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ORIGINAL ARTICLE

Gastric cancer in patients with type I gastric carcinoids

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Abstract
Background Atrophic body gastritis (ABG) is associated with both type I gastric carcinoids (T1-GCs) and intestinal-type gastric cancer. The occurrence of gastric cancer in ABG patients with type I gastric carcinoids has not yet been described.
Aim To describe the occurrence at follow-up of gastric cancer in ABG patients with type I gastric carcinoid in a retrospective case series in a single tertiary referral center.
Methods Between 1994 and 2012, 17 new cases of T1-GCs were diagnosed among a cohort of ABG patients in a single tertiary referral center for ABG. The clinical charts of these 17 T1-GC patients were retrospectively evaluated for the occurrence of gastric cancer at follow-up (median 4.2 years, range 0.5–13).
Results In 4 (23.5 %)/17 T1-GCs patients (3 females, age 40–78 years), gastric cancer occurred (median follow-up 5.9 years, range 5.1–13). Three cases were intestinal-type adenocarcinomas and one a signet-ring cell diffuse gastric cancer, localized in three cases in the antrum. In two patients, it was detected on random biopsies during follow-up gastroscopy; in the other two, gastroscopy was performed because of new symptoms. All patients with gastric cancer had associated autoimmune features (pernicious anemia, autoimmune thyroid disease and a spared antrum) compared to 77, 46 and 54 % of those without gastric cancer, although statistical significance was not reached.
Conclusions This case series shows that in patients with T1-GCs, gastric cancer may frequently occur at long-term follow-up. Thus, these patients should be monitored by a long-term surveillance program, including an accurate bioptic sampling of the antral mucosa.

Keywords Gastric cancer · Type I gastric carcinoids · Atrophic body gastritis · Pernicious anemia · Autoimmune gastritis

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Introduction

Type I gastric carcinoids (T1-GCs) are rare tumors that may arise in patients with atrophic body gastritis (ABG). These tumors are well differentiated with a low proliferative index (expressed as Ki67) and generally benign behavior; they constitute up to 80 % of all gastric carcinoids [1–3]. A major pathogenetic factor for T1-GCs is hypergastrinemia due to ABG. Gastrin acts as a growth type factor for enterochromaffin-like cells, which in ABG are chronically induced to proliferate through a multistep process passing from hyperplasia to dysplasia and then to carcinoids [3–5]. Long-term observational studies assessing the incidence of T1-GCs in ABG patients are scarce [6–8]. In a recent cohort study, ABG patients were followed up for 1,463 person-years, reporting an annual incidence rate of 0.4 % for type I gastric carcinoids [9]. An older

study reported an annual incidence of 2 %, observing 8 new cases of T1-GCs in 416 patient-years [7]. In the above cited study, pernicious anemia was present in almost 50 % of patients with T1-GCs [9], while previous studies exclusively included patients with this condition [7, 8, 10–12].

Atrophic body gastritis is a condition characterized by the loss of gastric glandular structures, which are replaced by connective tissue (non-metaplastic atrophy) or by glandular structures inappropriate for the location (metaplastic atrophy) [13]. Epidemiological data suggest that ABG is associated not only with T1-GCs, but also with intestinal-type gastric cancer. Atrophic body gastritis is considered a precursor condition for gastric cancer and non-invasive neoplasia [14, 15]. Previous studies reported a varying progression rate of ABG to gastric cancer up to 2 % per year [16–18]. Gastric cancer is still the fourth most common cancer worldwide and the second cause of cancer-related death [19]. It is accepted that the carcinogenesis involves a multistep progression from *Helicobacter pylori*-related chronic inflammation of the gastric mucosa to atrophic gastritis, intestinal metaplasia, dysplasia and finally intestinal-type gastric cancer [14].

