Chapter 3

Neuroendocrine Tumors of the Stomach: Gastric Apudomas

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Additional information is available at the end of the chapter

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Abstract

Anatomo-clinical studies of the neuroendocrine tumors of the stomach only can be well completed with a view of the basic characteristics of the elements of the so-called neuroendocrine system or gastrointestinal APUD system. Therefore, these gastric neoplasias cannot be studied in isolation because they are derived from a special line of endocrine cells that have many common biochemical bonds which are often involved in the clinical behavior of the tumor. These cells are called "APUD" for their biochemical and morphological characteristics, and their tumors as "apudomas." APUD cells store amines and regulatory peptides and are dispersed throughout the body and concentrated mainly in the digestive tract. Other names used for tumors of the same cell line, namely, "carcinoids," "endocrine tumors," and "neuroendocrine tumors," are not yet very well defined, although they are ostensibly used. The gastric apudomas do not escape of the basic rules of behavior of their counterparts of other sites of the digestive tract. Nevertheless, most of them present peculiar pathogenetic and pathophysiological characteristics whose knowledge is important to better understand the patient with this type of lesion.

Keywords: neuroendocrine tumors, gastric apudomas, gastric carcinoids, atrophic body gastritis, APUD cells

1. Introduction

Gastrointestinal neuroendocrine tumors make up a group of heterogeneous neoplasms of somewhat unpredictable biological and clinical behavior. These tumors arise mainly in the digestive tract but can occur in other organs that harbor neuroendocrine cells. They are considered complex tumors and of unpredictable clinical evolution due to the variety of attributes that they possess as the potential capacity of secretion of a large variety of peptides.

Although they may appear benign tumors for a certain period of time, they can originate tissue infiltration and give metastasis. All these pathophysiological attributes of neuroendocrine tumors, which may occur in varying degrees of intensity in different patients, arouse general interest, and so they are studied by professionals from different expertise. In this chapter, we will turn to the study of some relevant aspects of these tumors that originate in the stomach. However, since these neoplasias are part of a large family of gastrointestinal tumors, we will carry out a summary review of the main attributes of this family which should be useful to better understand some nuances of these tumors which originate in the stomach.

2. General aspects of neuroendocrine gastrointestinal system

The terms "neuroendocrine tumors," "carcinoid tumors," and "endocrine tumors" are widely used when referring to tumors of the digestive tract. These designations can be found simultaneously even as part of the same classification. Neuroendocrine tumors were firstly called as "carcinoid tumors" by the German pathologist Oberndorfer, in 1907 [1]. And until now, the term carcinoid has been used ostensibly, colloquially, and even in almost all current classifications [2, 3].

The term "apudoma" may also be considered as being a synonym of carcinoid tumor. The denomination of "APUD cells" was proposed by Pearse in the late 1960s as an acronym of *amine precursor uptake and decarboxylation* [4]. The term APUD summarizes some of the most important characteristics of these cells, which are (a) a high amine content and/or amine precursor uptake, (b) amino acid decarboxylase activity, and (c) characteristic ultrastructural pattern. Initially, the term "apudoma" was used mainly from the clinical point of view to designate those tumors of symptomatic patients due to the pathological secretion of bioactive products and afterward also for clinically asymptomatic tumors originating from APUD cells [5–7]. As we can see, unlike the roots of the other designations for these tumors, the term "apudoma" has been derived from consistent morphologic and biochemical basis.

Apudomas are derived from the APUD cell line and so they have characteristic ultrastructural pattern recognized due the presence in the tumor cells of secretory granules where the regulatory peptides are located as well as the biogenic amines that they produce [8, 9]. Normally, the APUD cells are rich in amino acid decarboxylase, which gives them the ability to capture 5-hydroxytryptophan and dihydroxyphenylalanine and produce, respectively, serotonin and dopamine. Although this property has not been demonstrated in all the cells morphologically characteristic of this system, this biochemical link may occur in all of them whatever their specific function is. This gives these cells a familial, morphological, and biochemical bond, which extends to a greater or lesser degree to the apudomas. In addition, these morphological and biochemical characteristics give to the term "APUD" a biologically more specific designation compared to the other denominations. Thus, the term "apudoma" is less vulnerable to temporal changes than those currently used, namely, "carcinoid," "endocrine tumor," and "neuroendocrine tumor." The latter denomination is being adopted in this article because of its extensive use in modern classifications and also throughout the medical literature indexing.

