CASE REPORT

A rare cause of obstructive jaundice and weight loss in Von Recklinghausen's disease

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ABSTRACT

We present the case of a patient with the rare triad of Von Recklinghausen's disease associated with a somatostatinoma and a gastrointestinal stromal tumour (GIST). The patient had recurrent jaundice, the typical somatostatinoma syndrome, positive MR imaging but negative ^{68}Ga-DOTATOC PET scanning in a histopathology-proven somatostatinoma tumour.

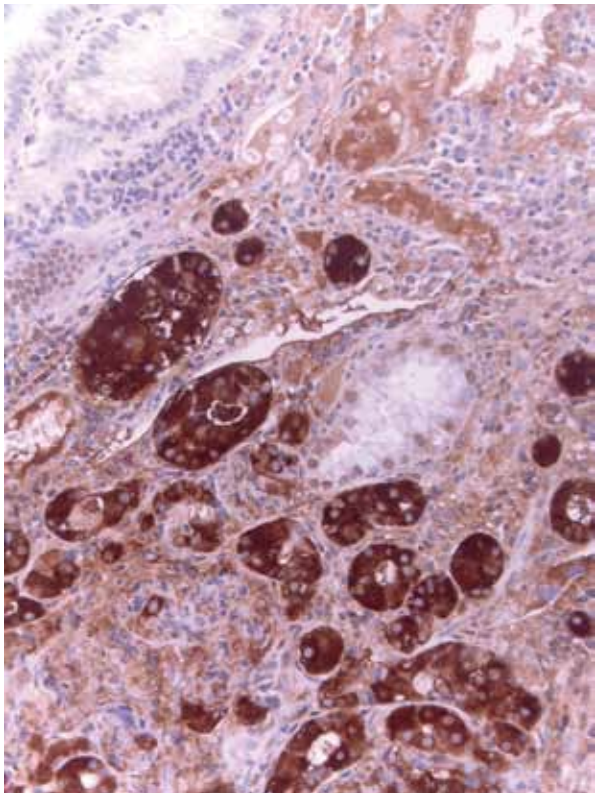
KEYWORDS

^{68}Ga-DOTATOC PET scan, gastrointestinal stromal tumour, MR imaging, somatostatinoma, Von Recklinghausen's disease

CASE REPORT

A 48-year-old male with a history of Von Recklinghausen's disease presented with recurrent, spontaneously resolving jaundice, diarrhoea and weight loss of 6 kg. Laboratory results showed serum bilirubin levels varying between 50 μmol/l and 165 μmol/l (normal <17 μmol/l) with corresponding fluctuations in cholestatic liver enzymes. Ultrasonography and CT scanning revealed a markedly dilated gallbladder (calculated fasting volume 240 ml; normal <50 ml) with sludge and multiple concrements, dilated intra- and extra-hepatic bile ducts, and a hypodense mass at the pancreatic head, near the distal common bile duct and duodenal wall. Additional lab investigations demonstrated marked steatorrhoea with faecal fat excretion of up to 90 g/day. Blood glucose levels were mildly elevated (9.2 mmol/l). Upper gastrointestinal endoscopy revealed a polypoid mass around the papilla of Vater. Immunohistochemical staining of biopsy specimens revealed a somatostatinoma (*figure 1*). A gastric emptying study with scintigraphy performed after the diagnosis of somatostatinoma showed delayed gastric emptying for a solid meal with $t_{1/2}$ of 103 min (normal values: 53 to 79 min). The somatostatinoma was functionally active

Figure 1. *During duodenoscopy, biopsies were taken from the polypous tissue near the papilla of Vater. After standard fixation and processing of the polypous tissue, immunohistochemistry with antisomatostatin antibody (somatostatin stain, red brown) was performed. Intense cytoplasmic labelling of somatostatin is evident and multiple psammoma bodies are identified (original magnification, x20)*



with an inhibitory syndrome (delayed gastric emptying, gallbladder stasis, diarrhoea and steatorrhoea, weight loss, diabetes mellitus). Plasma somatostatin concentrations were measured and appeared to be elevated, under fasting and fed conditions with values of 400 pmol/l and 600 pmol/l, respectively (normal value <150 pmol/l). The postprandial increase in serum levels of gastrointestinal peptides such as gastrin and pancreatic polypeptide (PP) was suppressed (normal postprandial increase of gastrin and PP: 40 to 100 pmol/l) and may have resulted from the inhibitory effect of somatostatin (*figure 2*).

