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Case report

Multiple, persistent gastropancreato-neuroendocrine tumours accompanying sigmoid bowel adenocarcinoma: A rare case report

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ABSTRACT

Introduction: Gastropancreato-neuroendocrine tumours (GETs) are rare, especially when they occur alongside colorectal adenocarcinoma. Furthermore, multiple GETs occurring within the small bowel are less frequent with only two cases described within the literature.
Presentation of case: A healthy 58-year old woman presented with severe gastrointestinal pain and faecal incontinence. Family history revealed consanguineous parents and a brother who had recently died of a gastric GET. First biopsy showed a sigmoid adenocarcinoma. Histology of the resected sigmoid revealed both adenocarcinoma and GET. After this, she presented with small bowel obstruction secondary to multiple ileal and jejunal GETs, also treated with resection. All imaging modalities gave no evidence of extra-intestinal metastasis. The patient received multiple operations and chemotherapy but died 18 months after the original presentation.
Discussion: A case of such persistent and multiple small bowel GET without extra-intestinal metastasis has yet to be reported within the literature. GETs are rare and typically asymptomatic with a small proportion giving the classical carcinoid syndrome. Surgery is usually reserved for smaller GETs with high five-year survival. Despite this, surgery and chemotherapy were performed and both proved to be ineffective. Furthermore, a genetic basis for GETs is supported in this case with her brother suffering a similar fatal tumour.
Conclusion: This case highlights a rare GET that has a likely underlying familial origin. It illustrates the non-specific presentation of these tumours and the importance of taking a thorough family history. It also demonstrates that these tumours can be fatal even in the absence of extra-intestinal metastasis.

1. Introduction

Gastropancreato-neuroendocrine tumours (GETs) are rare, with a prevalence of 35 per 100,000 [1]. Due to advancing imaging techniques and improving diagnostic ability their frequency is increasing. The name GET has recently replaced the term 'carcinoid' due to the multitude of cytokines and hormones they can release. As the name suggests, these tumours can occur anywhere along the gastrointestinal tract. Arising from the amine precursor uptake cells of the intestine, they can be metabolically active and are histologically distinctive from colorectal adenocarcinoma. To classify GETs further, they can be divided according to their source of origin, with 50% arising from the bowel and 50% arising from the pancreatic tract [2]. The commonest site in the bowel that GETs arise from is the appendix followed by ileum, rectum and stomach. The least common sites are the sigmoid, transverse and the descending colon, which comprise only 25% of all hindgut GETs [3]. Even more rare, are multiple small bowel GETs where there have been two published cases, both of which were associated with extra-intestinal metastasis [4].

Here, we explore a rare case of multiple GETs both in the small intestine and sigmoid colon alongside sigmoid colorectal adenocarcinoma with no extra-intestinal metastasis. Such a case is yet to be reported in the literature.

2. Presenting concerns

A 58-year-old healthy woman presented with severe gastrointestinal pain described as if her insides were being "wrung out". It

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occurred most days and her only relief was a hot-water bottle pressed onto her abdomen. She had loose bowel movements and on several occasions had become incontinent of faeces. There was no weight loss and her appetite was good. Her past medical history was unremarkable.

3. Clinical findings

Her family history included consanguineous parents and a brother who had recently died of metastatic gastric GET. On examination, she had a vague fullness to her abdomen but was otherwise unremarkable. Rectal examination and rigid sigmoidoscopy both appeared normal.

4. Diagnostic focus and assessment

Routine bloods showed a degree of normocytic anaemia. Plasma chromogranin A level was raised (12.4 nmol/L) but other cancer markers were within normal limits. Computerised tomography (CT) showed focal sigmoid wall thickening and biopsy taken at colonoscopy confirmed adenocarcinoma.

