagnosis of hepatic amyloid, and certainly in the context of the investigation of hepatomegaly of uncertain etiology this seems reasonable. However, if a diagnosis of amyloidosis had already been made or is strongly suspected, then a specific indication for performing a percutaneous liver biopsy is needed rather than for performing a more benign procedure such as a rectal biopsy.

8. Local infection

Infection in the right lung, pleural space, or peritoneal cavity may cause infectious organisms to be carried into the liver by the biopsy needle, with potential risk of causing infectious hepatitis or hepatic abscess.

Complications

Although the liver has a rich vascular supply, complications associated with percutaneous liver biopsy are rare, but are potentially fatal. The majority (60%) of complications occur within the first 2 hours, and 96% of complications occur during the first 24 hours after the procedure.[25,41] Potentially fatal complications generally occur within the first 6 hours, which is the reason for the standard 6-hour postbiopsy monitoring period. Approximately 2% (1-3%) of patients undergoing biopsy require hospitalization for the management of complications after a liver biopsy, especially if the procedure was performed with a Tru-cut biopsy needle. Vasovagal episode, hypotension and pain are the most common reasons for admission.[14,42]

Complications of percutaneous liver biopsy[43]

- Pain (0.056-22%)
  - o Pleuritic
  - o Peritoneal
  - o Diaphragmatic
- Hemorrhage
  - o Intraperitoneal (0.03-0.7%)
  - o Intrahepatic and/or subcapsular (0.059-23%)
  - o Hemobilia (0.059-0.2%)
- Bile peritonitis (0.03-0.22%)
- Bacteremia
- Sepsis (0.088%) and abscess formation
- Pneumothorax and/or pleural effusion (0.08-0.28%)
- Hemothorax (0.18-0.49%)
- Arteriovenous fistula (5.4%)
- Subcutaneous emphysema (0.014%)
- Anesthetic reaction (0.029%)
- Needle break (0.02-0.059%)
- Biopsy of other organs
  - o Lung (0.001-0.014%)
  - o Gallbladder (0.034-0.117%)
  - o Kidney (0.09-0.029%)
  - o Colon (0.003-0.044%)
- Mortality (0.008-0.3%)

1. Pain

Pain occurs in approximately 30- 50% of patients undergoing a liver biopsy. Immediately after the procedure, patients report localized discomfort at the biopsy site or mild, dull ache in the right upper quadrant. This typically is relatively short in duration, lasting less than 2 hours, and often responds to analgesics.[44] Approximately one fourth of patients have pain referred to the right shoulder, but is easily controlled with acetaminophen or mild narcotic analgesics. Unrelenting, severe abdominal pain is alarming, possibly indicating a more serious complication such as intraperitoneal bleeding or peritonitis.

2. Hemorrhage

Bleeding is another complication which is potentially lethal. Presentations include subcapsular or parenchymal hematoma, free intraperitoneal hemorrhage or hemobilia. Although very rare, clinically significant intraperitoneal hemorrhage is the most common fatal complication of percutaneous liver biopsy. Peritoneal hemorrhage may result from laceration of the liver caused by deep inspiration or patient movement during the biopsy, or may result from penetration of distended veins, aberrant arteries or branch of the hepatic artery or portal vein. It commonly manifests within the first 2-3 hours after the procedure[25,45] although it has been reported to present as long as 24 hours post-procedure. Late hemorrhage is associated

with a poor outcome. The overall rate of occurrence of peritoneal hemorrhage is around 0.3%. Older age, multiple needle passes (>3), and the presence of cirrhosis or hepatic malignancy have been described to be associated with increased risk of free intraperitoneal hemorrhage complicating liver biopsy.[25,42] Abdominal pain and persistent hemodynamic instability, presenting as tachycardia and hypotension, are typical of significant bleeding. Early diagnosis via ultrasonography or CT is preferred. Findings of free intraperitoneal fluid on ultrasonography or CT should be correlated with the clinical assessment of the patient.[46] If hemorrhage is suspected, immediate arrangements for blood, platelets, and plasma should be made, and an angiographer and surgeon should be alerted early in the process to facilitate rapid intervention if needed. Aggressive fluid management and blood and platelet transfusion, as indicated, may be sufficient in most cases to improve the patient's hemodynamic status. If hemodynamic instability persists despite aggressive resuscitative measures, angiographic embolization or surgical exploration is indicated to stop the bleeding. Angiography with potential embolization is the preferred intervention in most cases.

Intrahepatic or subcapsular hematomas are the most common bleeding complication and have been noted on approximately 23% of ultrasound images obtained following biopsy. Most of these are clinically asymptomatic and are often incidental findings.[47] The rate of occurrence have been similar after either blind or laparoscopy-guided modalities, but incidence may be influenced by needle type and imaging technique. Symptomatic hematomas require imaging by ultrasound, CT or MRI to establish the diagnosis. Large intrahepatic hematomas may cause pain along with tachycardia, hypotension, and a delayed decrease in the hematocrit.[45] Conservative treatment of hematomas is generally sufficient. Rarely, large hematomas may cause biliary obstruction which would require angiographic embolization or surgical management.

The least common of the hemorrhagic complications is hemobilia, or bleeding into the bile duct associated with the classic triad of gastrointestinal bleeding, biliary colic, and jaundice.[25] It is a rare complication of liver biopsy; one study of 68,276 biopsies reported only 4 instances of hemobilia.[25] Clinical presentation ranges from chronic anemia to rapid exsanguination. Hemobilia typically develops later than other complications. The average time to onset of symptoms is approximately five days after the biopsy, [48] but onset may occur earlier. Conservative treatment often is sufficient. However, if clinically significant hemobilia is present, angiography is the modality of choice because both diagnosis and intervention can be accomplished with a single procedure.

3. Transient bacteremia after percutaneous biopsy of a normal liver is a well recognized phenomenon and has been reported in 5.8 to 13.5% of patients after liver biopsy.[43] Although, such bacteremia is generally inconsequential, septicemia and shock can develop on rare occasions in patients with biliary obstruction and cholangitis. Currently, there are no recommendations for the routine use of prophylactic antibiotics in patients undergoing liver biopsy, including those with prosthetic valves or joints.[49]

4. Biliary peritonitis is another noteworthy complication, although rare. Severe abdominal pain and vasovagal hypotension herald its occurrence. Analgesics and fluid management usually are sufficient, but persistence of the condition may necessitate endoscopic retrograde cholangiopancreatography with stent placement

Other rare complications of percutaneous liver biopsy include biliary ascites, bile pleuritis, bile peritonitis, pneumothorax, hemothorax, subcutaneous emphysema, pneumoperitoneum, pneumoscrotum, subphrenic abscess, carcinoid crisis, anaphylaxis after biopsy of an echinococcal cyst, pancreatitis due to hemobilia, breakage of the biopsy needle, and accidental biopsy of other organs.[25,45,50]

The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10,000 to 1 in 12,000,[45,24] and is highest among patients who undergo biopsies of malignant lesions.

Procedure

Preparation:

A detailed history and physical are essential elements to obtain prior to performing a liver biopsy. This history will provide the indication or any contraindications for this procedure. The physician should ask the patient about any personal or family history of bleeding disorders or prior episodes of prolonged bleeding after procedures or operations. A detailed medication list should be obtained, particularly focusing on medications interfering with coagulation such as warfarin, aspirin and nonsteroidal anti-inflammatory drugs. A complete list of allergies to medicine should be obtained, with particular attention being paid to adverse affects related to anesthetic agents.

The patient should be given information prior to the procedure with explicit instructions on what to expect and how to prepare for the examination. Any medications affecting coagulation should be discontinued preferably one week prior to the biopsy. Typically, overnight fasting is requested prior to the procedure. On occasion, just prior to the procedure, the operator may ask the patient to ingest a food with high fat content to stimulate gallbladder contraction to lower the risk of gallbladder perforation.

Informed consent must be obtained by the physician from the patient or a designated conservator prior to the procedure. The physician should provide a detailed explanation about the risks and benefits of performing the biopsy. The physician should answer any questions the patient may have about the procedure itself and reassure the patient about the safety.

Equipment: The following equipment is necessary to have prior to performing the liver biopsy: signed informed consent, sterile gloves, a percutaneous liver biopsy device tray (which is available from multiple commercial medical device companies). Typically the device tray will include the following: an antiseptic skin preparation solution such as betadine, sterile gauze, sterile drape, 10 ml ampule of sterile saline solution, sterile surgical scapel, sterile core biopsy needle, 2 sterile injection needles (typically 21 and 25 gauge), formalin filled specimen container. Imaging equipment is not essential and may vary amongst institutions. However, we recommend ultrasound guidance and imaging prior to performing this procedure.

Timeout: Prior to the procedure beginning, a "timeout" should occur as final verification of correct patient, procedure, physician and site.

Patient Position: Upon entering the room, the patient should be positioned appropriately to allow optimal conditions for an adequate and safe biopsy. The patient should be in the supine position and up against the right edge of the bed. The patient's right arm is then positioned behind his or her head. We then ask the patient to angle their hips and lower extremities toward the left. This positioning applies forces to rotate the liver against the right body wall and toward the entry point for the biopsy needle. The patient should be comfortable enough to maintain this position for several minutes. Lastly, the height of the patient's stretcher should be adjusted to approximately the operator's elbow level.

Inspection and marking: Once the patient is positioned appropriately, the operator should inspect and palpate the patient's abdomen and liver edge. Percussion should be performed over the right upper quadrant in the midaxillary line. The percussion should focus on the intercostal spaces. The biopsy is typically performed in the 7th or 8th intercostal space, but location may vary. Percussion during inspiration and end expiration allows the operator to listen for lung resonance (during inspiration when the lungs are fully expanded and the diaphragm has shifted caudad) changing to liver dullness (after full exhalation when the lungs are collapsed and the diaphragm has shifted cephalad). The biopsy should be performed in an intercostal space which is dull to percussion at the end of exhalation. Instructing the patient to breathe in an appropriate manner to facilitate this process is key to a safe procedure. The patient should be instructed to inhale, and then exhale slowly and completely. At the end of exhalation, the patient should hold their breath, which will allow the operator the time to perform the biopsy with the liver in the proper plane.

Marking: Once an intercostal space has been chosen as a potential site, the patient should practice this breathing as the operator percusses the site to ensure appropriate dullness. A mark "X" is then placed on the biopsy site with a marking pen. The site should be marked on the superior border of the rib to avoid the neurovascular bundle which resides on the inferior border.

Ultrasound: At this juncture, ultrasound is used to verify the adequacy of the biopsy site. The gallbladder should be identified, if it has not been surgically removed, to ensure it is not in the plane of the impending biopsy. The patient is again instructed to inhale and fully exhale while the operator holds the ultrasound transducer at the designated biopsy site. At the end of exhalation, an adequate amount of liver parenchyma should be fully visible with no evidence of other organs in the biopsy plane. Doppler imaging can be applied to the field to ensure the absence of large blood vessels in this plane. One image of the liver parenchyma and one image of the parenchyma with doppler flow can be captured and saved for documentation.

Once adequate imaging of the liver has occurred, the operator should consider the directional plane of the biopsy needle. At the time of the biopsy, the needle should pass in the same directional plane as the ultrasound transducer signal. In an attempt to visualize this plane, we keep the transducer in place and use a flat edge to mark a line across the patient's abdomen in this plane. The operator should be sure not to vary too much in the cranial/caudal or the anterior/posterior direction as this can lead to unnecessary injury.

Sterilization

After fully marking the entry for the biopsy site and the directional plane of the needle, the operator should begin the sterilizing process. A topical povidone-iodine solution antiseptic should be used for this process. The antiseptic should be applied first at the point of entry, and then continued in the surrounding area by moving out in concentric circles. For this component of the procedure, non sterile gloves may be worn.

Once the area has been appropriately sterilized, the operator should open the cover to the biopsy tray and visually inspect the items to ensure that all of the items appear intact and are available. If all items appear intact, then the operator should place on a sterile gown, cap, mask with face shield and finally, sterile gloves. The sterile drape should then be placed on the patient, with the "X" marked biopsy site visible within the drape's central opening. All exposed areas within the sterile drape opening should be completely covered with the topical antiseptic. If possible, the crease from the drape's folding should align with the directional plane line of the biopsy. Sterile technique should be maintained throughout the entire procedure.

Anesthesia

Conscious sedation may be used for percutaneous liver biopsies. However, as previously stated, active patient participation is helpful to ensure the biopsy is performed during end expiration. In addition, the biopsy itself is performed so rapidly, that conscious sedation is rarely necessary. Therefore, we use primarily local anasthesia. Once the sterile drape is in place, local anasthetic should be used. 1 or 2% Lidocaine is aspirated into a syringe, and a 25 gauge needle is used to apply the medication to the dermal and subcuatenous tissue layers. The 25 gauge needle is then exchanged for a 21 or 22 gauge needle for deeper lidocaine injection. All tissue layers should be injected down to the capsule of the liver, and an adequate amount of lidocaine should be used to maximize local effect. Suction should be applied to the syringe prior to injection at each tissue layer. A small amount of blood may be seen within the syringe once the needle has reached the liver capsule and parenchyma. Once this is seen, the local anasthetic has been applied deep enough. Considerable effort should be made to provide adequate anasthetic to the portion of the capsule that will come in contact with the needle. This may be achieved by applying the deep layers of anasthesia during end expiration, or angling the anasthetic needle cephalad in anticipation of the motion that will occur with expiration.

Technique

Once adequate local anasthesia has been injected, palpation of this region should confirm positioning above the rib. A second syringe is then used to aspirate the provided sterile saline. The biopsy needle is then attached to the syringe. The needle must be attached securely. A loosely attached needle would negate the negative pressure essential during the biopsy.

A small, shallow incision is then made using the provided scalpel, allowing the biopsy needle to pass through the skin easily. The needle is introduced into the incision and slowly advanced toward the liver. The needle should passed through the anesthetized tract. Suction should be applied to the syringe as the needle passes through the tissue planes. There should be a popping sensation, with a lessening of resistance, as the needle passes through the peritoneum. A small amount of saline should then be flushed through the needle to expel any superficial tissue in the needle.

In final preparation for the biopsy, the operator should be sure the needle is aligned with the straight line drawn previously (which represented the direction displayed by the ultrasound transducer). In addition, the needle should be aligned and passed in a plane parallel to the floor. The operator should avoid passing the needle in a superior or posterior direction.

Suction is applied to the syringe. Some syringes have a locking mechanism to provide constant negative pressure. The patient is again asked to completely exhale and to hold their breath at end expiration. At this juncture, with constant suction being applied to the syringe, the needle is rapidly advanced into the liver and then withdrawn. The entire process of passing the needle should last no longer then approximately one second. The needle is removed completely from the patient, and a gauze is applied with pressure to the biopsy site.

The biopsy specimen is now within the needle or syringe. The specimen can be removed from the syringe by pulling the plunger out the back of the syringe and emptying the contents into a formalin containing bottle. The specimen may also be removed by pushing the syringe contents back through the syringe and needle into the formalin containing bottle. However, this in theory, may damage the specimen. If no specimen is obtained, the needle and syringe should be carefully examined again to ensure no problems exist. Another pass may be necessary. No more than three passes should be

performed, as the risk of bleeding and other complications increases significantly.