In the literature, there are some reports on single cases or very small case series of synchronous presentation of gastric adenocarcinoma and carcinoid [20–25] or descriptions of gastric composite tumors harboring adenocarcinoma and a carcinoid in the same lesion [26, 27]. To our knowledge, the occurrence of gastric cancer at follow-up in patients with T1-GCs has not yet been described. Thus, the aim of this case series was to describe the occurrence of gastric cancer at follow-up in patients with T1-GCs in a single tertiary referral center.

Materials and methods

Study population

In the study period between 1994 and 2012, 17 new cases of T1-GCs were diagnosed among a cohort of ABG patients in our unit, a tertiary referral center for ABG. These 17 ABG patients with T1-GCs were included in the study, and their clinical charts were retrospectively evaluated for the occurrence of gastric cancer at follow-up. Inclusion criteria were the diagnosis of T1-GC and at least one endoscopic-histological follow-up investigation. Exclusion criteria were the incompleteness of clinical charts, refusal of follow-up, or the presence of other neoplastic diseases or severe chronic illnesses. Baseline features of patients with T1-GC at baseline are given in Table 1. In slightly more than half of the patients, the gastric carcinoid was detected on a polypoid lesion (52.9 %), while in the remaining patients it was found on random biopsies with normal endoscopic appearance (47.1 %). As expected, in all cases the T1-GCs were detected in the gastric body. The majority were female (76.5 %), the median age was 49 years, and the median

Table 1 Baseline features of 17 atrophic body gastritis patients with type I gastric carcinoids diagnosed in the reference period between 1994 and 2012 at a tertiary referral center

Female gender, *n* (%)	13 (76.5)
Age, years, median (range)	49 (23–78)
Follow-up	
Months, median (range)	50 (6–156)
Years, median (range)	4.2 (0.5–13)
Number of follow-ups	
Median (range)	3 (2–13)
Mean ± SD	5 ± 3.4
Sydney score of corporal atrophy, mean ± SD	2.6 ± 0.6
Sydney score of intestinal metaplasia atrophy, mean ± SD	1.3 ± 0.9
Grading of corporal atrophy, *n* (%)	
Severe	12 (70.6)
Moderate	4 (23.5)
Mild	1 (5.9)
Grading of intestinal metaplasia, *n* (%)	
Severe	2 (11.8)
Moderate	5 (29.4)
Mild	7 (41.2)
Absent	3 (17.6)
Presence of antral gastritis, *n* (%)	7 (41.2)
Presence of antral atrophy, *n* (%)	3 (17.6)
Serum levels of chromogranin A, ng/ml, median (range)	241 (30–620)
Serum levels of fasting gastrin, pg/ml, median (range)	587 (110–4890)
Positivity to parietal cells antibodies, *n* (%)	17 (100)
H. pylori infection, *n* (%)	
Seropositivity to *H. pylori* antibodies (IgG)	5 (29.4)
Histological positivity to *H. pylori*	1 (5.9)
Actual or past smoking, *n* (%)	5 (29.4)
1st degree family history of gastric cancer, *n* (%)	2 (11.8)
1st degree family history of peptic ulcer, *n* (%)	7 (41.2)
Copresence of autoimmune thyroid disease, *n* (%)	10 (58.8)
Presence of anemia, *n* (%)	
Pernicious anemia	14 (82.4)
Iron deficiency anemia	3 (17.6)
Type of type I gastric carcinoids	
Intramucosal (in the absence of any endoscopic lesion)	8 (47.1)
On a polypoid lesion[a]	9 (52.9)

[a] In seven cases, the type I gastric carcinoid was detected on a micropolyp of the corporal mucosa (≤5 mm) and removed by biopsy forceps; in 2 cases, the polypoid lesion was >10 mm and endoscopic snare polypectomy was performed

follow-up was 50 months (6–156 months). Severe corporal atrophy was present in 70.6 %, while intestinal metaplasia was severe in only 11.8 % of patients. Six (35.3 %) patients were positive for *H. pylori*, and two (11.8 %) patients had a positive family history of gastric cancer. Pernicious anemia was present in 82.4 % of patients, while the remaining patients had iron deficiency anemia. More than half of patients (58.8 %) had copresence of autoimmune thyroid disease. In all 17 included patients, the T1-GCs were histologically classified as NET G1 in the WHO classification [2].

