Gastric carcinoids: Review a propos of two cases

C. Christopoulos¹³, E. Papavassiliou², V. Dimakopoulou¹, P. Economopoulos¹³

SUMMARY

Gastric carcinoids are neoplasms originating from the endocrine cells of the gastric wall and represent less than 1% of all gastric tumours. Their frequency appears to be rising in parallel with the increasing use of upper gastrointestinal endoscopy and the development of techniques for specific immunohistochemical study of gastric biopsies. The pathophysiological classification of gastric carcinoids into three types is clinically useful. The majority (75-80%) belong to Type I, which is associated with chronic atrophic gastritis type A. They develop as a response to chronic hypergastrinaemia, causing sequentially hyperplasia, dysplasia and neoplasia of the ECL (enterochromaffin-like) cells. They follow a benign clinical course and only exceptionally metastasize. Type II carcinoids (5-13%) are also associated with hypergastrinaemia and develop in patients with the Zollinger-Ellison syndrome as part of multiple endocrine neoplasia type 1 (MEN1). They have a slightly higher malignant potential than type I carcinoids. Type III includes the sporadic gastric carcinoids (14-25%) which are invasive tumours with metastases often present at the time of diagnosis. They are not associated with hypergastrinaemia and require more aggressive surgical treatment than types I and II. We review the current management approaches and report two cases of gastric carcinoids, one demonstrating that classification of these tumours is not always straightforward and the other highlighting the importance of extensive endoscopic sampling in the setting of multiple gastric polypoid lesions.

Key words: carcinoid, neuroendocrine tumour, gastric tumour, gastric polyp, atrophic gastritis, enterochromaffin-like cells, gastrin, gastrinoma

INTRODUCTION

Carcinoids are tumours originating from neuroendocrine cells of the gut, bronchial tree or thymus.¹² Lubarsch (1888)¹ is credited with the first detailed description of such tumours in the gastrointestinal tract (ileum) while Ranson (1890)³ described a patient with a tumour of the terminal ileum, hepatic metastases, diarrhoea and postprandial exacerbation of dyspnoea. In 1907, Oberndorfer introduced the term "carcinoid" (Karzinoid) to contradistinguish the more benign course of these rare tumours from that of the much commoner adenocarcinomas.³ Their incidence is estimated at 1-8.4 cases per 100,000 persons per year.⁶ The majority (67.5-73.7 %) are located in the alimentary tract, followed by the lungs.⁸,⁹

Gastric carcinoids can stem from any of the various neuroendocrine cells (Table 1), which constitute 1-2% of all epithelial cells of the stomach.¹⁰-¹² The majority (80%) originate from enterochromaffin-like (ECL) cells, the dominant gastric neuroendocrine cells, found mainly in the fundus and body of the organ.¹³-¹⁶ The first two cases were described by Askanazy in 1923¹⁷ and for a long time they were considered extremely rare tumours. In 1961, Christodoulopoulos and Klotz listed 79 cases published in the international literature,¹⁸ while by 1979 the number had risen to about 100.¹⁹ Their diagnosis was usually delayed and was often made at autopsy.¹⁹ The advent of endoscopy, in association with the development of more sophisticated techniques for pathological evaluation of gastric biopsies was followed by a rise in the relative frequency of gastric carcinoids.¹⁹ This varies significantly among published series, fluctuating between 3% and 41% of all gastrointestinal tract carcinoids.¹⁶,¹⁸,¹⁹,²¹,²²
Table 1. Neuroendocrine cells in the human stomach.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Main Location</th>
<th>Secretory product</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECL</td>
<td>Fundus-Corpus</td>
<td>Histamine</td>
<td>30-50</td>
</tr>
<tr>
<td>EC</td>
<td>Antrum</td>
<td>Serotonin</td>
<td>10</td>
</tr>
<tr>
<td>G</td>
<td>Antrum</td>
<td>Gastrin</td>
<td>30</td>
</tr>
<tr>
<td>D</td>
<td>Antrum</td>
<td>Somatostatin</td>
<td>20</td>
</tr>
<tr>
<td>A</td>
<td>Fundus-Corpus</td>
<td>Glucagon</td>
<td></td>
</tr>
<tr>
<td>X (A-like)</td>
<td>Fundus-Corpus</td>
<td>?Endothelin</td>
<td></td>
</tr>
<tr>
<td>?P/D1</td>
<td>Fundus-Corpus</td>
<td>?Ghrelin</td>
<td></td>
</tr>
</tbody>
</table>

ECL: Enterochromaffin-like cell, EC: enterochromaffin cell

Nevertheless, they remain generally rare, representing less than 1% of all gastric neoplasms. In this article we review the literature with the emphasis on the management of patients with gastric carcinoids, and present two cases highlighting possible pitfalls in the diagnosis and classification of these rare tumours.