Post Procedure Monitoring:

Once an adequate specimen is obtained, a bandage should be applied to the biopsy site. The patient should be instructed to lay in the right lateral decubitus position for at least 2 hours. Frequent vital signs should be monitored. The patient should be evaluated for any evidence of a complication. Post procedure monitoring should last at least 2 hours prior to discharge.

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GI Technique

Evaluation of hepatocellular carcinoma by contrast enhanced ultrasound : a novel technique

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Introduction

Characterization of focal liver lesions remains a diagnostic challenge for the radiologists, more so when there is associated underlying chronic liver disease (CLD). Imaging plays a vital role and there has been a constant endeavor to improve the diagnostic accuracy of liver lesions. The introduction of mutiphasic CT and MRI has revolutionized the diagnostic ability of liver lesions. With the advent of ultrasound contrast agents (UCAs), it is possible to evaluate liver lesions using the non-invasive imaging technique of "contrast-enhanced ultrasonography" (CEUS).[1-3] CEUS can overcome the limitations of grey scale and color doppler sonography[4,5] and has been used for characterisation of focal liver lesions.[2]. It can depict arterialisation of hypervascular hepatocellular carcinoma (HCC)[6,7] and can also help in assessment of the post-therapeutic response.[8,9]

We present two such cases of HCC evaluated by a recently available second generation ultrasound contrast agent, SonoVue (Bracco, UK).

Technique of CEUS

Initial grey scale ultrasound (US) was performed to look for a proper acoustic window, visibility of lesion and patient co-operation. CEUS was performed on Siemens S-2000 machine. The vial of SonoVue was prepared 5 minutes prior to CEUS by injecting 5 ml of saline into the powdered form of the vial and shaking vigorously. An intravenous antecubital access with 20-gauge venflon with a three-way connector was obtained.

After selecting contrast specific imaging mode, 2.4 ml of SonoVue per mass was injected intravenously followed by normal saline flush of 10 ml. The timer was started immediately following the contrast injection and findings recorded on cine mode. Enhancement of the mass was evaluated in three phases - arterial (15-25 seconds), portal venous (45-90 seconds) and delayed phase (180 seconds).The cine recordings were reviewed later and the pattern and peak enhancement of the mass in each phase was noted.

Case 1

A 45 years old female, known case of hepatitis C associated CLD presented with ascites. She was found to have deranged liver function tests. Serum a-feto protein was markedly elevated, 4392 ng/ml. US showed multiple focal, hypoechoic lesions in left lobe of liver, the largest one was isoechoic with a halo around and measuring 2.8 x 2.4 cm [**Figure 1a**].

CEUS was done for the largest mass.It showed intense enhancement on the arterial phase, retained contrast in the venous phase with relative washout in the delayed phase [**Figure 1b-d**], depicting the characteristic pattern of hypervascular HCC in the setting of CLD. MPCT confirmed the findings of HCC (**Figure 2a-b**) .

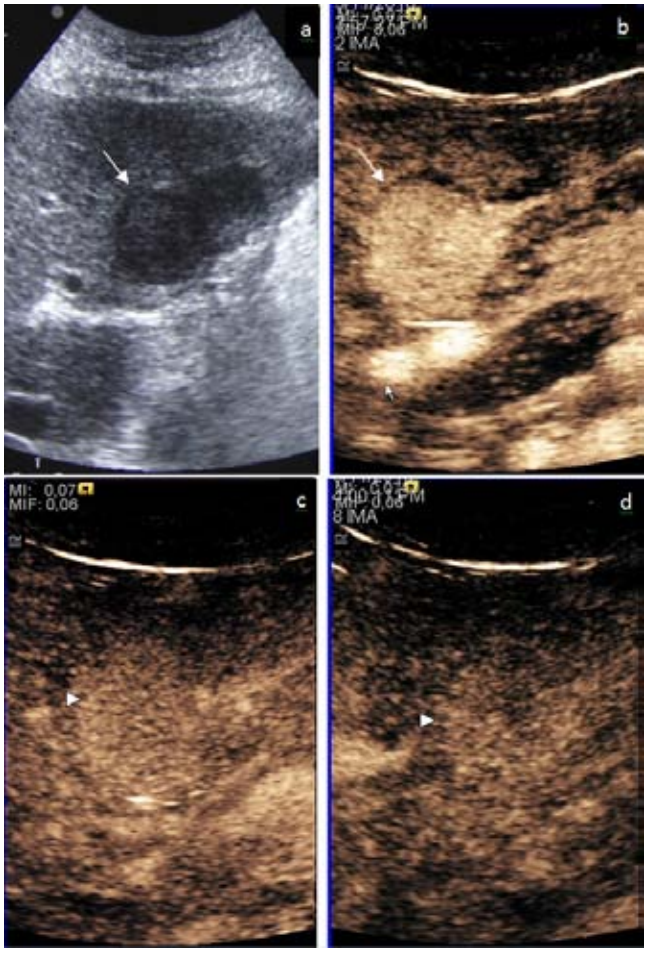

Figure 1: Grey scale (a) sonography of the mass studied by CEUS showing a well defined isoechoic lesion (arrow) with a halo in the left lobe of liver. CEUS was performed for characterisation of the mass. Arterial phase(b) of CEUS showing enhancement of the mass at 10 seconds (white arrow) followed by retained contrast (white arrowhead) on venous phase (c) [90 seconds] with relative washout (white arrowhead) on the delayed phase (d) [132 seconds] suggesting the classical enhancement pattern of hypervascular HCC.

Case 2

A 61 years old female, known case of hepatitis B related CLD with solitary large HCC who was treated with TACE was subjected to CEUS at one month following TACE. Grey scale ultrasound showed a large heterogenous HCC (4.5 X 2.5cm) in segment 6 (hyperechoic area superiorly and remaining hypoechoic) (**Figure 3 a**). CEUS showed an area of nodular enhancement superiorly within the mass in the arterial phase with washout in the delayed phase suggesting residual disease. The remaining tumor was non-enhancing [**Figure 3 b,c**]. MPCT confirmed the findings of CEUS. [**Figure 4a-c**].

Discussion

Imaging plays a vital role in the evaluation of liver lesions. With the advent of multidetector CT and newer MR sequences, multiphasic evaluation of liver is feasible, thus increasing sensitivity and specificity of the diagnosis of liver lesions. Another recent advance in this field is the introduction of CEUS.

Grey scale sonography is the first imaging modality for the evaluation of liver and widely recommended for surveillance of high risk patients for HCC detection.[10,11] However, gray scale and color doppler sonography have numerable limitations.[5] In order to improve the diagnostic ability, UCAs were developed. UCAs are microbubbles stabilized with galactose-palmitic acid or phospholipid shell containing either air (first generation agents) or other inert gases such as sulphur hexafluoride (second generation contrast agents). UCAs are blood pool

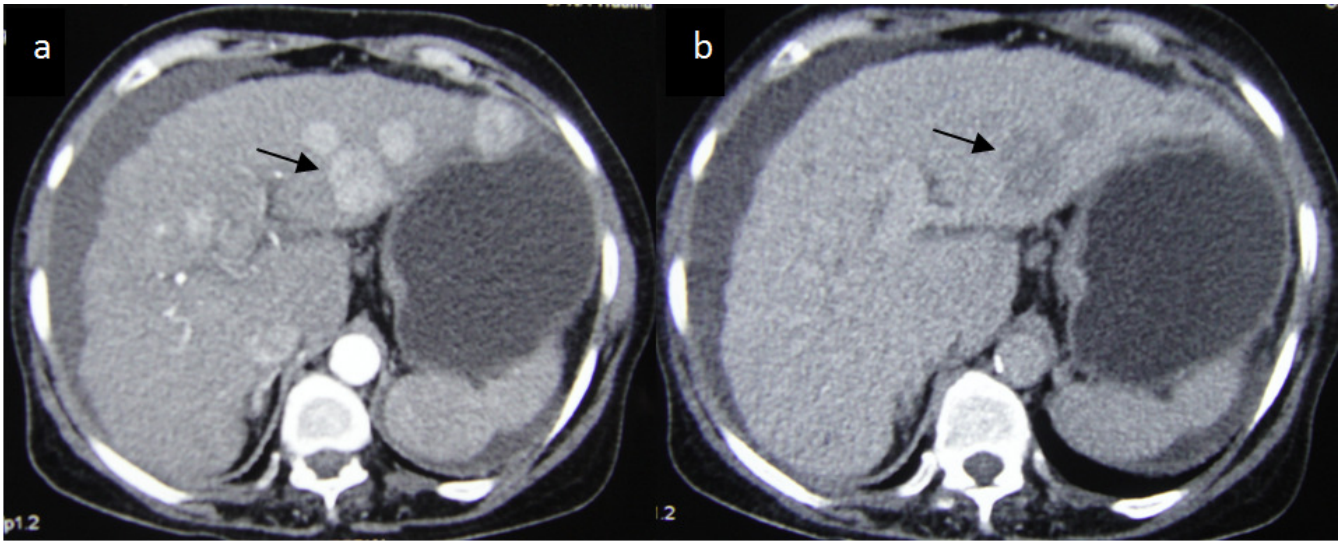

Figure 2: (a) Axial contrast enhanced MPCT scan of the same patient showing multiple enhancing masses in the arterial phase (a) with washout in the venous phase (b) characteristic of mutifocal HCC. The largest mass (depicted in a and b) was studied on CEUS (arrow). Features of CLD are also present, like, nodular liver surface, left lobe hypertrophy and ascites.

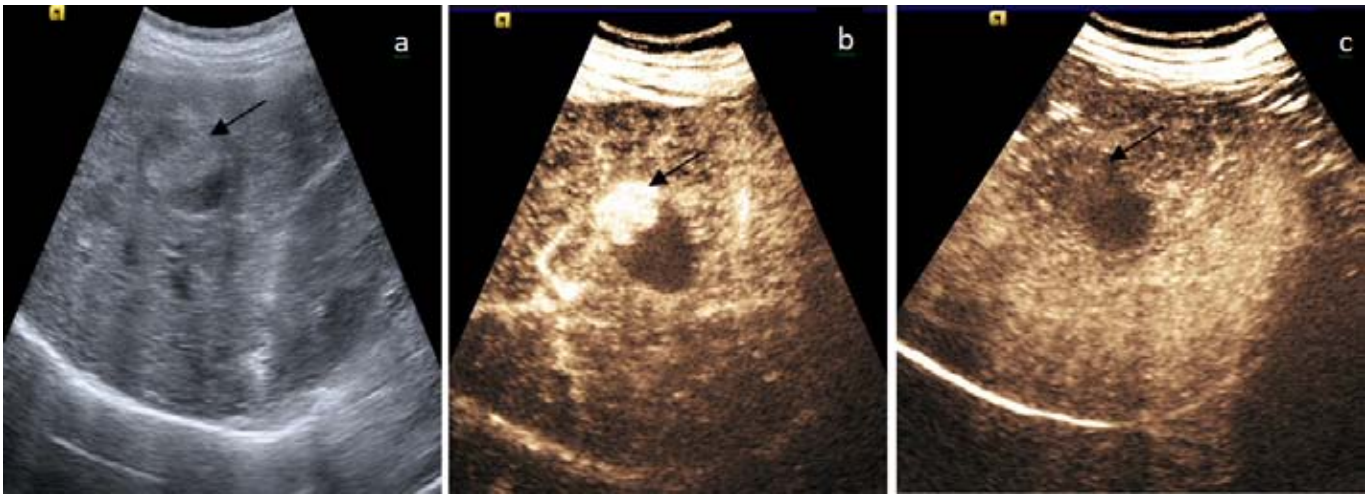

Figure 3: Grey scale ultrasound (a) following TACE showing a heterogeneous mass, hyperechoic area superiorly (arrow) with the remaining part as hypoechoic. CEUS was done which showed the same hyperechoic area showing intense enhancement (black arrow) on the arterial phase (b) [5 seconds] with washout (arrow) in the delayed phase (c) [190 seconds]. These findings were suggestive of residual disease at one month post TACE.

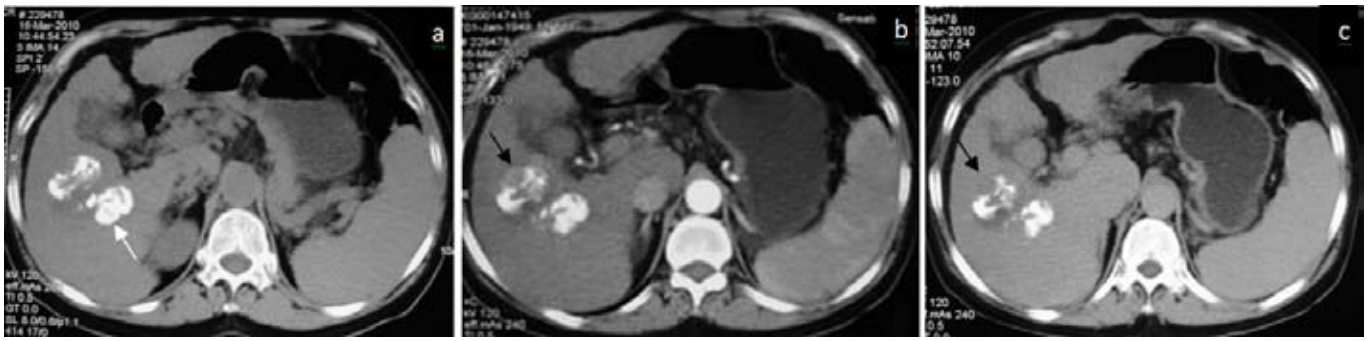

Figure 4: Post TACE axial image of MPCT noncontrast (a) showing dense scattered lipiodol (white arrow) within the segment 6 HCC . Following contrast, in the arterial phase (b) addditional area of enhancement was seen (black arrow) adjoining the lipiodol deposition which showed washout (black arrow) in the delayed phase (c). These findings of residual disease were similar to the CEUS observations.

agents and act by increasing the backscatter by virtue of its non-linear wide band harmonic response at low mechanical index[12] and facilitates better evaluation of liver lesions, compared with gray scale alone.[2,13-15]. The only contrast agent available in India is, SonoVue, Bracco (UK). SonoVue contains sulphur hexafluoride stabilized by phospholipid shell. It is a pure blood pool agent with no equilibrium phase. These features make SonoVue an ideal contrast agent for vascular phase (arterial, venous and delayed phase) imaging of liver lesions.[1,12]

The UCAs are safe and have few non specific side effects resolving spontaneously.[10,12] Rarely life threatening anaphylactoid reactions can occur which mandate precautionary measures to be ready. They can be safely used in patients with renal failure.[10] Sonazoid (GE Healthcare, Milwaukee, USA), another UCA, is available exclusively in Japan. Sonazoid differs from other agents in exhibiting post vascular phase till 60 to 120 minutes and helps in better lesion characterization.[16]

CEUS has high sensitivity in the detection and characterisation of liver lesions with diagnostic accuracy comparable to multiphasic CT.[6-8] It is useful for differentiating benign from malignant focal liver lesions[17] and exhibits classical enhancement patterns facilitating better characterization.[5,8,18]

Guidance of percutaneous ablative therapy for lesions not detected by gray scale sonography can also be achieved by CEUS.[19] Additionally, the assesment of treatment response in patients of HCC who have undergone tranarterial chemoembolization (TACE),radiofrequency ablation (RFA) or percutaneous acetic acid injection is also possible.[8,9]

The classical diagnosic pattern for HCC on multiphasic CT and MRI is the presence of enhancement in the arterial phase with washout of the contrast in venous or delayed phase. CEUS could successfully diagnose hypervascular HCC and depict the residual disease as nodular arterial enhancement with non-enhancing lipiodol very well in the two above cases, scoring over grey scale sonography on which this detection is not possible. Multiplanar computed tomography (MPCT) confirmed the findings of CEUS in both the cases of HCC.

