

## Clinical Aspects of ECL-Cell Abnormalities

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ECL cell hyperplasia results from hypergastrinemia, and in man this occurs due to achlorhydria in atrophic gastritis (pernicious anemia [PA]) and gastrinoma (Zollinger-Ellison syndrome [ZES]). Progression to neoplasia, i.e., ECL cell carcinoids (usually small, multicentric and non-functional), occurs in some five to 10 percent of patients with PA where they remain gastrin-dependent and reversible by normalization of serum gastrin by antrectomy. Even if untreated, the carcinoids are almost invariably benign and do not cause death. In ZES, ECL cell hyperplasia is progressive due to hypergastrinemia. However, carcinoids develop only in the MEN-I subtype but pose no additional threat of malignancy. A conservative approach is recommended for small multicentric carcinoids, and the tumors do not need removal. By contrast, single, large, non-gastrin-dependent carcinoids represent a different biological and clinical problem and are frequently malignant

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### INTRODUCTION

In the last 15 years, both Enterochromaffinlike (ECL)<sup>b</sup> cell function and ECL cell neoplasia have become the object of much attention [1]. ECL function is now recognized as being central to gastrin stimulation of acid secretion via release of histamine and the control and biology of the ECL cell has been extensively studied [1]. The clinical importance of ECL cell abnormalities derive more from their neoplastic than their functional implications. Gastric fundic carcinoids were first associated with pernicious anemia over 40 years ago [2] and were considered to be a curiosity accounting for 0.3 percent of all gastric tumors [3] and with a low rate of malignancy.

Neoplasia of the ECL cells was considered to be a minor and uncommon problem until the observations that omeprazole, the most specific and potent inhibitor of acid secretion with resultant hypergastrinemia, was found to greatly increase the incidence of gastric carcinoids in susceptible rats [4-16]. Because of the therapeutic importance of omeprazole and the possibility of a similar outcome in man [4], much effort was expended in understanding the process of ECL cell neoplasia. The human counterpart of the achlorhydria/hypergastrinemia rat model, pernicious anemia (PA), was known to develop carcinoids [2], and Rubin [7] identified endocrine cell hyperplasia associated with PA in 1969. Another human hypergastrinemia condition, but with high acid secretion, the Zollinger-Ellison syndrome (ZES), was felt to be at additional risk through the long-term use of omeprazole.

Extensive observations over the last 12 to 15 years of patients treated with omeprazole, which may cause modest elevation of fasting serum gastrin [8], has laid to rest the anxiety of the tumorigenic effect of omeprazole directly or through acid inhibition [8, 9].

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<sup>b</sup> Abbreviations: ECL, enterochromaffinlike; CAG, chronic atrophic gastritis; ZES, Zollinger-Ellison syndrome; PA, pernicious anemia.

ECL cell hyperplasia leading eventually to gastric carcinoids develops in rats with prolonged hypergastrinemia of  $>1000$  ng/l ( $>1000$  pg/ml), which may be induced by long-term administration of high-dose omeprazole [13-15], potent  $H_2$ -antagonists [16-18], antral exclusion [10], antral transplantation to the colon [11] or partial resection of the gastric fundus [12]. ECL cell hyperplasia is reversible with reversal of hypergastrinemia [14], and antrectomy, which prevents hypergastrinemia, also prevents ECL cell hyperplasia during long-term administration of omeprazole [13, 14]. Therefore, gastric ECL cells appear to be under the trophic control of gastrin in rats [12]. In mice, neither ECL cell hyperplasia nor carcinoids were found with prolonged omeprazole treatment, perhaps because of lower serum gastrin levels [13].

Two states of chronic hypergastrinemia of  $>1000$  ng/l are found in humans, chronic atrophic gastritis (CAG) and ZES. ECL cell hyperplasia is common both in CAG type A or pernicious anemia [19-21] and in the ZES, in which it is less often micronodular [22-24]. Gastric carcinoids, which are thought to evolve later [23], occur in up to five percent of patients with CAG [19-21] but rarely in ZES syndrome [24-28] and are then associated almost exclusively with multiple endocrine neoplasia [29]. In pernicious anemia, gastric ECL carcinoids are usually multicentric and occur in the gastric body and fundus. Earlier data suggested that a proportion of such tumors were potentially malignant [20, 22, 30], and before the present level of understanding, some authors recommended total gastrectomy [28, 31, 32]. This approach is now inappropriate, as the CAG-associated gastrin dependent carcinoids rarely, if ever, cause death [33].