CLASSIFICATION AND PATHOGENESIS

The considerable confusion in the literature regarding the classification of gastric carcinoids reflects the lack of an established classification system for carcinoids in general. So, the historic term “carcinoid” has been used loosely to describe a wide variety of tumours with neuroendocrine character, irrespective of anatomical site, histological grade of malignancy and clinical behaviour. The division, according to embryological origin, into foregut, midgut and hindgut carcinoids is of limited clinical use because it does not correlate well with the clinical behaviour and prognosis. In an effort to formulate a prognostically meaningful classification, Capella et al. proposed the division of neuroendocrine tumours (NET) into “well-differentiated NET” and “neuroendocrine carcinomas”. According to this classification, which was subsequently endorsed by WHO, the term “carcinoid” should be reserved only for well-differentiated neuroendocrine tumours of the stomach, bowel, bronchial tree and thymus, while the neoteric terms “malignant carcinoid” and “atypical carcinoid” were introduced for the description of well-differentiated neuroendocrine carcinomas at these anatomical sites.

Gastraic carcinoids are divided into two broad categories: gastrin-dependent, associated with hypergastrinaemia, and non-gastrin dependent or sporadic. Gastrin-dependent carcinoids are further subdivided into two groups: those associated with chronic atrophic gastritis type A (CAG-A) and those associated with the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1 (MEN1).

Carcinoids associated with CAG-A, also known as Type I gastric carcinoids, are the commonest (79.6%). Hypergastrinaemia is thought to be the main pathogenetic factor in this type of tumour. High gastrin levels lead to hyperplasia – dysplasia and finally neoplastic transformation of the histamine-secreting ECL cells of the gastric mucosa. This hypothesis is based on the observation of gastric carcinoids developing in laboratory animals with omeprazole-induced hypergastrinaemia. It should nevertheless be noted that no such lesions have been observed in man, despite prolonged use of proton-pump inhibitors. It appears that some genetic factor, possibly related to mutations of gene Regl-Æ also plays a role. The assumed physiological function of this gene is the suppression of ECL cell proliferation in response to gastrin.

Type I carcinoids:
- are usually diagnosed in older patients (mean age 63 years), mostly women (71%) and are often discovered during endoscopy for investigation of anaemia or abdominal pain,
- are usually multiple (in >50% of cases and small (usually <1 cm), and appear as polypoid lesions, occasionally with central ulceration,
- are located in the body and fundus of the stomach, and do not extend beyond the submucosa,
- are often asymptomatic and only rarely metastasize (2-14% of those larger than 2 cm, mainly to lymph nodes),
- are usually associated with pentagastrin-fast achlorhydria and hypergastrinaemia,
- are often associated with pernicious anaemia.

In view of the known association of pernicious anae-
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with malignant clinical behaviour, 59 – often metastasize 28,30 (>60% at time of diagnosis 16), – are not associated with hypergastrinaemia or specific clinical manifestations, apart from rare cases presenting with atypical carcinoid syndrome thought to result from histamine production.16,43
– are more common in men (75%), 16,27
– develop in middle-aged persons (mean age 53), 27 and
– contain ECL cells and a variety of other endocrine cells16,27 and often produce serotonin. 41

It is thought that a complex genetic background is involved in their pathogenesis, which does not involve hypergastrinaemia. Abnormalities of p53 and other genes have been implicated. 34

In view of its aggressive nature and significant mortality,27,60 this type of carcinoid should be treated with partial or total gastrectomy 52,43 (Figure 1).

The main characteristics of the three types of gastric carcinoids are summarised in Table 2.

