CLINICAL STUDY

Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study

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Abstract

Objective: To study the clinical presentation, diagnostic approach, response to treatment, and the presence of other pathologies in patients with gastric carcinoid type 1 (GC 1) tumors.

Design and methods: Retrospective analysis of 111 patients from four institutions and a mean follow-up of 76 months.

Results: The main indications for gastroscopy were upper gastrointestinal tract symptoms. The mean number of lesions, maximum tumoral diameter, and percentage of cells expressing Ki-67 labeling index were 3.6 ± 3.8 , 8 ± 12.1 mm and $1.9 \pm 2.4\%$ respectively. Serum gastrin and chromogranin A (CgA) levels were elevated in 100/101 and 85/90 patients respectively. Conventional imaging studies demonstrated pathology in 9/111 patients. Scintigraphy with radiolabeled octreotide was positive in 6/60 without revealing any additional lesions. From the 59 patients who had been followed-up without any intervention, five developed tumor progression. Thirty-two patients were treated with long-acting somatostatin analogs (SSAs), leading to a significant reduction of gastrin and CgA levels, number of visible tumors, and CgA immune-reactive tumor cells in 28, 19, 27, and 23 treated patients respectively. Antrectomy and/or gastrectomy were initially performed in 20 patients and a complete response was achieved in 13 patients. The most common comorbidities were vitamin B12 deficiency, thyroiditis, and parathyroid adenomas.

Conclusions: Most GCs1 are grade 1 (82.7%) tumors presenting with stage I (73.9%) disease with no mortality after prolonged follow-up. Ocreoscan did not provide further information compared with conventional imaging techniques. Treatment with SSAs proved to be effective for the duration of administration.

European Journal of Endocrinology 168 185–193

Introduction

Gastric carcinoids (GCs) are among the most common gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), with an annual incidence of 0.59–0.6275/100 000 inhabitants (1, 2). These tumors derive from the enterochromaffin-like cell of the gastric oxyntic mucosa and are classified in three main types based on clinicopathological characteristics, behavior, and prognosis (3). GC type 1 (GC1) are the most common (65–75%) gastric NETs associated with chronic atrophic gastritis and hypergastrinemia. Along with GC2 (5–10%), which are related to a gastrin-secreting neoplasm, they can be multiple and exert an indolent course compared with GC3 that are single lesions behaving in a malignant manner. However, a subset of GC1, up to 5%, may develop advanced disease, with lymph node and/or hepatic metastases (4).

The clinical presentation of GC1 is usually associated with nonspecific symptoms or they can be incidentally discovered. However, only a few studies evaluating relatively small cohorts have addressed in a specific and repetitive manner the exact pattern of their presentation (5, 6). Data derived from personal experience and consensus statements (7) suggest that the majority of GC1 can be easily sampled or removed by either biopsy forceps or endoscopic mucosal resection (EMR), being small (<15 mm), rounded, mucosal, or submucosal lesions (8). As these lesions are noninvasive, no further imaging studies are considered necessary to evaluate disease spread (9). However, there is paucity of data evaluating this approach in a large group of GC1 and no specific predictors exist that can identify the small percentage of patients who develop regional or distant metastases (10).

The therapeutic strategies for GC1 are based on risk stratification according to tumor size, number,

stage, and grading, ranging from close endoscopic surveillance to surgery (5, 11, 12). However, there are relatively few studies evaluating the effectiveness of different therapeutic modalities in patients with prolonged follow-up. Furthermore, although thyroid diseases, diabetes mellitus, hypertension, and gastrointestinal (GI) tumors have been reported to coexist with GC1 (5, 6), the exact incidence of concomitant pathologies still remains unclear.

The purpose of this multicenter study was to provide data regarding clinical presentation, pathological features, diagnostic approach, management, and response to different treatments in 111 patients with GC1 from four different institutions, and to record the incidence of concomitant diseases.

