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Searching The Culprit'-Multiple Gastrointestinal Neoplasms: Case Report with Literature Review

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Multiple primary malignant neoplasm (MPMN) occur frequently than can be explained on the basis of random chance. They are divided into two groups; synchronous and metachronous. Metachronous cancer is detected after 6 months of the first diagnosis and synchronous cancer within 6 months of the first diagnosis. The incidence of developing synchronous gastrointestinal malignancies is noted to rise with increasing age as the long-term survival for each cancer is increasing, more sophisticated treatments available and better application of screening programs. Synchronous cancers are clinically relevant with regard to their diagnosis and treatment.[1] The frequency of multiple primaries is reported to be in the range of 2-17%.[2] Synchronous cancer has an incidence of 3.4% in gastric cancer (GC)patients. The most common type of synchronous cancer in GC patients is colorectal cancer (CRC).[3] Most synchronous cancers consist of two lesions, rarely three or even four. In an exceptional case, Kibera *et al*. reported a case with 7 simultaneous colon cancers.[4]

Case Report

A male patient aged 72 years presented with recurrent non bilious vomiting, jaundice, itching, and anorexia and weight loss of 10 kg for 2 months. He developed increased stool frequency, which was small in volume, non-bloody for 15 days. Physical examination of the patient revealed pallor, icterus, cachexia, and a distended gall bladder. His background and family history were not significant. He was a chronic smoker and had a history of alcohol abuse for 20 years. There was no history of any chronic illness in the past. Blood investigations revealed a hemoglobin concentration of 9.2g/dl, leucocyte count of 12000/ul and a blood group O.Liver profile demonstrated total bilirubin 6 mg/dL, direct bilirubin 4 mg/dL, aspartate aminotransferase 124 U/L, alanine aminotransferase 119 U/L, and alkaline phosphatase 412 international U/L. Stool occult blood test was positive.Esophagogastroduodenoscopy showed a rigid stomach with uniformly thickened gastric folds from fundus to pylorus with few ulcerations creating a challenging duodenal intubation (**Figure 1A** and **B**). The first, second part of duodenum and ampulla was normal on esophagogastro-

duodenoscopy. Multiple gastric biopsies were taken with conventional forceps that revealed a poorly differentiated adenocarcinoma with signet-ring cell appearance and negative for *Helicobacter pylori* (**Figure 3A** and **B**). Multislice Computed tomography (MSCT) revealed marked wall thickening of the stomach with peri gastric lymph nodes, an abrupt cut off at distal common bile duct (**Figure 2A** and **C**),wall thickening of transverse colon, splenic flexure and rectum (**Figure 2B** and **D**). ERCP (endoscopic retrograde cholangiopancreatography) scope traversed with difficulty across the pylorus. A brush cytology and a distal common bile duct biopsy was taken after a precut sphincterotomy that revealed a moderately differentiated adenocarcinoma (**Figure 4B**). Colonoscopy revealed an ulcerative, partially obstructing circumferential mass in the rectum and an ulceroproliferative mass at splenic flexure that could not be traversed, with a normal intervening mucosa (**Figure 1C** and **D**). Carcinoembryonic antigen (CEA)level was 6ng/ml (normal range 5ng/ml). Thecolonoscopic biopsies from rectum and splenic flexure showed a poorly differentiated adenocarcinoma with signet ring appearance (**Figure 3C** and **4A**). The immunohistochemistry panel demonstrated the gastric neoplasm to be cytokeratin (CK)7 positive and negative for CK20 and CDX2 while the colonic neoplasm was positive for CK7/CK20/CDX2 (**Figure 5A-E**). The IHC proved the gastric and colonic lesions to be separate cancers and not metastatic lesions. He was diagnosed as a case of synchronous gastrointestinal neoplasm.

