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Original Article

Surgery Section

Varied Clinical Presentations of Small Bowel Malignancies Posing Diagnostic Uncertainty and their Management

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ABSTRACT

Introduction: Incidence of small bowel malignancy is lower compared to other parts of gastrointestinal tract for various reasons explained in literature. Adding to it, small bowel is not an easily accessible area by the commonly available endoscopic modalities. Clinical presentation may vary due to obscure behaviour of disease. Hence, a high index of suspicion is required for early diagnosis and treatment.

Aim: To evaluate the clinical behaviour of small bowel malignancies, its histological characteristics and to identify optimal imaging modality for early diagnosis and to assess its prognostic behaviour.

Materials and Methods: Retrospective data was collected of all patients who were diagnosed and treated as small bowel malignancy. The patient's medical records were reviewed. A literature review was also conducted on its clinical, pathological and treatment aspects by using terminologies mentioned in the heading keywords on PubMed, Google scholar. Total of 12 cases were managed over a period of four years with varied clinical presentations both in elective and emergency settings.

Paediatric cases and benign tumours were excluded from the evaluation. Those diagnosed with small bowel cancer and not willing for any form of treatment were not included. Only those who were treated under department of surgical oncology and completing atleast 2-3 monthly follow ups were included.

Results: Seven of the cases seen in our series were above age of 50 years, with male sex predominance. Jejunum was the most common subsite involved, with GIST being the most common histology. In the present series, majority presented with pain abdomen, two cases had chronic anaemia, one case presenting with mass per abdomen, and one case presented to emergency department with shock and massive haematemesis. Only in one case, small bowel was involved secondary to metastases from lung sarcoma. Resection and anastomosis was done in majority of cases and in one case of jejunal lymphoma infiltrating distal pancreas, en bloc resection of small bowel, distal pancreas and spleen was done.

Conclusion: Rarity of incidence, vague presentation, inaccessibility to commonly available endoscopic techniques, lack of accuracy in assessment of small bowel by commonly available simple imaging modalities makes the early diagnosis difficult. Hence, we hereby propose to consider small bowel as one of the primary source in case of uncertain clinical situations described above, due to the fact that it can be easily treated surgically in most of the situations.

Keywords: GIST, Lymphoma, Neuroendocrine carcinoma, Sarcoma, Small intestine

INTRODUCTION

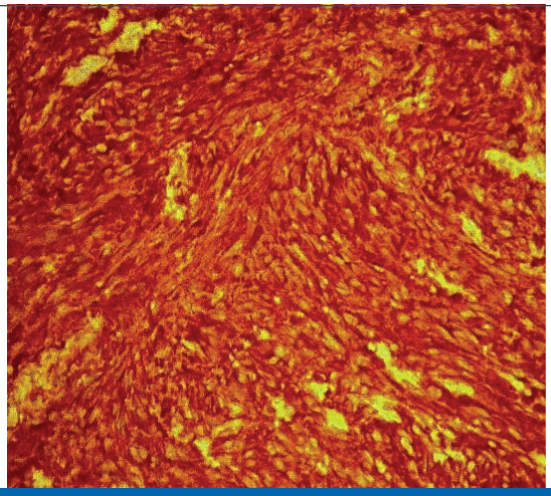
Small bowel malignancy accounts for less than 3% of gastrointestinal tract malignancies [1]. Histology wise, adenocarcinoma, carcinoid, stromal tumour accounts for 33%, 44%, 17% respectively of total small bowel malignancies [2], while primary gastrointestinal lymphoma constitutes only about 1%-4% of all gastrointestinal malignancies and is usually secondary to the widespread nodal diseases and most commonly involves stomach followed by small intestine and ileocecal region [3]. Risk factors proposed are alcohol [4], smoking [5], Familial adenomatous polyposis, lynch syndrome, peutz-jeghers syndrome, crohns disease [6]. Incidence of small bowel malignancies is rare when compared to colon cancer. Various reasons for low incidence being short contact time between small intestine and dietary carcinogens compared to the colon, shorter transit time, low concentrations of aerophilic grampositive bacteria noted in small bowel. The density of the microbiota is lower in small bowel than in the colon, where the microbiota produces xenobiotic transformation during which bile salts are deconjugated and dehydroxylated to form desoxycholic acid, which is a potential tumour promoter [7]. The epithelial cells of the small bowel are equipped with microsomal enzymes, including the benzopyrene hydroxylase, that may protect them against food-derived carcinogens [8]. The 5-year relative survival rate was 37.4% in one of the studies and it varied between 56.8% for endocrine tumours and 17.8% for sarcoma [9]. Methods of diagnosing the disease described in the literature are barium meal; contrast enhanced computed tomography, push enteroscopy, double balloon endoscopy, capsule endoscopy, intraoperative endoscopy, PET CT scan. Most of the cases can be managed by resection and anastomosis followed by adjuvant treatment when indicated.

