Rare disease

Gastric GIST with synchronous neuroendocrine tumour of the pancreas in a patient without neurofibromatosis type 1

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Summary

The gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract. These are rare tumours with an incidence of 15 new cases per million per year. The occurrence of neuroendocrine tumours of the pancreas is rare, representing 1–5% of pancreatic cancers, and it is estimated that its incidence does not exceed five to one million. GISTs are common in patients with neurofibromatosis type 1 (NF1); there are few reported cases of synchronous neuroendocrine tumours in these patients and most are pheochromocytomas. The case reports a 64-year-old woman referred to the General Surgery Outpatient for incidental finding of gastric and pancreatic tumours. She underwent a radical subtotal pancreatectomy + partial gastrectomy with jejunal transposition. The pathological examination revealed: gastric GISTs and a well-differentiated neuroendocrine carcinoma of the pancreas. This is the second case published so far of a patient with both tumours and without NF1. Posterior studies must be performed to evaluate if some other genetic disorder is involved in these patients without NF1.

BACKGROUND

The gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, and have an incidence of about 30/million/population/year.¹ Stromal tumours represent less than 1% of all of the gastrointestinal tract tumours. GISTs are mesenchymal neoplasms stemming from the interstitial cells of Cajal localised within the wall of the gastrointestinal tract. These tumours show a predilection for the stomach, usually the fundus, and they constitute 1–3% of the stomach neoplasms. Immunopositivity for CD117 (c-kit protein) is a distinctive immunohistochemical feature of these tumours, for which tumour size and mitotic activity are the most significant parameters regarding the prediction of clinical behaviour.² The majority, about 95% of the gastrointestinal stromal tumours, are characterised by the expression of c-kit receptor tyrosine kinase, whereas about 60–70% of the tumours express antigen CD34.³ They often occur in individuals over the age of 40 years, without gender predominance. The clinical behaviour is variable and benign tumours are most common. The primary treatment, when located, is the surgical resection, which can be complemented with the use of imatinib.

Neuroendocrine tumours (NETs) of the gastro-entero-pancreatic (GEP) system are rare and originate from the diffused endocrine system, representing about 2% of all gastrointestinal tumours. Their prevalence has increased substantially over the last three decades, only in part as a consequence of increased awareness and improved diagnostic techniques. The most recent estimates suggest a global clinical incidence of 2.5–5 cases/100 000 per year, with an autopsy incidence 2–5 times higher than the clinical one, and a slight predominance in females.⁴ The occurrence of NETs of the pancreas is also rare, representing 1–5% of pancreatic cancers, and it is estimated that its

incidence does not exceed five to one million. The tumours considered non-functioning (15–32% of pancreatic neuroendocrine tumours) are not associated with any syndrome, and are usually incidental. They have a slight predominance in males, and are more frequent in the 6th decade of life. Non-functioning tumours of islet cells are virtually all malignant tumours, and the treatment consists of surgical resection.

GISTs have been described to coexist with others neoplasms, the percentage of such cases ranging from 4.5% to 33%. In these cases, the stomach is the most frequent location of GIST. The most frequent concomitant tumour is adenocarcinoma of the gastrointestinal tract; other types include lymphoma, leukaemia, carcinomas of breast, prostate, pancreas or lung or adrenocortical adenoma (table 1). There are also few reports of familial GIST.³ The association between gastrointestinal NETs and synchronous or metachronous epithelial tumours account for about 10–46% of all cases.²

Table 1 Review of the literature on coexisting gastrointestinal stromal tumours (GISTs) and neuroendocrine tumours (NETs)

GIST	Neuroendocrine tumour	NF1	Reference
Stomach	Pancreas	–	1
Small bowel	Pheochromocytoma	+	12
Small bowel	Papilla of Vater	+	13
Small bowel	Pancreas	+	14
Small bowel	Duodenum	+	15
Small bowel	Pheochromocytoma	+	16
Small bowel	Pheochromocytoma	+	17
Small bowel	Pheochromocytoma	+	18
Small bowel	Pheochromocytoma	+	12
Large bowel	Pheochromocytoma	+	12
Ampulla de Vater	Ampulla de Vater	–	19

Figure 1 Upper endoscopy and ultrasound endoscopy.