Unlike the functional aspect of ECL tumors in *Mastomys* [1], where the oversecretion of histamine by the ECL cell tumors has even more deleterious effects than the malignancy, ECL cell proliferation and tumors (carcinoids) in man are overwhelmingly non-functional. The problem then is to place the neoplasia in a clinical perspective.

ECL cell proliferation and progression to dysplasia and then neoplasia [1, 5] offers the framework for classifying and understanding the clinical approach.

ECL cell hyperplasia occurs under several conditions of hypergastrinemia:

1. CAG [5, 34], mostly associated with pernicious anemia (PA) (CAG type A) [30, 34, 35], but also with non-PA atrophic gastritis (type B) [36].
2. Zollinger-Ellison syndrome, but almost exclusively in the MEN-I subset [37-39].
3. Patients treated long-term with omeprazole at doses that strongly suppress acid secretion [9].
4. Patients with *Helicobacter pylori* infection, especially those with long-term proton pump inhibitor acid suppression [40].

It is now felt that only patients in categories 1 and 2 (CAG, especially type A) and (ZES with MEN-I) may progress to dysplasia and may develop carcinoids, whereas in proton pump inhibitor therapy with or without *H. pylori* infection, ECL cell proliferation does not progress beyond the stage of hyperplasia or pseudohyperplasia [8] to dysplasia, and the risk of carcinoid evolution is virtually nonexistent [9].

Gastric carcinoid tumors may also develop in the absence of hypergastrinemia and these represent a more serious outcome [36, 41] and an entirely different therapeutic approach. These tumors are to be differentiated from the neuroendocrine carcinomas.

Based on improved histological and immunohistological criteria, several classifications of neuroendocrine tumors in the stomach have been presented [3, 5, 23, 36, 38], their precursor lesions identified [3, 33, 36], and their significance and natural history related to their background. These new perspectives have clarified and superseded the older literature [e.g., 42].

## CARCINOIDS ARISING IN CHRONIC ATROPHIC GASTRITIS

The majority of gastric carcinoids in man occur with CAG. Of the CAG cases with carcinoid up to 90 percent of the A type [5, 8, 36], i.e., secondary to PA and associated with hypergastrinemia [5, 34, 43] and precursor changes, hyperplasia and dysplasia, in the fundic mucosa [41]. These tumors are well differentiated [3], small (<10 mm) and in 80 percent are multiple [3, 5]. In one study [3], two-thirds were mucosal, only one-third sub-mucosal and none were invasive or metastatic, and in these and other series [5, 36, 41] none died of tumors. Only three of 91 cases collected by Solcia et al. [23] showed distant metastases from CAG-related carcinoid. Associated lesions in CAG type A include gastric carcinoma (up to 10 percent [41]), and antral hyperplastic polyps, which may cause chronic blood loss and may occur in as many as 20 percent of patients with carcinoids (personal observation). On the basis of such observations, a conservative or semi-conservative approach (see below) seems justified. Further support for a conservative stance comes from the observations of spontaneous regression of tumors in small numbers of patients for varying periods [44].

Based on the evidence that gastric carcinoids are the result of a hypergastrinemia and that reversal of a hypergastrinemia by antrectomy, at least in rats, resulted in reversal of carcinoids [14], such a surgical approach has been used in patients with CAG type A and multicentric small carcinoids. We have followed three patients for seven to eight years since antrectomy, which normalized gastrin. All showed rapid regression within six weeks of the carcinoids [35] and, except for one transient recurrence of a small carcinoid in two of the patients at one year, both of which resolved spontaneously, no further tumors have recurred, and all three now show only at most residual linear or nodular ECL cell hyperplasia. Similar results have been reported by Olbe et al. [45], Richards et al. [46], Solcia [47], Caruso [48], Sjoblom [49] and Kern [32]. By contrast, Eckhauser et al. [30] reported two cases, one of whom had a liver metastasis resected and the other a regional lymph node; in both, antrectomy normalized serum gastrin. The second patient had a gastric carcinoid recurrence at four to six months, while the first was free of tumor. In another case [51] with normalization of serum gastrin by antrectomy, multiple carcinoids developed after 23 months. However, that patient was secreting acid (MAO 6.8 mmol/hr) and the background was not apparently not CAG-type A (pernicious anemia). The case is thus not clear.