MATERIALS AND METHODS

It is a retrospective analysis done in the department of surgical oncology with review of medical records from June 2015 to June 2018. Retrospective data was collected of all patients who were diagnosed and treated as small bowel malignancy. A literature review was also conducted. Review was conducted on its clinical, pathological and treatment aspects by using terminologies mentioned in the heading keywords on databases PubMed, Google scholar and also through focused search using terminologies small bowel tumours and small bowel malignancy. Total of 12 cases were managed over a period of four years from June 2015-June 2018. Paediatric cases and benign tumours were excluded from the evaluation. Those diagnosed with small bowel cancer and not willing for any form of treatment were not included. Only those who were treated under department of surgical oncology and completing atleast 2-3 monthly follow ups were included and all the data was retrospectively evaluated. Ten cases were operated

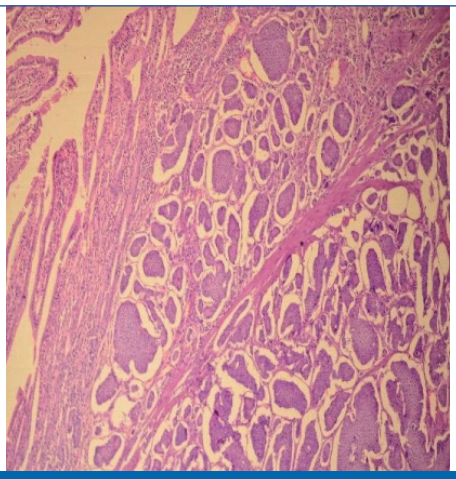
electively and one case operated in emergency setting. One case of duodenal lymphoma went to another hospital for a second opinion and was lost for follow up subsequently. Imaging was done in 11 cases. Upper GI endoscopy was done in eight cases and Colonoscopy was done in three cases when indicated. Intestinal resection and anastomosis was done in 10 cases and in one case of jejunal lymphoma infiltrating distal pancreas, en bloc resection of small bowel, distal pancreas and spleen was done. No significant postoperative complications were noted. Adjuvant treatment was given as per guidelines after tumour board discussion.

Case 1: Presented with mass per abdomen of three months duration. Imaging was suggestive of 15x15 cm growth probably arising from small bowel. Image guided biopsy and immunohistochemistry was suggestive of GIST. Neoadjuvant imatinib was given for four months and was operated. Patient is presently on adjuvant treatment [Table/Fig-1].



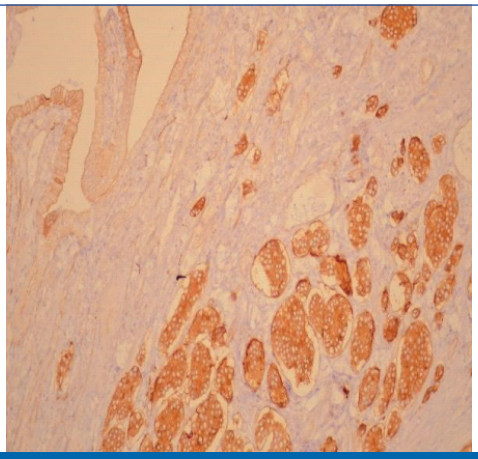
[Table/Fig-1]: IHC showing CD 117 positivity (40x).

Case 2: Presented with chronic pain abdomen of six months duration. USG abdomen was normal. CT abdomen was suggestive of thickening of small bowel for length of 18 cm with wall thickness of 13 mm. Exploratory laparotomy was suggestive of growth arising from small bowel, with final HPR was suggestive of well differentiated neuroendocrine tumour not involving serosa or lymph nodes. No adjuvant treatment given and presently is on follow up for 16 months without recurrence [Table/Fig-2,3].

