

# Association between pernicious anemia and gastric carcinoid tumor: apropos of a clinical case

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### Abstract

Gastric carcinoid tumors are uncommon, representing  $\leq 1\%$  of gastric tumors and 8.7% of all gastrointestinal carcinoid tumors.

Therefore, the authors present a case of a 32 year old woman, admitted in an Internal Medicine ward, for macrocytic anemia and whose etiological research revealed a pernicious anemia (PA). An upper gastrointestinal endoscopy revealed 6 polyps in the upper body of the stomach. All polyps were diagnosed as carcinoid using endoscopic biopsies. After exclusion of metastasis (by CT scan and Octreotide scan), and taking into account the multifocal

involvement of the tumor and the presence of complete intestinal metaplasia in the gastric body, the patient was proposed for total gastrectomy held without complications. It is under treatment with vitamin B-12, with excellent clinical and analytical response.

The presentation of this case alerts to the risk of the appearance of gastric carcinoid tumors in patients with PA and the need for upper endoscopy immediately after the diagnosis of the same. In carcinoids gastric type I disease, with no metastasis, the trend is benign.

Key words: Pernicious anemia, gastric carcinoid tumors.

### INTRODUCTION

Pernicious anemia (PA) is characterized by the presence of atrophic chronic gastritis type A (auto-immune), megaloblastic anemia with or without neurologic and/or psychiatric symptomatology. It is the most common cause of cyanocobalamin deficit through the loss of parietal cells secreting intrinsic factor in the gastric body and fundus. It is known at present that PA patients are at an increased risk of developing gastrointestinal neoplasms, such as gastric carcinoma, carcinoid tumor or esophagus cell pavement carcinoma.

Gastric carcinoid tumors are rare, usually well differentiated and represent  $\leq 1\%$  of gastric tumors and 8.7% of all gastrointestinal carcinoids. They are originated in the enterochromaffin cells of the gastrointestinal mucosa. According to the subtype they can present a variable prognosis. In

the last few years, 3 types of gastric neuroendocrine tumors were described: type I (associated to atrophic chronic gastritis, hypergastrinaemia and pernicious anemia), type II (associated to Zollinger-Ellison syndrome and multiple endocrine neoplasm type I) and lastly, type III, corresponding to an occasional form.

### CLINICAL CASE

We describe a clinical case of a 32 years old woman, previously healthy, without relevant personal background, admitted in the Medicine II Service of our Hospital due to a clinical condition of asthenia, adynamia, ease tiredness and palpitations, of progressive worsening, evolving for around 2 weeks, after returning from holidays. The patient was carrying the tests asked by her Family Doctor revealing Hb of 4,7g/dL with MCV of 123 fL, 123.000 / mm<sup>3</sup> platelets and ESR of 80 mm. She denied visible blood loss, usual consumption of drugs and/or alcohol, genetic-family character disease, changes in the intestinal movement, anorexia, weight loss, epigastralgia, paresthesia, changes in balance and/or awareness status. She was taking oral contraceptives and may have gone 4 months before the current admission to a trip to the Baltic countries (she denied ingesting raw

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fish). She is in a general diet.

In the objective exam she was afebrile, haemodynamically stable (with average blood pressure of 92 mmHg and heart frequency around 70 ppm), however with pale but hydrated mucosa, sub-icteric sclera and atrophic glossitis. In the heart exam, it was heard the presence of a systolic blow III/VI. Summary neurologic exam without changes. Without any other change worth of note in the physical exam. The blood tests (on admission), hemoglobin of 4.4 g/dL with MCV 117 fL; 110.000/mm<sup>3</sup> platelets; swab of peripheral blood with marked anisopoikilocytosis, some macro-ovalocytes and neutrophils with hypersegmented nuclei; CPR 1 mg/dL; ESR 80 mm; creatinine 0.5 mg/dL; LDH of 4861 U/L; AST/ALT 111/62 UI/L; Total bilirubin of 1.60 mg/dL; reduced vitamin B-12 ( $\leq 150$  pg/mL); negative serology for virus (HIV1,2; HVB; HVC); thyroid function, iron, transferrin, ferritin, folic acid, serum protein electrophoresis, intrinsic anti-factor Ab, immunoglobulin A (IgA) within the laboratorial values considered normal. The parietal anti-cell Ab was positive (1/80). The values for serum gastrin (1384 pg/mL; normal range from 13 to 115 pg/mL) and chromogranin A (346 ng/mL; normal range from 19 to 98 ng/mL) were increased. The value of 5-hydroxy-indole-acetic acid (5-HIAA), in 24 hours urine test, was not increased (2.10 mg/dL). Both the electrocardiogram and the thorax X Ray showed no changes. The EGD (oesophagogastroduodenoscopy) showed diffuse gastropathy with atrophic aspect; polypoid lesions (about 6) of the gastric body, great curvature and posterior face, with multiple biopsies carried out (Fig.1).