However, the simultaneous occurrence of gastric GIST and NET of the pancreas seems to be rare, and almost all cases reported are in patients with neurofibromatosis type 1 (NF1). Thereby, we present a case of synchronous occurrence of a gastric GIST and a well-differentiated NET of the pancreas, in a patient without NF1.

CASE PRESENTATION

A female patient, aged 64 years, with a history of modified radical mastectomy in 2005 for breast cancer, type 2 diabetes and arterial hypertension, was referred to the General Surgery Outpatient for incidental finding of gastric and pancreatic tumours (routine abdominal ultrasound). The breast cancer was an invasive ductal carcinoma pT2G3N2Mx (positive for c-erb2 and negative for receptors of oestrogen and progesterone), and was submitted to adjuvant chemotherapy and radiotherapy. To date, no signs of recurrence of the breast disease (during the current diagnosis, slides were reviewed and it was maintained the invasive ductal carcinoma diagnosis).

The abdominal ultrasound and CT performed demonstrated in the proximal region of the body of the pancreas a hypoechogenic nodular image with 17 mm diameter, and one node is also observed in prepancreatic topography with 28 mm diameter adjacent to the posterior region of the gastric body, greater curvature (GIST?) (figure 1). The upper endoscopy revealed in the posterior wall of antrum a

subepithelial formation covered by normal mucosa (ultrasound (US) endoscopy: ‘In the body of the pancreas is observed a hypoechoic nodule, well-defined and heterogeneous echotexture, with 15 mm in the sagittal plane, with no signs of invasion of adjacent structures (figure 2). Adenopathies were not observed. Biopsy of the pancreatic nodule was performed’). Posteriorly, a 111 in octreotide scintigraphy was performed that revealed a well-defined focus of increased uptake of the radiopharmaceutical in the region of the head of the pancreas, so the likelihood of neuroendocrine neoplasms is increased (figure 3). In the biopsy performed in the US endoscopy were observed cells without a definite arrangement, relatively abundant cytoplasm, round nuclei with slight pleomorphism and nucleoli less evident. These cell aggregates with dense hyaline stroma and artefacts stretch were similar to those seen in small-cell-type cancers. The immunohistoquimic examination showed positivity for cytokeratin 8 (CK8)/18, chromogranin and synaptophysin; and was negative for CK7, CK20 and CD45, favouring malignant epithelial neoplasm—pancreatic neuroendocrine carcinoma. So, the complementary studies suggested the presence of a gastric GIST and a neuroendocrine carcinoma of the pancreas.

In this sense, the patient underwent a radical subtotal pancreatectomy and partial gastrectomy with Roux Y jejunal transposition. Histologically, the gastric lesion was characterised by spindle cell proliferation with storiform

Figure 2 Abdominal ultrasound.

Figure 3 Octreoscan.

pattern and fasciculated arrangement, elongated nuclei with regular edges and with fine chromatin, without nucleoli or with a tiny nucleolus (figure 4). No mitotic figures were identified in 50 high-magnification fields. The dissected lymph nodes showed reactive changes. Immunohistoquimic examination was conducted for vimentin, CD117, PS100, desmin and muscle-specific actin. There was immunoreaction with anti-vimentin and CD117 (figure 5). The pancreatic nodule consisted of a tumour with solid, trabecular or cordonal growth pattern, consisting of elements with slight pleomorphism cytoplasm and well-defined limits, grainy texture, round or oval nuclei, with coarse chromatin and evident nucleoli (figure 6). Presence of 2 mitoses per 10 high-power fields (HPFs). Not identified venous or lymphatic vascular invasion. Together with the piece of pancreatectomy, only one of the excised lymph nodes was fully occupied by epithelial structures, compatible with metastasis of neuroendocrine carcinoma (figure 7). The excision of both lesions was complete. In conclusion, the pathological examination revealed a gastric GIST with 3 cm, with no mitotic figures in 50

Figure 4 Well-defined neoplasia of the gastric wall.