To conclude, CEUS is a simple, safe and promising imaging modality for characterization of focal liver lesions and for

assessment of post treatment response. Larger studies are needed to evaluate the diagnostic accuracy of this new imaging technique.

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Gossypiboma: Three cases

Introduction

Gossypiboma (retained surgical sponge) in the abdomen and pelvis is an uncommon occurrence but may have serious medico-legal implications and is under reported.[1-4] Three cases are reported here.

Case Reports

Case 1

A 26 years old female under went umbilical hernia repair. The surgery and immediate postoperative period was uneventful. The patient started having serous and thereafter purulent wound site discharge after 10 days and the wound was not healing with antibiotics. The first pus culture was sterile and later *E coli* was detected. On exploration of the wound, cotton threads were seen that led to a piece of gauge, which was removed. After the removal of gauge piece, there was frank enteric content discharge which spontaneously stopped in week's time and the wound healed.

Case 2

46 years old lady had under gone abdominal hysterectomy. The surgery was uneventful. All the stitches were removed after 7 days. But she continued to have gradually increasing fever. She was treated for urinary tract infection. In spite of antibiotics fever continued with chills and rigors. She was referred to our hospital 11 weeks after the surgery. On abdominal examination there was a tender lump around the umbilical area with exaggerated bowel sounds. Plain X-ray abdomen showed multiple air fluid levels. On USG there was a mixed echogenic mass adjacent to umbilicus. In view of past surgery, prolonged fever, and USG evidence of a mass, need for exploration was felt. The previous operating team was also present during the operation. On exploration there was an adherent mass of bowel. Separation of the bowel revealed a big surgical towel (**Figure 1**) eroding the ileum lumen at two places, causing luminal obstruction. The towel was removed. The eroded segment was resected and end-to-end small bowel anastomosis was done. The wound was closed after thorough toileting.

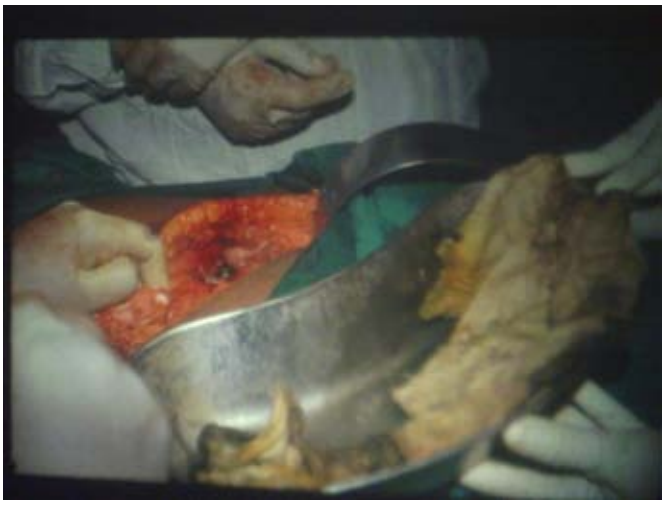

Figure 1: Removed towel

Case 3

A 47 years old lady had undergone abdominal hysterectomy for dysfunctional uterine bleeding. She developed high-grade fever in the post-operative period. Chest X ray revealed pneumonitis and she was treated for that. Ten days later she developed abdominal distention, vomiting and infrequent passage of flatus. Clinically there was a tender mass in periumblical area. Plain x-ray abdomen shows dilated bowel loops. CT scan had features of bowel obstruction with an additional mass lesion (**Figure 2**) with gas shadow within. In view of obstruction, emergency laparotomy was done. At surgery an abscess cavity was located with an abdominal sponge within. Peritoneal toilet was done and the bowel obstruction was relieved. The pus was sterile on culture. Post operatively she recovered well and is asymptomatic at 3 months of follow up.

Discussion

Gossypiboma can lead to significant medico-legal problems. Leaving a surgical sponge is considered a grave error by the chief surgeon of the operating team. It is under reported in the medical literature, as it gives negative publicity for the surgeon and the hospital.[2] Most of the publications are case reports, but in a series of 14 cases, thirteen of them were symptomatic with nonspecific abdominal pain and intestinal obstruction. Four patients required urgent surgery because the sponges were causing intestinal obstruction or intra abdominal sepsis.[3] In another study of 12 cases, gossypiboma was considered a lethal condition, and the presentations were intestinal

obstruction, (58.33%), discharging sinus, (41.67%), intra-abdominal abscess, (16.67%), peritonitis, (16.67%) and mass abdomen, (8.33%) with one fatality despite due care.[5] 2 of 3 our cases had presented with bowel obstruction with vague tender mass and one with wound discharge. Although gossypiboma is rarely seen in daily clinical practice, it should be considered in the differential diagnosis of acute mechanical intestinal obstruction in patients who underwent laparotomy previously.[6] At times it get encapsulated to form a foreign body granuloma (gauzeoma).[7] Transmural migration is seen when left for a long time.[8] Cross sectional imaging is essential for the diagnosis and management of retained abdominal foreign bodies [9] Typical CT findings of air density were not only seen in the uppermost part but also seen at the lower part of the retained surgical sponge (**Figure 2**). PET/CT gives a false positive report for cancer, which demonstrates a hypo metabolic area surrounded by increased 2-[fluorine-18] fluoro-2-deoxy-D-glucose uptake as if there is tumor necrosis.[10] Retained abdominal foreign body can be avoided by a thorough exploration of all quadrants of the abdomen, meticulous count of surgical materials at the termination of surgical cases and impregnation of surgical textile materials with a radio-opaque marker.[6, 8] Hand held radiofrequency identification device has been found to have 100% accuracy when performed correctly.[11]

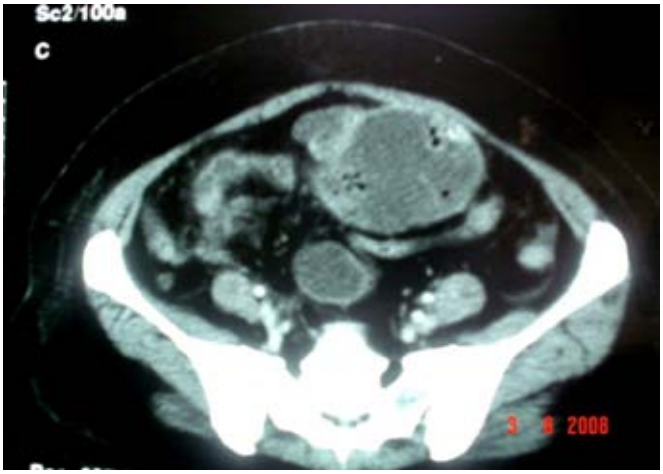

Figure 2: CT scan with trapped air in the foreign body

Conclusion

Retained foreign bodies have serious medicolegal and health implications. Gossypiboma should be ruled out when there is prolonged post operative fever with bowel obstruction.

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Intestinal obstruction in a child: internal hernia caused by an anomalous congenital band

Introduction

Intestinal obstruction is the commonest surgical emergency encountered in childhood.[1] Intestinal obstruction caused by an anomalous congenital band (ACB) is extremely rare.[2] We report a case of intestinal obstruction in a child due to internal herniation caused by an anomalous congenital band. To the best of our knowledge, this is only the second such case to be reported in literature.

Case Report

A 5 year old male child was brought to our emergency department with a history of pain abdomen, vomiting and abdominal distention of 5 days duration. He was being managed conservatively at another hospital for the same. He had constipation but was passing flatus occasionally and had no history of fever. He had a history of intestinal obstruction one year prior to the present episode when he was operated elsewhere. However, no relevant documents were available for perusal. He had then been put on anti-tubercular drugs which were discontinued by the parents after a few days on their own.

On examination, the child was afebrile, had tachycardia and was mildly dehydrated. The abdominal examination showed a well healed paramedian scar of previous surgery and no incisional hernia. The abdomen was distended but non-tender. No mass or free fluid was appreciated and bowel sounds were sluggish. Rectal examination revealed an empty rectum.

Laboratory investigations revealed leukocytosis (11400 cells/cu. mm) and normal electrolytes levels. Erect and supine abdominal radiographs demonstrated dilated small bowel loops and ultrasound of abdomen showed dilated fluid filled bowel loops with minimal ascites. A CT scan of abdomen also demonstrated dilated small bowel loops with stretched mesenteric vessels particularly at the attachment of mesentery at the ileo-caecal junction suggesting an internal herniation (**Figure 1**).

On laparotomy, there were minimal adhesions along with a small quantity of free fluid and no evidence of tuberculosis or malrotation. The small bowel was grossly dilated and when they were followed towards the ileo-caecal junction, the loops were found herniating through a hiatus formed by the ACB and its attachment to the ileum. The band was running from the right paracolic gutter and right lobe of liver to the anti-mesenteric border of the terminal ileum (**Figure 2**). The band was divided between ligatures to release the herniated loops of intestine. The site of attachment of the ACB to the terminal

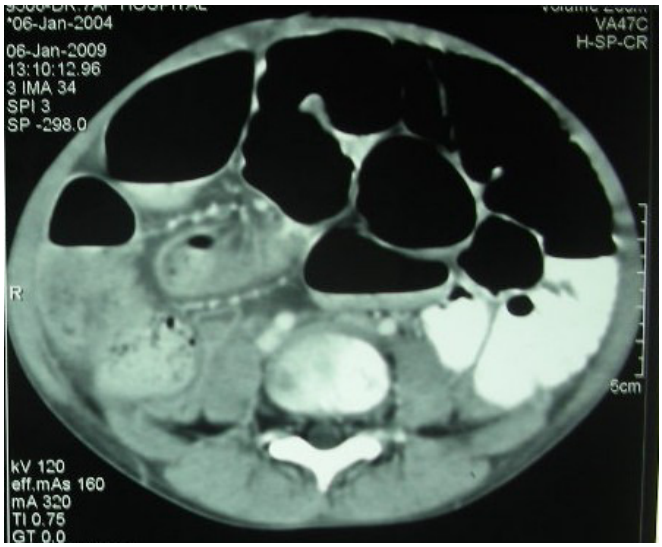

Figure 1: Abdominal CT showing stretched mesenteric vessels along with dilated small bowel loops.

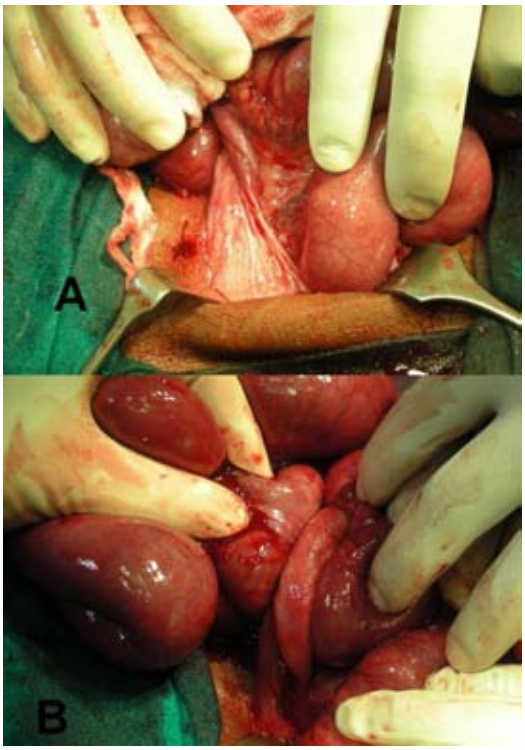

Figure 2: Intra-operative photograph. (A). Showing the broad based Anomalous congenital band arising from the right paracolic gutter and attached to terminal ileum. (B). Showing the herniation of small bowel loops through a hiatus formed by the ACB and its attachment to the ileum.

ileum was strictured and had to be resected. The child made an uneventful post op recovery. Histopathology of the band revealed blood vessels and nerves consistent with an ACB (**Figure 3**) and the resected ileum was unremarkable except for atrophic changes in the muscularis propria in the dilated portion.

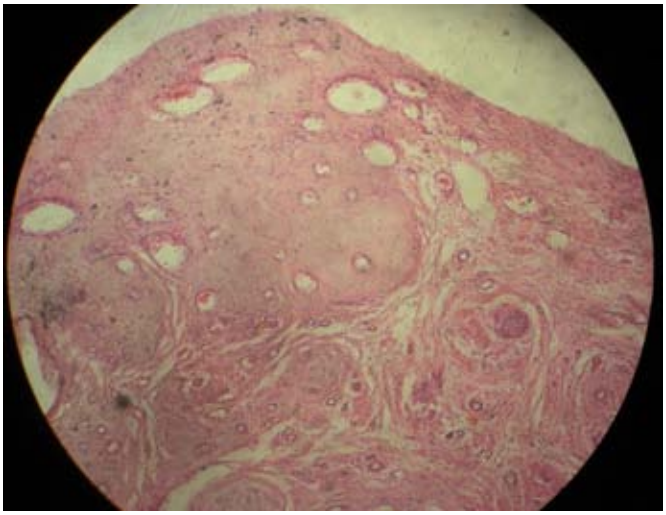

Figure 3: Histopathology of the ACB demonstrating blood vessels and nerve plexi.