Histology was compatible with Carcinoid tumor type I (Fig.2 and 3).

After excluding a secondary metastasis (CAT scan and octreotide scintigraphy <sup>111</sup>I), and, considering the multifocal tumor involvement, with a presence of a total intestinal metaplasia in the gastric body and fundus, a proposal for the patient to undergo a total gastrectomy emerged and it was carried out without intercurrent (Fig.4 and 5).

She started therapy with intramuscular B12 vitamin, with a clinical and analytical excellent response.

## DISCUSSION

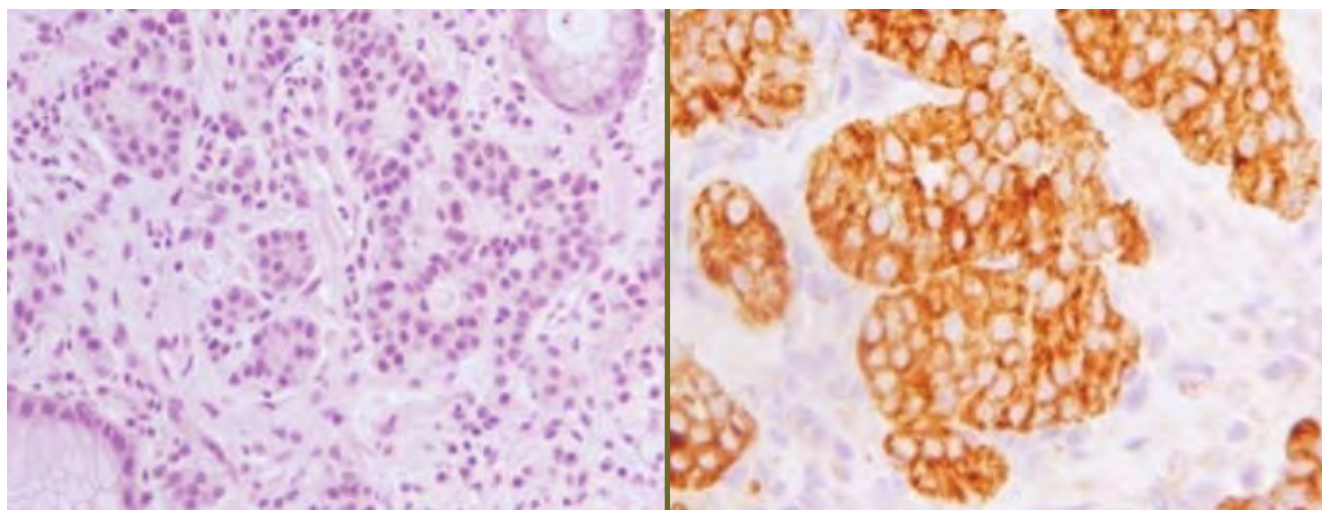
Gastric carcinoid tumors (GCT) are rare, representing around 8.7% of all gastrointestinal carcinoids.<sup>1</sup> These neuroendocrine tumors are classified in 3 types ac-



