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Quarterly Review

Peutz-Jeghers Syndrome: An outline on Diagnosis and Management

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ABSTRACT

Peutz-Jeghers Syndrome (PJS) is a rare inherited autosomal dominant disorder characterized by pigmented mucocutaneous melanotic macules and hamartomatous polyps. PJS arises due to mutations in STK11 gene located on chromosome 19q 13.3 and predisposes the patients to a multitude of malignancies with an estimated cumulative risk of 81% - 93%. Breast, gastrointestinal tract, pancreas, reproductive system and lung are common sites of development of malignancies in these patients. Anemia, rectal bleeding, abdominal pain, obstruction and intussusception are the usual complications in patients with PJS leading to multiple interventions. Upper GI endoscopy and Double Balloon Enteroscopy (DBE) allows screening of the gastrointestinal tract. Polypectomy of hamartomas more than 1 cm carried out at the time of surveillance endoscopy, abates the complications like bleeding, obstruction and intussusception. When DBE is not feasible, intraoperative endoscopy (IOE) is helpful to evaluate the entire gastrointestinal tract during surgery. IOE is also crucial for removal of all small intestinal polyps. Imaging techniques like magnetic resonance enterography and computed tomography enterography and video capsule endoscopy are non-invasive options for evaluation and screening in these patients. Sixty eight percent of the patients require emergency surgery during their lifetime. Regular cancer screening protocols should be instituted for early detection of malignancies. Genetic counseling and screening of other first degree family members helps in their preemptive identification and management. Chemoprevention using mTOR inhibitors, COX-2 inhibitors could be helpful in polyp reduction.

KEYWORDS: Intussusception, Double Balloon Endoscopy, Hamartomatous polyp, Intra-operative enteroscopy, Peutz-Jeghers Syndrome.

Introduction

Peutz-Jeghers syndrome (PJS) is a rare inherited disorder characterized by pigmented mucocutaneous melanotic macules and hamartomatous polyps in the gastrointestinal tract with varying degrees of cancer risk[1,2,3]. Jan Peutz first described this disorder in a Dutch family. Harold Jeghers subsequently described the relationship between

pigmented lesions, gastrointestinal polyposis and increased risk of carcinoma[4]. The eponym of Peutz-Jeghers syndrome was coined in 1954. PJS is a rare entity. Recently, there is considerable advancement in its diagnosis and management. This review focuses on the diagnosis and management of PJS.

Genetics

PJS is caused by mutation in the STK11 gene located on the short arm of chromosome 19 (19p13.3). Most mutations are small deletions, insertions or single base substitutions leading to an abnormal truncated protein with no enzymatic activity[1,3]. The STK11 gene encodes a serine threonine kinase and acts as a tumor suppressor gene. Mutation in STK11 gene leads to activation of mammalian target of rapamycin (mTOR) pathway leading to increase in protein synthesis by phosphorylating and inhibiting the mRNA translational repressor proteins[7,8,12]. Inheritance follows an autosomal dominant pattern with variable penetrance resulting in differences in presentation among family members[1,4,9]. In 10%-20% patients PJS arises due to de novo mutation without any family history. It is noteworthy that STK11 mutation could be identified only in 30% - 70% of the patients[10]. Variation in techniques of mutation analysis and patient selection are the cause for low detection rates. Newer techniques of mutation analysis such as Multiplex ligation dependent probe amplification (MLPA) have increased the identification rates up to 94%. The possibility of other gene mutations causing PJS is also being probed[11]. Identification of mutation in mTOR pathway in causation PJS have led to use of mTOR inhibitors for chemoprevention in PJS.[3]

Clinical Features

The prevalence of PJS varies from 1 in 8300 to 1 in 2.8 lakh population with equal male to female preponderance[1,3]. The median age of onset of presentation varies from 11-13 years[3]. Hyper pigmented macules are commonest symptoms. These macules are seen commonly around the mouth, lips, eyes, nostrils, and on the buccal mucosa and sparsely on the fingers, soles of the feet, palms, anal area and intestinal mucosa[1,2,3] (**Figure 1, Figure 2**). These are present in 95% of PJS patients. These arise due to clusters of melanocytes in the dermo-epidermal junction and have no malignant potential negating the need for biopsy. These hyper pigmentations may disappear by adolescence in many patients[4,6].

