CASE REPORT

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The value of the immunohistochemistry in a case of gastric neuroendocrine tumor and thyroid metastasis

CĂTĂLINA POIANĂ[1,2], MARA CARŞOTE[1], CARMEN ARDELEANU[3], DANA TERZEA[3,4], ELENA TAINA AVRAMESCU[5], M. C. NEAMŢU[6], RUCSANDRA DĂNCIULESCU MIULESCU[1]

[1]*Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest*

[2]*Department of Pituitary and Neuroendocrine Diseases, "Constantin I. Parhon" National Institute of Endocrinology, Bucharest*

[3]*Department of Pathology, "Victor Babeş" National Institute, Bucharest*

[4]*Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest*

[5]*Department of Medical Sciences, University of Craiova*

[6]*Department of Pathologic Physiology, University of Medicine and Pharmacy of Craiova*

Abstract

Thyroid metastasis is atypical. We present a 70-year-old female case that was first diagnosed as gastric cancer after surgical approach. Two years later a thyroidectomy was performed and the immunohistochemistry (IHC) profile revealed a neuroendocrine tumor (NET): poorly differentiated neuroendocrine carcinoma (with small cells), with positive reaction for SYN, CROMO, negative for calcitonin, TTF1 and thyreoglobulin. The Ki-67 index was 25%. Considering the unusual metastasis, the IHC exam of the stomach tumor was performed pointing the same features as the thyroid findings. This proved that the thyroid tumor was a metastasis from a primary gastric neoplasia. This is an unusual case of NET because of the thyroid involvement. Nevertheless, the IHC exam played the major role in elucidating the diagnosis and the prognosis of the case.

Keywords: gastric neuroendocrine tumor, immunohistochemistry, thyroid metastasis.

Introduction

The carcinoid tumors represent a diagnostic challenge because they are often innocuous at the time of presentation, and later their evolution needs a multidisciplinary diagnostic approach from biochemistry to imaging, nuclear medicine and histology. Similarly, treatment needs multidisciplinary approach, while surgery is the only curative modality [1].

Patient, Methods and Results

70-year-old female diabetic patient, without family disease background, had two years ago total gastrectomy for what was considered at that moment a gastric cancer.

The histological exam showed a tumor of 4 by 5 cm of the antrum, with microscopic aspect of poorly differentiated carcinoma, and wall invasion over the serosa. The peritumoral nodes had maximum 2 cm, associating carcinomatosis invasion into the inferior resection limit. There were small round or polygonal cells, poorly represented cytoplasm, hyperchromatic nucleus with intense mitosis (over 1–2/HPF), area of necrosis and ulceration (Figure 1).

The 17 local lymph nodes of maximum 2 cm had also carcinomatous invasion. Based on diagnosis of gastric carcinoma, the patient was referred to oncology, but refused the chemotherapy because of the poor prognosis.

Despite this prognosis of less than one year, two years later, at age of 70 years, the patient was clinically asymptomatic but a large recently increased goiter was accidentally discovered.

Thyroidectomy was performed because of the compression risk. The histological exam revealed a tumor of the left lobe and isthm, with extra-capsular invasion, a dens cellular proliferation, poorly narrowed, having trabecular areas, round-oval shaped cells, and intense eosinophilic cytoplasm of the tumor cells, and frequently giant tumor cells with an increased number of nucleolus, and atypical mitosis. Large areas of necrosis, hemorrhage, and sclero-hialinisation, and moderate interstitial inflammatory infiltrate and small vessels with intense subintimal and mural fibrous hyperplasia, with Monkeberg calcifications into the media are also described (Figure 2).

