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NEUROENDOCRINE TUMORS

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Abstract:

Introduction: *Gastric neuroendocrine tumors (gNETs) are cancers that arise from the enterochromaffin-like cells (ECL cells) of the stomach mucosa. They are considered rare cancers with a benign course and neuroendocrine differentiation. Though they are not common, the diagnosis is becoming higher, because of the high usage of endoscopy and the technical enhancement of endoscopies and physicians. The ECL cells bind to silver salts avidly and have a major role in the regulation and maintenance of the acid secretion. After eating, the G cells of the antrum produce gastrin and secret it which will stimulate the ECL cells and the histamine-producing parietal cells to produce hydrochloric acid (HCL). The negative feed-back is very important, it comes from the D cells, which are stimulated by the HCL and produce somatostatin which will reduce the secretion of gastrin. It is critical to understand the mechanisms in order to categorize and classify gastric gNETs in 4 clinical types, with distinct proper management plan and prognosis. It is also essential to emphasize that this classification system is different from the three histological grades recommended by the World Health Organization (WHO). Moreover, the WHO terminology for gNETs underwent changes in recent years, which amplified the difficulty to understand this complex disease.*

Aim of work: *In this review, we will discuss neuroendocrine tumors.****Methodology:*** *We did a systematic search for Neuroendocrine tumors using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.* ***Conclusions:*** *Gastric neuroendocrine tumors (gNETs) are cancers that arise from the enterochromaffin-like cells (ECL cells) of the stomach mucosa. They are considered rare cancers with a benign course and neuroendocrine differentiation. Though they are not common, the diagnosis is becoming higher, because of the high usage of endoscopy and the technical enhancement of endoscopies and physicians. Gastric NETs consist of a complex disease that includes different subtypes with distinct management and prognosis. The management of gNETs is based on the clinical type, disease extent, the differentiation of the lesion and the presence or absence of poor prognostic factors. According to the WHO, these cancers are categorized into 3 histologic degrees with distinct prognosis Correct identification of the clinical type and histological grade allows for a tailored management. Further studies will clarify the diseases biology and improve its treatment.*

Key words: *Neuroendocrine tumors, presentations, management.*

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INTRODUCTION:

Gastric neuroendocrine tumors (gNETs) are cancers that arise from the enterochromaffin-like cells (ECL cells) of the stomach mucosa. They are considered rare cancers with a benign course and neuroendocrine differentiation. Though they are not common, the diagnosis is becoming higher, because of the high usage of endoscopy and the technical enhancement of endoscopies and physicians4.

The ECL cells bind to silver salts avidly and have a major role in the regulation and maintenance of the acid secretion. After eating, the G cells of the antrum produce gastrin and secret it which will stimulate the ECL cells and the histamine-producing parietal cells to produce hydrochloric acid (HCL). The negative feed-back is very important, it comes from the D cells, which are stimulated by the HCL and produce somatostatin which will reduce the secretion of gastrin [1-2].

It is critical to understand the mechanisms in order to categorize and classify gastric gNETs in 4 clinical types, with distinct proper management plan and prognosis [3-4]. It is also essential to emphasize that this classification system is different from the three histological grades recommended by the World Health Organization (WHO). Moreover, the WHO terminology for gNETs underwent changes in recent years, which amplified the difficulty to understand this complex disease.

In this review, we will discuss the most recent evidence regarding the neuroendocrine tumors.

METHODOLOGY:

We did a systematic search for Neuroendocrine tumors using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Neuroendocrine tumors, presentations, management.

CLASSIFICATION AND DIAGNOSIS:

Type I

Type I represents the main type of gNETs it is the most common lesion, found in the gastric (about seventy five percent) and they are linked to autoimmune chronic atrophic gastritis. The patient has anti-parietal cell or anti-intrinsic factor antibodies, resulting in the damage of the gastric parietal cell, decreasing the level of HCL (achlorhydria), which will lead to higher production of the gastrin by G cells [5-6]. This higher production of hormones promotes ECL cells hyperplasia, supporting the appearance of multiple small lesions, often with little aggressive behavior and better outcome.

