Ischemic stroke as a presenting feature of VIPoma due to MEN 1 syndrome

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ABSTRACT

Introduction: Presentation of the ischemic stroke due to vasoactive intestinal peptide producing tumor (VIPoma) or Verner Morrison syndrome is rare. This is first of its kind case which we are reporting here which was later turned out to be multiple endocrine neoplasia type 1 (MEN 1) syndrome with diagnosis of primary hyperparathyroidism in the same patient in follow-up.

Description of the Case: A 13-year-old girl presented to our emergency department with features of disorientation, weakness of left sided extremities. She had watery high volume diarrhea and related dehydration with renal failure. Blood chemistry was suggestive of hypokalemia with metabolic acidosis. Patient had flushing on her face during this episode of illness. Magnetic resonance imaging (MRI) of brain suggested venous infarct. Computed tomography (CT) scan of abdomen done with high index of suspicion was suggestive of mass in tail of pancreas mostly a VIPoma. Patient was operated for the tumor after which there was no recurrence of diarrhea. Biopsy of tumor was consistent with VIPoma with chromogranin A positivity. Patient improved of her stroke episode with time. On follow-up she is diagnosed to have primary hyperparathyroidism with hypercalcemia due to left inferior parathyroid adenoma which improved with intravenous (IV) zoledronic acid therapy and now she is planned to undergo parathyroidectomy. Conclusion: VIPoma is a rare tumor but is well-described with MEN 1. Stroke as a presenting feature of VIPoma is first reported with this case.

Key words: Multiple endocrine neoplasia type 1, primary hyperparathyroidism, stroke, VIPoma

INTRODUCTION

Verner and Morrison described a syndrome of watery diarrhea, hypokalemia, and achlorhydria (WDHA) in 1958.[1] VIPomas producing high amounts of vasoactive intestinal peptide (VIP). These tumors commonly originate from the pancreas. Diarrhea with flushing may persist for years before the diagnosis and association with renal failure is reported. Morbidity from untreated WDHA syndrome is associated with long standing dehydration and with electrolyte and acid-base metabolism disorders. VIPoma cases may be associated with multiple endocrine neoplasia type 1 (MEN 1).[8] Here we report a case of VIPoma (as a component of MEN 1 syndrome) with stroke as a presenting complaint.

DESCRIPTION OF THE CASE

A 13-year-old girl child presented as disorientation, urinary incontinence, weakness of left sided extremities associated with diarrhea since 1 week duration to emergency department. Patient had history of repeated diarrheal illness since 1 year, but no history suggestive of transient ischemic attacks. There was no history of prior significant medical illness. She attained menarche 6 months back with regular menstruation. No history of similar disease reported in her family.

On clinical examination, she was disoriented and irritable at the time of presentation, severely dehydrated. Flushing
over face and body was observed. She was having tachycardia related to diarrhea with blood pressure (BP) of 90/70 mmHg which improved with hydration. Cardiovascular and respiratory systems were normal. Weakness of left sided extremities with irritability suggestive of stroke was observed.

Electrolyte imbalance in the form of hypokalemia, metabolic acidosis (14 mEq/L), and renal failure in the form of increased creatinine (2.3 mg/dl) value was seen. Her thyroid function tests were normal, serum calcitonin was 1.5 pg/ml, serum homocysteine was 6.87 μmol/l, factor V Leiden was negative, cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA) negative, perinuclear-ANCA (p-ANCA) negative, complement C3 was 86.5 mg/dl, C4 was 7.3 mg/dl normal; thus ruling out connective tissue disorders and prothrombotic states. Her serum corrected calcium was 8.7 mg/dl and serum prolactin was 11.9 ng/dl. She also had mild glucose intolerance. Her fasting blood sugar was 120 mg/dl which reverted to normal with treatment.

Colonoscopy was normal thus to rule out villous adenoma. Magnetic resonance imaging (MRI) of brain [Figure 1] was suggestive of flair hyperintensity showing diffusion restriction in right frontoparietal, occipital, temporal region suggestive of acute infarct and subacute infarct in left frontal region. MRI findings of infarct were not pertaining to any particular arterial territory suggestive of venous infarct. Patient was managed conservatively for stroke and renal failure following which she improved. Serum creatinine normalized (0.48 mg/dl) and weakness improved.

