AP&T Alimentary Pharmacology and Therapeutics

Review article: the investigation and management of gastric neuroendocrine tumours

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Publication data
Submitted 17 November 2013
First decision 4 December 2013
Resubmitted 19 February 2014
Accepted 20 February 2014
EV Pub Online 13 March 2014

This uncommissioned review article was subject to full peer-review.

SUMMARY

Background
Gastric carcinoids (GCs) or neuroendocrine tumours (NETs) are increasingly identified at endoscopy, and account for 0.6–2% of all gastric polyps identified. The SEER database in the US has demonstrated a rising incidence of gastric NETs amongst all NETs; from 2.2% between 1950 and 1969 to 6.0% between 2000 and 2007.

Aim
To review the literature and assist clinicians in managing patients with GCs.

Methods
A literature search was conducted through MEDLINE using search terms: gastric, carcinoid, neuroendocrine tumour, therapy, endoscopy, mucosal resection, submucosal dissection. Relevant articles were identified through manual review. The reference lists of these articles were reviewed to include further appropriate articles.

Results
There are three types of GCs with important epidemiological, pathophysiological, histological and endoscopic differences that affect prognosis and management. Type 1 and 2 GCs develop in the context of hypergastrinaemia that originates from achlorhydria in atrophic gastritis and a gastrinoma, respectively. Type 3 GCs occur sporadically and independent of gastrin. The histological type, grade and Ki67 index are used to determine prognosis and direct clinical management. Type 1 GCs >1 cm in size and type 2 GCs should be assessed for invasion beyond the submucosa with EUS prior to endoscopic resection with EMR or ESD. Type 3 GCs should be managed as per recommendations for gastric adenocarcinoma. The treatment of advanced disease is multimodal.

Conclusions
Patients with gastric carcinoids should be discussed in a specialist neuroendocrine tumour multidisciplinary meeting to ensure all treatment options are explored in localised and advanced disease. Areas of controversy exist that need further research.

Aliment Pharmacol Ther 2014; **39:** 1071–1084

doi:10.1111/apt.12698

INTRODUCTION

Gastric carcinoids (GC) or gastric neuroendocrine tumours (NETs) are increasingly diagnosed at endoscopy and account for 0.6–2% of all gastric polyps identified.[1–4] They arise in enterochromaffin-like (ECL) cells that play a role in the regulation of gastric acid production. GCs represent almost a quarter of all gastroenteropancreatic neuroendocrine tumours (GEP-NETs).[5] The majority are incidentally diagnosed from histology of 'simple' gastric polyps identified at endoscopy, which is the dominant diagnostic, therapeutic and surveillance modality for GCs.

There are three types of GCs as described in 1993 by Rindi *et al.*; type 1 and type 2 are related to the presence of hypergastrinaemia, while type 3 occurs sporadically and independent of gastrin.[6]

There are important epidemiological, pathophysiological, endoscopic and histological differences between each type that affects prognosis, management and follow-up.[7] The characteristics of the different types of GCs are discussed below and summarised in Table 1.

EPIDEMIOLOGY

Data from the SEER database in the US have demonstrated a rising incidence of gastric NETs amongst all NETs; from 2.2% between 1950 and 1969 to 6.0% between 2000 and 2007.[3, 4] The rising incidence can be explained by factors that have helped improve the diagnosis of GCs compared to other NETs; increased access to endoscopy (including repeated procedures and surveillance programmes), more widespread biopsying of 'simple' polyps, improved immunohistological assessment and greater understanding of GCs.[8, 9] However, the overall incidence of diagnosed GCs remains low at 0.2 cases per 100 000 population with a significantly higher prevalence resulting from a favourable prognosis.[5] Women are increasingly diagnosed with GCs, rising from 55% in 1970 to 66% in 2010, reflecting a changing gender distribution.[10, 11] This may relate to the increased use of endoscopy to diagnose 'incidental' type 1 GCs that are more prevalent in women.

PATHOPHYSIOLOGY

Type 1 and type 2 GCs develop because of hypergastrinaemia causing hyperplasia of precursor ECL cells. The hormone gastrin normally acts on ECL cells to regulate gastric acid production.[12] There is no evidence of hypergastrinaemia or abnormal gastric acidity in type 3 GCs.

On ingestion of a meal, G cells in the antrum of the stomach secrete gastrin that then binds to cholecystokinin-2 receptors [CCK-2 or gastrin-CCK(B)] on ECL cells in the gastric body and fundus. ECL cells release histamine to stimulate gastric parietal cells to produce hydrochloric acid. As part of a negative feedback loop in acid conditions, antral D cells secrete the hormone somatostatin that acts on G cells to inhibit the production of gastrin (Figure 1a). Hence, a lack of gastric acid production (achlorhydria), from conditions like atrophic gastritis, results in hyperplasia of G cells in the antrum in an attempt to secrete more gastrin. Hypergastrinaemia causes compensatory hyperplasia and proliferation of ECL cells through growth factors in an attempt to increase acid production.[13, 14] It is thought that hypergastrinaemia mediates the development of GCs

Table 1 | Clinical, histological and prognostic characteristics of the three types of Gastric NETs

