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## Disseminated neuroendocrine neoplasm with undetected primary tumor

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### ABSTRACT

Since the 19<sup>th</sup> century, neuroendocrine neoplasms (NEN) have been identified. Right up to the present day, the nomenclature is still under debate reflecting the heterogeneity of these tumors. Although some of them are slow growing, some can be fearfully aggressive and may develop in almost any organ of the abdomen, thorax, neck, skin, and gonads. The most commonly observed sites of NEN are the lung and the gastroenteropancreatic system (GEP), where more than 50 entities have been observed. In case of a NEN of unknown primary tumor, the histopathological diagnostic workup includes immunohistochemistry for chromogranin A and synaptophysin, followed by specific tissue markers. Clinical presentation is very diverse, depending on the primary site and functionality of the tumor. In the case of the GEP-NEN, the main symptoms are abdominal pain, diarrhea, weight loss, gastrointestinal bleeding, or bowel obstruction. The presence of neuropsychiatric symptoms is not insignificant in this group of tumors. The authors report a case of a 51-year-old man who sought medical attention because of a three-month history of a consumptive disease. The diagnostic workup disclosed a diffuse nodular infiltration of the lungs, hypokalemia, and hypercalcemia in a cachectic patient. The clinical investigation could not proceed because of an infectious intercurrent, which led to the fatal outcome. Autopsy findings showed a diffuse metastatic NEN. The primary tumoral site could not be demonstrated with the available immunohistochemical panel.

**Keywords:** Neuroendocrine tumor; Neoplasms, unknown primary; Neoplasms, metastasis; Diarrhea; Cachexia.

### CASE REPORT

A 51-year-old male patient sought medical attention complaining of pain for the past three months in the lower abdomen radiating to the right groin and inferior limb. More recently he referred watery diarrhea with up to three evacuations per day

without blood or mucus accompanied by anorexia and weight loss of 20 kg during this period. Since the onset of the symptoms, he has been presenting depression. His medical history included the diagnosis of epilepsy, alcohol consumption for seven

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years in his youth, and smoking for a long period right up to the date of admission. On admission, the physical examination showed an emaciated patient, but ruddy, hydrated, acyanotic, and anicteric. Vital signs were within normal limits. Examination of the lungs, heart, abdomen, and lower limbs was unremarkable. The admission laboratory tests are presented in Table 1.

The endoscopic examination of the upper gastrointestinal tract and colon were normal. The chest x-ray (Figure 1) showed the presence of tiny nodules, diffusely distributed throughout both lungs.

During hospitalization, the patient developed worsening of the depression symptoms followed by an altered level of consciousness and attention deficit. He started presenting with a cough and respiratory distress. When rales were detected on the lungs, vancomycin and imipenem were started. Because of the elevated serum calcium levels he was treated throughout hospitalization with

parenteral hydration associated with furosemide and pamidronate. After 13 days of hospitalization, he developed signs of septicemia. He died without diagnosis of the underlying disease. An autopsy was performed.

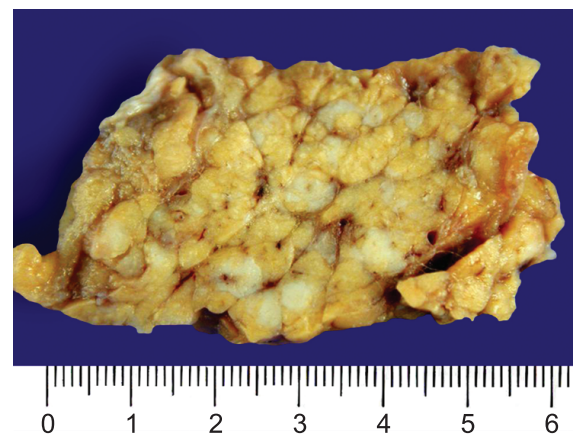
## AUTOPSY FINDINGS

On external examination, the anthropometric measures revealed the body of a man 176 cm in height, which weighed 47 kg (Body Mass Index = 15). The pancreas weighed 170 g (RV = 103-186 g) and showed multiple grayish nodules, with up to 0.5 cm in diameter (Figure 2).

