CASE REPORT

Duodenal somatostatinoma presenting as obstructive jaundice with the coexistence of a gastrointestinal stromal tumour in neurofibromatosis type 1: a case with review of the literature

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SUMMARY

Somatostatinomas are rare neuroendocrine tumours, mostly located in the pancreas or duodenum, with an estimated incidence of 1 in 40 million. Duodenal somatostatinomas (DSs) are usually found in association with neurofibromatosis type 1 (NF1), tuberous sclerosis and Von Hippel-Lindau syndrome. Gastrointestinal stromal tumours (GIST) have also been described in NF1, but the association with somatostatinoma is very uncommon. We report the case of a patient with NF1 who presented with obstructive jaundice due to multiple firm nodules around the ampulla of Vater. A pancreaticoduodenectomy was performed and revealed a 1 cm duodenal/ampullary mass which stained positive for somatostatin, together with a GIST also found on the duodenal wall. Despite its rarity, ampullary somatostatinomas should be considered in the differential diagnosis of biliary tract dilation in patients with NF1.

BACKGROUND

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder resulting from a mutation of the *NF1* gene that codifies for neurofibromin. Patients with NF1 have an increased risk of developing benign and malignant tumours.^{1,2} Gastrointestinal tumours associated with NF1 include mucosal and myenteric nerve hyperplasia, gastrointestinal stromal tumours (GIST), carcinoid tumours and other neuroendocrine tumours (NETs), including somatostatinomas.³ Usually, somatostatinomas are located in the pancreas or duodenum. Forty per cent of cases of duodenal somatostatinomas (DSs) occur in patients with NF1, but the incidence of somatostatinomas in these patients is only 1% to 3%.^{4–7} The incidence of GISTs in patients with NF1 is 7%,⁸ and to our knowledge, the co-occurrence of DS and GIST has only been reported in 16 cases (table 1).^{5,9–22} We report a case of a patient with NF1 who presented with abdominal pain and jaundice due to DS associated with a GIST in the duodenum.

CASE PRESENTATION

A 44-year-old woman with NF1 presented to the emergency department with right upper quadrant

abdominal pain of 1-month duration. The pain was described as dull, intermittent, moderate in intensity, non-radiating and exacerbated by eating. She denied fever, nausea, vomiting, diarrhoea, heartburn and weight loss. Her vital signs were within normal limits on presentation. On physical examination, she had icteric scleras and skin. Diffuse café-au-lait spots and neurofibromas were present on her trunk and all extremities. She had tenderness in the right upper quadrant and epigastrium.

INVESTIGATIONS

Initial laboratory testing suggested biliary tract obstruction: total bilirubin 3.4 mg/dL (n: 0.4–2.0), aspartate transaminase 71 UI/L (n: 15–41), alanine transaminase 34 UI/L (n: 14–54) and alkaline phosphatase 414 UI/L (n: 43–122). Complete blood count, electrolytes and lipase were all within the normal range. Abdominal ultrasound was significant for bile duct dilatation and cholelithiasis.

TREATMENT

The patient underwent laparoscopic cholecystectomy. An intraoperative cholangiogram showed a dilated common bile duct without stones. A post-operative endoscopic retrograde cholangiopancreatography revealed multiple firm nodules around the ampulla and a dilated common bile duct and pancreatic duct. A biopsy of the ampullary mass revealed cells that stained positive for synaptophysin, chromogranin and CK7, with a Ki-67 of 2% consistent with a low-grade neuroendocrine tumour (NET). A CT with contrast and a MRI of the abdomen and pelvis revealed dilatation of the common bile duct and the pancreatic duct (double duct sign) with a hypodensity lesion of 1×1.3×3 cm at ampulla of Vater that infiltrated the surrounding fat (figures 1 and 2). The patient underwent pancreaticoduodenectomy with lymph node resection. Histopathology showed a 1 cm mass that stained positive for somatostatin with scattered psammoma bodies in the duodenal wall (figure 3, figure 4). Two out of 10 lymph nodes were positive for tumour invasion. A 4 mm GIST was also incidentally found in the duodenal wall (figure 5). Somatostatin levels and functional positron-emitting tomography/CT (PET/CT) using radiolabelled somatostatin analogues

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Table 1 Demographic data, clinical presentation and tumour characteristics of reported cases of DS coexistence with a GIST in NF1

