

# Recent Studies on Digestive System Anatomy

## Chapter 1

# Study on Morphology and Pathogenesis of Type 1 ECL- Cell Gastric Carcinoids

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## 1. Introduction and Aim

Gastric carcinoids develop from neuroendocrine cells. There are a few types of neuroendocrine cells in the stomach, mainly G, D, ECL, D1, Ec, P and X cells [1-5]. Gastric carcinoids in the stomach derive from ECL cells, the dominant type of endocrine cells of the corpus and fundus mucosa realising histamine which is responsible for parietal cell stimulation [6-8]. Autoimmune atrophic fundic gastritis induces both hypergastrinemia and pernicious anemia (PA), as well as the changes in both epithelium and endocrine cells in gastric mucosa [6-9]. The most important complications of hypergastrinemia are: gastric cancer and enterochromaffin-like cell (ECL- cell) carcinoid [7-10]. Gastric carcinoids (GCs) constitute 4% of all gastrointestinal endocrine tumors and 0.3% of gastric neoplasia [6-10].

The aim of this study was to examine both type ECL-cell carcinoid morphology and their histogenesis in A gastritis.

## Methods

During the period from 2013-2015, 40 patients with PA and 20 patients of control group were examined. Histopathological examination was done in endoscopic biopsies of gastric antral and corpus/ fundic mucosa, fixed in 10% formaldehyde. Paraffin sections were stained with classic HE, histochemical (AB-PAS), cytochemical argiophilic Sevier- Munger and Grimelius methods and immunocytochemical ABC method, with antibody to gastrin for analysis antral G cells and with Chromogranin A for the detection of gastric ECL- cell carcinoids. Basal gastrin serum levels were examined by using RIA method.

## 2. Clinical and Micromorphological Features

Marked antral G cell hyperplasia (**Figure 1a**) is associated with hypergastrinemia induced by atrophic corporal autoimmune gastritis; G cells in control (**Figure 1b**) ECL-cell hyperplasia of simplex, linear (**Figure 1c**) or adenomatoid type or, type 1 ECL- cell carcinoids. Carcinoids were divided into four types [6-10]. The first three originate from the ECL cells located in the corpus /fundic gastric mucosa. These cells have been identified earlier as the histamine- containing argyrophil cells in rat gastric mucosa of the mastomas [2-6]. They are of closed type and the most numerous in the inferior third of fundic glands. However, now, there are also reports on the distribution of ECL- cell in human stomach, proved by specific cytochemical argyrophilic Sevier-Munger,s method (**Figure 1c**).

Autoimmune corpus atrophic gastritis with diffuse intestinal and pyloric metaplasia (**Figure 2**) is followed by hipergastrinaemia and by ECL-cell hyperplasia (**Figure 1c**), displasia and neoplasia.

Gastric carcinoids have been shown to be increasing [10-16]. Today, the incidence of Gcs in relation to all gastric neoplasms both benign and malignant growths, has also increased from 0.4 to 1.8% [15-18].

Type 1 Gcs accounts for 70-80% of all gastric. Gcs are developed as a result of the trophic effect of gastrin on the ECL cells [17]. These tumors are associated with autoimmune chronic atrophic gastritis. The loss of hydrochloric acid producing parietal cells leads to achlorhydria which in turn stimulates the G-cells of the antrum to produce gastrin. We have found the significant difference in serum gastrin levels between controls and pernicious anemia ( $p < 0.001$ ). Hypergastrinemia promotes the growth of the ECL cells- first resulting in hyperplasia out of which multiple ECL - cell tumors arise [17-21].

Type1 Gcs are typically multiple, usually small ( $< 2$  cm ) and because of their association with autoimmune AG occur more frequently in females aged 50 years or greater, commonly associated with  $B_{12}$  malabsorption and pernicious anemia [9-14]. Histologically, trabecular with hyalin stroma, nest and microglandulat structure, with eosinophilic cytoplasm and without nuclear atypia and mitotic activity (**Figure 3**). Immunohistochemical marked reaction with Chromogranin A antibody, has confirmed the type 1 ECL-cell carcinoid (**Figure 4**).