On light microscopy, there was a trabecular proliferation of cells with mild atypia displaying "salt and pepper chromatin" (Figure 3). The immunohistochemical panel revealed positivity for chromogranin, synaptophysin, cytokeratin



**Figure 1** – Chest radiography showing diffuse bilateral nodules.



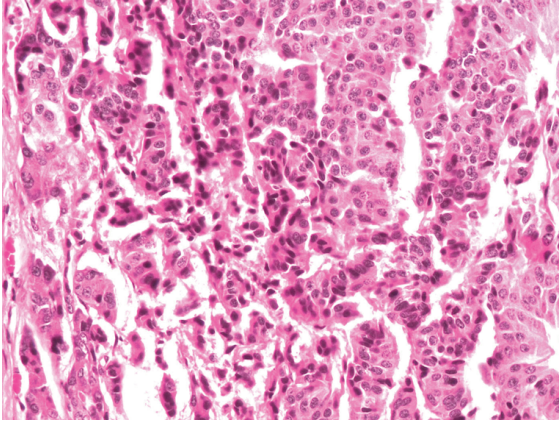
**Figure 2** – Gross examination of the pancreas showing multiple grayish nodules measuring up to 0.5 cm in diameter spread throughout the organ.

**Table 1** – Laboratory diagnostic work up at admission

Exam	Result	RV	Exam	Result	RV
Hemoglobin	13.7 g/dL	13.0-18.0 g/dL	Creatinine	0.58 mg/dL	0.7-1.0 mg/dL
Hematocrit	35.5%	40.0-52.0%	BUN	23 mg/dL	10-50 mg/dL
Leukocytes	9.16.10 <sup>9</sup> /mm <sup>3</sup>	4.0-11.10 <sup>9</sup> /mm <sup>3</sup>	Calcium	12.5 mg/dL	8.60-10.20 mg/dL
Neutrophils	68.2%	46-75%	PTH	<3 pg/mL	16-87 pg/mL
Eosinophils	0.9%	1-4%	K <sup>+</sup>	2.1 mEq/L	3.5-5.0 mEq/L
Basophils	0.5%	0-2.5%	Na <sup>+</sup>	132 mEq/L	135-145 mEq/L
Lymphocytes	22.0%	18-40%	Glucose	154 mEq/L	70-99 mEq/L
Monocyte	8.4%	2-9%	AST	22 U/L	<37 U/L
Platelets	356.10 <sup>9</sup> /mm <sup>3</sup>	140-450.10 <sup>9</sup> /mm <sup>3</sup>	ALT	26 U/L	<41 U/L

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; Na<sup>+</sup> = sodium; K<sup>+</sup> = potassium; PTH = parathyroid hormone; RV = reference value.

35BH11, and focal positivity for glucagon and somatostatin (Figure 4). The immunohistochemistry for insulin, pancreatic polypeptide, and the specific transcription factor markers TTF-1 and CDX-2 were negative. The tumor cell proliferation, assessed by Ki67 antigen, was estimated at 3-20%, which corresponds to the well-differentiated grade 2 of the WHO classification.

