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Review Article

Neuroendocrine Tumour of the Ileum Presenting As Intestinal Obstruction in a 23 yr Old Female: A Case Report and Literature Review

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Abstract
Primary small bowel tumors are rare and constitute only 1-3% of GI malignancies. Neuroendocrine tumors are rare tumors that arise from enterochromaffin cells in GI Tract. These may present with non-hormonal features due to partial obstruction of bowel or with hormonal features due to secretion of serotonin and other biochemical substances into circulation. WHO in 2010 classified these tumors according to Ki 67 index and mitotic count which is believed to be a useful prognostic factor and related with tumor size, invasion and metastasis. Treatment is mainly surgical comprising of segmental resection of small bowel with associated lymph node clearance.
We present a case of a who grade 2 neuroendocrine tumor presenting in a 23 year old female as intestinal obstruction without metastasis. We are reporting this case because of early age of onset and its presentation as intestinal obstruction which lead to early diagnosis of the disease before it metastasised, hence improving the prognosis. Review of literature done to emphasise the clinicopathological features, diagnosis and treatment of the disease.

Introduction

Primary tumours of small intestine are extremely rare and constitute 1-3% of all gastrointestinal intestinal (GI) tract malignancies.[1] These are most commonly diagnosed after the 5th decade of life with peak occurrence in the 6th and 7th decades.[2]
Neuroendocrine tumors (NET) are neoplasms of enterochromaffin cells which display neuroses-retory capacity and may result in the carcinoid syndrome.[3] These tumors are uncommon but the most common primary tumors of the distal small intestine. These usually do not grow to a big size to cause intraluminal obstruction, but they usually cause obstruction by local desmoplastic reaction.[4]
We present a case of a 23yr old female who presented in emergency as intestinal obstruction

due to a WHO grade 2 neuroendocrine tumor present in proximal ileum. We present this case due to its rarity and clinical significance.

Case Report

A 23-year-old female presented to us in casualty with pain upper abdomen severe and colicky in nature, associated with vomiting and distension of abdomen since 3 days. Patient had history of on and off pain abdomen for 3 months, also associated with altered bowel habits (in form of alternating diarrhea and constipation) with decreased appetite. No history of associated fever, jaundice, weight loss or GI bleed was there. Patient was diagnosed as Kochs abdomen and was started on antitubercular medicine since 3 months from a private hospital.

General physical examination was unremarkable.

On local examination abdomen was grossly distended, Tenderness was present in periumblical area, tympanic note was present on percussion, b/l flank dullness was present, shifting dullness was positive and there was visible peristalsis. Per rectal examination was within normal limits.

Other systems were within normal limits.

A clinical diagnosis of acute intestinal obstruction was made, a ryles tube inserted and routine blood investigations with chest and abdominal x rays with ultrasound abdomen was ordered. All haematological investigations were within normal limits. Abdominal x rays showed multiple air fluid levels and dilated bowel loops. On usg abdomen e/o dilated bowel loops with calibre of small bowel loops = 3.3cm was seen.

A CECT abdomen done to ascertain the cause of intestinal obstruction, showed – jejunal gut loops were dilated with maximum calibre of 42mm. distal gut loops are collapsed. There was heterogeneously enhancing growth in relation to proximal ileum with CT value of 80-140 HU with size of 2.1 X 2.8 cm. (Fig 1) Subcentimetric lymph nodes seen in prepara-aortic region with free fluid in pelvis.

Patient was taken up for emergency surgery to relieve intestinal obstruction. On opening abdomen proximal small bowel was dilated upto around 12cm in calibre whereas distal small bowel and large bowel was collapsed. There was a circumferential growth 3 X 2cm in size, hard, approx. 150 cm proximal to ileocaecal junction (Fig 2). Adjacent structures were not involved. No liver metastasis, omental/mesenteric/ pelvic deposits or abdominal lymphadenopathy were seen. Resection of the growth bearing segment with margins of approximately 10cm both proximally and distally with side to side anastomosis was done (Fig 3).