Discussion

The most common etiology of small bowel obstruction is adhesions followed by inguinal hernias, tumours, intussusception, foreign bodies and inflammatory bowel disease.[2] Tuberculosis is incriminated in a sizeable proportion of cases in this part of the world.[3] However, amongst the pediatric population, in the post neonatal age group, the more common causes are intussusception, incarcerated hernias, malrotation with midgut volvulus and post-operative adhesions.[4] Of all the causes less than 1% of cases have been ascribed to internal hernias and predisposing factors are congenital bands, congenital anomalies of the intestinal rotation and congenital defects in the mesentery or omentum, post-surgical or traumatic defects of the mesentery and omentum.[5,6] ACBs causing intestinal obstruction are very rare and to the best of our knowledge only one case of internal hernias caused by an anomalous congenital band has been reported in literature previously.[7]

An ACB is one which has no identifiable embryological or acquired basis.[8] During embryogenesis, abnormal adhesion of the peritoneal folds can induce congenital bands as anomalies of the mesentery that can cause intestinal obstruction and their location is different from that of the well-known embryogenic remnants such as vitelline vessels or omphalomesenteric ducts.[8] Such bands cause obstruction by entrapment of the intestine between the band and mesentery or by compression of the bowel.[8] However, it is possible that these bands lead to an internal herniation as in our case. The broad based band, running from the right paracolic gutter and right lobe of liver to the anti-mesenteric border of terminal ileum formed a bridge underneath which the small bowel loops had herniated in addition to causing compression at its site of attachment. There are reports of a similar presentation caused by the adhesion of the tip of Meckel's diverticulum to the adjacent mesentery and or an inflamed appendix epiploca and greater omentum.[9,10]

Though the patient had a previous surgery for similar complaints and was started on anti tubercular therapy (discontinued by the parents after a couple of days), we believe that this is an ACB rather than an inflammatory band. This is explained by the absence of evidence of tuberculosis either current or past in the peritoneal cavity, the location and attachment of the band and further supported by the histopathological findings where in blood vessels and nerve plexi were seen.[8]

Though the diagnosis of intestinal obstruction is straight forward with the typical presentation and clinical findings aided by imaging studies, the cause of obstruction may be difficult to establish pre-operatively despite the availability of modern imaging techniques. A barium study may point towards a congenital band as an etiology. An abdominal CT is a very useful modality to pick up an internal hernia as was in our case but bands are usually identified on exploratory laparotomy. With the advent of minimal access surgery, diagnostic laparoscopy may be a safe and feasible modality to diagnose congenital bands and also to deliver definitive treatment.[11] In our case, in view of grossly distended bowel loops and a prior history of abdominal tuberculosis and laparotomy, a diagnostic laparoscopy was not considered.

Surgery is the cornerstone in the management of ACB causing obstruction. This can be accomplished through an exploratory laparotomy with division of the band which would release the trapped bowel and resection of non-viable bowel if any. A quick decision to proceed to surgery is vital to prevent strangulation of bowel and to reduce the morbidity and mortality associated with it. As brought out earlier, laparoscopy is increasingly being used in the definitive management of such cases and would offer patients maximum benefit with minimum risk.[11]

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Eosinophilic enteritis-A rare case of chronic diarrhoea in a child

Introduction

Eosinophilic enteritis (EE) is a rare disease that is characterized by tissue eosinophilia. The clinical signs and symptoms depend on the layer of the gut predominantly involved. Klein and Tally et al. have classified this disorder into mucosal, submucosal and subserosal disease, based on the layer of the gut predominantly involved.[1-3] The most prevalent form is the one with predominant involvement of the mucosal layer with symptoms of colicky abdominal pain, nausea, vomiting, diarrhoea and weight loss. The exact pathogenesis of the disease remains unknown but, at least in some of these patients with predominant involvement of the mucous layer, high serum IgE levels has been documented. Most patients will have history of food allergy or family history of allergy.[4]

Case Report

A six year old female child born of non consanguineous parents was admitted with a history of abdominal distension with vague pain and loose stools of two months duration. She had 6-8 loose motions per day associated with borborygmi with occasional vomiting. She had loss of appetite with low grade intermittent fever. There was no history of contact with open case of tuberculosis, drug intake, or worm infestation. Physical examination revealed grade I protein malnutrition, mild anemia and pedal edema. Abdomen was distended with a doughy feel. Investigations revealed a total count of 14,800 cells/cu mm, differential count of 20% polymorph, 28% lymphocytes, 52% eosinophils. Hemoglobin was 9 gm% and peripheral smear showed hypochromic microcytic anemia. Stool examination showed no ova or cysts. Occult blood was negative. Serum albumin was 3 gm/dl. Chest X ray was normal. HIV test and mantoux tests were negative. Ultrasound (USG) abdomen revealed minimal free fluid with thickened bowel wall. Barium meal follow through showed thickened bowel wall with features suggestive of malabsorption. Upper gastrointestinal endoscopy showed no visible abnormality and duodenal biopsy of the mucosa from the 3rd part of duodenum was done. Histopathology showed partial villous atrophy, intra epithelial infiltration with lymphocytes and dense tissue eosinophilia of more than 50/HPF (**Figure 1**). She had elevated serum IgE levels (196 IU/l). A final diagnosis of eosinophilic enteritis was

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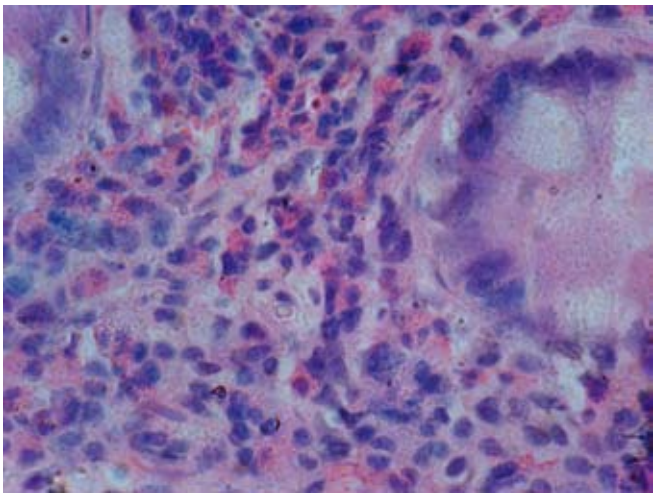

Figure 1: Photomicrograph of duodenal biopsy specimen stained with hematoxylin and eosin stains showing partial villous atrophy, intra epithelial infiltration with lymphocytes and dense tissue eosinophilia of more than 50/HPF

made. Our patient had involvement of mucosal and subserosal involvement as she had diarrhoea and ascites. . The child was started on oral prednisolone 2mg/kg and tapered over a period of three months. The child showed dramatic response to oral steroid therapy. The child improved clinically with reduction in diarrhoeal frequency and gain in weight. Currently the child is doing well.

Discussion

Chronic diarrhoea in children encompasses a wide variety of causes. When our patient presented with diarrhoea for two months duration, the initial evaluation was carried to rule out some of the conditions peculiar to tropical countries like giardiasis, tuberculosis and persistent infectious diarrhoea. She had peripheral eosinophilia. Upper gastroscopy with duodenal biopsy confirmed the diagnosis of EE. Elevated serum IgE is seen more often in paediatric population than adults with EE.[5] Eosinophilic enteritis is an uncommon disorder that has been documented mainly in adulthood[3] and characterized by infiltration by eosinophils of gastrointestinal tract. Patients with mucosal involvement present with nausea, vomiting, diarrhoea and weight loss. Muscular involvement usually presents with intermittent obstructive symptoms or with complications like perforation. Serosal involvement presents with ascites. Rarely, other organs like pleura, pericardium, gall bladder, biliary tree and liver can be affected. The exact etiology is not known although few of these patients may have food allergy or family history of allergy. Canine hookworm, Ankylostoma infestation, drugs like carbamazepine, cotrimoxazole and heavy metals like gold have been incriminated as causes in enterocolitis with tissue eosinophilia. The defects in mucosal integrity may be responsible for localization of various antigens in gut wall resulting in infiltration of eosinophilia in blood and tissues. Favourable response to steroids suggest the possibility of type I hypersensitivity reaction. Eosinophil through toxic cationic protein (MBP) plays a role in pathogenesis of this disease.[3] Food allergy has been noticed in 50% of cases.[6]

Allergic mechanism has been implicated in most of these patients.[7] A viral etiology has also been suggested in some cases.[8] Peripheral eosinophilia is noticed in 80% of patients.[2] The diagnosis is established by demonstration of tissue eosinophilia on endoscopic, laparoscopic or surgical specimens. However, the endoscopy may be normal or may show mild erythema to nodularity, thickened mucosal folds or even frank ulcerations. Full thickness surgical biopsies may be needed for diagnosis if the disease process is confined to the muscular layer. Ultrasonography, barium contrast studies, computerised tomography of the abdomen may show bowel thickening, nodularity or evidence of gastric outlet obstruction. Stomach is the most common site.[2] Duodenum and rest of the small bowel may be involved.[9] Steroids form the mainstay of therapy and nearly 90% will show favourable response. Mast cell stabilizers like sodium chromoglycate can be used to prevent mast cell degradation and release of histamines and leukotrines. Eosinophilic gastroenteritis in general has good prognosis.

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Blunt abdominal trauma, acute mesenteric venous thrombosis and small bowel stricture

Introduction

Thrombosis of the portal vein (PV) or its tributaries following blunt abdominal trauma is very rare and most of the reported cases of injury to the portal venous system have been the result of penetrating wounds. Further portal vein thrombosis after blunt abdominal trauma, which is followed by intestinal obstruction, has not been previously reported. We present what we think is the first such case.

Case Report

A 43-year-old army officer presented with a history of having had a road traffic accident when the car he was driving was hit by a truck. He lost consciousness for a few minutes and after being taken to a casualty department underwent computerized tomograpy (CT) of the head which was normal. He also had abdominal pain and a CT scan of the abdomen was done at the same time which was also normal. He was managed conservatively and discharged after four days. He remained well for one week after which he started having recurrent episodes of colicky abdominal pain, vomiting and obstipation. He was investigated with another CT scan of the abdomen with oral (water) and intravenous contrast which showed an altered echotexture of the liver with an occlusive fresh thrombus involving the PV, extending into its right branch and proximally into the superior mesenteric vein (SMV) (**Figure 1&2**). There was luminal narrowing of the distal small bowel with proximal dilatation, suggestive of an ischaemic stricture (**Figure 3**). There was no evidence of any other visceral injury. He was referred to our unit for further management. His complete blood counts, liver function tests, renal function tests and procoagulant screening were all within normal limits. Upper gastrointestinal

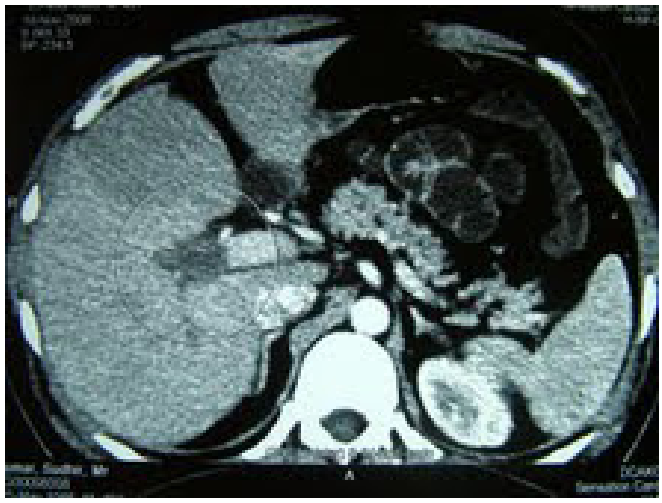

Figure 1: CT scan of the abdomen showing hypodense thrombus in the lumen of the portal vein extending into superior mesenteric vein.

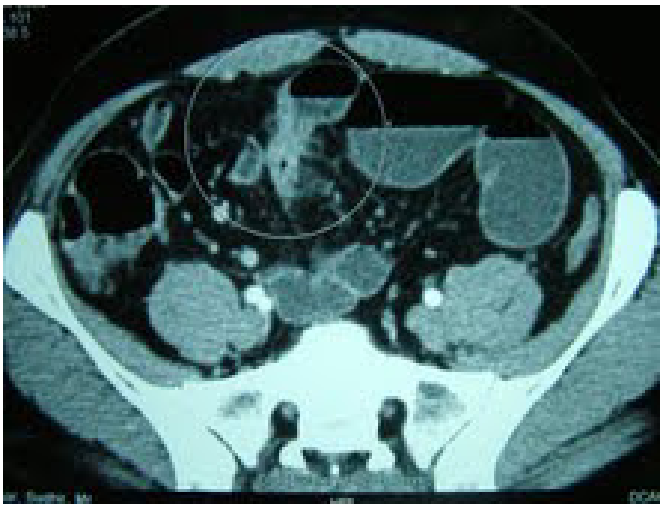

Figure 2: CT scan showing thrombus in the right PV

Table 1: Literature review of causes and presentation of PV & SMV thrombosis

Previous reports	Cause of thrombosis	Clinical presentation	Extent of thrombosis
Duvoux C et al, 1994[6]	Blunt trauma abdomen	Asymptomatic	Rt & Lt PV
Gopal SV, 2009[11]	Blunt trauma abdomen	Asymptomatic, on follow up CT	SMV& PV thrombosis
Uribe et al, 1999[13]	Antithrombin III deficiency, OCP, smoking	Segmental small bowel stenosis	SMV& PV thrombosis
Eugene C et al, 1995[14]	Drug addiction (cocaine), antiphospholipid antibody	Segmental small bowel stenosis	SMV thrombosis
Gonzalez F et al 2006[15]	Blunt trauma abdomen, G202102A factor 2 gene mutation	Pain, portal hypertension	PV thrombosis
Present report, 2010	Blunt trauma abdomen	Small bowel stricture	SMV& PV thrombosis

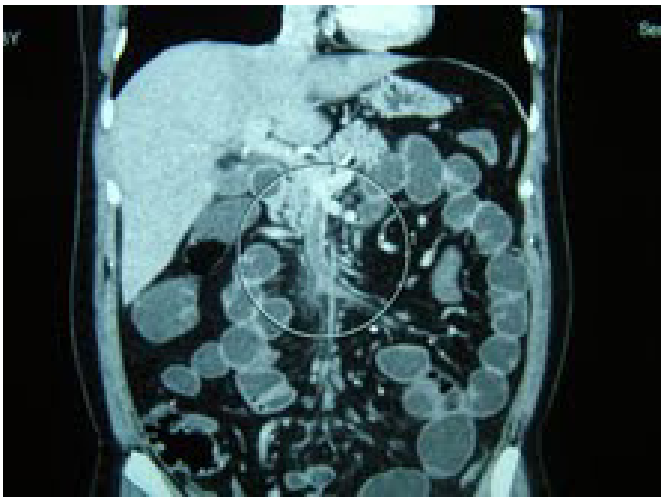

Figure 3: CT scan of the abdomen showing ileal stricture with dilated fluid filled proximal bowel loops with thickened walls.

endoscopy (UGIE) showed only mild duodenitis. The patient was started on low molecular weight heparin and was planned for surgery for his small bowel stricture. On laparotomy, there was a stricture 15 inches from the ileocaecal region which was resected and a side-to-side ileoileal anastomosis was performed. He had an uneventful postoperative course. Histopathological examination of the resected specimen showed that large areas of the mucosa had ulcers and was replaced by inflammatory granulation tissue. There was diffuse, transmural chronic inflammation and fibrosis with nodular fibroserositis. He is presently doing well one year after the operation and the anticoagulants have been continued.

Discussion

The various factors implicated for PV thrombosis include a decrease in portal flow as in cirrhosis, hepatobiliary malignancies and inflammation in the abdomen, or endothelial lesions which initiate thrombus formation such as trauma or surgical injury.[1,2] It is believed that portal vein thrombosis follows a combination of systemic and local insults.[3,4] The various systemic risk factors that have been implicated include coagulation disorders and the use of oral contraceptives.[4] This has been supported by Fried et al[5] who reported a case of superior mesenteric vein thrombosis following blunt abdominal trauma in a patient with primary antiphospholipid syndrome. However, our patient had no coagulation abnormality and the cause of thrombosis was solely attributed to the blunt trauma to his abdomen.