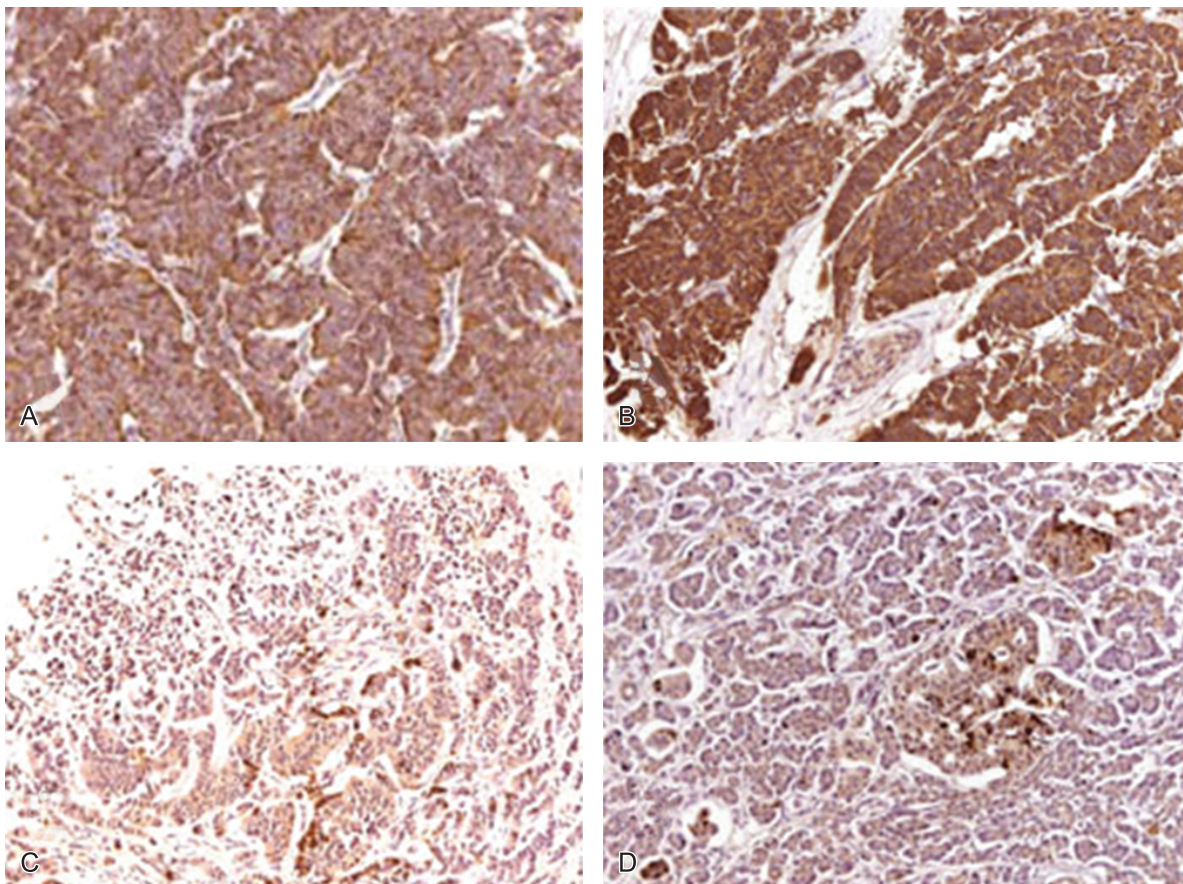


**Figure 3** – Photomicrography of the pancreas showing trabecular proliferation of cells with mild atypia displaying “salt and pepper chromatin” (H&E, 400x).

The right and left lungs weighed 670 (RV = 360-570 g) and 534 g (RV = 325-480 g), respectively. Both lungs exhibited a gray and smooth external surface, with anthracotic deposits. The pleural surface showed multiple grayish nodules (Figure 5). On sectioning, the parenchyma was aerated and exhibited a spongy consistency. Reddish areas of consolidation were detected in both inferior lobes. No pleural effusion was detected. On histological examination, the grayish nodules corresponded to neuroendocrine tumors in the pleura as well as within the alveolar spaces, besides multiple areas of exudative pneumonia (Figure 6).

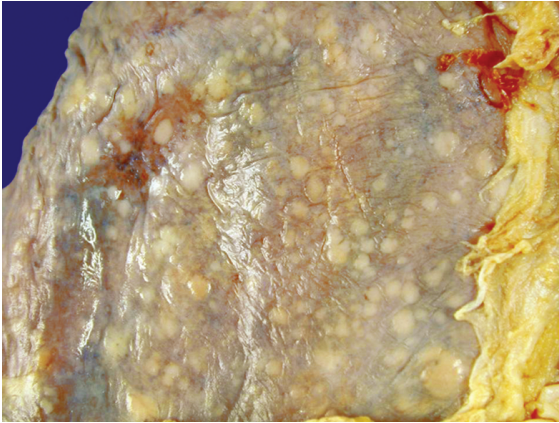
The microscopic examination of the spleen showed reactive splenitis. The heart weighted 354 g (RV = 270-360 g) and also showed multiple grayish nodules throughout the pericardial surface and within the myocardium (Figure 7).