Figure 5 Fascicular spindle cell, marked for CD117.

high-magnification fields, favouring a benign behaviour; and a well-differentiated neuroendocrine carcinoma of the pancreas with 1.1 cm, with the presence of one metastatic lymph node.

The Oncology Group decision was to carry out surveillance and to undertake a positron electron tomography (PET) scan and octreoscan to assess the need for adjuvant treatment. Since neither PET CT nor Octreoscan showed evidence of metastatic focus, the patient did not carry out adjuvant therapy.

DIFFERENTIAL DIAGNOSIS

- ▶ Pancreatic adenocarcinoma with gastric invasion
- ▶ Gastric lymphoma with peri-pancreatic lymph nodes
- ▶ Gastric and pancreatic neuroendocrine tumours.

OUTCOME AND FOLLOW-UP

The 24-month follow-up (gastroscopy, radiology, abdominal and pelvic CT, PET scan and octreoscan) has not demonstrated relapse of any neoplasm.

DISCUSSION

GISTs most commonly occur sporadically, but show an increased tendency in patients with NF1. A small number

Figure 6 Detail of the neoplastic cells (above). Evidence of neuroendocrine differentiation (bottom).

Figure 7 Lymph node completely metastasised, with scanty residual lymphoid tissue.

of pancreatic neuroendocrine tumours have been described in NF1 patients. There were only nine reports of GISTs associated with neuroendocrine tumour of the pancreas and almost all of these have been diagnosed in patients with NF1.¹

In summary, this is the second case report of a non-NF1 patient that had a pancreatic neuroendocrine tumour coexistent with a gastric GIST.

GISTs, thought to arise from interstitial Cajal cells of the gastrointestinal wall, demonstrate no clear gender predilection; the affected individuals are mainly adults between the 6th and 8th decade. Gastric GISTs can be incidentally detected during endoscopy, an imaging study or in a surgical specimen, given that they are slowly growing tumours localised within a deeper layer of the gastrointestinal wall. Although our patient was asymptomatic, GISTs usually manifest with non-specific symptoms, such as nausea, vomiting and abdominal pain or, most often, with bleeding, due to protrusion of the tumour and stretching of the overlying mucosa; metastasis may sometimes constitute the initial symptom. Optimal therapy includes surgical excision and treatment with imatinib. The latter is appropriate for non-operable tumours, cases where total excision is impossible or for recurrences, its use as adjuvant therapy in high-risk patients is still controversial. Concerning prediction of clinical behaviour, the initial proposal formulated by the National Institute of Health (NIH) GIST Workshop in 2001 defined the risk for aggressive behaviour based on tumour size (single largest dimension) and mitotic count (the number of mitotic figures per 50 HPF), classifying GISTs into very low, low, intermediate and high risk categories. This classification is widely used for predicting postoperative malignant potential. However, other pathological factors may help in the prediction of the prognosis, including c-kit mutation, cellular necrosis, interstitial necrosis and lesion site. In our case, the GIST was classified as of the low risk (2–5 cm; <5/50 HPF) category according to the NIH criteria. If the clinical malignancy has been assessed as low, the metastatic risk is estimated at 0%.³