Only nine cases of portal vein injury following trauma have been reported in the literature[6-9] and in 8 of them penetrating trauma was responsible.[10] The time interval between trauma and thrombosis varied between 7 days and 6months.[11] Our patient presented one week of trauma with intestinal obstruction. In fact portal vein thrombosis after blunt trauma is exceedingly rare. In a study by Mattox et al[12] involving 2000 patients, who experienced trauma requiring surgery only 1% (n=22) had portal vein injury - 17 after gunshot wounds, 3 after stab wounds and only two of these had blunt abdominal trauma. Pearl et al[9] reported that out of 18,900 patients who sustained injury during a 10-year period only 15 patients sustained portal vein injury which was the result of penetrating abdominal trauma.

Previous reports (**Table 1**) have described clinical presentations with abdominal pain, hepatic functional abnormalities and haematemesis.[13] There have been no cases reported of small bowel stricture following portal vein and superior mesenteric vein thrombosis. There has been only one report of superior mesenteric vein thrombosis with jejunal stenosis secondary to antithrombin III deficiency, oral contraceptive use and smoking. Although there have been isolated case reports of ischaemic intestinal stricture following mesenteric venous thrombosis,[14] to our knowledge this is the first report of small bowel stricture with PV and SMV thrombosis following blunt abdominal trauma which was managed successfully with resection-anastomosis and anticoagulation.

We suggest that an ischaemic stricture may follow mesenteric venous thrombosis which has resulted from blunt trauma to the abdomen.

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Unusual occurrence of sigmoid volvulus in a young adult

Introduction

Sigmoid volvulus is the most common form of volvulus of the gastrointestinal tract. Its prevalence among patients who present with acute intestinal obstruction varies geographically, ranging from fewer than 10% in the US to as high as 80% of cases from the Bolivian and Peruvian Andes. Sigmoid volvulus, if complicated carries high risk of mortality and/or morbidity, hence low threshold and early detection is required.[1-3]
The true incidence of sigmoid volvulus in Saudi Arabia, and its presentation as acute intestinal obstruction has not been studied, and has not been published in Saudi national journals. We share our experience of patients with sigmoid volvulus presenting with acute intestinal obstruction at King Fahad Medical City due to the fact its rarity to occur in young adulthood and few reported cases in the gulf areas.

Case Reports

Case 1

A 22 year old patient presented to emergency room (ER) complaining of abdominal pain associated with distension and non projectile vomiting for three days. The pain was intermittent, localized mainly in the lower abdomen with no radiation. On examination, his abdomen was distended and tender in the lower quadrants. His vitals were stable.

Case 2

A 25 year old patient arrived to ER with sudden abdominal pain. On examination, his vitals were stable, and abdomen was distended with the absence of guarding and rigidity. He had a familiar episode 2 years ago, and at that time he underwent colonoscopy and his symptoms were relieved.

Both patients were diagnosed of sigmoid volvulus based upon clinical presentation and radiological findings (**Figure 1,2**). They did not have signs of peritonitis, nor perforation. Both underwent colonoscopic decompression to reduce the sigmoid volvulus. Later, they were offered sigmoid colectomy to prevent recurrence but both refused.

Discussion

Sigmoid volvulus is common in elderly persons, in individuals with neurologic conditions, and in patients in nursing homes

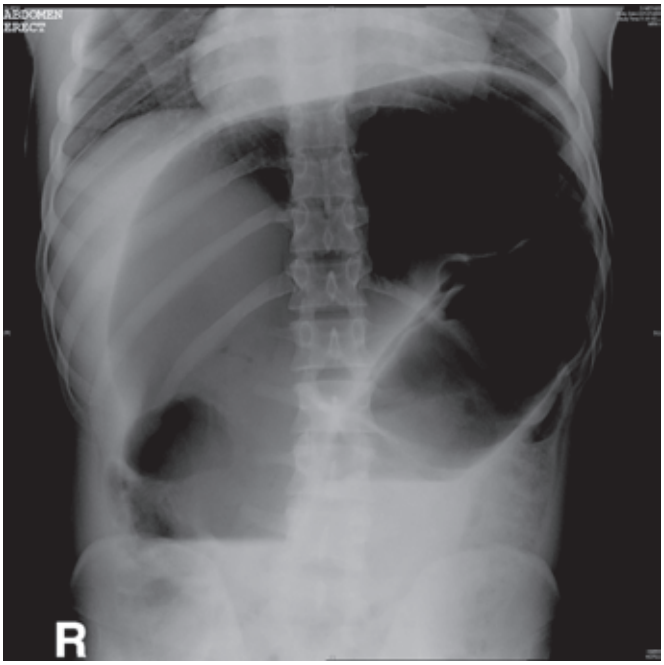

Figure 1: X-ray of abdomen showing volvulus (case 1)

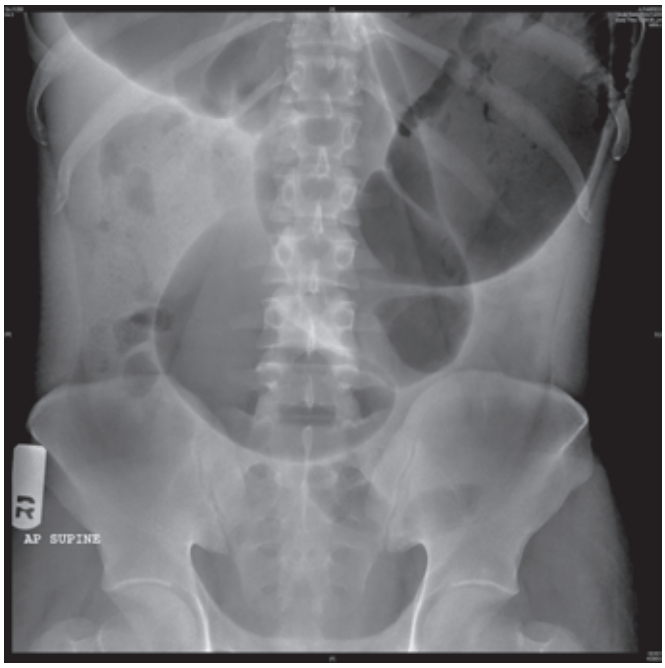

Figure 2: X-ray abdomen showing sigmoid volvulus (case 2)

or mental health facilities. The reasons why sigmoid volvulus is more common with advancing age are not well-understood. Lengthening of the sigmoid colon and its mesentery is not a feature of normal ageing. One possible explanation is colonic dysmotility, which could predispose to torsion of the sigmoid colon. In a report of 40 patients from England, the average age was 72 years.[4]

In children, sigmoid volvulus can be the initial presenting feature of Hirschsprung's disease.[5] The majority of patients with sigmoid volvulus present with abdominal pain, nausea, abdominal distension, and constipation; vomiting is less common. However, some patients (particularly younger patients) may have a more insidious presentation with recurrent attacks of abdominal pain, with resolution presumably due to spontaneous distortion.[2] The diagnosis is often suspected based upon the clinical presentation and physical examination. The pain associated with sigmoid volvulus is usually continuous and severe, with a superimposed colicky component occurring during peristalsis. The abdomen is usually distended and tympanitic.

A plain film of the abdomen can establish the diagnosis in approximately 60 percent of patients.[6] The distended sigmoid colon appears as an ahaustral collection of gas that extends from the pelvis to the right upper quadrant as high as the diaphragm. Distended large bowel proximal to the sigmoid and air-fluid levels in the small bowel are often present. A barium enema using water-soluble contrast may be helpful in certain cases.

The diagnosis can also be made by CT scan. Typical findings include a whirl pattern, caused by the dilated sigmoid colon around its mesocolon and vessels, and a bird-beak appearance of the afferent and efferent colonic segments.[7] Many endoscopists choose to leave a rectal tube in place with its proximal end beyond the area of twisting. However, a rectal tube may lessen colonic distension and reduce the chance of recurrent volvulus in the acute setting. Sigmoidoscopy is used to detorse the volvulus, which can be accomplished by advancing a flexible or rigid sigmoidoscope through the twisted segment. Reduction of the sigmoid volvulus using this technique has been successful in 85 to 95 percent of cases in some series.[6,8] The major problem is recurrence in up to 60 percent of patients.[7,9] The time to recurrence can vary from hours to weeks; as a result, definitive treatment soon after sigmoidoscopic reduction is advised. Although surgical resection without decompression has been used at some centers with acceptable outcomes,[10] most favor preoperative decompression whenever feasible. The surgical approaches to prevent recurrent volvulus include mesosigmoidopexy and resection with primary anastomosis or a Hartmann's procedure.[1,9,10]

In these two cases, both patients were young adults with no predisposing factors. The precise incidence of sigmoid volvulus in Saudi populations, and the risk factors for its development in relatively younger patients needs to be studied.

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Saccharomyces cerevisiae as a cause of oral thrush & diarrhoea in an HIV/ AIDS patient

Introduction

Saccharomyces cerevisiae is a commensal inhabiting the gastrointestinal tract of humans, considered important to maintain the normal homeostasis of the lower gastrointestinal tract. A vast majority of patients with AIDS and low CD4 counts present with manifestations involving the gastrointestinal tract in the form of oral thrush, oesophagitis, duodenitis, jejunitis, colitis, and protracted diarrhoea. *Saccharomyces cerevisiae* though considered a commensal, has been seen to cause infections in immunocompromised patients. Here, we present a case of an HIV positive patient who presented with hitherto unreported pangastrointestinal involvement due to *Saccharomyces cerevisiae*.

Case Report

A 15 year old HIV positive female patient presented to the internist with complaints of recurrent oral thrush, abdominal pain and protracted diarrhoea. The HIV status of the patient was known for the last 10 years and her CD4 count at the time of presentation was 100 cells/ml and absolute lymphocyte count was 1800 cells/µl. She acquired HIV infection from her parents via mother to child transmission and both her parents who had HIV, died few years back.

She had a history of oral ulcers of 1 year, associated with painful swallowing, dry mouth and burning sensation. The patient had significant weight loss and loss of appetite. The patient also complained of diarrhoea which was recurrent and intractable with abdominal pain since 3 weeks. On examination, the oropharynx showed white patches and ulcers (numerous and of varying size) and cervical lymphadenopathy, the abdomen was rigid and guarded with exacerbated bowel sounds. Endoscopy showed oesophagitis and duodenitis and mucosal biopsy revealed focal villous abnormalities. The patient was not on antiretroviral therapy or any systemic antifungal therapy at the time of presentation. Patient was taking nystatin gargles and symptomatic treatment before presenting to the hospital but showed no improvement on the current therapy, instead the ulcers increased in size and diarrhoea

persisted. There was no history of any probiotic intake in the past year by the patient.

Swabs were obtained from the lesions in the mouth and subjected to a direct gram's staining and culture on Sabouraud's dextrose agar (SDA) and SDA with chloramphenicol. Three stool samples were collected and processed separately on three consecutive days. The stools were watery and mucoid with no blood on gross examination. Saline and iodine wet mount preparation was prepared, a modified acid fast staining done using 0.5% H_2SO_4, and the cultured on SDA and SDA with chloramphenicol in duplicate. Bacteriological culture was done after enrichment in selenite F broth on xylose lysine deoxycholate agar, bile salt agar & MacConkeys agar. A blood culture was also done in brainheart infusion broth and subcultured on blood agar, chocolate agar, and brain heart infusion agar.

Direct gram stain from the swab showed predominance of gram positive budding yeast cells though no pseudohyphae were seen and the culture revealed creamy white yeast like growth on both the agar medium. The grams from the colony showed budding yeast cells without any capsule, the organism was identified using corn meal agar and carbohydrate assimilation test, as *Saccharomyces cerevisiae*. Wet mount preparation and modified acid fast staining did not show any parasitic ova or cyst in the stool sample. Bacterial culture revealed no pathogenic organism, but on each occasion *Saccharomyces* was isolated in the fungal culture. Blood culture was also sterile. The patient was started on Amphotericin B and there was a dramatic response in symptoms.

Discussion

There have been many reports of *Saccharomyces sp.* causing systemic infections in immunocompromised hosts. There have been several reports of fungemia caused by *Saccharomyces* in debilitated patients previously but none have reported a local mucosal involvement with *Saccharomyces* which became so extensive that it involved the whole of the GI tract as seen in this case.[1-4] Also there have been reports of cases developing fungemia following probiotic preparations containing this organism.[5,6]

In this patient *Saccharomyces* seems to be the pathogenic organism involving the whole GIT of the patient. The symptoms, signs and the endoscopic findings of the patient suggested a pan GI involvement. The patient was highly immunocompromised having a CD4 count of 100 cells/µl, and an absolute lymphocyte count of 1800 cells/µl and there was no history of any long term antibiotic intake. Repeated isolation, along with patient's dramatic response to Amphotericin B confirmed our diagnosis of *Saccharomyces* as the causative agent of this patient's condition retrospectively.

To the best of our knowledge, pangastrointestinal mucosal involvement caused by *S. cerevisiae* in AIDS or immunocompromised patients has not been reported. High degree of suspicion, continuous study and identification of atypical presentations such as these is necessary, especially in those not responding to conventional treatment to formulate new strategies to combat morbidity and mortality in patients suffering from HIV/AIDS.

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Telipressin induced peripheral ischaemic gangrene and skin necrosis

Introduction

Terlipressin is a synthetic vasoconstrictor which is used in hepato-renal syndrome and variceal bleed. The safety profile of terlipressin is better than vasopressin. Therefore, the use of terlipressin has increased over the last few years. We report a case of terlipressin induced ischemic peripheral gangrene and ischemic necrosis of skin. Very few cases have been reported in literature. This report should increase awareness regarding the complications of this commonly used drug.

Case Report

A 50 year old male, known diabetic and alcoholic was admitted with fever of 6 days duration along with upper respiratory tract infection. He had received artesunate and ciprofloxacin. Investigations revealed Hb - 9.3g/dl, TLC - 21,000/cu mm, Platelet - 1.23 lakhs/cu mm, DLC : N-62 L-33 E-04 M-01, peripheral smear for malarial parasite – negative, , blood urea-24 mg/dl, serum creatinine-2.8 mg/dl, Na-137 mEq/L, K-4.8 mEq/L, random blood sugar- 150mg/dl, serum bilirubin-2 mg/dl, (direct - 0.4 mg/dl), SGOT-982 u/L, SGPT-413 u/L, Alk. Phos. - 208 u/L, LDH - 350 u/L, S. proteins.-6.1gm/dl, S. albumin-3.5gm/dl, ECG-Normal, CXR(chest X-ray)-normal.He was provisionally diagnosed as having severe sepsis and piperacillin- tazobactum was started. empirically. He developed seizure on day one of admission and went into anuria. Injection phenytoin was started and he underwent hemodialysis.