CLINICAL MANIFESTATIONS

Epigastric pain, vomiting, upper gastrointestinal haemorrhage and iron deficiency anaemia are common clinical manifestations of symptomatic gastric carcinoids,29,40 although in the majority of cases these tumours represent incidental endoscopic findings. The clinical picture depends on the size and location of the tumour, its secretory products, the presence of hepatic metastases and the coexistence of associated conditions (e.g. pernicious anaemia and other autoimmune disorders in Type I carcinoids, ZES and MEN1 manifestations in Type II carcinoids). Large tumours (usually Type III carcinoids) can present with symptoms of gastric outlet obstruction.81

In contrast to small bowel carcinoids, development of the typical carcinoid syndrome is unusual (5%).18 Atypical carcinoid syndrome manifesting as episodic flushing due to histamine release can occur in Type III (sporadic) carcinoids.16 Isolated cases of ectopic ACTH production by gastric carcinoids manifesting as Cushing’s syndrome have also been described.82-64

DIAGNOSIS AND STAGING

The diagnosis is usually made by endoscopic biopsy. The tumours appear as submucosal masses or small, yellowish (a result of cholesterol and lipid accumulation
within the tumour) polypoid protuberances, occasionally with a central erosion or ulceration. Because of their submucosal location, a standard biopsy may be insufficient to obtain adequate diagnostic material, and a partial polypectomy with endoscopic snare excision or a ultrasonographically guided needle biopsy are preferable. It is also rewarding to take biopsies from the surrounding gastric mucosa in order to confirm or exclude the presence of atrophic gastritis.

Microscopy reveals the typical appearances of foregut carcinoid consisting of monomorphic, small or medium sized, round or polygonal cells with variably eosinophilic cytoplasm and uniform, central, round nuclei with fine chromatin pattern, small nucleoli and absent or scanty mitoses. Features of cellular atypia are present in Type III carcinoids and include nuclear polymorphism,
Measurement of plasma gastrin levels allows the differentiation of gastrin-dependent (Types I and II) from sporadic (Type III) gastric carcinoids. Hypergastrinaemia in the absence of evidence of CAG-A requires further investigation in the direction of ZES-MEN1, including a secretin-provocation test.

Staging begins with the assessment of the depth of gastric wall infiltration. This can be achieved in 90% of cases with endoscopic ultrasound (EUS), while the same technique allows detection of infiltrated perigastric lymph nodes in 75% of cases. Information about both gastric wall infiltration and extragastric extent of disease can also be obtained by CT, which has a reported sensitivity of 87% in hepatic metastases detection, and MRI. Modern CT-based imaging techniques like dedicated multi-detector CT of the stomach allow high-quality multiplanar reformation and three-dimensional reconstruction of gastric images and are promising, high sensitivity tools to be used as an adjunct to endoscopy for preoperative staging. Positron emission tomography (PET-scanning) can be helpful and has been used for diagnosis and follow-up of carcinoid tumors but experience with this method remains limited.

Carcinoids are usually rich in somatostatin receptors, Table 2. Main characteristics of gastric carcinoids. Modified from Modlin IM, Lye KD, Kidd M.

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>68-83 %</td>
<td>5-13 %</td>
<td>14-25 %</td>
</tr>
<tr>
<td>Mean age</td>
<td>63 years</td>
<td>45-50 years</td>
<td>49-53 years</td>
</tr>
<tr>
<td>Sex</td>
<td>F:71 % F:M=2:3:1</td>
<td>F:M=1:1</td>
<td>F:M=1:3</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Fundus or body</td>
<td>Fundus</td>
<td>Antrum or fundus</td>
</tr>
<tr>
<td>Tumor characteristics</td>
<td>Usually multicentric, polypoid</td>
<td>Usually multicentric</td>
<td>Single, solitary</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Usually &lt; 1</td>
<td>&gt; 1 cm (usually 1-2 cm)</td>
<td>&gt; 1 cm (usually 2-5 cm)</td>
</tr>
<tr>
<td>Histopathology</td>
<td>ECL cell lesion; progression: hyperplasia to dysplasia to neoplasia</td>
<td>ECL cell lesion; progression: hyperplasia to dysplasia to neoplasia</td>
<td>Any gastric endocrine cell without preneoplastic status, lesion normal adjacent mucosa</td>
</tr>
<tr>
<td>Biological behavior</td>
<td>Slow growth; rarely metastasizes (2-14%)</td>
<td>Slow growth; may metastasize (30% lymph nodes, 10% distal)</td>
<td>Relatively aggressive; frequent metastases to regional nodes (55%) and liver (24%)</td>
</tr>
<tr>
<td>Coexistent diseases</td>
<td>Autoimmune diseases (thyroiditis, Addison’s disease, diabetes, pernicious anaemia, vitiligo, rheumatoid arthritis)</td>
<td>MEN-1 (Manifestations from pituitary, parathyroid glands, and endocrine pancreas)</td>
<td>Non-specific clinical manifestations. Rarely atypical carcinoid syndrome</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Often asymptomatic</td>
<td>Possibly manifestations of MEN-1 syndrome</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma gastrin level</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Gastric acid output</td>
<td>Low or absent</td>
<td>High</td>
<td>Normal or low</td>
</tr>
<tr>
<td>Secretin test</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