Anemia, rectal bleeding, abdominal pain, obstruction and/or intussusception are the other common complications in patients with PJS in the first three decades.[4,5]

Ninety percent of affected individuals eventually develop small intestinal polyps[13]. In the small intestine, jejunum is the most common site for polyps followed by ileum and duodenum. Involvement of colon, stomach and rectum are seen in the decreasing order of incidence[15]. In a minority of patients, gallbladder, common bile duct, nasal mucosa, bladder, uterus and vagina[2,15] are also affected by polyps. These polyps are hamartomatous polyps and characterized by complex glands with presence of arborizing smooth muscle bands in the lamina propria (arrows) on microscopy (**Figure 3**). The glands are lined by columnar epithelium and goblet cells primarily in the

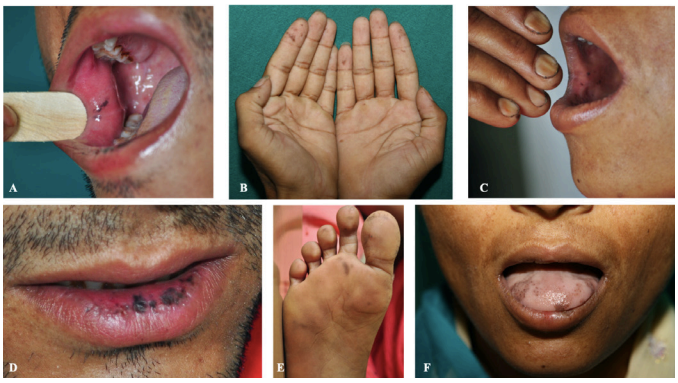

Figure 1 (A): Patients with pigmented macules in the buccal mucosa; (B): palm; (C): Koilonychia due to chronic bleeding; (D): Pigmented lesion on lip; (E) Sole; (F): Tongue.

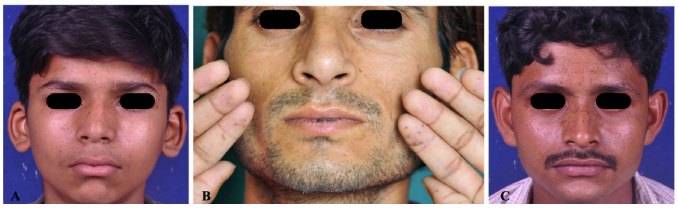

Figure 2: Facial pigmentations, occasionally these are subtle and around the eyes.

superficial portion and on the surface of the polyp. At the base, Paneth cells and endocrine cells may be seen.[1,3]

PJS is associated with increased risk of gastrointestinal and non gastrointestinal malignancies. The cumulative risk of development of malignancies is estimated between 81% - 93%.[13,16]. Breast cancer poses the highest specific risk affecting 32% - 54% of the females with PJS. Colon (39%) is the most common site of GI tract malignancy followed by pancreas (36%), stomach (29%), small intestine (13%) and esophagus[13,19]. Few cases of Cholangiocarcinoma and carcinoma of gallbladder are also reported[3,21]. Sex cord tumors of ovary is seen in 36% of female patients while sex-cord testicular tumors occur in 9% of male PJS patients[13,15]. PJS is associated with lung, uterine and cervical cancers with prevalence of 15%, 10% and 9% respectively. Surveillance and early detection hence play a crucial role in the management of PJS patients[13,16].

Diagnosis and Treatment

In patients with a family history of PJS, diagnosis can be made with any number of PJS polyps, or characteristic prominent PJS mucocutaneous pigmentation [20].

