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A case study of the multifaceted therapeutic approach of VIPomas

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Abstract

Neuroendocrine tumors, arising from neuroendocrine cells, a group of malignant tumors capable of secreting peptides and biogenic amines, are differentiated as either diffuse endocrine system (DES) or gastroentero-pancreatic neuroendocrine tumors (GEP-NET). The latter are rare tumors that synthesize various substances, leading to the onset of certain generalized symptoms, qualifying these tumors as hormonally active. Increased hormone levels, whether in blood, urine or other fluids, constitute biochemical markers aiding in their diagnosis. This study examines a female patient initially treated as a nephrological inpatient for symptoms of AKI and severe hypokalemia. However, her overall clinical state deteriorated. An abdominal CT yielded a tumor along the head and body of the pancreas, whereupon the patient was transferred to a surgical department. It was decided not to excise the tumor due to unfavorable in situ conditions in the vicinity of the celiac trunk; therefore, a biopsy was performed instead. The patient was then admitted to an endocrinological department for fatigue, bouts of watery diarrhea, as well as non-respiratory acidosis. The diagnosis of VIPoma with elevated hormonal activity was suspected and Lanreotide was administered, resulting in a reduction in symptom severity, and a blood vasoactive intestinal peptide was performed. Following discharge, the diagnosis of VIPoma was confirmed by elevated levels of serum vasoactive intestinal peptide >60 pmol/L. In this investigation, the persistence of the initial symptom of watery diarrhea was an indication for the expansion of the diagnostic approach. While many modern laboratories are capable of performing a diverse range of diagnostic methods, a timely diagnosis can prevent life-threatening complications and extend both the life expectancy and quality-adjusted life-years of patients.

Keywords: Neuroendocrine tumors; Pancreatic tumors; VIPoma; Diagnosis; Treatment.

Introduction

Neuroendocrine tumors consist of a diverse group of malignant tumors, which can arise from neuroendocrine cells throughout the body. They are highly differentiated cells capable of producing, storing and secreting peptides and biogenic amines. These differentiations can be limited to certain organs and spread across the entire gastric system, or be restricted to the pancreas, wherein they form a part of the diffuse endocrine system (DES) and are categorized as gastroentero-pancreatic neuroendocrine tumors (GEP-NET). Neuroendocrine tumors of the pancreas include insulinomas, gastrinomas, glucagonomas and VIPomas. They constitute approximately 2-3% of all pancreatic tumors [1-3].

GEP-NET can produce one of a number of peptide hormones that are transported to various target organs upon their release into the circulation, where they bind to their corresponding receptors and thus elicit numerous biochemical reactions. Tumors that autonomically secrete vasoactive intestinal peptides (VIPomas) are very rare neuroendocrine tumors, occurring in 1 in 10 million individuals annually. They are most frequently diagnosed in children aged 2-4 years and adults aged 30-50 years [4,5]. Known also as Verner-Morrison Syndrome or WDHA Syndrome, they are named after the most frequently occurring symptoms: watery diarrhea, hypocalcemia, hypochlorhydria and achlorhydria [4].

Case description

This investigation examines the case of a female patient aged 45 years, admitted to a nephrology department with symptoms consistent with acute kidney injury. The history of the present illness includes watery diarrhea, based upon which the patient was prepared for a diagnostic colonoscopy. The patient received polyethylene glycol and sodium sulfate in preparation for this procedure. The past medical history also revealed a previous appendectomy, cesarean section, bilateral oophorectomy due to the presence of ovarian cysts, as well as the patient's having undergone a laparoscopic cholecystectomy many years prior.

Nephrological inpatient treatment

The patient presented to the Nephrology Department in a disoriented, overall severe and acute hypotensive (90/50 mm Hg) state with diminished cognitive contact. There were numerous well-demarcated erythematous changes on the skin of the hands. In addition, a recurrent yet spontaneous erythema of the skin of the face was observed.

The results of the laboratory tests performed are presented in Table 1.

The laboratory test results illustrated severe hypokalemia – 2.14 mmol/L (normal: 3.50-5.10), hyponatremia – 132 mmol/L (normal: 136-146), creatinine level – 1011 µmol/L (normal: 49-90), glomerular filtration rate (CKD-EPI) – 3.7 mL/min/L/1.73m (normal: >60), urea – 42.43 mmol/L (normal: 2.8-7.2), as well as symptoms of severe non-respiratory acidosis.