Diagnosis of type I gastric carcinoid and atrophic body gastritis

At baseline and at follow-up, esophagogastroduodenoscopy (EGD) was performed under sedation with an Olympus video gastroscope GIF-Q165. During each EGD, all polyps found were resected, and a complete bioptic gastric mapping was performed according to a previously described protocol [9]. T1-GCs were treated with endoscopic management and/or by endoscopic/histological follow-up, as appropriate [6, 9]. All patients with a diagnosis of T1-GCs underwent at least one imaging procedure for tumor staging (CT-scan, Octreoscan, Gallium-68 PET scan) [6, 9]. In case of T1-GCs presenting as polyps >1.5 cm in diameter or suspected incomplete resection, endoscopic ultrasonography (EUS) was performed after sedation by intravenous propofol using a Pentax EG-3630UR endoscope to assess the polyp's complete removal and to exclude lymph nodal involvement [1]. The specimens were formalin-fixed and routinely processed. Five-µm-thick mucosal gastric sections were stained with hematoxylin-eosin for routine examination and Giemsa staining for *Helicobacter pylori* (*H. pylori*). Immunohistochemistry was performed using monoclonal antibody anti-chromogranin A (Clone DAK-A3; Dako, Glostrup, Denmark), Ki67 (Clone MIB1, Dako, Glostrup, Denmark) and rabbit polyclonal antibody anti-gastrin (Dako Code A 0568), and visualized by Envision-Flex (Dako) in a Dako Autostainer instrument according to the manufacturer's instructions [6, 9].

Serological assays were performed in every patient, evaluating: fasting serum gastrinemia (nv <40 pg/ml), chromogranin A (nv <98 ng/ml), anti-parietal cell antibodies and IgG *H. pylori* antibodies (nv <21 UI/ml). Gastrin and chromogranin A were measured by radioimmunoassay (RIA), pepsinogen I was assessed by an RIA commercial kit (Pepsik; Sorin, Saluggia, Italy), anti-parietal cell antibodies were evaluated in serum using a solid-phase immunosorbent assay commercial kit (Autostat, Cogent Diagnostic Ltd., Edinburgh, UK), while *H. pylori* IgG antibodies were measured by a commercial enzyme-linked immunosorbent assay kit (GAP test IgG; Biorad, Milan, Italy) [6, 9].

The anemia pattern was also assessed, evaluating hemoglobin, MCV, ferritin and vitamin B_{12} values.

Pernicious anemia was defined as low hemoglobin concentration and MCV >100 fl together with low B_{12} vitamin levels, responding to intramuscular B_{12} vitamin treatment. Iron deficiency anemia was defined as a low hemoglobin concentration, MCV <80 fl and ferritin <30 ng/ml [28, 29]. The diagnosis of autoimmune thyroid disease was based on the presence of thyroid autoantibodies and thyroiditis signs at ultrasound evaluation irrespective of thyroid function, as previously described [30].

Atrophic body gastritis diagnosis was based on the presence of hypergastrinemia and atrophy of the body mucosa as confirmed by histological evaluation. According to the updated Sydney system, gastric body atrophy was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands; this variable was graded on a four-grade scale represented by the absence of replacement (score 0), replacement to a mild degree (score 1), moderate degree (score 2) or severe degree (score 3), as previously reported [6, 9, 28]. Personal and clinical data, family history of gastric neoplasia and smoking habit were recorded for all patients during a structured clinical interview [9, 18]. Diagnosis of T1-GCs was performed when enterochromaffin-like cell proliferation was >500 µ [31], classified according to the 2010 WHO criteria [2].