5. Theraputic focus and assessment

The case was discussed at the colorectal multidisciplinary team meeting. The surgical team performed an urgent sigmoid resection with anastomosis. Intra-operatively, no peritoneal metastases were seen. 180 mm of sigmoid was resected and histology confirmed a 55 mm adenocarcinoma in situ that extended 2 mm beyond the muscularis propria, shown in Fig. 1. Examination of 20 resected lymph nodes revealed no metastatic lymph node involvement. Unexpectedly, two serosal nodules were noted that were histologically distinct from the adenocarcinoma. Staining showed that they were positive for CD56, chromogranin and synaptophysin where the adenocarcinoma was not, shown in Fig. 2a and b. These lesions both had a Ki67 index of greater than 30% indicating a grade 3 GET. This raised Ki67 index indicates that this was a likely metastasis from elsewhere and therefore further investigation was sought.

An ocreotide scan was performed in addition to magnetic resonant imaging (MRI) of the pancreas and CT of the abdomen and pelvis. These did not show any obvious intra or extra-intestinal lesion present. Follow up MRI four months after surgery showed normal small bowel but a 20 mm spiculated mass in the mesentery, shown in Fig. 3a–c. Again, no extra-intestinal metastases were noted.

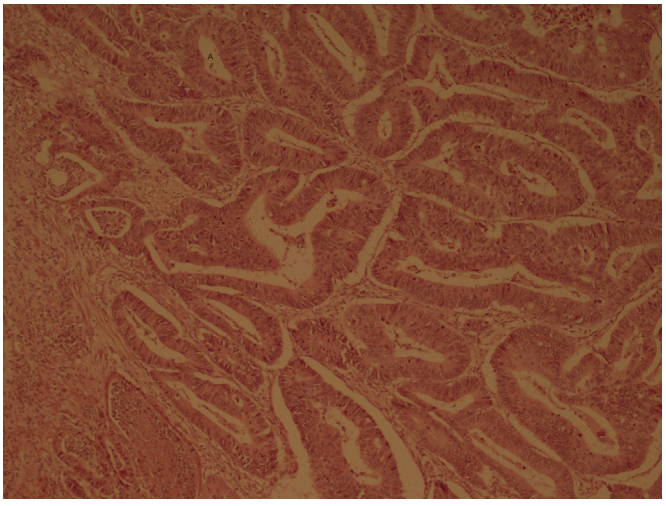

Fig. 1. Histology showing the sigmoid adenocarcinoma. 'A' marks glandular forming tissue which is indicative of adenocarcinoma.

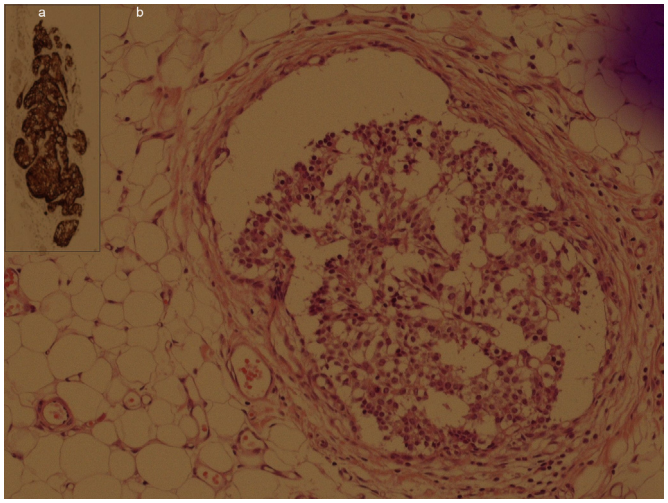

Fig. 2. a. this indicates the chromogranin stain that was used. It is dark which indicates that the chromogranin was taken up readily by the neuroendocrine tumour. b. this indicates the carcinoid tumour within the sigmoid colon.