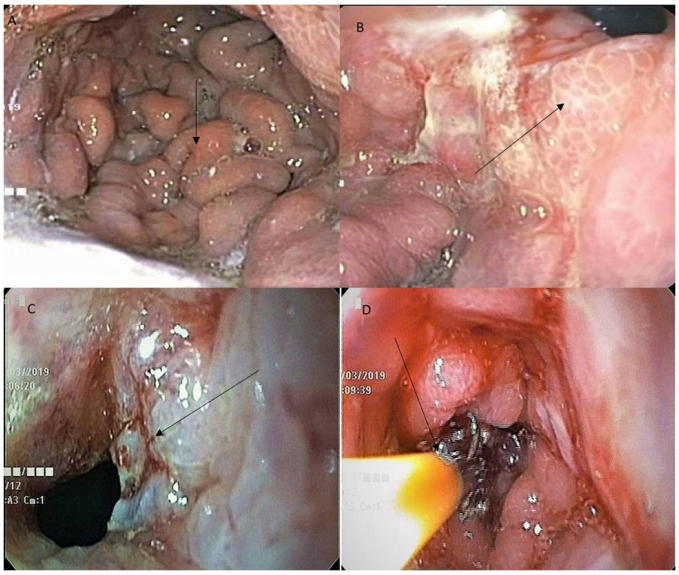

Figure (1A): Body and antrum (1B): (Fundus in retroflexed position) showing gastric mucosa with linitusplastica appearance on conventional white light esophagogastroduodenoscopy (red arrow). (1C): Conventional white light colonoscopy showing circumferential partial lumen occluding rectal growth (red arrow). (1D): Complete lumen occluding growth in the splenic flexure and biopsy forceps for tissue biopsy (red arrow).

Discussion

In patients with a gastric neoplasm there is also an increased risk of second tumor, mainly during the first year after the diagnosis of the index neoplasm, with an important decrease in survival[5]. The incidence

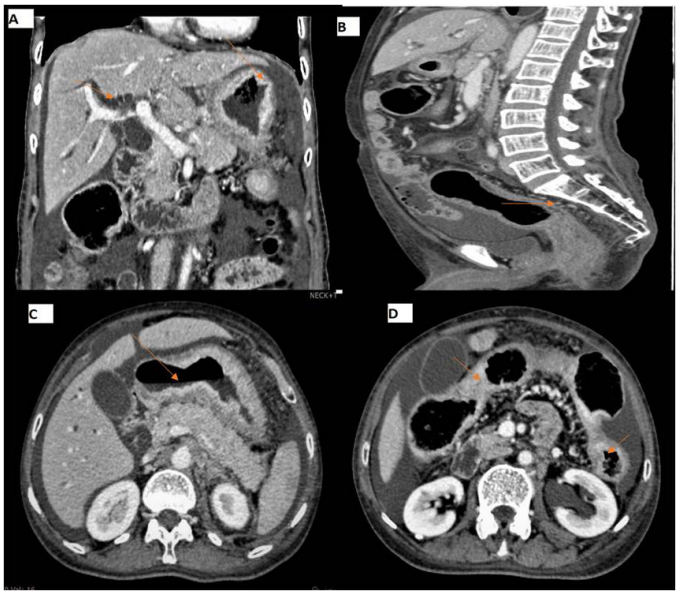

Figure (2A): CT abdomen demonstrating diffuse gastric wall thickening with strong contrast enhancement and a dilated common bile duct (CBD) with abrupt cut off at distal CBD (red arrow). (2B): CT abdomen demonstrating long segment concentric bowel wall thickening in rectum with perirectal infiltration and partial lumen occlusion and thickening at splenic flexure (red arrow). (2C): CT abdomen demonstrating gastric wall thickening with contrast enhancement and perigastric lymph nodes (red arrow). (2D): CT abdomen demonstrating transverse colon and splenic flexure thickening with pericolonic infiltration (red arrow).