2.1. Tumor sites and staining

One of the first steps, both in pathology and clinics, when we are faced with the possibility to do the diagnosis of a gastrointestinal apudoma, is the knowledge of its possible primary location (**Table 1**). It may seem like an unimportant detail, but this can be very valuable as a first step to better understand the biology of the tumor [10, 11].

Sometimes, we deal with an unknown primary site metastasis. But knowing which segment of the digestive tract derives the tumor may be helpful because this information gives an idea on the possible evolution of the apudoma. Regarding the gastric apudomas, this is a crucial knowledge as we will see later on. In addition, the pathologist gains confidence in the study of the diagnostic possibilities, including for the evaluation which stain techniques or which neuroendocrine marker should be used [12]. Most of the gastric apudomas do not produce serotonin and are negative for argentaffin staining; on the other hand, they usually are positive for argyrophilic and chromogranin staining (**Figure 1**). These properties of apudoma, in relation to certain staining techniques, often depend on their place of origin (**Table 2**) [13–15].

Currently, immunohistochemistry techniques have been used as tools of choice for the specific histologic diagnosis of apudomas. Through this methodology, it is sought to mark the presence of antigenic products typical of APUD cells and also frequently present in apudomas (**Figures 2** and **3**). Neuron-specific enolase (NSE) was the first immunohistochemical marker for histological diagnosis of apudomas [16]. Before the discovery of this marker, the most commonly available methods were silver staining. Synaptophysin is also a neuroendocrine marker, located on the membrane of the synaptic vesicles, and present in neurons, neuroendocrine cells and in many neuroendocrine tumors [17, 18]. Chromogranins comprise a group of acidic polypeptides that make up about 40–50% of the soluble protein content of the suprarenal medullar granules. The chromogranin A is the most widespread; it is present in varying amounts in the secretion granules of neuroendocrine cells and in neuroendocrine tumors [15, 18]. If the tumor is less differentiated and with fewer secretory granules in the cytoplasm, the staining can give doubtful results or even a false-negative reaction. Chromogranin is one of the main markers used for the histological diagnosis of gastric apudomas presenting high index of sensitivity and specificity. It is also tentatively used as a serologic marker of apudoma evolution [19]. It is always appropriate to remember that the antibodies used against apudoma antigens are derived from different clones and are provided by different companies. This may result in differences in sensitivity and specificity of each set of reagents, and these different properties must be under the control of each laboratory.

Foregut	Midgut	Hindgut
Esophagus	Jejunum/ileum	Distal colon
Stomach	Appendix	Rectosigmoid
Duodenum	Cecum	

Apudomas can arise in any region of the gastrointestinal tract. These regions are known as foregut, midgut, and hindgut. Apudomas from these different sites frequently present different clinical behaviors.

Table 1. Primary sites of the gastrointestinal apudomas.

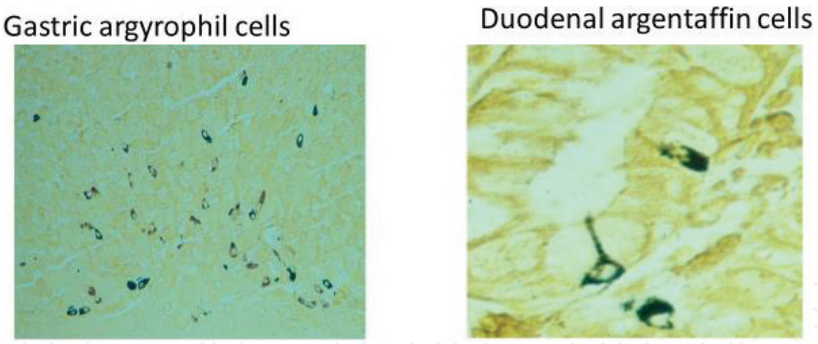

Figure 1. Although it is nonspecific staining for APUD cells and apudomas, the argentaffin and argyrophilic stains may be useful for the demonstration of these elements [13].