Characteristic	Type 1	Type 2	Type 3
Percentage of gastric NETs	70–80%	5–10%	<20%
Associations	Chronic atrophic gastritis Pernicious anaemia	MEN-1 Zollinger–Ellison syndrome	
Epidemiology	Typically women 50–70 years	Family history of MEN-1	Male preponderance
Mean age at diagnosis	63	50	55
Number of tumours	Multiple	Multiple	Solitary
Size of tumours (usual)	<1 cm	<1 cm	2–5 cm
Site of tumours	Fundus/Body	Fundus/Body	Fundus, Body or Antrum
Likelihood of metastases	Low <5%	<10%	>50%
Histological appearance	Well differentiated	Well differentiated	Usually poorly differentiated
WHO grading Ki67	≤2%	≤2%	>2%
WHO grading Mitotic count	<2	<2	>2
Angioinvasion	Rare	<10%	>50%
Plasma gastrin levels	↑↑	↑↑	Normal
Gastric pH	↑↑	↓↓	Normal
Plasma chromogranin A	Elevated	Elevated	Normal
Prognosis	Excellent	Good	Poor

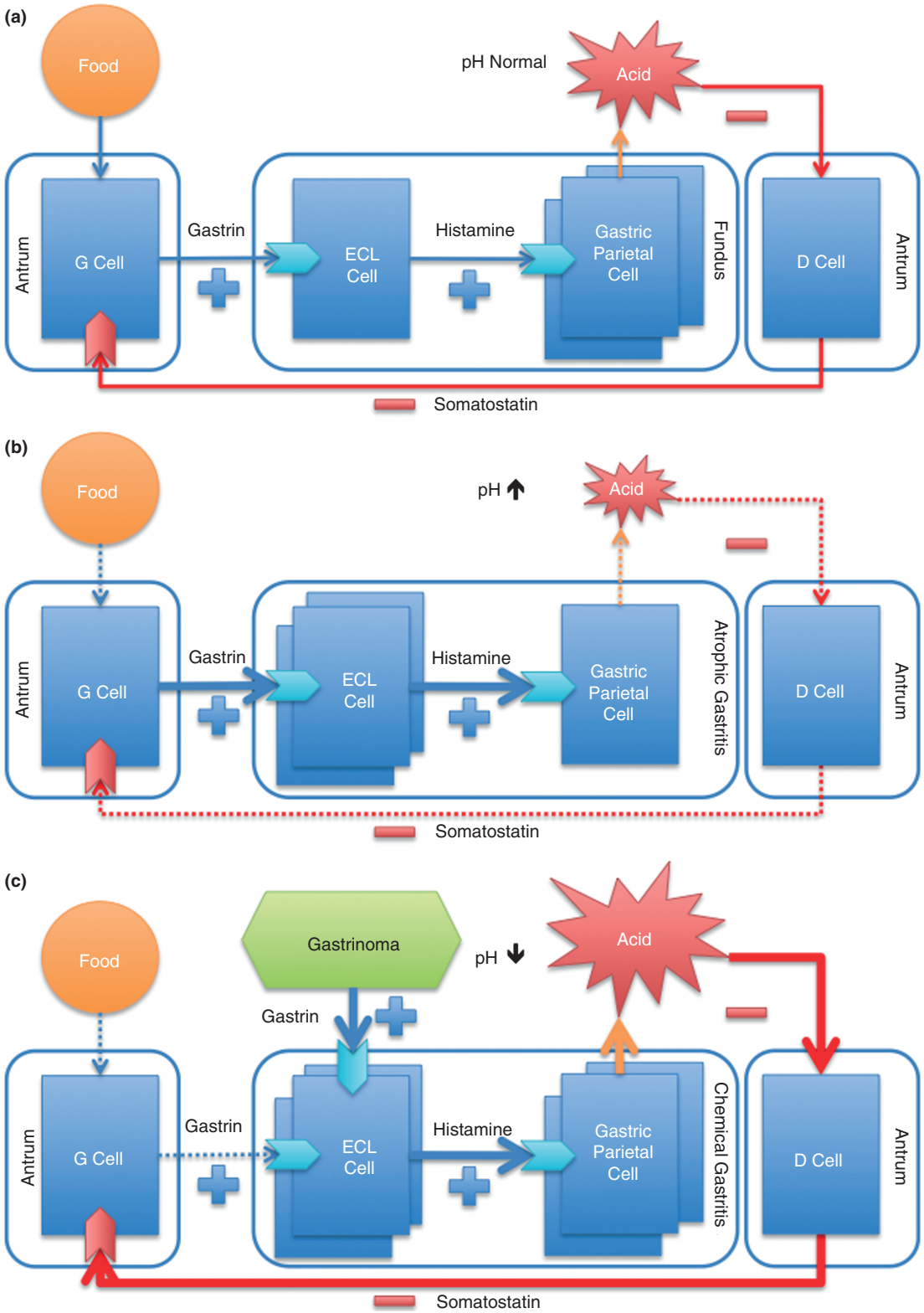

Figure 1 | The role of gastrin in normal (a) gastric acid homoeostasis, chronic atrophic gastritis (b) and in Zollinger–Ellison syndrome (c) from a gastrinoma.

from ECL cells, though other cofactors play a role.[15] Type 1 and 2 GCs develop through a 'hyperplasia–dysplasia–neoplasia' sequence.[16, 17]

Type 1 GC: hypergastrinaemia, atrophic gastritis and achlorhydria

Conditions associated with achlorhydria, such as chronic atrophic gastritis, vagotomy and chronic acid suppression treatment, result in hypergastrinaemia (Figure 1b), though not all are associated with an increased prevalence of GCs.[18] Cases of chronic atrophic gastritis with known ECL-cell dysplasia have a significantly higher risk of developing type 1 GCs than those with nondysplastic changes, with an incidence of 6.3 and 0.3 per 100 person-years respectively (hazard ratio of 20.7).[19] The presence of severe hyperplasia is also associated with a significantly increased risk of GC development (hazard ratio of 13.0).