In context of history, clinical examination and investigation findings with high index of suspicion for pancreatic tumor, we did CT scan of abdomen [Figure 2] and it was suggestive of bulky tail of pancreas with well-defined heterogeneous enhancing area in the tail of pancreas suggestive of endocrine tumor of pancreas most likely VIPoma, we could not perform serum VIP levels as the test is not performed in India.

With visualization of tumor, patient underwent surgical removal of the tumor following which clinical and biochemical features normalized. Histopathologic analysis was confirmative of VIPoma with the findings of well-circumscribed capsulated nodule of 3.5 × 3.5 × 4 cm size. Microscopically features [Figure 3] of tumor cells having round to oval vesicular nuclei with prominent nucleoli and prominent eosinophilic cytoplasm, invading capsule but without extra pancreatic invasion and on immunohistochemistry tumor cells were positive for chromogranin A. These features were suggestive of neuroendocrine tumor, VIPoma.

On follow-up she was given vitamin D supplementation with which her calcium levels increased to 12.3 mg/dl with high Parathyroid hormone value 133.6 pg/ml. Her ultrasound of neck was suggestive of well-defined lesion in left inferior pole of thyroid. 99m-methoxyisobutylisonitrile (MIBI) parathyroid scintigraphy [Figure 4] was suggestive of adenoma of left inferior parathyroid gland. Patient received one dose of zolindronic acid following which serum calcium normalized and now the patient is planned for parathyroidectomy.

**DISCUSSION**

Verner-Morrison syndrome and pancreatic cholera. VIPoma is exceptionally rare, with an annual reported incidence between 0.2 and 2 cases per million people.[3,4] The majority of tumors are malignant, and most patients present with metastatic disease.[3] VIPomas are slow growing and generally cause symptoms due to their excessive production of VIP, a physiologically active hormone. In patients with VIPoma, the most common manifestations are chronic secretory diarrhea, hypokalemia, and metabolic acidosis.[3,4] These tumors may be difficult to localize by conventional radiographic studies. Surgery remains the mainstay of treatment for lesions localized to the pancreas and offers the best chance of a cure.[3,4]

Our patient’s presentation was most consistent with VIPoma syndrome because she had the typical symptoms of a large volume of diarrhea, hypovolemia, and refractory
hypokalemia. The etiology of her diarrhea was secretory because it was voluminous and failed to improve with fasting. Stool output in patients with VIPomas ranges from 1 L to more than 3 L daily, leading to profound dehydration and acidosis. Hypokalemia is a universal finding, resulting from fecal loss of potassium and from secondary hyperaldosteronism. Acute renal failure resulting from the dehydration caused by WDHA syndrome also has been reported. But stroke is not yet reported as presenting feature of this syndrome. High hematocrit caused by diarrhea is a well-known risk factor for stroke which may be the possibility in our case as coagulation profile was reported normal. Stroke has been reported in up to 7% of adults with primary hyperparathyroidism.

The most common symptoms of VIPoma include diarrhea, dehydration, weight loss, hypokalemia, and achlorhydria. In a series of 31 patients reported by Peng and colleagues, all patients had diarrhea, significant weight loss, and dehydration. Of these patients, 68% had hypokalemia and 64% had diarrhea. She also had mild glucose intolerance. Her fasting blood sugar was 120 mg/dl which reverted to normal with treatment. Hyperglycemia was also noted in 28% of patients in Peng and colleagues' review. This is thought to be secondary to VIP’s stimulation of hepatic glycogenolysis.

Surgical resection can offer immediate improvement in symptoms and may increase survival. Matthews and colleagues reported the surgical outcome of 20 patients with functioning pancreatic endocrine tumors. Of these patients, 90% had complete resolution of their symptoms and normalization of their neuroendocrine markers postoperatively. Our patient also started immediate improvement postoperatively.

Histopathology predominantly reveals ganglioneuroblastoma or ganglioneuroma. Immunohistochemistry of the tumor cells was positive for chromogranin A is a typical description of VIPoma. Our patients tumor cells having round to oval vesicular nuclei with prominent nucleoli and prominent eosinophilic cytoplasm, invading capsule but without extra pancreatic invasion and on immunohistochemistry tumor cells were positive for chromogranin A; features suggestive of neuroendocrine tumor.

CONCLUSION

VIPoma is a rare tumor but is well-described with MEN 1. Stroke as a presenting feature of VIPoma is not yet reported. Thus high suspicion is the key, for diagnosis of VIPoma and MEN 1 syndrome.

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