The World health organization (WHO), Mayo Clinic, and Tomlinson and Houston have independently proposed guidelines for diagnosis of PJS (**Table 1**)[17,20,22]. Among these, WHO criteria are commonly used. It states that in patients without a family history of PJS, a diagnosis

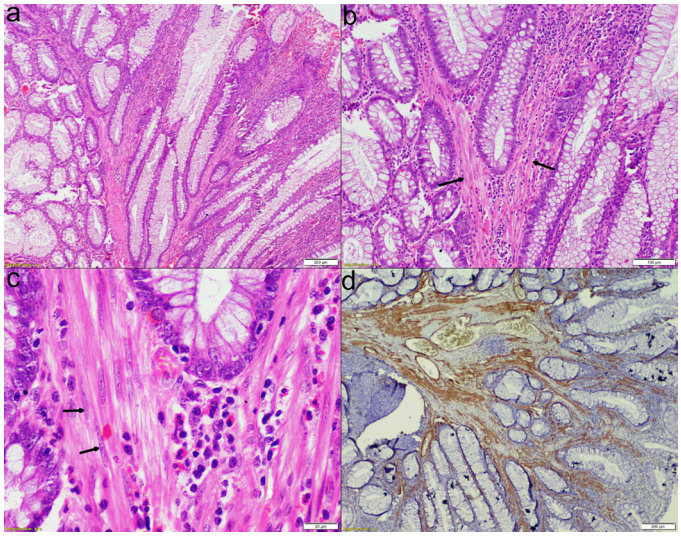

Figure 3: Hematoxylin and eosin stained (HE) section shows a polyp (a, HE; 40x) with an arborization of smooth muscle bundles (arrows) within the lamina propria (b, HE; 100x). The cells have elongated nuclei with eosinophilic cytoplasm (c, HE; 400x). Immunohistochemistry with smooth muscle actin confirms the display of smooth muscle fibers in the lamina propria (d, 40x).

Table 1: Criteria for diagnosis of PJS.

Sl. No.	Name	Criteria
1	World Health Organisation	**Patients without family history of PJS** Presence of 3 or more histologically confirmed PJS polyps or, any number of PJS polyps with characteristic melanotic macules **Patients with family history of PJS** Any number of PJS polyps or, characteristic melanoticmacules
2	Mayo Clinic	**Patients without family history of PJS** Characteristic melanotic macules and 1 or more polyps withPJS histology or, Two intestinal polyps with PJS histology **Patients with history of PJS in sibling or child** Characteristic melanotic macules or,One or more intestinal polyps with PJS histology or, LKB1 mutation
3	Tomlinson and Houston	Two or more intestinal polyps with PJS histology or,One intestinal polyp with PJS histology with either melanotic maculesor,a family history of PJS and characteristic melanoticmacules

PJS: Peutz-Jeghers syndrome, LKB1: Liver Kinase B1

of PJS is made if there are three or more histologically confirmed PJS polyps, or any number of PJS polyps and characteristic PJS mucocutaneous pigmentation. In patients with a family history of PJS, diagnosis can be made with any number of PJS polyps, or characteristic prominent PJS mucocutaneous pigmentation[20].

Genetic testing helps in confirming the diagnosis. STK11 mutation is identified in around 94% of clinically diagnosed patients[11]. Genetic testing should be carried out by 8 years of age in high risk first degree relatives of PJS patients without any clinical stigmata of PJS. First degree relatives of PJS patients with identified STK11 mutation should undergo testing for the specific mutation. Negative report for the mutation rules out PJS in the relatives, while a positive report confirms the disease and should follow the treatment protocol. If mutation could not be identified in the index case further testing of the relatives are futile and should be avoided[1].

Imaging

Multi-detector Computer Tomography (MDCT), Magnetic resonance imaging (MRI) and Video capsule endoscopy (VCE) are used as non-invasive modalities for diagnosing PJS. Both CT and MR enterography have good sensitivity for larger polyps; however, the accuracy drops for sub-centimetric lesions.