Endocrine tumours of the pancreas can occur with typical syndromes due to hormonal hypersecretion, such as insulinoma, gastrinoma, VIP-oma, glucagonoma and somatostatinoma, but in a percentage of 40–50 they are non-functioning or secrete peptide with a low biological impact, such as pancreatic polypeptide and neurotensin. Histopathological examination is the main criterion of the WHO classification, which takes into account: tumour size, the number of mitoses, presence of cellular atypias, proliferative index and angioinvasion.⁴ By this classification, the tumours are divided into three grades. Briefly, grade 1 (G1) ETs were characterised by a variable structure, either with insular, trabecular, acinar, diffuse or mixed patterns, and by a monomorphic cytology with low atypia and rare if any mitosis (<2/10 HPFs). Grade 2 (G2) ETs showed focal moderate cytological atypia with a few scattered mitotic figures (2–10/10 HPFs) and spotty necrosis. Grade 3 (G3) ETs demonstrated a solid growth pattern; the tumour cells were small, round or oat-cell-like with marked nuclear pleomorphism, brisk mitotic activity (>10/10 HPFs) and sizeable areas of tumour necrosis.⁵ In our case, the neuroendocrine tumour of the pancreas presented a solid or trabecular growth pattern, and two mitoses per 10 HPFs. Despite having an intermediate mitotic index, it already had lymph node metastasis at diagnosis. Some studies have suggested a limitation of the current WHO classification in the assessment of the metastatic behaviour of GEP NETs. They demonstrated that small, low-grade NETs, with a low proliferative index, which met the criteria of the WHO classification criteria for benignity, behaved in a highly aggressive manner. On the other hand, large, and high-grade, with a high proliferative index NETs, which met the WHO classification criteria for malignancy, behaved in a benign manner, that is, without metastatic disease. Previous studies suggest that tumours with a short cell cycle may grow rapidly but without necessarily manifesting numerous mitotic figures at any moment.^{5–6} In addition, reports indicate that nuclear survivin and valosin-containing protein (p97) are useful prognostic factors in NETs.^{7–8} Additionally, some studies defend an increased risk of synchronous malignancies in GEP NETs and the need for a thorough search for additional neoplasms in these patients.^{9–11}

In the case of familial GIST, the family members present a mutation of c-kit protooncogene. These individuals are characterised by particular genotypic features including nuchal, neck, hand, perianal and perioral skin hyperpigmentation. Moreover, a number of other syndromes associated with c-kit mutation and multiple stromal tumours have been described, and they manifest dysphagia, skin hyperpigmentation or histologically confirmed hyperplasia of Cajal cells or myenteric ganglion cells.³

GEP NETs are usually sporadic, but they may also be multiple and may occur in some genetic syndromes such as multiple endocrine neoplasia type 1, von Hippel–Lindau syndrome, NF1 and tuberous sclerosis. Their frequency in these syndromes varies from very low (<1%) for carcinoid to high (80–100%) for pancreatic endocrine tumours (insulinomas 5–20%, gastrinomas 25–30% and non-functioning >50%).⁴

Thus, certain familiar conditions and syndromes favour the development of multiple neoplasias. However, there are very few cases of NF1-related concurrent GEP NETS

and GISTs and also a very little understanding of the prognostic implications of such concurrent tumours. Available evidence suggests that mutations in the NF1 gene might be involved in the pathogenesis of GIST in NF1 patients.¹ However, it is unknown whether the same mutation exists in NF1 patients with coexistent GISTs and GEP NETs, and more importantly, it is unknown whether there are such mutations in non-NF1 patients with coexistent GISTs and GEP NETs.¹ A meticulous follow-up (along with a well-scheduled initial therapeutic approach) should be performed for all patients suffering from the aforementioned neoplasms so that the devastating consequences of a metastatic disease are avoided.²

In patients with NF1, NF1 gene mutation occurs and its gene product—neurofibromin—acts as a tumour suppressor. Functionally, neurofibromin reduces cell proliferation by accelerating the inactivation of the proto-oncogene p21-ras, which plays a cardinal role in mitogenic intracellular pathways. It is therefore understandable that multiple cancers arise in these patients. However, further studies are needed to determine whether in patients who do not possess this genetic disorder there will exist another that can favour the concomitant appearance of these two neoplasms. Only in this way can we predict more accurately the prognosis of these patients.

Learning points

- ▶ The presence of a neoplasm in an organ in itself should not undermine a thorough study to the exclusion of a second cancer in another organ.
- ▶ Gastrointestinal stromal tumour (GIST) can occur simultaneously with gastro-entero-pancreatic neuroendocrine tumours (NETs) in the absence of neurofibromatosis-1.
- ▶ Gastroenterologists and pathologists, in particular, should be aware of this rare phenomenon given that even single well-differentiated, sporadic (unrelated to hypergastrinaemia or A-CAG) NETs of small size may coexist with GISTs.
- ▶ The tumour grade, tumour size and mitotic activity do not accurately predict malignant behaviour of gastro-entero-pancreatic NETs.
- ▶ A meticulous follow-up should be performed for all patients suffering simultaneously from GIST and gastro-entero-pancreatic NETs.

Competing interests None.

Patient consent Obtained.

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