Icterus appeared on fifth day of admission. LFT revealed S. bilirubin -17.8 mg/dl, (direct - 9.7 mg/dl), SGOT-419 u/L, SGPT-131 u/L, Alk. Phos-225 u/L, S.proteins- 5.38 g/dl, S. albumin-2.6 g/dl. He was provisionally diagnosed as a case of alcoholic hepatitis with hepatorenal syndrome, diabetes mellitus along with severe sepsis. Inj terlipressin was advised but not started. On Day-12 the liver function tests worsened with an increase in S. bilirubin to 32 mg/dl (direct-16.6 mg/dl). The other parameters were : SGOT-215 u/L, SGPT-95 u/L, alk. phos-839 u/L, S.protein-5.5 g/dl, S.Alb-2.4 g/dl, PT-INR 2.4, HAV, HEV, HBsAg & HCV were negative. Inj terlipressin 1 mg 8hrly IV was started. On Day 14 ecchymosis was noticed all over body. SpO2 was not recordable in right index finger. Subsequently

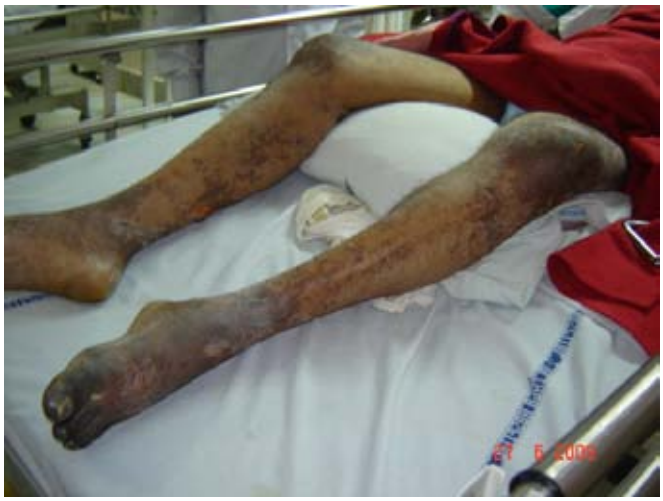

Figure 1: Skin necrosis over right knee & digital gangrene both toes.

Figure 2: Skin gangrene & ischaemic necrosis over both legs

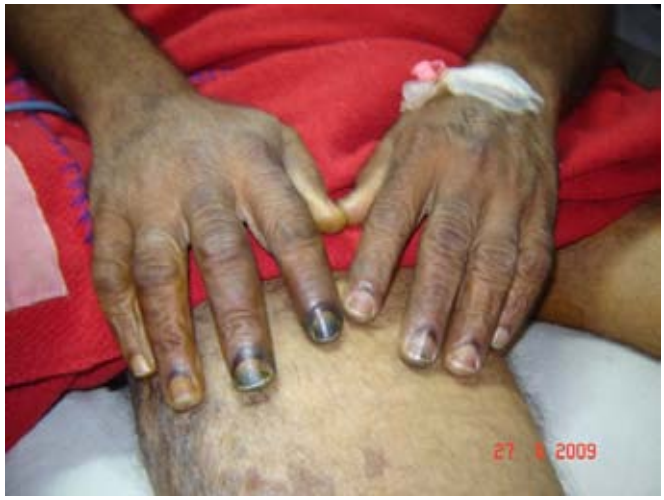

Figure 3: Digital gangrene right index & middle finger.

peripheral gangrene appeared in all four limbs. (**Figure 1, 2 & 3**)

Terlipressin was stopped. The hepatic failure gradually improved. (Day 15 PT/INR - 1.2. Day 16 PT/INR - 1.14). S.bilirubin-12.4 mg/dl (direct-5.8 mg/dl), SGOT-265 u/L, SGPT-

58 u/L, Alk. Ph-1121 u/L, S. protein-6.5 g/dl, S.alb-2.7 g/dl. USG abdomen revealed hepatosplenomegaly. Patient was ventilated for 16 days, underwent 14 hemodialysis and had ICU stay of 26 days.

Discussion

Since its introduction in the early 1990s, terlipressin has revolutionized management of liver disease with a role in the treatment of variceal haemorrhage and hepatorenal syndrome. Terlipressin has proven to be safe, with a lower incidence of side-effects compared with vasopressin and other synthetic analogues. Although, terlipressin is selective for the spanchnic circulation, it can exert vasoconstrictor effects on the systemic circulation. Undesirable effects are usually mild and include headache, abdominal pain and bradycardia. More serious complications are uncommon, but cases of ischaemic colitis, myocardial infarction and skin necrosis[1-4] have been reported.

We believe that the skin lesion seen in this patient occurred as a result of terlipressin therapy. There is evidence for a temporal relationship between terlipressin and the observed skin necrosis. The manufacturers of terlipressin (Ferring Pharmaceuticals Ltd, Saint-Prex, Switzerland) have received 10 reports of skin necrosis related to terlipressin use. The majority of cases are related to skin necrosis affecting the extremities, but there are also a small number of cases of foreskin and scrotal necrosis in males. Ischaemic complications as a result of vasoconstrictor medication usually affect peripheral areas such as the digits of the hands and feet.

This case suggests extra vigilance is warranted while administering terlipressin. Although ischemic complication with terlipressin is rare, we should be aware of it and detect it early.

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Biliary pancreatitis secondary to stones from a gall bladder remnant

Introduction

Laparoscopic cholecystectomy is now accepted as the "gold standard" for treatment of biliary pancreatitis to prevent further attacks.[1] When dissection of the Calot's triangle is difficult, partial cholecystectomy has been proposed as a safer operation.[2] The remnant stump, which includes the Hartmann's pouch, should be cleared of residual gall stones at the time of surgery.[3] However, some of these remnants may retain stones, or form new ones in the post operative period.[3,4] These patients may present with "post cholecystectomy pain" at varying intervals from the primary surgery due to the residual or recurrent stones.[5] The remnant gall bladder and cystic duct stump must be kept in mind while evaluating these patients, especially if a history of partial cholecystectomy is available.[5] We present four such patients who presented with post cholecystectomy biliary pancreatitis, with a view to highlight this problem.

Case Report

The patients details are provided in **Table 1**. There was one female and three males with a mean age of 56.6 years (range 45-69 years). Two patients had undergone open partial cholecystectomy and two, laparoscopic cholecystectomy as

Table 1: Details of patients who presented with delayed biliary pancreatitis after partial cholecystectomy

Case	Age (yrs)	Sex	Cholecyst-ectomy	Indication for cholecy-stectomy	Onset of biliary pancreatitis after chole-cystectomy	Severity of pan-creatitis	Imaging for detection of gall bladder remnant	Treatment	Outcome	Follow Up
1	45	F	Open, partial	Biliary pancreatitis	16 months	Mild	USG normal, EUS showed GB remnant with stones	Excision of remnant	No recurrence	48 months
2	54	M	Laparoscopic	Biliary pancreatitis	12 months	Mild	USG - GB remnant & long cystic duct stumpwith stones EUS - GB remnant with stones in it and in cystic duct	Excision of remnant	No recurrence	12 months
3	69	M	Laparoscopic	Biliary pancreatitis	24 months	Mild to moderate (pseudocyst)	USG normal, MRCP – sludge in remnant	Sphincter-otomy with Pseudocyst drainage	No recurrence	24 months
4	58	M	Open, partial	Empyema gall bladder	14 months	severe	CT- pancreatic necrosis MRCP – stump with sludge	Necrosect-omy done	awaited	-

the index operation. The details of laparoscopic surgery done (complete/ partial) and the indication for partial cholecystectomy as done in the two open cases were not available. The time of presentation after primary surgery ranged from twelve to twenty-four months. All these patients had a residual gall bladder stump detected on imaging. The gall bladder was detected on Ultrasonography (USG) in one patient, Magnetic Resonance Cholangio Pancreatography (MRCP) showed sludge in the remnant in two patients. Computerized Tomography (CT) was used only in one patient with necrotizing pancreatitis. Endoscopic Ultrasonography (EUS) showed the remnant gall bladder with stones in two patients. In all the patients, the common bile duct did not reveal stones or sludge. Two of these patients had severe pancreatitis. One patient presented with a pseudocyst of the pancreas and was treated with sphincterotomy and pseudocyst drainage. Two patients who presented with mild pancreatitis were treated with excision of the stump. None of the patients who underwent stump excision or sphincterotomy has had a further attack (mean follow up 28 months).

Discussion

In laparoscopic cholecystectomy, the cystic duct is divided close to the gall bladder to avoid bile duct injury, leading to a longer cystic duct remnant compared to open cholecystectomy.[6] In patients who undergo a partial cholecystectomy, in addition to the cystic duct remnant, a portion of the gall bladder is left behind, to avoid Calot's triangle dissection.[3,7] Cystic duct remnant, defined as a residual duct or gall bladder remnant greater than 1cm in length, in the presence of stones, can cause post-cholecystectomy syndrome and complications including biliary pancreatitis.[8] The incidence of PCS is reported to be between 10-40%.[5,9]

Routine imaging such as USG may not be able to detect the remnant stump, as was the case in two of our patients, due to the small size, unless gross dilatation of the stump has taken place or a large filling defect is clearly visualized.[5] Hence, when patients who have undergone laparoscopic or open partial cholecystectomy present with biliary pancreatitis, it is advisable to use modalities like MRCP and EUS, along with ERCP and sphincter of Oddi (SOD) manometry.[1,4,5] Both MRCP and EUS have been found to be useful in imaging the remnant stump.[6,8,10-12] The differential diagnosis of a cystic lesion in the extra hepatic biliary tree, after cholecystectomy, includes a gall bladder remnant, secondary dilatation of the cystic duct stump, gall bladder duplication and type II choledochal cyst.[4]

In patients who have biliary pancreatitis after cholecystectomy, the differential diagnosis includes residual or recurrent bile duct stones, cystic duct stones, remnant gall bladder stones and SOD dysfunction. EUS has been shown to be accurate for the identification of gallbladder sludge, common bile duct stones, and pancreatic disease. ERCP and sphincter

of Oddi manometry should generally be reserved for patients with multiple unexplained attacks and negative EUS results, who have previously undergone cholecystectomy.[13-15]

The treatment option in case of recurrent pancreatitis following a previous cholecystectomy could be an endoscopic sphincterotomy or resection of the remnant. There are increasing numbers of reports favouring resection of the residual cystic duct/ gall bladder remnant in patients suffering from post cholecystectomy syndromes.[6,8] Completion cholecystectomy or "recholecystectomy" is now gaining importance as the definitive treatment for residual gall bladder remnant and can be performed laparoscopically when feasible.[1,10,16,17] However, resurgery can be technically challenging. In our patients, the two who underwent completion cholecystectomy had demonstrable stones in the remnant stump. Neither of them has had a recurrence of symptoms after removal of the residual gall bladder. A sphicterotomy was performed in the patient who had sludge seen in the remnant on MRCP as this patient had already undergone pseudocyst drainage after the laparoscopic cholecystectomy and we thought it would be difficult to approach the stump surgically. There are some conceptual advantages of remnant excision over sphincterotomy. Besides eliminating other problems associated with remnant stones (e.g. post cholecystectomy pain), it avoids the side effects as well as the long term recurrent stenosis associated with a sphincterotomy.[18]

In conclusion, in patients who have undergone partial cholecystectomy for biliary pancreatitis, recurrence of the pancreatitis may be due to stones in the remnant gall bladder.

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Spontaneous Splenic Rupture in Complicated Malaria: Non – Operative Management

Introduction

Malaria still continues to be a major health problem in many parts of the world. An enlarged spleen is considered to be one of the cardinal physical signs. Though splenic rupture in malaria is rare but yet it is a important life threatening complication specially of *Plasmodium vivax*. Spontaneous splenic rupture has been described in conditions such as infectious mononucleosis, haematological malignancies[1-3] but malaria continues to be the most common aetiology.[4,5]

Traditionally all types of splenic rupture have been treated with splenectomy but with the emerging trend of splenic conservation in splenic trauma similar approach has been applied to a ruptured malarial spleen also. We report a patient with combined *P.falciparum* and *P.vivax* malaria who developed spontaneous splenic rupture and was managed successfully non–operatively.

Case Report

A seventeen year old girl presented to the emergency department with history of intermittent high grade fever for the last eight days. The fever was associated with chills and rigors. This was followed by abdominal pain, distension and repeated episodes of non bilious vomiting for the last 3 days. At presentation she had a pulse of 102 per minute, respiratory rate of 24 per minute, and mild hypotension (98/60 mm) .On examination, abdomen was distended with tenderness in left hypochondrium. Spleen was palpable 3 cm below the left costal margin and liver was palpable 4 cm below the right costal margin. There was evidence of free fluid in the abdomen and the bowel sounds were sluggish. On investigations her haemoglobin was 7.2 g% with thrombocytopenia (platelet count of 42,000 per cu mm) and marked leukocytosis (total leukocyte count of 25,000 per cu mm). The blood urea was 184 mg/dl and serum creatinine was elevated {5.7 mg% (normal 0.8-1 mg %)}. A peripheral blood smear showed gametocyte of *Plasmodium falciparum*(**Figure 1**). An antibody enzyme linked immunosorbent assay (ELISA) was positive for both *P.falciparum* and *P.vivax*. Ultrasonography and non contrast computerised tomography scan (**Figure 2**) revealed a wedge shaped infarct in the spleen with free fluid in the abdomen suggestive of splenic rupture. The patient was put on conservative management with monitoring of vitals, laboratory parameters and clinical signs. An infraumblical abdominal drain was inserted which drained about 600 ml of non clotting blood. Patient was started on injection artesunate 120 mg and broad spectrum antibiotic (imepenem 1 gram and cilastatin 500 milligrams). She was transfused blood and blood products and underwent one haemodialysis. Subsequently she went into

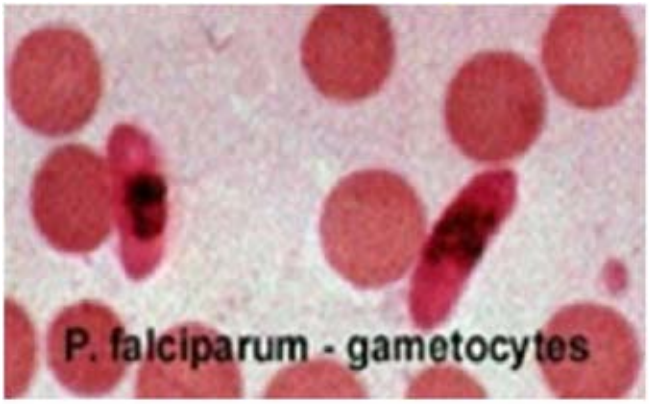

Figure 1: Peripheral blood smear showing gametocytes of Plasmodium falciparum

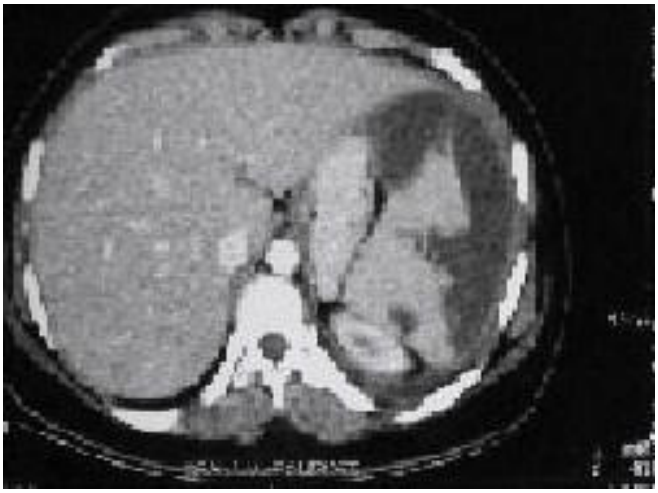

Figure 2: Non-contrast computerized tomography scan showing perisplenic fluid collection

diuretic phase of renal failure and her renal parameters improved within next two weeks. Her general condition gradually started improving. Peripheral blood smear showed a decrease in gametocyte counts (200/cu mm). The anti malarials and antibiotics were stopped after 2 weeks and patient made an uneventful recovery .She is on regular follow up and a contrast enhanced CT scan done after 4 weeks showed a collection around the spleen . A repeat ultrasound after three months showed complete resolution and no collection and patient is asymptomatic after 9 months of follow up.