Gastrointestinal apudomas and silver staining properties			
	Foregut	**Midgut**	**Hindgut**
Argyrophilic tumors	+++	+++	++
Argentaffin tumors	+	+++	+

+, seldomly positive; ++, sometimes negative; +++, much frequently positive

Table 2. Almost all the gastric apudomas are demonstrated by argyrophilic staining and/or by argentaffin methods.

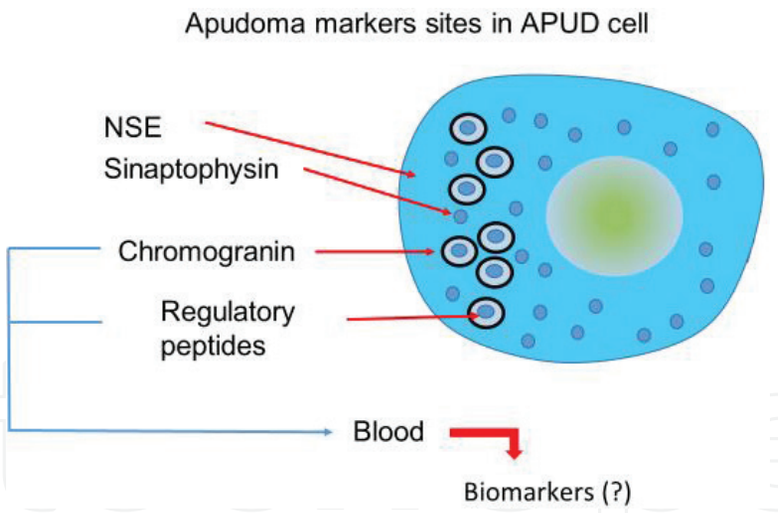

Figure 2. Some of the neuroendocrine markers are scattered in the cytoplasm of apudoma cells such as PGP 9.5, synaptophysin, and neuron specific enolase. Chromogranin and the regulatory peptides are stored in secretory granules. The amount of these granules in the neoplastic cells will determine weaker or stronger staining of the tumor.

2.2. General view on pathology of gastrointestinal apudomas

We have now reached a point which concerns more directly the attending physician. Since the apudomas frequently present unpredictable clinical evolution, how could the histopathology help on this matter? In fact, all the factors shown in **Table 3** are important to evaluate the possible clinical behavior of a given gastrointestinal apudoma. However, the two first, i.e., degree