Additional MR imaging showed a large mass in the ampullary region extending to the pancreatic head (*figure 3A* and *B*). A ^{68}Ga-DOTATOC PET scan was performed for staging and detection of possible metastases. ^{68}Ga-DOTATOC (tracer) is a somatostatin receptor agonist which reflects the expression of somatostatin receptors on the tumour surface. The ^{68}Ga-DOTATOC PET scan showed a lack of abnormal tumoural ^{68}Ga-DOTATOC uptake (*figure 3C*). Co-registered MR-PET imaging showed ^{68}Ga-DOTATOC hyperactivity in the kidneys because of physiological excretion, but no specific hyperactivity at the site of the tumour (*figure 3D*).

During laparotomy, a lesion in the ampullary region extending to the pancreatic head was palpated. In addition, a 0.6 x 0.6 cm tumour was observed on the outer surface of the jejunum. A pylorus preserving pancreaticoduodenectomy and resection of the jejunal tumour was performed. Histological examination revealed a somatostatinoma in the pancreatic specimen with a diameter of 3.5 cm and one positive lymph node ($pT_3N_1M_x$ stadium). The presence of a high amount of somatostatin was confirmed by immunohistochemistry. The jejunal lesion with CD117/c-kit expression revealed a gastrointestinal stromal tumour (GIST) (*figure 4*). Postoperative recovery was uneventful. After a follow-up period of two years (clinical follow-up every six months and yearly CT imaging), we have not observed any sign of recurrence.

Figure 2. *Results of a nutrition challenge test: Plasma somatostatin, gastrin and pancreatic polypeptide (PP) levels, fasting and after ingestion of a fat-rich 600 kCal meal. The meal was ingested at time 0 min. Fasting and postprandial plasma somatostatin is increased (normal value <150 pmol/l). The postprandial response of gastrin and PP is impaired (normal postprandial increase of gastrin and PP: 40 to 100 pmol/l)*

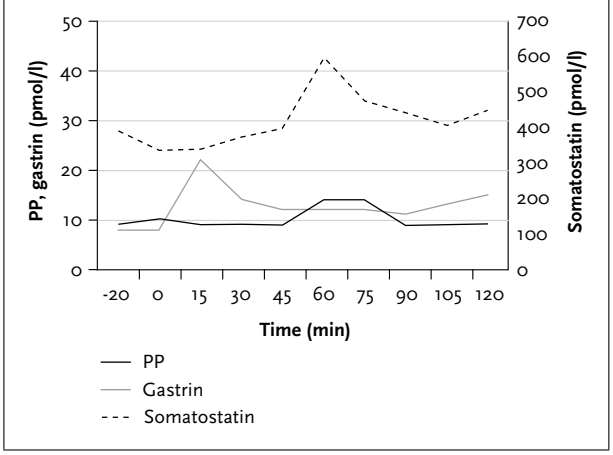
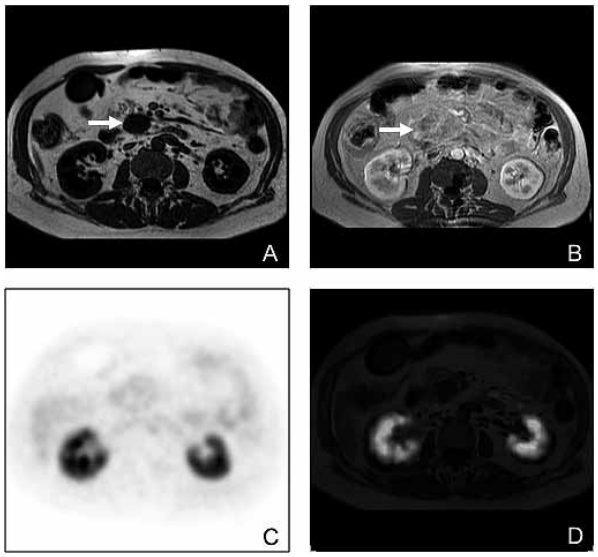