A dialysis line was inserted into the right interior carotid vein upon admission. The patient then underwent the first hour-long hemodialysis treatment without complications. The overall clinical state of the patient was observed to have improved. Nevertheless, a decrease in potassium and an increase in troponins was determined to have taken place. The patient negated experiencing sensations of dyspnea or stenocardial pain.

The patient was then consulted cardiologically due to increased levels of the following parameters pathognomonic for myocardial injury: creatinine kinase (CK) – 174 U/L (normal: 0 – 145), CK-MB – 12.7 ng/mL (normal <2.88), troponin T hs – 216 ng/L, NT-proBNP – 740.9 pg/mL (normal: <125), D-dimers 1.69 mg/L FEU (normal: <0.50). Bedside echocardiography revealed characteristics of left ventricular hypertrophy with mild mid-ventricular stenosis but with a nominal ejection fraction (65-70%) without any segmental contractility aberrations. Due to the above, acute coronary syndrome was ruled out as the cause of these symptoms. The elevated levels of the cardiac markers were most likely caused by severe kidney injury and CNS complications.

On the following day of hospitalization, having taken into account the deteriorating clinical state of the patient, computed tomography of the head without contrast was performed. This test revealed characteristics of generalized cerebral edema, most likely due to an osmotic imbalance. The patient was consulted neurologically and neurosurgically with conversative treatment with the anti-edemic drugs mannitol and furosemide being recommended. As a result, the patient's clinical state was observed to have improved: a subsequent CT scan revealed no cerebral edema. A USG examination of the area surrounding the body of the pancreas illustrated a smoothly demarcated, well-perfused hypoechogenic space, based upon which the suspicion of a presence of a pancreatic tumor in need of further diagnosis was ruled out.

Based on the irregular structure described in the results of the abdominal ultrasound, a computed tomography scan of the abdomen was performed and the presence of an irregular isodense growth 54x42x45 mm in size was exhibited along the border of the head and body of the pancreas, mildly increasing in density after the administration of contrast. A significant decrease in the parenchyma of the body and tail of the pancreas, as well as a dilated pancreatic duct, were observed proximally to this growth. Furthermore, a hypodense growth, mildly intensifying under contrast, approximately 25x20 mm in size, was observed along the inferior border of segment VI of the liver. Based on the above results, it was impossible to rule out the possibility of metastasis (Figure 3).

Taking the overall clinical state of the patient into account, it was suspected that the observed disorders were hormonal in origin. Therefore, it was decided to pursue further endocrinological diagnosis, the results of which are presented in Table 2. The following marker levels were obtained: chromogranin A – >1000 ng/mL (normal: <100), neurospecic enolase (NSE) – 11.7 ng/mL (normal: <16.3), 5-hydroxyindoleacetic acid – 6.8 mg/24h (normal: 2-9). These data strengthened the suspicion of this structure's being a neuroendocrine tumor. Having stabilized the patient's biochemical parameters, she was transferred to a surgical department for further diagnosis of this growth.

Surgical inpatient treatment

The patient was admitted to the Surgery Department for the purpose of resection of the tumor. During the laparotomy

performed, the tumor was found to be a solid growth, approximately 7 cm in size, having infiltrated the celiac trunk, while allowing for the detection of a strong pulse on palpation of the hepatic artery. No evidence of dissemination of the tumor was found. It was decided not to perform a radical resection of the tumor due to the lack of conditions allowing for the safe preparation of the celiac trunk. Instead, a needle biopsy was performed. No complications arose during the surgical procedures or the post-operative period.

Table 1: General and specific markers utilized in the diagnosis of neuroendocrine tumors (NET) [1,3].

General markers	Specific markers
Chromogranina A	Carcinoid • 5-hydroxyindoleacetic acid (5-HIAA), in 24-hour urine collection, • Serotonin
Neurospecific enolase	Insulinoma • Fasting insulin level, • Peptide C
Pancreatic polypeptide	Gastrinoma • Gastrin, • Gastrin stimulation test
Chromogranin B	Glucagonoma • Glucagon
Pancreostatin	VIPoma • Vasoactive intestinal peptide (VIP)
Chorionic gonadotropin	Somatostatinoma • Somatostatin (SST)

Table 2: Symptoms suggestive of a neuroendocrine tumor [1,4].

Persistent watery diarrhea lasting more than 3 days
Electrolyte disturbances (severe hypokalemia), non-respiratory acidosis
Severe abdominal pain, indigestion, gastrointestinal bleeding
Weight loss
Personality disorders, depression

Table 3: Criteria for assessing the degree of histological maturity of neuroendocrine neoplasms [3,12].