Publication Year	Age/Sex	Presenting symptoms	Size of somatostatinoma	Metastasis site	GIST location	Size of GIST tumour	Treatment	Outcome	Author
2000	36/Female	GI bleeding, jaundice	1.2 cm	Lymph node	Duodenum	3.5×3.5 cm	Pancreaticoduodenectomy with regional lymph node resection.	24 months alive	Karatzas <i>et al</i> ¹⁴
2002	64/Female	Pancreatitis, cholangitis	1.5 cm×0.8 cm	N/A	Stomach, duodenum, jejunum	Multiple, 0.5–3 cm	Duodenum and jejunum resection	12 months alive	Usui <i>et al</i> ²⁰
2004	62/Female	Anorexia, weight loss	5.0 cm	Liver	Stomach, jejunum	Multiple, 1 cm	Gastrojejunal bypass	12 months alive	Suzuki <i>et al</i> ⁹
2005	43/Female	GI bleeding	1.5 cm	Lymph node, pancreas	Jejunum	3.5 cm in diameter	Pylorus-preserving pancreaticoduodenectomy	12 months alive	Kramer <i>et al</i> ¹⁵
2006	45/Female	Heartburn, dysphagia and intermittent abdominal pain	1.6×1.6×1.1 cm	N/A	Duodenum	1.5×0.8×0.8 cm	Excisional mass biopsy	Not described	Juergens <i>et al</i> ¹³
2007	47/Male	GI bleeding	1.7×1.2 cm	Liver, lymph node	Jejunum	7.0 cm	Pancreaticoduodenectomy, hepatic wedge resection	16 months alive	Bentini <i>et al</i> ¹⁰
2008	59/Female	None (high hepatobiliary enzymes)	3.0×2.5 cm	Lymph node	Duodenum	Multiple, 0.5–1.0 cm	Pylorus-preserving pancreaticoduodenectomy	48 months alive	Ikedo <i>et al</i> ¹²
2008	49/Female	None (dilated biliary duct)	5.0 cm	N/A	Stomach	5.0 cm in diameter	Pancreaticoduodenectomy	72 months alive	Sakorafas <i>et al</i> ⁶
2009	36/Male	Jaundice	3.5×3.4×2.2 cm	Lymph node	Jejunum	0.5×0.5×0.4 cm	Pancreaticoduodenectomy with partial jejunum resection	1 year alive	Chetty <i>et al</i> ¹¹
2010	43/Male	GI bleeding	1.8×2.0×2.0 cm	N/A	Duodenum, jejunum	Multiple, 0.2–0.7 cm (largest one is 2 cm)	Pylorus-preserving pancreaticoduodenectomy with proximal jejunal resection	18 months alive	Relles <i>et al</i> ¹⁸
31/Male		Dysphagia, abdominal discomfort	0.7×0.4×0.4 cm	N/A	Duodenum, jejunum	0.5 cm, 1.2 cm	Duodenal and jejunal mass resection with reconstruction	6 months alive	
2012	67/Female	None (dilated biliary and pancreatic duct)	two masses, 2.3 cm and 1.8 cm in dimension	Lymph node	Duodenum	3.0 cm	Pylorus-preserving pancreaticoduodenectomy	12 months alive	Yoshida <i>et al</i> ²²
2013	51/Female	Abdominal discomfort	Not described	N/A	Duodenum, jejunum	Not described	Pancreaticoduodenectomy and imatinib	Alive	Afsar <i>et al</i> ⁹
2014	68/Female	Incidental finding from an autopsy	2 cm	N/A	Small bowel (unspecified location)	Not described	N/A	N/A	Njei <i>et al</i> ¹⁷
2016	81/Female	Diarrhoea	2.0×1.5 cm	Liver, lymph node	Duodenum	Not described	Subtotal stomach-preserving pancreaticoduodenectomy, hepatic wedge resections	49 days later dead (complication after surgery)	Yamamoto <i>et al</i> ²¹
2016	50/Female	GI bleeding	Multiple, 0.5–2.5 cm	N/A	Duodenum	0.4×0.4×0.3 cm	Pylorus-preserving pancreaticoduodenectomy	10 days later dead (complication after surgery)	Kumar <i>et al</i> ¹⁶
Our case	44/Female	Abdominal pain, jaundice	1 cm in dimension	Lymph node	Duodenum	0.4 cm	Pancreaticoduodenectomy	12 months alive until now	N/A

DS, duodenal somatostatinoma; GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1.