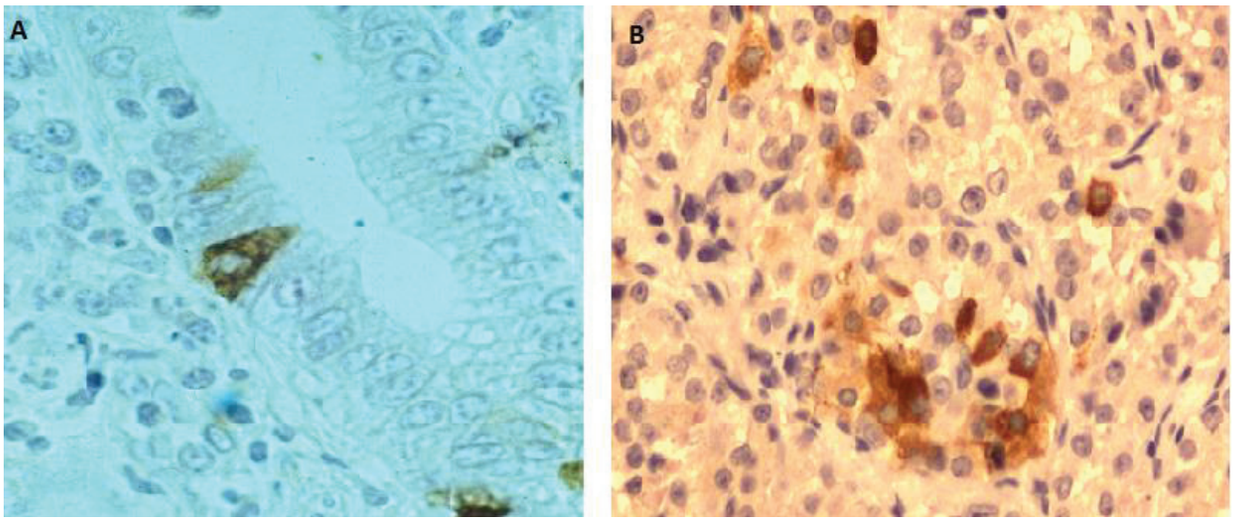

Figure 3. (A) G cell of the gastric mucosa stained specifically with antibody against gastrin. The staining is very specific by observing that the background elements, i.e., other cells and surrounding tissues, are completely negative. The very strong contrast between the positive and negative elements of tissue confers confidence of the final result in relation to the specificity of the staining reaction. (B) The staining contrast is not always very clear in regard to apudomas which may exhibit cells with various degrees of differentiation. A variable number of neoplastic cells with low secretory granule density could present a dubious or completely negative reaction. As a result, a given gastrinoma may exhibit cells strongly reactive to the gastrin antibody alongside others completely negative.

of histologic tumor differentiation and the proliferative activity of the neoplastic cells, depend exclusively on the pathologist interpretation. And unlikely, the last four parameters shown in **Table 3** depend on the opinion of different expert professionals to reach more reliable conclusions about the clinical course of the tumor.

In general pathology, the degree of differentiation of a given epithelial tumor, evaluated by histology, has always been, and still is, a criterion that together with other ones, gives an idea about the grade of malignancy that a particular carcinoma must have: a less aggressive evolution, more common among the well-differentiated ones, or a more aggressive evolution more common in those poorly differentiated (**Figure 4**). This histopathological criterion continues to be applied

PATHOLOGY (Histopathology)	Tumor histopathology Well differenciated Pourly differenciated
	Proliferative activity
IMAGE METHODS ENDOSCOPY SURGERY PATHOLOGY	Primary tumor site
	Tumor size
	Degree of tumor infiltration
	Metastasis (TNM Classification)

Table 3. Main criteria to determine the malignant potential of the apudoma.

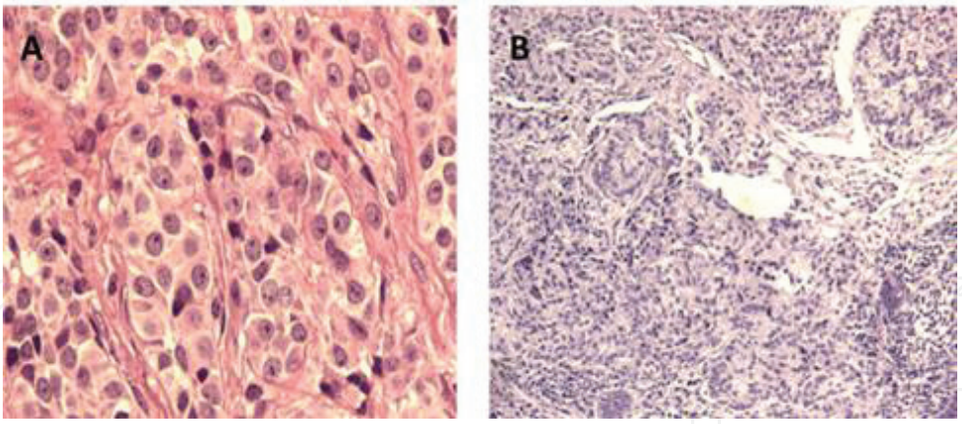

Figure 4. Well-differentiated type 1 (A) and poorly differentiated type 2 (B) gastric apudomas. Although the degree of tumor differentiated could have some importance regarding the degree of malignancy, the proliferative activity remains as a better histopathological indicator for this purpose.

mainly in relation to the nonendocrine carcinomas. Concerning the apudomas, this parameter, as an isolated element, has little value. Differently, the well-differentiated apudoma can present unpredictable clinical behavior. However, when the tumor is histologically poorly differentiated, the prognosis is often worse. In this respect, this criterion of cellular differentiation may be helpful. In addition, apudomas present varying densities of membrane receptors for different regulatory peptides, including somatostatin. And, a high density of these receptors in apudoma cells acquires current medical importance for the patient treatment. Some data indicate that the somatostatin receptor density would be dependent on the degree of tumor grade [20].