Figure 3. *T1-weighted MR image shows a large mass (with low signal intensity, arrow) in the ampullary region extending to the pancreatic head (A). Post-gadolinium contrast enhanced T1-weighted MR imaging shows an intense arterial enhancement of the tumour (arrow), which reflects the abundant blood supply characteristic of neuroendocrine tumours (B). Transverse ^{68}Ga-DOTATOC PET (C) and co-registered MR-PET image (D) show only specific uptake in the kidneys but not in the somatostatinoma tumour area*



DISCUSSION

Somatostatinomas are malignant, somatostatin-producing neuroendocrine tumours (NETs). They are rare with an estimated annual incidence of one per 40 million and a median age at onset of 54 years. In over 90% of patients these tumours are symptomatic.[1] The classical syndrome in a patient with a somatostatinoma is characterised by diabetes mellitus, cholelithiasis, diarrhoea with steatorrhoea and hypo- or achlorhydria resulting from the inhibitory actions of somatostatin on gastrointestinal motility and secretion. Somatostatin inhibits the secretion and the action of various regulatory peptides and hormones, such as insulin, cholecystokinin (CCK), glucagon, gastrin, and PP. Thereby, motor and secretory functions as gallbladder contraction, pancreatic enzyme secretion, and gastric acid secretion are impaired.[2]

The incidence of a GIST is 4 to 22 per 1,000,000. Somatostatinomas as well as GISTs are increasingly being recognised in association with Von Recklinghausen's disease. Of the somatostatinomas that have been reported to originate in the peri-ampullary region 40% were associated with Von Recklinghausen's disease. GISTs occur in up to 3.9 to 25% of patients with Von Recklinghausen's disease.[3,4] The prevalence of Von Recklinghausen's disease in patients with GIST is up to 6%.[5] A review of the literature revealed seven previously reported cases of this rare clinical triad presented here.[3,4,6-10]

Most NETs demonstrate low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Moderate or intense early enhancement of portions of the primary NETs reflects the abundant blood supply of these tumours.[11-13] The complete spectrum of MR imaging (*figure 3*) confirms the above-mentioned imaging features. Positive and negative predicted values for MR imaging in the detection of 22 NETs reported by Semelka *et al*. were 96 and 100%, respectively.[11] For this reason, we suggest a more prominent future role for MR imaging in the diagnosis and evaluation of suspected NETs.

^{68}Ga-DOTATOC PET is increasingly used as it is superior for the detection of NETs compared with conventional somatostatin receptor scintigraphy (SRS) with SPECT and diagnostic CT.[13-15] Evaluation of the diagnostic value of ^{68}Ga-DOTATOC PET compared with SRS with SPECT and CT in 84 patients with known or suspected NETs by Gabriel *et al*. resulted in 97% sensitivity for PET, 52% for SPECT and 61% for CT; 92% specificity for PET, 92% for SPECT and 71% for CT and 96% accuracy for PET, 58% for SPECT and 63% for CT. These differences in diagnostic efficacy were statistically significant in favour of ^{68}Ga-DOTATOC PET ($p<0.001$). The combined use of PET and CT showed the highest accuracy.[15] DOTATOC PET scanning is important in the preoperative work-up as it provides information on possible metastases. Although several authors reported positive SRS and ^{68}Ga-DOTATOC PET scans in cases of somatostatinomas, the tumour in our patient lacked uptake on the DOTATOC scan.[13-17] We postulate that the reason for the absence of radiolabelled somatostatin uptake in our case may be due to locally high somatostatin concentrations that resulted in either down-regulation of the somatostatin receptors on the tumour surface reducing the binding potential for the small fraction of radiolabelled DOTATOC, or in competitive binding with the labelled somatostatin.

CONCLUSION

Although somatostatinomas and GISTs are rare tumours, they should be considered in patients with Von Recklinghausen's disease with unexplained gastrointestinal symptoms. Our patient had a functional somatostatinoma with clinically overt inhibitory somatostatinoma syndrome. Although ^{68}Ga-DOTATOC PET is superior for the detection of NETs compared with SPECT and CT, the tumour in our patient lacked uptake of ^{68}Ga-DOTATOC. Diagnostic accuracy of MR imaging in detecting NETs is promising and combined with ^{68}Ga-DOTATOC PET scanning may provide the most accurate diagnostic tool for preoperative staging of gastrointestinal neuroendocrine tumours, including somatostatinomas.

ACKNOWLEDGEMENTS

We thank our colleagues B. Brans, for his critical revision of the manuscript and his useful comments and Ms. N. Helgers, for developing the co-registered MR-PET image (both working at the Department of Nuclear Medicine at Maastricht University Medical Centre, the Netherlands).

