Profuse watery diarrhea capable of causing circulatory instability is a known hormonally mediated effect of pancreatic neuroendocrine tumors that secrete vasoactive intestinal polypeptide. Surgical resection provides the only possibility of cure, and recent developments in somatostatin analogues have helped to stabilize these patients preoperatively.

**Case Report**

A 63-year-old man was first seen in Sault Ste. Marie in December 1992, complaining of a change in bowel habit. Stools had become more frequent and looser but with no observable blood or mucus. Colonoscopy revealed only a sessile villous adenoma 1.5 cm in dimension in the ascending colon. The patient had upper gastrointestinal bleeding, found by endoscopy to be due to peptic esophagitis, and was treated with histamine blocking agents.

After surgical resection for rectosigmoid carcinoma a 63-year-old man had secretory diarrhea causing severe metabolic acidosis, hypokalemia, hypercalcemia and dehydration. Subsequent investigations revealed a mass measuring 4 x 5 cm in the uncinate process of the pancreas and an elevated vasoactive intestinal polypeptide concentration. The diarrhea responded to treatment with the somatostatin analogue, Sandostatin, and remained under control during a prolonged preoperative period. The patient underwent a Whipple procedure with immediate lessening of his diarrhea. This report illustrates a classic case of vipoma and demonstrates the need to consider this condition in the differential diagnosis of secretory diarrhea, even in the presence of other gastrointestinal lesions. The effectiveness of somatostatin analogues in stabilizing the diarrhea preoperatively is also well illustrated.
10.0 mmol/L, with a normal anion gap. He was also hypercalcemic (serum calcium greater than 3.0 mmol/L) and was treated with bisphosphonates.

Subsequent investigations, including computed tomography (CT), revealed a mass in the uncinate process of the pancreas. Magnetic resonance imaging (MRI) confirmed the presence of an enhancing mass in the inferior aspect of the uncinate process, which was isointense with $T_1$ weighting and hyperintense with $T_2$ weighting (Fig. 1).

On the basis of the patient’s clinical course and the presence of a pancreatic mass, a clinical diagnosis of pancreatic cholera was made and Sandostatin (Sandoz Canada Inc., Whitby, Ont.) (100 µg subcutaneously) was given three times daily. There was immediate improvement in the diarrhea. The serum VIP level was markedly elevated (228 pg/mL, normal less than 75 pg/mL), confirming the diagnosis of a vipoma. Because he was markedly malnourished, total parenteral nutrition was begun and he was transferred to the Sunnybrook Health Science Centre.

After transfer he was found to have a right lower lobe pneumonia, secondary to aspiration, that developed during transport. His pneumonia progressed to an empyema requiring thoracostomy drainage. Because of this, the preoperative period was prolonged, with episodes of systemic sepsis requiring treatment in the intensive care unit. Throughout the 12-week preoperative period the diarrhea was controlled with Sandostatin, although the dosage had to be progressively increased, up to 900 µg three times a day.

When the empyema resolved the patient underwent resection of the mass in the uncinate process of pancreas through a Whipple pancreaticoduodenectomy (Fig. 2). A right hemicolectomy was also performed to resect a 2 × 3-cm sessile villous adenoma of the ascending colon that could not be removed endoscopically. There were no intraoperative complications.

The postoperative course was complicated by a prolonged ileus, and intra-abdominal fluid collections that grew Escherichia coli from percutaneous drainage. There was no radiologic evidence of anastomotic leakage, and he responded to antibiotic therapy.

The final pathology report described the pancreatic lesion as consisting of tumour cells with a low nuclear–cytoplasmic ratio, round to oval bland nuclei and neurosecretory-like granules, consistent with an endocrine VIP-secreting tumour. There was no vascular invasion, and all resection margins were free of tumour, although nests of tumour were seen beyond the tumour capsule. Postoperatively the serum VIP level returned to normal and was less than 30 pg/mL. One year postoperatively the patient was clinically well with no diarrhea.

**DISCUSSION**

The terms watery diarrhea, hypokalemia, achlorhydria (WDHA) syndrome, Verner–Morrison syndrome and pancreatic cholera all describe a watery diarrhea syndrome associated with the overproduction of VIP.

Pancreatic tumours are the primary but not sole origin of VIP secretion. It may also be produced by neuroblastomas, bronchogenic carcinomas, ganglioneuromas or pheochromocytomas. VIP is an ectopic tumour product; it is not normally produced by the islet cells. Pancreatic VIP production occurs from a discrete tumour in 80% of cases and from hyperplasia or a microadenoma in 20% of cases. In adults, excess VIP production is
pancreatic in 90% and extrapancreatic in 10% of cases. In children 80% of cases are extrapancreatic. Vipomas themselves can be equally benign or malignant.

VIP is thought to function physiologically as a local paracrine neuro-modulator, which only functions hormonally when produced in excess. VIP is a member of the secretin-glucagon peptide family. It acts on the gut as a potent secretagogue, using a cAMP (adenosine 3′,5′-cyclic phosphate)-mediated mechanism, among others, to produce a massive isosmotic chloride secretion with no mucus or fat that persists during fasting.

Hypokalemia may be severe because large quantities of potassium are drawn into the gut with the chloride secretion. VIP also stimulates renin secretion, augmenting aldosterone production, which is often already stimulated due to volume contraction.

Achlorhydria, part of the complete syndrome, occurs because VIP inhibits gastric mucosal secretion; due to a secretin-like action. The esophagitis our patient exhibited was not consistent with a typical vipoma. Hypercalcemia due to increased bone resorption is found in 25% to 75% of cases and abnormal glucose tolerance in 20% to 50% of cases due to a glucagon-like action of VIP. Flushing, without hypersecretion is seen in 15% to 20% of cases.

The diagnosis is suspected on the basis of the clinical symptoms and confirmed with the demonstration of an elevated serum VIP level. This should be drawn during an episode of diarrhea, as levels may be normal when the patient is not having diarrhea. Resuscitation of the often severely dehydrated patient is essential. Large quantities of intravenous fluids and potassium may be required. Before octreotide was produced, the voluminous diarrhea often necessitated urgent resection of the tumour in very ill patients because of the intractability of the diarrhea. Sandostatin (octreotide) is a longer-acting analogue of somatostatin that can be given by subcutaneous injection beginning at a dose of 50 to 100 µg every 6 hours. At least 85% to 90% of patients will experience clinical improvement, allowing a more controlled preoperative workup. Many patients will become tolerant and require higher doses with treatment, or become unresponsive altogether. Corticosteroids, formerly first-line medical therapy for control of the diarrhea, may enhance the response to Sandostatin. Other medications that may be considered in the management of the diarrhea include clonidine hydrochloride, indomethacin, lithium, and calcium channel and beta-blocking agents.

Methods of localizing a suspected vipoma preoperatively include imaging with ultrasonography, CT, MRI, angiography or portal venous sampling. Occasionally, the tumour may be found only by careful inspection at operation. The majority of lesions are reported to be located in the distal two-thirds of the pancreas. The pancreas should be widely mobilized. Ultrasonography should be used intraoperatively because the malignant mass may be hard to identify. Formal resection is recommended rather than enucleation because of the multifocal nature of the lesion and the difficulty in determining pathologically whether the tumour is benign or malignant. Even obvious metastatic and bulky disease should be debulked since the tumour is often slow growing. Tumour debulking also may provide symptomatic relief.

Patients with the inherited syndromes of multiple endocrine neoplasia, type 1, are more likely to have multiple islet cell tumours. The use of portal venous sampling has been described but it has been reported that this investigation only confirmed that the dominant tumour was functioning and did not change the operative strategy.

Rebound gastric hypersecretion may occur when the inhibitory effect of VIP on the gastric mucosa is relieved after resection.

**CONCLUSIONS**

Although vipoma is a rare tumour, with a rare constellation of symptoms, it can be treated satisfactorily and even cured by surgical resection. It should be suspected in cases of severe metabolic disturbance due to fasting watery diarrhea. The diagnosis can be confirmed by determination of serum VIP levels and by improvement in diarrhea in response to Sandostatin administration. Somatostatin analogues are extremely effective in preoperative stabilization of these patients and their use should obviate the need to operate prematurely when patients have circulating instability or concomitant medical problems.

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References


SESAP VIII Critique
Critique SESAP VIII

ITEM 46

This patient shows clinical evidence suggesting peritonitis associated with sudden contamination of the peritoneal cavity by gastrointestinal contents. In view of her laparoscopic cholecystectomy three days previously, delayed intestinal perforation as a complication of the laparoscopic procedure seems likely. Such perforations usually occur as a result of damage to bowel wall from electrocautery or laser instruments. Bowel wall damage may not be recognized at the time of operation. Subsequent necrosis of the bowel wall at the site of the injury produces perforation and subsequent sudden, severe abdominal symptoms as described in this patient. The interval between operation and peritonitis from this cause is typically several days. Upright abdominal roentgenograms may demonstrate free air but usually provide little help in the diagnosis.

The clinical picture is not consistent with subphrenic abscess. Pancreatitis can present suddenly and masquerade as a perforated viscus but has not been associated with laparoscopic cholecystectomy. Bile peritonitis is not likely to produce this clinical picture in the circumstances described.

References