Materials and methods

Data from 111 patients (30 from Greece, 28 from Israel, and 53 from Sweden) with GC1 were retrospectively collected from medical records, using a uniform specially designed investigational protocol according to the European Neuroendocrine Tumor Society (ENETS) guidelines suggestions. All patients were analyzed with respect to their presenting symptoms/signs, serum gastrin and chromogranin A (CgA) levels, biochemical and hormone profile, findings at endoscopy, imaging studies, and histopathology. Tumor-node-metastasis staging was based on the published ENETS guidelines (7) and patients gave their consent according to the Local Bioethical Committee requirements. The symptoms leading to the diagnosis of GC1 were recorded along with other comorbidities and neoplasias.

Endoscopy

Upper GI endoscopy was performed after an overnight fast in all patients. The general appearance of gastric mucosa was characterized and accessible lesions were removed. Tissue specimens were obtained from the lesions along with multiple biopsies from nontumorous mucosa. The size of the lesions and the number of biopsies from each site were recorded.

Gastrin and CgA assays

Serum gastrin and CgA levels were assessed after an overnight fast. Gastrin levels were measured with a commercial RIA (GammaDab [125 I] Gastrin RIA Kit, DiaSorin, Stillwater, OK, USA). In all four institutions, the upper normal gastrin levels were considered as 108 pg/ml. In the first institution, CgA levels were measured using CgA-RIA CT, CIS Bio International (Gif-sur-Yvette Cedex, France); reference range, 19.4–98.1 ng/ml. In the remaining institutions, CgA levels were measured with another commercial RIA Kit: CgA-RIA CT, Cis Bio International (Bagnols-Ceze,

France), employing the same reference range. Gastrin and CgA kits for patients from Uppsala were from Euro-Diagnostica (Malmö, Sweden; upper normal limit, 60 pmol/l and 4 nmol/l respectively). Gastrin levels in picomole per liter were converted to picogram per milliliter by multiplying 2.1 and CgA levels in picomole per liter to picogram per milliliter (1 ng/ml = 1000 pg/ml) by multiplying 49.

Imaging studies

Conventional imaging studies, including computerized tomography (CT) scanning and/or magnetic resonance imaging (MRI) of the abdomen and pelvis were used to assess local spread and distant metastases. Additional imaging studies such as pituitary MRI and chest CT were used for the evaluation of concomitant tumor-related diseases and for the exclusion of patients with MEN1 syndrome. Radionuclide imaging studies included 111 In-octreotide scintigraphy (Octreoscan, $n = 60$), 68 Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic-acid-D-Phe1-Tyr3-octreotide positron emission tomography CT (68 Ga-DOTATOC-PET CT, $n = 11$) scintigraphy, 18 F-fluorodeoxyglucose-PET (18 FDG-PET, $n = 2$) scanning, and 11 C-5-hydroxytryptophan PET (11 C-5-HTP-PET, $n = 5$) scintigraphy and were used to verify tumor progression or restaging and discordant biochemical and imaging findings.

Endoscopic ultrasound (EUS) was performed in 35 patients, as a tool to provide additional information regarding the location and depth of the lesions. Suspicious findings from abdominal imaging studies and submucosal lesions were further investigated with EUS and biopsy when indicated.

Histopathology

The tissue specimens were fixed in 10% buffered neutral formalin for 18–20 h at room temperature, followed by routine processing to paraffin wax. Approximately 4 μ m thick sections were cut and routinely stained with hematoxylin–eosin and immunostained for CgA (104/111 patients), synaptophysin (79/111), neuron-specific enolase (77/111), and Ki-67 labeling index (LI; 98/111). Nontumorous mucosa was examined for the presence of widespread glandular atrophy, immune cell infiltration, parietal cell alterations, *Helicobacter pylori* (*H. pylori*) infection (88/111 patients), and intestinal metaplasia. Gastritis, atrophy, and immunostaining were semi-quantitative characterized by the same pathologist at each institution as mild, moderate, and severe using uniformly accepted criteria (13, 14). Foci of endocrine cell hyperplasia were considered to be present in different, previously well-described patterns (diffuse, linear, or nodular) (15).

Table 1 Reasons for endoscopic evaluation leading to the diagnosis of gastric carcinoid type 1.