The majority of these tumors are benign, but metastases have been reported in 3-5 % of patients [18]. Small tumors can be removed endoscopically while larger tumors or those demonstrating invasion, require surgical excision. Ongoing endoscopic surveillance is required every six months since recurrence remains high. Somatostatin analogues have been utilized to reduce the gastrin levels and have been shown to reduce recurrences. Five-year survival rates, approaching 98% illustrate the benign nature of this type tumour.

Type 2 Gcs, like type 1, are gastrin dependent and often multifocal. These carcinoids develop secondary in the context of high gastrin hormone levels due to gastrin secreting tumor (gastrinoma or Zollinger-Ellison syndromes- CES) associated with MEN I: these patients have elevated gastric acid and present with the clinical manifestations of ZES. Type 2 gastric tumors represent 50% of gastric carcinoids and equally distributed between males and females. Histologically, they appear similar to type 1 tumors, however, their malignant potential is greater. Regional lymph nodes have been reported in up to 30% of cases and liver metastases in 10% [19]. Treatment of those tumors is focused on removal of the source of gastrin (typically a duodenal gastrinoma), together with resection of the gastric carcinoid if it is large and unable to be resected endoscopically. The 5-year survival is approximately 90% for type 2 gastric carcinoids [19].

Type 3 Gcs, or sporadic tumors, account for 20% of gastric carcinoids: they are not associated with elevated gastric levels, They are usually solitary, large (> 2 cm) and occur most frequently in male over age of 50. Regional lymph node involvement is found in up to 50% of cases and liver metastases develop in over two thirds of the patients. An ‘atypical ‘carcinoid syndrome can develop in 5 to 10% in patients with type 3 carcinoids: it is a result of histamine levels. Serum CgA serve as tumor markers and can be useful in following response to therapy. This kind of gastric carcinoid should be treated similar to the more common adenocarcinoma of the stomach, with an enblock resection and an appropriate lymph node clearance. Unfortunately, unlike type 1 and 2 carcinoid, type 3 has a 5-year survival of only 50% overall and 10% in those patients with distant metastases.

Type 4 Gcs: consist of poorly different endocrine carcinomas and mixed exocrine - endocrine carcinoids. The tumors are usually greater than 5 cm, often ulcerating and surgical unresectable. The prognosis is poor with the median survival of only 8 months reported in the literature [11]. Chemotherapy has been attempted in a limited number of patients yet the rarity of these tumor does not allow for standard therapeutic protocols.

### 3. Etiology

Role of “A gastritis” in type 1 ECL- cell carcinoid (enterochromaffin-like ECL cell carcinoid) pathogenesis:

Autoimmune gastritis is a chronic inflammatory disease with destruction of parietal cells of the corpus and fundus of the stomach. The known consequence is vitamin B<sub>12</sub> deficiency and, consequently, pernicious anemia. The ECL cells specifically produce histamine and histidine decarboxylase, which are difficult to demonstrate by immunohistochemical methods in routinely processed specimens [15]. They have been commonly labelled as “ ECL cacinoids “ although minor cell subpopulations expressing serotonin, ghrelin, gastrin, somatostatin, pancreatic polypeptide (PP), or alfa human chorionic gonadotropin (alfa- hCG) have been

detected. The rest carcinoids are : ECL cell, histamine-producing NET, EC cell , serotonin producing NET, Gastrinoma (Gastrin -producing NET), NEC and MANEC producing [15-19].

#### 4. Precursor lesions

ECL cell NETs arising in the successive stages of hyperplasia are termed simple, linear, micronodular and adenomatoid, aprgastrinaemic conditions (types I and II) develop through a sequence of hyperplasia-dysplasia-neoplasia that is well-documented [19].