Because of the low risk of tumor invasion and death from metastatic tumor [33, 41] carcinoids may be approached on the basis of background disease, tumor size and age of the patient. Patients older than 65 or 70 should probably be watched expectantly if initial evaluation shows (multiple) small tumors. In younger individuals, it is reasonable to recommend antrectomy [5, 32, 35, 45, 47-49, 53] with expectation of long-term cure. Solitary tumors greater than 1.5 cm should be excised.

If the sequence of the gastrin-dependent development of carcinoids is hyperplasia → dysplasia → neoplasia (i.e., carcinoid) and neoplasia is defined as tumor progression beyond the point at which the ECL proliferation becomes independent of gastrin [1], then one would expect none of the gastric carcinoids to regress after normalization of the gastrin. Yet, 80 to 90 percent of cases reported have regressed permanently with normalization of gastrin after antrectomy. Is the definition of neoplasia then still valid, or are there stages of carcinoid (e.g., defined by size, or cell characteristics) in which carcinoids are irreversible?

The cost/benefit of screening CAG type A by endoscopy for tumors, including carcinoma, is discussed by Borch [19]. In patients with known carcinoids, follow-up endoscopy at one to two year intervals is advisable because of possible associated lesions such as carcinoma [41], though no one has suggested that carcinoids are a marker for the development of carcinoma in the same stomach.

The role of gastrin in promoting hyperplasia of ECL cells clearly follows from the physiological principle [45] that an agonist may cause both secretion and proliferation of the target cell [43]. For most such agonists, these two actions are mediated by receptors of differing affinity, and this is also true of the effect of gastrin on ECL cells [52]. An additional mechanism that could be involved in the apparent hyperplasia of ECL cells in hypergastrinemic CAG (i.e., PA) or in ZES-MEN-I is the prolongation of life span of the cells [5]. Such a prolongation may result from inhibition of apoptosis as previously suggested [43]. Several candidate oncoproteins, e.g., myc [53] or BCL-2, are possible. BCL-2 has been reported to be increased in ZES-MEN-I and increased more in CAG type A, both conditions in which proliferation, atypia and neoplasia occur with intermediate and high risk, respectively [54]. By contrast, in ZES (not MEN) BCL-2 is normal [54].

Withdrawal of gastrin would then be expected to reverse the process, and evidence of apoptosis should be sought in stomachs shortly after antrectomy. Experimentally this could be tested in rats being treated with omeprazole [14].

A small proportion of apparently well-differentiated carcinoids in CAG type A stomachs are larger (1.6-2 cm) and locally invasive [3, 5, 23]. It is not clear how these would behave with antrectomy alone and may in fact represent the cases that did not regress [30, 55] because they had progressed beyond gastrin dependence [1]. It is also unclear whether the larger tumors represent a different subset or an unusual growth of one or more multicentric tumors, which by my observations and those of others [23, 44] rarely change from year to year. Because of the complexity of morphology of endocrine cell tumors, it is not always clear from published data that the exact cell type makeup of questionable tumors was known, especially in the older literature. Some may in fact be neuroendocrine carcinomas [5]. Such cases would obviously not be expected to benefit from antrectomy.

### GASTRIC CARCINOIDS ASSOCIATED WITH ZES

With the hypothesis in hand that hypergastrinemia causes carcinoids, as appears clear from the rat data [10-17] and from the case of the hypergastrinemic CAG with PA, it was expected that the high gastrin levels in patients with ZES would cause carcinoids to develop. In fact, ECL cell density in ZES is higher (i.e., ECL cell hyperplasia) than in controls and duodenal ulcer, even in those DU patients with acid secretion in the ZE range [5, 9, 56-58] and carcinoids do occur in patients with ZES [24-28]. However, it is now apparent that the carcinoids that do develop in ZES are almost exclusively seen in the MEN-I subtype [2, 38, 59]. Cadiot [39] reported that five of 17 cases (30 percent) with MEN-I had carcinoids, compared to none of 31 with sporadic ZES. Solcia et al. [3] have collected 19 such cases and describe the whole spectrum from simple hyperplasia to invasive tumor. Two of 6 cases reported by Rindi et al. [29] had lymph node spread, but no patient died of ECL carcinoid in follow-up. These carcinoids do not require special intervention. Rarely carcinoids may be found in MEN-I without the ZES component [23].

