**ABSTRACT**

Neuroendocrine tumors (carcinoids) are tumors originating from neuroendocrine cells. The distinction between different types of gastric carcinoids is important for their management. We present the case of a 38-year-old woman with type 1 gastric neuroendocrine tumors (NETs) associated with autoimmune atrophic gastritis. The management of these tumors has not been yet codified and different therapeutic strategies have been suggested. A proper evaluation before therapy is indicated in order to rule out both the malignant transformation as well as the presence of synchronous lesions, such as dysplasia or gastric adenocarcinoma. We describe our diagnostic and therapeutic strategies with references to previously published reports.

**Key words:** gastric carcinoid – pernicious anemia – atrophic gastritis – neuroendocrine tumor (NET)

**INTRODUCTION**

Carcinoids are tumors of the diffuse endocrine system hosted in the digestive and bronchial mucosa. The term “neuroendocrine tumor” (NET) has been introduced by the World Health Organization (WHO) to define “carcinoids” and a classification system has been adopted [1]. The reported incidence of the gastric NETs has increased in recent years, possibly related to the increasingly widespread use of upper endoscopic evaluation of patients with dyspeptic complaints and improvement of methods of histopathological diagnosis [2]. The development of a tumor grading system and the availability of specific immunohistochemical techniques allows better assessment of these lesions. Important attributes for gastric carcinoids’ diagnosis include distinguishing between different types based upon the presence of associated conditions (such as atrophic gastritis, pernicious anemia, multiple endocrine neoplasia MEN 1), the number and size of the tumors, the depth of invasion, the distribution of proliferation markers (ki-67 index), and the presence of metastases.

**CASE REPORT**

A 38 year old female with persistent dyspepsia was admitted to our department. Her past medical history was significant for a history of pernicious anemia, diagnosed three years ago in another medical facility and treated with B12 vitamin. Upper endoscopic evaluation performed at that time showed atrophic gastritis and three small nodules (< 4 mm in size) on the greater curvature. Histological examination of the biopsy specimens revealed atrophic gastritis, intestinal metaplasia, low-grade dysplasia. The patient had been non-compliant with follow-up endoscopic surveillance.

On admission, laboratory tests showed normal hemoglobin levels (12.6 g/l, hematocrit 39.7%). Fasting serum gastrin levels were elevated: 1232 pg/ml (normal levels: 13-115 pg/ml), as well as serum antibodies to gastric parietal cells > 100 U/ml (normal values < 10 U/ml). Gastroscopy revealed corporeal atrophic gastritis and multiple erythematous nodules on the greater curvature and on the anterior wall of the gastric body: one lesion of 10 mm in size, five lesions smaller than 10 mm (Figs. 1, 2). One 10 mm polyp was also identified in the gastric antrum. Magnifying endoscopy showed specific, modified patterns of the corporeal lesions (Fig. 3). Targeted biopsies were taken from the lesions and also from the antral and corporeal mucosa. Biopsies were stained for chromogranin A
and synaptophysin and the proliferative activity (ki-67 index) was assessed. The histopathological evaluation revealed well-differentiated tumors showing positive immune-staining with chromogranin and synaptophysin. The surrounding mucosa showed atrophic gastritis, intestinal metaplasia and hyperplasia of the enterochromaffin-like (ECL) cells (Fig. 4). The antral polyp was an adenoma. A diagnosis of autoimmune atrophic gastritis, type 1 gastric carcinoid and gastric adenoma was made.

Endosonography was performed in order to evaluate the depth of infiltration. Tumors were limited to the muscularis mucosae with no evidence of lymph node involvement.

The patient underwent endoscopic polypectomy of the largest corporeal tumor (10 mm diameter) and of the antral polyp. Histological examination of the resected lesions showed well-differentiated carcinoid (G1) in the corpus, limited to the mucosa and submucosa, with one mitosis per 10 high-powered fields, ki-67 index < 2% (Fig. 5). The antral polyp was found to be a tubular adenoma.

We recommended endoscopic surveillance with biopsies. At reevaluation, the patient had persistent complaints of dyspepsia. Endoscopy revealed multifocal small nodular lesions. Serum gastrin levels were high (1000 pg/ml). With the patient's consent, an antrectomy was performed. A reevaluation six months after surgery showed normal gastrin levels (110 pg/ml). Gastroscopy revealed a gastric remnant without detectable nodular lesions.
Histological evaluation of multiple biopsies showed chronic atrophic gastritis, intestinal metaplasia, enterochromaffin-like (ECL) cells hyperplasia and no detectable carcinoid tumor. In this case, a regression of lesions was achieved in the absence of the hypergastrinemic stimulus.