The liver weight was normal and also presented multiple nodules in the parenchyma (Figure 8). The adrenals weighted 10 g each (RV = 9.7 each) and showed a yellowish cut surface with multiple grayish well-defined nodules

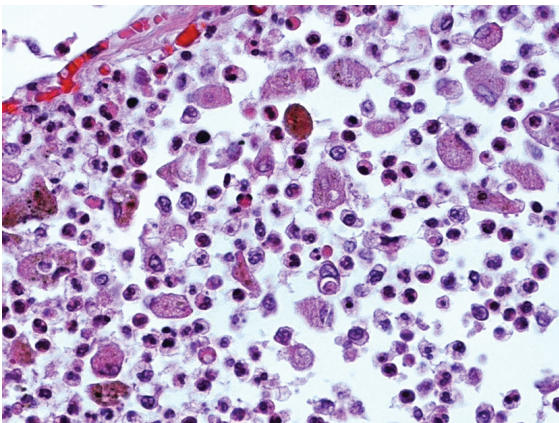


**Figure 4** – Photomicrography of the pancreatic tumoral nodule. The immunohistochemical panel revealed positivity for chromogranin (A), synaptophysin (B), and focal positivity for glucagon (C) and somatostatin (D) (100x).

(Figure 9). As well as the pancreas, the lungs, heart, liver, adrenals, thyroid, prostate, kidneys, and bone marrow showed microscopic neuroendocrine tumors on light microscopy. In the dorsum, the patient had a subcutaneous well-defined nodule, measuring 5.0 cm in its longest axis, which had a yellowish and homogeneous cut surface.



**Figure 5** – Right pleural surface showing multiple grayish nodules.



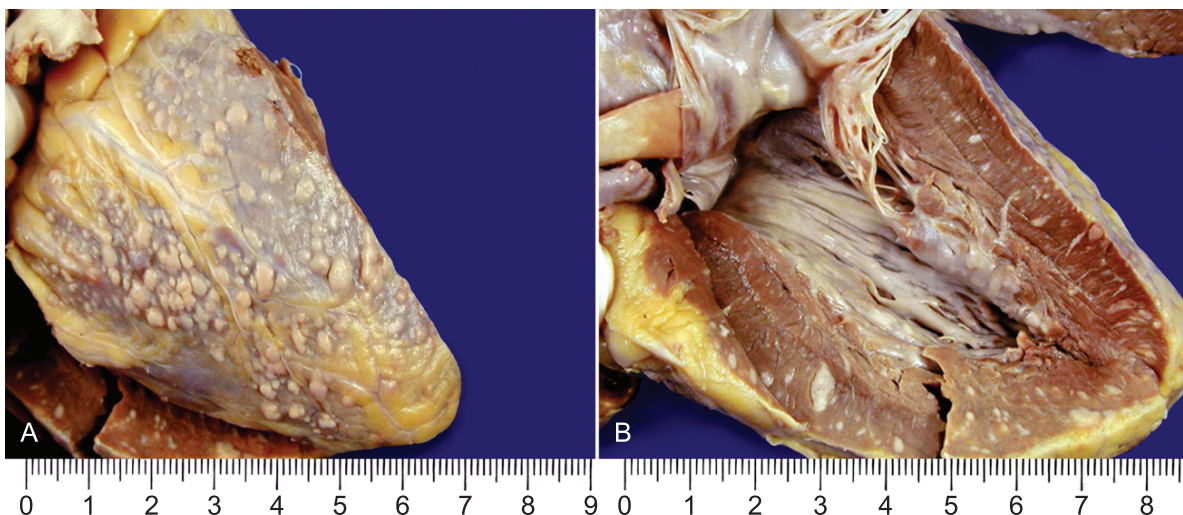
**Figure 6** – Photomicrograph of the lung showing areas of intra-alveolar exudative pneumonia (HE, 400x).

The histological examination revealed a lipoma with a neuroendocrine nodule within the adipose tissue, with the same histological characteristics of the tumor cited above. The clinical data added to the autopsy findings concluded that sepsis and pneumonia were the immediate cause of death.