Figure 1 An axial (A) and coronal (B) CT scan of upper abdomen with contrast demonstrated a hypodensity lesion with infiltration of surrounding fat (white arrow) and dilatation of both common bile duct and pancreatic duct (double duct sign; white asterisks) with suspected mass at the area of ampulla of Vater.

were not performed preoperatively as somatostatinoma was not anticipated in this patient.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful. After surgery, somatostatin levels were 25 pg/mL ($n < 30$ pg/mL) and screening for pheochromocytoma was negative. Somatostatin levels, CT scan and MRI of the abdomen and pelvis have been followed for surveillance and have shown no evidence of recurrent disease or metastasis. The patient remains free of disease 1 year after surgery. Considering the reported correlation between MEN (multiple endocrine neoplasias) and somatostatinomas, it is important to note that although the patient was not screened for MEN1 mutation, she did have normal parathyroid hormone and other minerals levels. Moreover, there was no pituitary lesion noted on a recent head MRI.

DISCUSSION

Patients with the NF1 have an increased risk of developing benign and malignant tumours, with a cumulative cancer risk of 20% in affected patients who are older than 50 years of age.^{1 2 6 23 24} This is thought to be in part mediated by loss-of-function mutations in neurofibromin which regulates cell proliferation.²⁵ A reduction or complete loss of normal function of neurofibromin results in activation of the RAS signal transduction pathway and ultimately in stimulation of cell proliferation and survival.²³ Deletion of cyclin-dependent kinase inhibitor 2A and mutations in tumour protein 53 have also been reported in these patients and are thought to contribute to their increased risk of tumour formation.^{24–27}

Figure 2 An axial (A) and coronal (B) section of abdominal MRI T2 showing a dilatation of both common bile duct and pancreatic duct (double duct sign; black asterisks) with hypodensity lesion suspected mass on a coronal view (size 1×1.3×3 cm) obstructed at the ampulla of Vater (white arrow).

Figure 3 (A), (B) This is a H&E stain of well-differentiated duodenal neoplasm composed entirely of the somatostatin-producing cell as polygonal cells with abundant eosinophilic cytoplasm arranged in solid nests and pseudoglandular foci (black asterisks) with psammoma bodies (C) and (D) (black arrow) located in the duodenal wall.

Somatostatinomas are rare gastrointestinal NETs that develop from enteric endocrine cells and that are believed to originate from endodermal cells. Histologically, they are similar to other well-differentiated NETs, staining positive for synaptophysin and chromogranin A; somatostatinomas specifically usually have psammoma bodies and show diffuse staining for somatostatin.^{4 28} Pancreatic somatostatinomas tend to be larger in size (typically >4 cm) and often have a more aggressive course than the DSs.²⁹ Pancreatic somatostatinomas usually cause somatostatin syndrome, presenting with hyperglycaemia, abdominal pain, gastrointestinal bleeding, jaundice, diarrhoea, steatorrhoea and weight loss.^{23 30} In contrast, DSs are about 2–3 cm in diameter at the time of diagnosis and patients present with non-specific symptoms including abdominal pain (25%), jaundice (25%) and cholelithiasis (19%).^{29 31} Most cases of DSs occur in association with NF1.

The main peptide released from somatostatinoma is somatostatin, which should be measured at diagnosis and followed thereafter as a tumour marker for surveillance. These tumours express somatostatin receptor types 2 and 5 and therefore, can be localised using somatostatin receptor-based imaging techniques. Gallium 68 DOTA-D-Phe¹-Tyr³-Octreotate (⁶⁸Ga-DOTATATE) is the radiotracer with the highest sensitivity,³¹ and the use of ⁶⁸Ga-DOTATATE PET/CT, along with upper gastrointestinal endoscopy, endoscopic ultrasound, CT scan and MRI should be considered for the localisation, staging and

Figure 4 (A) and (B) demonstrated immunohistochemistry staining (brown colour) of somatostatin-producing cell in duodenum tissue under duodenal mucosa.