Degree of histological maturity (G-grading scale)	Number of resolved figures/10 wide fields-of-view	Ki-67 proliferation index [%]
G1 – Low grade or well differentiated	< 2	< 3
G2 – Intermediate grade or moderately differentiated	2 - 20	3 – 20
G3 – High grade or poorly differentiated	> 20	> 20

The histopathological analysis revealed clusters of monomorphic cells among the vitreous fibrous connective tissue: synaptophysin – positive, chromogranin – positive, Ki-67 proliferation index – low, below 1%. Taking into account the general clinical state of the patient as well as the result of the histopathological assessment, a neuroendocrine tumor NET – G1 was diagnosed. The patient was discharged from the department and referred for further endocrinological treatment.

Endocrinologic inpatient treatment

The patient was admitted in an overall moderate clinical state to the Endocrinology Department, having experienced fatigue resulting from bouts of diarrhea increasing in severity. Laboratory testing revealed acid-base and electrolyte imbalances as well as hypokalemia – 1.8 mmol/L (normal: 3.5-5.5), including symptoms of non-respiratory acidosis. Due to the suspicion that the tumor was a VIPoma with elevated hormonal activity, the first dose of a long-acting somatostatin analog (Lanreotide 120 mg s.c.) was administered. The diarrhea subsided and the kidney markers stabilized fully on the second day of treatment. For the purpose of expanding the scope of the diagnosis, a blood vasoactive intestinal peptide (VIP) test was performed. Three weeks following the course of treatment, an increase in the number of bowel movements was observed. However, hypokalemia was also detected in laboratory testing. It was decided to administer a second dose of Lanreotide, after which the clinical symptoms were observed to have subsided.

The patient was discharged in an overall stable clinical state, without having experienced further bouts of diarrhea or distress, and referred for subsequent hospitalization after four weeks for the purpose of continuing the previously implemented course of treatment. Subsequent to being discharged, the diagnosis of VIPoma was confirmed by elevated levels of serum vasoactive intestinal peptide >60 pmol/L (normal: <30 pmol/L). Table 1 presents the changes in the laboratory parameters throughout the three hospitalization periods.

Discussion

GEP-NET are rare, atypical tumors, capable of synthesizing many substances, which are capable of manifesting many generalized symptoms. Such clinical presentations qualify these tumors as hormonally active. Increased hormone levels, whether in blood, urine or other fluids, constitute biochemical markers, aiding in their diagnosis. The diagnosis of GEP-NET involves a number of compounds divided into general (non-specific, elevated in all NETs) and specific markers (Table 1). Chromogranin A is the most significant general marker and testing for its blood concentration is recommended in all cases of suspected NETs. A significant proportion of tumors are clinically silent (that is, hormonally inactive) and are therefore diagnosed incidentally during routine surgical procedures or in their advanced stages, wherein they cause “mass effects”.

VIP functions as a smooth muscle regulator, water and electrolyte secretory stimulator in the gastrointestinal tract, as well as an inhibitor of gastric acid secretion. It also serves as a blood vessel dilator, which may lead to a generalized peripheral vascular effect. However, current literature does not corelate the presentation of these characteristics with the onset of hypotension or shock [9]. In the case of the patient presented in this investigation, periodic reddening of the hands and face were observed. This was most likely related with the detected elevation in hormone levels. WDHA Syndrome triggered by the VIPo-

ma and characterized by severe diarrhea six months in duration, was observed in this patient. This was due to the binding of VIP particles to intestinal epithelial cells, which increased their synthesis and utilization of cyclic AMP, causing an increase in electrolyte concentrations in the intestinal lumen, leading to the onset of diarrhea. In the majority of cases, diarrhea constitutes the main, indeed sometimes the only, symptom associated with VIPomas [5,8]. Table 1 presents symptoms characteristic in the diagnosis of neuroendocrine tumors.

Based on the duration of the exhibited symptoms, the classification of the tumor as well as its localization, patients may present in a range of clinical states, from a mild electrolyte imbalance to severe multiorgan complications: renal failure, arrhythmias or disseminated intravascular coagulation [10]. This constitutes a significant difficulty in the selection and implementation of appropriate diagnostic procedures, invariably prolonging the timeframe of the diagnosis of the tumor. In the case of the patient described in this investigation, the only alarming symptom was chronic diarrhea, which could have been pathognomonic for a variety of disease states. Many elements compounded one another in this case, for which reason the patient presented in such a severe initial clinical state.