Indication for endoscopy	Number of patients (%)	Time elapsed (months) ^a (mean ± S.D.)
Upper gastrointestinal tract symptoms ^b	56 (50.4)	13.9 ± 15.9
Assessment of longstanding anemia	41 (37.3)	21.2 ± 32.3
Other ^c	14 (12.6)	18.6 ± 32.2

^aBetween onset of related symptoms and definite diagnosis.^bChronic epigastric pain, dyspepsia, bloating, nausea, increased salivation, gastroesophageal reflux, and early satiety.^cLaparoscopic adjustable gastric banding for severe obesity (1/111), high calcitonin/gastrin levels (3/111), hepatocellular carcinoma (1/111), weight loss (3/111), carcinoid syndrome (2/111), hoarseness (2/111), and retro-sternal pain (2/110).

Management

From 1983 to 2002, 32 patients were sequentially treated according to each center's expertise. From 2003 to 2012, 79 patients underwent polypectomy or EMR (16) if lesions were smaller than 10 mm, five or fewer and did not extend beyond the submucosa. Patients with larger lesions who denied surgical treatment were advised to be closely followed-up, with or without somatostatin analogs (SSAs) therapy. Informed consent was obtained from all patients treated with SSAs; 15 of these patients have participated in a previous study (17). Conservatively treated patients were followed-up with tumor marker measurements and

gastroscopy. Following tumor progression, surgical resection including antrectomy, partial, subtotal, or total gastrectomy was applied depending on the extent of the disease.

Follow-up

The mean duration of follow-up period was 76 months (range, 12–348 months). Patients underwent the second upper GI endoscopy within 6 months following initial diagnosis and every 6 months (range, 4–12 months) thereafter. Each visit included clinical assessment and tumor markers measurements. Imaging studies and further hematological/biochemical evaluation were performed when indicated. The initial approach to the patients with a biochemical GC1 recurrence was clinical re-evaluation, upper GI tract endoscopy, and abdominal MRI or CT if indicated. Positive findings from conventional imaging studies were further evaluated with EUS and fine-needle aspiration cytology when necessary.

Statistical analysis

Spearman's nonparametric test was used to correlate gastrin and CgA levels before diagnosis with age, time between onset of related symptoms and definite diagnosis, number of lesions, percentage of Ki-67 expression, and maximum tumor diameter. Nonparametric ANOVA (Kruskal–Wallis one-way ANOVA) was

Table 2 Common medical comorbidities encountered in the 111 patients with type 1 gastric carcinoids.

Benign diseases	n	Percentage (%)	Tumor-related diseases	n	Percentage (%)	Incidence (cases/100 000 per year)	
						Current study	European community ^a
Medical comorbidities							
Anemia (B12 deficiency)	47	42.3	Parathyroid adenoma	6	5.4	853.9	2
Hashimoto's thyroiditis	41	36.9	Papillary thyroid carcinoma	3	2.7	426.9	10
Hypertension	22	19.8	Colon cancer	2	1.8	284.6	75
Hyperlipidemia	12	10.8	Breast cancer			287.8	110.3
Diabetes mellitus type 2	11	9.9	Lung cancer			284.6	23.9
Anemia (iron deficiency) and osteoporosis	10	9	Prolactinoma				30
Diabetes mellitus type 1	7	6.3	Endometrial carcinoma	1	0.9	143.9	5
Multinodular goiter	6	5.4	Acute myelogenous leukemia			142.3	8
Obesity, rheumatoid arthritis, and coronary heart disease	4	3.6	Prostate cancer			137.7	78.9
Ischemic attack, Sjögren's syndrome, and systemic lupus erythematosus	3	2.7	Medullary thyroid carcinoma			142.3	1
Premature ovarian failure, impaired fasting glucose, renal transplantation, and psoriasis	2	1.8	Hepatocellular carcinoma				8.9
Addison's disease, Graves' disease, vitiligo, depression, chronic autoimmune hepatitis, and lymphocytic colitis	1	0.9	Midgut carcinoid				0.9

^aData retrieved from reference 2 and European Society of Medical Oncology (references (18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29)).

