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Case Report

Small bowel adenocarcinoma: revisited

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ABSTRACT

Small bowel malignancies are rare despite it representing 75% of the gastro intestinal (GI) length and 90% of the mucosal surface area. Even then small bowel adenocarcinoma (SBA) accounts for only 30-40% of all small intestine malignancies. Etiology is multifactorial and risk factors include hereditary mutations, inflammatory bowel diseases, coeliac disease. Presenting symptoms are vague and nonspecific and cannot usually be diagnosed by conventional upper and lower GI endoscopy as it is in an inaccessible location. This leads to delayed diagnosis and hence poor prognosis. Mainstay of treatment is surgical resection with adjuvant chemotherapy in advanced disease. We present a case study of a 74 years old woman who presented to the emergency department with small bowel obstruction and radiological features suggestive of underlying small bowel malignancy. She underwent urgent laparotomy with segmental small bowel resection and had intraoperative evidence of wide spread metastasis which was confirmed on subsequent tumor staging scans. She received adjuvant chemotherapy with complete metabolic response at one year post resection. SBA is generally diagnosed at advanced stage due to its anatomical location. Complete surgical resections should always be targeted. However, adjuvant chemotherapy plays a role in advanced disease even though clinical data of evidence is scarce.

Keywords: Small bowel malignancy, Small bowel adenocarcinoma, Small bowel resection, FOLFOX

INTRODUCTION

The small bowel forms 75% of intestinal length and 90% of the gastrointestinal (GI) surface.[1] Despite this primary small bowel malignant tumours are rare and only constitutes 1-3% of all GI tract malignancies and less than 2% of total malignancies.[2] Small bowel malignancy has four common histological types: carcinoid tumour (35-42 %), adenocarcinoma (30-40 %), lymphoma (15-20%) and sarcoma (10-15%).[3] In occurs in decreasing frequency from duodenum (64.5%), jejunum (20.5%), and ileum (15%).[4]

CASE REPORT

A 74-year-old woman presented to the emergency department with progressively worsening nausea and the bilious vomiting on a background of similar symptoms associated with anorexia and weight loss of 8 kg over the past 2 months. She had passed a bowel motion the day prior and was still passing flatus on day of admission. She never had abdominal pain. She did not have any other medical illness except for a previous laparoscopic appendicectomy. On her abdominal examination, she had gaseous distended abdomen which was soft and non-tender. Rest of her physical examination were unremarkable, and her vital signs were normal.

Her blood investigations were; WCC 18.3, neutrophils 15.3, CRP 218, urea 13.9, creatinine 202 (new), albumin 48, pH 7.4, lactate 1. A portal venous phase CT scan was performed which showed a transition point in the proximal jejunum with mural thickening and multiple

surrounding enlarged mesenteric and retroperitoneal lymph nodes (Figure 1 and 2).

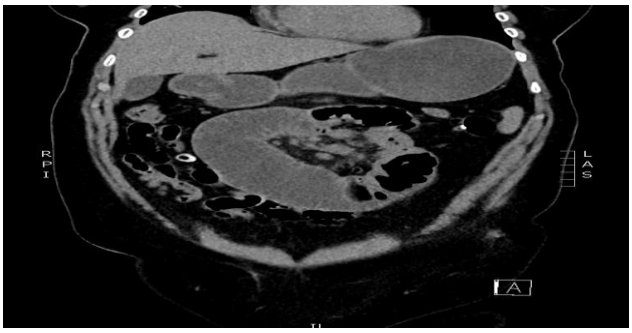

Figure 1: CT image of stricture in small bowel.

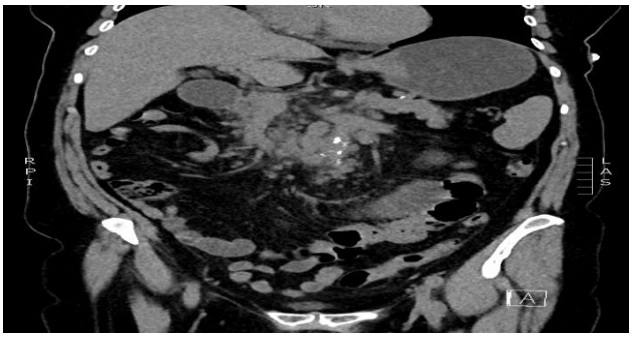

Figure 2: CT image of multiple enlarged lymph nodes.

