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Case Report

Surgery Section

Ileal Neuroendocrine Tumour Causing Carcinoid Syndrome in Absence of Hepatic Metastasis

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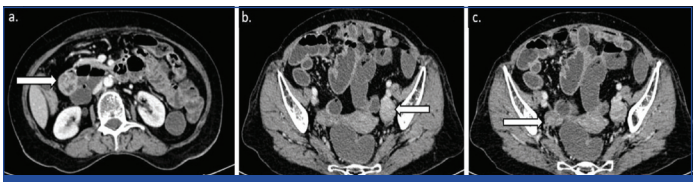
ABSTRACT

Carcinoid syndrome consists of the classic symptom triad of flushing, diarrhoea, and valvular heart disease. It occurs in the majority of patients with liver metastases. This report presents a 68-year-old female who suffered from chronic diarrhoea with a history of multiple admissions for the same. On evaluation, a Computed Tomography (CT) scan showed a terminal ileal lesion and bulky ovaries. Suspecting Neuroendocrine Tumour (NET) with carcinoid syndrome, a Gallium 68 DOTANOC (DOTA-1-Nal3-octreotide) scan was done which revealed somatostatin receptor expression in enhancing soft tissue lesion in terminal ileum as well as in bilateral adnexa. This confirmed the diagnosis of NET of the ileum and bilateral ovarian metastases. The patient underwent laparoscopic curative resection of the primary tumour along with bilateral oophorectomy. The patient was diagnosed with ileal NET and presented with clinical symptoms of carcinoid syndrome, yet did not have evidence of hepatic metastasis, but instead had bilateral ovarian metastasis which itself is a rare entity.

Keywords: Diarrhoea, Ileal carcinoid, Laparoscopic resection, Ovarian metastasis

CASE REPORT

A 68-year-old postmenopausal female presented with recurrent episodes of watery diarrhoea for the last 18 months. There was no history of fever, blood in stools, weight loss, flushing, breathlessness, or wheezing. She had multiple Outpatient Department (OPD) consultations and admissions where she received symptomatic treatment without definite relief. Her physical examination and routine haematological and biochemical parameters were unremarkable. The stool examination was normal. CT scan of the abdomen revealed a focal non obstructive submucosal lesion in the terminal ileum showing homogenous enhancement and measuring 17 mm in maximum thickness and 2.8 cm in length. It also showed bulky ovaries (left>right) [Table/Fig-1].

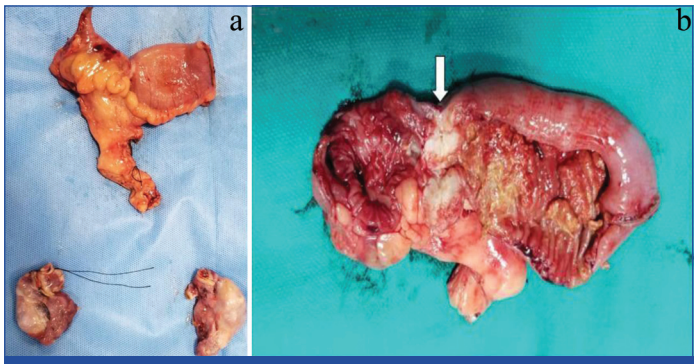


[Table/Fig-1]: Axial CECT images: a) Showing submucosal enhancing lesion in terminal ileum; b and c) Bilateral bulky enhancing ovaries (white arrow).

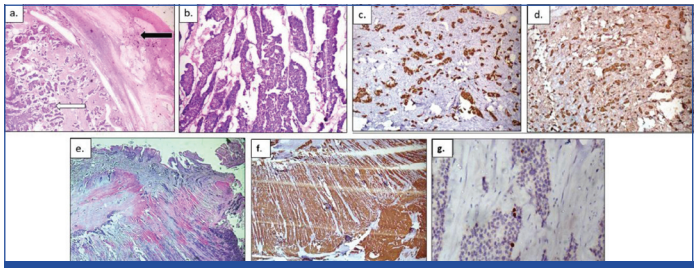
With suspicion of NET, a Ga-68 DOTANOC scan was done, which revealed somatostatin receptor expression in enhancing soft tissue lesion in the terminal ileum as well as in bilateral adnexa, which confirmed the diagnosis of NET of the ileum with bilateral ovarian metastases. Furthermore, serum chromogranin A levels and 24 hours urinary 5-Hydroxyindoleacetic Acid (5-HIAA) levels were elevated- 2580 ng/mL (normal <108 ng/mL) and 12 mg (normal 2-9 mg), respectively. Echocardiography was normal.