Multi Detector Computed Tomography (MDCT)

MDCT enterography has high spatial resolution and is usually performed for the evaluation of small-bowel tumors and surveillance in patients with PJS. The polyps appear as well-defined hyper-dense enhancing lesions. These are usually multiple, often pedunculated lesions of varying size and more frequently involve the small bowel (**Figure 4)**. CT enterography involves distending the small bowel loops that have neutral contrast enabling high lesion detection rates. The exposure to ionizing radiation however makes CECT a suboptimal candidate for repeat imaging which is needed for surveillance[24,26]. CT also shows polyp-related complications such as intussusception and bowel obstruction. Bowel within a bowel sign, target-like appearance or sausage shaped mass are imaging features of intussusception.

MR Imaging

MR enterography is also based on a similar principle of optimally distending the small bowel loops to increase the sensitivity in the detection of polyps. MR however has better contrast resolution and provides multiple paradigms in the form of various pulse sequences to assess bowel polyps. The fluid used to distend the small bowel appears hyper intense on T2W images and hypointense on post-gadolinium images. Thus, luminal polyps appear dark inT2-weighted images and bright in post-contrast images (because they enhance) (**Figure 5**). The overall concordance rate between MR enterography and VCE is

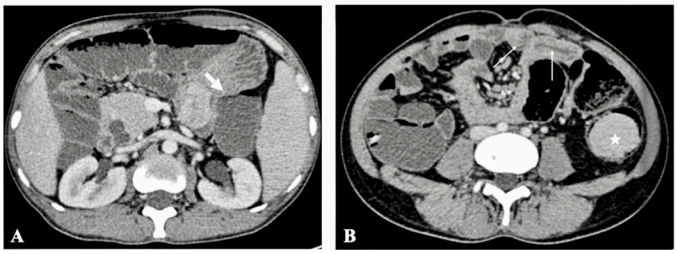

Figure 4: Axial contrast-enhanced CT enterography images (a and b) show large polyps in duodenum (thick arrow) and descending colon (asterisk) in a case of Peutz-Jeghers syndrome. Segments of small bowel intussusception (thin arrows) are also seen because of other smaller polyps.

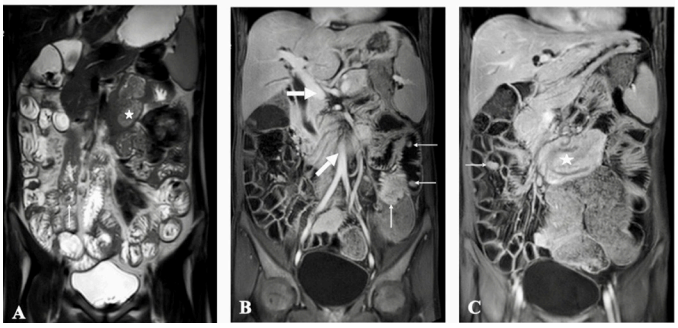

Figure 5: Coronal BTFE image (a) and post-gadolinium images (b and c) in a patient with Peutz-Jeghers syndrome show a large intraluminal polypoidal mass in third part of duodenum (asterisk) with associated duodenal intussusception (short thick arrow) and dilatation of the bile duct (arrowhead). There were multiple smaller polyps in jejunum and ileum (thin arrows)

70% and polyps measuring 15mm or higher have a better concordance rate of 93%. However, VCE has better rates of identification of polyps measuring 6mm to 9 mm. MR enterography appears to be a safe alternative to VCE for small bowel evaluation in PJS patients[5,24]. Being radiation-free, MR is a good method for follow-up and surveillance of these patients, especially since majority of these are young children and adults.