Animal studies in rats have demonstrated the development of type 1 gastric NETS following prolonged therapy with H2-receptor antagonists.[20] In humans, chronic PPI therapy is associated with ECL-cell hyperplasia, which is seen in 10–30% of patients who are infected with *Helicobacter pylori*.[21] These infected patients have a greater prevalence of atrophic gastritis and markedly higher gastrin levels. In animal models, *H. pylori* lipopolysaccarides and peptidoglycans stimulate and activate proliferation of ECL cells.[22] The impact of PPI therapy on hypergastrinaemia, ECL hyperplasia and GC development is discussed later.

Type 2 GC: hypergastrinaemia, gastrinoma and peptic ulcers

Autonomous gastrin secretion from a gastrinoma (Zollinger–Ellison syndrome – ZES), in the context of normal parietal cell function, results in hypergastrinaemia (see Figure 1c) that leads to marked gastric acidity and associated peptic ulcers. Gastrinomas are located in the wall of the duodenum in 50–88% of sporadic ZES patients and 70–100% of MEN1/ZES patients.[23–25]

Enterochromaffin-like-cell changes are invariably seen in both sporadic and MEN-1 related cases of ZES.[26–28] Advanced hyperplasia and GCs are seen in 53% and 23% respectively of cases with MEN-1/ZES cases. Risk factors for developing GCs in patients with MEN-1/ZES include elevated fasting serum gastrin (>490 pg/mL), gastric nodules (present in 44% of patients), severe ECL-cell changes and long disease duration (>7 years).[26] Type 2 GCs associated with ZES invariably show loss of heterozygosity at the MEN-1 gene locus 11q13.[29, 30]

Type 3 GC: sporadic with normal gastrin levels

These lesions occur sporadically without evidence of a predisposing condition, like atrophic gastritis or a gastrinoma, that lead to hypergastrinaemia. There is an absence of ECL hyperplasia in the corpus mucosa that is evident in type 1 and 2 GCs.[31] Although these tumours do not develop in MEN-1 patients, there is loss of heterozygosity at the MEN-1 gene locus 11q13 in 25–50% of type 3 GCs.[30] However, there is limited research on molecular genetics pathways in sporadic type 3 GCs.

DIAGNOSIS AND INVESTIGATIONS

Specific information is required to establish the type, prognosis and management of a GC lesion. The critical factor predicting prognosis is the type of GC, though other variables that predict malignancy include size, invasion and grade.[32]

Baseline endoscopic assessment of GC

Careful inspection of the mucosa for multiple small lesions is advised, as type 1 and type 2 GCs are commonly multifocal. The size of the largest lesion should be recorded as type 1 GCs <1 cm do not require additional assessment or resection. Type 1 GCs >1 cm require assessment with EUS and imaging for locally invasive, nodal and metastatic disease prior to resection.

Biopsies should be taken from the suspected GC lesion plus two nonlesion biopsies from antrum and four biopsies from the body/fundus to help identify the GC type by assessing for the presence of atrophic gastritis and intestinal metaplasia.[7, 33] An assessment of *H. pylori* status should be made as infection is associated with atrophic gastritis in type 1 GC as well as sporadic type 3 GC.[34] pH testing of gastric fluid may offer clarification when there is uncertainty over the GC type; type 1 have a higher pH (>4) and type 2 have a lower pH (<2) than normal. The simplest method for assessing pH is to aspirate gastric secretions at the time of endoscopy and test with pH indicator strips. An alternative would be to perform a 24-h gastric pH study off PPI therapy.

Histological assessment of GCs

The diagnosis of GCs is confirmed by histology. All gastric NETs are identifiable at histology by their characteristic appearance and immunohistochemical staining for the neuroendocrine markers chromogranin A (CgA) and synaptophysin.[35, 36]

The histological classification of GCs is based on grade and differentiation. The mitotic count in 10 HPF (1 HPF = 2 mm^2) and the Ki67 index are used to

determine the grade of NETS. The 2010 WHO histological classification utilises the Ki67 index to grade GCs as part of gastroenteropancreatic NETs. Well-differentiated GCs (Neuroendocrine Tumours – NETs) have a low (G1) grade with a Ki67 of ≤2% or intermediate grade (G2) with Ki67 of 3–20%. Poorly differentiated GCs (Neuroendocrine Carcinoma – NEC) have a high grade (G3) with a Ki67 of >20%.[37]

Biochemical investigations for GCs

Fasting serum gastrin levels are elevated in type 1 and 2 GCs but not in type 3 GCs. Levels are also elevated in patients treated with acid suppression therapy. Levels >1000 pg/mL with a pH <2 are diagnostic of ZES, although the majority of cases do not reach these levels. CgA is secreted by ECL cells, particularly under the influence of gastrin, and is the most useful serum diagnostic marker for NETs with high sensitivity and correlation with tumour burden and liver metastases.[38–40] However, CgA can be raised in patients on PPI therapy as well as in the presence of chronic atrophic gastritis alone.

Additional imaging: EUS and nuclear medicine

The investigation of GCs is dependent on the histological type and the associated risk of locally advanced or metastatic disease. The role of more specialised investigations, like endoscopic ultrasound (EUS) and somatostatin receptor scintigraphy again depends on histological type.[41] Positive somatostatin receptor imaging with Indium In-111 labelled Pentetreotide (OctreoScan; Mallinckrodt Medical B.V, Petten, The Netherlands) may help with tailoring therapy. The role of FDG-PET remains unclear in G1 or G2 tumours, but is of more utility in highly metabolically active G3 NEC. The diagnosis, investigation and management of the three types of GCs are discussed with an algorithm outlined in Figure 2.