Biopsy revealed - Section of small bowel with presence of a neoplasm comprising of nests of cells with vesicular nuclei and moderate amount of cytoplasm (Fig 4). 5-8 mitosis/10hpf noted. No areas of necrosis present. Tumor seen infiltrating up to the serosa. Resection lines free from tumor invasion. Mesenteric lymph nodes free from tumor deposits.

On IHC – CD 34 – Negative, CD 117 – Negative, CD 45- Negative, Pan Cytokeratin – focal weak positive, Vimentin – positive, KI- 67 – 10-12%, Smooth muscle actin – Negative, Desmin – negative, synaptophysin – positive and chromogranin – positive.

So a final diagnosis of who grade 2 neuroend-ocrine tumor of proximal ileum was made.

Follow up after 1-month patient is doing well with no complications.

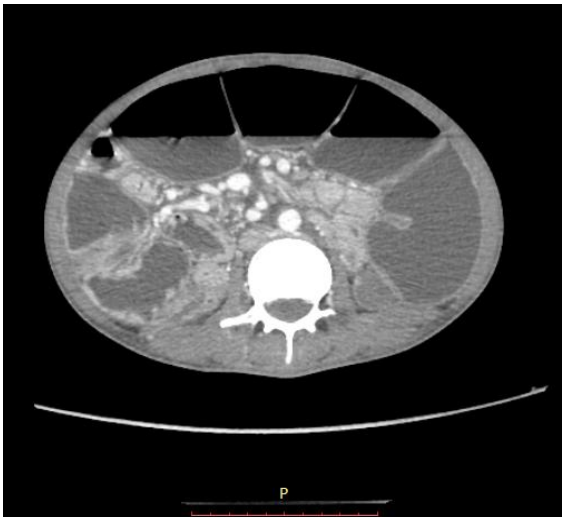

Fig 1: CECT abdomen of the patient

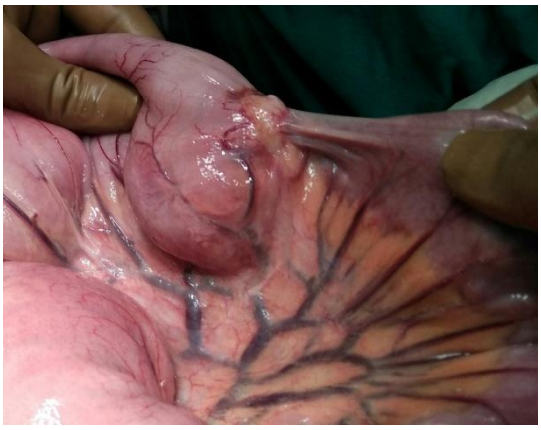

Fig 2: Intraoperative photograph showing the growth

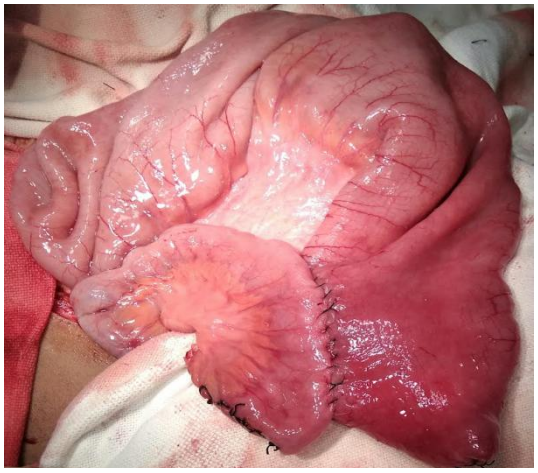

Fig 3: Resection with side to side anastomosis done

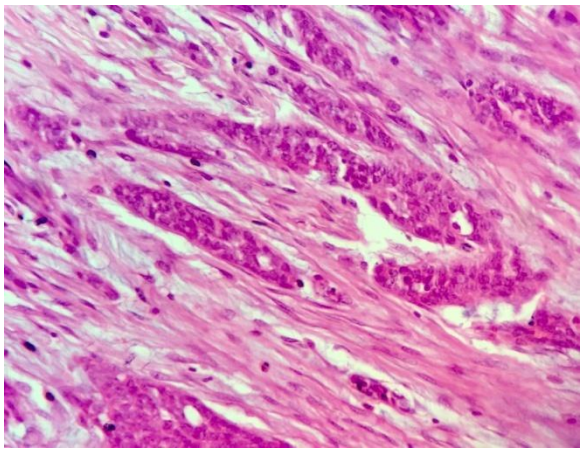

Fig 4: Histopathological examination of the tumor showing nests of cells

Discussion

Although the small bowel represents 75 % of the length of the GI tract and 90 % of the absorptive mucosal surface area, tumours of the small bowel are rarer than other GI malignancies.[5]

The possible explanations include lumen of small bowel is largely free of bacteria so bacterial metabolites implicated in genetic alterations are absent, dilute character and relatively rapid transit of small bowel contents, reducing exposure to luminal carcinogens, high levels of luminal IgA and greater distribution of lymphoid tissue in small intestinal epithelium, high level of benzpyrene hydroxylase produced by enterocytes of brush border epithelium that detoxifies carcinogens.[6]

Small bowel cancer has four common histological types: adenocarcinoma (30–40 %), neuroendocrine tumour (35–42 %), lymphoma (15–20 %), and sarcoma (10–15 %).[7]

Neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract were originally called carcinoid tumors (Karzinioide) by Oberndorfer.

He noted from his autopsy work that they were often multiple, had less gland formation than adenocarcinomas, and initially appeared to be harmless.

NETs from the GI tract (67%) are more common than the ones from tracheobronchial tree (23.5%).In the GI tract these arise from the enterochromaffin cells of Kulchitsky i.e. neural crest cells situated at the base of crypts of Lieberkuhn. These may arise in appendix, small bowel, rectum, caecum, stomach and rarely even in pancreas, esophagus and liver.[9,10]