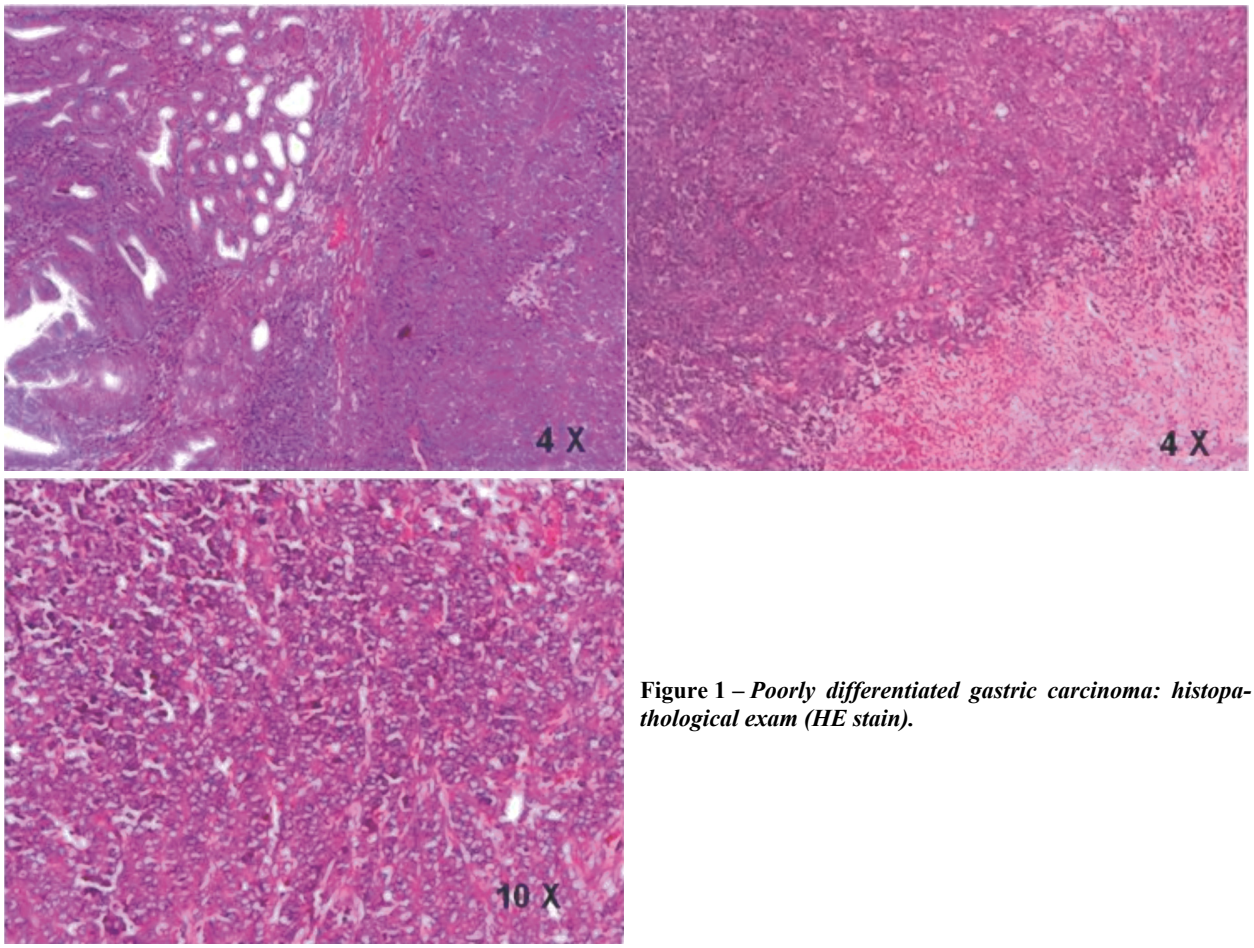

Figure 1 – ***Poorly differentiated gastric carcinoma: histopathological exam (HE stain).***

