CASE REPORT

Four tumours including neuroendocrine tumour of the ileum

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SUMMARY

Gastroenteropancreatic neuroendocrine tumours are associated with development of further primary tumours. Certain conditions give an inherited predisposition to developing neoplasia. To the best of our knowledge, this is the first paper to report a patient with neuroendocrine tumour and three other tumours: a further bowel cancer, a brain tumour and a skin cancer. We report a case of a 42-year-old Caucasian man presenting with clinical features of intestinal obstruction who on histopathology of surgical specimen was found to have two distinct tumours of the bowel: a colonic adenocarcinoma at the splenic flexure and a well-differentiated neuroendocrine tumour of the terminal ileum. His history included a basal cell carcinoma and a benign brain tumour. He had extensive family history of neoplasia suggesting an inherited predisposition. Our case demonstrates the importance of investigating patients with known neuroendocrine tumours for further malignancy and suggests that patients with multiple primary malignancies should be referred for genetic testing.

BACKGROUND

Neuroendocrine tumours (NETs) are a rare form of neoplasia, though reviews suggest increasing prevalence over the past 30 years, possibly due to improved diagnostic techniques.^{1–3} Intestinal NETs arise from enterochromaffin cells in the crypts of Lieberkuhn.^{3,4}

The incidence of gastroenteropancreatic (GEP) NETs is estimated at about 2.5–5 cases per 100 000.^{1,2} NETs are reported to be the most frequent neoplasm of the small intestine and indeed studies report that they account for 17–46% of all malignant small bowel neoplasms.^{1,3,5,6} The ileum, where our patient's tumour was discovered, is the most common location, composing 28% of all NETs.^{1,5,6} Jeuno-ileal NETs have a poor 5-year survival rate (60.5%) compared with other gastrointestinal NETs and commonly metastasise to the liver.^{1,2,5}

GEP NETs are commonly non-functioning and present late with symptoms of metastases or mass effects such as vague abdominal pain.⁵ They are often an incidental diagnosis.^{5,7–9}

Although they are usually sporadic, GEP NETs other than tumours of ileal origin can be due to a familial syndrome, for example, neurofibromatosis type 1, multiple endocrine neoplasia type 1 or von Hippel-Lindau syndrome.²

Studies have found a significant association between NETs and other tumours, such as in our patient.^{5,10,11} This may be due to the production

by NETs of a growth factor agent that promotes neoplastic transformation.^{5,10} Indeed, second primary malignancies are reported in up to 55% of patients with gastrointestinal NETs.⁹

Rates of patients with multiple primary colorectal cancers are calculated at 3.5–7%.^{12,13}

To the best of our knowledge, this is the first paper to report a patient with the combination of an intestinal NET, a further bowel malignancy, a brain tumour and a skin cancer.

CASE PRESENTATION

A 42-year-old Caucasian man presented with acute worsening of lower abdominal pain and altered bowel habits. On questioning, he also reported weight loss of two stones over 12 months.

In medical history, he had a childhood ependymoma of the fourth ventricle, which was treated with surgical excision and radiotherapy. He suffered from seizures thought to be a frontal lobe epilepsy and had previously had a basal cell carcinoma removed.

There was an extensive history of cancer within the family. His brother suffered from breast cancer, his maternal grandmother had a brain tumour and his maternal grandmother's sister was also diagnosed with malignancy.

OUTCOME AND FOLLOW-UP

CT of the abdomen and pelvis revealed an 8 cm stricture suggestive of a neoplastic lesion at the proximal descending colon causing large bowel obstruction with perforation leading to diffuse peritonitis. The patient had an emergency laparotomy and subtotal colectomy with end ileostomy. Operation findings included an obstructing splenic flexure colon tumour adherent to the left kidney.

Histopathology of the surgical specimen reported two distinct tumours of the bowel. First, a moderately differentiated adenocarcinoma at the splenic flexure staged pT4b N2 Mx, which displayed microsatellite instability. Second, a well-differentiated pT1 N1 Mx NET in the terminal ileum, which stained positive for chromogranin and synaptophysin. This was a low-grade (grade 1) NET, mitotic count was less than 2 mitoses/10 high-power fields and the index of proliferation marker Ki67 was less than 2%.

Subsequent imaging revealed four liver metastases. Following discussion at a multidisciplinary meeting, the patient was to be considered for colorectal chemotherapy; however, sadly, he passed away shortly thereafter.

