CLINICAL CASE

GASTRIC CARCINOMA BETWEEN HIGH GRADE NEUROENDOCRINE FEATURES AND ADENOCARCINOMA: A CASE REPORT AND BRIEF REVIEW OF LITERATURE

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Abstract

Mixed adenoneuroendocrine carcinoma (MANEC) is an exceptionally rare type of cancer associated to the gastrointestinal tract, without a clearly established and optimal therapeutic management. These tumors present with non-specific symptoms or histopathological findings to distinguish them from pure adenocarcinomas. We report the case of a 64-year-old male diagnosed with a high grade mixed adeneuroendocrine carcinoma of the gastric antrum, stage T2N3Mx. The patient underwent radical gastrectomy and the histopathological examination of the surgically resected specimen revealed a tumor mass containing both adenocarcinoma and poorly differentiated neuroendocrine components. Immunostaining for Chromogranin A and Synaptophysin was positive in the neuroendocrine component and negative in the adenocarcinoma component, which was positive for CK7 and CK20. Ki67 proliferation index was 95%. Using this report as reference, we also discuss the imunohistopathological features, clinical behavior and therapeutic management of mixed adenoneuroendocrine carcinomas, presenting a brief review of literature regarding this rare, yet highly aggressive tumor.

Keywords: *MANEC, gastrectomy, immunostaining*

Introduction

The concept of mixed adenoneuro-endocrine carcinoma (MANEC) was first described by Lewin in 1987. He classified these neoplasms in three different categories: collision tumors, combined tumors and amphicrine tumors [1]. In 2000, the World Health Organization (WHO) introduced the term mixed exocrine-endocrine tumor which was changed in 2010 to the currently acknowledged terminology of MANEC (Table 1) [2]. This type of cancer represents a highly malignant, two-in-one tumor, with dual morphological differentiation, usually represented by an adenocarcinoma with neuroendocrine features, with either component exceeding 30% and having various degrees of differentiation, from well to poorly differentiated. Therefore, in order to establish the diagnosis of MANEC, immunostaining for various neuroendocrine markers is required. Examination by electron microscopy would reveal large dense-core neurosecretory vesiclesin the neuroendocrine cells, but this method is not routinely used in clinical practice [2,3].

Classification of WHO 2010	
NET G1	Carcinoid – well-differentiated endocrine tumor
NET G2	Well-differentiated endocrine carcinoma
NEC	Poorly-differentiated endocrine carcinoma – large cell or small cell type
MANEC	Mixed adenoneuroendocrine carcinoma
	Hyperplastic and preneoplastic lesions

NET G1 (Neuroendocrine Tumor grade 1), NET G2 (Neuroendocrine Tumor grade 2), NEC (Neuroendocrine Carcinoma)

Table 1- Classification of WHO 2010. Adapted from N. D. T. Fred T. Bosman, Fatima Carneiro, Ralph H. Hruban, "WHO Classification of tumours of the digestive System," 2010.

Case presentation

A 64-year-old male presents to the University Emergency Hospital Bucharest due to nausea, hematemesis, weakness and strong stomach cramps which were suspected to be caused by an ulceration of the gastric mucosa or a gastric neoplasm. The patient was known with chronic gastritis in the background of an active Helicobacter pylori infection which led to high levels of gastrin in the past 2 years since he was diagnosed. Meanwhile, he lost 10 kilos in the last 2 months and presented noticeable abdominal pain located especially in the epigastrium, nausea, vomiting once a month, symptoms ameliorated with Omez (containing the active substance Omeprazole).

Gastroscopic examination showed a tumoral mass as a polypoid lesion in appearance, located in the gastric antrum. Biopsy revealed an admixture of high grade adenocarcinoma with neuroendocrine features which classified the tumoral lesion a high-grade type of gastric MANEC. The patient underwent a subtotal gastrectomy. The resected specimen was sent to the Department of Pathology for further evaluation. Gross examination of the specimen revealed an infiltrative tumoral mass measuring about 5 centimeters in greatest diameter, that microscopically appeared to infiltrate the muscular layer. The tumor was composed of two histological components: a high grade adenocarcinoma with both papillary and discohesive (signet ring cell) patterns, as well as a neuroendocrine carcinoma associated with a diffuse non-specific inflammatory reaction. 10 out of the 15 evaluated lymph nodes presented invasion of both components (Figures 1 and 2).