The probable basis for carcinoid development is not, therefore, hypergastrinemia alone [3] but the possible loss of one or more tumor suppressing genes in MEN-I [60] with the result of abnormal secretion by EC or ECL cells [3] of growth factors like gastrin or  $\beta$ -fibroblast growth factor [1], which is abnormally elevated in patients with MEN-I [61, 62].

It has been suggested that *H. pylori* may contribute to ECL cell proliferation, perhaps through a mechanism demonstrated *in vitro* showing stimulation of ECL cells and proliferation by *H. pylori* lipopolysaccharide [63], especially with hypergastrinemia or acid suppression by lansoprazole [40]. We have re-examined this question in hypersecretors (BAO > 15 meq/hr), both ZE (n = 31) and non-ZE (n = 12) and found that infection with *H. pylori* had no effect on ECL cell counts before or after up to seven years of lansoprazole

treatment to control acid secretion, and following a pre-treatment history that averaged over 12 years, i.e., over a probable time-span of nearly 20 years [58]. Only one instance of carcinoid was found, a ZE MEN-I patient (one of four such patients, 25 percent), who was also *H. pylori*-negative.

### SPORADIC ARGYROPHIL CARCINOIDS

These generally single tumors arise in the gastric body mucosa in patients with normal serum gastrin and are, thus, different from the generally multicentric small benign carcinoids seen in CAG and ZES-MEN-I [3, 36, 38, 41, 64]. These tumors represent 13 percent of the gastric endocrine tumors reported by Solcia et al. [3, 36] and by Bordi et al. [41]. They differ in other respects as well, being generally larger (median 2 cm diameter) with a distinct tendency to invasion [3] and metastasis which is generally size-dependent [64], features absent in gastric-dependent carcinoids [3]. Fewer than 10 percent of single tumors <1 cm metastasized vs. 66 percent of tumors >3 cm [42]. Invasion into deeper gastric layers, vessels or lymphatics indicates aggressive behavior and poor prognosis. Those with atypical morphology tend to be larger (>3 cm) and have poorer prognosis (5-year, 20 percent survival vs. 79 percent of the remainder [64]). The dominant cell type in these tumors are also ECL cell type. The tumors are generally non-functional with some tumors containing EC, X and G cells; occasionally an atypical carcinoid syndrome may be seen when the tumor metastasizes to liver [3]. These isolated, non-gastrin-related carcinoids thus have features in common with neuroendocrine carcinomas [36], unlike the gastrin-dependent carcinoids should, thus, be treated aggressively by surgical removal [1, 41]. Local invasion or deep penetration may be estimated by endoscopic ultrasound, which should be supplemented by CT scan and detailed immunohistochemical and electron microscopic analysis of the tumor. Once metastasized, prognosis is very poor [1] and the options more limited with removal if possible of metastases and symptomatic treatment of carcinoid syndrome with octreotide as needed.

### CONCLUSION

Much has been learned in recent years about the ECL cell and its role in acid secretion. How the ECL cell and the six or more other types of gastric mucosal endocrine cells affect gastric physiology, growth or repair remains obscure. Thus, the role of pancreostatin, gastrin, somatostatin and growth factors such as TGF $\alpha$  and gastrin-releasing peptide, as well as currently unknown functions of gastrin and histamine are still conjectural [1].

The causes and course of hyperplasia, dysplasia and progression to neoplasia are incompletely understood [1], particularly in man. The progression from hyperplasia to dysplasia to neoplasia appears to occur only or nearly only in limited cases of hypergastrinemia—CAG, especially type A and ZES-MEN-I. *H. pylori* appears irrelevant in this context, as does treatment with proton pump inhibitor.

The progression to neoplasia is more clearly defined in *Mastomys* as defined by gastrin independence [1, 65]. It is unclear whether the same occurs in man. In the one model, CAG type A, reversal of hypergastrinemia results in regression of carcinoids in nearly all cases. Further evaluation of the biology of the tumors that fail to respond appears warranted. The relatively low level of malignancy and absence of function allows one to adopt a conservative approach to multicentric small carcinoids that are the rule. The solitary non-gastrin-dependent large carcinoid, however, does not in the first place fit the gastrin model and is clearly a different biological and clinical problem.

*Acknowledgement: I am grateful to Ms. Deddie Poe for typing the manuscript.*

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