The patient underwent laparoscopic segmental resection with primary anastomosis of the distal ileum and bilateral oophorectomy [Table/Fig-2]. To prevent carcinoid crisis intraoperatively, the surgery was performed under octreotide infusion cover at 50 µg/hr started 12 hours before surgery, and continued for 24 hours postoperatively.

Histopathological examination showed a well-differentiated NET (World Health Organisation (WHO) Grade-2) [1] in the ileum and bilateral ovaries. On Immunohistochemistry, tumour cells were positive for synaptophysin and chromogranin [Table/Fig-3]. On the four week follow-up, the patient was completely asymptomatic.



[Table/Fig-2]: Resected gross specimen.
a) Distal ileum and bilateral ovaries; b) Cut section of ileum showing the tumour.



[Table/Fig-3]: Photomicrographs of ovarian and ileal tumour: a) Section from the ovarian tumour shows a normal ovary (black solid arrow) at the periphery along with a tumour (white arrow) with atypical cells seen in nests and clusters (Haematoxylin & Eosin (H&E) X40); b) Higher magnification shows tumour present in cords, nests, and islands of monomorphic cells with scant cytoplasm, stippled chromatin, and no mitotic activity or necrosis (H&E) X200. Immunohistochemical analysis revealed tumour cells to be diffusely reactive for; c) Synaptophysin (X100); and d) Chromogranin (X40); e) Sections show normal ileal mucosa with the submucosa infiltrated by a tumour having an architectural pattern of cords and nests with scant cytoplasm, stippled chromatin, and no mitosis (X40). Immunohistochemical analysis revealed tumour cells to be diffusely reactive for; f) Synaptophysin (X40) with; g) low proliferation index of 3% (Ki 67 X400).

DISCUSSION

Gastrointestinal NETs (GI-NETS), frequently called carcinoid tumours, are tumours derived from diffuse amine and acid-producing cells of the GI tract with different hormonal profiles, depending on the site

of origin. Small Intestinal (SI) NETS comprise >50% of all SI tumours with an annual incidence of approximately, 0.8/100,000 [2]. The ileum is the most common site of origin. Patients with GI-NETs must have liver metastasis before they develop carcinoid syndrome unlike ovarian or bronchial tumours, which may have carcinoid syndrome even in absence of liver metastasis [3].

Among the NET ectopic hormonal syndromes, carcinoid syndrome is the second oldest to be described, after insulinoma, with the earliest publication in 1954 [4]. Approximately, 30-40% of patients with well-differentiated NETs present with carcinoid syndrome [5].

The occurrence of Carcinoid syndrome associated diarrhoea among NET patients is as high as 60-80%. One of the main secretory products of GI-NETS is serotonin. It acts on 5-HT3 receptors, stimulating intestinal motility and secretion and inhibiting absorption. High levels of serotonin cause increased frequency of bowel movements and decrease stool consistency, clinically seen as diarrhoea [6].

Two plausible explanations have been given to explain why carcinoid syndrome in such a case cannot occur in absence of liver metastasis [7]:

- The liver contains a huge amount of monoamine oxidase activity, which inactivates most of the serotonin produced by the tumour [7].
- Primary GI-NETs are usually small and secrete a lesser amount of hormones than a metastatic liver lesion, which is much larger in size and secretory function [7].