## DISCUSSION

The neuroendocrine system, a fascinating chapter of histology, is represented by scattered cells throughout the body identifiable by their reactivity for chromium and silver salts. Named as enterochromaffin cells, argentaffin cells, clear cells, enteroendocrine cells, and Kultschitsky cells by several investigators, they may give rise to the neuroendocrine neoplasm (NEN). In the 19<sup>th</sup> century, Langhans (1867), Lubarsch (1888), and Ransom (1890) described tumors exhibiting neuroendocrine characteristics.<sup>1</sup> In 1907, Siegfried Oberndorfer coined the term *karzinoide* (“carcinoma-like” in German), to describe the feature of behaving like a benign tumor despite the microscopically malignant appearance.<sup>1</sup> Even till now, the nomenclature is still under debate reflecting the heterogeneity of these tumors.<sup>2</sup> Although the tumors are often slow growing, compared with adenocarcinomas, they can also be extremely aggressive.<sup>3</sup>

The incidence of NENs ranges from 2.5 to 5 cases per 100,000 in the Caucasian population.<sup>4</sup> This has substantially increased over recent decades, partially due to improved diagnostic techniques and clinical awareness.<sup>5-8</sup>

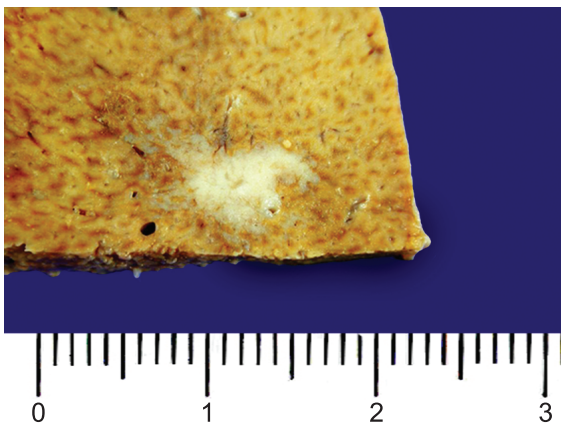


**Figure 7** – Gross examination of the heart showing multiple grayish nodules throughout the pericardial surface and within the myocardium.

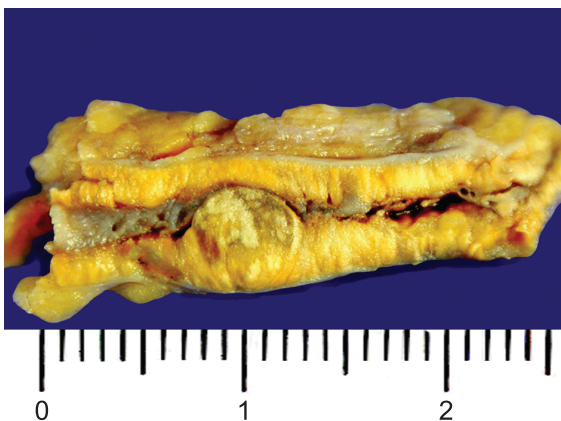
NENs seem to be homogeneous in terms of morphology, but depending on their localization, these neoplasms reveal distinct phenotypes with respect to pathology, immunohistochemistry, and hormonal syndromes.<sup>9</sup> They may develop in almost any organ of the abdomen, thorax, neck, and skin. The most commonly observed sites of NEN are the lungs and the gastroenteropancreatic system (GEP), where more than 50 entities have been observed.<sup>10</sup> There are rare sites of occurrence, which include the larynx, thymus, thyroid, adrenal, gonads, kidney.<sup>11,12</sup> The incidence of primary site may vary with gender and race.<sup>5</sup> In the National Cancer Institute (USA) survey, from 1950 until 1999, 13,715 cases were retrieved. The incidence of gastrointestinal (GI) NEN was 67.5% and bronchopulmonary 25.3%. Within the GI-NEN 41.8% were localized in the small intestine, 27.4% in the rectum, and 8.7% in the stomach.<sup>12</sup> A cohort study conducted in southern Spain<sup>4</sup> comprised 837 patients and 907 GEP-NET tumors. In this study, gastrointestinal sites represented 55% of cases followed by nonfunctional pancreatic tumors (20%). Among the functional tumors, the enteric

