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Pernicious Anemia and Gastric Carcinoid Tumor: A Case Report and Literature Review

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Abstract We present the case of a 77-year-old female patient, who is derived from her primary care physician to our department with fatigue and laboratory exams that revealed hemoglobin 7.8 g / dl, leukocytes 6.3000/mm3, platelets 210000/mm3, total bilirubin 3.8 mg/dl, indirect bilirubin 2.09 mg/dL, LDH 936 U/I, Vitamin B12 <100, VCM 118 fl, folic acid > 24 ng/ml, total iron 215 mcg/dl, ferritin 187 ng/ml and antibodies against parietal cells, so pernicious anemia (PA) was diagnosed. She later received reposition treatment of vitamin b12 and was scheduled for endoscopic studies. Colonoscopy showed the presence of two diverticula in the sigmoid colon; while her upper endoscopy revealed a 2.5 cm stomach polyp. A biopsy was performed and it resulted positive for synaptophysin, with a Ki67 index <1%, so gastric neuroendocrine tumor (NET) type I was diagnosed, and it was subsequently resected by partial gastrectomy. Patients with a diagnosis of pernicious anemia have a higher risk of developing NETs in the gastrointestinal (GI) system, however, endoscopic screening is not performed in all patients with this disease. The purpose of this report is to encourage medical professionals to perform complete studies of the GI system to all patients that are diagnosed with PA.

Keywords: *pernicious anemia, neuroendocrine tumor, gastric carcinoid*

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1. Introduction

At the 1907 annual meeting of the German Pathology Association, the German physician Siegfried Oberndorfe presented 6 cases where the term karzinoid was used for the first time. He used this term to refer to ileus lesions that had histology similar to neoplastic lesions, but did not infiltrate or metastasize like the latter. This difference was proved wrong in 1929 by Oberndorfe himself, when faced with carcinoid tumors with malignant behavior [1]. Despite this lack of precision in terms of the clinical signs of tumors and due to not having been the first to describe lesions with these histological features, Oberndorfe has a distinctive place in the Pathology, since its description would lay the foundation for descriptions. and future updates regarding neuroendocrine tumors.

Neuroendocrine tumors (NET) are considered rare, since they correspond to 0.46% of all neoplasms and 8% of all endocrine tumors of the digestive system. The incidence of neuroendocrine tumors is between 2.5 - 4.5 / 100000 [2], which has been described to have increased in the last 3 decades, which may be due to a greater availability of diagnostic tools.

The literature describes NETs as intramural masses when they occur in the intestinal tube, however, when they are presented in the appendix, they appear as bulbous lesions. It is worth noting the importance of the topographic location of the tumors since their behavior is partly related to the topography location, in which the most frequent will be the gastric while the appendicular ones will be the least frequent [3]. These masses are formed by neoplastic cells of similar appearance, which are characterized by having cytoplasmic granules of neuronal secretion that gives the name "chromatophins" or "argentaffines", depending on their affinity for certain dyes.

Neuroendocrine tumors manifest clinically by compressive effect, by local fibrosis or by the effect of the secretion of their intracellular components, generating the so-called carcinoid syndrome. This syndrome occurs in 3-5% of patients, in which the existence of liver metastases is described [4]. The classic carcinoid syndrome presents with diarrhea, flushing, hypotension and bronchospasm; All symptoms of increased serotonin secretion. Due to a large existence of serotonergic receptors in the right heart and a large metabolism of serotonin in the left heart due to the passage through the lungs, left valvular pathologies also occur in the carcinoid syndrome [5].

Due to the asymptomatic nature of NETs, the diagnosis is usually made incidentally during an endoscopy, but in cases where the presence of a TNE is suspected, the diagnosis is made by studying different specific neuroendocrine markers, in which the most useful it is 5-HIAA (24-hour 5-hydroxyindoleacetic acid in urine). Endoscopy is added to these studies in order to perform an extraction with a future confirmatory and stratified histological study of the tumor [4].

Tumor mass resection is usually the treatment of choice in NETs, and in patients with advanced disease it usually provides a better quality of life. Together with these surgical procedures, octreotide, a somatostatin analogue, could be added to mitigate the symptoms of carcinoid syndrome [6].

