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Original Research Paper

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NOTHING BUT NET: CHRONIC DIARRHEA AS A MANIFESTATION OF A NEUROENDOCRINE TUMOR

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ABSTRACT Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that originate in endocrine cells with the ability to secrete amines and hormonal polypeptides. Pancreatic neuroendocrine tumors (PNETs) can be functional or non-functional. Functional PNETs secrete common hormones such as gastrin, insulin and glucagon and much less frequent hormones such as vasoactive intestinal peptide (VIP). Vipomas are characterized by chronic diarrhea of secretory characteristics that usually lead to Electrolytes and metabolic disturbances that leads to more severe complications. This article describes the case of a 50-year-old man who had suffered chronic diarrhea with frequent hospitalization for electrolytic disturbances for two months due to severe hypokalemia and acute renal damage due to dehydration. After multiple investigations, a diagnosis of secretory diarrhea due to NET was considered. Empirical therapy with Octreotide was begun to control diarrhea and correct the electrolytic disorder after which patient was treated surgically.

KEYWORDS : Chronic diarrhea, secretory diarrhea, neuroendocrine tumor, vipoma.

INTRODUCTION

Diarrhea is defined as a significant reduction in stool consistency or an increase in stool volume to more than 200 g/d. Chronic diarrhea is considered last more than 4 weeks.

Chronic diarrhea is classified into three main groups:

1. Watery diarrhea: osmotic, secretory, and functional diarrhea. In osmotic, diarrhea, intraluminal water is retained by unabsorbed substances. In secretory diarrhea, absorption of water is reduced while functional diarrhea is generated by hypermotility.
2. Fatty diarrhea (steatorrhea) is subdivided into malabsorption syndromes and maldigestion.
3. Inflammatory diarrhea (exudative diarrhea) occurs with leukocytosis and leukocytes in stool. Purulent material and blood may also be present in stool.

Secretory diarrhea, a type of watery diarrhea, is caused increased secretion of electrolytes, especially sodium and chlorine, in the intestinal lumen.

Clinically, secretory diarrhea is not related to intake, so patients frequently say it is predominantly nocturnal. Consequently, it does not respond to fasting. Fecal volume neither decreases nor increases, and its osmolarity is similar to that of plasma (fecal osmotic gap <50 mOsm/kg). Furthermore, secretory diarrhea is voluminous with as much as 1 Liter in 24 hours. It is usually associated with electrolyte disorders such as hypokalemia and metabolic acidosis due to the concomitant loss of bicarbonate.

Within this context, NETs are neoplasms that occur relatively infrequently and whose clinical presentation varies. Initially, they may go unnoticed. However, they do have malignant and metastatic potential.

Eighty-five percent of all NETs originate in the gastrointestinal tract, while 10% occur in the lungs and manifest as bronchial carcinoids. PNETs are mostly non-functional, but some can secrete hormones that lead to unique clinical syndromes such as vipomas.

CASE REPORT

We reported a case of 50 years old male known case of hypertension on treatment, who was brought to Civil Hospital, baroda with c/o severe profuse watery diarrhea, not containing blood or mucous since last 6-8 weeks. Episodes persisted despite fasting . At admission to our institution, he continued to suffer from large volume diarrhea, moderate dehydration and electrolyte disorder. The initial stool and blood reports were negative for infection despite multiple previous antibiotics regimens , patient had not improved , HIV infection was also ruled out . He was evaluated by gastro-enterology service, where he underwent upper and lower GI-SCOPY, with BIOPSY. This test ruled out IBD and other MALABSORBTION SYNDROMES.

Given the characteristics of the patient's diarrhea, severe hypokalemia, metabolic acidosis with severe depletion of bicarbonate levels, and hypercalcemia, we requested S.CHROMOGRANIN-A LEVEL by considering Neuroendocrinal origin of secretory diarrhea. . Which turn out to be positive .

After which we confirmed our diagnosis of suspecting NET by performing PET-CT (DOTA-NOC), which suggestive of SUB-CENTIMETER SIZED LESION AT DISTAL BODY OF PANCREASE. Which further confirmed by EUS-guided FNAC ,which suggestive of NET.

Table 1. Principal tests done.

Parameter	Report	Reference value
Potassium	1.3 mEq/L	3.5-5.0 mEq/L
Chlorine	123 mEq/L	97-107 mEq/L
Sodium	132 mEq/L	135-145 mEq/L
Ionized calcium	1.92 mEq/L	1.12-1.32 mEq/L
Arterial gases	pH: 7.22; pO2: 90; pCO2: 18; HCO_3: 7 EB: −18.3	pH: 7.35-7.45; pO_2: >90; pCO_2: 35-45; HCO_3: 22-30
Creatinine	1.9 mg/dL	1-1.4 mg/dL
Blood Urea Nitrogen	45 mg/mL	14-40mg/mL
Potassium in urine	7.26 mEq/L	–
Thyroid-stimulating hormone (TSH)	3.1 mU/L	0.5-4.0mU/L
Parathyroid hormone (PTH)	16	16-60pg/ml.
Chromogranin A	57.4 ng/mL	
Albumin	4.1 g/dL	–
IgA TTG level	Not reactive	–

DISCUSSION:

PNETs are infrequently occurring neoplasms that arise from multipotent stem cells in the epithelium of the pancreatic duct. Fifty percent of them are non-functional or secrete peptides of low biological power such as pancreatic polypeptide (PP) or neurotensin. The other 50% are functional. Production of gastrin (gastrinoma) and insulin (insulinoma) is most common.

