Somatostatin-producing Endocrine Tumour of the Duodenum Associated with Type 1 Neurofibromatosis

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Type 1 neurofibromatosis (NF1) is an autosomal dominant neurocutaneous disorder resulting from mutations of the *NF1* gene located on chromosome 17q11.2, which encodes neurofibromin, a GTPase activating protein (GAP) that negatively regulates p21-RAS signalling involved in cellular proliferation and differentiation control (1). Mutations of *NF1* lead to abnormal tumour suppression function with increased prevalence of benign and malignant neoplasms, including neuroendocrine tumours. Gastrointestinal lesions are reported in 25% of NF1 patients. They include: (*i*) hyperplasia of the gut neural tissue, (*ii*) gastrointestinal stromal tumour (GIST), and (*iii*) endocrine tumours of the duodenum and periampullary region (2). Duodenal somatostatin-producing neuroendocrine tumour (or duodenal somatostatinoma (DS)) is a rare malignant tumour that may be associated with NF1 (2–5). We report here a case of such association and discuss its management.

CASE REPORT

A 47-year-old man has been followed in our department since 2005 for NF1. He displayed the "classical" features of NF1, e.g. café au lait macules, multiple cutaneous and subcutaneous neurofibromas, axillary and inguinal freckling, and bilateral Lisch nodules. He was otherwise in good health.

In 2007, he was admitted for investigation of abdominal pain, transit changes with diarrhoea alternating with constipation and one episode of gastrointestinal bleeding.

Laboratory tests, including full blood cell count, C-reactive protein, and liver function tests, were within normal ranges. Pancreatic enzymes were not screened. Abdominal ultrasound was normal. Abdominal computed tomography scan revealed a 25 mm mass located in the second portion of the duodenum. There was no other anomaly involving the liver, the spleen or any lymph node enlargement. Oesophagoduodenoscopy and endoscopic retrograde cholangiopancreatography showed a polypoid tumour extending to the pancreas head. Two endocrine tumour markers, neurone-specific enolase and chromogranin A, were elevated at 14.6 ng/ml (normal < 12.5 ng/ml) and 82 ng/ml (normal < 70 ng/ml), respectively. A cephalic duodenopancreatectomy associated with cholecystectomy was performed in June 2008. Pathological examination of the resected mass revealed a duodeno-pancreatic highly differentiated endocrine carcinoma. No vascular embolism or perineural infiltration was observed. Immunohistochemistry showed that the tumoural cells expressed endocrine markers such as synaptophysine, chromogranin A, CD56 and somatostatin, which was consistent with the diagnosis of somatostatinoma. Mitotic index, measured by Ki-67 labelling was below 5%. Six out of the 15 resected regional lymph nodes were invaded by tumoural cells without capsule effraction. According to these findings and the World Health Organization (WHO) classification of gastroenteropancreatic neuroendocrine tumours (6), a final diagnosis of well-differentiated somatostatin-producing carcinoma of the ampulla with lymph node metastases was made. The post-operative course was uneventful. There was no indication of adjuvant treatment. No recurrence occurred during the first 10 months of follow-up.

DISCUSSION

To date, more than 100 cases of DS have been reported in the literature. They display positivity for endocrine markers, especially synaptophysine and chromogranin A, and most cells have somatostatin receptors (4). DS tend rapidly to produce local symptoms related to local mass effects: jaundice, abdominal pain and gastrointestinal bleeding (7, 8). Classic somatostatinoma syndrome (steatorrhoea, cholelithiasis, diabetes mellitus-like symptoms), often observed in pancreatic tumours, is rarely present in DS. It occurs in only 10% of cases and is always incomplete (2, 9).

Approximately 14–43% of DS develop in NF1 patients (4, 5). In NF1, somatostatinomas typically occur in the duodenum, in the vicinity of the ampulla of Vater (10) and rarely in the pancreas (4, 5). When associated with NF1, DS appears to be smaller, because of an earlier recognition related to local symptoms, well-differentiated with a low grade of malignancy (8). However, liver or lymph nodes metastases have been reported in 35% of DS and risk of metastases significantly increases when tumours are larger than 20 mm (11). A diagnosis of duodenal tumour may be suspected based on the results of conventional imaging, such as computed tomography, ultrasound and magnetic resonance imaging.

The final diagnosis is confirmed by pathological examination and immunohistochemistry of surgical

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specimens. There is a high incidence of psammoma bodies (psammomatous calcifications) in the duodenal lesions of patients with NF1, which may be helpful in establishing the diagnosis (4).

Somatostatin-receptor scintigraphy can be useful for follow-up after surgical resection in order to detect incomplete tumour removal or metastases (12); however, its sensitivity does not allow us totally to rule out metastatic disease in the absence of marker uptake. Surgical resection is the gold standard treatment. Liver metastases do not contraindicate surgery, owing to the slow progression rate of these tumours (13). Surgical treatment results in long-term survival with an overall postoperative 5-year survival rate of 75% (4, 9).

Finally, it is of interest to note that the incidence of pheochromocytoma is higher in the subpopulation of NF1 patients with DS (approximately 15%) compared with both NF1 patients without DS (1%) and the general population (7). This triple association suggests an inherited endocrinopathy and represents a particular form of multiple endocrine neoplasia syndrome (9, 14).

DS should be suspected in any patient with NF1 who presents with gastrointestinal symptoms. NF1-associated DS has a good prognosis and does not require adjuvant therapy after surgery. Our observation acts as a reminder of the utmost importance of regular clinical evaluation of NF1 patients to examine for any clinical symptoms that may be related to a malignancy, as proposed in French guidelines for the management of NF1 (15).

The authors declare no conflict of interest.

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