#### 5. Prognosis

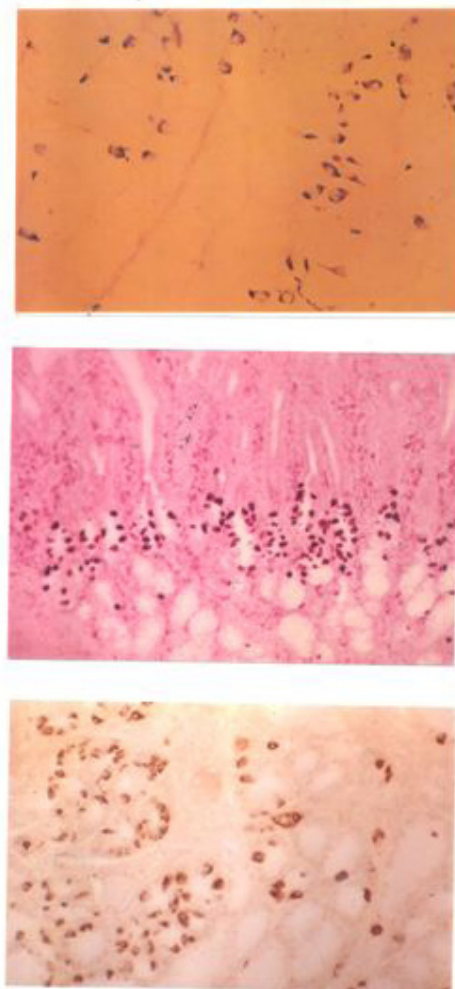
The prognosis for patients with gastric NETs is highly variable. A striking difference exists between ECL cell NETS, which are mostly indolent or low grade malignant, and NECs, which invariably high-grade malignant. In ECL cell NETS, favourable prognosis associates will growth within mucosa-submucosa, absence of angioinvasio, size < 1cm, absence of endocrine syndrome.

#### 6. Conclusion

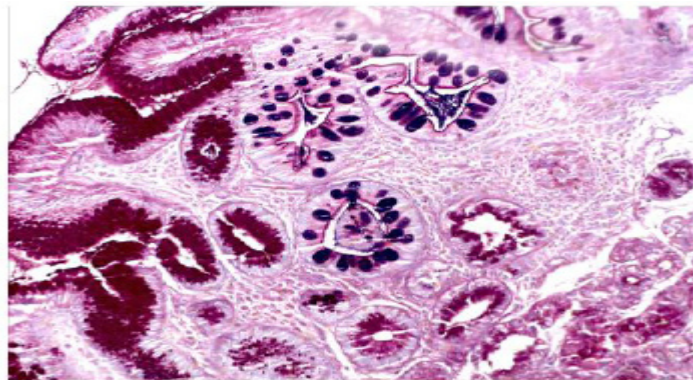
We have concluded that

- the most frequent, type 1 ECL- cell carcinoid is associated often with both autoimmune chronic atrophic A gastritis and autoimmune Hashimoto thyroiditis;
- ECL- cell carcinoid diagnosis is made incidentally on upper endoscopy;
- loss of hydrochloric acid producing parietal cells leads to achlorhydria, which in turn stimulates the G cells of the antrum to produce gastrin;
- role of gastrin in etiology of gastric cancer implies caution in the long- term treatment with inhibitors of gastric acid secretion, inducing secondary hypergastrinemia, antral G cell hyperplasia, corpus ECL-cell hyperplasia, type 1 ECL-cell carcinoids in the corpus / fundic mucosa and neuroendocrine gastric cancer;
- interest for the genesis of ECL –cell corpus / fundic carcinoids is dramatically increased, since drug Omeprazole (PROTON PUMP Inhibitor) was so commonly used;
- degree and duration of hypoacidity, as well as secondary hypergastrinemia
- determine the risk of tumor development;
- suggestion that carcinoma of diffuse type (signet ring cell type) probable originates from the ECL cells by dedifferentiation and that represents neuroendocrine carcinoma [21], is only new provocative research field for the future.