Under the view of histopathological diagnosis, the malignancy potential of a particular apudoma rests mainly on the degree of tumor cell proliferation. This criterion can be applied to all apudomas regardless of their origin. There are two histopathological tools to assess the degree of cell proliferation: (i) the number of observable mitoses in the routine preparations stained by *hematoxylin* and *eosin* and (ii) the index of cell immunoreactivity for Ki-67 antibody. The Ki-67 reactive protein is only expressed in the nucleus of cells that are in the various phases of the active cell replication cycle. This protein is not expressed in resting cells, that is, the cells that have not yet entered the active mitotic cycle. Moreover, there is not always any correspondence between the degree of differentiation of a given apudoma and the degree of cell proliferation [21, 22].

Concerning proliferative activity, the low-grade (G1) tumors present very few numbers of mitosis in routine HE preparation or otherwise less than 3% of neoplastic cells stained by Ki-67 antibody. The high-grade (G3) tumors should present more than 20 mitoses per 10 microscopic high-power field (hpf) or more than 20% of the neoplastic cells positive to Ki-67 antibody. Finally, tumors with intermediate degree of cell proliferation that lie between these two extremes are considered to be G2.

2.3. Gastric apudomas

Almost all apudomas of the stomach are derived from the endocrine cells of the body mucosa and rarely from the endocrine cells of the antral mucosa. They represent approximately 2–4% of all gastric neoplasias and 7.2% of all apudomas of the gastrointestinal tract [10].

In recent decades, there has been evidence that favors believing in an increase in the incidence of gastric apudomas. To a great extent, this increase must be occurring due to the technological evolution of the instruments connected to endoscopy of the upper digestive tract because these tumors are mostly often discovered incidentally during endoscopy. However, a real increase in the prevalence of these tumors cannot be ruled out [11, 23, 24].

The apudomas of the stomach are generally divided into three different groups based on their clinical and physiopathological characteristics: type 1, apudomas of the stomach associated with atrophic body gastritis (ABG), with or without pernicious anemia; type 2, apudomas of the stomach associated with Zollinger-Ellison syndrome, sporadic or familial; and type 3, sporadic apudoma not associated with known predisposing disease [25].

2.4. Gastric apudoma type 1

These are the most frequent gastric neuroendocrine tumors. They are characteristically associated with atrophic body gastritis (ABG) and are the most frequent of the gastric apudomas constituting about 70–80% of them. The criterion adopted for the classification of these tumors in type 1 is the recognition of the presence of established chronic autoimmune gastritis, with or without pernicious anemia, or just the presence of atrophic body gastritis confirmed by histopathology. This type of tumor appears to be more prevalent in women as well as the prevalence of the underlying disease (**Figure 5**).