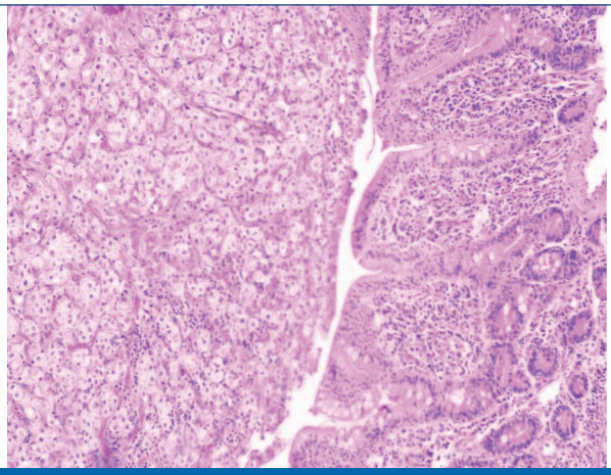


[Table/Fig-2]: A 10X H&E showing small bowel mucosa infiltrated by tumour.

Case 3: A 47-year-old female diagnosed case of sarcoma left thigh with pulmonary secondaries presented with h/o dizziness and melaena to emergency department. On evaluation, found to have bleeding tumour from jejunum. No imaging was possible as the patient's vitals were not stable. On Exploratory laparotomy, tumour arising from mid jejunum was adherent to retroperitoneum and was resected without any complication. Final histology was suggestive of alveolar soft part sarcoma which was resembling that of primary sarcoma arising from thigh with lung metastases. Patient is presently on palliative chemotherapy [Table/Fig-4].



[Table/Fig-3]: Synaptophysin positivity (20 x).



[Table/Fig-4]: The tumour cells are polygonal with abundant granular eosinophilic cytoplasm arranged in nests of tumour cells separated by thin fibrous septae Central degeneration and loss of cohesion of cells in the center of the nests creates the characteristic "pseudoalveolar" pattern (20x).

Case 4: A 60-year-old female with chronic anaemia of three years duration was being evaluated under department of haematology. Upper GI endoscopy and colonoscopy was normal. Had received multiple blood transfusions and iron supplements. MRI abdomen and pelvis was suggestive of mass probably arising from proximal jejunum. On surgical exploration, tumour was arising from proximal jejunum and final histopathology was suggestive of Gastrointestinal stromal tumour and is presently on adjuvant imatinib.

Case 5: A 62-year-old female presented to department of gynaecology with mass in left iliac fossa.

Ultrasound abdomen was suggestive of mass probably arising from left adnexa. On exploration, mass was arising from ileum and surgical oncology consultation was sought. Final HPR was suggestive of GIST and is presently on adjuvant treatment.

Case 6: A 64-year-old male presented to department of gastroenterology with history of vomiting since two weeks. Upper GI endoscopy was suggestive of ulceroproliferative growth arising from duodenum. Biopsy was suggestive of Diffuse large B-Cell lymphoma. Patient was advised for gastric bypass and chemotherapy. Patient went to another hospital for second opinion and was lost for follow up.

Case 7: A 23-year-old male presented with bilious vomiting and weight loss to department of gastroenterology. Upper GI endoscopy was normal. CECT abdomen was suggestive of mass probably arising from small bowel/pancreas. On exploration, growth was arising from jejunum infiltrating pancreas. Distal pancreatectomy with intestinal resection and anastomosis was done. Final histopathology

was suggestive of Lymphoma arising from intestine. Patient was referred to medical oncology team for further management.

RESULTS

Majority of the cases in our series were of male sex (seven) and above age of 50 years (10). Jejunum was the most common subsite involved, with GIST being the most common histology. In our series, majority presented with pain abdomen, two cases had chronic anaemia, one case presenting with mass per abdomen and one case presented to emergency department with shock and massive haematemesis. Only in one case, small bowel was involved secondary to metastases from lung sarcoma. Resection and anastomosis was done in 10 cases and in one case of jejunal lymphoma infiltrating distal pancreas, en bloc resection of small bowel, distal pancreas and spleen was done. No major post operative complications were observed. Adjuvant treatment with Tab. Imatinib 400 mg was advised for those cases diagnosed as gist and CHOP (Cyclophosphamide, hydroxyadriamycin, oncovin and prednisolone) regimen was used for lymphoma cases. Survival duration was measured from time of diagnosis to last follow up. Ten patients were under regular follow up. Nine patients were without any recurrence till date and one patient is on palliative chemotherapy, while two patients are lost for follow up. Clinicopathological profile and tumour characteristics are shown in [Table/Fig-5,6].