FIG. 1

ording to their clinical-pathological features.<sup>2-4</sup> The most common GCT type I, are associates to hypergastrinaemia in the context of atrophic chronic gastritis in PA, and usually they are benign. In the atrophic chronic gastritis, the loss of parietal cells producing acid in the gastric body and fundus, usually caused by a destructive process of auto-immune origin, leads to the permanent reduction of gastric acid secretion and intrinsic factor. Consequently the production of gastrin by the antrum G cells is not disrupted. The trophic effect of a sustained gastrin release which is seen in achlorhydria produces a proliferation of enterochromaffin cells (ECL), which will evolve from hyperplasia to dysplasia and lastly for neoplasia.<sup>5</sup> Several mechanisms have been proposed to explain the transformation of ECL hyperplasia into carcinoid tumor. The increased expression of bcl-2 protein increases the cell survival, blocking apoptosis, extending thus the length of time in which the genetic and environment factors have a stimulating effect on the tumor.<sup>6</sup> Controversial studies refer that a *Helicobacter pylori* infection, is responsible for the hypergastrinaemia and GCT induction in animals and seldom in humans.<sup>6</sup>

There is a predominance by the female gender, with an average diagnosis age around 48 years old.<sup>7</sup> Although most patients are asymptomatic, dyspepsia, abdominal pain, nausea, unexplained weight loss, digestive hemorrhage and/or anemia, may be present. In around 33% of patients, the diagnosis is an endoscopic finding.<sup>8</sup> Besides, the increasing use of EDA in the observation of PA patients may lead in the future to an increasing incidence.<sup>8</sup> The symptoms of



Microscopic images of polypoid lesions in the gastric body and fundus (HE and A Chromogranin).

### FIG. 2 and 3

classic carcinoid syndrome (flushing, tachycardia and diarrhea) are rare, ranging from 0 to 2%.<sup>8</sup>

These tumors tend to be small ( $\leq 1$  cm), multifocal and limited to the mucosa and/or submucosa. They are surrounded by hyperplastic ECL cells, predominantly in the gastric body and fundus. They are relatively benign with a risk of ganglionic and hepatic secondary cancer lower than 5%.<sup>9</sup>

The use of CAT scan and scintigraphy with octreotide routinely to exclude secondary lesions did not show a cost-benefit ratio unless in cases where there is a high suspicion of metastatic disease.<sup>7</sup>

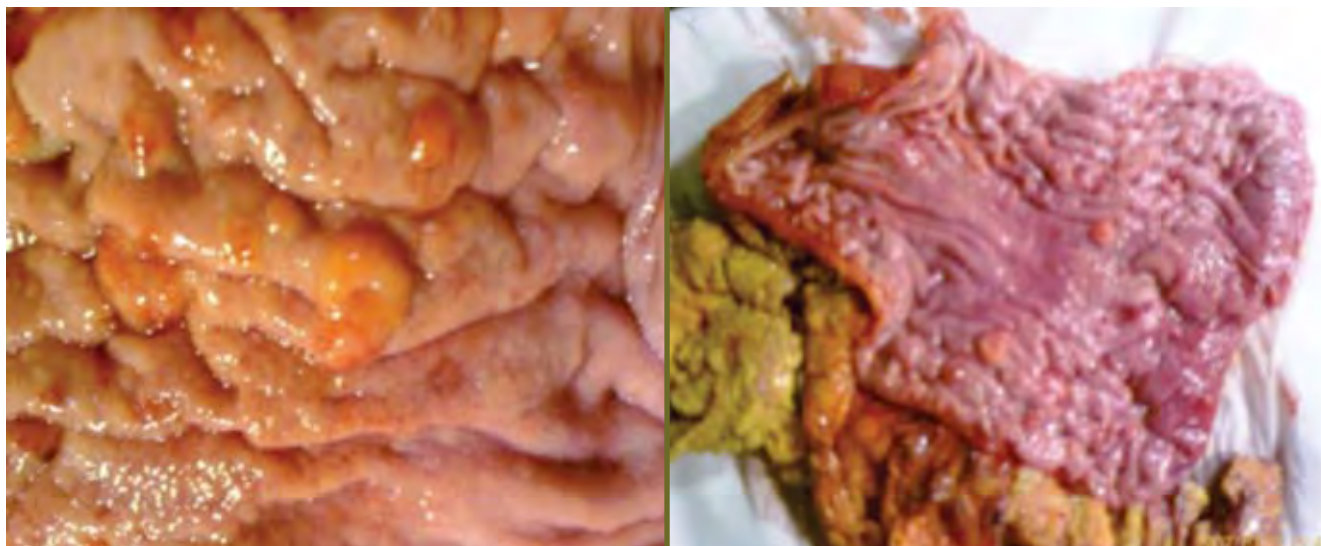
At present, it is recommended as therapy the simple endoscopic polypectomy small and isolated Type I GCT (keeping an annual follow-up with endoscopy and CAT scan), reserving laparoscopic antrectomy for bigger tumors ( $\geq 1$  cm), whether multicentric or recurrent and associated to the abdominal symptomatology as unexplained weight loss or worsening anemia.<sup>8</sup> In a recently published study, some authors recommend a total gastrectomy in patients with tumors  $\geq 2$  cm in size, regardless of gastrin serum value, in situations where antrectomy was not effective to control the disease, a cataclysmic digestive hemorrhage or in a situation of exuberant gastric carcinoid.<sup>8</sup>