used to compare mean levels of gastrin and CgA at diagnosis, during SSAs therapy and following surgical treatment. *Post hoc* comparisons were made using Mann–Whitney *U* test. Kaplan–Meier statistical method for estimating 'survival' was used to calculate the time needed for the 50% of patients to remain alive and to calculate the progression-free survival period. Log-rank test was used to compare the percentage of progression-free survival of conservatively treated, SSAs treated, and operated patients. As all patients were of European origin, we compared the incidence of other neoplasias to the corresponding of the normal European population (18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). Calculations were performed using the Number Cruncher Statistical System, Power Analysis System (NCSS/PASS 2004, Dawson Edition), and Statistical Package for Social Sciences (SPSS V.13.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Patients' demographics and clinical findings

In total 111 patients (82 female) with GC1, with a mean age of 58.5 ± 12.7 years (range, 29–84 years) were studied. The most common reasons for endoscopic evaluation were upper GI tract symptoms (Table 1).

The most common medical comorbidities were anemia due to vitamin B12 deficiency (47/111),

Hashimoto's thyroiditis (41/111), and hypertension (22/111) (Table 2). Other neoplasias included primary hyperparathyroidism due to a single parathyroid adenoma (6/111), papillary thyroid carcinoma (3/111), and breast cancer (2/111). The age- and sex-adjusted incidence of relative tumors of the corresponding European population are shown in Table 2.

Biochemistry

High levels of anti-parietal cell antibodies were initially detected in 70/87 patients. Pretreatment gastrin, but not CgA, levels were statistically correlated with the maximum tumor diameter ($P = 0.01$) at endoscopy; however the r_s value was only 0.26. No correlation was found with the time interval between the onset of related symptoms and confirmation of definite diagnosis, number of lesions, percentage of Ki-67 expressing cells, and age at diagnosis.

Imaging studies

Abdominal CT scanning and/or MRI studies were negative in 102/111 patients performed. In three patients treated with SSAs, abdominal CT showed increased thickness of the gastric wall, also shown in scintigraphy studies. In two operated patients, CT showed liver metastases. In a further four operated patients, CT findings were confined to the gastric area.

Table 3 Findings from anatomical and functional imaging studies performed in the 111 patients with gastric carcinoid type 1 tumors.

	Conventional imaging studies ^a			Functional imaging studies					
	Octreoscan			⁶⁸ Ga-DOTATOC-PET CT		¹¹ C-5-HTP-PET		¹⁸ FDG-PET	
	Positive findings	Positive findings	Additional information ^b	Positive findings	Additional information ^b	Positive findings	Additional information ^b	Positive findings	Additional information ^b
Follow-up without any medication									
$n = 30$	0	ND		ND		ND		ND	
$n = 23$	0	2	No	ND		ND		ND	
$n = 2$	0	0	No	ND		0		ND	
$n = 2$	0	0	No	ND		1	No	ND	
$n = 1$	0	0	No	ND		ND		1	No
$n = 1$	0	0	No	ND		ND		0	No
Long-acting somatostatin analogs									
$n = 18$	2	2	No						
$n = 3$	0	ND							
$n = 9$	1	ND		1	No	ND		ND	
$n = 2$	0	0	No	0	No	ND		ND	
Surgical treatment									
$n = 9$	2	1	No	ND		ND		ND	
$n = 8$	2	ND		ND		ND		ND	
$n = 1$	1	ND		1		ND		ND	
$n = 1$	0	0	No	ND		0	No	ND	
$n = 1$	1	1	No	ND		1	No	ND	

Octreoscan, ¹¹¹In-octreotide scintigraphy; ⁶⁸Ga-DOTATOC-PET CT, ⁶⁸Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic-acid-D-Phe1-Tyr3-octreotide positron emission tomography computed tomography; ¹¹C-5-HTP-PET, ¹¹C-5-hydroxytryptophan positron emission tomography scintigraphy; ¹⁸FDG-PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; ND, not done.

^aCT and MRI of abdomen and pelvis, and endoscopic ultrasonography.

^bFor gastric carcinoid type 1 tumor recurrence, as compared with conventional imaging studies.