6. Follow-up and outcomes

Despite the removal of the sigmoid bowel, the patient still suffered with constant diarrhoea, nausea and severe abdominal pain with no evident cause. She was trialled on cyclizine, domperidone and even acupuncture with no success. She did gain some relief from ondansetron and metaclopramide. Somatostatin therapy was commenced but provided little symptomatic relief.

One month later, the patient was admitted with small bowel obstruction. Emergency laparotomy was performed and 500 mm of small bowel was resected. This small bowel showed multiple GETs with the largest being 28 mm in diameter and having a Ki67 index of 8%. Histology of this is shown in Fig. 4. Two smaller jejunal lesions were noted, both less than 10 mm in diameter. There were multiple deposits within the mesentery up to 18 mm in size in addition to further ulceration throughout the portion of resected small bowel. After this operation, chemotherapy was commenced with a regime of Cisplatin and Etoposide for six cycles on a q21 day schedule.

Five months after starting chemotherapy, the patient presented with symptoms of large bowel obstruction. CT showed multiple large bowel lesions, likely due to further tumour involvement. As before, CT gave no evidence of extra-intestinal metastasis.

The final diagnosis was two sigmoid GETs and adenocarcinoma, multiple small bowel GETs and questionable further large bowel GETs. Histology indicated well-differentiated and aggressive tumours. The timeline of events is depicted in Fig. 5. Despite rigorous chemotherapy and intensive surgical procedures, the patient became increasingly weak and died 18 months after the original presentation.

7. Discussion

We have presented an unusual case of multiple GETs. Treatment was both medical and surgical, with two operations being performed. On post-operative imaging, no further lesions were reported and yet there was future recurrence to a different portion of the bowel. A case of such persistent GET has not yet been reported in the literature.