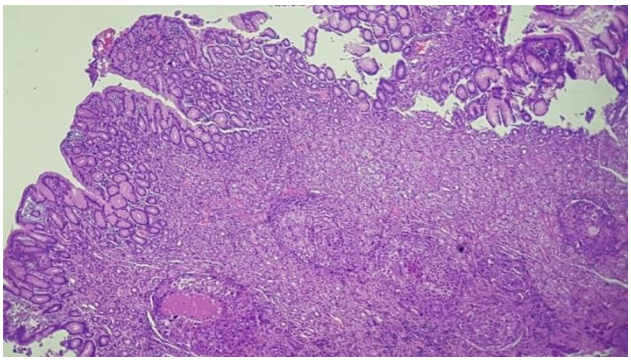

Figure 1 - Mixed adenoneuroendocrine carcinoma of the gastric antrum, H.E., 40x

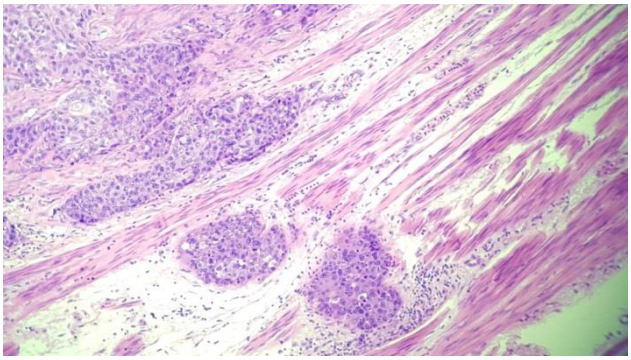

Figure 2 - Neuroendocrine component composed of large tumor cells with vesicular nuclei, coarse chromatin, prominent nucleoli and a moderate to abundant cytoplasm, H.E., 100x

In order to establish the final diagnosis, immunostaining for CK7, CK20, CDX2, pan-cytokeratin AE1/AE3, Ki67, Chromogranin A and Synaptophysin were performed. In our case, CK7, CK20 and CDX2 showed strong and diffuse membranar positivity in the adenocarcinomatous component. Ki-67 proliferation index was extremely high, staining 95% of all tumoral cells. Positive Chromogranin

and Synaptophysin staining confirmed the presence of neuroendocrine differentiation (Figures 3 and 4). Based on these results, the final diagnosis of gastric MANEC stage T2N3Mx has been established. The patient did not received chemotherapy after the surgical treatment that also involved the removal of all lymph node metastasis.

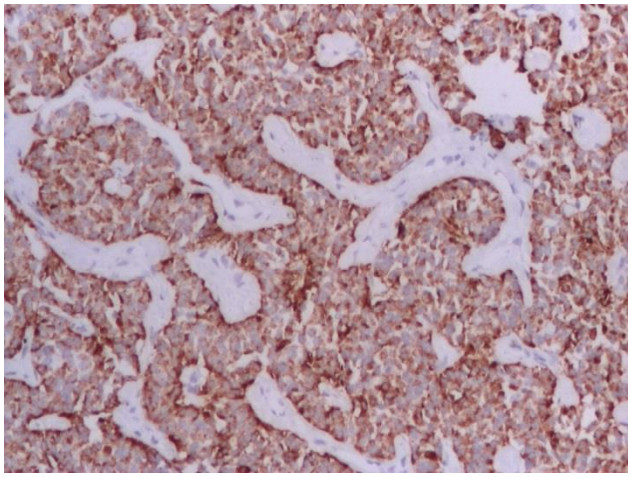

Figure 3 - Strong immunoexpression of Chromogranin A in the neuroendocrine component of gastric MANEC, 200x.