2. Case Presentation

We present the case of a 77-year-old female patient, whose only pathological history is a cholecystectomy, who was referred by her primary care physician due to laboratory tests that demonstrated macrocytic anemia. The patient reported feeling fatigue and denied the presence of any other symptoms, and the cause of her anemia began to be investigated. Several laboratory parameters were requested, which presented: hemoglobin 7.8 g / dl, leukocytes 6.3000 / mm3, platelets 210000 / mm3, total bilirubin 3.8 mg / dl, indirect bilirubin 2.09 mg / dl, LDH 936 U / I, Vitamin B12 < 100, VCM 118 fl, folic acid> 24 ng / ml, total iron 215 mcg / dl, ferritin 187 ng / ml. It was concluded that the patient had macrocytosis and vitamin B12 deficiency; subsequently, anti-parietal cell antibodies were requested, which showed a positive result, indicating the diagnosis of pernicious anemia (PA). A dose of intramuscular vitamin b12 (1000mcg) was prescribed and gastroenterology interconsultation was performed for endoscopy and colonoscopy assessment.

The patient is subjected to both procedures; the findings were: stomach presented sessile polyp of approximately 2.5 cm in diameter on the anterior face without signs of bleeding (Figure 1), proximal body, heart, antrum and pylorus, normal; while the colonoscopy showed the presence of 2 diverticula in the sigmoid colon; A biopsy is taken and the sample is analyzed by pathological anatomy with the following findings: epithelial neoplasia characterized by proliferation of compact nests of different shapes and sizes, which occasionally draw small lights that give it a tubular appearance. Synaptophysin staining was used which was intensely positive in a diffuse and complete manner in all neoplastic nests (Figure 2), revealing the presence of hyperplasia of neuroendocrine cells with linear growth. Ki67 immunostaining was performed, proving a proliferation rate well below 1%, so that the diagnosis of neuroendocrine tumor type I was reached. At the same time, two samples were obtained from the gastric fundus that underwent microscopical examination revealing atrophic gastritis.

Subsequently, it was indicated to perform a positron emission tomography (PET Scan) with Gallium 68 on the patient, which was negative. Finally, the patient underwent resection by partial gastrectomy without complications and she was instructed to go to subsequent endoscopic controls every 6 months to assess her evolution, as well as receiving vitamin B12 replacement therapy as necessary.

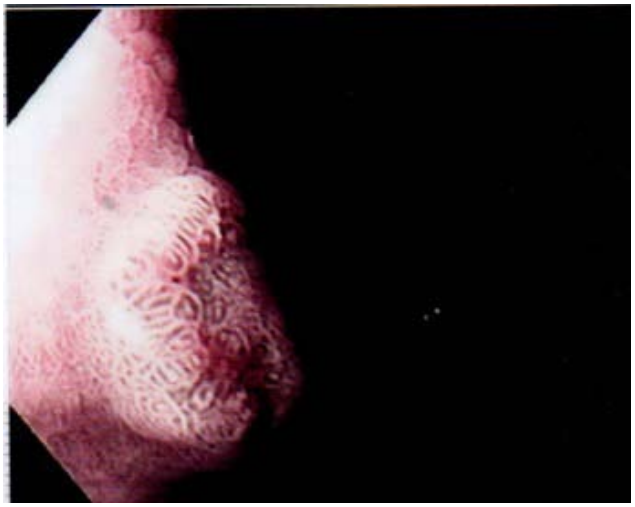

Figure 1. Sessile polyp of approximately 2.5 cm in diameter on the anterior stomach