TYPE 1 GC: DIAGNOSIS, INVESTIGATION AND MANAGEMENT

Diagnosis

Type 1 GCs represent 74–78% of all GCs and are more common in women.[6, 31] They are associated with pernicious anaemia and autoimmune chronic atrophic gastritis. However, only 5% of patients with chronic atrophic gastritis develop type 1 GC with 2.4% at the time of diagnosis and a low annual incidence (0.4%).[31, 33, 42] They are nonfunctioning tumours and only cause symptoms when they ulcerate, which can result in bleeding and anaemia. The associated atrophic gastritis can cause both B12 and iron deficiency as well as dyspepsia from slow gastric emptying.[43] Endoscopists need to have a high index of suspicion for gastric polyps in patients referred with atrophic gastritis and/or B12 and iron deficiency.

Type 1 GCs are often found in the gastric fundus (see Figure 3) and are mostly polypoid (78%), small (size 5–8 mm) and multicentric (68%, mean number – 3).[44, 45] Characteristic features include an irregularly shaped erythematous depression or central ulcers.[46] Almost a quarter of type 1 GCs are microcarcinoids that are diagnosed at histology, though narrow band imaging and high-resolution magnification endoscopy have been reported to assist in their diagnosis.[47–49] Gastric pH is elevated (>4) because of a lack of parietal cells secreting acid. CgA is more specific (55–85%) than serum gastrin (35–55%) in type 1 GC as hypergastrinaemia is also present in chronic atrophic gastritis.[44, 50]

Most type 1 GCs are G1 tumours (82.7%) with a low Ki67 that present with stage I (73.9%) disease limited to the mucosa or submucosa.[44, 51] They rarely invade the muscularis propria or metastasise to local lymph nodes if <1 cm. Patients diagnosed with type 1 GC have an excellent prognosis, even with metastatic disease, with normal life expectancy and no associated mortality.[34, 44, 51, 52] Type 1 GCs are recurring tumours (median time 24 months), due to persistent antral-mediated hypergastrinaemia, with 3% developing poorly differentiated G3 NEC.[16]

Rarely composite carcinoid-adenocarcinoma lesions are found in lesions >2 cm and represent two pathophysiological processes associated with atrophic gastritis; GC development from ECL-cell hyperplasia and adenocarcinoma development from *H. Pylori*-associated intestinal metaplasia.[53–58] Nonlesion gastric biopsies identify atrophy in 82% of patients, with severe atrophy found in 64%.[45] Gastric pH testing (>4) can help differentiate type 1 GCs in cases where atrophy is not readily demonstrated.

In addition, associated autoimmune conditions like pernicious anaemia, diabetes mellitus, Hashimoto's thyroiditis and primary biliary cirrhosis should be considered and appropriately investigated. *H. pylori* status should be also assessed because of its association with intestinal metaplasia and gastric adenocarcinoma.

Additional investigations

For lesions ≤1 cm there is no indication for further assessment as they are invariably confined to the