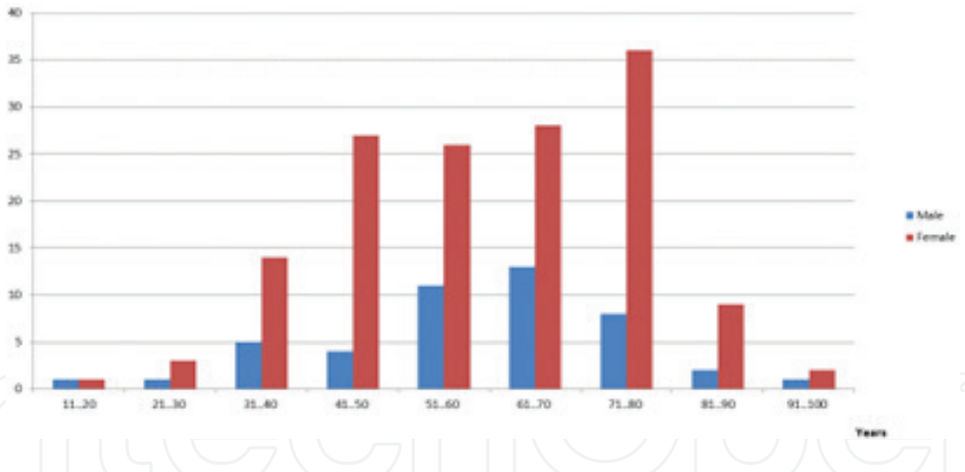

Figure 5. Distribution of 196 consecutive patients with atrophic body gastritis according to the age and gender. Patients were from a general hospital in Belo Horizonte, Brazil [26].

Therefore, it can be assumed that this type of tumor is a direct consequence of the atrophic body gastritis. According to this diagnostic criterion, we can conclude that the different types of apudomas of the stomach cannot be diagnosed based only on their endoscopic and histopathological pattern. Therefore, for the inclusion or exclusion of a gastric apudoma as type 1, it is necessary that in addition to histological samples of the tumor itself we also have samples of the gastric mucosa of the antral and body regions of the stomach to confirm or rule out the possibility of atrophic body gastritis. Recognizing an endocrine tumor as type 1 opens a range of possibilities to better understand the set of pathophysiological changes that may be occurring in the patient:

a. Gastric apudoma type 1 occurs in the mucosa of the fundus or the gastric body generally as multiple nodules, smaller than 1 cm in most cases. As they are generally multiple, they may occur according to an irregular distribution in the gastric body, the gastric fundus, or in the two regions simultaneously (**Table 4**). Usually, these nodules are projected into the lumen of the stomach and are frequently diagnosed by endoscopy as "gastric polyps." This diagnosis is not always incorrect because in ABG hyperplastic polyps are relatively frequent.

b. The neoplasia usually consists of well-differentiated neuroendocrine cells with a low Ki-67 index (G1) indicating low levels of cell proliferation. This characteristic is in agreement with the indolent evolution of these tumors; only a small number of them present metastases when diagnosed and rarely take the patient to death (**Table 4**).

c. Due to atrophy of the oxyntic mucosa these patients present hypochlorhydria or achlorhydria.

d. Since the gastric mucosa of the corpus is atrophic and the antral mucosa is preserved, the G cells are usually hyperfunctioning, and these patients frequently present hypergastrinemia (**Table 4** and **Figure 6**).

e. Even without the occurrence of high levels of serum gastrin, the constant trophic stimuli of this hormone will lead to hyperplasia of the endocrine cells of the gastric body. These hyperplastic cells are believed to be enterochromaffin-like (ECL) cells. However, other types of neuroendocrine cells may be participating in this hyperplastic process, including ghrelin-producing cells [26]. The areas of neuroendocrine cell hyperplasia can be found in almost all cases of well-established atrophic body gastritis (**Figures 7–9**). As we have already said, these areas of endocrine hyperplasia occur along the atrophic mucosa and according to their morphological aspect can be classified as (i) diffuse, (ii) linear, and (iii) nodular [27].

f. Based on these general aspects of atrophic body gastritis, it is possible to conclude that the areas of neuroendocrine hyperplasia are probably the precursor lesion of type 1 gastric apudoma. However, there are no histological signs that highlight where the hyperplasia ends and where the neoplasm begins. In this regard, the large, confluent hyperplastic nodules with a diameter about 300–500 μm associated with infiltration of mucosa tissues would already be classified as indicative of emerging neoplastic lesion (**Figure 9**). Just for comparison, 500 μm is equivalent, on average, to half thickness of normal oxyntic mucosa in formalin-fixed histologic sections.

g. The infiltration of the submucosa by the hyperplastic endocrine cells is already a sign of malignant behavior. However, for the most part, these type 1 gastric apudomas present indolent evolution, and few of them present metastasis at the time of diagnosis (**Table 4**).