Case	Age in years	Sex	Subsite	Clinical presentation	Histopathology	Primary (P)/Metastatic (Met)	Staging (TNM)	Treatment	outcome
1.	68	M	Jejunun	Abdominal mass	Gist	P	T2N0M0 (H)	RA+TP	A
2.	75	F	Ileum	Pain abdomen	NEC	P	T3N0M0	RA	B
3.	65	F	Ileum	Pain abdomen, weight loss	Gist	P	T3NOMO (H)	RA+TP	A
4.	59	M	Jejunum	Chronic anaemia	Gist	P	T3N0M0 (H)	RA+TP	A
5.	47	F	Jejunum	Haematemesis with shock	Alveolar soft part sarcoma	Met	T4NOM1	RA+CT	R
6.	60	F	Jejunum	Chronic anaemia	Gist	P	T4N0M0 (H)	RA+TP	A
7.	68	M	Ileum	Melaena	Gist	P	T3N0M0 (H)	RA+TP	A
8.	62	F	Ileum	Mass per abdomen	Gist	P	T3N0M0 (H)	RA+TP	A
9.	64	M	Duodenum	Vomiting	Lymphoma	P	2E*	X	
10.	60	M	Ileum	Pain abdomen, melaena	Lymphoma	P	1E*	RA+CT	C
11.	23	M	Jejunum	Bilious vomiting, weight loss	Lymphoma	P	2E*	DP+RA	D
12.	62	M	Jejunum	Pain abdomen	NEC	P	T3N0M0	RA	B

[Table/Fig-5]: Clinicopathological profile of representative cases.
M: Male; F: Female;GIST: Gastrointestinal Stromal Tumour; NEC: Neuroendocrine Carcinoma; A: Presently on adjuvant Imatinib 400mg without any recurrence till date; B: On regular follow up (No chemo-therapy given, as it was not indicated); C: Completed chemotherapy and presently on follow up; D: Defaulted treatment and was lost for follow up; R: On palliative chemotherapy; X: Lost for follow up; RA: Resection and Anastomosis; TP: Targeted therapy with Tab; Imatinib 400mg.H: High mitotic rate; *- Ann arbor staging system was used

Grade	(n)	Stage	(n)
Well	2	1	1
Moderate	-	2	4
Poor	1	3	6
Not applicable	9**	4	1

[Table/Fig-6]: Tumour characteristics.
**- Mitotic rate was used for gist and not applicable for lymphomas

DISCUSSION

Approximately, about 75 percent of the length and over 90 percent of the surface of gastrointestinal tract is represented by small bowel, however, small bowel malignancy accounts for only about 3 percent of all gastrointestinal tract neoplasms [10,11] due to various reasons described in the introduction. Duodenum and jejunum are most commonly affected by adenocarcinoma which represents about two thirds of duodenal neoplasms [12].

Carcinoid tumours are the most common malignant neoplasms of the SI, while carcinoid tumours are more commonly found in the ileum [13]. Ileum is the most common site (60%-65%) involving small intestine lymphoma followed by jejunum (20%-25%) [14]. If the carcinoid tumour extends beyond small bowel, it leads to desmoplastic reaction in mesentry, which appears as tethering, angulation or fixation of small bowel on imaging [15]. Criteria used by Dawson IM et al., is used for labeling primary gastrointestinal lymphoma [16], while Ann Arbor staging with modification is employed to stage gastrointestinal lymphoma, AJCC TNM Staging is used for adenocarcinoma, Gist and neuroendocrine tumour. Disadvantage of inaccessibility of small bowel by commonly done endoscopic techniques can be overcome by use of other modalities like push enteroscopy, capsule endoscopy, Contrast enhanced CT scan (CECT), PET-CT scan.

CECT scan has high sensitivity (81%-94%) and specificity (96%) for determining the level and cause of small bowel obstruction and is the investigation of choice in such situation [17]. Ultrasound imaging is reliant on operator skill and experience and may also fail to fully delineate complications and exclude disease in deep abdominal loops [18]. MR enteroclysis has a high accuracy in excluding inflammatory and neoplastic disease and incase of a negative MR enteroclysis, an arteriovenous malformation is likely to be the cause of bleeding and enteroscopy may be required [19]. MR enteroclysis has been proposed to be more sensitive than CT enteroclysis for detecting mucosal lesions of the small bowel [20,21]. Capsule endoscopy is the another option available with limiting factors being availability, inaccuracy for imaging proximal segment of bowel due to rapid transit time and bile and/or bubble artefact, also poor description of large lesion in distal bowel and chances of capsule retention in case of obstructive lesions [22,23]. PET/CT is useful in initial diagnosis, disease staging, evaluating response to treatment, and restaging [24].