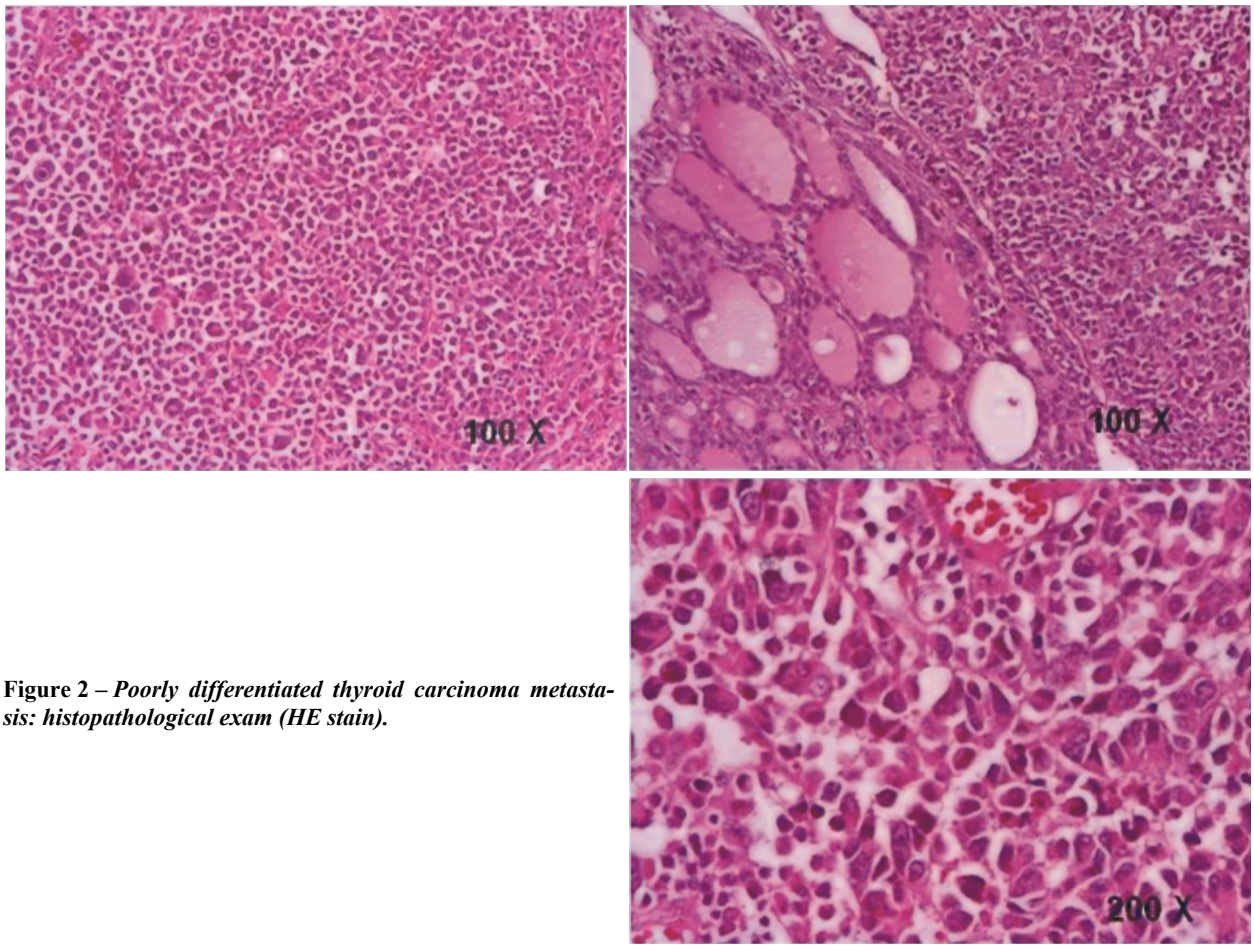

Figure 2 – ***Poorly differentiated thyroid carcinoma metastasis: histopathological exam (HE stain).***

Four lymph cervical lymph nodes and nine pretraheal and anterior mediastinal lymph nodes were collected, but they were not invaded. The IHC profile showed tumor cells that were positive for synaptophysin, chromogranin A, AE1–AE3, CD56 and negative for calcitonin, TTF1, and thyreoglobulin, CLA, CD3, CD20, CD138, S100, CK20, and neurofilaments (Figure 3). These suggested a neuroendocrine phenotype (synaptophysin, chromogranin A), excluding a thyroid or follicular papillary (TTF1, and thyreoglobulin), medullar thyroid cancer (calcitonin) or microcellular pulmonary cancer (TTF1). At this moment, the IHC was performed for the gastric tumor. The same phenotype was found: positive reaction for CK7 (zonal), SYN and CROMO into the tumor, CEA negative, CK20 positive in the focal gastric epithelium. The value of Ki-67 index was high (25%). Based on these, the diagnosis of poorly differentiated carcinoma (with small cells) was established (Figure 4). According to TNM system, the disease was stage IV (T3N1M1) [2].

The serum neuroendocrine markers were increased (twice as normal chromogranin A). The serum serotonin, neuron specific enolase as well was 24 hours urinary 5-hydroxy-indolacetic acid were first normal but three months later they also increased. No other metastasis was found by CT scan. Based on increased neuroendocrine markers, therapy with monthly octreotidum LAR 20 mg was started. It is difficult to establish if the thyroid metastasis were presented now of gastric tumor diagnosis. Also, a whole body octreoscan would be useful to provide additional information about other secondary determinations. The patient will be followed-up.