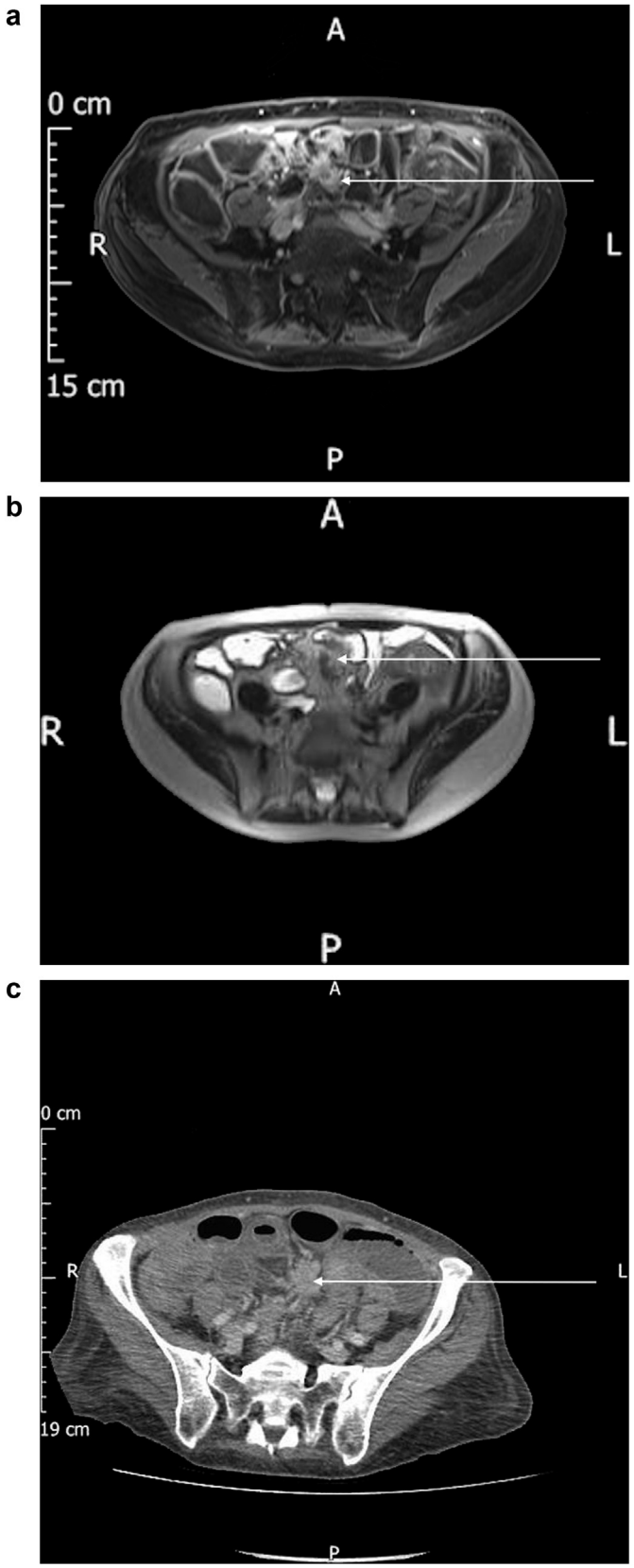

Fig. 3. a. T1 weighted MRI post-gadolinium showing the spiculated 20 mm mass within the mesentery. This lesion is arrowed. b. T2 weighted MRI also illustrating the speculated 20 mm mass within the mesentery. The lesion is arrowed. c. CT of the mesentery mass that was taken 1 month after the MRI in a and b. The lesion is arrowed.

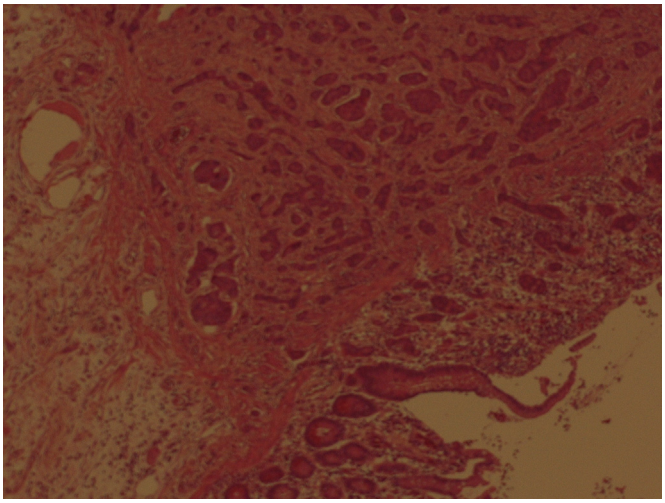

Fig. 4. This indicates the presence of carcinoid through the muscularis mucosa within the small bowel lumen.

The patient initially presented with multiple sigmoid tumours, complaining of symptoms of anaemia, diarrhoea and abdominal pain. This can be characteristic of any mass present either in the rectum or sigmoid colon due to overflow. The classical carcinoid syndrome comprises flushing, diarrhoea and bronchospasm. This only occurs in around 10% of patients and is caused by secretion of bioactive compounds such as serotonin and bradykinin. It is unknown whether the symptoms were caused by the adenocarcinoma or the GET. After resection of the sigmoid colon, the symptoms still persisted making it likely that the cause was from the yet unidentified lesions within the small bowel. Rectal and sigmoid GETs can present with change in bowel habit and anaemia. Extra-intestinal metastatic disease is not common on presentation, occurring in 20% of patients [5]. However, as many as 90% of patients with GETs are asymptomatic at the time of discovery and the diagnosis is incidental to other investigations [6].

Prompt investigation resulted in diagnosis and allowed early surgical resection. Due to their slow growing nature, the mean survival time for GETs is longer than other GI malignancies [7]. The Ki67 index is a marker that has been indicated in survival for patients with GETs with an index of greater than or equal to 10% indicating poorer prognosis (19 months as opposed to 72 months) [8]. However, no absolute threshold value has been defined. This fits with the case, where a Ki67 index of 38% was noted on admission and the patient's survival time was 18 months from diagnosis. The Ki67 is a useful marker for the primary tumour rather than metastasis and in our case the primary's origin was never confirmed. It is possible that the primary was in the large bowel metastasising to the small bowel and the sigmoid colon.