Type II GCT, are the rarest, representing 5-10% of all GCT. They are associated to Zollinger-Ellison syndrome in association to Type I multiple endocrine neoplasia (MEN-I). Gastric carcinoids are rarely found in an occasional Zollinger-Ellison syndrome, without

MEN-I, as the allele loss of the suppressing gene MEN-I is needed to induce the transformation of hyperplastic ECL cells in carcinoid tumors.<sup>10</sup> It is established that similar genetic defects are present in patients with MEN-I and AP and, carcinoidosis can only evolve in both conditions if hypergastrinaemia is present. Therefore, gastrin acts in ECL cells genetically changed to promote the tumoral growth. The genetic defect in patients with MEN-I is the loss of the closest heterozygosity to locus MEN-I in chromosome 11q13. The PA defect is thought to be in the same neighborhood.<sup>8</sup> They are multicentric, of variable size (1-2 cm) and able to metastasise into regional lymphatic ganglions. The carcinoid syndrome and direct mortality by the tumor are rare. Therapeutic indications are also a target of speculation; modalities include total gastrectomy, tumors surgical resection, endoscopic polypectomy, treatment with somatostatin analogues or even a simple clinical observation. The proton pump inhibitors, often used to inhibit a gastric acid secretion in these patients, in spite of causing hypergastrinaemia and subsequent ECL cells hyperplasia, do not lead to a transformation in neoplasia in humans.<sup>10</sup>

The average survival rate at 5 years in Type I and II GCT can go from 60 to 75%.<sup>10</sup>

Type III GCT, are occasional, around 13% of all GCT and are not associated to hypergastrinemia.<sup>4</sup> They are highly proliferating and have an increase expression of p53 protein, codified by a tumoral suppressive gene and that is responsible for the apoptosis



Macroscopic images of a total gastrectomy piece.

FIG. 4 and 5

of damaged cells. They are isolated, big, ulcerated tumors, usually invasive with distant metastasis. Tumor with  $\geq 3$  cm size cause metastases in 66% of patients, whilst the smaller than 1 cm can only become secondary in 10%.<sup>1</sup> It is verified a clear predominance of the male gender (80%).<sup>4</sup> A carcinoid syndrome can be seen in patients with hepatic metastasis. The prognosis is reserved, with a survival rate of 20% at the end of 5 years.<sup>4</sup> They are more aggressive tumors, which should be treated with total gastrectomy with a removal of all regional lymphatic ganglions in the absence of hepatic metastases. If the latter are present, chemotherapy is recommended.<sup>4</sup>

In our patient, PA was diagnosed by the association of megaloblastic anemia, a decrease of vitamin B-12 value and atrophic gastritis. The histologic exam of polyps' biopsy by EDA revealed a GCT. The value of serum gastrin and A chromogranin was increased and 5-HIAA was normal. Without clinic-laboratorial semiology of carcinoid syndrome. Through hypergastrinaemia, in the absence of Zollinger-Ellison syndrome and MEN-I, the final diagnosis was Type I GCT.

In spite of excluding a secondary metastasizing (CAT scan and octreotide scintigraphy), considering the tumor multifocal involvement, with a presence of a total intestinal metaplasia in the gastric body and fundus, the patient was proposed to total gastrectomy which has evolved without interurrences.

The presentation of this case aims to alert to the risk of appearing gastric carcinoid tumors in patients with anemia by a vitamin B12 deficit and the need to perform EDA immediately after the diagnosis. In Type I gastric carcinoids that do not show the disease at a distance (as it is the case of our patient), the evolution is benign. ■

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