Video capsule endoscopy (VCE)

VCE have shown increased sensitivity in polyp detection when compared to conventional radiological techniques. VCE is a safe and diagnostically sensitive method for small bowel surveillance in patients with PJS including children. It causes substantially less patient discomfort than barium enterography or double balloon enteroscopy. VCE has been useful in diagnosing patients with occult gastrointestinal bleeding. VCE demonstrated higher polyp detection rate than small bowel follow-through in a blinded comparison in patients with PJ syndrome. In another study, the number of polyps >10 mm detected by VCE were greater than by MRE. However, the positive predictive value of detecting a polyp at subsequent balloon enteroscopy was lower with VCE than MRE (60% vs 100%). MRE was also more accurate in terms of size estimation and localization of polyps. In comparison with double balloon enteroscopy, VCE has a comparable polyp detection rate. Duodenal and proximal small intestinal polyps and lesions are missed in VCE due to lesser transit time. The other major drawback of VCE is the inability to accurately estimate polyp size and location. VCE is also contraindicated in patients presenting with obstruction[33,34].

Endoscopy

The two basic techniques in the diagnosis and management of hamartomas include Double balloon enteroscopy (DBE) and Intra-operative endoscopy (IOE)[3,23].

Double balloon enteroscopy was introduced as a modification of push enteroscopy by Yamamoto et al. in 2001 and has become the investigation of choice for evaluation of small bowel lesions and can evaluate the entire small bowel. It consists of an endoscope and a soft flexible over-tube, each having an inflatable balloon attached to its distal end[27,29,30]. Study comparing DBE with IOE showed similar polyp detection rates irrespective of size. In a comparative study of 18 consecutive patients, DBE demonstrated more polyps than small bowel follow-through and had comparable accuracy to VCE. Complications with DBE are rare with diagnostic procedures and 4.3% for therapeutic procedures. DBE however possesses a disadvantage of being a prolonged invasive procedure and in PJS patients its maneuverability is hampered as most patients had prior abdominal surgery[3,5,24].

Intraoperative endoscopy (IOE) is the combination of laparotomy or laparoscopy with endoscopy. During laparotomy or laparoscopy, an enterotomy is made on antimesenteric border on the small bowel and the endoscope is passed through it. Small bowel is inflated with air for better evaluation. It was the accepted method for complete evaluation of small bowel before the era of DBE. Also, large polyps obscuring the lumen will pose difficulty in DBE and mandate a conversion to IOE. Intraoperative endoscopy reduces the need for frequent enterotomies and also increases polyp detection rate.[3,34,35] (**Figure 6**). Attempt should be made to clear all polyps in these patients utilizing IOE. Endoscopic therapy in the small intestine should be performed with special care to avoid complications such as bleeding and perforation[5,23,35].

In a comparative study of DBE and IOE, both techniques had comparable accuracy in removing small bowel polyps and the authors concluded that polypectomy with DBE may obviate the need for repeated surgeries and DBE would be less invasive and convenient for the patient.

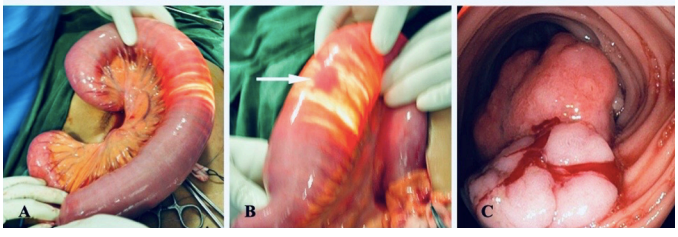

Figure 6: Intra operative enteroscopy done through a small enterotomy already done for removal of polyp. During IOE, the polyps are seen outside as dark shadow against the endoscopic illumination (white arrow)

Single Incision Laparoscopic (SILS) assisted DBE are currently being carried out in few centers and need further validation. It helps in easier conversion to IOE when DBE fails[37].