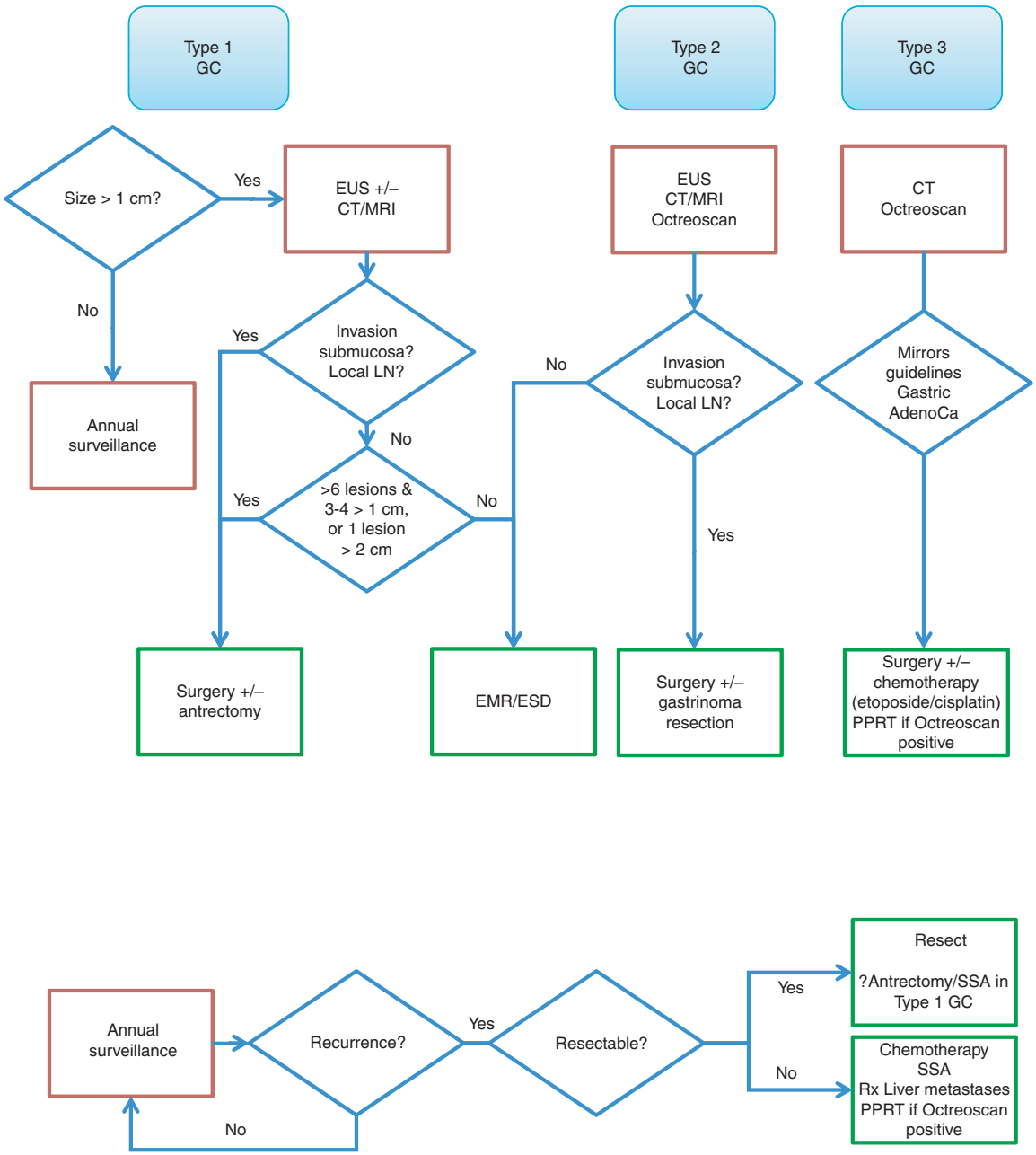

Figure 2 | Algorithm for investigating and treating Gastric NETs dependent on histological type.

mucosa or submucosa. For lesions >1 cm EUS is useful to assess for invasion beyond the submucosa prior to resection.[45, 59] For lesions >2 cm CT or MRI is recommended to assess for invasion and nodal disease. Functional imaging with Octreoscan is unlikely to reveal any additional lesions above conventional imaging in early resectable disease.[44] Somatostatin receptor imaging positivity may indicate a role for somatostatin analogues (SSA) in advanced, unresectable or residual disease.[60]

Treatment and surveillance

The majority of type 1 GCs are managed by endoscopy. Lesions <1 cm should undergo annual endoscopic surveillance as they have a low risk of invasion or metastasis at this size.

Lesions >1 cm should be resected, as there is a small risk of lymph node metastases. Endoscopic resection is indicated if EUS demonstrates the lesion to be localised to the mucosa or submucosa. This should be performed by someone with experience of gastric Endoscopic

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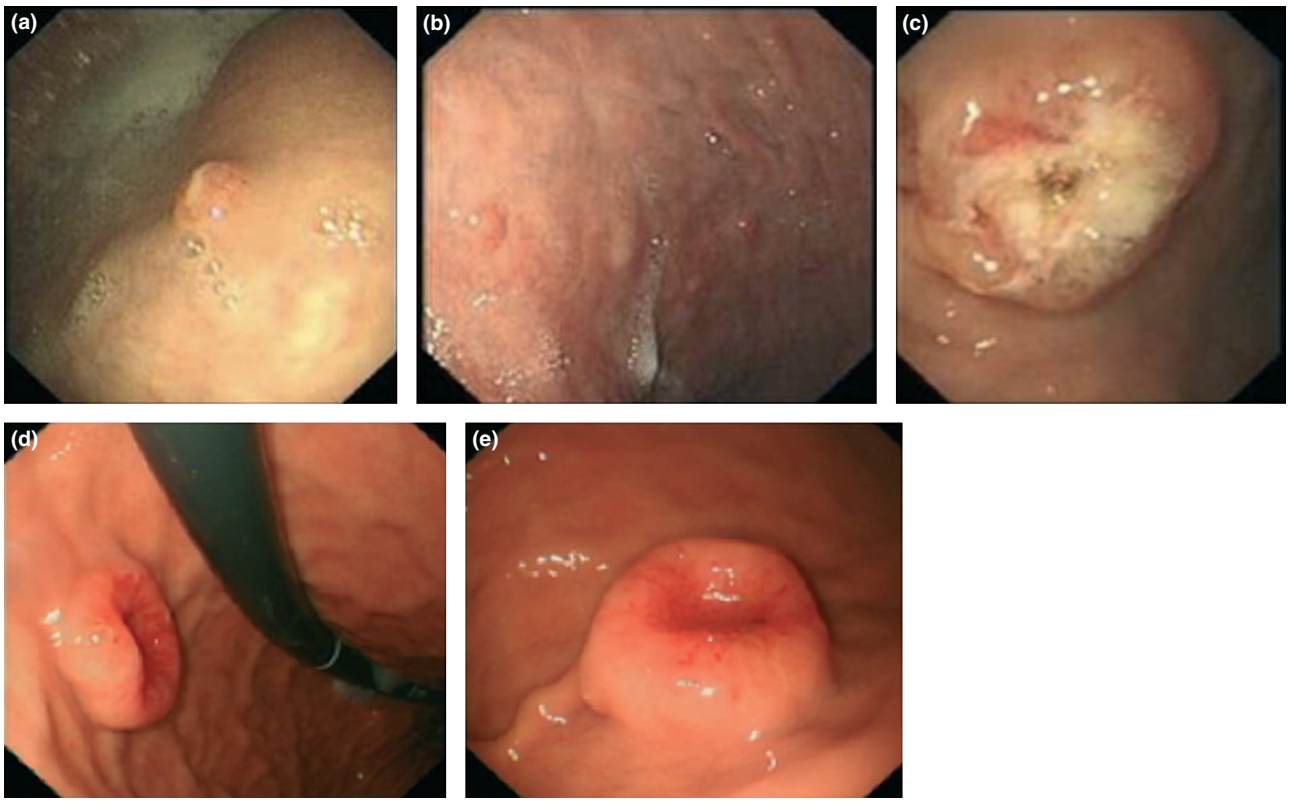