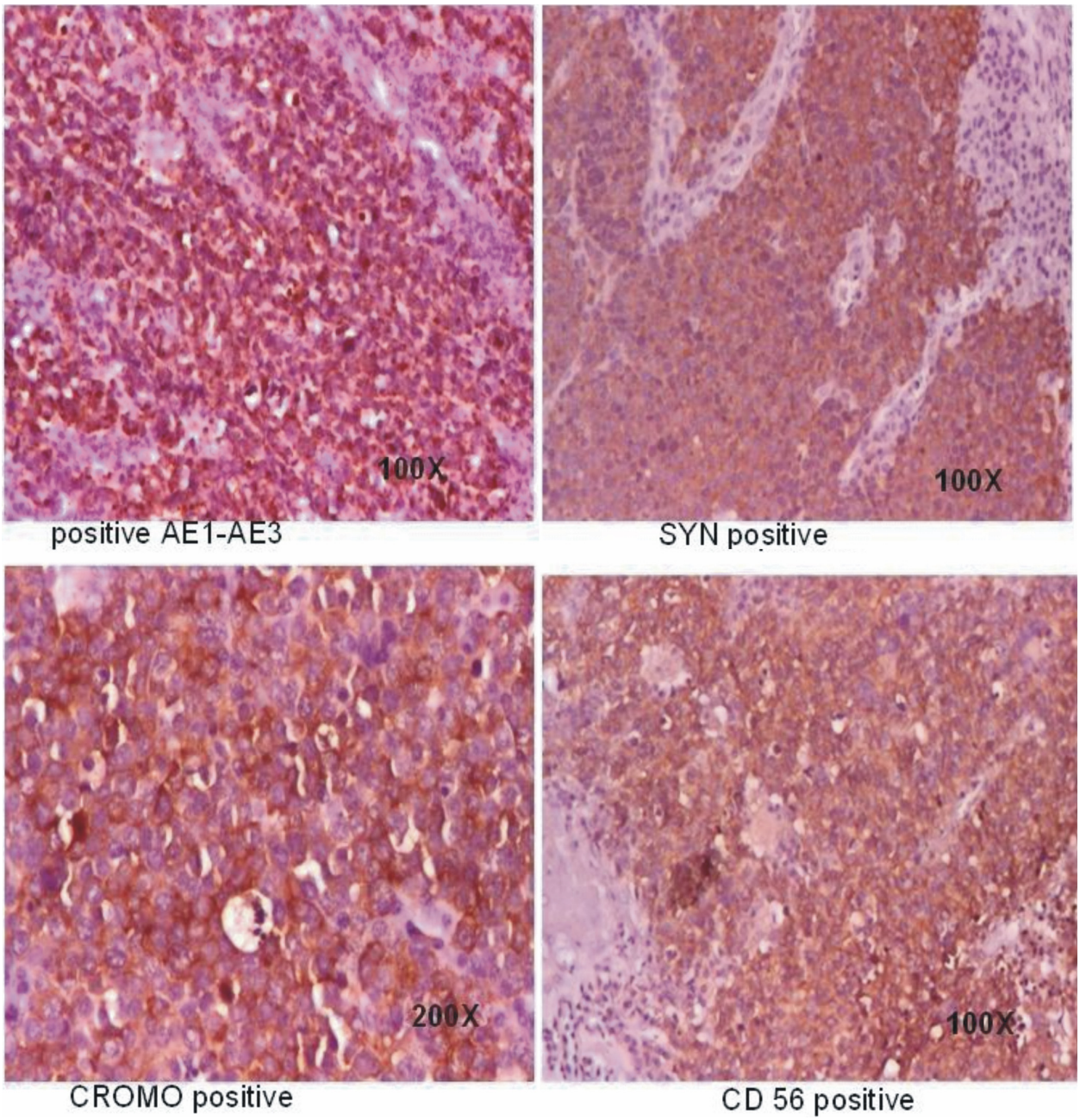

Figure 3 – ***Poorly differentiated neuroendocrine thyroid metastasis: the immunohistochemistry profile.***