NEN (10%), insulinomas (8%), and gastrinomas (4%) were the most common. Glucagonoma, VIPoma, and somatostatinoma totaled less than 2%. In this study, 44% of patients presented with widespread disease at the time of diagnosis, which is different from the North American series where 12.9% of patients showed this stage at the time of diagnosis.<sup>12</sup> The patient reported in this case study presented a widespread and advanced-stage disease, evidenced by the necropsy findings and clinically by the cachexia that became symptomatic three months before medical attention.

Neuroendocrine carcinoma of unknown primary (NCUP) accounts for 9-13% of all NEN, and 5% of all malignant neoplasm.<sup>4,5,13</sup> These tumors arise from an occult or clinically undetectable primary site, which can be located in the liver, bronchus, pancreas, colon, rectum, or elsewhere. Two different clinicopathologic subsets of these tumors have been described. The first subset includes low-grade neuroendocrine carcinomas (metastatic well-differentiated NEN) usually involving the liver or presenting with symptoms due to the secretion of vasoactive peptides (functional tumors). This subset of tumors presents an indolent behavior. The second subset includes high-grade poorly differentiated carcinomas, which present rapidly growing biological behavior.<sup>2</sup> It cannot be identified if these tumors arise from an occult primary gastrointestinal or pulmonary site or even from multipotent stem cells.<sup>13</sup> The tumor presented in this case study belongs to the first group, with a proliferation cell index classified as G2. Unfortunately, the available immunohistochemical panel could not precisely elucidate the primary tumor, but in accordance with the available results and the literature data the tumor most probably belongs to the GEP-NEN group.



**Figure 8** – Gross examination of the liver presenting nodules in the parenchyma.



**Figure 9** – Gross examination of the right adrenal gland, showing a yellowish cut surface with multiple grayish well-defined nodules.

The WHO classification of 2010 presumes that all NEN are potentially malignant, but differs markedly in respect of their likelihood to develop metastases. The classification takes into account the tumor proliferative activity measured by immunostaining for the cell cycle-dependent marker Ki67 antigen, and/or by number of mitoses per unit area of tumor (usually expressed as mitoses per 10 high-power microscopic fields or 2 mm<sup>2</sup>).<sup>14</sup> Therefore the tumor is distinguished between well-differentiated and poorly differentiated neoplasms.<sup>15-17</sup> All well-differentiated neoplasms, graded G1 (Ki67 < 2%) and G2 (Ki67 2-20%), regardless of their biological behavior, will be called neuroendocrine tumors (NETs). All poorly differentiated neoplasms, graded G3 (Ki67 > 20%), will be termed neuroendocrine

carcinomas (NECs).<sup>17,18</sup> The WHO classification for lung and thymus NETs relies only on the mitotic rate,<sup>19</sup> whereas the European Neuroendocrine Tumor Society (ENETS) as well as the WHO recommend either mitotic rate or Ki67 labeling index for gastroenteropancreatic NETs.<sup>20</sup>

The NEN histopathological workup includes the use of the neurosecretory markers, chromogranin A (CgA) and synaptophysin. CgA is part of the membrane of neurosecretory hormone granules, and its positivity depends on the number of these intracellular granules being evident in the well-differentiated tumors while mild reactions are observed in the poor-differentiated, due to the scarcity of granules in these tumor cells. CgA may even lack in NEN of the lung and rectum. Synaptophysin, on the other hand, can be demonstrated in all NEN, independently of the number of neurosecretory vesicles.<sup>10</sup>