Medical treatment of GETs is dependent on whether they are hormone secreting or not. Hormone secreting tumours can usually be suppressed by somatostatin analogues. Chemotherapy agents, usually reserved for after somatostatin or interferon have been trialled, include 5-flurouracil and streptozocin although the response is limited [9]. In this case three cycles of cisplatin and etoposide chemotherapy were commenced, but as before, the tumour was unresponsive and the symptoms persisted. The choice of cisplatin was made because tumours with particularly high Ki67 indexes having a greater response to platinum based chemotherapy [10]. Radiation is also of limited use except in the case of bone metastasis where it can be used for symptom control [9].

The patient's brother also suffered a fatal GET. In contrast to the presented case, this tumour was found in the foregut and

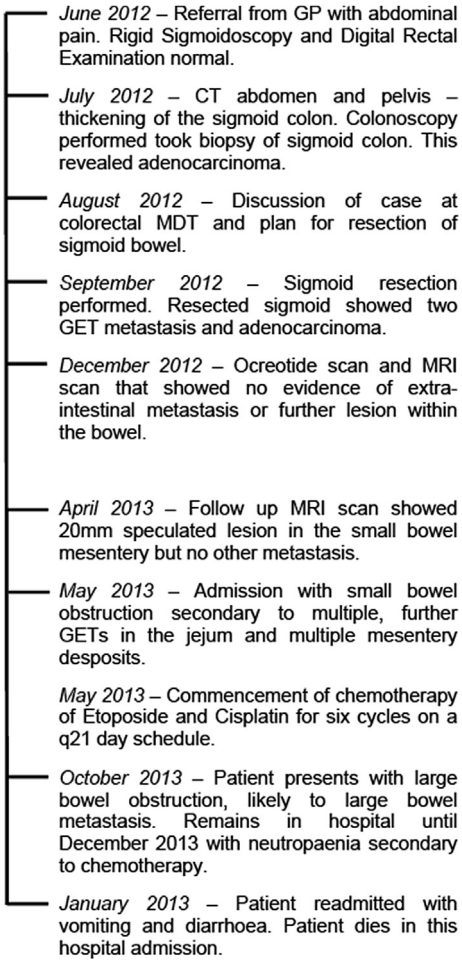

Fig. 5. Timeline of events.

presented with metastatic disease and also did not respond well to medical or surgical intervention. This leads to a potential genetic aetiology for the GET where Individual genes and chromosomal abnormalities have already been implicated [11]. Specific genetic associations most commonly manifested as aneuploidy in chromosome 18 followed by chromosome 13 and then 21 [12]. It was noted that 69% of ileal GETs were associated with chromosome 18 abnormalities, specifically polymorphisms on locus 18q22.1 [13]. Furthermore, it should be noted that in this case, the parents were consanguineous, a risk factor for mortality and increasing the chance of familial association, especially in these chromosome that are indicated [14].

In summary, we have presented a rare case of multiple GETs seen throughout large and small bowel in addition to a sigmoid adenocarcinoma with likely genetic association. Due to recent increases in detection and incidence of GETs, different management approaches must be considered. This case has illustrated that with multiple and persistent GETs, even without extra-intestinal metastasis, prognosis can still be poor.

Conflicts of interest statement

The authors have disclosed no conflicts of interest, financial or otherwise.

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None.

Consent

Written informed consent was obtained from the patient's husband (next of kin) for the publication of this case report.

De-identification

All demographic data on images and potential patient identifiable information has been removed.

Key learning points

- Diagnosis of GETs with metastasis can be incidental
- Genetics are an important aetiological factor for small bowel GETs
- Surgery is the only curative option for GETs but is not always successful.

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