VIPoma syndrome: challenges in management

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ABSTRACT

Vasoactive intestinal peptide-producing tumour (VIPoma) or Verner-Morrison syndrome is a very rare neuroendocrine tumour. It occurs in less than ten percent of pancreatic islet cell tumours, and about 70 percent to 80 percent of these tumours originate from the pancreas. Diagnosis is characteristically delayed. The first-line treatment is surgical. It may be curative in forty percent of patients with benign and non-metastatic disease. Palliative surgery is indicated in extensive disease, followed by conventional somatostatin analogue (octreotide) therapy. Somatostatin analogues improve hormone-mediated symptoms, reduce tumour bulk and prevent local and systemic effects. We present a female patient with VIPoma syndrome, which had metastasised to the liver at diagnosis. The patient underwent palliative Whipple procedure and subsequent cytoreductive radiofrequency ablations to her liver metastases. Unfortunately, after symptomatic improvement for three years, her disease progressed. Currently, she is on daily octreotide, achieving partial control of her symptoms.

Keywords: neuroendocrine tumour, radiofrequency ablation, somatostatin analogue, VIPoma, Whipple procedure

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INTRODUCTION

Neuroendocrine tumours (NETs) are extremely rare tumours. In a recent nationwide epidemiological study from Sweden, the incidence of NET was estimated to be approaching three per 100,000 individuals per year, with a slight predominance in women,[1] while the annual incidence of vasoactive intestinal peptide-producing tumour (VIPoma) in the United States has been reported as 0.05–0.2 per one million adults.[2] These tumours have a strong predilection for the gastrointestinal tract. VIPomas affect the pancreas in 90% of the cases and the tissues of neural crest origin in the remaining cases. Therefore, most of the NETs may share common clinical presentations. Unfortunately, 40%–70% of the VIPoma cases have already metastasised at presentation, commonly to the lymph nodes, liver, bone or lung.

VIPoma, also known as WDHA (watery diarrhoea, hypokalaemia, achlorhydria syndrome) was first described by Verner and Morrison in 1958.[3] These tumours secrete excessive amounts of vasoactive intestinal peptide (VIP), a hormone which stimulates adenosine 3',5'-cyclic phosphate (cAMP) production by the intestinal tract, resulting in profuse diarrhoea manifesting as water and electrolyte loss, especially potassium. Tremendous advances have been made in the management of VIPoma. Even with metastatic disease, surgery for tumour clearance or debulking is still the first-line treatment. Recently, adjuvant therapy, such as octreotide and interferon-α, has been used concurrently to control symptoms and disease.

CASE REPORT

Our patient is a 58-year-old Chinese woman, who presented in 2004 with intermittent epigastric discomfort unrelated to meals. This was associated with loose stools four to five times per day. There was no associated vomiting or weight loss. An abdominal ultrasonography revealed a suspicious epigastric mass. The patient had sought several surgical opinions, all of which reached the consensus that her disease was advanced and that she should be managed conservatively.

The patient presented at our hospital in 2006 with progressively worsening diarrhoea of up to 20 times per day and symptomatic hypokalaemia associated with generalised body weakness. She denied having other associated symptoms such as flushing, and she had never been hypertensive. Her concurrent serum potassium was 2.3 mmol/l. The patient was admitted and rehydrated, and her hypokalaemia was corrected.

An abdominal ultrasonography revealed a large mixed, echogenic irregular soft tissue mass in the head and uncinate process of the pancreas measuring 5.9 cm × 6.2 cm, with dilatation of the pancreatic duct. There was also a cystic lesion measuring 4.1 cm × 3.3 cm with

