CASE REPORT

VIPoma with multiple endocrine neoplasia type 1 identified as an atypical gene mutation

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SUMMARY

A 47-year-old man presented with persistent diarrhoea and hypokalaemia. CT revealed 4 pancreatic tumours that appeared to be VIPomas, because the patient had an elevated plasma vasoactive intestinal polypeptide level. MRI showed a low-intensity area in the pituitary suggestive of a pituitary tumour, and a parathyroid tumour was detected by ultrasonography and ⁹⁹Tc-MIBI scintigraphy. Given these results, the patient was diagnosed with multiple endocrine neoplasia type 1 (MEN1) and scheduled for surgery. MEN1 is an autosomal dominant disorder associated with *MEN1* mutations. Genetic testing indicated that the patient had a *MEN1* gene mutation; his 2 sons had the same mutations. Most MEN1 tumours are benign, but some pancreatic and thymic tumours could become malignant. Without treatment, such tumours would result in earlier mortality. Despite its rarity, we should perform genetic testing for family members of patients with MEN1 to identify mutation carriers and improve the patients' prognosis.

BACKGROUND

Multiple endocrine neoplasia type 1 (MEN1) is diagnosed clinically by the presence of neoplastic disease in at least two of the commonly affected organs, such as the parathyroid, anterior pituitary and pancreas. Some patients with MEN1 can remain undiagnosed for years because there is no evidence of more than one endocrine tumour, or no clinical manifestations. If there is a family history of MEN1, a diagnosis can be established with evidence of only one lesion. More accurate diagnosis of the disorder can result in a more favourable patient prognosis. Genetic testing for the proband and his or her family members is very important in the management of MEN1.

CASE PRESENTATION

In April 2013, a 47-year-old man with a 1-year history of persistent severe diarrhoea presented to our hospital. His medical history was significant for acute pancreatitis and carcinoid of the rectum. He presented thirst and was found to have dehydration and hypokalaemia (K, 1.9 mEq/L) prior to arrival. An extensive diagnostic evaluation was initiated.

Contrast-enhanced CT revealed four tumours in the pancreas—one in the pancreatic head (32×21 mm, [figure 1](#)), one in the body (14×12 mm) and two in the tail (9×7 mm and 8×7 mm, respectively). Pathological examination of specimens obtained by endoscopic ultrasonography-guided fine-needle biopsy of the

tumour in the pancreatic head revealed that the mass was suspicious for a neuroendocrine tumour of low historical grade. Blood testing revealed an elevated plasma vasoactive intestinal polypeptide (VIP) level (748 pg/mL; normal range <100 pg/mL). The patient was diagnosed with VIPoma and scheduled for surgery.

Cervical ultrasonography and CT showed a 16×9×7 mm mass around the left inferior lobe of the thyroid gland. The detected mass was positive on ⁹⁹Tc-MIBI scintigraphy ([figure 2A, B](#)). The patient's serum calcium and intact-parathyroid hormone (iPTH) levels were 12.5 mg/dL and 165 pg/mL, respectively, consistent with primary hyperparathyroidism. Gadolinium-enhanced MRI revealed a 5×5 mm low-intensity area in the anterior pituitary ([figure 2C, D](#)), but levels of anterior pituitary hormones remained within normal limits. On the basis of these results, the patient was diagnosed with VIPoma associated with MEN1.

TREATMENT

We performed pylorus-preserving pancreatoduodenectomy and resection of two tumours. Immunohistochemical staining of the resected tumours was positive for chromogranin A, synaptophysin, natural cell adhesion molecule (NCAM) and VIP ([figure 3A, B](#)). The patient's postoperative VIP level decreased to <5 pg/mL. His diarrhoea improved within several days and the postoperative course was uneventful.

OUTCOME AND FOLLOW-UP

The patient is scheduled to have follow-up including blood testing for all pituitary functions every 6 months, as well as MRI of the pituitary and

Figure 1 VIPoma contrast-enhanced CT scan revealing a mass in the pancreatic head (arrow).

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Figure 2 Parathyroid tumour and pituitary tumour. (A and B) Dual-phase ^{99m}Tc -MIBI scintigraphy representing hyperfunctioning parathyroid gland ((A) early phase, (B) delay phase). (C and D) Gadolinium-enhanced MRI showing a pituitary mass ((C) coronal section, (D) sagittal section).

abdominal CT every year. To date, no metastases have been found and his VIP level has remained below the detectable limit.

DISCUSSION

VIPoma is a rare endocrine tumour, first reported in 1957,¹ with an annual incidence of 1 per 10 million.² Approximately 60–80% patients already have metastatic disease at the time of diagnosis. It has been reported that 68-DOTA-TATE fusion positron emission tomography/CT is more sensitive for detecting metastasis than conventional CT or MRI.^{3,4} In general, MEN1 may have a favourable prognosis because of its slow progression. Patients are typically diagnosed around age 30–50 years. Timely surveillance for the development of additional malignancies affects prognosis.

MEN1 is a disorder characterised by multiple tumours of the parathyroid, pancreatic islet cells and anterior pituitary gland. The prevalence of MEN1 in Western countries has been estimated to be approximately 1–2/100 000, and its incidence might be similar among individuals of Japanese and Caucasian

descent.⁵ Some patients also develop thymic endocrine neoplasias, adrenal cortical tumours and bronchial carcinoids.

MEN1 is a highly penetrant disorder inherited in an autosomal-dominant fashion. More than 95% patients develop some clinical manifestations of primary hyperparathyroidism, such as hypercalcaemia, before the age of 50 years. *MEN1* was isolated in 1997 and has enabled physicians to recommend pre-symptomatic genetic testing for high-risk family members. *MEN1* consists of 10 exons that encode a 610-amino acid protein known as menin. Genetic tests in our patient indicated that he had a novel gene mutation in the exon8-intron9 boundary region (c.1350+1_1350+14delinsCT),^{6,7} which seems to have caused abnormal splicing. Most MEN 1 tumours are benign but some pancreatic and thymic tumours can become malignant and be associated with poor prognosis. We can establish early surveillance with genetic screening for relatives, especially children and grandchildren of the proband. Despite the atypical gene mutation, presymptomatic genetic testing of our patient's two sons revealed the same mutation. As a result of genetic screening, early identification of mutation carriers can be expected to permit pre-symptomatic diagnosis of each neoplasia and interventions that

Figure 3 Immunohistochemical staining of the resected VIPoma. The brown colour represents immunochemical detection of vasoactive intestinal polypeptide in the resected pancreatic specimen. Magnification: (A) $\times 40$ and (B) $\times 200$. Scale bars 500 μm .

will improve the prognosis of MEN1. Genetic testing plays a crucial role in early detection and treatment of this syndrome.

Learning points

- ▶ VIPoma should be considered as a differential diagnosis for persistent diarrhoea with hypokalaemia.
- ▶ Pancreatic endocrine tumours such as VIPomas can be associated with multiple endocrine neoplasia type 1, regardless of its rarity.
- ▶ Genetic tests to make a presymptomatic diagnosis should be performed.

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