She was initially managed conservatively with nasogastric tube, IV fluids and IV antibiotics. She passed a bowel motion on the following day. However due to possible features of malignancy on imaging, decision was made for exploratory laparotomy in the emergency operative list.

Operative findings were; proximal jejunal stricture 20 cm from DJ flexure with multiple abnormal mesenteric lymph nodes and multiple mattered para-aortic lymph nodes. The features were in keeping with a malignant small bowel stricture. There were a few tumour deposits on the omentum but no palpable liver metastasis. 20 cm length of involved small bowel was resected along with adjoining mesentery and lymph nodes. Samples of omental deposits were taken for histology. Small bowel continuity restored with side-to-side functional end to end anastomosis with TLC 75 linear stapler cutter. Mesenteric defect was closed with 3/0 PDS. She had an uneventful recovery and was discharge 5 days post operation

Histology confirms primary small bowel adenocarcinoma with the tumour cells showing positive staining for CDX2, CK19 and negative staining for TTF-1, pax 8, GATA3, and ER. The tumour extends to the serosal surface and 4 out of 5 lymph nodes were positive for tumour. Omental deposits were confirmed to be metastatic disease. Disease was staged at T4N2M1. CEA and CA 19.9 were later added on and came back as 2 and <5 respectively. She subsequently had a PET scan performed as an outpatient. It showed extensive nodal disease throughout the abdomen and pelvis with further mediastinal and left supraclavicular nodal disease involvement. In addition to omentoperitoneal metastases, there is a segment VIII liver metastasis and innumerable pulmonary metastases (Figure 4).

Patient was referred to the medical oncologist and has been started on palliative chemotherapy with FOLFOX (folinic acid, fluoroucil and oxaliplatin) and Avastin. After cycle 10, oxaliplatin was omitted and she continued with maintenance fluorouracil and Avastin. After cycle 27, Avastin was ceased due to proteinuria. She is currently on maintenance fluorouracil only. Under the medical oncologist, she has been getting surveillance PET scans and has shown complete metabolic response to therapy (Figure 5).

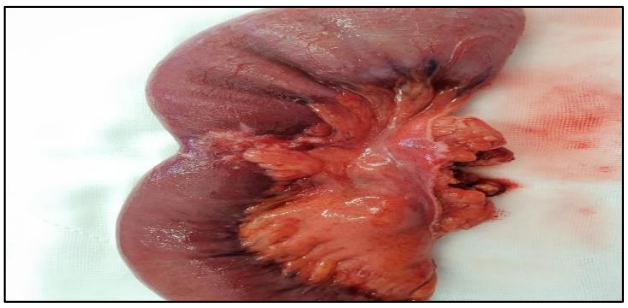

Figure 3: Resected specimen of stricture and enlarged mesenteric lymph nodes.

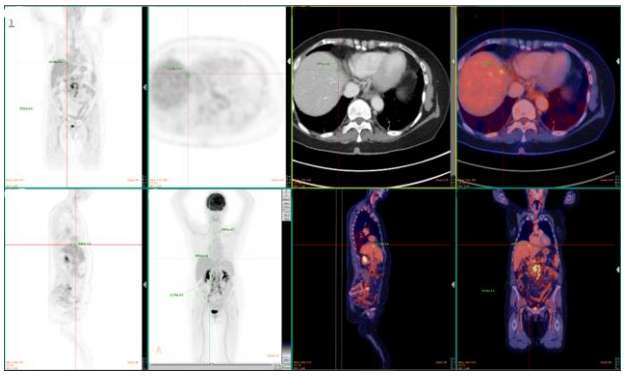

Figure 4: Pre chemotherapy PET scan.

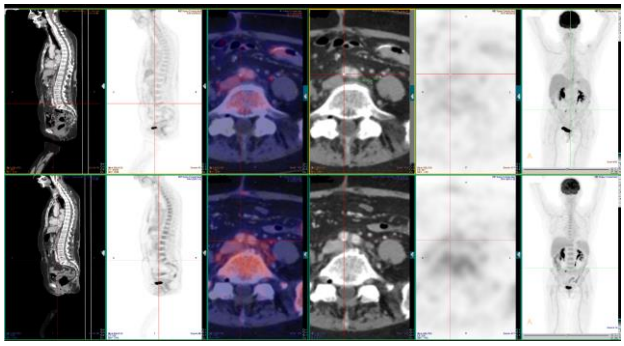

Figure 5: 1 year post chemotherapy PET scan.