Figure 5 (A) H and E stain of 4 mm of GIST tumour in the duodenal wall (black arrow). (B) Presence of GIST with spindle cell arrangement showing immunoreactivity for CD117 (black arrow). GIST, gastrointestinal stromal tumour.

preoperative assessment of NETs and somatostatinomas specifically.³² ⁶⁸Ga-DOTATATE PET/CT has the added benefit of allowing the assessment of somatostatin receptor status which is relevant to predict the tumour's response to somatostatin analogues and peptide receptor radioligand therapy.³¹

Surgical resection is recommended considering its malignancy potential. Local lymphadenectomy should be considered in tumours that are >1 cm since they are more likely to invade beyond the submucosa and tend to metastasise to lymph nodes. Whipple's operation with regional lymphadenectomy should be considered for more aggressive or larger tumours. Radiation and chemotherapy are also treatment options, but most metastatic NETs are unresponsive to chemotherapy.^{33–37} For tumours <1 cm, there is no consensus regarding management, although endoscopic excision is considered a reasonable approach because of the low incidence of metastasis and lymph node involvement.

GISTs are rare mesenchymal tumours that arise from the digestive tract, with a reported incidence of 7 to 20 per million, accounting for <1% of all gastrointestinal tumours.³⁸ They commonly occur in patients with NF1, and autopsy studies have reported as many as one of three patients with NF1 to have GISTs.³⁹ Histologically, they are composed of mesenchymal spindle, epithelioid or pleomorphic cells and are usually CD117 or CD34 positive on an immunohistochemical stain. Its presentation can vary from simple abdominal pain, vomiting, bowel obstruction to gastrointestinal bleeding or it can be found incidentally in asymptomatic patients. The standard treatment is also surgical excision and possibly adjuvant chemotherapy (imatinib) on advanced stages.^{40 41}

The coexistence of somatostatinoma and GISTs in a patient with NF1 is uncommon; after a literature review on MEDLINE, Cochrane and EMBASE from inception to June 2018, we identified 16 reported cases as shown in table 1.

Seventy-six per cent of the patients were women, with ages ranging between 30 and 80 years. Presenting symptoms were mainly associated with the local effect of the somatostatinoma tumour and included abdominal pain, gastrointestinal bleeding and signs of biliary obstruction. The size of the somatostatinomas from pathological reports ranged from 2 to 3 cm, with only two cases >5 cm. Lymph nodes are a common location site of metastasis, and eight cases had lymph node involvement. In most cases, GISTs were incidentally found and generally located in the duodenum (11 cases), others less common location included the stomach and jejunum. Almost every patient (12 cases) underwent a Whipple procedure. Thirteen patients (82%), including ours, were reported to be alive after 6 months; 2 patients deceased due to complications after surgery, and 2 cases were incidentally found in the autopsy.

It is unknown whether the coexistence of somatostatinomas and GISTs in patients with NF1 is a coincidental finding or a rare association resulting from a common underlying molecular event. Mutations in the KIT and platelet-derived growth factor receptor alpha genes that are found in >80% of GISTs are lacking in patients with NF1.³⁹ Instead, loss of heterozygosity of neurofibromin 1 gene consequencing to have negative regulation in the RAS signal transduction pathway has been found in GISTs associated with NF1.^{39 42} Similar findings in insulinomas of patient with NF1 suggest that the same mechanism underlies tumourigenesis of neuroendocrine tumours (NETs), such as somatostatinomas, in this population. Along these lines, and making it more likely that they might share common pathogenesis with somatostatinomas, GISTs have been found to express synaptic-like microvesicle proteins, as is commonly found in NETs.⁴³ In addition, GISTs have been reported in patients with MEN1 and 2,^{44 45} supporting the possible neuroendocrine nature of GISTs.

Establishing an association between GISTs and DSs in patients with NF1 can be a hint to help determine the genetic mechanisms behind the development of these tumours in patients with NF1. If this relationship is indeed proven, acknowledging and recognising would allow for better preoperative planning and intraoperative evaluation, helping avoid multiple operations with unrecognised lesions at the time of initial surgery.

Learning points

- The patient with neurofibromatosis type 1 (NF1), who presents with jaundice and abdominal pain similar to cholelithiasis, should consider duodenal somatostatinoma (DS) as a possible diagnosis.
- DSs do not cause somatostatinoma syndrome and tissue specimens are needed to establish the diagnosis.
- Coexistence of gastrointestinal tumour with DS in NF1 should be investigated.
- In NF1, physicians should be aware of the risk of developing associated cancers. Surveillance and monitoring investigation possible are considered being beneficial.

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