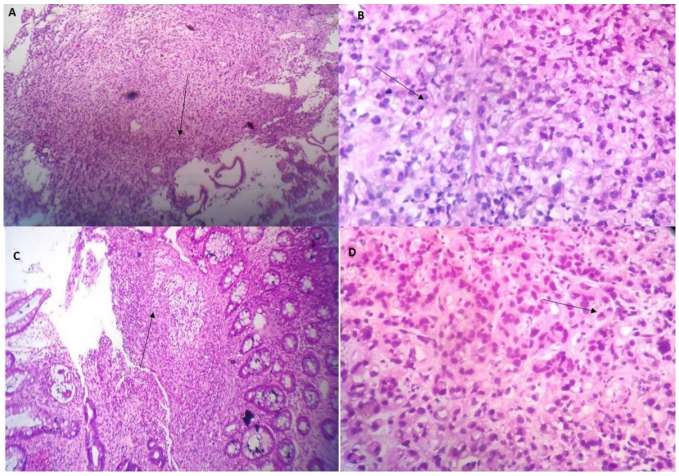

Figure (3A and 3B): (10x) (Stomach H and E stain) Intramucosal diffuse carcinoma with neoplastic cells displaying a pure signet ring cell phenotype within extracellular mucin pools. (3C): (H and E stain)-Poorly differentiated carcinoma with signet-ring cell features extending into the serosal surface involving the rectum. (3D): (H and E stain) (10x)-Majority of cellularity composed of single and clusters of poorly differentiated signet ring cells floating within extracellular mucin pools in rectal mucosa.

of synchronous or metachronous cancer in gastric carcinoma is 3.4%[6]. Synchronous triple neoplasms of gastrointestinal tract involving the stomach, common bile duct and colon is extremely rare. The median age at diagnosis of gastric cancer is 67 years (range, 37-84 years), 69 years for patients with synchronous tumors versus 60 years for those withmetachronous tumors[7]. Patients with synchronous GC and CRC present in older age, with higher comorbidities, and advanced cancer stage than with metachronous CRC and GC. The incidence of synchronous cancers is significantly higher in men than in women, and it also generally increased with age[8]. The presented patient clinical profile coincided with the epidemiological characteristics described in the literature. Signet ring cell cancer (SRCC) is a rare entity representing less than 14% of GC and 1% of CRC[9]. It is a subtype of poorly cohesive carcinoma (WHO classification)[10]. Due to decreased expression of E-cadherin, the signet cells do not adhere to each other leading to migration and invasion of adjacent tissues. In patients with gastric cancer diagnosed with MMPN, most

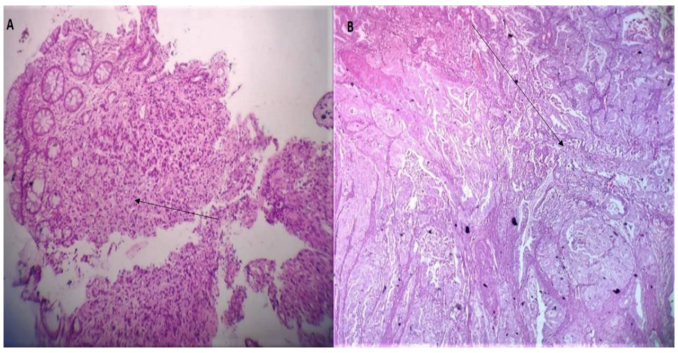

Figure (4A): (H and E stain)-Neoplastic cells infiltration involving the splenic flexureImage. (4B): (H and E stain) (10x)-Cholangiocarcinoma of extrahepatic bile duct (distal CBD)-moderately differentiated adenocarcinoma.

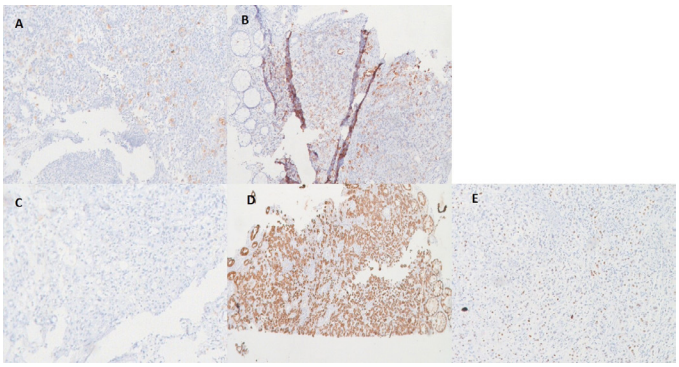

Figure 5: (20X)-Immunohistochemistry demonstrating gastric (A): and colonic carcinoma (B): with immunoreactivity for CK7 and gastric (C): showed absent reactivity to CK20 and colonic carcinoma (D): showed strong immunoreactivity to CK20. (E): CDX2 nuclear expression in colonic carcinoma.