DISCUSSION

There are four types of gastric NETs. The differentiation is important from the point of view of prognosis and therapeutic approach. Type 1 NETs are multiple polypoid lesions, usually small (< 10 mm), localized in the corpus and/or fundus of the stomach. These tumors occur most frequently in 40-60 year old women, in association with chronic atrophic gastritis. Type 2 gastric NETs are also multiple small nodular lesions in the gastric body and fundus. They are associated with MEN 1 syndrome, or Zollinger-Ellison syndrome, with an equal distribution between the genders and with a peak incidence at age 45. Both type 1 and 2 NETs are well-differentiated tumors. Tumors greater than 10-20 mm in size can potentially infiltrate the muscularis propria and progress to angio-invasion and lymph nodes metastases.

Type 3 NETs are solitary polypoid tumors, which occur in any part of the stomach, with a peak incidence at age of 50. They are not associated with other gastric conditions or hypergastrinemia. Usually these are larger lesions, greater than 10 mm in size, well-differentiated, which infiltrate muscularis propria with angio-invasion and lymph nodes and liver metastases.

Type 4 NETs are solitary, poorly differentiated neuroendocrine carcinomas, larger in size, arising in any part of the stomach, with a peak incidence in men over 60 years of age. They are typically accompanied by vascular invasion, metastases, and have a poor prognosis [3].

Gastric NETs are rarely associated with carcinoid syndrome. There have been, however, published cases with atypical symptoms including purplish flushing of the extremities and the trunk [4].

In our patient, the diagnosis was type 1 gastric NET, associated with autoimmune atrophic gastritis. Hypergastrinemia results in hyperplasia of the ECL cells and the development of carcinoid tumors. Autoimmune atrophic gastritis (type-A gastritis) is a risk factor for gastric cancer [5] and patients with type 1 gastric NETs can go on to develop gastric adenocarcinoma. Multiple antral and corporeal biopsies (gastric mapping) should be taken in order to detect synchronous lesions, such as dysplasia or early cancer. In our patient, histological evaluation of multiple biopsy specimens allowed the detection of premalignant lesions which required continued endoscopic surveillance: atrophic gastritis, intestinal metaplasia, low-grade dysplasia, and tubular adenoma.

Treatment of gastric NETs is based upon the evaluation of the malignant potential, meaning the evidence of invasive growth, regional or distant metastases, and the presence of proliferation markers (ki-67). Metastatic potential is related to the size and the depth of the tumor.

The therapy of choice for type 1 NETs is controversial [6]. Different types of treatment have been reported: surgical (gastrectomy, gastric antrum resection, fundic resection) or endoscopic therapy - polypectomy or endoscopic mucosal resection (EMR), endoscopic surveillance at 1 to 2-year intervals without therapy [7], long-term octreotide therapy [8].

In Japan, most carcinoids have been treated by gastrectomy [9]. Recently, EMR was used in the management of type 1 and type 2 gastric carcinoids in Japan. Tumors limited to the mucosa/submucosa, less than 10 mm in size can be managed by endoscopic resection (polypectomy or EMR) or by endoscopic surveillance [3]. Japanese authors recommended EMR in patients with three to five tumors, measuring 10 mm or less in diameter, followed by an accurate histologic assessment of the resected specimens. Surgery is recommended if there is evidence of invasion of the muscularis propria, vascular invasion, high proliferation rate or residual tumor after resection [10]. Surgical therapy is also an option for type 3 or type 4 gastric NETs.

Some authors recommended antrectomy with local resection with subsequent endoscopic surveillance of the gastric remnant, for patients with three to five carcinoid lesions, where one or more lesions are 10 mm or more in diameter [11]. In some cases, they reported regression of lesions after antral resection, likely due to the elimination of the trophic stimulus that promotes tumor growth. We noticed a similar evolution after surgical therapy in our patient.

CONCLUSION

The distinction between different types of gastric NETs is essential for the management of these patients. Endoscopic evaluation should include multiple biopsies from visible lesions and the surrounding mucosa. The best therapeutic option for NETs type 1 (endoscopic or surgical treatment) is based upon clinical and histological data, and thus on the estimation of behavior of the tumor. Endoscopic surveillance is mandatory due to the associated risk of developing of gastric adenocarcinoma.

Conflicts of interest: None to declare.

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