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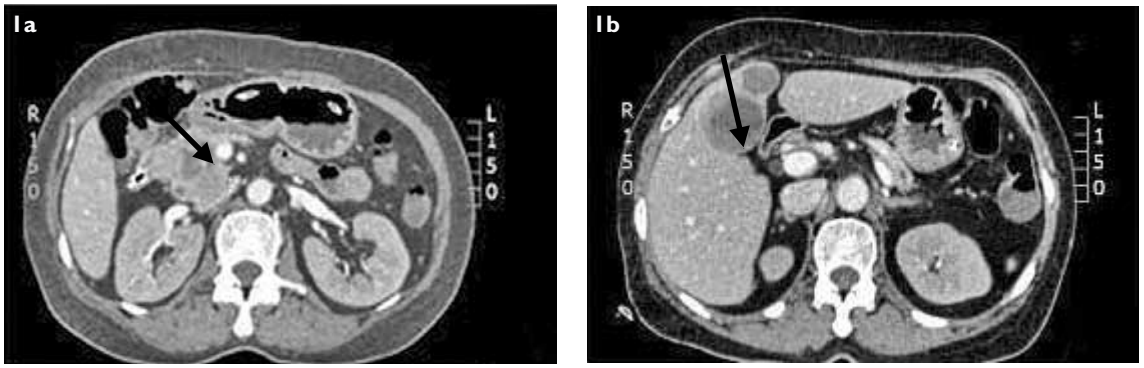

Fig. 1 Contrast-enhanced CT images of the abdomen show (a) the primary pancreatic mass (arrow); and (b) liver metastasis in the segment (arrow).

variable wall thickness seen in segment 3 of the liver, with smaller solid nodular projections arising from the wall of the lesion, while another hyperechoic lesion measuring 2.4 cm × 2.5 cm was seen in segment 7. Contrasted computed tomography (CT) of the abdomen confirmed a 5.6 cm × 5.1 cm heterogeneous mass in the head of the pancreas, with a hypodense lesion within causing partial compression of the inferior vena cava (IVC) and right renal vein (Fig. 1a). The mass displaced the second part of the duodenum laterally. Several enhancing liver lesions were also seen in segment 5 (largest 1.1 cm × 1.7 cm) and two lesions in segment 6 (largest 3.5 cm × 3.7 cm) that contained a fluid level (Fig. 1b). In addition, there were multiple sclerotic bone lesions in the L3 vertebral body, both the iliac bones and the right acetabulum. However, a bone scan that was performed was negative for metastasis.

Other investigations, including full blood count, liver function test and fasting plasma glucose, were all normal. Alpha-foetoprotein (AFP), carcinoembryonic antigen (CEA) and CA-125 were within normal limits. The 24-hour urine hydroxyindoleacetic acid (HIAA) level was 6.0 (normal range 0.0–6.0) mmol. Clinical features and biochemical tests for endocrinopathies, such as Cushing's syndrome, Conn's syndrome and hyperthyroidism, were excluded.

Endoscopic ultrasonography-guided fine needle aspiration cytology revealed sheets of cuboidal cells with slightly pleomorphic nuclei, moderate cytoplasm and ill-defined cell borders. There was no mitosis or necrosis. However, a few groups of columnar epithelial cells were seen, while immunohistochemistry stained for neuron-specific enolase (NSE) and chromogranin were positive. The results implied the presence of a possible pancreatic NET.

Despite the extensiveness of the patient's disease, palliative debulking surgery was performed followed by cytoreductive therapy. Whipple procedure was performed, which included pancreaticojejunostomy, choledocojejunostomy and gastrojejunostomy. Preoperatively, the patient was administered subcutaneous octreotide 150 mcg daily for two weeks. Intraoperatively, the head of the pancreatic mass was found to be adherent to the portal vein and had invaded the middle colic gutter, with possible invasion into the uncinate process.

Histopathology of the pancreatic mass revealed a well circumscribed tumour measuring 2 cm × 2 cm. Histology showed a malignant necrotic tumour with some viable areas (Fig. 2a) that consisted of sheets of relatively rounded cells forming trabeculae and ribbons separated by highly vascular thin fibrous stroma. The tumour cells displayed scanty pink granular cytoplasm and round to oval stippling, with a few having mitotic activity (Fig. 2b). Immunohistochemistry confirmed that the tumour cells expressed synaptophysin and chromogranin. A diagnosis of metastatic advanced NET suggestive of VIPoma was made.