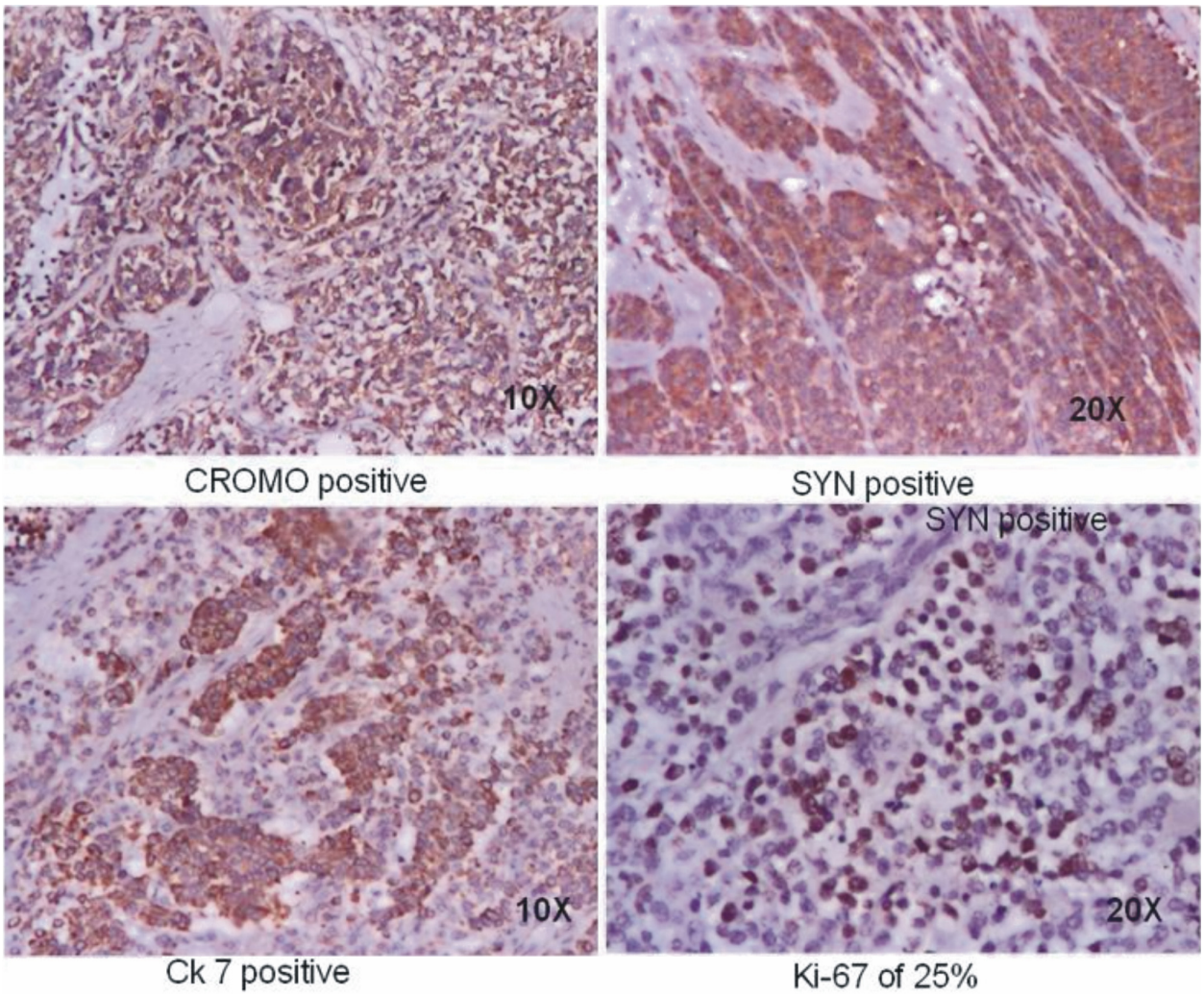

Figure 4 – ***Poorly differentiated gastric carcinoma: the immunohistochemistry profile of the neuroendocrine gastric tumor.***

Discussion

Our case refers to a neuroendocrine tumor with thyroid metastasis. The gastric NET arises from the endocrine cells comprised all over the stomach. There are six types of endocrine cells: the majority is represented by histamine-producing enterochromaffin-cells (in the corpus and fundus of the stomach), and gastrin-producing cells (G-cells of the antrum). Rarer cells without a particular distribution are somatostatin-producing cells (D-cells), serotonin-producing enterochromaffin cells, and ghrelin-producing cells (P-cells) [3].

According to *WHO*, there are several categories of NET (based on histology and prognostic parameters as Ki-67 index or protein p53): well-differentiated endocrine tumor, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinoma, mixed endocrine-exocrine tumor and tumor-like lesions [4]. The poorly differentiated carcinoma (with small cells) of the stomach as our case represents less than 10% of gastric NET [5]. They are high grade malignant, usually nonfunctioning, and rarely associate paraneoplasic Cushing's syndrome. In this case, the basal plasma cortisol was normal and no clinical features suggested hypercorticism.