prominent nucleoli, slight increase in mitotic activity and small areas of necrosis. Occasionally entirely different cell types, e.g. plasmacytoid, spindle-shaped and poorly differentiated cells may be present, making difficult the differential diagnosis from other tumours, including lymphoma, leiomyoma, hamartoma or carcinoma. The tumour shows various patterns of growth including trabecular or ribbon-like with anastomosing features, solid, nodular or insular cords, nest, rosette-like or pseudoglandular formations or any combination of the above. The majority are confined within the mucosa and submucosa but more aggressive tumours can infiltrate the muscularis propria and serosa, expanding to the mesentery. Local lymph node metastases as well as distant metastases, mainly to the liver can also be present at the time of diagnosis.

Histochemically gastric carcinoids are argentophilic. Nowadays staining with silver salts is only of historical interest as it has been superceded by immunostaining with antibodies to a variety of molecules contained in the neuroendocrine granules of carcinoid tumours. Among them, staining for Chromogranin-A is the most useful, being positive in practically all cases, followed by synaptophysin and neuron-specific enolase.
mainly of subtype 2 (SSTR2), for which octreotide, a synthetic somatostatin analogue, has high affinity. Scintigraphy with radioactively labeled (indium-111 diethylenetriamine pentaacetic acid) octreotide (In-111 DTPA Octr), or OctreoScan, is a sensitive and specific tool enabling not only the mapping of regional and distant metastases but also the intraoperative detection of neuroendocrine tumours using hand-held gamma cameras. OctreoScan has now displaced the previously popular but of low specificity iodine-131 metaiodobenzylguanidine (MIBG) scanning. An other alternative to somatostatin receptor scintigraphy (SRS) is immunoscintigraphy, which employs monoclonal antibodies to chromogranin-A and can be used for diagnostic and staging purposes, especially in cases of tumours poor in somatostatin receptors. Plasma Chromogranin-A is the most useful peptide marker in the diagnostic work-up and the follow-up after treatment of gastric carcinoids, while urinary 5-HIAA measurement is not helpful in view of the low serotonin content of foregut carcinoids.

**TREATMENT**

Due to the rarity of these tumours, evidence from large, randomized studies is lacking and the recommendations are based on small, uncontrolled series. As mentioned above (see discussion of individual carcinoid types in the classification section), endoscopic or surgical resection is the initial approach in all types of gastric carcinoid. Surgery is the only potentially curative treatment for patients with carcinoid tumors in general, and this applies even in the presence of metastases. In the case of metastatic gastric carcinoid, gastric surgery has the additional theoretical advantage of ameliorating hypergastrinaemia, which represents the main trophic stimulus for many of these tumours. An algorithmic description of the recommended management of patients with a newly diagnosed gastric carcinoid is presented in Figure 1.

All patients with gastric carcinoids will need regular, life-long follow-up, the kind of which may vary depending on the initial treatment. It may include endoscopy, measurements of plasma levels of markers of disease activity and a range of imaging methods, most notably the highly sensitive SRS. It is important to avoid depending on one modality alone to assess disease status. For example, falsely negative SRS can occasionally be a result of either down-regulation of SSTR on carcinoid cells following administration of steroids, chemotherapy or prolonged courses of somatostatin analogues or the emergence of clones of tumour cells lacking somatostatin receptors. It should also be noted that, beside monitoring the original tumour, follow-up should include thorough screening for common cancers (colon, breast, lung, prostate), as it is known that synchronous or metachronous second malignancies occur commonly in patients with gastrointestinal carcinoids.