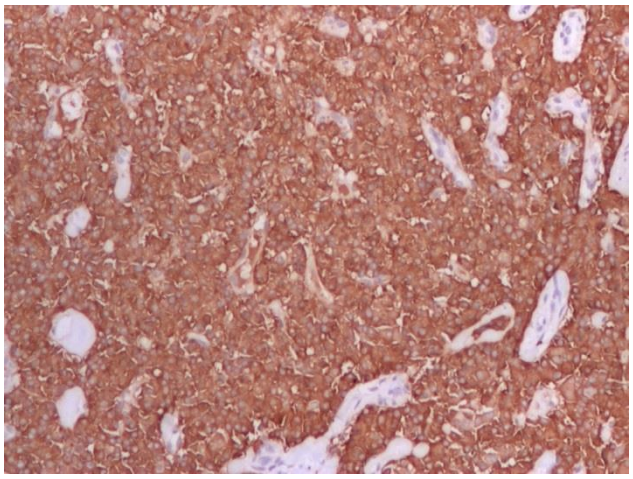

Figure 4- Strong immunoexpression of Synaptophysin in the neuroendocrine component of gastric MANEC, 200x.

Discussions

Gastric MANECs are described as gastric neuroendocrine tumors with specific adenocarcinoma cells despite the fact that a small part of neuroendocrine cells in gastric adenocarcinomas should not restrict to classify it as MANECs. This explains why neuroendocrine differentiation is usually required only for large cell component. [2-4]

In general, there are three types of gastric neuroendocrine tumor, presented in Table 2 [2]. Type 1 and 2 of gastric neuroendocrine tumors are related to high levels of gastrin hormone (hypergastrinemia). Hypergastrinemia is always associated with a pH less than 2. In fact, the hypersecretion of the gastrin hormone by G cells is the consequence of a deficiency in gastric acid, which inhibits the gastrin secretion in the normal conditions. The lack of cobalamin in autoimmune disorders that lead to pernicious anemia, chronic inflammatory changes related to gastric Helicobacter pylori infection, metaplasia of the gastric mucosa and specific gastric surgery, cause achlorhydria (the trigger of premalignant conditions in gastrointestinal pathology) [5,8]. The level of the principal forms of gastrin in the stomach (G-34, G-17, G-14) are required to put the diagnosis of Zollinger-Ellison syndrome (ZES), characterized by severe diarrhea, peptic ulcer disease and gastric acid hypersecretion [2,6]. Some cases of ZES are associated with autosomal dominant inherited disorder- multiple endocrine neoplasia type 1 (MEN1) [10]. Mutations of MEN 1 gene locus may occur sporadically in the patient's family. The loss of heterozygosity of 11q13(location of the MEN 1 gene usually show the character of type 2 gastric neuroendocrine tumors, but it also can describe type 1 cases [3]. Hypergastrinemia related to MEN 1 is determined by an ectopic secretion of gastrin hormone, named gastrinoma that is more commonly found in the duodenum than in the stomach [10-12]. For distinguishing not-G cells from G cells it is necessary the gastrin immunostaining with neuroendocrine markers. Highlight the suspect neuroendocrine cells from the other cell population it is also about evidence the background of their proliferation. The lesions may come as polyps which cover the mucosa which can regress without any treatment. Some patients need somatostatin analogues, also known as inhibiting growth hormones for decreasing the high level of gastrin hormone or surgical treatment to remove the source of the excess of gastrin [14]. Type 3 cases have a more aggressive behavior with metastases in more than 50% cases. Even though their background

could not be completely elucidated yet, type 3 has not hypergastrinemia [3]. In this case report, the patient can have as a possible diagnosis the gastric neuroendocrine tumor type 1 due to the high levels of gastrin which may be caused by chronic gastritis and Helicobacter pylori infection, but we should also include the occurrence of type 2 in ZES associated with hypergastrinemia..