A reduction in the intrinsic factor with decrease of vitamin B12 absorption also occurs resulting in macrocytic anemia (pernicious or megaloblastic) [7]. The Diagnosis of type I can be made by upper gastrointestinal (GI) endoscopy with biopsy. The endoscopic findings could be pale, yellowish and transparent blood vessels of the antral mucosa, contrasting with the smooth and reddish mucosa of normal areas. Neuroendocrine tumors can be seen as small, reddish polyps and often being multiple.

The histological exam would reveal atrophy of the mucosa cells, absence of parietal cells and neuroendocrine cell hyperplasia. It can also assert the diagnosis of NET. hgiher serum gastrin and low serum vitamin B12 can often be concluded. Anti-parietal cell and anti-intrinsic factor antibodies can be detected [8]. Finally, the gastric acidity dosage shows high pH (more than seven) [9].

Type II

Type II are believed to be caused by gastrinomas (gastrin-producing tumors), which os also known as Zollinger-Ellison syndrome. In many situations the patient has multiple endocrine neoplasia type I (MEN-1) and must be evaluated with serum sequencing for MEN1 gene [10].

The rate of type II gNETs is around seven percent and the lesions are usually tiny and multiple. The metastatic potential is considered low, though it is higher than in type I [11]. To confirm the diagnosis, upper Gastrointestinal endoscopy with gastric biopsy shows normal or hypertrophic gastric mucosa29. Hypergastrinemia and gastric pH more than two (hyperchlorhydria) are usually seen. Serial measurement of gastrin levels after intravenous administration of secretin could also be done showing an elevation in gastrin levels for patients with gastrinoma, while they lower in healthy adults.

Following confirmation of the diagnosis, research should remain on in order to localize the gastrinoma and, possibly, eradicate it with surgery. Most of these types are seen in the triangle of gastrinomas verified by the junction of the cystic duct with the common hepatic duct, the transition from 2nd to 3rd duodenal portions and the pancreatic cervix [12]. Computed tomography (CT) scan, magnetic resonance imaging (MRI), endoscopic ultrasound, scintigraphy with

octreotide, selective angiography, positron emission tomography and intraoperative ultrasonography are helpful tools that can aid localizing the lesion.

Type III

Type III gNETs comprise a sporadic lesion and characterized by the highest ability to generate metastasis. The survival of these patients is much worse (about eighty percent at 5 years compared to ninety percent for type I.

Generally speaking, the lesion is distinctive and more than one centimeter, with normal gastrinemia. The diagnosis can be made by upper GI endoscopy with biopsy, observing a single lesion in normal gastric mucosa. though it is uncommon, carcinoid syndrome could be the first presentation.

Type IV

It is worth noting that 3 recent studies suggested a 4th type of gNET. It consists of multiple small lesions and the histological examination shows hypertrophy and hyperplasia of parietal cells with vacuolated cytoplasm. A structural abnormality prevents the HCL, produced by these cells, from being secreted. Eventually, achlorhydria, hypergastrinemia and hyperplasia of neuroendocrine cells occur [13].

Immunohistochemistry

Immunohistochemical analysis is critial in NETs. It permits diagnostic confirmation and allows classifying the lesion according to the histological grades defined by the WHO [14]. To confirm the diagnosis chromogranin A and synaptophysin are essential, wheras for prognostic definition the proliferative index Ki-67 and the number of mitoses per high magnification field are needed. Other markers, like p53, have being evaluated, and can predict the prognosis and risk of metastasis [15].

Staging

CT scan of the abdomen is highly suggested for type I and II gNETs larger than two cm and for all type III lesions. MRI of the abdomen, octreotide scintigraphy and PET-CT may be usefull in specific cases34.

Management

The management of gNETs is based on the clinical type, disease extent, the differentiation of the lesion and the presence or absence of poor prognostic factors. Accordingto the WHO, these cancers are categorized into 3 histologic degrees with distinct prognosis.

Carcinoid crisis should also be prevented before and after any tumor manipulation or anesthesia. This can be done by giving intravenous or subcutaneous octreotide [16].

Type I

Because most of the lesions are small, well-differentiated and with excellent prognosis, management often comprises in the serial endoscopic resection of these lesions12. Supplementation of vitamin B12 is highly recommended.

