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BRIEF ARTICLE

Metastatic type 1 gastric carcinoid: A real threat or just a myth?

Simona Grozinsky-Glasberg, Dimitrios Thomas, Jonathan R Strosberg, Ulrich-Frank Pape, Stephan Felder, Apostolos V Tsolakis, Krystallenia I Alexandraki, Merav Fraenkel, Leonard Saiegh, Petachia Reissman, Gregory Kaltsas, David J Gross

Simona Grozinsky-Glasberg, David J Gross, Neuroendocrine Tumor Unit, Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, 91120 Jerusalem, Israel
Dimitrios Thomas, Krystallenia I Alexandraki, Gregory Kaltsas, Endocrine Unit, Department of Pathophysiology, National University of Athens, 11527 Athens, Greece
Jonathan R Strosberg, Moffitt Cancer Center, Tampa, FL 33612, United States
Ulrich-Frank Pape, Stephan Felder, Department of Internal Medicine, Division of Hepatology, Gastroenterology, Endocrinology and Metabolism, Charité Universitätsmedizin, DE-13353 Berlin, Germany
Apostolos V Tsolakis, Department of Medical Sciences, Section of Endocrine Oncology, Uppsala University, 75185 Uppsala, Sweden
Merav Fraenkel, Institute of Endocrinology, Soroka Ben Gurion University Hospital, 84965 Beer Sheva, Israel
Leonard Saiegh, Institute of Endocrinology, Bnei Zion Hospital, 33394 Haifa, Israel
Petachia Reissman, Department of Surgery, Shaare-Zedek Medical Center, The Hebrew University School of Medicine, 93722 Jerusalem, Israel
Author contributions: Grozinsky-Glasberg S contributed to study concept and design, interpretation of data, drafting of the manuscript, statistical analysis, study supervision; Thomas D, Strosberg JR, Pape UF, Felder S, Tsolakis AV, Alexandraki KI, Fraenkel M and Saiegh L contributed to acquisition of data; Reissman P and Kaltsas G contributed to critical revision of the manuscript; Gross DJ contributed to study concept and critical revision of the manuscript.
Correspondence to: Dr. Simona Grozinsky-Glasberg, MD, Neuroendocrine Tumor Unit, Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, PO Box 12000, 91120 Jerusalem, Israel. simonag@hadassah.org.il
Telephone: +972-2-6776788 Fax: +972-2-6437940
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Abstract

AIM: To describe disease characteristics and treatment modalities in a group of rare patients with metastatic gastric carcinoid type 1 (GCA1).

METHODS: Information on clinical, biochemical, radiological, histopathological findings, the extent of the disease, as well as the use of different therapeutic modalities and the long-term outcome were recorded. Patients' data were assessed at presentation, and thereafter at 6 to 12 monthly intervals both clinically and biochemically, but also endoscopically and histopathologically. Patients were evaluated for the presence of specific symptoms; the presence of autoimmune disorders and the presence of other gastrointestinal malignancies in other family members were also recorded. The evaluation of response to treatment was defined using established WHO criteria.

RESULTS: We studied twenty consecutive patients with a mean age of 55.1 years. The mean follow-up period was 83 mo. Twelve patients had regional lymph node metastases and 8 patients had liver metastases. The primary tumor mean diameter was 20.13 ± 10.83 mm (mean ± SD). The mean Ki-67 index was 6.8% ± 11.2%. All but one patient underwent endoscopic or surgical excision of the tumor. The disease was stable in all but 3 patients who had progressive liver disease. All patients remained alive during the follow-up period.

CONCLUSION: Metastatic GCA1 carries a good overall prognosis, being related to a tumor size of ⩾ 1 cm, an elevated Ki-67 index and high serum gastrin levels.

Key words: Metastatic gastric carcinoids; Gastrin; Chromogranin A; Somatostatin analogues; Stomach neuroendocrine tumor

Core tip: Metastatic gastric carcinoid type 1 (GCA1) are extremely rare and there is no data regarding their natural history, treatment and prognosis. Based on our study, metastatic GCA1 carries a good overall prognosis. Metastatic spread appears to be related to a tumor size of ⩾ 1 cm, an elevated Ki-67 index, and to high serum gastrin levels. Endoscopic surveillance is extremely important for follow-up. Surgical resection should be performed only in patients in whom total tumor excision is expected. Although still controversial, somatostatin analogues could be considered as first line treatment to lower the elevated gastrin levels and suppress enterochromaffin like cell hyperplasia.

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INTRODUCTION

Gastric carcinoids (GCAs) are neuroendocrine tumors (NETs) of the gastric mucosa originating from enterochromaffin like (ECL) cells[1]. GCAs arise either spontaneously or in response to a chronic hypergastrinemia state; due to their rarity (only 2% of all carcinoids and 8.7% of gastrointestinal carcinoids)[2,3], the predictors of metastatic disease have not been systematically addressed.

GCAs are divided into three distinct types. Type 1 (GCA1) represents the majority (approximately 75%) and is associated with chronic atrophic gastritis and autoimmune destruction of parietal cells. Type 2 (GCA2) (approximately 5%-10%) occurs almost always in the context of Multiple Endocrine Neoplasia type 1 (MEN1). Both types 1 and 2 GCAs occur in the setting of elevated serum gastrin which exerts a trophic effect on gastric enterochromaffin-like (ECL) cells leading to neuroendocrine cell hyperplasia and multifocal polypoid carcinoid tumors. These tumors are well differentiated and carry an excellent overall prognosis. Type 3 GCAs (15%-25%) are not related to hypergastrinemia and follow an aggressive course[4-6].

Type 1 GCAs are usually discovered during upper gastrointestinal tract (GIT) endoscopy performed for non specific symptoms (nausea, abdominal pain, dyspepsia)[7], or during investigation of anemia[8-10]. In the past, type 1 GCA was frequently diagnosed in women in their 5th to 7th decades; however, with the more extensive use of endoscopy, the diagnosis occurs at a younger age[11].

Traditionally, GCA1s are endoscopically removed[12,13]; antrectomy could be considered to remove the source of excessive gastrin secretion[14]. Importantly, somatostatin analogues (SSAs) have been increasingly used in the treatment of patients with GCA1 or GCA2[15], based on their capability to inhibit gastrin release, reduce the ECL cell hyperplasia[16-20], and to substantially decrease tumor load[21-23].

Metastatic GCA1 are extremely rare and little is known about their natural history, treatment and prognosis. We conducted a multicenter, retrospective analysis to describe disease characteristics and treatment modalities in a group of rare patients with metastatic GCA1.

MATERIALS AND METHODS

Twenty consecutive patients with metastatic GCAs1 treated in five tertiary referral centers for at least 6 mo were studied. Information on clinical presentation, biochemical profile, imaging, histopathological findings and disease extent (using the TNM classification)[24] were recorded. The use of varying therapeutic modalities and the long-term outcome of these patients were also recorded. Patients' data were assessed at presentation, and thereafter at 6-12 monthly intervals both clinically and biochemically, but also endoscopically and histopathologically.

Clinical assessment

Patients were evaluated for the presence of symptoms such as abdominal pain, nausea, vomiting and dyspepsia; the presence of autoimmune disorders associated with pernicious anemia and the presence of other gastrointestinal malignancies in other family members were also recorded.

Biochemical evaluation

Pernicious anemia was defined as a low serum vitamin B_{12} level (normal range 180-670 pmol/L) and at least one positive antibody against parietal cells, intrinsic factor or proton-pump antigen. Serum gastrin and chromogranin A (CgA) were measured after an overnight fast, and thereafter at regular intervals (3-6 mo) during the study period. Treatment with proton pump inhibitors (PPIs) was discontinued for at least 3 wk before blood samples were taken. Serum CgA and gastrin were measured using commercially available radioimmunoassay kits: CGA-RIACT, CISBIO International, France (normal reference range of 19.4-98.1 ng/mL), or Euro-Diagnostica, Malmö (upper normal limit 4 nmol/L) for CgA, and DiaSorin, Stillwater, Minnesota 55082-0285, United States (normal reference range of 40-108 mU/L) or EURO-Diagnostica, Malmö (upper normal limit 60 pmol/L) for gastrin, respectively.

Imaging assessment

All patients underwent imaging assessment at diagnosis, including either ^{111}In-pentetreotide scintigraphy (Octreoscan) or (68)Gallium-DOTA-TATE/-TOC/-NOC

Table 1 Clinical and histopathological characteristics of the study patients

Patient No.	No. of lesions	Size, largest lesion (mm)	Ki-67%	CT before Tx	SRS/^{68}Ga before Tx	Distant mets	Gastrin (40-108 mU/L)		Surgery	Residual disease	SSA/monthly dosage (mg)	Outcome	F/U Period (mo)
							at Dx	Last					
1	multiple	15	2%	-	Uptake (stomach, LN)	no	1811	125	wedge resection	no	Som A 90	cure	108
2	solitary	35	2%	Liver mets	Uptake (stomach, Liver)	liver	-	-	Billroth 2 + LN	liver	no	SD	84
3	multiple	21	2%	Liver mets	Uptake (stomach, Liver)	liver	2204	325	none	liver	San LAR 30	CR	36
4	multiple	55	20%	Stomach lesion	Uptake (stomach)	diaphragm	1800	-	Billroth 2 + LN	no	San LAR 30	cure	24
5	multiple	25	1%	Stomach lesion	Uptake (stomach, LN)	no	1403	-	Billroth 2 + LN	no	no	cure	18
6	multiple	-	15%	Hepato-gastric ligament LN	no data	no	-	-	ER	no	no	cure	12
7	solitary	17	4%	LN	Uptake (stomach, LN)	no	700	600	wedge resection	no	no	cure	132
8	multiple	15	1%	Liver mets and LN	Uptake (LN, Liver)	liver	407	190	ER, largest	liver	San LAR 30 + INF 50 mcg/wk	PR	36
9	solitary	10	1%	Liver mets and LN	no data	liver	-	-	wedge resection	no	no	cure	360
10	solitary	30	5%	Stomach lesion	no uptake	no	5130	43	Billroth 2 + LN	no	none	cure	120
11	multiple	17	1%	-	no uptake	no	-	-	Billroth 2 + LN	no	none	cure	168
12	multiple	14	5%	-	no uptake	no	-	-	Billroth 2 + LN	no	none	cure	72
13	solitary	47	15%	-	Uptake (stomach, Liver)	liver	5470	45	ER	liver	none	SD	120
14	multiple	30	2%	-	Uptake (LN, Liver)	liver	1336	335	ER, recurrent	liver	none	SD	48
15	multiple	10	2%	No pathology	no uptake	no	3500	-	Billroth 2 + LN	no	none	cure	48
16	multiple	30	2%	Stomach lesion	no data	no	-	-	Billroth 2 + LN	no	none	cure	36
17	solitary	-	1%	Liver mets	Uptake (liver)	liver	1612	10	Billroth 2 + LN	liver	none	SD	36
18	multiple	20	-	Stomach lesion, mesenteric and gastro-hepatic LN	no data	no	506	-	wedge resection	no	none	cure	60
19	multiple	20	-	No pathology	no uptake	no	1600	-	Billroth 2 + LN	no	none	cure	72
20	multiple	15	-	Liver mets	Uptake (stomach, Liver)	liver	458	336	ER	liver	San LAR 30	SD	72

Nr. of lesions, solitary: one lesion seen on endoscopy, multiples ⩾ 2 lesions seen on endoscopy; CT: Computerized tomography; SRS: Somatostatin receptor scintigraphy (Octreoscan); (68)Ga: (68)Gallium-DOTA-TATE/-TOC/-NOC PET; Tx: Treatment; SSAs: Somatostatin analogues; LN: Lymphadenopathy; mets: Metastases; SomA: Somatuline Autogel; SanLAR: Sandostatin LAR; INF: Interferon α; Billroth 2 + LN: Gastro-jejunostomy and lymph nodes dissection; wedge resection: wedge resection (triangular resection) of a part of the stomach; ER: Endoscopic resection; SD: Stable disease; PR: Partial response; CR: Complete response.

PET (17 patients), computerized tomography (CT) of the abdomen (13 patients), or both modalities (11 patients) (Table 1).

Endoscopic and histopathological assessment

All patients underwent upper GI endoscopy and 6/20 also underwent endoscopic ultra-sonography (EUS). Upper GI endoscopy with multiple biopsies was performed in order to assess the lesions and map surrounding gastric mucosa for changes of atrophic gastritis; the "dominant" lesions were biopsied and removed if possible. EUS was performed to assess invasion of the muscularis propria, regional lymph node involvement and/or visible metastases. Histopathological diagnosis was performed using biopsies taken from both the tumors and the surrounding mucosa at diagnosis or periodically during the follow-up period, or, in case of tumor excision - from the surgical specimen. Sections were immunostained for chromogranin (CG), neuron specific enolase (NSE), synaptophysin (SYN), and the Ki-67 proliferative index using the MIB-I antibody. The diagnosis of NETs was confirmed morphologically during endoscopy together with a positive immunocytochemical staining for NSE, SYN and/or CG.

Table 2 Factors of significance in the suspicion of metastatic gastric carcinoid type 1 *n* (%)

Characteristics	All GCA1 patients (*n* = 254)	Metastatic GCA1 patients (*n* = 20)	*P* value at diagnosis (metastatic *vs* all GCA1)
Age (yr), mean ± SD	58.5 ± 12.7	55.1 ± 12.8	0.050
Size of largest tumor (mm, mean ± SD)	7.9 ± 12.1	20.14 ± 11	< 0.001
Ki-67 (%, mean ± SD)	1.9 ± 2.4	6.8 ± 11.2	< 0.001
Symptomatic	112 (44)	18 (90)	< 0.001
Gastrin levels (mI/L, mean ± SD) at diagnosis	898 ± 418	2138.4 ± 1562	< 0.001

GCA1: Gastric carcinoid type 1.

Table 3 Demographic and clinical characteristics of the patients included in the study *n* (%)

Characteristics	All patients *n* = 20
Age (yr), mean ± SD	55.1 ± 12.8
Male:female, *n*	9:11
Caucasians	95%
Size of primary tumor (mm), mean ± SD	20.14 ± 11
Symptomatic	18 (90)
Atrophic gastritis	20 (100)
Other autoimmune diseases	2 (10)
Familial aggregation	3 (15)

Evaluation of response to treatment

Disease response was defined using established WHO criteria[24].

Patients were considered in remission if symptoms disappeared, gastrin and CgA levels were substantially reduced (> 50% reduction) or returned to normal range and if there was no evidence of residual disease following treatment. The study was approved by the local institutional ethical committees and informed consent was obtained from all patients.

Statistical analysis

Results were expressed as mean ± SD. Nonparametric ANOVA (Kruskal-Wallis one-way ANOVA) was used to assess and compare different parameters (such as the mean age at diagnosis, the size of the largest tumor, the Ki-67 *etc*.) at diagnosis (Table 2), or the levels of gastrin at diagnosis and following surgical treatment/at last visit (Table 1). Post hoc comparisons were made using Mann-Whitney *U* test. A *P* value of < 0.05 was considered significant.

RESULTS

The clinical characteristics of all patients included in the study are shown in Table 3. The cohort included 9 men and 11 women with a mean age of 55.1 years. Whereas women are usually at higher risk for autoimmune atrophic gastritis, our cohort included patients of both genders, showing only a slight preponderance in the number of female patients. The mean duration of follow-up was 83 mo (range 12-360 mo). Other autoimmune diseases (*e.g.*, Hashimoto's thyroiditis, Sjögren's syndrome) were diagnosed in two patients (10%). In three patients (15%) there was a first-degree relative with history of gastric (2 patients) or pancreatic (one patient) adenocarcinoma.

Basal evaluation (at diagnosis)

At diagnosis gastroscopy revealed macroscopic gastric carcinoid tumors (described as "nodules", "ulcers" or "polyps") in all patients, with a mean diameter of 20.13 ± 10.83 mm (mean ± SD) (range 4-55 mm). The tumors were single in 6/20 patients (30%), and multiple (defined as ⩾ 2 tumors seen on gastroscopy) in the remaining 14 (70%). ECL cell hyperplasia was observed in all patients. The mean Ki-67% proliferation index was 6.8% ± 11.2% (range 1%-20%). None of the patients included in the present series presented with ZES and the associated MEN1 syndrome or with characteristics of type 3 gastric carcinoids (Tables 1 and 4).

EUS was intended to be performed in all patients in order to reveal any residual and/or sub-mucosal tumors. Signs of aggressiveness or invasiveness at first biopsy were demonstrated in seven out of 12 patients with available data (58%) and included: ulceration of the primary lesion in two patients (17%); vascular invasion in two patients (17%); invasion of the muscularis mucosa and lamina propria in four patients (33%). Peri-gastric/gastro-hepatic ligament lymph node invasion was observed in 9 patients (45%) as demonstrated by CT scan and/or Octreoscan or (68)Ga-DOTATOC/NOC/TATE PET-CT; distant metastases were present at initial diagnosis in 9 patients (45%), and included liver metastases in eight and diaphragmatic metastases in one out of the 20 patients.

Treatment

Ten out of the twenty patients (50%) underwent total gastrectomy or a Billroth 2 operation (gastro-jejunostomy) and lymph node dissection, another 4 patients (20%) underwent antrectomy and wedge resection, whereas endoscopic resection of the dominant lesion was performed in 5 patients (25%). One patient underwent only primary tumor biopsy (Table 1, patient No. 3).

Histopathological analysis following tumor resection demonstrated positive staining by immunohistochemistry (IHC) for neuroendocrine markers (chromogranin and synaptophysin) in all patients (100%), for vesicular monoamine transporter 2 (VMAT2) in two patients (10%), and for neuron specific enolase (NSE) in seven patients (35%). Ki-67 indices were available in 17 out of the 20 patients included; eleven tumors were defined as ENETS grade 1

Table 4 Features associated with the diagnosis of gastric carcinoid type 1 in our patients

Patient No.	Vitamin B12 levels (n. 180-670 pmol/L)	APCA	Gastrin levels (n. 40-108 mU/L)	Prior use of PPIs	1st gastroscopy (macroscopic)	Histo-pathology	*H.Pylori*
1	45	positive (1/20)	1811	no	multiple	CAG + IM	negative
2	165	positive	-	no	solitary	CAG + IM + NECH	-
3	333	positive (1:160)	2204	no	multiple	CAG + NECH	negative
4	186	positive (1:20)	1800	no	multiple	CAG + NECH	negative
5	104	positive (1:20)	1403	no	multiple	CAG + NECH	negative
6	122	positive (1:80)	-	no	multiple	CAG	-
7	121	-	700	no	solitary	CAG + IM + NECH	-
8	86	-	407	no	multiple	CAG + IM + NECH	-
9	50	-	-	no	solitary	CAG + NECH	-
10	-	positive (1:40)	5130	no	solitary	CAG	-
11	-	-	-	no	multiple	CAG	-
12	-	-	-	no	multiple	CAG	-
13	184	positive (1:160)	5470	no	solitary	CAG	-
14	121	positive	1336	no	multiple	CAG	-
15	215	-	3500	no	multiple	CAG	-
16	-	-	-	no	multiple	CAG + IM + NECH	-
17	345	-	1612	no	solitary	CAG	-
18	130	-	506	no	multiple	CAG	-
19	181	-	1600	no	multiple	CAG	negative
20	167	positive	458	no	multiple	CAG	-

APCA: Antiparietal cells antibodies; PPIs: Proton pump inhibitors; CAG: Chronic atrophic gastritis; IM: Intestinal metaplasia; NECH: Neuroendocrine cells hyperplasia; *H. pylori*: *Helicobacter pylori*.

(Ki-67 ⩽ 2%) and six tumors as grade 2 (Ki-67 between 2%-20%). The final value for the mean Ki-67 proliferation index measured 4.8%, slightly lower than the Ki-67 value at first endoscopy (6.8%); interestingly, the Ki-67 was significantly higher in the liver/lymph node metastases than in the primary tumor in 4/20 patients.

Based on local team decision, five out of the 20 patients assessed were treated with somatostatin analogues (SSAs): in four patients Sandostatin LAR (Novartis, Basel, Switzerland) 30 mg/month, in one patient Somatuline Autogel (Ipsen, Paris) 90 mg/month, whereas in one patient pegylated interferon alpha was added to the SSA at a dosage of 50 micrograms per week, as anti-secretory and anti-proliferative therapy.

Treatment related adverse events were reported in only 3 patients and included diarrhea (one patient), fatigue (in the patient treated with interferon alpha) and gastrectomy-related dumping syndrome in one patient.

None of the patients received chemotherapy or peptide receptor radioligand therapy, to date.

Laboratory and imaging assessment at diagnosis

Gastrin and CgA levels were elevated at diagnosis in all patients with available data (14/20 patients for gastrin, and 13/20 patients for CgA) and reached 2138.4 ± 1562 mU/L for gastrin (normal range 40-108 mU/L) and 507.6 ± 403.7 ng/mL for CgA (normal range 19.4-98.1 ng/mL), respectively. No clear correlation was found between initial gastrin and CgA serum levels and the number or size of the tumors.

High levels of anti-parietal cells antibodies were found in all patients in whom their titer was determined. The levels of vitamin B_{12} were low in all but six patients, with a mean value of 162 ± 87 pmol/L (normal range 180-670 pmol/L) (Table 4).

Data on functional imaging - ^{111}In-pentetreotide scintigraphy (Octreoscan) or (68)Ga-DOTATOC/NOC/TATE PET-CT (performed based on local availability) were available at diagnosis in 17/20 included patients: in 12 patients (71%) there was increased tracer uptake by the gastric lesions as well as by the perigastric metastatic lymph nodes and liver lesions. Twelve patients underwent (68)Ga-DOTATOC/NOC/TATE-PET-CT demonstrating an increased uptake by the tumor and metastases in 9 patients, and no pathological uptake in the remaining 3 patients. Five patients performed an Octreoscan, showing increased uptake by the tumor in 3, and no pathological uptake in 2.

Interestingly, in the five patients with no pathological uptake by either functional imaging method, the Ki-67 index of proliferation was ⩽ 2% and the tumor size was > 1 cm.

Follow-up assessment and treatment outcome

All patients remained alive during the follow-up period. During follow-up after the first intervention, the disease was stable in all patients: in the subgroup who underwent total gastrectomy or Billroth 2 operation (gastro-jejunostomy) and lymph node dissection (10 patients, 50%), as well as in the subgroup of the 4 patients (20%) who underwent antrectomy and wedge resection, the disease did not progress or recur during follow-up. The same was observed in the other patients in the present series, including those who underwent repeated endoscopic resection of the largest lesions. In the seven patients with persistent liver disease, somatostatin analogue treatment was administered in three patients: in two Sandostatin LAR 30 mg/month alone, (inducing disease stabilization in

one patient and complete response in the other), whereas in the third patient pegylated interferon α (PegIntron) at a dosage of 50 micrograms/week was added to Sandostatin LAR 30 mg/month, and induced partial response of the liver metastases. All patients tolerated treatment with SSAs well and none discontinued treatment during the follow-up period. Apart from a slight perturbation in the control of pre-treatment diabetes mellitus in one patient (Table 1, patient 3), there were no other adverse effects associated with somatostatin analogue treatment. Eighteen patients (90%) had symptoms attributed to the disease (such as abdominal pain, nausea, vomiting or dyspepsia) that improved in all following treatment.

Serum gastrin decreased progressively in all patients with available data, from 2138.4 ± 1562 mI/L pre-treatment to 223 ± 193 mI/L at the last visit (normal range 40-108 mI/ L, $P < 0.005$). The levels of serum CgA also significantly decreased, from 507.6 ± 403.7 ng/mL to 57 ± 44.7 ng/mL (mean ± SD) (normal range 19.4-98.1 ng/mL, $P < 0.005$).

DISCUSSION

GCAs are rare neoplasms, accounting for about 1.25% of all malignancies[25]. Their incidence, however, is increasing, most probably as result of the widespread use of endoscopy and imaging. Despite the relatively indolent biological behaviour of GCA1 tumors, approximately 8%-23% have been reported as presenting with an aggressive clinical course, metastasizing to regional lymph nodes and rarely to the liver[7].

The European Neuroendocrine Tumor Society (ENETS) consensus guidelines on GCA1 treatment are based on tumor size (less or more than 1 cm) and specify that, despite a preference for a conservative approach, based on endoscopic follow-up, lesion resection is recommended whenever possible[26]. Specifically, in patients with lesions of more than 1 cm, EUS should be performed to assess gastric wall and lymph nodal involvement before the decision about the type of excision (endoscopic mucosal resection, EMR, or subtotal gastrectomy/wide resection) is taken. Although biotherapy with somatostatin analogues (SSAs) is still a matter of debate according to the ENETS guidelines, we and others have recently demonstrated the beneficial effect of long acting SSAs monthly administration on inhibition of gastrin and CgA levels and of tumor progression, as shown from the regression of ECL-cell hyperplasia and tumor disappearance observed in the great majority of treated patients[21,27,28]. The combination of octreotide and α-interferon has been also reported to be of value in a patient with metastatic disease to the liver[7].

As the therapeutic modalities to inhibit tumor progression in metastatic GEP-NETs are still unsatisfactory, new approaches are under investigation. Recent preclinical data demonstrated possible beneficial effects of interferon-beta (IFN-β) in inhibiting cell proliferation and stimulating apoptosis in a PNET cell line model[29-31]. Moreover, a new gastrin/CCK2 receptor antagonist molecule, YF476, appears to induce potent inhibition of ECL cell proliferation compared with dopamine agonists or dopamine/somatostatin chimera molecules, and to provide new insights for the therapy of hypergastrinemic gastric NETs associated with low acid states, such as in our patients[32]. Noteworthy, a recent phase Ⅱ study demonstrated good tolerability for the multi receptor ligand SSA pasireotide (SOM230) in patients with GEP NETs refractory to available SSAs[33].

In the present study we sought to define risk factors for increased malignant potential at the time of diagnosis in patients with GCA1. From a total of 254 consecutive patients with GCA1 followed and treated at 5 tertiary referral medical centers, we identified 20 patients with metastatic disease to locoregional lymph nodes or liver at presentation (7.9%). In our series, the patients with metastatic GCA1 were younger, had larger tumors, had a higher Ki-67 proliferation index, and presented with higher gastrin levels compared with the group of patients with non-metastatic GCA1 tumors (Table 2). These results are in accordance with a recent study published by Saund MS and coworkers[34], demonstrating that in a group of 984 patients with localized GCA1, tumor size and depth predict lymph node metastasis; they recommended endoscopic resection for intraepithelial tumors < 2 cm and perhaps tumors < 1 cm invading into the lamina propria or submucosa.

In the present series, most of the patients with metastatic GCA1 were symptomatic, with presence of epigastric or abdominal pain, dyspepsia, bloating, nausea, loose stools or early satiety. A possible explanation for these symptoms may be the presence of atrophic gastritis together with achlorhydria in all patients with GCA1, as well as the increased levels of gastrin[35,36].

Of note, there was a clear correlation between the size of the tumor at diagnosis and tumor metastatic spread in our study, as in all patients included the tumor size was ⩾ 1 cm. Moreover, the mean Ki-67 index of proliferation in the metastatic GCA1 was significantly higher than in the localized tumors (Table 2), most probably due to an increased number of patients with grade 2 tumors in our series (6/20 patients, 30%) and indicating the utmost importance of performing immunohistochemical staining for this marker in all patients with GCA1. Findings of aggressiveness and/or invasiveness at diagnosis (*e.g.*, ulceration of the lesion, vascular invasion, muscularis propria or lamina propria invasion) are all predictive factors for an aggressive biological behaviour, in parallel with a tumor size of ⩾ 1 cm. In this high risk group, EUS or cross-sectional imaging should be performed to assess the presence of lymph nodes/liver metastatic disease.

Regarding the imaging characteristics of metastatic GCA1, it appears from our study that no radiological parameters, tumor number or tumor uptake on somatostatin receptor scintigraphy could distinguish between local and metastatic tumors. All of the metastatic GCA1 patients accomplished tumor resection with a low compli-

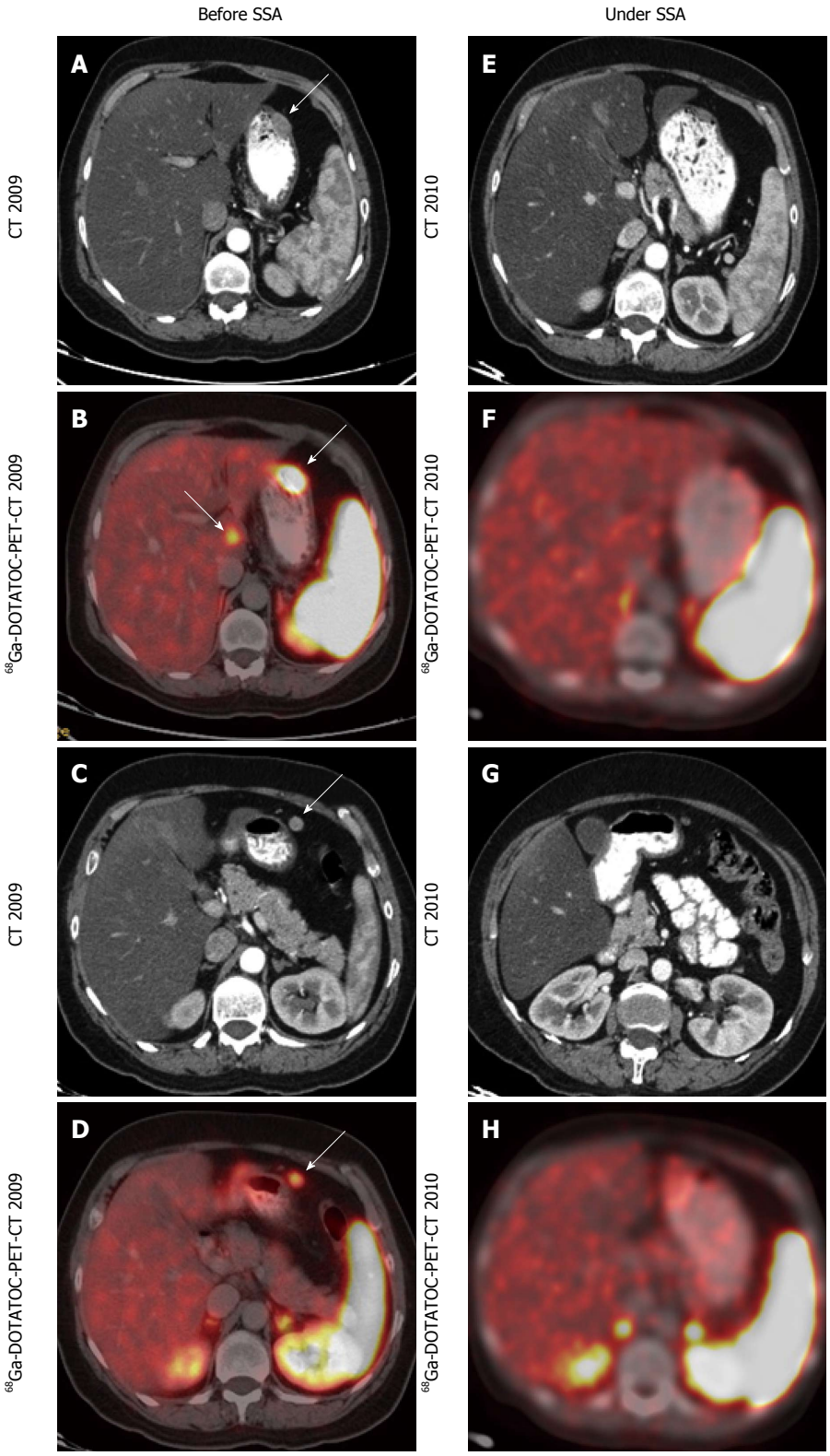

Figure 1 Computed tomography and ^{68}Ga-DOTATOC-PET-Computed tomography images before and during treatment with somatostatin analogue (sandostatin LAR 30 mg/mo). Pathologic uptake in the gastric and hepatic lesion (A + B) adjacent lymphadenopathy and liver lesion (C + D), disappeared on follow up imaging (E - H).

cation rate, and with an excellent outcome. Following or in parallel with tumor resection, medical therapy was administered in five patients, based on clinical experience. Importantly, under treatment with SSAs, the disease stabilized in 3 patients, in one patient the primary tumor, the metastatic lymph nodes and the liver metastases regressed and completely disappeared (Figure 1 and Table 1), whereas in another patient, pegylated interferon α

was added to the SSA and induced disease stabilization. In none of the twenty patients with metastatic GCA1 was disease progression observed over a mean follow-up period of 54 mo.

Based on the results of our study, metastatic GCA1 do exist, are extremely rare, and carry a good overall prognosis. Metastatic spread appears to be related to a tumor size of ⩾ 1 cm, and therefore endoscopic ultrasound evaluation is recommended in such patients. Elevated Ki-67 index of tumor proliferation, as well as high serum gastrin levels, represent additional risk factors for metastatic disease. Endoscopic resection and/or subtotal gastrectomy are recommended by the ENETS guidelines in all patients with gastric carcinoids of ⩾ 1 cm; however, in our personal opinion[21], SSAs might be considered as possible treatment in order to lower the elevated gastrin levels, suppress ECL cell hyperplasia, and obviate the need for surgical excisions, particularly in patients with multiple or relapsing tumors, as well as in those with metastatic disease of the liver. Treatment with SSAs could be theoretically continued as long as gastrin/CGA levels are suppressed, in parallel with disease stabilization observed on regular endoscopic follow-up. However, this approach is still problematic by the lack of controlled trials, the high cost of these drugs as well as the limited accessibility to SSAs in some areas. Although the potential role of SSAs ("cold" SSAs, as monthly injections, or radioactive "hot" SSAs, PRRT) cannot be denied - it remains still controversial and it has to be confirmed in larger studies. Moreover, surgical procedures should be most probably performed only in patients in whom total tumor excision can be expected. Therefore, in these patients, endoscopic surveillance (as well as repeated oncological surveillance by imaging in metastatic cases) is the most important measure. Prospective multicenter randomised studies, including larger number of patients, would be optimal for definition of the best therapeutic approach, the duration of treatment and its efficacy in terms of long-term survival. However, due to the extreme rarity of this condition, the probability for such trials is remote, and therefore clinicians who manage these patients will most probably have to rely on personal experience and data from retrospective studies, such as ours.

COMMENTS

Background

Gastric carcinoids (GCAs) are rare neuroendocrine tumors (NETs) of the gastric mucosa originating from enterochromaffin like (ECL) cells. Type 1 (GCA1) represents the majority, and usually carries an excellent overall prognosis.

Research frontiers

Metastatic GCA1 are extremely rare and little is known about their natural history, treatment and prognosis. The present study represents a multicenter, retrospective analysis aiming to describe disease characteristics and treatment modalities in a group of rare patients with metastatic GCA1.

Innovations and breakthroughs

The authors demonstrated that the metastatic potential of GCA1 appears to be related to a tumor size of ⩾ 1 cm, an elevated Ki-67 index and high serum gastrin levels. Endoscopic ultrasound is recommended in patients with these risk factors. Somatostatin analogues may be used, particularly in patients with multiple relapsing tumors, and with metastatic disease. Surgical procedures should be performed only in patients in whom total tumor excision is expected.

Applications

By understanding the potential malignant behavior of these rare tumors, this study may represent a future strategy for therapeutic intervention in patients with metastatic GCA1.

Peer review

This is a useful multicenter, retrospective analysis of a rare disease and provides helpful information on risk factors, tumor characteristics, treatment procedures and prognosis in a wide and rare group of patients with metastatic GCA1.

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