Figure 3 | (a) Type 1 carcinoid tumour of 2 mm with surrounding atrophic gastritis. (b) Multiple gastric small nodules with associated atrophic gastritis. (c) Gastric carcinoid of 8 mm with evidence of central ulcers. (d and e) Large type 1 gastric carcinoid with central ulcers.

Mucosal Resection (EMR) due to the risk of complications such as perforation and to maximise complete resection rates. Endoscopic Submucosal Dissection (ESD) has been shown to be safe for larger lesions and those not amenable to EMR, with high en bloc complete resection rates in experienced centres mostly in Japan.[61–64] However, it is not widely available in the UK and the majority of evidence for ESD for NETs is from the rectal carcinoid literature.[65–69] Endoscopic resection of nonmetastatic localised lesions <2 cm with ≤6 lesions has been demonstrated to be as effective as surgical resection. For more advanced lesions >1 cm, with EUS-assessed involvement of the muscularis propria and/or local lymph nodes, surgical resection is indicated. Surgical oncological resection is indicated if there are >6 lesions with 3–4 >1 cm, or if there is a single lesion >2 cm. PPI therapy should be stopped as it has little effect in the context of achlorhydria from atrophic gastritis.

Gastric antrectomy for type 1 GC is recognised as a therapy option in patients with multifocal (>6 lesions, 3–4 lesions >1 cm or 1 lesion >2 cm), invasive or recurrent disease. Antrectomy removes G cells-mediated hypergastrinaemia that leads to regression of GC lesions in over 90%.[31, 44, 70]

Small single centre studies suggest that somatostatin analogues (SSA) may have a role in reducing tumour burden and progression in type 1 GCs, particularly if there are multiple lesions.[71, 72] SSA act on G cells to suppress gastrin secretion that drives ECL hyperplasia and may have a direct anti-proliferative effect on ECL cells via somatostatin receptors. The treatment is well tolerated with a reduction or normalisation in gastrin and CgA levels in all patients. The majority of patients will have complete regression of lesions or a reduction in tumour size at follow-up endoscopy, though lesions soon recur after cessation of SSA therapy. Importantly, there is no proven outcome advantage from using SSA therapy in type 1 GCs. Netazepide (Trio Medicines Ltd, London, England) is a new orally active selective antagonist of the gastrin/CCK-2 receptor that has been shown to reduce gastric acid secretion.[73, 74] It shows promise for treating Type 1 GCs with a reduction in the number and size of the largest lesions at 12 weeks post-treatment.[75, 76]

Endoscopic surveillance is recommended annually for unresected lesions <1 cm and for recurrent GCs. The interval may be increased to 2 yearly endoscopies in nonrecurrent cases. Moreover, chronic atrophic gastritis is an independent risk factor for gastric adenocarcinoma and requires surveillance. If a new lesion is diagnosed at surveillance, it should ideally be resected endoscopically as discussed previously with new biopsy mapping of antral and gastric mucosa.

TYPE 2 GC: DIAGNOSIS, INVESTIGATION AND MANAGEMENT

Diagnosis

These are the least common type of gastric NET, comprising <5% of all gastric NETs, and result from hypergastrinaemia caused by gastrinomas, invariably in patients with Multiple Endocrine Neoplasia type 1 (MEN-1) although some arise sporadically.[77–79] Almost 30% of patients with MEN-1 develop GCs and up to 50% will if ZES is present.[80, 81] The majority of patients have symptoms of peptic ulcers refractory to treatment as a result of increased gastric secretion.[29] However, the GC lesion itself rarely causes symptoms. As previously described, the gastrinoma is frequently located in the wall of the duodenum.

The endoscopic appearances are usually of multiple small polypoid tumours that are usually <1 cm in size. In some instances type 2 GCs may affect the entire fundus and, more rarely, be located in the antrum. There may also be endoscopic evidence of peptic ulcers from excess gastric acid secretion.

Type 2 GCs are usually well differentiated (G1 or G2), though invasion beyond the submucosa and metastases (5–12%) to abdominal lymph nodes and liver are more common than in type 1.[6] The prognosis is good with a mortality rate of less than 10%. In contrast to type 1 GC, the background gastric mucosa may demonstrate signs of chemical gastritis or ulcers, rather than atrophy, because of increased gastric acidity (pH <2). Measuring random or overnight gastric pH may help classify the particular type of GC because of these pH differences. Serum gastrin levels are elevated with 63.5% of patients having levels greater than 1000 pg/mL.[29] Serum CgA levels are invariably elevated in all patients, often greater than 10 times the upper limit of normal.

Genetic testing for MEN-1 gene mutations can also be helpful as mutations are seen in 25% of cases with ZES. In addition, screening for parathyroid and pituitary tumours associated with MEN-1 is recommended.[29]

Additional investigations

Imaging with EUS, CT, MRI and scintigraphy is helpful as there is increased likelihood of locally advanced and metastatic disease. In addition, these modalities may help identify the site of the gastrinoma. Octreoscan and EUS can reveal the gastrinoma in nearly two-thirds of patients in whom CT or MRI demonstrates no abnormality.[29] Selective angiography with calcium stimulation may be necessary to identify small tumours that are not visible on cross-sectional imaging or EUS.[82] PET CT with 68 Ga-DOTA-NOC may be of additional value and can help localise occult gastrinomas.[83]

Treatment and surveillance

All lesions should be resected, as there is a greater risk of lymph node involvement and metastases. Endoscopic resection is indicated for all localised lesions and surgery for those with invasive or metastatic disease. Multiple lesions can be managed with both endoscopy and surgery. In addition, the site of the gastrinoma should ideally be identified and resected. There is no role for antrectomy as the hypergastrinaemia does not originate from the gastric antrum. Annual endoscopic surveillance is advocated for recurrence, particularly if ZES persists from an in situ gastrinoma. Acid hypersecretion in ZES should be controlled to prevent complications.[25] High-dose PPI therapy is the preferred choice to control acid secretion, although long-acting SSAs have also been used.

TYPE 3 GC: DIAGNOSIS, INVESTIGATION AND MANAGEMENT

Diagnosis

Type 3 GCs account for 15–20% of gastric NETs and have the worst prognosis with the highest rate of metastases.[84] They occur sporadically, unrelated to gastrin and are more frequently observed in men over the age of 50 years.[6, 16, 32, 85, 86] Patients may present with pain, weight loss, gastrointestinal haemorrhage and iron deficiency anaemia. It may be associated with an atypical form of carcinoid syndrome due to high levels of histamine released from ECL cells that cause itching, cutaneous wheals and bronchospasm.[87]

These are usually large (>2 cm) solitary lesions arising in normal gastric mucosa (Figure 4a,b). They may have an ulcerated appearance and can cause significant haemorrhage. They are commonly associated with *H. pylori* related gastritis.[34] There is no associated gastric atrophy or significant peptic ulcers that are commonly seen with type 1 or 2 GC respectively.

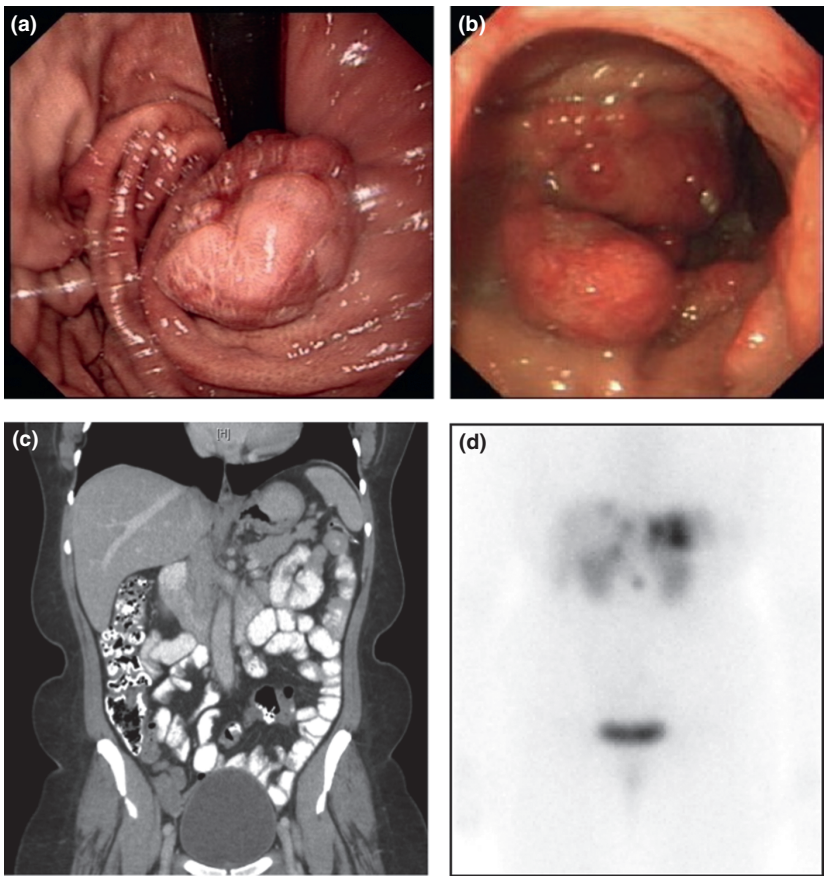

Figure 4 | (a) A large type 3 gastric carcinoid viewed on retroflexion in the gastric cardia. (b) A large type 3 gastric carcinoid in the fundus. (c) CT scan of type 3 gastric carcinoid shown in b. (d) Octreoscan of type 3 gastric carcinoid shown in b with uptake in fundus.

Type 3 GCs can vary in histological grade and differentiation, though G3 tumours (gastric NEC) are more common. Invasion beyond the submucosa is common with metastases present in 50–100%.[6, 88] The prognosis is poor with a mortality rate of 22–30%.[34] Concurrent gastric adenocarcinoma can be present in 5–10% of these cases.[36, 58, 89] In contrast to other GCs, the gastric pH is normal and there is poor correlation with serum gastrin and CgA levels.

Additional investigations

Type 3 Gastric NETs behave like gastric adenocarcinomas and should be similarly investigated and staged with CT (Figure 4c). Octreoscans are usually negative in poorly differentiated high-grade tumours (G3 NEC) but occasionally highlight the extent of disease (Figure 4d).