The enterochromaffin cells are involved in several types of well differentiated neuroendocrine tumors: the majority are type I associated with chronic atrophic gastritis, the other are type II, involved in genetic forms as MEN 1 syndrome and Zollinger–Ellison syndrome, and type III (the less frequent) [6]. Type 1 is typically seen in women of the 7th decade, having a neoplasm limited to the gastric mucosa. The metastasis is atypical [7]. The type III tumors are more frequent in men of 6th decade. They are single, large tumors, with local invasion into the wall [5]. This classification is useful for the approach of the disease. Type I carcinoids can be considered to be benign lesions, with exceptional risk of metastases, type II may have distant metastases, as well as type III carcinoids.

The therapy is mainly endoscopic resection and somatostatin analogues in types I and II, or surgery in type III [8]. Total gastrectomy is reserved for patients with extensive tumor involvement of the gastric wall or for emergency bleeding [9]. The poorly differentiated carcinoma as our case is a difficult diagnosis to establish; the IHC plays a major role. The tumors have usually IHC positive for synaptophysin and neuronal specific enolase, but rarely positive for chromogranin A, as in our case [7]. The carcinoid syndrome is rare. That

is why recent opinions refer to the term of "carcinoid" as inadequate, and probably a more adequate term would be "endocrinocarcinoma" [10]. They are large tumors (more than 4 cm), usually associate metastasis, and they are found in patients of 7th decade of either sex [5, 7, 11]. Our case was an antral, single, large tumor of 4 by 5 cm, having an invasion into the wall (G3) and also into 17 local lymph nodes, at the moment of diagnosis, in a 7th decade female patient. It is atypical the long-standing evolution of more than two years because the prognosis is a few months.

The prognosis depends of the size, histological grading, mitotic count, and Ki-67 index. The poorly differentiated carcinoma has a severe prognosis because they are extremely aggressive and they often associate metastasis now of diagnosis. In our case, it is difficult to evaluate if the metastasis (except for the local lymph nodes) were presented now of gastric resection. The size of the tumor pointes a benign behavior in case of a tumor of less than 1 cm, and 80% probability of benign type in case of less than 2 cm diameter [4]. The small size does not exclude metastasis. For example, in a Japan study of 1914 gastrointestinal neuroendocrine tumors, 449 were located into the stomach. The tumors of less than 1 cm had 16.4% metastasis rate and a 5-year survival rate after curative resection of 89.6%. The gastric tumors between 5 and 10 mm had 9.6% metastasis rate [12]. A diameter of more than 3 cm usually is seen in type III well differentiated tumors and more than 4 cm in poor differentiated carcinomas [5]. Tumor size (especially in gastric and appendiceal carcinoids) and, also, the spreading of disease, highly predict the evolution of the patients [13]. The grading depends on the mitotic count and the value of Ki-67 index [2]. A value of 25% involves a G3 grading, with the poor prognosis. Histological, G3 involves also necrosis, atypical structures, and an increased number of mitosis. The gastric G3 tumor is the less frequent compare to G1 or G2. Serum chromogranin-A seems a very useful tumor marker for the diagnosis and follow-up of the patients with gastrointestinal carcinoids [13].

Also, gastro-entero-pancreatic neuroendocrine tumors are rare neoplasms. Gastrointestinal NET constitutes 0.5–1% of cancer [14]. Their prevalence has increased over the past three decades. Also, it increased clinical recognition and methods of their diagnosis [15]. Gastric carcinoids account for 2.4% of all carcinoids [16]. The frequency in surgical reports increased from 0.5 to 1.77% of all gastric cancer and from 2.4 to 8.7% of all gastrointestinal NET [17]. The frequency in endoscopies reports varies from 11 to 41% of all gastrointestinal NET [18]. The higher frequency is related to the larger use of endoscopies and the larger use of IHC exams [19].

The gastric carcinoid associates very rarely a thyroid metastasis. Generally, the thyroid is not involved in second determinations of a primary malignancy. Differential diagnosis issue must be considered. For example, a recent reported case found cervical PET uptake in the case of woman diagnosed with gastric carcinoid. However, the histological report pointed a tuberculosis lymphadenitis [20].

Conclusions

In patients with neuroendocrine tumors, the thyroid involvement as secondary determination is atypical. The thyroid examination has a special role in selected cases of neuroendocrine tumors patients. The major role in elucidating the diagnosis and prognosis is played by the histological exam and especially by the immunohistochemistry.

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Corresponding author
Cristian Neamţu, MD, PhD, Department of Pathologic Physiology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareş Street, 200349 Craiova, Romania; e-mail: drcristianneamtu@yahoo.com

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