Routine preparation for colonoscopies in the case of this severely dehydrated patient led to advanced renal failure, requiring the implementation of emergency renal replacement therapy. Despite the utilization of a very precisely tailored first round of dialysis, cerebral edema nevertheless ensued, which is presently a very rarely observed complication.

The diagnosis of NET requires the presentation of characteristic symptoms, an increase in biochemical markers as well as localized growths visible in imaging tests, such as ultrasonography, computed tomography or magnetic resonance imaging. They constitute the basis for the assessment of the degree of severity of the tumor and the monitoring of its response to treatment.

In nearly 60-70% of patients, metastases are already present at the time of diagnosis, the most common of which is to the liver, as in the case of the patient described in this investigation (a 25x20 mm growth along the inferior border of segment VI of the liver, as visible under CT). However, there are other metastatic targets for NETs as well, such as the lymph nodes, kidneys and lungs [1,3,5,7]. Due to the high probability of metastasis, liver lobe resection and embolization or targeted ablation of hepatic arteries may be required and indeed prove effective, however this approach was not pursued in this case [8].

The gold standard of treatment for this type of tumor is surgical resection [4]. According to current literature, 75% of this type of tumor is localized in the tail of the pancreas and 25% in the body of the pancreas, as in the case presented. Partial pancreatectomy undertaken via laparotomy was once the preferred procedure for tumors localized in the body or tail of the pancreas. The surgical approach is dependent upon the localization and size of the tumor. In the past decade, the minimally invasive approach has become the standard, allowing for the preservation of the largest mass of the pancreatic parenchyma and minimalizing the incidence of endocrinological complications [11].

The majority of NETs exhibit an over-expression of cell surface somatostatin receptors. This biological characteristic is harnessed in imaging techniques based on the analysis of somatostatin receptors, such as 111. In octreotide scintigraphy and 68Ga DOTATATE positron emission tomography (PET). This also lends somatostatin analogs a therapeutic role in the treatment and restoration of insufficiencies or disorders related with NETs [2,6]. They are utilized in the treatment of diarrhea, reduction of the blood VIP level as well as in the decreasing or stabilization of tumor size, owing to their antiproliferative properties [4].

Octreotide and Lanreotide are long-lasting, synthetic SSTR analogs, which effectively inhibit the secretion of VIP by tumor cells. Their mechanism of action is primarily based on their binding target cell receptors. Under circumstances in which radical tumor resection is ineffective or impossible (as in this investigation), they constitute a pharmacological role in the management of symptoms in VIPoma patients [9]. The patient in this investigation responded very well to the course of treatment implemented, which is essential in the maintenance of optimal acid-base parameters and electrolyte concentrations, as well as in the prevention of the appearance of severe complications such as subsequent acute kidney injury. In certain situations, the administration of their higher doses intravenously may be required due to the possibility that the subcutaneous route may be ineffective in patients suffering from severe diarrhea [6]. Based on the clinical state of the patient, the presentation of certain symptoms in the initial phase of treatment allows optimal dose titration.

One of the most critical histopathological characteristics of neuroendocrine tumors that plays a role in their prognosis is the histological grading of the tumor. It is determined on the basis of the Ki-67 proliferation index as well as the number of resolved figures [3,12]. Table 3 presents the criteria along with the corresponding breakdown of the grading of neuroendocrine tumors. In the case presented in this investigation, the histopathological analysis yielded a very low Ki-67 index, below 1%. This allowed for the classification of the tumor as G1, that is, well differentiated and of a low degree of malignancy.

Conclusion

Despite the exhibition of many highly characteristic symptoms, the diagnosis of neuroendocrine tumors often presents a challenge for clinicians of many specializations. In every case of severe, watery diarrhea that does not subside upon fasting and lasts for an extended period of time, it is essential to broaden the scope of the diagnostic approach. It is possible to perform modern diagnostic methods in many, although not necessarily highly specialized, laboratories. A timely diagnosis is essential in the prevention of life-threatening complications, as well as in the extension of the life expectancy and quality-adjusted life-years of the patient.

Declarations

Patient consent: Written informed consent was obtained from the patient for publication of this case report.

Conflict of interest: The authors have no conflicts of interest to declare.

Author contributions: Each of the seven authors of this case report provided substantial contributions to its conception and drafting, exercised final approval of the version to be published, and agree to be accountable for all aspects of the work.

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