The detection of metastatic carcinoid should not be seen as a catastrophic event, in view of the fact that many of these tumours are slow-growing and patients can remain asymptomatic for years. A period of observation may therefore allow for a decision to be made concerning optimal supportive care or more specific antitumour treatments. On the other hand, it is becoming increasingly apparent that an appreciable percentage of the tumours are more aggressive, necessitating the development of effective treatment protocols. The approach to the treatment of metastatic gastric carcinoid is generally similar to that of the much commoner metastatic intestinal carcinoid.

The advent of somatostatin and its analogues has generated new prospects for medical treatment of SRS-positive metastatic carcinoid. Somatostatin is a 14-aminoacid peptide that inhibits the secretion of growth hormone and most gastrointestinal hormones by binding to G-protein-coupled transmembrane receptors (of which there are 5 subtypes, SSTR1-5). Octreotide, a 8-aminoacid long-acting somatostatin analogue has a plasma half-life of 1.5-2 hr and acts by binding mainly to SSTR2. Other long-acting analogues are lanreotide and the more recently introduced octreotide acetate. Octreotide at low doses was used in the 1980s for symptomatic control of carcinoid syndrome and it was later realized that these analogues given at higher doses might also retard carcinoid tumour growth. Ferraro et al showed that administration of octreotide controlled the growth of ECL cells in the setting of atrophic gastritis-related hypergastrinaemia. Other investigators have shown that somatostatin analogues could induce regression of both hypergastrinaemia-related and sporadic gastric carcinoid tumours. It therefore appears that somatostatin analogues are well suited for the management of metastatic gastric carcinoid, as they exert inhibitory action on both the trophic stimulus (gastrin) and the tumour itself. These agents have an excellent safety profile but cannot be used in children for fear of stunt linear growth, which is a major adverse effect. Other adverse effects include steatorrhea, which may require pancreatic enzyme replacement, and development of
gallstones. Local irritation at the site of injection is a common complaint. Some therapeutic regimens have successfully combined somatostatin analogues with interferon, an immunomodulating agent shown to benefit some patients with advanced carcinoid tumours even when used as monotherapy.

Receptor-targeted therapy with a radioactive isotope attached to a somatostatin analogue or MIBG, is currently being used on an experimental basis in patients with unresectable tumours. Encouraging preliminary results have been reported with $^{111}$In-labelled octreotide, $^{123}$I-labelled MIBG and $^{90}$Yttrium-labelled octreotide.

Various chemotherapeutic agents alone or in combination have been employed for treating metastatic carcinoids. Most protocols have included classical cytotoxic drugs like 5-fluorouracil (5-FU), streptozotocin, anthracyclines, alkylating agents, cisplatin and etoposide, but the results in general have been poor, as is the case with slow-growing, well-differentiated tumours. Selecting the most effective chemotherapy for the individual patient by means of drug resistance testing on cells cultured from tumour biopsies, is a promising technique currently under investigation.

Many aggressive approaches have been applied to the treatment of hepatic metastases, ranging from simple resection of isolated lesions to liver transplantation. Successes have also been reported with radiofrequency ablation and hepatic artery chemoembolization, while multimodality treatment protocols are becoming increasingly popular. Finally, irradiation should be considered in cases with metastatic bone or CNS disease.

**CASE REPORTS**

**Case 1**

A 66-year-old man with recurrent upper GI bleeding underwent oesophago-gastro-duodenoscopy, which revealed the presence of a small (<1 cm) polypoid lesion in the body of the stomach near the antrum, without signs of bleeding. Histology of the endoscopically excised polyp was compatible with a carcinoid, showing mucosa and submucosa infiltration by tumour consisting of small, uniform cells with regular, normochromatic nuclei and scanty mitoses, forming microglandular, trabecular and insular patterns. Tumour cells were immunoreactive for chromogranin-A, synaptophysin, neuron-specific enolase and gastrin. Because of continuing melaenas, the patient underwent surgery leading to the discovery and resection of an ulcerated leiomyoma of the jejunum, to which the GI bleeding was eventually ascribed. Laboratory investigations including biochemical profile, 24-hour urinary 5-HIAA estimation and computerized tomograms of the abdomen were within normal limits. Seven years later the patient was remaining in excellent health, although endoscopic ultrasonographic examination of the stomach was showing a 6.9 x 5.3 mm hypoechoic submucosal lesion at the site of the originally excised carcinoid, with no perigastric lymphadenopathy. There was associated hypergastrinaemia at 557 pg/ml (normal range 0-110 pg/ml) with no evidence of either atrophic gastritis (normal histology and serum B12 levels, absent autoantibodies to parietal cells and intrinsic factor) or MEN1 syndrome (normal hormonal profile and CT imaging) and therefore a tentative diagnosis of sporadic, gastrin-producing NET of the stomach was made. In view of the small tumour size and absence of invasiveness, no further action was undertaken beyond close endoscopic monitoring.