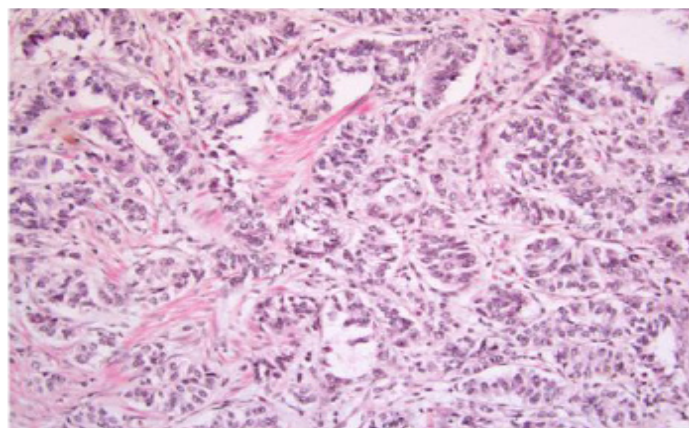
## 7. Figures



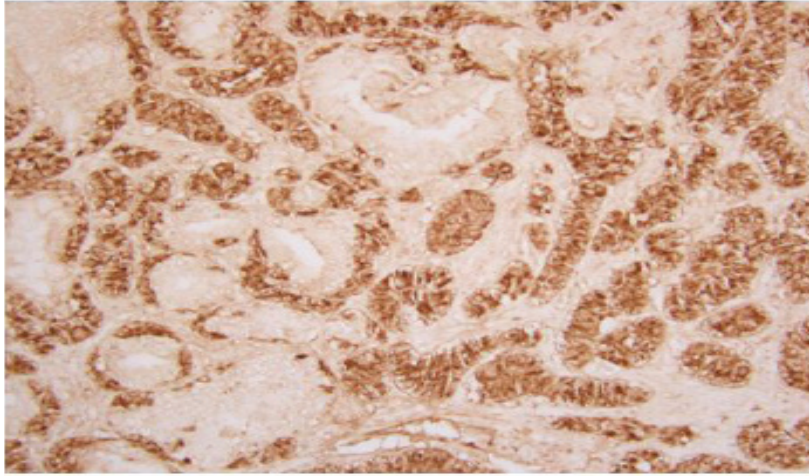
**Figure 1:** (a,b,c)\_a- adenomatoid G cell hyperplasia ( ABC x 300); b- antral G cells in control ( ABC x 200); c- linear ECL–cell hyperplasia ( Sevier-Munger x 300)



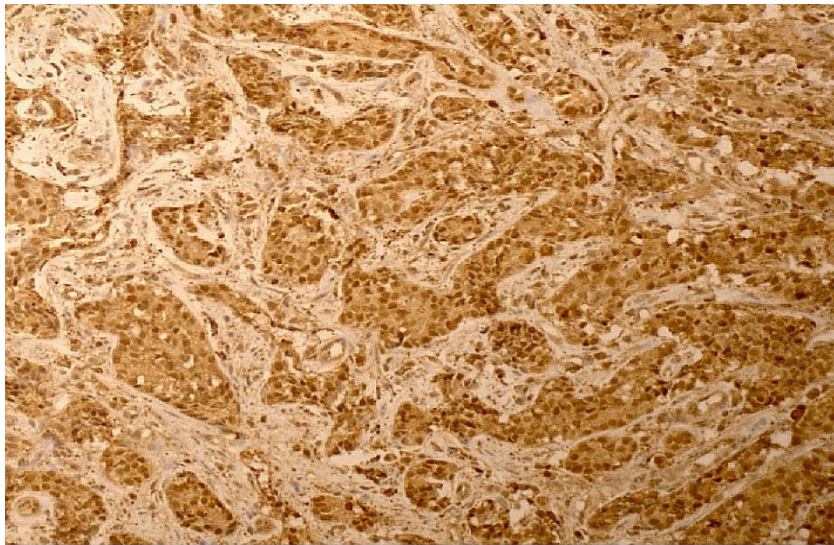
**Figure 2:** Chronic corpus/fundic atrophic gastritis with intestinal and pyloric metaplasia AB-PAS x 300



**Figure 3:** Type 1 ECL – cell carcinoid HE X 300



**Figure 4:** Strong Chromogranin A activity. ABC x 300



**Figure 5:** Carcinoid of the stomach: Submucose localisation. Grimelius x 200

## 8. References

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