Octreoscan was positive in 6/60 patients and in two was considered to be false positive based on other imaging studies and prolonged follow-up. True positive findings were observed in 4/6 patients who had normal abdominal CT findings, and in whom EUS revealed submucosal lesions and a further patient with liver metastases. As compared with conventional imaging studies, Octreoscan revealed no additional information in any of the 60 patients examined (Table 3).

⁶⁸Ga-DOTATOC-PET CT scintigraphy was performed in 12 patients and was negative in 10. In the two positive patients, CT findings were also apparent (Table 3). ¹¹C-5-HTP-PET scintigraphy was positive in 2/4 patients examined: true positive in one patient in whom conventional imaging modalities also revealed pathology and false positive in a patient who had no evidence of tumor progression on prolonged follow-up. ¹⁸FDG-PET was positive in two patients with rheumatoid arthritis. EUS to the restaging of two patients with stage III–G2 disease.

Histopathological findings

From the 111 patients, 58 had single and 53 multicentric lesions. The mean maximum diameter of excised tumors was 7.9 ± 12.1 mm (range, 0.2–100 mm) and the mean percentage of cells expressing Ki-67 LI was $1.9 \pm 2.4\%$ (range, 0.1–15%). Chronic *H. pylori* infection and intestinal metaplasia were found in 17.1 and 68.5% of patients respectively. Mild, moderate, and severe chronic gastritis or atrophy was detected in 48.6, 39.6, and 11.7% of patients respectively. Diffuse, linear, and nodular pattern of endocrine cell hyperplasia was detected in 48, 75.7, and 81.1% of patients respectively.

Follow-up according to the therapeutic modality applied

Without any intervention Fifty-nine patients (38 female), with a 3.2 mean number of lesions (range, 1–15), were followed-up, without any additional treatment, for a mean period of 90.3 ± 72.5 months (range, 12–348 months). Forty-seven patients were categorized into stage I–G1, one into stage I–G2, nine into stage IIa–G1, and two into stage IIa–G2. Following endoscopic removal of all visible lesions, five patients had a complete response (CR; complete regression of all clinical, radiological, and hormonal evidence of the tumor), nine a partial response (PR; a 50% or greater reduction in all measurable tumor, clinical symptoms, and hormonal levels, without appearance of new lesions), and 40 stable disease (SD; <50% reduction or no greater than 25% increase in the same parameters). Five patients (8.5%) had progressive disease (PD) within 48 ± 7.9 months of the initial diagnosis. Serum gastrin and CgA levels normalized in

one and six patients respectively, most probably due to the resection of the lesions during endoscopy.

Long-acting somatostatin analogs Thirty-two patients (30 female), with a 3.8 mean number of lesions (range, 1–13), were treated with SSAs. Eighteen patients were categorized into stage I–G1, seven into stage I–G2, five into stage IIa–G1, and two into stage IIa–G2. Patients selected for SSA therapy presented with larger size tumors (number of visible lesions, 3.6 ± 2.5 vs 2.26 ± 2.4 , $P=0.084$ and tumor diameter, 6.2 ± 4.5 vs 3.5 ± 3.5 mm, $P=0.042$), higher gastrin (1360 ± 642 vs 606 ± 778 pg/ml, $P=0.001$), and CgA levels (356 ± 178 vs 195 ± 140 ng/ml, $P=0.007$), compared with patients treated conservatively. Of the 32 SSA-treated patients, eight had a CR, 15 a PR, three a SD, and six patients (18.7%) had PD. During treatment, serum gastrin levels significantly reduced (from 1373 ± 649 to 290 ± 221 pg/ml, $P<0.001$) and in four patients normalized. CgA levels also significantly reduced (from 359 ± 175 to 129 ± 99 ng/ml,

Table 4 Alteration of tumor characteristics during therapy with somatostatin analogs.

