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Case Reports

Hypercalcemia as the Presenting Finding in VIPoma

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Hypercalcemia is typically associated with primary hyperparathyroidism, malignancy, vitamin D intoxication, and granulomatous disease; however, it can also be associated with a neuroendocrine tumor that secretes vasoactive intestinal polypeptide (VIP). A 74-year-old woman with a history of hypothyroidism and nephrolithiasis presented to her primary care physician with a chief complaint of diarrhea and was found to have mild hypercalcemia. A Hypercalcemia workup was initiated, and the patient was ultimately found to have elevated VIP. Although a discrete pancreatic mass was not identified, an endoscopic ultrasound with fine needle aspiration revealed a VIPoma. She was then referred to hepatobiliary surgery for the removal of the tumor. As VIPoma has a poor prognosis, early recognition and treatment are essential for improving patient outcomes.

BACKGROUND

VIPoma is a rare neuroendocrine tumor that produces vasoactive intestinal polypeptide (VIP). It is most often found in middle-aged adults and toddlers. Most tumors arise in the pancreas; however, in children, they can form more often in the sympathetic chain or adrenal glands.[1] We present an older adult with subacute diarrhea, hypokalemia, hypotension, and hypercalcemia who was eventually diagnosed with VIPoma.

CASE PRESENTATION

A 74-year-old woman with a history of hypothyroidism treated with levothyroxine and recent nephrolithiasis presented with fatigue, persistent subacute diarrhea, and hypokalemia. She was found to have hypotension, which resolved with intravenous (IV) fluid administration. The patient was encouraged to maintain oral intake and was given potassium supplementation.

Due to persistent symptoms over the next few months, additional work-up was completed. Infectious stool work-up was negative, but a complete metabolic panel was notable for calcium of 11.9 mg/dL (normal range 8.7-10.3 mg/dL). Her PTH was 19 pg/mL (normal range 15-65 pg/mL), 25 hydroxy vitamin D 44.1 ng/mL (normal range 30.0-100.0 ng/mL), and PTHrp <2.0 pmol/L (normal value <2.0 pmol/L). Serum protein electrophoresis and immunofixation were normal, and she did not have an M spike (**Table 1**). Further history revealed generalized bone pain, polydipsia, nocturia, and memory loss. In addition, she noted difficulty swallowing, prompting her to eat less, and in the setting of her ongoing chronic diarrhea, she lost 20 pounds over five months.

The VIP level came back high at 982 pg/mL (normal range 0-58 pg/mL) with a repeat value of 388.4 pg/mL (**Table 1**). A CT of the abdomen and pelvis with pancreatic protocol did not reveal pancreatic abnormalities. However, a 2-centimeter uncinate pancreatic mass was found on endoscopic ultrasound evaluation. Pathology was consistent with VIPoma (**Figure 1**). She was started on octreotide. A follow up CT scan of the abdomen and pelvis revealed multiple low-density lesions in the liver. She received a partial hepatectomy, and the results were consistent with metastasis (**Figure 2**). She received a partial hepatectomy and is planned for a Whipple procedure to remove the primary tumor.

DISCUSSION

Vasoactive intestinal polypeptide acts locally on the gastrointestinal tract to induce intestinal electrolyte and water secretion. An excess of this hormone can thus cause secretory diarrhea and electrolyte abnormalities such as hypokalemia. In addition, surplus VIP can cause hypochlorhydria or achlorhydria by inhibiting the parietal cells in the stomach. This constellation of symptoms and laboratory abnormalities: **W**atery **D**iarrhea, **H**ypokalemia, and **A**chlorhydria is known as WDHA syndrome or Verner Morrison Syndrome. The inhibition of parietal cells can also cause vitamin B12 or iron deficiency. VIP secretion also causes hyperglycemia by inducing glycogenolysis and cutaneous flushing from prostaglandin release and vasoactive properties.

Another laboratory finding from having increased pancreatic secretion of VIP is hypercalcemia. Diarrhea (and to a lesser degree, polyuria from hyperglycemia) can cause severe dehydration, leading to increased serum albumin concentration and elevated serum calcium. Bone lytic lesions can lead to increased serum calcium. While most VIPomas are solitary tumors, they can be associated with multiple endocrine neoplasia 1 (MEN1) syndrome about 5% of the time.[2] Family history or personal history of other MEN1 associated conditions, such as primary hyperparathyroidism or pituitary adenomas, would warrant genetic testing (**Figure 3**).