frequent locations of second neoplasms are, in order of frequency: colorectal (19%), uterus and ovarian (16%) and breast (13%)[5]. Kibera *et al*. showed that the incidence of synchronous cancer with multiple gastric cancers was statistically higher than that of synchronous cancer with single gastric cancer[11]. In the 23 year study by Malgorzata GC patients with second primary were more commonly blood group O (50%) and blood group A (27%) and a significant association between older age and blood group O prevailed. Gastric cancer without second primary was associated with blood group O[12]. Another study found that 27% of patients with Gastric cancer with second primary was blood group O and the rest were blood group A who

were *Helicobacter pylori* positive[13]. Our patient was in the extremes of age with blood group O and *Helicobacter pylori* negative. There is need to include gastric cancer patients with blood group O as controls in the study of synchronous neoplasms.

The dominant symptoms in the patient addressed pointed towards gastric etiology and obstructive jaundice and the presence of colonic disease was incipient. In most of cases of patients with synchronous cancers, there was the dominance of obstructive colon symptoms, while the gastric disease symptoms were moderate or overlapping[14]. Recent studies indicate that after a diagnosis of GC, older patients in particular should be investigated for second malignancies. The detection of synchronous GC and CRC can be obtained by easily available diagnostic methods. Synchronous CRC was detected with a high prevalence of 4% by Saito *et al*. when colonoscopy was selected as the screening method of choice in gastric cancer patients. Saito *et al* detected synchronous colorectal adenoma (39%) and CRC (4%) in patients of GC who were older than 50 years through screening colonoscopy. Therefore, it is recommended that if possible, a colonoscopy screening is performed before treatment of patients older than 50 years with GC[15]. The use of colonoscopy in asymptomatic elderly men for CRC is beneficial to identify patients with synchronous colonic neoplasia[16]. CT colonography is valuable in those patients with stenosis that leads to incomplete colonoscopy. In our case scenario CT colonography guided us in detecting the transverse colon lesion due to an incomplete colonoscopy.

A favorable prognosis in early GC but a poor or similar prognosis for SRCC in advanced GC has been reported in literature[17,18]. Patients with multiple metachronous primary neoplasms showed better survival rates in contrast to patients with synchronous neoplasms[19,20]. Metachronous gastric and colon cancer is an independent predictor of survival and it had a better prognosis than synchronous cancer[21].

CDX2 expression is an excellent marker of adenocarcinomas arising in the GI tract, particularly colon and high levels (> 75% positive cells) of CDX2 expression were found almost exclusively in adenocarcinomas of the colorectum[22]. The CK7-/CK20+ pattern was identified in 65% to 95% of the colorectal adenocarcinomas and gastric cancers are CK7+ in different series. Few cases of colorectal carcinomas demonstrate CK7+ pattern[22,23]. The immunohistochemistry in our patient differentiated the colorectal cancer from metastatic gastric cancer and directed toward a synchronous malignancy. Patients with colorectal tumors with MSI (microsatellite instability)are usually young and have longer survival times than patients with tumors without MSI and correlated with the tumor location in the proximal colon[24]. Kim *et al*. in their study concluded that the presence of microsatellite instability (MSI) in gastric cancer may be a predictor of synchronous gastric and colorectal neoplasms. MSI-H (microsatellite high) GC prevalence in Asians is commonly < 10% of all GC cases[25]. The patient in our case had no family history of cancer, was in the extremes of age, had a distal colonic malignancy and capitulated to the aggressive nature of the neoplasm. The case highlights theneed for early diagnosis of synchronous cancer and awareness of clinicians about this aggressive form of tumors and enlightens the role immunohistochemistry in synchronous neoplasms.

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