Spiral enteroscopy is a newer technique that uses a special over-tube called Discovery Small Bowel (DSB) to pleat small bowel. Spiral enteroscope consist of an overture with helical spirals of 5mm at the end[39,40]. This could be rotated independently from the enteroscope and can be engaged or disengaged when advancing. The technique of spiral enteroscopy is thus helpful in the diagnostic and therapeutic evaluation of small bowel by rotating and clockwise movement of enteroscope. However spiral enteroscopy needs further validation in polyp detection[23,38,39].

Virtual enteroscopy by use of MDCT technique is also being evaluated in the detection of polyps in PJS patients. Virtual enteroscopy has shown promising results in the detection of small bowel tumors[40]. Virtual enteroscopy involves inserting a duodenal tube under fluoroscopy followed by inflation of the small intestine with 2000ml of air. Air acts as a contrast medium to achieve small bowel expansion. This helps in better identification of raised lesions such as polyps compared to enterography[40,41].

Screening

Screening for malignancy is pivotal in managing patients with PJS. For first degree relatives of PJS patients, screening should start at birth followed by annual history and physical examination. Special attention should be given to identification of mucocutaneous macules, precocious puberty and testicular tumors which appear at an early age.[1,5]

Multiple screening protocols have been elucidated by various institutions including Danish polyposis Registry, St Marks Hospital, Johns Hopkins Hospital, The Mayo Clinic for follow up of PJS patients[3,5,42-47]. Breast cancer poses the highest specific risk and screening in female PJS patients should be along the lines of screening of BRCA1 and BRCA2 patients. It includes monthly breast self-examination starting at 18 years of age and semiannual clinical breast examination and annual mammography starting at the age of 25 years.

Baseline UGI endoscopy and colonoscopy have been suggested at 8 years of age. If polyps are present then colonoscopy and UGI endoscopy to be carried out 3 yearly. If no polyps were detected at the baseline investigation then reinitiate follow up at 18 years with colonoscopy and UGI endoscopy carried out every 3 years. Colonoscopy frequency to be increased after 50 years, conducted every 1-2 years. Pancreatic cancer is third most common cancer in PJS patients, however there are no evidence for routine screening protocols as cost benefit analysis showed poor cost effectiveness.

Screening with pelvic examination and pap smear should be carried out yearly to rule out cervical and uterine malignancies starting at 21 years. The mean age of development of testicular cancer is 9 years prompting an annual examination from birth and attention to development of precocious puberty. Ultrasound examination to be done in case of any suspicious findings on examination.[1,3,5,45-47]

The surveillance protocol is outlined in **Table 2**.

Chemoprevention

PJS being a rare disease, chemopreventive human studies are difficult to conduct due to lack of participants[49]. Animal studies have shown promising results. Rapamycin is a macrolide antibiotic and acts as a mTOR inhibitor after binding to its cytoplasmic receptor[3,12]. Rapamycin studies in mice models showed reduction of polyp burden and polyp size[48]. Rapamycin analogues including sirolimus and everolimus approved for various cancer treatment could be helpful in PJS patients[12]. Another frontier in chemoprevention is the use of COX-2 inhibitors based on the observation that hamartomas and carcinomas in PJS patients expressed COX-2 receptors. Celecoxib, a COX-2 inhibitor, showed decreased vascularity and reduction in tumor burden in mice models[50,51]. Metformin, an oral hypoglycemic drug, has also shown inhibition of mTOR pathway in experimental models, and needs further validation[51].

Surgery

Laparotomy or laparoscopic surgery is the treatment for polyps related complications and for endoscopically

Table 2: Surveillance protocol for follow up in PJS patients.