Discussion

Spleen plays an important role in the host defence against number of intravascular parasites including Plasmodium. Traumatic splenic rupture is a well described entity but spontaneous splenic rupture has also been described. It has been described in few diseases such as infectious mononucleosis, splenic neoplasm and haematological malignancies.[1-3] However, malaria is by far the most common cause of spontaneous splenic rupture. Splenic involvement in malaria causes splenomegaly which makes it more prone to rupture.[6,7] Other splenic complications of malaria that have been described include the hyperactive malarial spleen (tropical splenomegaly syndrome), hypersplenism, splenic cysts and splenic torsion.

The incidence of spontaneous rupture of spleen in malaria has been estimated to be about 2%[8-10] and it has been reported that the incidence is higher in induced malaria (via blood transfusions) as compared to natural malaria (mosquito bite/ transplacental). A total of 22 cases have been reported since 1960[5,6,13-19]. This spontaneous rupture almost exclusively occurs during the stage of acute infection and most commonly during the primary attack[11,12] as seen in our case. The malarial species most commonly involved is *P.vivax* though rare cases of *P falciparum* and malaria have also been reported.[11] However no case of spontaneous rupture has been described in combined *P.falciparum* and *P.vivax* malaria as in our case.

The exact mechanism of spleen rupture in malaria is not known. The following three mechanisms are implicated:(i) increase in intrasplenic tension due to cellular hyperplasia and engorgement; (ii) spleen may be compressed by the abdominal musculature during physiological activities such as sneezing, coughing, defecation, etc.; and (iii) vascular occlusion due to reticulo-endothelial hyperplasia, resulting in thrombosis and infarction. This leads to interstitial and subcapsular haemorrhage and stripping of the capsule, which lead to further subcapsular haemorrhage. The distended capsule finally gives way.[11]

The common presenting features are fever, tachycardia, vomiting, generalized abdominal pain, progressive weakness. However splenic rupture in malaria continues to be a real pitfall for practitioners for it can happen without any preceding attacks or trauma. Physical examination may reveal tenderness in left hypochondrium, enlarged spleen and signs of diaphragmatic irritation (Kehr's sign). Signs of hypotension and hypovolemic shock may also be present. The tests usually carried out for diagnosis of splenic rupture include abdominal sonography, Contrast Enhanced CT scan of abdomen which will reveal enlarged spleen, capsular tear and perisplenic hematoma.

Historically the treatment of splenic rupture has been splenectomy[7]. With the emergence of splenic conservation in splenic trauma similar concept has been applied to spontaneous rupture in other conditions. As our patient was young, haemodynamically stable and considering the immunological role of spleen in pneumococcal and malarial infection , we opted for a non-operative management.

The conservative management consists of observation for 7-14 days in hospital with strict bed rest, administration of blood and blood products,[6,7] serial monitoring of haemoglobin and haematocrit along with monitoring of vital parameters. Regular abdominal ultrasonography should be done to assess the progress of the patient. Splenectomy should be reserved for patients with uncontrolled bleeding and haemodynamic instability.

In conclusion, spontaneous splenic rupture of malarial spleen is rare and requires high degree of clinical suspicion to arrive at a diagnosis. Most of these cases, like traumatic splenic injuries, can now be managed non-operatively. Splenic salvage should be the aim in the management of these patients.

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Encapsulating sclerosing peritonitis

Introduction

Sclerosing encapsulating peritonitis is a rare cause of small bowel obstruction, and can be classified as idiopathic or secondary (most importantly and most frequently due to chronic ambulatory peritoneal dialysis). The idiopathic form (also known as abdominal cocoon) was first described by Foo et al in 1978.[1,2] It affects mainly young females from tropical and subtropical regions, but adult case reports from temperate zones can be encountered in literature. It is characterized by a thick, fibrotic, cocoon-like membrane, partially or totally encasing the small bowel. Clinically, it presents with recurrent episodes of acute or sub acute small bowel obstruction, weight loss, nausea and anorexia, and at times with a palpable abdominal mass.[2] Most cases are diagnosed incidentally at laparotomy, as in the case presented, although a preoperative diagnosis is purported feasible by a combination of barium follow-through (concertina pattern or cauliflower sign and delayed transit of contrast medium) and computed tomography of the abdomen (small bowel loops congregated to the center of the abdomen encased by a soft-tissue density mantle).[3,4] However, preoperative diagnosis requires a high index of clinical suspicion. Surgery (membrane dissection and extensive adhesiolysis) is the treatment of choice, and there is usually no need for bowel loop resection, especially when a preoperative diagnosis is feasible. Resection of the bowel is unnecessary and it increases morbidity and mortality. Resection is indicated only if the bowel is non-viable. An excellent long-term postoperative prognosis is most of the times guaranteed.[5]

Case Presentation

A 70 year-old man was presented with 24-hour history of colicky abdominal pain and bilious vomiting. He reported to have 6 similar episodes, attributed to small bowel obstruction in the past 4 years, which required hospitalization and resolved with conservative treatment. He also admitted chronic constipation for the last 6 years, anorexia and 15 kg weight loss since his last admission. He had no surgical or other medical history. On examination, he was in distress, but afebrile and haemodynamically stable. His abdomen was distended but non-

tender, with increased bowel sounds in pitch and frequency. No palpable abdominal mass or organomegaly and no external hernias were present. Laboratory blood analyses were within normal limits. Plain abdominal X-ray showed few air-fluid levels centrally located, without free intraperitoneal gas. Ultrasound of the abdomen did not reveal any abnormalities. Contrast-enhanced CT scan of abdomen (**Figure 1,2**), performed on the same day, confirmed the diagnosis of small bowel ileus without providing any diagnostic clues. The patient was admitted and ileus resolved by day 3 conservatively. Endoscopy of upper and lower gastrointestinal tract and biopsies from the duodenum and colon provided normal findings. Although symptoms of obstruction had abated, the history of multiple relapses, the patient's complaints for poor quality of life and multiple admissions, as well as the undefined origin of the underlying pathology led to an exploratory laparotomy on day 7. On surgery, a fibrous capsule covering all the abdominal viscera was revealed, in which small bowel loops were encased, with the presence of interloop adhesions (**Figure 3**). The liver, stomach, appendix, right and left colon, as well as the sigmoid, were also covered and the greater omentum looked hypoplastic and encased in fibrous tissue. Incision of the thick membrane and extensive adhesiolysis of small bowel loops were performed without loop resection. Histology of the membrane showed thickened fibrocollagenous tissue without inflammation. A diagnosis of idiopathic sclerosing encapsulating peritonitis (abdominal cocoon) was established, due to intraoperative findings and by ruling-out any other condition explaining the patient's pathology. Postoperatively, a forgotten small bowel follow-through performed elsewhere was brought to our attention by the patient, showing ileal loops bunched and confined in the lower

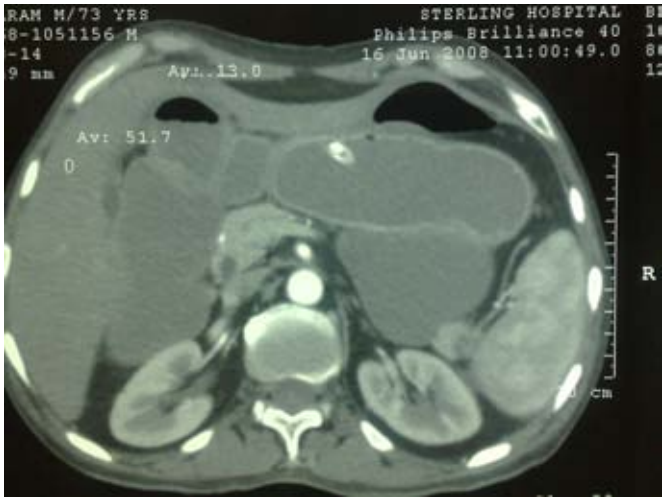

Figure 1: CT dilated bowel loops

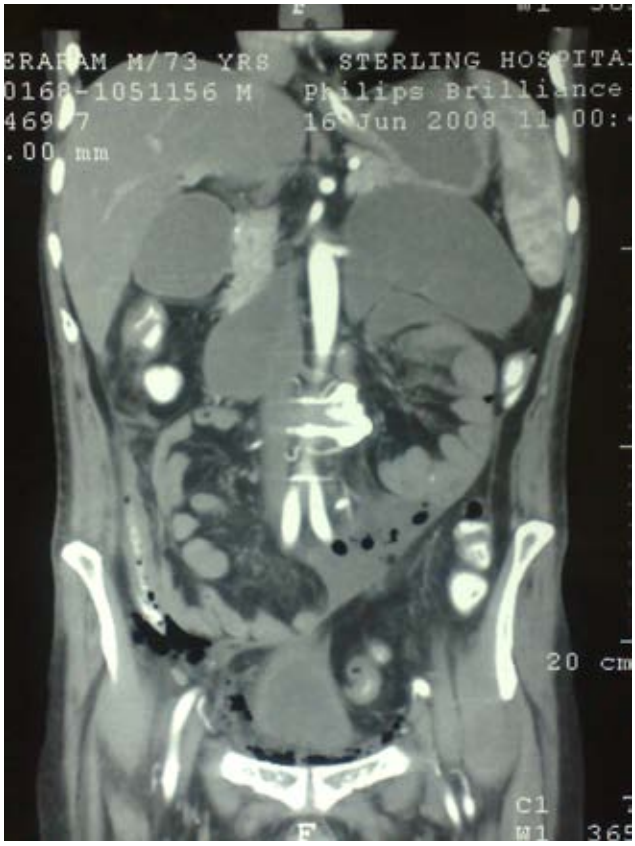

Figure 2: CT dilated bowel loops with cocoon

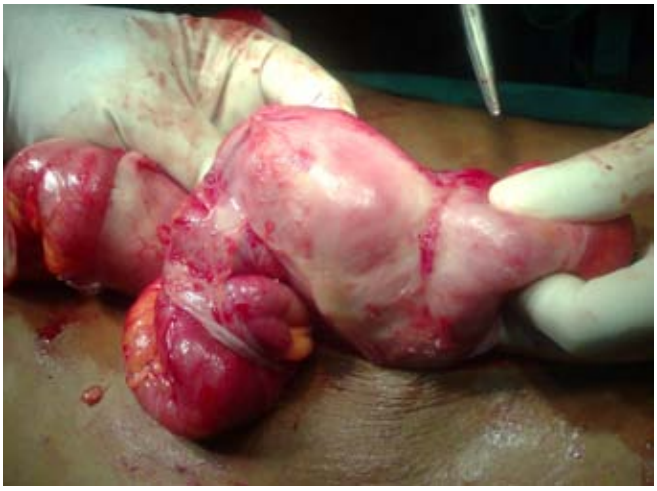

Figure 3: Bowels covered by fibrous membrane

abdomen and pelvis apparently due to adhesions. Postoperative recovery was uneventful and one year after the operation he is in good health.

Discussion

In the presented case, an intra-operative diagnosis of idiopathic sclerosing peritonitis was made in an adult male patient with a history of recurrent bouts of small bowel ileus. Pre-operative findings were inconclusive in his current admission. Although

final surgical management would not have been modified, if results from imaging investigations during prior admissions were accessible in time, a pre-operative diagnosis could have been made possible. Idiopathic sclerosing encapsulating peritonitis or abdominal cocoon, although a rare cause of a common surgical emergency such as small bowel ileus, may be responsible, especially in cases with recurrent attacks of non-strangulating obstruction in the same individual. A high index of clinical suspicion may be generated by the recurrent presentation of small bowel ileus combined with relevant imaging findings and lack of other etiologies. Preoperative diagnosis must be pursued, as it may prevent a "surprise" upon laparotomy and unnecessary procedures for the patient, such as bowel resection.

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Spontaneous rupture of spleen in dengue virus infection

Introduction

Dengue virus infection is a common mosquito- borne disease found in tropic and subtropic regions of the world. It is transmitted to humans by the bite of *Aedes aegypti*, and rarely by *Aedes albopictus* mosquitoes. Dengue virus infection may be asymptomatic or lead to undifferentiated fever, dengue fever (DF) or dengue hemorrhagic fever (DHF). The increasingly widespread distribution and rising incidence of dengue virus infection is related to the increased distribution of *Aedes aegypti*, and its increase in urban areas of Southeast Asia and due to air travel.[1]

All four dengue serotypes cause DF are characterized by sudden onset fever, headache, retro-orbital pain, general malaise, myalgias, leucopenia with lymphocytosis, thrombocytopenia, and mild elevation of liver enzymes. It may also cause rash, mild hemorrhagic manifestations; and rarely severe hemorrhage leading to shock through blood loss.[2] In a small percentage of dengue virus infections, a more severe form of disease, known as DHF, is characterized by acute fever associated with a hemorrhagic diathesis and a tendency to develop dengue shock syndrome (DSS). Treatment of both classic DF and DHF/DSS is symptomatic and supportive.[2,3] There has been an apparent increase in the complications of dengue infection seen among adults in our practice. We describe a case of spontaneous splenic rupture in a patient with DHF.

Case Report

A 25-year-old man was admitted with a 7-day history of fever, myalgia, and headache. He was febrile and anicteric. No pallor, rash or lymphadenopathy was evident, and a tourniquet test was negative. Mild hepatomegaly was present. The neck was supple with no neurologic deficit. Platelet count was 90,000/dL, and hematocrit was 33% before the admission which dropped to 35,000/dL and 30% at the admission. A peripheral blood smear did not show malarial parasites, and blood cultures were sterile. Dengue virus specific IgM antibodies were found to be positive. On day 2, the patient had sudden hypotension with abdominal pain and distension; hematocrit dropped to 15% and platelet count to 25,000/dL. Paracentesis yielded

frankly hemorrhagic fluid. Contrast-enhanced computed tomography (**Figure 1**) showed ascites and an organized, non-enhancing collection over the posterosuperior aspect of spleen, suggestive of splenic rupture. After resuscitation with colloids and packed red cells, he was taken for emergency surgery. Exploratory laparotomy with splenectomy and lavage of peritoneal cavity was done. Spleen was ruptured at the lower pole and at the hilum (**Figure 2**). Over the next few dayshe recovered uneventfully. His fever and platelets normalized in 10 days after the surgery. At present he is doing well six months after the surgery.