The mean age at diagnosis of NETs is around 60 years[11] though it has rarely been reported in young.[12] These are more commonly seen in males with male to female ratio is 1.4/1.0.[13]

Neuroendocrine tumors progress slowly and remain clinically silent in most of cases. While many of the other GI NETs are found incidentally on endoscopy, owing to their small size and lack of specific symptoms, small-bowel NETs can present with hormonal or non hormonal symptoms; Non hormonal symptoms are mostly secondary to partial mechanical obstruction of the small bowel with symptoms such as vague abdominal pain. These obstructive features may be due to peritumoral fibrosis or invasion which may cause characteristic kinking of bowel or

secondary to desmoplastic reaction leading to ischemic changes. Anorexia, weight loss, fatigue and occasionally a palpable abdominal mass are the other non-hormonal symptoms that might be present.[10,14] Hormonal manifestations of neuroendocrine tumors are grouped under the term "Carcinoid syndrome" and occurs because of secretion of serotonin, bradykinins and prostaglandins. This syndrome occurs when these substances enter the systemic circulation. Midgut NETs are those most associated with the classic carcinoid syndrome of diarrhea, flushing, and right heart fibrosis/damage, most likely because even small tumors have a stronger tendency to metastasize to local lymph nodes and to the liver, compared to other GI NETs.[15] In absence of hepatic metastasis serotonin undergoes degradeation in liver to non active substances thus manifestations of carcinoid syndrome do not occur.

In our case the patient had a history of vague abdominal pain for approximately 3 months and now presented with complete intestinal obstruction. No hormonal symptoms were noted in our patient as there was no metastasis.

In tropical countries small intestinal obstruction is usually associated with bowel adhesions in a previously operated patient or strangulated hernia ortuberculosis of ileocecal region. Ileoileal or ileocolic intussusceptions and Meckel's diverticulitis are also other causes though rare. Small bowel tumors are extremely rare as a cause of intestinal obstruction.[16]In our case the patient was on Anti tubercular treatment for 3 months for suspected ileocaecal tuberculosis.