2.5. Gastric apudoma type 2

Type 2 gastric apudomas are those associated with sporadic or familial Zollinger-Ellison syndrome. They account for only 5–6% of the gastric apudomas. Almost always these tumors

	Type 1	Type 2	Type 3
Frequency (%)	70–80	5–10	10–15
Endoscopic view	Multiple and small	Multiple and small	Single (>2 cm)
Site	Gastric body/fundus	Gastric body/fundus	Any region
Cellular proliferation index	G1	G1/G2	G3
Gastrinemia	Generally high	Generally high	Normal
Metastasis (%)	2–5	10–30	50–100

Table 4. Differential profiles between the three groups of gastric apudomas.

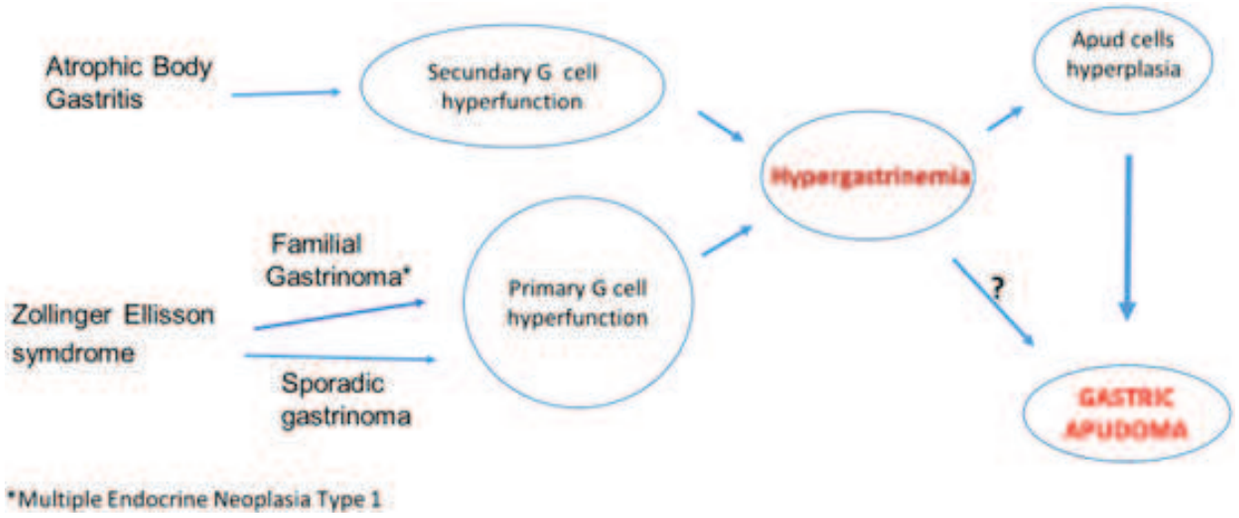

Figure 6. Drawing showing the pathogenetic mechanisms of the gastric apudomas type 1 and type 2. The pathophysiological central mechanism associated with these two types of tumors is the occurrence of hypergastrinemia or a persistent supra-basal gastrinemia.

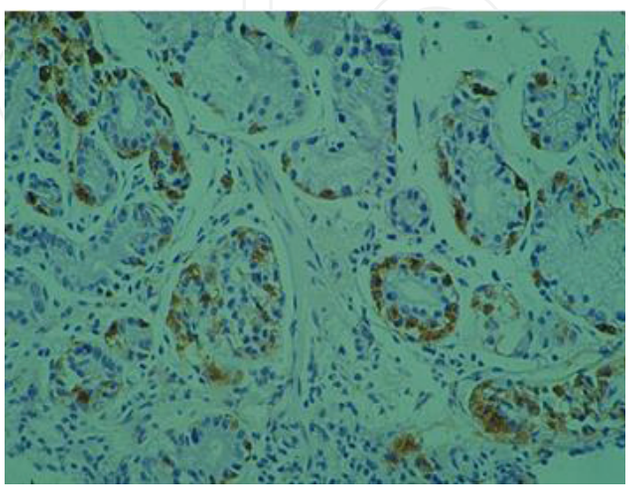

Figure 7. Diffuse and linear types of endocrine cell hyperplasia in atrophic body gastritis. The hyperplastic cells are stained for chromogranin.