By the time of VIPoma diagnosis, most tumors are over 3 centimeters in size and more than 50% have metasta-

Table 1. Laboratory Test Results

Laboratory Tests		Reference	Value	Interpretation
	Calcium	8.7-10.3 mg/dL	11.9	H*
	1,25(OH)2 vitamin D	19.9-79.3 pg/dL	75.6	
	25(OH) vitamin D	30.0-100.0 ng/mL	44.1	
	Vitamin A	22.0-69.5 ug/dL	88	H**
	PTH	15-65 pg/mL	19***	
	PTHrp	pmol/L	<2.0	
	ACE	14-82 U/L	28	
	Gastrin	0-115 pg/mL	<10	
	ACTH	7.2-64.4 pg/mL	12.7	
	VIP	0.0-58.5 pg/mL	982.8	H
	VIP (second draw)	0.0-58.5 pg/mL	388.4****	H
Electrophoresis	Albumin electrophoresis	2.9-4.4 g/dL	2.9	
	Alpha 1	0.0-0.4 g/dL	0.4	
	Alpha 2	0.4-1.0 g/dL	0.9	
	Beta globulin	0.7-1.3 g/dL	1	
	Gamma globulin	0.4-1.8 g/dL	1	
	M component		Not seen	
Stool Studies	Campylobacter culture		Negative	
	Salmonella/Shigella screen		Negative	
	E.coli, Shiga toxin assay		Negative	
	C.diff toxin B		Negative	

*Value at which hypercalcemia workup was initiated
**Not high enough to cause hypercalcemia
***Appropriately low-normal, low concern for hyperparathyroidism/MEN1
****Second value needed to confirm as VIP levels fluctuate

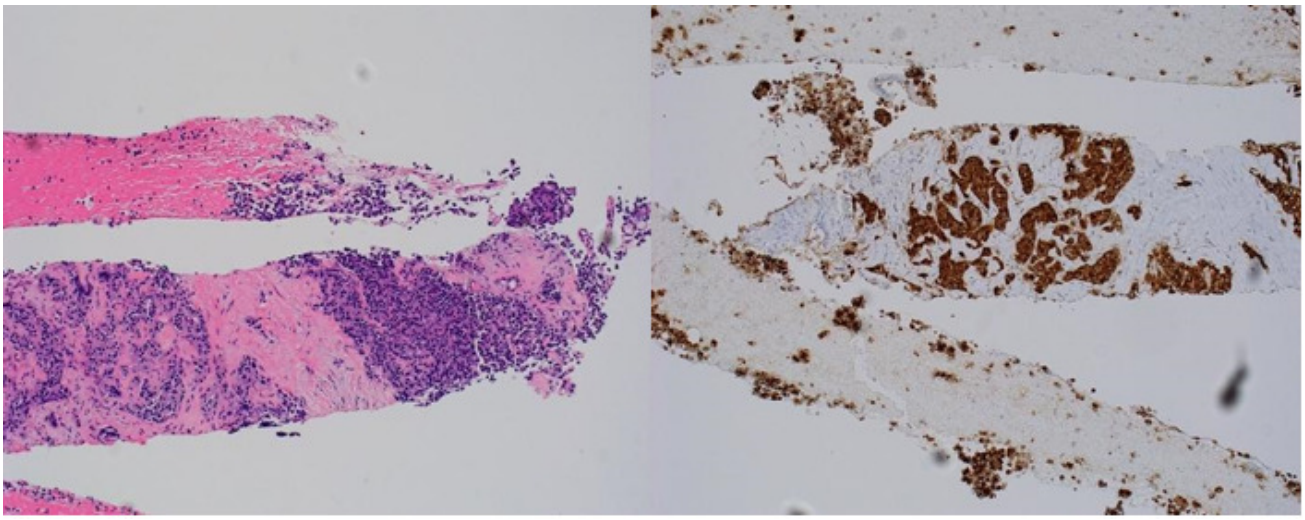

Figure 1. (left) H&E stain of endoscopic ultrasound fine needle aspiration results (100x) revealing well differentiated neuroendocrine tumor admixed with clusters of lymphoid cells. (right) Synaptophysin stain of endoscopic ultrasound fine needle aspiration results (100x) revealing strong positive staining in the tumor cells consistent with neuroendocrine tumor.

sized.[3] Diagnosis is made with two separate elevated serum VIP levels. Localization of the tumor can be made with computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. In cases where initial imaging does not identify the tumor, endoscopic ultrasound, or positron emission tomography (PET) imaging can be utilized. Additionally, PET scans can help locate foci of metastasis.

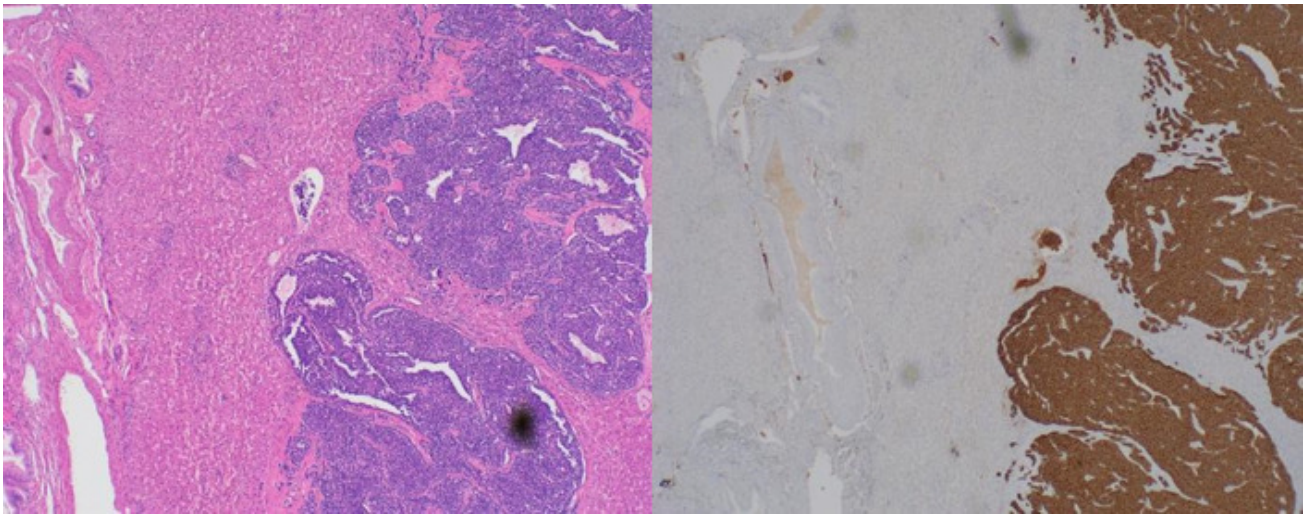

Figure 2. (left) H&E stain of the partial hepatectomy (200x) revealing unremarkable liver parenchyma involved by metastatic neoplasm with neuroendocrine morphology. (right) Synaptophysin stain of the partial hepatectomy (100x) revealing strong positive staining in the metastatic cells and negative staining in the liver parenchyma consistent with neuroendocrine tumor

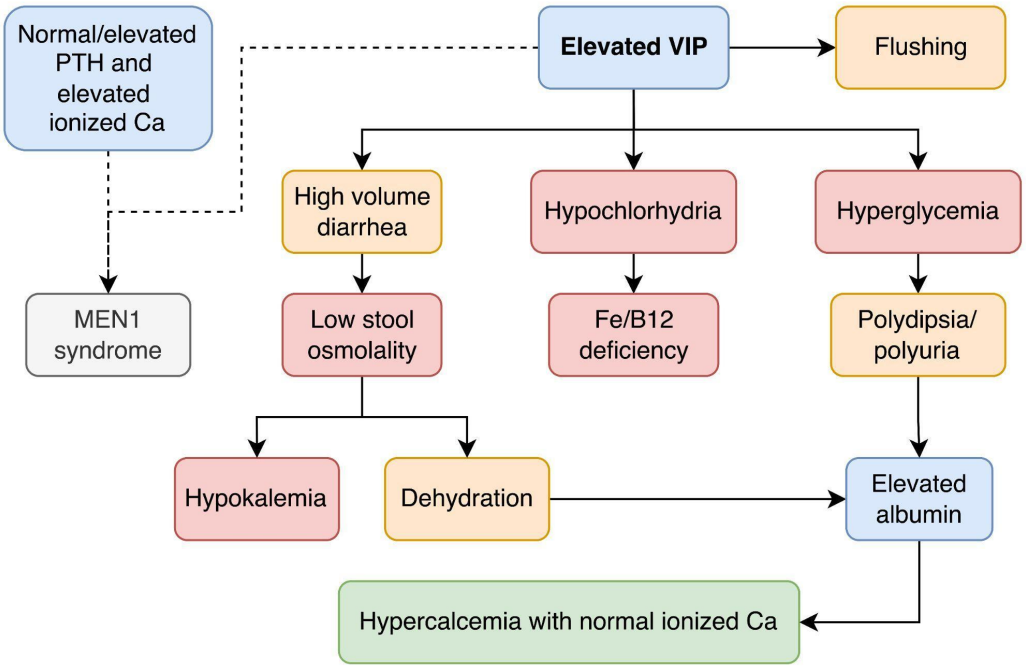

Figure 3. Clinical Features of VIPoma

This case illustrates the need to pursue further work-up when lab abnormalities are inconsistent with a clinical syndrome. Hypercalcemia is typically associated with constipation; therefore, the constellation of hypercalcemia and diarrhea should prompt additional investigation. While VIPoma has an incidence of one per million, it has a median survival of 96 months due to the late presentation of the disease with most cases already with metastasis.[4,5] Early identification and referral to surgery is imperative for better outcomes.

Treatment of VIPoma begins with fluid and electrolyte repletion. Somatostatin analogs such as octreotide inhibit VIP release and treat symptoms such as diarrhea. However, definitive treatment occurs with resection. Staging of the disease as well as patient comorbidities would determine the approach. Common locations of metastases include the liver, kidneys, bone, and lymph nodes.[2] After resection, surveillance for recurrence is performed via VIP and abdominal imaging measurements for up to 10 years.

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- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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