The primary tumor is rarely diagnosed radiologically. Plain abdominal x ray is the initial screening modality and it may show curvilinear calcification but is usually non specific. Barium studies (enteroclysis, follow through examination) may show intramural or intraluminal filling defects in the distended ileum. It may also show stricture formation, thickening of the valvulaeconiventes and increase in the interbowel loop distance due to wall thickening. Ultrasound may reveal wall thickening, lymphnode metastasis or hepatic metastasis. But all these findings are too non specific to make a diagnosis.[17] However ct scan may prove very helpful in these cases. It may reveal a soft tissue mass with spiculated borders and radiating strands with or without calcification. It may also reveal lymphadenopathy and hepatic metastasis.[18]Somatostatin receptor scintigraphy with Indium III Octreotide, Indium III pentetrotide and Iodine 123 meta iodobenzylguanidine is a sensitive and non-invasive technique for imaging these tumors and their metastatic spread.[10]

The principal management approach in these cases is surgical resection of the primary lesion and is the only curative option. For GI – NETs size greater than 2cm is usually associated with lymphnode metastasis. However in jejunoileal tumors nodal metastasis usually occurs even in lesions more than 1cm. So in lesions less than 1cm local resection is usually adequate. However, with lesions over 1 cm there is a high risk of recurrence and thus segmental resection is required with extensive clearance of the associated mesenteric lymph nodes. Surgery has been shown to be of benefit even in patients with metastatic disease, both to gain symptomatic relief and improve survival.[19]

Drugs such as somatostatin analogs may also be used for symptomatic management of patients with hormonal symptoms. [20]These are also believed to stabilise the tumor growth. Therefore, these are used as first-line treatment in inoperable functioning tumors.

Typical histopathology specimen shows clusters of uniform cells with scant cytoplasm and nucleus exhibits salt and pepper chromatin pattern under electron microscopy.

Current classifications of NETs are the 2000 and 2010 who classifications. The 2000 classification was based on histological parameters such as size, depth of invasion, angiolymphatic invasion and metastasis. This divides NETs into well differentiated neuroendocrine tumors, well differentiated neuroendocrine carcinomas and poorly differentiated neuroendocrine carcinomas.[21]

The WHO 2010 classification which is also recommended by the European Neuroendocrine Tumor Society (ENETS) divides NETs into: Low-

grade (G1) tumors show a mitotic index less than 2%, or mitotic activity of fewer than 2 per 10 HPFs. Intermediate grade (G2) tumors have a mitotic index from 3% to 30% or mitotic activity of 2 to 20 per HPF and grade 3 high grade neuroendocrine carcinomas have a mitotic index greater than 20% or mitotic rate greater than 20 per HPF.[22]

Mitotic rate should be based upon counting 50 high-power (40x objective) fields in the area of highest mitotic activity and reported as number of mitoses per 10 HPF. The mitotic index should be calculated by counting at least 500 and preferably 2000 cells.

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling although the precise method of assessment has not been standardized. It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.[23]

Grade assigned based on Ki-67 index may be higher than that based on mitotic count. Thus, reporting the higher grade by either method is preferred if both are performed.

G1 and G2 are well-differentiated tumors with diffuse intense chromogranin/synaptophysin positivity. G3 tumors are high-grade poorly differentiated neuroendocrine carcinomas.

It was found that proliferative activity, which included mitotic activity and Ki67 proliferation index, is a useful prognostic indicator that correlated with other features, such as tumor size, invasion, and metastasis. Miller HC et al in a review of 161 patients with neuroendocrine tumors found that 46.1% of G1, 77.8% OF G2 and 100% had metastatised tumors.[24]

Our case was diagnosed as a who grade 2 neuroendocrine tumor based on ki index and mitotic rate.

Conclusion

Neuroendocrine tumors are rare tumors of the GI tract. Most of them have an indolent course but may also present with obstructive features. Prognosis can be improved with early diagnosis and surgery at an early stage is usually curative. As late diagnosis is associated with poor prognosis carcinoid tumor should be kept as a differential diagnosis in patients presenting with non-specific symptoms of partial bowel obstruction.

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