Primary ovarian carcinoid tumours or ovarian metastasis as in this case, release serotonin or other vasoactive substances directly into the systemic circulation bypassing the liver and thus, can produce carcinoid syndrome. To the best of our knowledge, there have been only a limited number of such cases in the literature so far. A review of the literature yielded 19 cases of GI-NET with features of carcinoid syndrome in the absence of liver metastasis [Table/Fig-4] [7-18]. As mentioned in the table, the site of primary tumours in these patients was the middle and distal ileum, jejunum, caecum, appendix and mesentery. All the patients had evidence of carcinoid syndrome in the absence of hepatic metastasis. Only eight patients had metastatic deposits in the ovaries (Case 2,3,4,5,6,8,9,10), while in others the most common site of tumour spread was lymph nodes (Case 1,11,12,13,14,15,17). Most of the patients received surgical management and five patients (Case 5,10,12,14,17) showed complete remission without any postoperative complications or recurrence.

S. No.	Study	Cases	Patient Age (years)/Sex	Primary tumour	Metastasis	Surgery performed	Outcome
1.	Feldmann MJ and Jones SR [7]	3	57/M 60/M 28/F	Mid-jejunum Terminal ileum Ileum	Retroperitoneal Lymph nodes Peritoneum Adjacent Lymph nodes	Resection and anastomosis	Information not available
2.	†Robboy SJ et al., [8]	1	40/F	Ileum ? cecum†	Para-aortic LN, B/L ovaries	BSO, ileocolectomy	Died after 1.8 years
3	*Kenneth E Droulard [8]	1	72/M	Ileum	B/L ovaries, extensive peritoneal metastasis	BSO, Resection and anastomosis, omentectomy	Intestinal obstruction Died after 3.8 years
4	Quinn BF [9]	1	61/M	Caecum	B/L ovaries	Bilateral salpingo-oopherectomy, hemicolectomy	Information not available
5.	*Mary Ellen Kirk [8]	1	52/F	Ileum	Right ovary	Right oopherectomy, resection	Complete remission
6.	Morris JM and Scully RE [10]	1	59/M	Ileum	Peritoneum, B/L ovaries	BSO	Information not available
7.	*Pines DJ [8]	1	58/F	Ileum	Uterine serosa	Hysterectomy, resection and anastomosis	Intestinal obstruction
8.	*Casella JV [8]	1	44/F	Jejunum	B/L ovaries	Resection and anastomosis, BSO	Developed mesenteric mass after 3 months
9.	*Mulvey Rj [8]	1	25/F	Ileum	Mesentery, B/L ovaries	Resection, BSO	Died after 0.7 years
10	Hopping RA et al., [11]	1	47/M	Appendix	Right ovary	Right oophorectomy+appendectomy	Complete remission
11	Rosenberg JM and Welch JP [12]	1	51/M	Mid-ileum	Lymph nodes	Resection and anastomosis+Lymph node dissection	Information not available
12	Hossain J et al., [13]	1	31/M	Jejunum and ileum	Para-aortic lymph nodes	Resection and anastomosis	Complete remission
13.	Zavras N et al., [14]	1	73/M	Pancreas	Adjacent Lymph nodes	Conservative due to extensive lymphadenopathy	Succumbed to heart failure
14.	Datta S et al., [15]	1	80/M	ileal mesentery	Mesenteric lymph nodes	En bloc excision	Complete remission
15.	Jahagirdar V et al., [16]	1	64/F	Ileum	Lymph nodes and heart	Conservative	Succumbed to septicaemia
16.	Shogbesan O et al., [17]	1	64/F	Mesentery	NIL	Information not present	Information not available
17.	Famerée L et al., [18]	1	25/F	Terminal ileum	Common iliac nodes	Resection of the midgut lesion with superior mesenteric axis lymph node dissection	Complete remission

[Table/Fig-4]: Reported cases of carcinoid syndrome without liver metastasis [7-18].
[1*]These cases were sourced from reference article 8. No direct refereces for the same were found in the article and literature.
[2†]As mentioned in the references article 8

CONCLUSION(S)

Management of chronic diarrhoea can challenge clinicians and the possibility of a carcinoid syndrome should be entertained in them. Further, carcinoid syndrome in absence of liver metastasis, though rare, can occur when vasoactive substances are released directly into systemic circulation as in this case with ovarian metastasis.

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