H. pylori status was considered positive when a positive *H. pylori* immunoglobulin G titer was detected and/or bacteria were revealed at histology (Giemsa stain) [28, 32]. Bismuth-based triple regimen eradication therapy was prescribed in the case of *H. pylori* positivity, and, after 6 months, the absence of *H. pylori* at histology and a decrease of at least 50 % in the initial titer of *H. pylori* IgG was the criterion for the successful cure of infection [32].

Follow-up

Median endoscopic follow-up of the study population was calculated as the time interval between the first and last endoscopy performed by each patient. After the first diagnosis of T1-GCs in ABG patients, gastroscopy with extensive bioptic sampling after 6 and 12 months was performed. If T1-GC was not confirmed at two following gastroscopies, patients were followed up by the general follow-up protocol for ABG patients, that is, a follow-up gastroscopy scheduled at 4-year intervals with the standard bioptic sampling (at least three biopsies taken in the gastric antrum and corpus). Polypoid lesions up to 5 mm were removed by forceps; otherwise, an electrocautery snare was used [9, 18].

Table 2 Patients with type I gastric carcinoid who developed an epithelial neoplastic lesion

Patient	Gender	Age, years	Type of lesion	Diagnosis of gastric cancer	Localization/ TNM	Time of occurrence after diagnosis of type I GC, months (years)	Outcome
1	F	40	Low-grade dysplasia (intramucosal, endoscopically normal mucosa, detected on random biopsies)	Gastroscopy according to follow-up protocol	Antrum	17 (1.4)	
			Diffuse gastric cancer (signet-ring cells) in situ (endoscopically normal mucosa, detected on random biopsies)		Antrum T1N0M0	156 (13)	Gastric surgery alive
2	M	78	Intestinal-type adenocarcinoma (gastric ulcer, 3 cm)	New onset of anemia	Angulus T1N0M0	80 (6.7)	No surgery due to comorbidities dead
3	F	58	Intestinal-type adenocarcinoma (gastric ulcer, 2 cm)	New onset of epigastric pain	Antrum T1N0M0	63 (5.2)	Gastric surgery dead (complications of surgery)
4	F	49	Intestinal-type adenocarcinoma in situ (endoscopically normal mucosa, detected on random biopsies)	Gastroscopy according to follow-up protocol	Antrum TisN0M0	61 (5.1)	Gastric surgery alive

Results

During a total median follow-up period of 4.2 years (range 0.5–13 years) in 4 (23.5 %) out of 17 T1-GCs patients, gastric cancer occurred at a median follow-up of 5.9 years (5.1–13 years). Table 2 summarizes the features of the four patients in whom gastric cancer occurred. Three patients were female, and their ages ranged from 40 to 78 years. In two patients, the neoplastic lesion was detected on random biopsies during a scheduled follow-up gastroscopy, while in the remaining two patients gastroscopy was performed because of the new onset of symptoms: epigastric pain in one case and anemia in the other. In three cases, the gastric cancer was localized in the antrum and in one case at the angulus. All lesions occurred at long-term follow-up between 5.1 and 13 years after the first diagnosis of T1-GCs. In one patient, a low-grade dysplasia in the antrum had been detected previously (at 1.4-year follow-up). In three cases, the histological diagnosis of gastric cancer was intestinal-type adenocarcinoma (Fig. 1), and in one case, it was a signet-ring cell diffuse gastric cancer (Fig. 2). This latter case had a negative family history for gastric cancer, while among the three cases with intestinal-type adenocarcinoma, one had a positive family history of gastric cancer.