Post surgery, the patient underwent a total of three rounds of radiofrequency ablation (RFA) therapy to the liver metastases. She was followed up with serial CT of the abdomen. Unfortunately, the latest CT abdomen did not show any improvement in the liver metastases. The diarrhoea improved after surgery, and its frequency was reduced to 5–8 times a day compared to twenty times preoperatively. The patient denied hypokalaemic symptoms. Unfortunately, her symptoms eventually progressed over the next three years, with worsening diarrhoea and symptomatic hypokalaemia. Investigations revealed recurrent hypokalaemia, hyperchloraemia, post-prandial hyperglycaemia with metabolic acidosis and hypercalcaemia with serum intact parathyroid hormone 2.3 (normal range 1.1–7.3) pmol/l. However, blood for PTHrp was not sent for testing due to the unavailability of the test. The patient was treated with

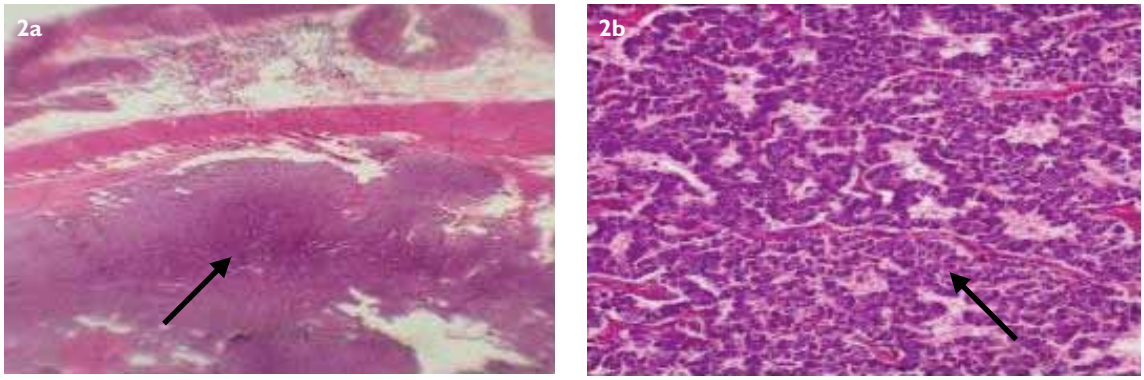

Fig. 2 Photomicrographs show (a) central necrosis of the primary pancreatic tumour (arrow) (Haematoxylin & eosin, x 200); and (b) the primary pancreatic tumour (arrow) (Haematoxylin & eosin, x 200).

saline hydration and potassium replacement. Insulin was initiated to control hyperglycaemia. Diarrhoea was controlled with diphenoxylate and subcutaneous octreotide 50 mcg tds initially, and titrated down to 50 mcg daily thereafter.

The option of chemotherapy was discussed, but the patient was reluctant to undergo the treatment. Therefore, octreotide was initiated for symptomatic control of her diarrhoea and to arrest the liver metastasis. A clinical response was generated, with more manageable diarrhoea and a normalisation of serum potassium. However, the patient continued to require insulin for glycaemic control.

DISCUSSION

VIPoma is a very rare NET. Up to 80% of these tumours originate from the pancreas, mostly in the tail. The majority of the cases are sporadic. About 50%–60% of the cases have metastasised by the time the diagnosis is made, as was the case with our patient. Most patients have secretory watery diarrhoea, resulting in electrolyte disturbance, such as hypokalaemia, hypophosphataemia, hypomagnesaemia and metabolic acidosis. Hypochlorhydria or achlorhydria occurs in 75% of cases due to the inhibition of gastric acid production by VIP. Hyperchloraemic acidosis can also occur due to low bicarbonate levels from severe intestinal loss. Occasionally, hypercalcaemia, glucose intolerance and hypotension may be present. During attacks of diarrhoea, the flushing that is similar to that observed in carcinoid syndrome can occur, although rarely. The VIP level is elevated in almost all cases, but it can also be normal between episodes of diarrhoea. The serum for VIP was not sent for testing as the facilities to analyse VIP were unavailable.