**Comment:** Classification of gastric carcinoids based on the presence (Types I and II) or absence (Type III) of hypergastrinaemia can be difficult in the exceptional case of a sporadic, gastrin-producing, gastric NET. It should be noted that, although sporadic gastric carcinoids are usually comprised of ECL cells, they often exhibit a mixed cell population including gastrin-positive cells, the significance of which is unclear. The finding of high levels of expression of precursor and mature gastrin peptides in gastric carcinoids, together with the gastrin receptor, suggests that these tumours express the gastrin autocrine-paracrine pathway and could explain why some carcinoids do not regress after surgical procedures that lower serum gastrin.

**Case 2**

A 41-year-old female was referred for upper GI endoscopy during the course of investigations for incidentally discovered iron deficiency anaemia. She had a history of a radiologically diagnosed duodenal ulcer, for which she was taking omeprazole and was asymptomatic at the time of the examination. Endoscopy revealed the presence of multiple friable polyps, sized 0.2-1.5 cm, in the fundus and body of the stomach, while the surrounding mucosa appeared normal. Histological examination of the biggest (maximal diameter 1.5 cm) of four endoscopically removed polyps was compatible with a hyperplastic/regenerative gastric polyp with no evidence of neoplasia. Examination of the other three polyps (maximal diameter 0.4 cm) showed infiltration of the mucosa and submucosa by tumour consisting of small,
uniform cells with a trabecular or glandular pattern of growth and mild cellular atypia. Mitoses were less than 2 per 10 high-power optical fields and Ki-67 positivity was present in less than 2% of neoplastic cells. Immunocytochemical staining was positive for chromogranin-A and synaptophysin. A diagnosis of well-differentiated NET was made and on further investigation the patient was also found to have low levels of serum vitamin B12 (129 µg/L, normal range 270-900 µg/L) combined with high titres of anti-parietal cell autoantibodies. Extensive endocrinological investigation excluded the presence of multiple endocrine neoplasia type 1 (MEN1). 24-hour urinary 5-HIAA excretion was within normal levels and CT-scanning of abdomen and thorax was negative for metastases. The tumour was classified as Type 1 gastric carcinoid and the patient was advised to have regular endoscopic follow-up and further polypectomies as necessary.

Comment: This case of gastric carcinoids coexisting with hyperplastic/regenerative polyps highlights the need for thorough endoscopic sampling in the setting of multiple polypoid lesions of the stomach. Even in endoscopically unremarkable mucosae, extensive sampling of both the lesser and greater curvatures is recommended in hypergastrinaemic patients, as it has been shown that the rate of diagnosis of dysplastic and carcinoid lesions correlates with the number of specimens examined.104

REFERENCES

27. Rindi G, Bordi C, Rappel S, et al. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology,
37. Lehy T, Mignon M, Cadiot G, et al. Gastric carcinoid cell behaviour in Zollinger-Ellison patients on long term
genetique de la NEM1: donnees physiopathologiques re-
centes et applications cliniques. Dans le cadre du GENEM. Groupe d'Etude des Neoplasies Endocriniennes Multi-
terology 1997; 113:773-781.
40. D'Adda T, Keller G, Bordi C, Hofler H. Loss of heterozy-
gosity in 11q13-14 regions in gastric neuroendocrine tu-
41. Granberg D, Wilander E, Stridsberg M, et al. Clinical symp-
45. Marcus FS, Friedman MA, Callen PW, Churg A, Har-


96. Warner RR. Carcinoid case presentation and discussion: