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Case 2: A 66-Year-Old Man With Chronic Watery Diarrhea

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PRESENTATION OF CASE 2

Dr. Ji Eun Shin: A 66-year-old man was admitted to this hospital because of diarrhea, weight loss and hypotension.

The patient had been well until a month before this admission, taking medication well for underlying diseases such as hypertension and diabetes. Diarrhea occurred four weeks before admission to this hospital. Diarrhea was watery, 4 to 5 times a day, even at night, and mild diffuse abdominal pain was accompanied without tenderness. He had no known allergies and had no history of ingestion of contaminated foods or raw meats. He did not take any new medications. Symptoms got worse on the day of visit, which was followed by severe general weakness and weight loss of 4 kg.

On examination, the temperature was 35.1°C, the heart rate 99 beats per minute, the blood pressure 66/29 mmHg, the respiratory rate 20 breaths per minute, and an oxygen saturation of 100% while he was breathing ambient air. Skin was dry and both extremities were cold. Lung sounds were clear, and there was mild abdominal tenderness. He complained of general weakness, but his consciousness was alert enough to communicate.

There were no specific findings in the complete blood count. In blood chemistry, urea nitrogen (117.6 mg per deciliter) and creatinine (11.62 mg per deciliter) were elevated. The patient had no history of chronic renal disease, and no abnormal findings were noticed in his previous laboratory findings performed three months before admission. In addition, serum glucose was 204 mg per deciliter and total ketone bodies was 909.8 μmol per liter. In the arterial blood gas panel, pH was 6.985 and HCO3 was measured below 10 mmol per liter, suggesting that severe metabolic acidosis was accompanied. Anion gap was calculated at 22.3 mmol per liter; other test results are shown in **Table 1**.

Six liters of isotonic crystalloid solution containing sodium chloride were transfused rapidly through two peripheral intravenous catheters after four hours of arrival. However, systolic blood pressure was not maintained above 90 mmHg, so vasopressors, norepinephrine and vasopressin were administered. Anuria persisted despite continuous fluid resuscitation

Table 1. Laboratory data of the patients

Parameters	Reference range, adults[a]	On admission	7 Days after admission
Hematocrit, %	41.0–53.0 (men)	31.9	22.8
Hemoglobin, g/dL	13.5–17.5 (men)	10.4	8.0
White-cell count (per mm)	4,500–11,000	16,550	16,040
Differential count, %			
Neutrophils	40–70	88.7	72.0
Lymphocytes	22–44	4.7	14.8
Monocytes	4–11	6.5	9.3
Eosinophils	0–8	0.0	3.7
Platelet count (per mm)	150,000–450,000	211,000	147,000
Prothrombin time, sec	11.0–13.7	13.4	13.6
Sodium, mmol/L	135–145	135	140
Potassium, mmol/L	3.4–4.8	4.5	3.1
Chloride, mmol/L	100–108	105	109
Urea nitrogen, mg/dL	8–25	117.6	11.2
Creatinine, mg/dL	0.60–1.50	11.62	0.86
Estimated glomerular filtration rate (mL/min/1.73m)	> 60	4	91
Glucose, mg/dL	70–110	204	209
Protein, g/dL			
Total	6.0–8.3	6.5	5.6
Albumin	3.3–5.0	4.1	3.2
Osmolarity (mOsm/kg of water)	275–300	332	290
Calcium, mg/dL	8.5–10.5	8.4	7.9
Phosphorus, mg/dL	2.6–4.5	4.2	2.9
C-reactive protein, mg/L	0–0.5	1.08	
ABGA-PH	7.35–7.45	6.985	7.382
ABGA-PCO2, mmHg	35.0–48.0	20.4	25.4
ABGA-PO2, mmHg	83–108	102	87.9
ABGA-HCO3, mmol/L	21–28	< 10	14.8
Lactic acid, mmol/L	0.5–1.6	4.2	1.0

[a]Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Seoul St. Mary's Hospital are for adults who do not have medical conditions that could affect the results.

Author Contributions

Conceptualization: Park SJ. Data curation: Shin JE, Park SJ, Yoon SY, Kim Y. Supervision: Lee MA. Writing - original draft: Shin JE, Park SJ, Yoon SY, Kim Y. Writing - review & editing: Shin JE, Park SJ.

and metabolic acidosis did not improve in the following arterial pH test. The patient was admitted to the intensive care unit due to hemodynamic instability accompanying anuria and metabolic acidosis, and continuous renal replacement therapy was initiated.

While renal replacement therapy was continued five days after hospitalization, uremia improved, but diarrhea got aggravated and the amount reached 10 liters per day. Despite renal replacement therapy, severe metabolic acidosis with hypokalemia of less than 3.0 mmol per liter of potassium lasted due to persistent massive watery diarrhea.

No pus cells suggestive of any inflammation in gastrointestinal (GI) tract were observed in the stool examination. No enteric pathogen and parasites were observed in stool specimen. Polymerase chain reaction testing for entero-pathogen and testing for *Clostridium difficile* toxin were negative.

CLINICAL IMPRESSION

Dr. Ji Eun Shin: Chronic diarrhea due to hormone-producing tumor.

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IMAGE PRESENTATION

Dr. Ji Eun Shin: We performed computed tomography (CT) of abdomen and colonoscopy to examine structural disease in the GI tract, including inflammatory bowel disease and intestinal carcinoid tumors. May we review imaging studies?

Dr. Seo Yeon Youn: Enhanced abdominal CT showed a 5.2 cm sized well-defined mass with avid enhancement and central low-density portion in the pancreas tail (**Fig. 1A**), and there were no other findings suspicious of intestinal malignancy, acute enterocolitis, or ischemic colitis. On enhanced pancreas biliary magnetic resonance imaging (MRI), this pancreatic tail mass showed hemorrhagic and cystic change in central portion, and diffusion restriction in peripheral solid portion of the tumor (**Fig. 1B**). The differential considerations for solid tumors of the pancreas should include pancreatic adenocarcinoma, neuroendocrine tumor (NET), and metastases from other primary cancer. In this patient, duct dilatation of the pancreas, a classic finding of pancreatic adenocarcinoma, was not observed. The pancreatic tail mass was enhanced at peripheral solid portion with central cystic change and hemorrhage with fluid-fluid level, which findings were consistent with NET of pancreas. In colonoscopy, no specific lesions were found suggestive of inflammatory bowel disease, and no stool in a general form other than intestinal fluid was observed.

DIFFERENTIAL DIAGNOSIS

Dr. Ji Eun Shin: This 66-year-old man presented with 4-week-history of chronic diarrhea. When he was hospitalized, he had a rapidly worsening clinical course with profuse watery diarrhea, severe enough to cause hypovolemic shock and acute renal failure.

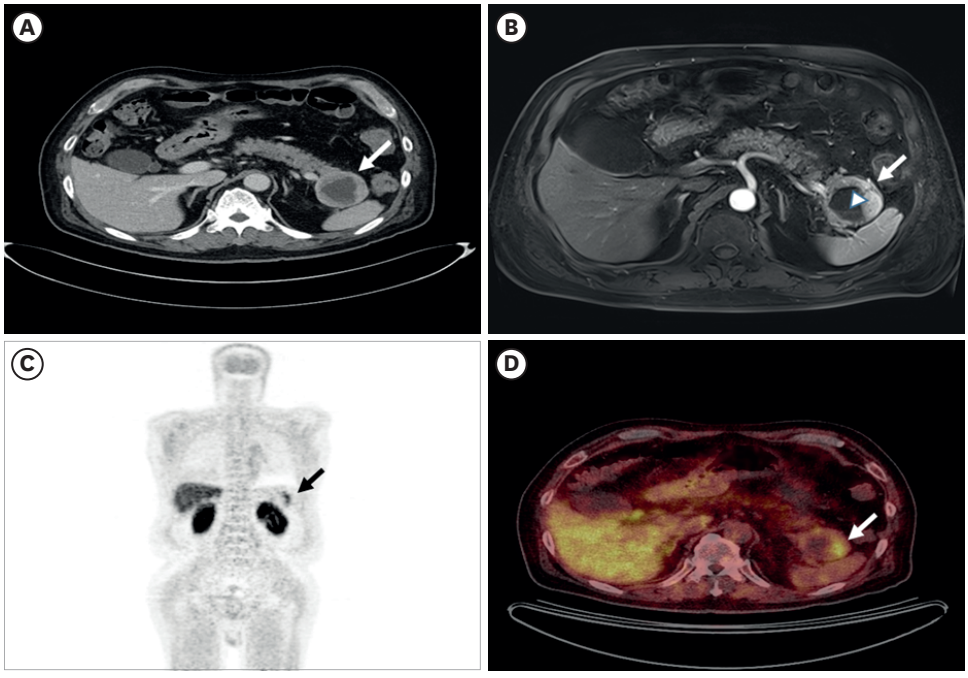

Fig. 1. Abdominal imaging and ^{18}F-DOPA PET/CT. An axial image from a contrast enhanced CT scans of abdomen and pelvis (**A**) shows a 5.2cm sized pancreatic tail mass (arrow) with central hypodense portion. Axial arterial phase T1-weighted fat-suppressed magnetic resonance image (**B**) shows the mass (arrow) with marked enhanced peripheral solid mass with central cystic change and hemorrhage with fluid-fluid level (arrowhead). ^{18}F-DOPA PET/CT image (**C**, **D**) clearly depicts a pancreatic tail tumor (arrow) with peripheral uptake and central photon defect.

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Although acute diarrhea is commonly caused by infection, the etiology of chronic diarrheal disease is more elusive.[1] Differential diagnosis can be made upon detailed history taking, physical examination, and appropriate imaging and blood tests.

Chronic watery diarrhea

Differential diagnosis of watery diarrhea starts with discriminating whether the mechanism of diarrhea is secretory or osmotic. The initial step to differentiate between these two is figuring out the presence of an osmolar gap by measuring stool electrolytes and osmolality in a stool specimen.[1] Unfortunately, in this case, the stool electrolyte was not examined. Considering that the patient's symptoms did not improve even with fasting and only a large amount of intestinal fluid was observed without stool at colonoscopy, his clinical course is more suitable for secretory diarrhea. There are several conditions that can cause secretory diarrhea, such as motility disorder, inflammatory bowel disease, endocrinopathy, and peptide-secreting tumors.

Looking at the patient's medical history, none of the medications being taken had a known mechanism of causing diarrhea. There were no clinical symptoms suggestive of irritable bowel syndrome. He denied any food history causing chronic diarrhea. Colonoscopy performed 2 years before admission showed no findings suggestive of inflammatory bowel disease or GI malignancy. There were no findings in the stool examination and colonoscopy, suggestive of acute enterocolitis or inflammatory disease. In any laboratory test performed during hospitalization, there were no findings suggestive of endocrinologic diseases such as hyperthyroidism and adrenal insufficiency which are known to commonly cause watery diarrhea. Abdominal CT showed no findings consistent with acute infectious enteritis or ischemic colitis.

Diarrhea with hormone-secreting tumor

Dr. Se Jun Park: Peptide-secreting functional NET is a very rare disease entity causing chronic watery diarrhea, but it must be considered when the etiology of diarrhea is not clear, and the symptoms are severe. Peptide-secreting functional NET could be detected by measuring serum levels of chromogranin, gastrin, vasoactive intestinal polypeptide (VIP), or calcitonin, as well as urine levels of 5-hydroxyindoleacetic acid.[2]

In this patient, a 5.2 cm sized well-enhancing pancreatic tail mass with predominant cystic change was observed on the abdominal CT, which was typical imaging findings of pancreatic NET. Considering these imaging findings, we decided to evaluate whether the patient's main complaint was due to hormone-secreting tumor. Among pancreatic NET, those that can cause watery diarrhea include gastrinoma, vasoactive intestinal peptide-secreting tumor (VIPoma), and rare functioning tumor causing carcinoid syndrome. Serum specific peptide levels were identified to differentiate them.[3] The chromogranin A measured in the patient's serum was 152.3 ng per milliliter, which was higher than normal, suggesting the possibility of pancreatic NET.

Gastrinoma, also known as the Zollinger-Ellison syndrome, a rare tumor of duodenum (70%) and pancreas (25%), causes ectopic hypersecretion of gastrin.[3] Excessive secretion of gastric acid leads to severe peptic ulcer disease, esophageal reflux symptom, and diarrhea. However, this patient had normal serum gastric level, even though he had not taken any proton pump inhibitors that could lower serum gastrin level.

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Table 2. Laboratory tests to detect peptide-secreting neuroendocrine tumor

Test items	Reference range, adults	7 Days after admission
Blood		
Chromogranin A, ng/mL	19.4–98.1	152.3
VIP, pg/mL	< 70	290.00
Gastrin, pg/mL	25.00–111.00	54.84
Urine		
5-HIAA, mg/d	< 10	9.74

VIP = vasoactive intestinal peptide, 5-HIAA = 5-hydroxyindoleacetic acid.

Carcinoid syndrome is one of the common hormone-producing diseases causing diarrhea.[3] However, pancreatic NETs causing carcinoid syndrome are very rare (< 1% of all carcinoids), and the patient did not have any typical symptoms such as, flushing, edema, or wheezing suggestive of carcinoid syndrome other than diarrhea. To differentiate it, 5-hydroxyindoleacetic acid in the urine was measured, and the value was 9.74 mg per day, which carcinoid syndrome could be excluded.

VIPoma is another pancreatic NET that is rare and known to cause watery diarrhea. Diagnosis can be made upon an elevated VIP level with radiologic evidence of a pancreatic lesion. The VIP level was 290 pg per milliliter, which was suitable for the diagnosis of VIPoma (**Table 2**).[4]

PATHOLOGIC FINDINGS

For pathologic confirmation, we performed endoscopic ultrasound–guided biopsy and appropriate tissue was obtained.

Dr. Younghoon Kim: Pathological examination of biopsy specimens showed tumor cells with round to oval nuclei with salt and pepper chromatin arranged in a trabecular pattern, which features are consistent with NET. We also received a specimen from the surgical resection of the pancreatic mass. The specimen consisted of a 5.0 × 4.8 × 4.4 cm sized tumor of the pancreas tail (**Fig. 2A**). The pancreatic mass was circumscribed and was composed of soft, pale gray tissue with focally observed necrotic and hemorrhagic areas (**Fig. 2B**).

Microscopically, tumor cells with small, round to ovoid nucleus and disperse chromatin is arranged in nesting and trabecular pattern (**Fig. 2C**). Mitosis was up to 1 per 10 high power fields. Immunohistochemistry revealed positivity for synaptophysin (**Fig. 2D**) and CD56 and negativity for chromogranin (**Fig. 2E**). Glucagon staining was focally positive. Ki-67 index was 2% (**Fig. 2F**). The tumor was diagnosed as NET grade 1. Lymphovascular or perineural invasions and regional lymph node metastases were not observed. Based on the tumor size and the involvement of peripancreatic tissue, the pathologic stage was determined to be pT3N0Mx.

Serum VIP levels measured at the time of diagnosis were markedly elevated. After surgery, the VIP levels have remained normal. Therefore, the final diagnosis in this case is pancreatic VIP-secreting neuroendocrine neoplasm (VIPoma).

FINAL DIAGNOSIS

Dr. Se Jun Park: Vasoactive intestinal peptide-secreting tumor (VIPoma) of pancreas.

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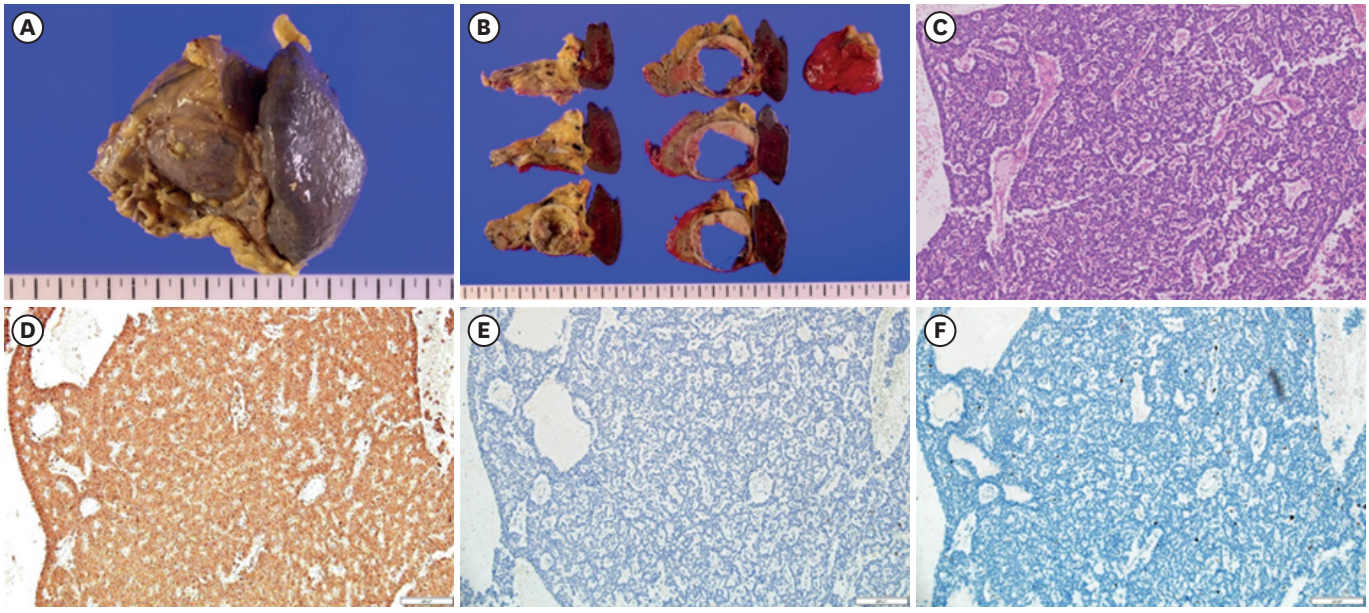

Fig. 2. Pathological findings. A specimen obtained from surgical resection of the pancreatic tail shows cystic mass that measured 5.0 × 4.8 × 4.4 cm (**A**, **B**). Microscopical examination of a section of the pancreatic mass shows tumor cells with small, round to ovoid nucleus and disperse chromatin which arranged in nesting and trabecular pattern (**C**, hematoxylin and eosin, ×100). Mitosis was up to 1 per 10 high power fields. Immunohistochemical staining revealed positivity for synaptophysin (**D**) and negativity for chromogranin (**E**). Ki-67 proliferation index was 2% (**F**).

GENERAL INTRODUCTION OF THE DISEASE MANAGEMENT

Dr. Se Jun Park: VIP is known to function primarily as a neurotransmitter and neuromodulator. VIP receptors have been identified in abundance in the GI tract and central nervous system and the effect of this hormone on GI tract is as follows; epithelial secretion and absorption in the GI tract mucosa and the biliary mucosa, smooth muscle relaxation including the lower esophageal sphincter and colon, and growth promoting effect in certain tumors. Some studies showed that VIP does not cause intestinal motility disturbances but contributes to diarrhea mostly because of the secretory activity.[4]

VIPoma is a non-beta pancreatic islet cell tumor secreting VIP, resulting in a syndrome of watery diarrhea, hypokalemia, and achlorhydria which together are known as the WHDA syndrome.[5] Many patients with VIPoma often present with severe, profuse, intermittent, or continuous secretory diarrhea; involving substantial fluid and electrolyte secretion that exceeds the absorptive capacity of the distal small intestine. The patient complained of massive diarrhea enough to cause hypovolemic shock and acute renal failure during hospitalization and was accompanied by hypokalemia and hyperchlorhydria with a potassium level of 2.8 mmol per liter and chloride 113 mmol per liter measured in blood, which is consistent with the clinical course of VIPoma.

Most VIPomas, ranging from 70% to 90%, are malignant with 40% to 70% having metastasized at time of diagnosis, especially to the liver, lymph nodes or bone. As accurate staging is necessary to determine treatment method for functioning or non-functioning pancreatic NET. Integrated PET/CT using Gallium-68-DOTA-0-Phe1-Tyr3-Octreotate (^{68}Ga-DOTATATE) or Ga-68-DOTA-0-Phe-Tyr-Octreotide (^{68}Ga-DOTATOC) should be performed to identify the tumor and its location.[6] Because of its greater sensitivity, ^{68}Ga-DOTATATE or

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^{68}Ga-DOTATOC PET/CT is preferred over conventional somatostatin receptor scintigraphy. However, those modalities were not available at our institution, we performed ^{18}F-dihydroxyphenyl-alanine (^{18}F-DOPA) PET as staging modality in this patient. In ^{18}F-DOPA PET, there was ^{18}F-DOPA-avid tumor with central necrosis in pancreas tail which is suggestive of NET. There was no evidence of distant metastases (**Fig. 1C and D**).

The patient in this case had serious complications related to severe diarrhea such as renal failure and hypovolemic shock. Initially, fluid resuscitation with electrolytes supplement is warranted in these patients. However, in this case, the patient's symptoms worsened despite adequate fluid supply and conservative treatment. It is well known that octreotide and other somatostatin analogues are useful for the treatment of secretory diarrhea in VIPoma patients, by adhering somatostatin receptors expressed on VIPoma, thus inhibiting hormone excretion from the tumor.[6] After 10 days of hospitalization, VIPoma was clinically diagnosed through blood tests and imaging. We started octreotide 100 ug subcutaneously twice a day and diarrhea improved immediately after administration.

Apart from the medical management, surgery is the mainstay of curative treatment for pancreatic NET for patients with localized disease. Also, reduction of tumor burden by surgical resection has been recommended as management of refractory symptoms in previous cases with VIPoma.[5] After discussing the surgical treatment with department of general surgery, it was decided to perform distal pancreatectomy in consideration of the size and location of the pancreatic NET mass. He underwent a surgery four weeks after admission, and, he was discharged with improvement of all clinical symptoms including diarrhea and acute renal failure.

Three weeks after surgery, at the outpatient visit, the patient did not complain of any specific symptoms, including diarrhea. In the blood chemistry, renal function was also well maintained with urea nitrogen 6.5 mg per deciliter, creatinine 0.90 mg per deciliter. Following serum VIP level was measured 50.00 pg per milliliter or less.

Prognosis

After surgical resection, it is recommended that patients be followed up after 3 to 9 months with serum tumor markers and imaging, and interval of follow-up can be changed depending on patients' disease status. There are several reports on how to assess the prognosis of pancreatic NET, however, there is no definitive consensus about a distinct predictor. Yet, it is a common opinion that the grade of histology and the presence of distant metastasis are important factors in predicting prognosis.[6] In patients with advanced pancreatic NETs, the best prognosticator for progression was Ki-67 index.[6] Several studies reported that in pancreatic NET patients the presence of positive lymph nodes and their number have important prognostic value.[7,8] These results support the recommendation that a systematic removal of regional lymph nodes should be conducted for any pancreatic NET operation.

According to histological finding of this patient, he had a grade 1 pancreatic NET with a Ki-67 index of 3% or less and a mitotic index of 2 or less, without regional lymph nodes involvement, suggesting a low risk of recurrence. For functioning NET, long survival is expected even when the late stage is detected. In a previous study, the median survival of VIPoma was found to be 7.9 years in all stages.[4]

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DISCUSSION

The incidence of pancreatic NET is known to be 1 to 5 per million per year, and accounts for 1–2% of pancreatic tumors. Of these, more than 90% occur sporadically, but the remainder occur in hereditary syndrome, well-known as multiple endocrine neoplasia 1.[4]

Pancreatic NETs can be classified into functioning pancreatic NETs and nonfunctioning (N-F) pancreatic NETs depending on their ability to secret hormones. Functioning pancreatic NETs secrete large amounts of peptide hormones and other bioactive compounds leading to hypersecretion clinical syndromes.[3] According to a recent study, N-F pancreatic NETs account for 60–90% of pancreatic NETs, and in most cases, they are diagnosed in delay because they usually grow slowly and exhibit fewer symptoms.[6]

After diagnosis of pancreatic NET, imaging studies are required for accurate localization of the tumor. CT or MRI of the abdomen can localize the location of the tumor and the extent of disease. Recent studies have shown that ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET/CT is highly sensitive and specific for pancreatic NETs, including gastrinomas, and N-F pancreatic NETs.[6] Therefore, preoperative imaging with ^{68}Ga-labeled somatostatin analogue with PET/CT should be considered as a first-line diagnostic imaging method for staging pancreatic NET patients, if available. If unavailable, somatostatin receptor scintigraphy with SPECT or ^{18}F-DOPA PET could be useful in staging for pancreatic NETs. In case of rapid tumor progression, 18-fluorodeoxyglucose (^{18}FDG) PET/CT may be considered to assess tumor location and burden.

Dr. Ji Eun Shin: How can we establish perioperative management for patients with VIPoma accompanied with electrolyte imbalance and acute renal impairment due to extensive volume loss?

Dr. Se Jun Park: Curative resection is recommended for patients with VIPoma without evidence of non-resectable or metastatic disease. However, secretory diarrhea is commonly extensive, with loss of bicarbonate and potassium leading to severe metabolic acidosis and hypokalemia. Therefore, patients with VIPoma need to be resuscitated with preoperative somatostatin analog treatment and intravenous fluid and electrolyte therapy before being subjected to surgery.[9]

Dr. Ji Eun Shin: What are the treatment options for patients with locally advanced or metastatic pancreatic NET?

Dr. MyungAh Lee: For patients with locally advanced or metastatic functioning pancreatic NETs, somatostatin analogues (octreotide, lanreotide) remain the first-line treatment. For patients with advanced N-F pancreatic NET, not only somatostatin analogues, but targeted treatment and cytotoxic chemotherapy could be considered. According to recent studies, peptide receptor radionuclide therapy (PRRT) using 177 Lu-DOTATATE showed favorable outcome for patients with NETs including pancreatic NETs with distant metastases. PRRT can be considered in both functioning pancreatic NETs and N-F pancreatic NETs with high expression of somatostatin receptors. The European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines Update for Management of Patients with Functional Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors, updated in 2016, provides a basic idea for developing a diagnostic method and therapeutic strategy.[6]

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In this case, the patient with chronic watery diarrhea was pathologically diagnosed with pancreatic NET grade 1, and serum VIP level elevation was confirmed. Finally, this patient was diagnosed with pancreatic VIPoma classified as pancreatic functioning NET.

Related questions

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