Insulinomas, clinically characterized by hypoglycemia with neuroglycopenic symptoms, are benign in up to 90% of cases. Gastrinomas are characterized by peptic ulcers, severe diarrhea, and gastroesophageal reflux secondary to production of large amounts of gastrin. Glucagonomas manifest through diabetes mellitus, thrombosis, depression and a skin rash known as migratory necrolytic erythema. This rash is red-brown, exfoliative and erythematous with superficial necrolysis and occurs mainly in the lower limbs.

Vipomas (or Verner-Morrison syndrome), first described in 1958, are very rare. Their incidence is just 1 case per 10,000 people per year. They occur in non-insulinproducing pancreatic islets B and are usually large (72% measure more than 5 cm) and malignant (64% to 92%) at the time of diagnosis. They generate profuse diarrhea, hypokalemia and classical achlorhydria due to the secretion of VIP in plasma. They also produce a 28 amino acid polypeptide that is widely distributed in the gastrointestinal tract and the brain. It relaxes vascular and visceral smooth muscle. All of this leads to the secretion of fluids and electrolytes in the intestinal lumen.

Secretory diarrhea, unlike osmotic diarrhea, persists during fasting. It is produced by increased secretion of water and electrolytes into the intestinal lumen to the point that it exceeds absorption capacity. It is secondary to external factors such as VIP which stimulate production of cyclic adenosine monophosphate (AMP).

When in NETs secrete large quantities of VIP, patients often experience severe diarrhea, dehydration, erythema, and weight loss. VIP also promotes hepatic glycogenolysis that results in hyperglycemia, dilates peripheral systemic blood vessels, and inhibits hydrochloric acid secretion.

Imaging studies play important diagnostic roles since they make it possible to determine the extent of the lesion, involvement of neighboring organs, infiltration, and its relationship with vascular and nerve structures. Transabdominal ultrasound's sensitivity varies between 20% and 86% depending on tumor size, but it is difficult to visualize tumors on the surface of the pancreas and duodenum. Consequently, this test is useful as a guide for percutaneous biopsy, if indicated.

Endoscopic ultrasound (EUS) is very useful for tumors located in the head of the pancreas and in the duodenal wall, but it does not allow evaluation of extrapancreatic lesions given the potential of pNETs for malignancy.

On the other hand, computed tomography (CT) scans can locate the primary tumor and possible secondary lesions and has a sensitivity of 30% for tumors of 1 to 3 cm, and 95% for tumors larger than 3 cm. Its performance improves notably with the use of multiphase techniques.
In the case of small lesions, gadolinium MRI has the highest sensitivity (91% to 94%). Either multiphasic CT scans, MRI, or both can be used to plan the surgical approach and subsequent follow-up.

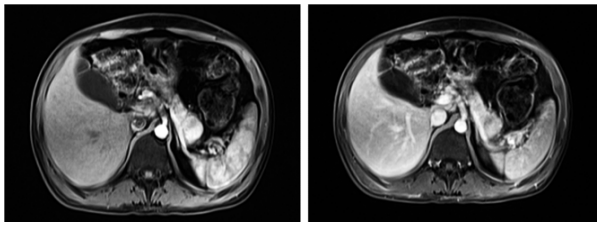

Figure 1. A. Contrast abdominal MRI. Solid 09 mm lesion in the tail of the pancreas with posterior enhancement by intravenous administration of contrast. Normal-sized pancreas. **B.** Solid 09 mm lesion in the tail of the pancreas, hypointense in T1, isointense in T2, hyperintense in diffusion, with enhancement after intravenous administration of contrast.

Essential initial treatment is correction of potentially fatal hydroelectrolytic disorders. Once the compromise has been defined by imaging, surgical resection is the next step. If a tumor cannot be completely removed, surgical reduction may have a palliative benefit especially when combined with treatment with somatostatin analogues which have antisecretory and antiproliferative effects, with tyrosine kinase inhibitors such as sunitinib, or with mTOR inhibitors such as everolimus.

CONCLUSION:

Vipoma is very rare: its incidence is 1 per 10,000 people per year. Profuse secretory diarrhea is the main symptom, and it frequently leads to hypokalemia, weight loss, and achlorhydria. This pathology may or may not be malignant, but it is always vitally important to recognize that this entity is potentially fatal given its severe hydro-electrolyte disturbances.

Surgical resection, the mainstay of treatment, has achieved complete remission of symptoms as occurred in the case described here. Our final objective is to encourage publication of cases with similar characteristics in order to unify early diagnosis approaches in a way that minimizes complications.

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