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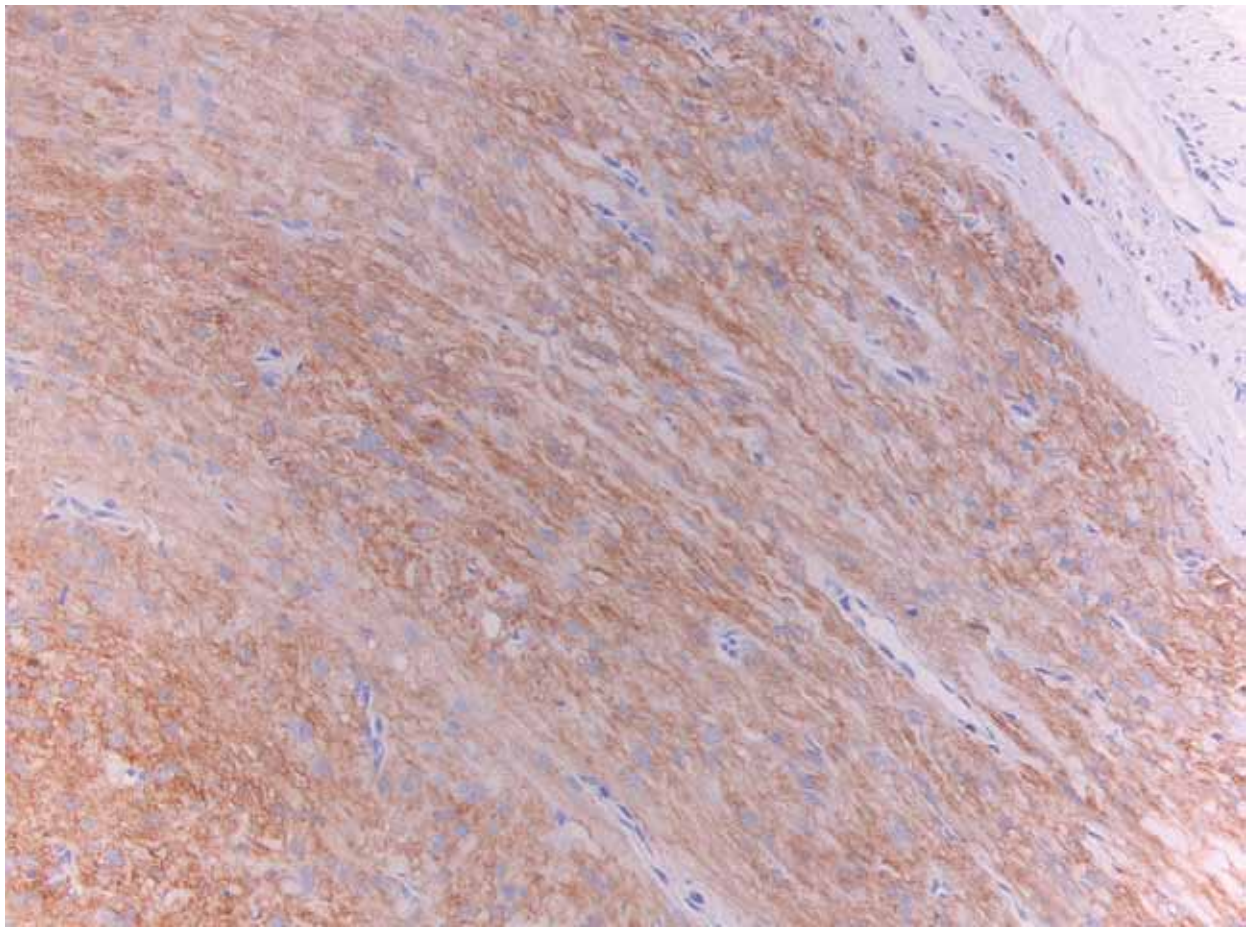
Figure 4. *After standard fixation and processing of the jejunal tissue, immunohistochemistry with anti-c-kit protein (CD117) was performed. CD117 stain is the product of the c-kit proto-oncogene that encodes a tyrosine-kinase receptor, which is responsible for cellular proliferation in GISTs. Positive CD117 stain (red-brown) revealed a gastrointestinal stromal tumour (original magnification, x20)*



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