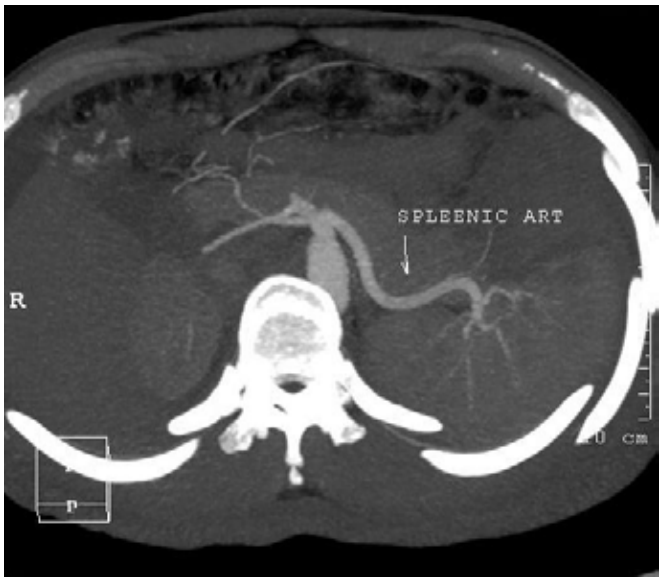

Figure 1: CECT abdomen showing splenic rupture with haemoperitoneum

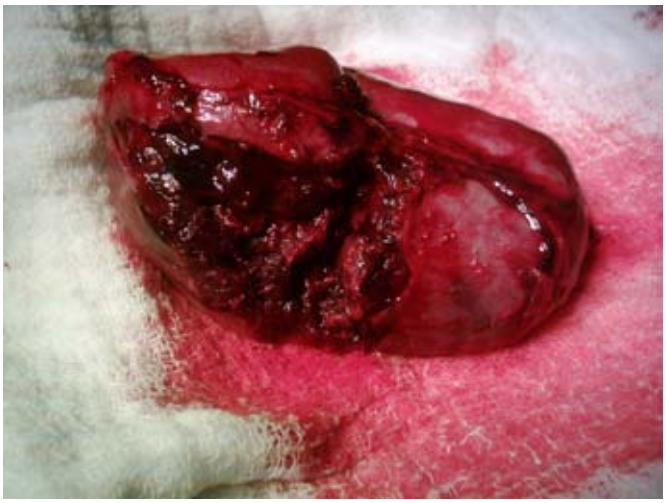

Figure 2 : Ruptured splenic specimen

Discussion

Often considered more common in children, DHF is now being seen more frequently in adults as a consequence of shifting patterns of infection and immunity.[4,5] Although the pathogenesis and pathophysiology of severe dengue infection remains incompletely understood, possible contributory factors to increased disease severity have been described.[5,6] Age, sex, race, pre-existing co-morbidities, and viral-specific features have been noted to play a role in disease outcomes.[3,7] The mainstay of treatment remains prompt fluid resuscitation to counteract massive plasma leakage. Timely and effective intravenous crystalloid replacement of plasma losses results in a favorable outcome in most cases.[8] In its severest form, dengue virus infection is associated with hemorrhagic complications, plasma leakage, shock, liver failure, and disseminated intravascular coagulopathy.

Dengue virus infections are rarely fatal in adults, although fatal infections do occur.[5,9] Bleeding, one of the major problems encountered in DHF, contributes to worsening morbidity. The pathogenesis of hemorrhage may be multifactorial and include vasculopathy, platelet deficiency and dysfunction, and blood coagulation defects.[10] The most common hemorrhagic manifestations are epistaxis, skin hemorrhages, and gastrointestinal hemorrhages. [5,11] Bleeding can occur in any organ. Spontaneous splenic ruptures are rare but life-threatening complications of infectious diseases. The typical presentation is acute, but progressive forms are described.[12,13] The spleen, which frequently has congestion, bears subcapsular hematomas in 15% of DHF cases.[14]

Splenic rupture in patients with hemorrhagic dengue is uncommon but can happen spontaneously or as a result of trauma, which may be minor or unnoticed. There are only three previously reported cases of spleen rupture in patients with dengue fever: a 35-year-old white man with dengue fever who underwent splenectomy in French Polynesia and had a favorable clinical outcome;[15] a 23-year-old woman who lived in Venezuela, had severe illness and died after splenectomy with gramnegative sepsis and multiorgan failure;[16] and a 52-year-old woman with dengue fever who underwent splenectomy in Brazil and had a favorable clinical outcome.[17] In the first and third cases, the ruptured spleen developed in patients without the classical symptoms of DHF/DSS. We presume the splenic rupture in our patient was due to factors, such as the level of severity of DHF/DSS (grade IV) the presence of consumption coagulopathy and severe thrombocytopenia.

In conclusion, a case of spleen rupture may be misdiagnosed as shock syndrome seen in DHF/DSS. Physicians should be aware of the possibility of splenic rupture in areas where dengue infection is endemic. Early diagnosis and treatment are needed to avoid a fatal outcome.

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La Voix

'Ghosts and witches' – Cholecystectomy and Colonic injury

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I am a 57 year old woman. I am the principal of a girls' college in a small town, Jaunpur, in UP. In the months of September and October 2009, I had stomach ache, nausea and vomiting. After ultrasound (USG), it was diagnosed that there were stones in my gall bladder. I could have been easily operated in Jaunpur itself or a nearby bigger town, but my nephew, who is a doctor in Aligarh (University Health Services), asked me to come there and get my gall bladder removed in Aligarh.

I was admitted to a nursing home in Aligarh on 28th October 2009. Next morning at 7 AM, the operation (laparoscopic cholecystectomy) was done. After the operation, I felt deep pain in my abdomen which became severe. On 30th October evening, the operating doctor sent me to the medical college hospital in Aligarh. Throughout the night, I cried with pain and the next morning I felt very weak. Due to vomiting I could not take anything by mouth. Many injections were given but there was no relief. Gradually, my heart beat increased and reached above 140/ minute. A senior physician suspected a heart attack and suggested TROP T test which was done but was negative. It became difficult for me to breathe and I began to lose consciousness. By the evening of 31st October, my doctors decided to shift me to the Cardiac care Unit (CCU). So my husband decided to take me to another private hospital in the town. I became unconscious (my husband was told that I had developed abdominal sepsis) and was put on ventilator at once. Because of sepsis and unconscious state, my memory faded and I could not even recognize my husband and my son. It was after about 7 days on 8th November, that I regained my consciousness and memory and could recognize my daughter who had arrived from Lucknow to see me. Because of lying straight on my back in the bed for 9 days, a bed sore had developed at my lower back.

At this hospital US, CT and blood tests were done but abdominal pain and distension continued and there was no sign of relief. Two senior surgeons visited me but of no avail. After taking liquid diet from 10th November to 14th November, my condition grew from bad to worse. On the request of my husband and on my doctors' advice, I was shifted to Lucknow by an ambulance.

On 15th November, a surgeon in Lucknow examined me and sent me to a Gastroenterologist, who at once referred me to SGPGIMS. I was immediately admitted to SGPGIMS and was operated that very night when a perforation was found in my transverse colon and a colostomy was done. I faced several problems with the stoma. I had to be very careful in lying on either side as the bag could disconnect or leak. Many a times, my bed sheets and dress would become soiled with stools. I could not take bath. My son had to clean and change the stoma frequently, sometimes even three to four times in a day; he could not go anywhere for long. Day and night, my husband remained with me. The feeding pipe in the stomach gave me much trouble and hurt me. Sometimes, I would have pain in the abdomen and would need painkillers. The open wound of about 10 inches had to be cleaned and dressed daily. I had to bear the pain and the discomfort at the time of these dressings. The stoma was finally closed on 18th February 2010.

I stayed for 3 days at Aligarh nursing home, 24 hours at medical college in Aligarh, 14 days at critical care hospital in Aligarh and 24 days at SGPGIMS. We had to stay at my elder brother's home in

Lucknow from 8th December 2009 to 20th January 2010 to go for regular checkups at SGPGIMS. On 21st January 2010, we came back to Jaunpur for some time. I was admitted at SGPGIMS again from 9th February to 26th February 2010 for the second operation. Then I stayed at my brother's home in Lucknow again till 2nd March and finally returned to Jaunpur on 2nd March 2010.

On my behalf, my husband informed the manager of my college about my illness and I remained on medical leave for more than 4 months from 24th October 2009 to 4th March 2010. As I am a Principal of a college, teaching and administration at the college were disturbed. My husband took long leave from his college. Due to long leave from the college, the students of my husband suffered. My daughter, a student of MBA in Lucknow came to Aligarh and visited me several times in SGPGIMS at the cost of her classes and studies. My son, who has completed his engineering studies, could not appear in competitive exams. My younger brother, the manager of a bank, took emergency leave to help us at Aligarh and then again to see me at Lucknow. My other brother, a railway employee, also took leave to see me at Lucknow. My sister-in-law remained with me all the time; her daily routine and household works were disturbed.

The treatment at Aligarh was too costly for us. We had brought 30,000 rupees with us and my husband had another 60,000 in his ATM. Soon, we ran out of money. My husband requested his friends and relatives in Jaunpur, Varanasi, Pratapgarh and Lucknow to send him money through his bank account. My sister-in-law, my sisters and brothers all helped us. My younger brother came to Aligarh and lent us 70,000 rupees. Money gradually poured in and we spent about 3 lakhs rupees in Aligarh. We had to pay 25,000 rupees for the ambulance, attendants, oxygen, etc. when I was transferred from Aligarh to Lucknow. As we both are earning (I get Rs. 30,000 per month and my husband gets Rs 34,000), my relatives were assured that the amount lent by them to us in this period of crisis would be positively returned to them, and in time. Luckily, a fixed deposit in bank matured to around 2 lakhs rupees in February 2010 and we have repaid half of the borrowed money. My husband has applied for 2 lakhs loan from his provident fund and soon rest of the debt would be repaid by April 2010. At SGPGIMS, costly injections had to be given to save my life; the stoma bags and plates were also very costly. We have spent more than 5 lakhs rupees on my treatment at Aligarh and Lucknow. This amount does not include other expenses e.g. travel, hotel stay, food and lodging, and many other daily expenses.

During this period, our life was full of torment, torture and turmoil. Our house looked haunted and deserted as it remained locked for three months. It seemed as if the sweetness of life and the joy of living had vanished. Our friends, family members and near and dear ones prayed for me night and day with tears. After the second operation to close the stoma, I am fine now but my health has gone down. We thank all those who give relief and comfort to the suffering.

We are trying to forget this time but it will not be possible for me forget that in my subconscious state, I felt as if I were in another world imprisoned by 'ghosts and witches'.

Comment (Dr V.K. Kapoor):

The commonest intra-operative injury during cholecystectomy is bile duct injury (BDI), diagnosis and management of which is well documented. Laparoscopic cholecystectomy can, however, be associated with bowel (duodenal and colonic) injury also – almost always caused by injudicious and careless use of electro-cautery. Since these injuries are less common, they are not thought of and because they are usually thermal, they present late and are often missed, as happened in the case of Mrs. Arjumand Bano. She was lucky to survive severe intra-abdominal sepsis –mainly due to the prayers and support of her friends and relatives, but many other patients may not be so fortunate. Any patient, who is not comfortable (sitting up in the bed having her morning cup of tea and wanting to go home), does not have stable vital signs (pulse, temperature and respiratory ate) and does not have a settled (soft and non-tender) abdomen the day after laparoscopic cholecystectomy, should be strongly suspected to have sustained an intra-operative injury (usually to the bile duct but may be to the duodenum or the colon) and appropriately investigated and managed. We ourselves have had mortality because of a duodenal injury caused during laparoscopic cholecystectomy which was missed. Mrs. Bano has forgotten and forgiven, but it is the duty of all of us, the surgeons, to take every precaution to make each and every cholecystectomy a 'safe cholecystectomy' so that 'ghosts and witches' stay away from our patients.

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The cover photograph has been taken from the GI Techniques: The new and the old, 'Evaluation of hepatocellular carcinoma by contrast enhanced ultrasound : a novel technique'*, Page 214, Figure 1 a,b.*

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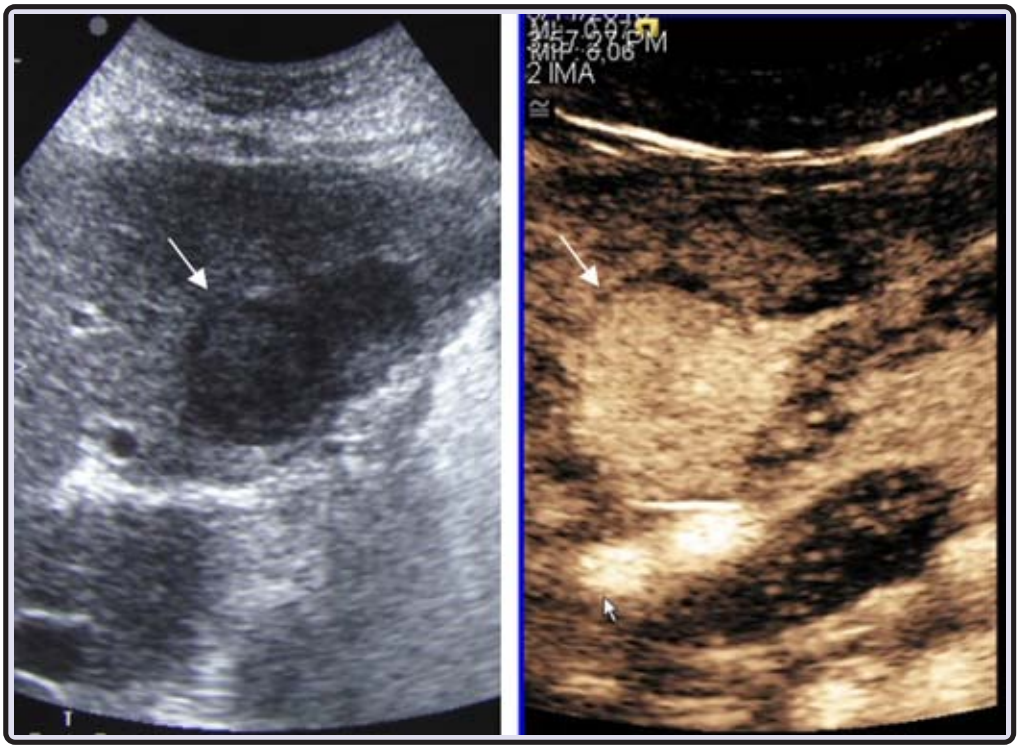

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