Our patient had chronic diarrhoea and recurrent hospital admissions for symptomatic hypokalaemia. She also exhibited biochemical abnormalities such as metabolic acidosis, hypercalcaemia and glucose intolerance. The mechanism of hypercalcaemia is thought to be due to the release of PTHrp by the culprit tumour, while the mechanism for hyperglycaemia preoperatively is still unknown to date.[4] The diagnosis of VIPoma was very likely in view of our patient's classical symptoms, electrolyte abnormalities, metabolic acidosis, radiological evidence (incidental finding of tumour in the head of pancreas and liver metastases) and positive histopathology of a NET. This was unlikely to be a carcinoid tumour, as tumours derived from foregut cells (bronchial, pancreatic, duodenal or biliary carcinoid) produce a large amount of serotonin, which is oxidised within the tumour to 5-HIAA. Moreover, in the absence of flushing (which occurs in 90% of carcinoid patients) and an elevated 24-hour urinary 5-HIAA (which occurs in 86% of carcinoid patients), the diagnosis of carcinoid tumour was remote. Colonic villous adenoma was another differential diagnosis; however, it usually presents with rectal bleeding and very rarely, secretory diarrhoea. Furthermore, the colonoscopy performed was reported to be normal.

VIP level is elevated in almost all cases of VIPoma, but it can also be normal between diarrhoeal episodes. However, although the serum tests for VIP levels were not performed, a diagnosis of VIPoma syndrome was more appropriate as there is a considerable overlap between VIPomas and other NETs, such as carcinoid tumours, gastrinomas, glucagonomas and others. Despite this limitation, the diagnosis of VIPoma was still the most reasonable diagnosis, given the presentation, clinical course and biochemical abnormalities.

Surgery remains the mainstay of treatment in tumours presenting with VIPoma-like syndrome. Cytoreductive surgery includes debulking palliative surgery of the primary tumour, while RFA and

cryotherapy are indicated for the management of distant metastases. These measures reduce tumour bulk, improve hormone-mediated symptoms and prevent local and systemic tumour effects. Palliative debulking surgery, followed by multiple RFAs was performed in our patient to improve her status. However, not unexpectedly, her disease progressed over the next three years with recurrence. It is unfortunate that the patient was not offered surgery in 2004; a more favourable outcome may have been attained then as her disease was less extensive at that time.

Medical therapy with the somatostatin analogue, octreotide, was administered for symptomatic relief. It has been noted in recent publications that octreotide 250–450 mcg per day is associated with a 60% symptomatic, 70% biochemical and 5%–10% tumour response.[5] Stabilisation of tumour growth documented by CT has been observed in 30%–50% of patients. However, due to financial constraints, our patient was treated with a suboptimal dose of octreotide 150 mcg daily, which was subsequently titrated down to 50 mcg daily. Fortunately, her diarrhoea improved and the biochemical abnormalities were corrected. However, tachyphylaxis may develop after prolonged treatment with octreotide, and thus dose escalation or combination with other agents such as interferon-α is required. The newer somatostatin analogue, pasireotide or SOM-230, has a more prolonged half-life and higher affinity for somatostatin receptors, which may be considered in the future.

In conclusion, VIPoma syndrome is very rare, and the disease would have usually metastasised at the time of diagnosis. A high index of suspicion in patients with chronic diarrhoea would aid early recognition of this rare disease. A complete resection of the primary tumour improves the prognosis tremendously. However, patients with metastatic disease should also not be denied palliative debulking surgery as it improves the patients' outcomes. Adjuvant treatment with somatostatin analogues can be offered in addition to debulking surgery, and if cost is an issue, as was the case with our patient, suboptimal dosing can provide adequate symptomatic relief, controlling hormone-mediated symptoms and enabling a better quality of life.

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