Patient	Number of visible tumors		Maximum diameter of the tumor (mm)		Follow-up (months)
	Diagnosis	SSA therapy ^a	Diagnosis	SSA therapy ^a	
1st	5	3	2	2	40
2nd ^b	1	9	5	5	85
3rd	4	5	3	3	40
4th	2	1	6	3	38
5th	7	5	0.3	3	77
6th	1	0	3	0	42
7th ^b	3	3	1.5	5	82
8th	1	0	0.3	0	26
9th	1	2	1.5	5	18
10th	5	0	15	0	35
11th	5	4	15	4	57
12th	7	0	11	0	45
13th	1	0	5	0	57
14th	5	0	11	0	35
15th	4	0	3	0	45
16th	5	6	3	2	57
17th	5	0	2	0	57
18th	6	0	10	0	33
19th	5	0	9	0	37
20th	8	0	5	0	34
21st	1	0	1	0	46
22nd	2	0	8	0	18
23rd	1	0	12	0	28
24th	10	2	10	2	24
25th	3	0	4	0	24
26th	1	0	15	0	27
27th	1	0	5	0	18
28th	2	1	4	2	18
29th	1	0	8	0	22
30th	1	0	2	0	23
31st	6	0	4	0	18
32nd	13	0	5	0	60

^aLast follow-up visit.

^bThe patient was operated due to disease progression.

Figure 1 Box plot indicating the median levels (black arrows) of gastrin (A) and chromogranin A (B) at diagnosis, in patients who were followed-up, without any medication, in patients treated with somatostatin analogs (SSAs), and in surgically treated patients. Horizontal bars show statistically significant differences between groups. Open circles represent extreme values (beyond the 75th percentile) of gastrin levels (Panel A) or extreme values (beyond the 75th percentile) of chromogranin A levels (Panel B).

$P<0.001$) and normalized in 12 patients. Number of visible tumors, maximum tumor diameter and number of CgA immunostained tumor cells was decreased in 26/32, 25/32, and 24/32 patients respectively (Table 4). All patients tolerated treatment well, but two patients discontinued treatment and were operated due to histological and biochemical tumor progression.

Surgical treatment Twenty patients, with a 4.8 mean number of lesions (range, 1–13), were operated. Three patients with GC1 stage I–G1, one with stage II–G1, one with stage IV–G1 and liver metastases at presentation, and one with stage I–G1 underwent total gastrectomy; five had a CR and one a PR. Three patients underwent a subtotal gastrectomy and had a CR, whereas nine underwent a partial gastrectomy (four had a CR, two a PR, two SD, and one developed PD 12 months after the operation). Two patients had an antrectomy. Compared with the patients treated with SSAs, operated patients

had statistically higher mean percentage of Ki-67 LI expression (7 ± 5.8 vs 2.3 ± 1.2 , $P=0.05$), and higher mean maximum tumor diameter (31.9 ± 32.4 vs 6.2 ± 4.5 mm, $P=0.026$). Following surgical treatment, gastrin and CgA levels normalized in 9/14 and 8/13 patients respectively, and were statistically lower than any other treatment (Fig. 1).

The percentage of patients who developed relapses over time was 8.5% (without any medication), 6.2% (SSAs treated), and 5% (operated) patients respectively ($P=0.694$, log-rank test, Fig. 2A). One hundred and nine patients still remain alive and two died from GC1-unrelated reasons (hepatocellular carcinoma and myocardial infarction; Fig. 2B).

Figure 2 Kaplan–Meir analysis of the 111 gastric carcinoid type 1 (GC1) patients included in the study. (A) The percentage of patients with complete or partial response or stable disease over time is plotted. (B) Survival analysis. Black arrows indicate two patients who died after 53 and 84 months from the diagnosis of GC1 from apparently unrelated reasons (hepatocellular carcinoma grade II and myocardial infarction respectively).

Discussion

Although relatively rare, GCs1 were recently shown to be the most common GEP carcinoid tumors in a prospective study (2). GCs1 are usually indolent tumors diagnosed during endoscopic evaluation for nonspecific symptoms, attributed to the presence of the lesions. Similarly to previous small-sized studies (5, 6), this study confirmed that nonspecific upper GI symptoms were the commonest presenting complaints. By contrast, symptoms implying local GI invasion, such as GI bleeding, were found to be extremely rare.