Type	Serum Gastrin Levels	Pathogenic Mechanism	Clinical Course
1	Hypergastrinemia resulting from absence of hydrochloric acid	Autoimmune gastritis	Spontaneous regression or endoscopic removal of polyps in superficial mucosa, rarely invasive
2	Hypergastrinemia resulting from ectopic gastrin secretion	ZES MEN 1	Treatment with somatostatin analogues effective
3	No hypergastrinemia	Undetermined	Aggressive behavior with deep lesions, metastatic

Table 2- Clinical Features of Gastric Neuroendocrine Tumors. Adapted from J. R. G. Robert D. Odze, Odze&Goldblum Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas, 3E. Elsevier Saunders, 2015.

The previous treatment with Omeprazole reduces the acid gastric secretion by inhibiting the proton pump. The proton pump inhibitor can also be associated with the suppressed activity of the urease. Due to one study, the survival of Helicobacter pylori is restricted in the absence of an urease-independent mechanism, but the bacteria is not destroyed [16]. We take this into consideration because the patient known with Helicobacter pylori used Omez for a long time to relieve the epigastric pain and it may lead to an inactive bacterial infection that could reduce the chance of a gastric neuroendocrine tumor type 1. Another concern of this proton pump inhibitor is a potential adverse effect which can induce parietal gastric cells hyperplasia and gastric carcinoid development that can also be a cause of the described gastric MANEC in this article [15,16].

To distinguish gastric MANECs from neuroendocrine neoplasms it is necessary to make an immunostain display with specific neuroendocrine markers. Synaptophysin, Chromogranin and CD56 are the most specific neuroendocrine markers. Chromogranin A-secretory protein is found in large dense-core vesicles of neuroendocrine tumors [18]. Synaptophysin-glycoprotein is located in the membranes. The antibodies to Synaptophysin can also be found in the neurons, adrenal medulla, pancreatic islets in non-pathological situations. The occurrence of Synaptophysin in neoplasms as Chromogranin is unlikely sure because a minimum number of tumors are not related to the presence of Synaptophysin, respectively the Chromogranin in immunohistochemistry which raise the question of the possible heterogeneity of these tumors. CD56 is another reliable neuroendocrine marker in confirming a neuroendocrine carcinoma expressed on natural killer cells, neurons and others [19]. Cytokeratin 7(CK7) and Cytokeratin 20 (CK20) are low molecular weight cytokeratins with an anatomic distribution generally restricted to epithelial tissue and its neoplasms [20]. Their diverse and unique expression has been found useful in the differential diagnosis of some carcinomas with epithelial origin. CDX2 is a human homeobox gene that encodes a nuclear transcription factor critical for intestinal embryonic development, which is relatively specific for intestinal epithelium [17,18]. Ki-67 is a marker of cell proliferation that is usually over 60%, increased 95% for this neuroendocrine tumor.

Hereinafter, immunostaining the antrum gastric tumor shows an intestinal epithelial origin by CDX2, CK7 and CK20 positive, an adenocarcinoma component because of the presence of pan-cytokeratin AE1/AE3 and a neuroendocrine component revealed by specific markers: Synaptophysin and Chromogranin. The specific characteristics of the immunostain display reveal the diagnosis of gastric MANEC.

The first-line treatment in gastric MANECs is a subtotal or total gastrectomy. According to their location, metastases, cell-differentiation, nutritional status, a palliative treatment with somatostatin analogues or chemotherapy is usually requested, although the optimal treatment strategy is unclear yet [1]. For the 64-year-old patient we evaluated the subtotal gastrectomy to a good prognosis due to the extent of still early diagnosed tumor. Chemotherapy may be a good option for this highly invasive type of cancer, but in a further approach the patient already has a poor nutritional status which puts in question the benefits of anti-cancer drugs.

Conclusions

Understanding the history of Helicobacter pylori infection at this patient enables to make differential diagnosis and identify the cause, risks and treatment of the gastric MANEC. It is an atypical type of cancer associated to gastrointestinal tract with an unsure disease management, described closely to a literature review in the background of an accurate anatomo-pathological examination of the surgically resected specimen.

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