Sl. No.	Cancer type	Age (years)	Surveillance
1	Breast	18 25	Monthly Self Breast examination Annual mammogram/ MRI and 6 monthly Clinical Examination
2	Colon	8 18	Baseline Colonoscopy if polyps present then 3 yearly colonoscopy every 3 yearly, increase frequency after 50 yrs
3	Stomach	8 18	Baseline UGI endoscopy, 2-3 yrly endoscopy if polyps present UGI endoscopy every 2-3 years
4	Small Intestine	8 18	VCE or CT or MR enterographyevery 3 yearly if polyppresent VCE or CT or MR enterographyevery 3 yearly if polyppresent
5	Uterus and cervix	21	Pelvic examination with pap Smear annually
6	Testis	at birth	History and Physical examination annually Ultrasound of testis if any abnormality

MRI: Magnetic Resonance Imaging, UGI: Upper Gastrointestinal endoscopy, VCE: Video Capsule Endoscopy, CT: Computed Tomography .

irretrievable symptomatic polyps. About 30% of PJS patients required laparotomy before 10 years of age and by 20 years 68% of patients had undergone a laparotomy, mostly as an emergency procedure for complications as mentioned earlier[3,14]. Usually, the surgeon resorts to removal of the symptomatic polyp. However, in PJS patients the concept of "clean sweep surgery" in which all polyps are removed at the time of laparotomy have proven benefits by reducing need for subsequent laparotomies and increasing overall survival[1,5,52]. The clean sweep surgery could be carried out with the help of intraoperative endoscopy or by multiple enterotomies at centers where intraoperative endoscopy is unavailable. Laparoscopy, enterotomy and polyp excision is also a viable option in these patients[46]. Intraoperative milking of small bowel drags the polyp and produces dimpling on the bowel wall and can be used as an adjunct in identifying and locating the base of polyps. Enterotomy is performed at the site of the dimple and the poly is excised including its base (**Figure 7**). Duodenal polyps arising near the papilla favors towards surgical resection. Endoscopic snaring or cautery ligation can lead to injury of papilla and should be avoided. Mucosectomy and papilla reconstruction is a viable surgical option in these patients. Irreducible intussusception, large polyp, multiple polyps in a short segment of bowel, vascular compromise due to obstruction require segmental resection of the bowel. Repeated laparotomy with extensive small bowel resections

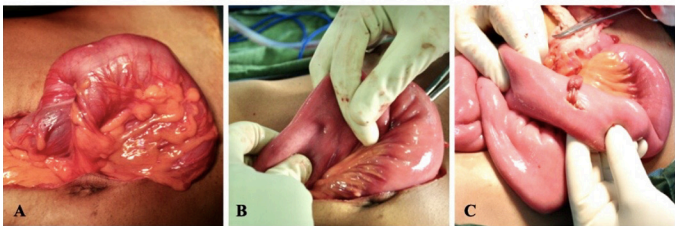

Figure 7 (A): Intraoperative image with intussusception of colon due to polyp; (B): dimpling of serosa during milking of small bowel. This dimpling indicates the site of attachment of the pedunculated polyp to the bowel wall; (C): enterotomy at polyp base for excision of polyp.

can eventually lead to short-bowel syndrome in these patients. Mostly resections are done for intussusception, and this could be avoided by prophylactic polypectomy of polyps measuring more than 1 cm during surveillance enteroscopy or doing a clean sweep surgery during the primary laparotomy[3,14,45,46].

Road Ahead

The major deterrent in the management of these patients is the lack of awareness among patients and medical fraternity delaying diagnosis and early referral. Lack of national and international databases for collection and compilation of data of rare disorders including PJS

hamper the progress. Strict adherence to surveillance protocols will prolong the life expectancy in these patients. Genetic counseling should be mandated for all patients. A centralized organization at national and international level may be set up for disseminating information to patients and health professionals, testing, diagnosing, follow up and clinical research for all rare inherited disorders. All diagnosed patients should be counseled for participating in clinical trials to deduct better treatment protocols.

The advent of novel Clustered Regularly Interspaced Palindromic Sequences (CRISPR) technology and CRISPR associated protein 9 (Cas 9) mediated genetic editing as a cure is promising for PJS patients. Editing the mutated STK11 gene offers a radical and permanent cure for PJS patients. Still in the embryonal stages of development gene editing could hold the future to treat these rare inherited disorders[53-55].

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