It has previously been suggested that patients with GC1 are at increased risk of developing other GI tract malignancies (5). In our patients an increased prevalence of parathyroid adenomas, thyroid carcinomas, and adrenal adenomas was observed that was 10 times higher compared with the corresponding European population (2, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29). However, this finding should be interpreted with caution, as it may be attributed to the extensive investigations and periodical assessment performed and to the mixed populations living in different European countries. Primary hyperparathyroidism due to a parathyroid adenoma was the commonest neoplasia. Although the exact etiology of this finding is not known, it is plausible to consider that these tumors may develop as a result of the stimulatory effect of gastrin (30). As most patients had autoimmune gastritis, other autoimmune endocrine disorders, such as Hashimoto's thyroiditis, premature ovarian failure, vitiligo, and diabetes mellitus type 1 were also found to be prevalent (31).

H. pylori infection was found in 17% of patients, a lower infection rate than in the general population (32), probably related to the extensive atrophic changes of the gastric mucosa that inhibit *H. pylori* colonization (33). However, the exact impact of *H. pylori* infection in autoimmune gastritis and GCs pathogenesis is still under investigation (34).

We mainly used upper GI tract endoscopy and conventional imaging studies for the diagnosis, follow-up, and initial therapeutic approach of recurrences. Although Octreoscan has a detection rate of 67–91% for all primary and metastatic NETs, it is considered to be of limited value when applied to small GC1 (35). This view was confirmed for the first time in this study, as Octreoscan did not reveal additional pathology not obvious with other imaging modalities used, particularly EUS. On the basis of these findings, this imaging modality should not be applied for the evaluation of disease extent in patients with GC1.

The majority of patients treated conservatively had a relatively higher recurrence rate on endoscopic surveillance compared with operated or SSA-treated patients. SSAs were associated with an important reduction of tumor markers and improvement of tumor histopathological characteristics compared with patients followed-up without any intervention. Previous clinical studies

have demonstrated the anti-proliferative effect of octreotide on tumor load in patients with GC1 for at least a short period of treatment (36, 37). Although gastrin levels reduced significantly following treatment with SSA, the long-term effects of this form of treatment are still unknown. Pending more data on patients treated with SSAs, biotherapy is currently recommended in functioning tumors and in cases with metastatic disease in reference centers (38).

In surgically treated patients, a 65% CR rate was observed, relatively lower compared with other studies (39). Neither the appearance of new lesions, increase in tumor size, nor the clinical and radiological evidence of the presence of a tumor identified partial responders. Although antrectomy has been proved effective in abolishing hypergastrinemia (39), it was performed in only two of our patients, while 9/20 patients underwent subtotal or total gastrectomy. It is probable that patients with GC1 tumors have been over-treated in the past, mainly due to the absence of specific therapeutic guidelines. Based on the findings of this study and the fact that these tumors remain mainly stationary, or even regress over time (40), a more conservative approach seems advisable. In our relatively large cohort, only two patients were found to have metastatic disease, diagnosed 1 and 7 years after initial presentation; these patients still remain alive, with SD on prolonged follow-up. Furthermore, no GC1-related deaths were observed during the follow-up period. However, we did not find any specific predictors that could identify patients with a trend for metastasis.

In conclusion, vitamin B12 deficiency and Hashimoto's thyroiditis are the most common diseases, while neoplasias of parathyroids, thyroid, adrenals, and digestive organs are more prevalent in patients with GC1. Most GCs1 are grade 1 tumors presenting with stage I disease. As no GC1-related deaths were recorded after a mean follow-up period of 76 months, these findings reflect the relatively indolent nature of the disease. Radionuclides, although they could be useful in selected patients, did not prove to be necessary as they did not detect additional disease. Long-term survival benefit of SSA therapy and aggressive surgical resection for patients with metastatic disease needs further investigation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the Selander Foundation.

Acknowledgements

The authors are grateful to Prof. Lars Grimelius for evaluating a part of the specimens.

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Received 23 September 2012

Revised version received 30 October 2012

Accepted 6 November 2012