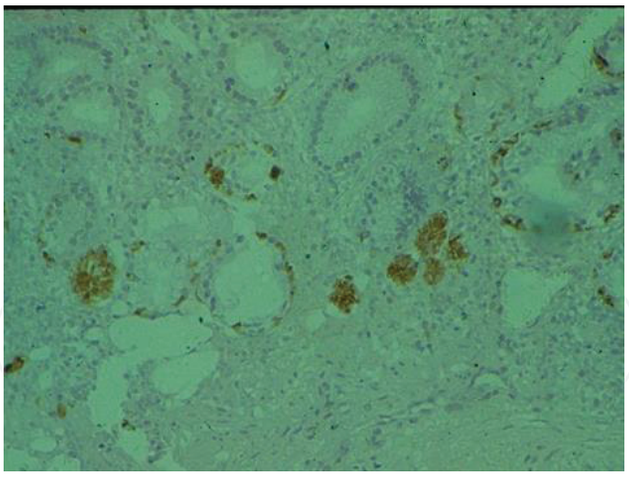

Figure 8. Nodular type of endocrine cell hyperplasia in atrophic body gastritis. The hyperplastic cells form small nodules in the lamina propria. Chromogranin staining.

occur in patients with multiple endocrine neoplasia (MEN) type 1. Rarely, there is also a Zollinger-Ellison syndrome (ZES) not associated with multiple endocrine neoplasia (MEN) which leads to gastric apudoma development. In this case the ZES may be due to the presence of a sporadic gastrinoma, the main location of which is believed to be the tail of the pancreas. Thus, most frequently, the patient presenting a type 2 gastric apudoma may be a carrier of the genetic transmission of MEN syndrome. MEN-1 is an inherited autosomal dominant syndrome caused by an inactivating mutation of the MEN-1 gene, which is a tumor suppressor gene. MEN-1 syndrome may include the development of primary hyperparathyroidism, pancreatic islet tumors, and pituitary adenomas. In addition, some patients may develop other neoplasms such as thyroid tumors, adrenal adenomas, pheochromocytomas, and neuroendocrine tumors mainly of the gastroduodenal area.

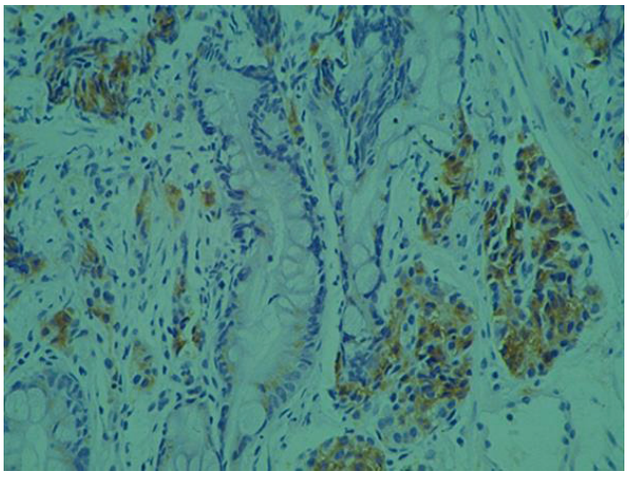

Figure 9. Endocrine cell forming large hyperplastic nodules in the lamina propria. This type of lesions may be indicative of an emerging gastric apudoma. As these tumors may be multicentric, it is possible that more strongly suspected lesions occur in other areas of the gastric mucosa. Chromogranin staining.

2.6. Gastric apudoma type 3

Type 3 gastric apudomas are known as sporadic gastric tumors, representing about 10–15% of all gastric apudomas, and develop independently hypergastrinemia as well as gastric endocrine cell hyperplasia (**Table 4**). More frequently they present as a single polypoid tumor usually greater than 2 cm in size [28]. These tumors are composed mainly by enterochromaffin-like cells, and differently from the other gastric apudoma, they have an aggressive clinical evolution. These tumors present histopathological signs corresponding to the clinical evolution of worse prognosis such as angioinvasion, rapid growth, mitotic activity, and high Ki-67 index.

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