DISCUSSION

The risk factors for small bowel malignancies are as follows;

Ethnicity

In the United States, African Americans are 1.6-1.8 times more likely to be diagnosed with small bowel malignancy compared to other ethnicities and also have a proportionally higher mortality.[5]

Age

The median age of diagnosis is 62 in the United states and this is comparable to the United Kingdom. After the age of 40, the risk begins to increase and does not level out until the age of 90.[5,6]

Sex

Males are more likely to be diagnosed with, and die from, small bowel malignancy than females. In the United States, the gender discrepancy in incidence is about 1.3:1 and in mortality about 1.6:1, suggesting lower survival rates among men.[5]

Hereditary mutations

Familial adenomatous polyposis (FAP) increases the risk of small bowel adenocarcinoma (SBA) by 330 times compared to the general population.[7] In a study of 1255 patients with FAP, about 5% had been diagnosed with SBA with half of it being found in the duodenum.[8] In fact, duodenal adenocarcinoma was the primary cause of death among FAP patients who had undergone a coloproctectomy.[9] Other predisposing mutations include lynch syndrome, Peutz-Jeghers syndrome, multiple endocrine neoplasia syndrome type 1, and neurofibromatosis type 1.

Inflammatory bowel disease (IBD)

The relative risk for SBA among those with Crohn's disease ranges from 17 to 41.[10] The cumulative risk is estimated at 0.2% after 10 years of Crohn's disease, but 2.2% after 25 years.[11] The SEER study suggested a lifetime risk of 1.6% of SBA among those with Crohn's disease, almost 3 times that of the average American.[12]

Coeliac disease

Has been shown to increase the risk of SBA and small bowel lymphoma. A British study of 395 cases of small intestine cancer found celiac disease was implicated in 13% of SBA cases (mostly in the jejunum) and 39% of lymphomas.[13]

SBA tend to present with vague and nonspecific (Table 1) symptoms. This generally leads to a delay in diagnosis and eventual treatment. An analysis of 77 cases has been done on this.[14] The delay in presentation to primary heath care physicians was 2 months; delay to appropriate investigation was 8.2 months and it was 12 months until definitive diagnosis was made.

There are multiple different modalities to investigate for small bowel malignancies. Barium contrast studies are simple yet an effective method with up to 83% detection rate.[15] For duodenal tumours, diagnosis can be made easily with an endoscopic examination. However, as the tumour goes further distally, it can be a challenge to make an endoscopic diagnosis. Push enteroscopy is not readily available in most centres and may not visualise the entire small bowel mucosa. Video capsule endoscopy also has value in diagnosis and has been shown to be more accurate than push enteroscopy.[16] Computer tomography (CT) has the advantage on detecting extra mucosal spread, lymphadenopathy and distant metastases. Neoplastic disease is suspected when small bowel thickness exceeds 1.5 cm (normal:4 mm),[17] discrete mesenteric masses are >1.5 cm in diameter or there is eccentric or asymmetrical thickening of the small bowel.[18] The accuracy of CT in detecting small bowel malignancy is approximately 47%.[18] Magnetic resonance enteroclysis (MRE) has been shown to have good sensitivity and specificity in a retrospective study of 67 patients with 2 separate readers. Sensitivity of 87.5 and 91.6%, with specificity of 93 and 97.6% respectively.[19]

Table 1: Symptoms and signs of small bowel malignancy.

Symptoms	Frequency (%)
Pain	15-58
Nausea and vomiting	10-39
Weight loss	10-42
Anaemia	18-24
Abdominal mass	8-21
Abdominal tenderness	8
Distension	8
Hepatomegaly	8
Asymptomatic/normal examination	10-42
Diarrhoea/constipation	3-5
Jaundice	3-18

The mainstay of treatment of SBA is resection. This may be curative or palliative. In early duodenal tumours, endoscopic resection can be performed. This is either with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). EMR is a procedure that uses a snare and if required, injection of fluid to the submucosa space to lift the lesion. ESD is performed by injecting fluid into the submucosa space and creating an incision around the perimeter of the lesion, and then dissecting the lesion from the deeper layers achieving en bloc resection. EMR is more commonly used in duodenal lesions. This is partly due to ESD being more technically challenging and equipment not being readily available in

some centres. Lesions over 20mm tend to require piecemeal resection with EMR, which causes a higher rate of recurrence.[20] In this instance ESD should be considered.