Surgical treatment is essential only when endoscopic resection is not possible or when poor prognostic factors are present. While the surgical indication is clear when deep invasion is seen, for those cases with lymph node metastasis or for lesions not suitable for endoscopic resection, there is no clear evidence that suggests or not surgery when there is only necrosis, vascular invasion or an elevated Ki-67. A recent study validated the WHO classification, showing the presence of a lymph node metastasis in a patient with a small and superficial type I gNET whose only poor prognostic factor was a Ki-67 of seven percent [17]. This also underlines the need for diligent analysis of all resected lymph node.

It is also not clear when surgery should be done for patients with frequent recurrences or when there is a high number of lesions. At this moment there is no evidence in the literature that allows a strong recommendation, since there is no consensus of what is a “frequent recurrence” or a “high number” of lesions. So the treatment of these cases should be tailored and discussed with the patient.

The best kind of surgery for type I gNETs is considerd controversial37. Antrectomy has been suggested to eliminate the gastrin-producing G cells; but, it may fail because of improper removal of these cells or due to the ECL cells became autonomous. For these reasons subtotal or total gastrectomy are recommended and better available options. Subtotal gastrectomy allows sufficient removal of G cells, while total gastrectomy is preserved for those cases with substantial disease in the gastric fundus.

It is worth noting the clinical management of type I gNETs, though this will scarcely be an efficient choice in the long term. Some authors used somatostatin analogues (octreotide) to lower gastrinemia in small groups of patients. But, following discontinuation of the management with serum gastrin rose again in a 1 year follow-up, although no new lesions were observed in the short term [18]. So, this management must be reserved for those patients unfit for surgical resection.

Type II
Treatment of type II gNETs consists in localizing and resecting the gastrinoma. As for gastric lesions, unless there is some factor of poor prognosis, endoscopic resection is enough.

Type III
These lesions must be treated aggressively with total or subtotal gastrectomy associated with lymphadenectomy. If there is resectable metastatic disease, it should also be managed. For unresectable liver disease, local therapies like arterial embolization or radioablation have a success rate of fifty percent. If there is extrahepatic metastasis or recurrent symptomatic disease, systemic therapy with cytotoxic chemotherapy (streptozocin combined with 5-fluorouracil or cyclophosphamide, doxorubicin mono drug or with 5-fluorouracil, dacarbazine or temozolamide, oxaliplatin with capecitabine or 5-flurouracil with leucovorin) or molecular targeted agents.

Carcinoid syndrome
This is considered a rare event in gNETs and its clinical manifestation is atypical consisting exclusively of redness due to histamine production26. Symptoms control is achieved with somatostatin analogs (octreotide or lanreotide) and interferon alfa in low doses for refractory cases [19].

Follow up
Disease development is very heterogeneous, with a median survival ranging from 13 months to more than 10 years. The recommendation of the National Comprehensive Cancer Network (NCCN) for follow-up consists of anamnesis, physical examination, upper GI endoscopy, abdominal CT scan or MRI and serum chromogranin A, every 6 months for one to two years, yearly for four more years and then every two years until ten years after surgery [20].

Trends
The presence of somatostatin receptors in NETs have been implemented as initial point for the development of new diagnostic techniques and therapeutic methods. A less expensive and more rapid octreotide scintigraphy has been obtained after labeling it with technetium instead of indium [21]. Another recent innovation is the use of gallium marked octreotide, which can be captured by positron emission tomography scans (PET and PET-CT).

A new marker that could aid the diagnosis are also being studied. Serum enolase which is most usually produced by aggressive undifferentiated tumors is an example. From this knowledge more, specific follow-up tests for each histological tumor type may be achieved.

CONCLUSIONS:

Gastric neuroendocrine tumors (gNETs) are cancers that arise from the enterochromaffin-like cells (ECL cells) of the stomach mucosa. They are considered rare cancers with a benign course and neuroendocrine differentiation. Though they are not common, the diagnosis is becoming higher, because of the high usage of endoscopy and the technical enhancement of endoscopies and physicians. Gastric NETs consist of a complex disease that includes different subtypes with distinct management and prognosis. The management of gNETs is based on the clinical type, disease extent, the differentiation of the lesion and the presence or absence of poor prognostic factors. According to the WHO, these cancers are categorized into 3 histologic degrees with distinct prognosis Correct identification of the clinical type and histological grade allows for a tailored management. Further studies will clarify the diseases biology and improve its treatment.

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