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DISCUSSION

Our patient did not have a family history of bowel cancer nor was he known to have an inherited predisposition, however, by a relatively young age he had suffered four tumours, three of which were malignant. Furthermore, as cancer had been diagnosed in several members of his family in multiple generations, and of rare types such as brain tumour and male breast malignancy, we must consider the possibility of a hereditary cancer susceptibility syndrome. These are thought to account for 5–10% of all cancers and increase the risk of benign as well as malignant tumours.¹⁴

Lynch syndrome, the most common form of hereditary colorectal neoplasia, results from microsatellite instability and increases risk of synchronous bowel malignancy.^{12–14} Lynch syndrome also increases risk of basal cell carcinoma, small intestine adenocarcinoma and brain tumours such as those suffered by our patient.^{12–14} However, loss of expression of mismatch repair proteins is not thought to be a significant factor in GEP NETs.^{15 16}

Multiple endocrine neoplasia type 1 predisposes to enteropancreatic endocrine tumours, but not ileal NETs; indeed, non-functional tumours of the enteropancreas are seen in up to 20% of patients.¹⁴

Familial adenomatous polyposis increases the risk of synchronous bowel malignancy, and cancer of the small intestine and central nervous system.^{12–14 17} In Li-Fraumeni syndrome, which gives a predisposition to brain and colon tumours, multiple primary cancers are found in up to 50% of patients.^{14 18 19} Juvenile polyposis and Peutz-Jeghers syndrome also increase the risk of malignancy of the colon and small intestine.^{14 20}

As our patient is sadly no longer alive, we are unable to perform genetic testing to confirm an inherited susceptibility; however, this is strongly suggested by the history.

Learning points

- Patients with known neuroendocrine tumours should be investigated for further malignancy.
- Patients with multiple primary malignancies should be referred for genetic testing.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934–59.
- 2 Modlin IM, Oberg K, Chung DC, *et al.* Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008;9:61–72.
- 3 Sembawa H, Lamoureux E, Gologan A, *et al.* Multiple carcinoids of the ileum: case reports. *Can J Surg* 2007;51:225–6.
- 4 Eggenberger JC. Carcinoid and other neuroendocrine tumors of the colon and rectum. *Clin Colon Rectal Surg* 2011;24:129–34.
- 5 Modlin IM, Kidd M, Latich I, *et al.* Current status of gastrointestinal carcinoids. *Gastroenterology* 2005;128:1717–51.
- 6 Gabos S, Berkel J, Band P, *et al.* Small bowel cancer in western Canada. *Int J Epidemiol* 1993;22:198–206.
- 7 Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. *Acta Pathol Microbiol Scand A* 1976;84:322–30.
- 8 Greenstein AJ, Balasubramanian S, Harpaz N, *et al.* Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. *Am J Gastroenterol* 1997;92:682–5.
- 9 Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. *J Surg Oncol* 2000;75:310–16.
- 10 Modlin IM, Tang LH. The gastric enterochromaffin-like cell: an enigmatic cellular link. *Gastroenterology* 1996;111:783–810.
- 11 Norheim I, Oberg K, Theodorsson-Norheim E, *et al.* Malignant carcinoid tumors. An analysis of 103 patients with regard to tumor localization, hormone production, and survival. *Ann Surg* 1987;206:115–25.
- 12 Papadopoulos V, Michalopoulos A, Basdanis G, *et al.* Synchronous and metachronous colorectal carcinoma. *Tech Coloproctol* 2004;8:s97–s100.
- 13 Arai T, Sawabe M, Takubo K, *et al.* Multiple colorectal cancers in the elderly: a retrospective study of both surgical and autopsy cases. *J Gastroenterol* 2001;36:748–52.
- 14 Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene* 2004;23:6445–70.
- 15 Arnason T, Sapp HL, Rayson D, *et al.* Loss of expression of DNA mismatch repair proteins is rare in pancreatic and small intestinal neuroendocrine tumors. *Arch Pathol Lab Med* 2011;135:1539–44.
- 16 Arnold CN, Sosnowski A, Schmitt-Graff A, *et al.* Analysis of molecular pathways in sporadic neuroendocrine tumors of the gastro-entero-pancreatic system. *Int J Cancer* 2007;120:2157–64.
- 17 Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. *Int J Colorectal Dis* 2001;16:63–75.
- 18 Freiburg T, Abel A, Bonaiti-Pellie C, *et al.* Li-Fraumeni syndrome: update, new data and guidelines for clinical management. *Bull du Cancer* 2001;88:581–7.
- 19 Krutikova V, Trkova M, Kodet R, *et al.* Li-Fraumeni syndrome. *Ceskoslovenska Pediatr* 2003;58:552–5.
- 20 Jarvinen H, Franssila KO. Familial juvenile polyposis coli; increased risk of colorectal cancer. *Gut* 1984;25:792–800.

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