For more advanced duodenal tumours, a pancreaticoduodenectomy should be performed for a tumour in the second segment of the duodenum or for an infiltrating tumour in the proximal or distal duodenum.[21] Additionally, resection of the peri-duodenal, peri-pancreatic, and hepatic lymph nodes should also be performed, as well as resection of the right side of the coeliac and superior mesenteric arteries. A duodenal resection alone could be performed for a proximal duodenal tumour or a distal duodenal tumour with no infiltration of adjacent organ, despite the fact that this procedure is associated with poor prognosis.[22,23] A complete resection is preferred, as incomplete resections are strongly associated with poor prognosis.[24] For jejunal and ileal tumours, a complete segmental resection with adjacent lymph nodes and jejuno-jejunal or ileo-ileal anastomosis should be performed. If the last ileal loop or Bauhin's valve are involved, an ileocecal or right hemicolectomy should be performed with ligation of the ileocolic artery so as to allow for lymph node resection. In palliative cases, surgery should still be considered to avoid obstruction or to prevent recurrent GI bleeding.

The 5-year overall survival for all SBA patients ranges from 14-33%.[1] Prognosis is related to the stage of the disease. 6-12% of the patients have stage I disease at diagnosis, 27-37% stage II, 21-27% stage III and 32-37% stage IV. Compared to colon cancer, where 20% of patients were diagnosed at stage 1 and 20% at stage 4.[25] This reflects the delay in diagnosis with small bowel adenocarcinoma. The 5-year overall survival for specific stages in SBA is 50-60% for stage I, 40-55% for stage II, 10-40% for stage III and 3-5% for stage IV.[26]

Table 2: Ongoing clinical study of systemic therapy for SBA.

Drug regimen	Phase	Type of adenocarcinoma	Line of treatment	N	NCT identifier
5-FU vs FOLFOX vs observation	III	Small bowel	adjuvant	100	NCT02502370
Gemcatibine, oxaliplatin and erlotinib	I	Biliary, pancreatic, duodenal and ampullary	1st	28	NCT00987766
Panitumumab	II	Small bowel and ampullarya	1st	27	NCT01202409
Nab-paclitaxel	II	Small bowel	≥2nd	10	NCT01730586
Pembrolizumab	II	Small bowel	≥2nd	40	NCT02949219
Avelumab	II	Small bowel	≥2nd	25	NCT03000179

The relapse pattern for SBA is predominantly systemic.[21] At present, no randomised studies evaluating the benefit of adjuvant chemotherapy in SBA has been completed. Data are gathered from retrospective studies and extrapolation from colorectal cancers. Table 2 shows the current ongoing clinical studies of systemic therapy for SBA.[27] The BALLAD trial is an international trial currently in phase 3 which compares adjuvant treatment with either 5-fluorouracil and leucovorin or a combination of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) compared to observation only. In advanced disease i.e., unresectable or metastatic, there has been multiple retrospective studies demonstrating a significant survival benefit for systemic chemotherapy.[28-34] In these studies, overall response rates of 6-50% and disease control rates of 37-67% were observed. Systemic chemotherapy was associated with significantly higher median progression-free survival and overall survival (6 months vs. 1 month and 9-19 vs. 2-13 months, respectively). Although, retrospective comparative studies may be significantly biased and the number of patients per regimen was usually considerably small, it seems that the best results in means of response, survival and toxicity have been recorded for FOLFOX.[34-38] This has been shown by our case study, who has demonstrated excellent response to the FOLFOX regime.

CONCLUSION

SBA is often diagnosed at an advanced stage due to atypical and late symptoms, its low index of suspicion, difficult endoscopic access and poor detection by radiological imaging. Surgical resection is the mainstay of therapy for locoregional disease and complete resection offers the best prognosis. The exact role of adjuvant chemotherapy is unclear at present but it seems that it is associated with significantly better outcome in more advanced stages of disease. The combination of a fluoropyrimidine and oxaliplatin (FOLFOX or CAPOX) seems to be the most appropriate front-line systemic chemotherapy for disseminated disease.

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