Treatment and surveillance

The decision to surgically resect type 3 GCs should mirror the principles and guidelines for gastric adenocarcinomas. Partial or total gastrectomy with local lymph node resection is often performed.

In patients with metastatic disease at presentation, systemic therapy is often first line therapy and is discussed below. Surveillance with CT and endoscopy following a resection of type 3 GC mirrors that of gastric adenocarcinomas.

THERAPIES IN ADVANCED DISEASE

The treatment of metastatic liver disease from NETs is multimodal, including surgical, loco-regional and systemic treatment modalities.[90, 91] SSA may have a role as an anti-proliferative agent in advanced but low proliferative (G1) GCs that are Octreoscan positive.[92–95] They also have a role in patients with functioning tumours causing carcinoid syndrome as an anti-secretory agent.[91, 96] Systemic chemotherapy is indicated in G3 NEC with etoposide and cisplatin, particularly if Octreoscan negative.[97] Peptide Receptor Radionuclide Therapy (PRRT) with 90 Y- and/or 177 Lu labelled SSA has a role in patients with a positive Octreoscan and advanced extrahepatic disease.[98, 99]

THE ROLE OF THE MULTIDISCIPLINARY MEETING AND SPECIALIST CENTRES

Though the incidence of GCs is increasing, the majority of clinicians will have limited experience of the condition. The management of GCs (and NETs in general)

requires input from a range of disciplines, including gastroenterology, surgery, histopathology, radiology, oncology and nuclear medicine. For this reason, cases should be discussed in a specialist NET multidisciplinary meeting (MDM) to ensure all investigation and treatment modalities are appropriately explored.[100] Importantly, a histopathologist with an interest in NETs should review all cases to ensure accurate subtyping and grading given the direct impact on clinical management. Studies from centres with experience in managing NET patients have shown improved survival.[101] Institutional experience and case volume are important factors that have led to the development of specialist NET referral centres.

CONTROVERSIES IN PATHOGENESIS, DIAGNOSIS AND MANAGEMENT

The original Rindi classification still serves well to describe the pathophysiological differences between GCs. However, it does not adequately describe differences in disease behaviour that are seen in clinical practice. Similarly, the Ki67 index has been criticised because of intra- and inter-observer variability as well as inconsistency in differentiating between G1 and G2 tumours.[102] Indeed, a Ki67 cut-off of 5% has been suggested as a more discriminatory threshold between G1 and G2 in predicting survival and recurrence in other NETs.[103, 104]

Sporadic type 3 GCs appear to have a diverse pathophysiology, extending from a well-differentiated group with slow disease progression to a poorly differentiated group with rapid disease progression. Current guidance suggests that all type 3 GCs should be treated with oncological resections irrespective of grade and stage. In addition, a further distinct GC subset (type 4), unrelated to existing GC types, has been proposed that describes poorly differentiated G3 NECs that invariably present with metastases.[31, 86] This may be a clinically useful subtype as management strategies for G1/G2 and G3 GCs can differ. For instance, EMR and ESD of well-differentiated type 3 GCs limited to the submucosa and <2 cm has been shown to be efficacious in a retrospective analysis.[105] Incomplete resection, with involved margins or lymphovascular invasion, was seen in 20% of cases, although no disease recurrence was reported at follow-up.

There have been case reports of gastric NETs in patients taking PPI therapy with associated ECL hyperplasia but without atrophic gastritis. Acid suppression therapy can lead to hypergastrinaemia that acts as a trophic factor on ECL cells.[18, 106, 107] In one case report, PPI use was associated with a poorly differentiated neuroendocrine carcinoma.[108] Stopping PPI therapy led to ECL hyperplasia regression in two patients, with regression of a well-differentiated NET in one case.[109] The impact of PPI therapy on the rising incidence of GCs is not clear but merits further assessment.[110, 111]

Current guidance advocates that all >1 cm type 1 GC should undergo resection even though there is an excellent prognosis. An argument exists for an expectant approach with surveillance for lesions <1.5 cm as these have a low risk of invasion and metastasis. Patient specific factors, like comorbidities and choice, should play a significant part in the discussion around resection or surveillance. Moreover, the morbidity associated with locally advanced and metastatic type 1 GCs has not been adequately determined to strongly advocate empirical oncological resection. The use of antrectomy to remove the trophic effects of hypergastrinaemia in multifocal, invasive and recurrent disease remains controversial with only limited published data. ECL hyperplasia can persist in 50% of patients and tumour progression can still occur following antrectomy.[31, 70] However, antrectomy is efficacious in reducing gastrin and chromogranin A when compared to medical therapy.[112]

FUTURE PERSPECTIVES AND DEVELOPMENTS IN DIAGNOSIS AND THERAPY

At present there is no validated immunohistochemical panel of markers that can augment histological analysis to improve subtyping and risk stratification of NETs.[113] A better understanding of the molecular genetic pathogenesis of GCs and NETs may help with the development of useful biomarkers for both tissue and serum analysis. Advances in functional imaging may detect additional disease for more accurate staging. Somatostatin receptor imaging with 68 Ga-DOTATATE PET has a higher sensitivity than Octreoscan and can identify additional lesions in well-differentiated NETs beyond those seen with conventional cross-sectional imaging.[114] The role of netazepide in managing type 1 GC needs further exploration with randomised controlled trials to establish long-term efficacy and to define patient selection. For instance, it may play a role in abolishing hypergastrinaemia in cases where antrectomy is currently advocated, or in the cohort of patients who are not fit enough for resection.

AUTHORSHIP

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ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

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