The search for hormones, biogenic amines, and transcription factors is useful in identifying the primary tumor in the case of metastases of unknown origin. In this setting among the GEP system, the vesicular monoamine transporter 2 (VMAT2) is a marker for enterochromaffin-like cells of the stomach. It can be positive also in the adrenal medulla and paraganglia cells. NEN in the duodenum commonly produces gastrin and somatostatin. Serotonin-forming NEN is predominant in the ileum and appendix. Pancreatic NEN primarily produces insulin, glucagon, pancreatic polypeptide, and somatostatin, as well as calcitonin, adrenocorticotrophic hormone (ACTH) or vasoactive intestinal polypeptide (VIP). VIP can also be found in adrenal NEN, such as pheochromocytoma. These peptide hormones may be revealed by immunohistochemistry; however, these positive reactions are not necessarily correlated with endocrine syndromes.<sup>21,22</sup> The immunohistochemical research of this case allowed the diagnosis of a NEN through the positivity to CgA and synaptophysin. The focal positivity to glucagon and somatostatin enabled the localization of the tumor as being identified from the GEP system. Although classified as well differentiated, the grade 2 NETs may fail to express strong positive immunohistochemical reactions for specific markers. The evidence of specific transcription factors is also noteworthy for the determination of the primary GEP-NEN. In this context, CDX-2 is positive in 90% of NEN in the ileum and appendix; Islet-1 is highly specific for pancreas; TTF-1 is expressed in about 50% of bronchopulmonary NEN.<sup>10,22</sup> In the case

reported here, the immunostaining was negative for both CDX-2 and TTF-1.

A primary neuroendocrine tumor originating from the skin (Merkel cell carcinoma) is unlikely since the tumor cells were small and well differentiated.

The clinical picture of NEN depends on its primary tumor, the presence of metastases, and the production of hormones or peptide of clinical significance. Among the latter are the insulinoma, glucagonoma, gastrinoma, somatostatinoma, VIPoma, thymic producing ACTH tumors, and others.

In a series of 241 patients with the diagnosis of GEP-NEN, the most common symptoms were abdominal pain (29.5%), diarrhea (8.7%), weight loss (7.5%), gastrointestinal bleeding (5.4%), flushing (3.7%), and bowel obstruction (3.3%). In this series, neurological and psychiatric symptoms were reported in 2.1% of patients, among whom 9.1% presented pancreatic NENs. Diarrhea can be the manifestation of the carcinoid syndrome, which is most prevalent in the GEP-NEN and some tumors of the bronchopulmonary origin. The syndrome becomes evident when metastases are present. The diarrhea in these cases occurs due to the overproduction of serotonin by the tumor, which is responsible for the bowel hypermotility and intestinal mucosa hypersecretion. The patient of this case study featured a history with few clinical data, but abdominal pain, diarrhea, weight loss, and a depressed mood were present. The diarrhea could be part of a carcinoid syndrome, even in the absence of the other carcinoid syndrome symptoms. Diarrhea can also be observed in glucagonoma, but is often associated with diabetes mellitus and the presence of necrolytic migratory erythema (involving the face, perineum, or extremities), which were lacking in this case. The somatostatinoma also present diarrhea, but diabetes mellitus, again, was also present. The VIPoma that present clinically with watery diarrhea associated with hypokalemia, hypercalcemia, and eventually hyperglycemia could be a likely diagnosis for this case once the electrolytic disturbances were present. Tumors producing calcitonin are not usually associated with hypercalcemia, unless bone metastases are present.

The laboratory diagnostic workup in functional NEN may include the hormonal dosages (gastrin, insulin, peptide C, somatostatin, pancreatic polypeptide, glucagon, ACTH, cortisol, VIP and urinary 5-hydroxy-indol-acetic acid (5HIAA),

depending on the functional status of the tumor, clinical symptoms, and histological features.<sup>23</sup> Even with respect to the diagnosis, the computed tomography scan of the chest, abdomen, and pelvis complemented by somatostatin receptor scintigraphy (SRS) are indicated. Over 90% of gastroenteropancreatic NENs, including nonfunctioning islet cell tumors and carcinoids, have high concentrations of somatostatin receptors, and can be imaged using octreotide, a radiolabeled form of the somatostatin analog. SRS has also been used to help provide information regarding the primary tumor location. The endoscopic examination is fundamental for the diagnosis of NEN, which is included for the determination of the primary tumor in case of liver metastasis.<sup>23-25</sup> Unfortunately, in this case study, this investigation was not undertaken because of the lack of clinical suspicion of NEN and the short period of hospitalization.

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