Most of the cases reported were of elderly age group [25,26]. Majority of the cases seen in the present series were above age of 50 years, with male sex predominance, which is in agreement with study done by Mirna et al., [25-27]. CECT was done in 10 cases, Magnetic resonance imaging was done in one case and no imaging was possible in one of the case. Ultrasound scan was done as the initial imaging modality in three cases, of which, failed to pick up the disease in two cases and was able to hint at the possible site of pathology in one case. CECT was able to pick up the diagnosis in all 10 cases and was found to be more useful. PET-CT scan was done in one of the case who was on adjuvant Imatinib during follow up period. Jejunum was the most common subsite involved, with GIST being the most common histology in the present series unlike the other published series, where ileum was the most common site involved [27,28] with lymphoma, adenocarcinoma and carcinoid tumours being the commonly reported histologies [27,28], while the present study is in agreement with case series reported by Alves Junior AJT et al., [25]. Lymphoma was the second most common

histology observed in our series. Histopathological features are shown in [Table/Fig-2] (small bowel mucosa infiltrated by tumour), Immunohistochemical features of GIST is shown in [Table/Fig-1] (CD117 positivity). Synaptophysin positivity for neuroendocrine carcinoma is shown in [Table/Fig-3], and characteristic pseudoalveolar pattern of alveolar soft part sarcoma is shown in [Table/Fig-4]. Commonly described presentations in the reported cases are melaena, pain and distension of Abdomen [25,26], iron deficiency anaemia [29,30], abdominal cramps and signs of intestinal obstruction [25,31], unexplained diarrhea [32]. In the present series, majority presented with pain abdomen, two cases had chronic anaemia, one case presenting with mass per abdomen and one case presented to emergency department with shock and massive haematemesis. Only in one case, small bowel was involved secondary to metastases from Thigh sarcoma. Bidirectional endoscopy have failed to diagnose the cause in one of the recently reported case series [26], while in one retrospective study of large series of patients who underwent capsule endoscopy for various reasons, only seven cases of malignant small bowel tumours were diagnosed, with mean age of 50 years [23]. Such rarity is the incidence. In our series, similarly bidirectional endoscopy was able to detect the site of pathology in only two cases, while CECT scan was able to pick up the site of pathology in 10 cases. Similarly, CT scan abdomen was able to hint at the diagnosis where bi-directional endoscopy have failed in the reported case series [25,29]. Majority of the cases (seven) presented in advanced stage, which matches that of the reported studies [27]. Since mitotic rate was used in latest AJCC staging system, rather than traditional grading system and no grading system was applicable for lymphomas, grading was applicable in only three cases. All the cases were operated in elective setting except in one case, which is unlike the study reported by Haoues N et al., [28].

Resection and anastomosis was done in majority of cases and in one case of jejunal lymphoma infiltrating distal pancreas, en bloc resection of small bowel, distal pancreas and spleen was done. No significant postoperative complications noted. Adjuvant treatment given was given when indicated and most of the cases are under Follow up. Clinical diagnosis was delayed or was not possible in few cases due to the fact that in one of the case, patient was in unstable condition and imaging was not possible, wherein push enetroscopy was attempted, but the field was obscured by bleeding. Another case was evaluated for long time in department of haematology, but on imaging, tumour was found involving bowel loops. Chronic anaemia for evaluation was the situation in another case, where in both upper GI endoscopy and colonoscopy failed to demonstrate the lesion. And on imaging with MRI, lesion was found in jejunal loop. In few cases presenting with pain abdomen, Ultrasound abdomen was not helpful. Hence, higher imaging modality was used. With this background, in certain clinical situations like chronic anaemia where cause cannot be found out, or in case of chronic pain abdomen, especially in elderly age group which cannot be fitted into any clinical diagnosis, higher imaging modality needs to be considered with small bowel being possible primary source. Stage and grade of the tumour, adequate surgery with proper lymph node clearance when indicated and appropriate adjuvant therapy determines the long term survival.

CONCLUSION

Rarity of incidence, vague presentation, inaccessibility to commonly available endoscopic techniques, lack of accuracy in assessment of small bowel by commonly available simple imaging modalities makes the early diagnosis difficult. Hence, we hereby propose to consider small bowel as one of the primary source in case of uncertain clinical situations described above, due to the fact that it can be easily treated surgically in most the situations, and also due to the fact that no specific tumour marker is available to hint at the diagnosis.

LIMITATION

Small sample size, short follow up period, single center study is the main limitations of our study. Further comparative studies are needed to evaluate mainly the significance of higher imaging modality and also the ideal diagnostic modality for early diagnosis of small bowel pathologies.

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