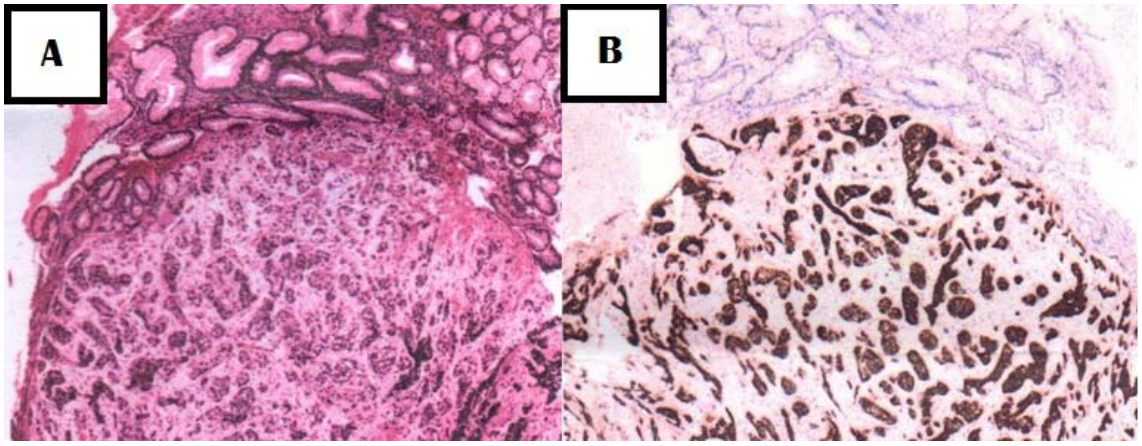

Figure 2. A) Proliferation of compact nests of different shapes and sizes, which occasionally draw small lights that give it a tubular appearance. B) Hyperplasia of neuroendocrine cells with linear growth, positive for synaptophysin

3. Discussion

Gastric neuroendocrine tumors are rare neoplasms and represent less than 1% of total gastric tumors and approximately 9% of gastrointestinal neuroendocrine tumors [7]. The World Health Organization classified them in 2010 into three categories of 1-3; the first are well-differentiated low-grade NET with a Ki-67 index <3%, the second are well-differentiated intermediate-grade NET with a Ki-67 index of 3 to 20%, and finally the third are poorly differentiated TNE with Ki index -67> 20% [8]. From this classification, type 1 NETs represent 70-80% of all gastric NETs and are directly related to the presence of chronic atrophic gastritis and pernicious anemia. These conditions prevent the secretion of gastric acid, which allows hyperplasia of the cells Stomach G and gastrin hypersecretion, which binds to the cholecystokinin-2 receptor in enterochromaffin cells (ECF) promoting its proliferation and the formation of a TNE [9].

Pernicious anemia (PA) is characterized by autoimmune atrophic gastritis, secondary to the presence of anti-parietal cell antibodies, preventing the absorption of vitamin B12, resulting in macrocytosis. Several international analyzes in the last 5 years have shown that the relative risk of developing gastric malignancy in patients with PA compared to the healthy population is 6.8 (95% CI: 2.6-18.1) [10]. Type 1 gastric NETs are detected in 1-7% of patients with pernicious anemia. Likewise, the presence of PA has been related to several gastrointestinal malignancies; in 2015, a case-control study was conducted in the United States in patients aged 66 to 69 years, which showed a high odds ratio (OR) for gastric adenocarcinoma (OR 2.2, 95% CI: 1.9-2.5); gastric carcinoid (OR 11.4, 95% CI: 8.9-14.7); and small bowel cancer (OR 1.6, 95% CI: 1.3-2.0) [11].

The treatment of gastric NETs type 1 and 2 is only endoscopic resection of the polyp and subsequent endoscopic controls every 6 to 12 months; while type 3 require more aggressive treatment such as partial or total gastrectomy with resection of local lymph nodes due to their ability to cause metastases [12]. However, there are several indications to perform partial gastrectomy in TNE 1 and 2: extensive tumor involvement of the gastric wall (due to increased risk of adenocarcinoma), tumor> 2cm (increased risk of metastasis), poorly differentiated histology, or emerging bleeding [13].

Although the American Society of Gastroenterology and Enodoscopy recommends that every patient with PA should undergo an endoscopy after their diagnosis, it has been shown that approximately only 25% of patients with this condition are subjected to endoscopic studies [14].

According to the guidelines of the National Comprehensive Cancer Network, post-treatment surveillance of type 1 TNE and 2 under 2 cm, includes a history and physical examination with gastro-endoscopy every 6 months for 3 years and then once a year. Meanwhile, in NETs greater than 2 cm, it is recommended to add imaging tests such as abdominal computed tomography, or magnetic resonance imaging, depending on the clinical criteria of the specialist. Likewise, determination of blood values of chromogranin A and urinary 5-hydroxyindoleacetic acid (5-HIAA) can be included [15].

Although NETs are rare entities, it is necessary to relate them to AP, and include endoscopy and colonoscopy in the diagnostic process, even if the patient does not report gastrointestinal symptoms due to the risk of presenting neoplasms at the level of the digestive system.

Conflict of Interest

None.

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