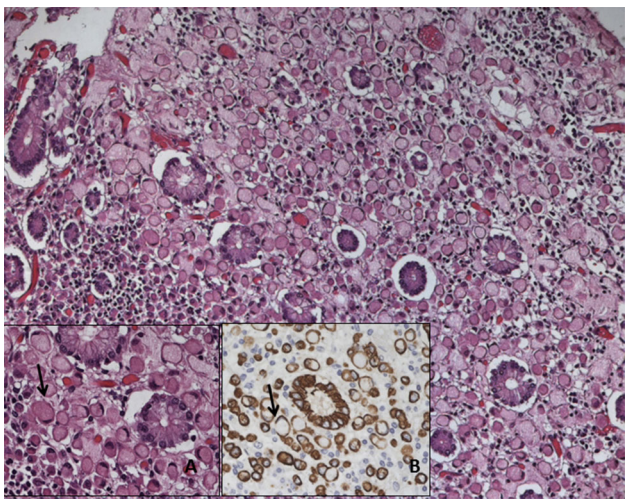

Fig. 1 Gastric adenocarcinoma (tubular type, see WHO 2010), moderately differentiated (G2) (H&E ×10)

With regard to *H. pylori*, only one case with an adenocarcinoma had a positive titer of antibodies to *H. pylori*, and the infection was cured. At the time of diagnosis of gastric cancer, the tumor lesion was classified as T1 or less (one case was classified as Tis), and in none of the cases were lymph node or distant metastases detected (T1/Tis N0 M0). With regard to outcome, in one case neither gastric surgery nor chemotherapy could be performed because of severe comorbidities, and the patient died because of the progression of gastric cancer. In three cases, gastrectomy was performed; two patients are alive, but one patient died because of surgical complications. In the three cases who underwent surgery, the histopathological diagnosis was confirmed on the surgical specimen.

With the limits of the small sample size in the two groups, we tried to compare the clinical and histological features of

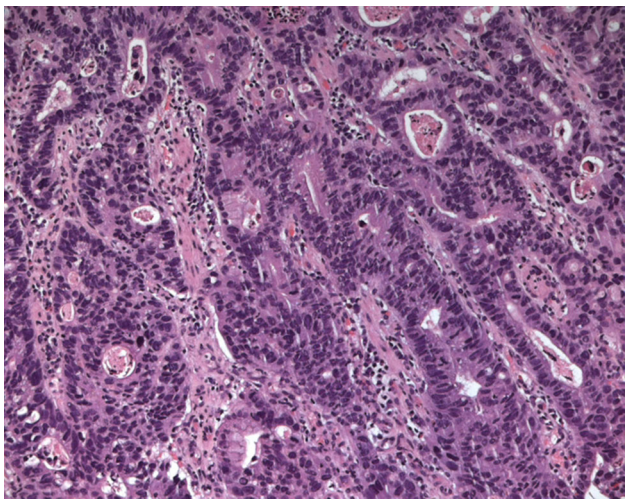

Fig. 2 Poorly cohesive/signet ring gastric carcinoma (see WHO 2010). Inset A shows high magnification (H&E ×40) of signet ring cells in the lamina propria (*arrow*) that show cytokeratin expression. (Inset B, IHC ×40)

T1-GC patients with and without gastric cancer. The two groups were similar with regard to age, gender and histological scores of ABG and presentation type of T1-GCs. In the four patients in whom gastric cancer developed, the overall follow-up was longer compared to the other patients (71.5 versus 41 months, $p = 0.0542$). Antral gastritis and antral atrophy, two features associated with increased risk of gastric cancer, were absent in all four patients with gastric cancer compared to seven and three patients, respectively, without gastric cancer ($p = 0.18$ and 0.76). All four patients with gastric cancer had an associated autoimmune thyroid disease and pernicious anemia compared to 46.1 and 76.9 % of patients without gastric cancer ($p = 0.18$ and 0.76).

Of these four patients who developed gastric cancer at follow-up, in one case the T1-GC was detected on a polyp, which was removed endoscopically. In this case, no coexistence of both tumor lesions (adenocarcinoma and T1-GC) at the same time point was observed. In the other three cases, the T1-GCs were intramucosal and were detected at random biopsies without any endoscopic lesion. Only in one case in one mucosal specimen of the gastric biopsies taken at the moment of the diagnosis of gastric cancer was the presence of an intramucosal T1-GC described. Because the intramucosal T1-GCs of the other two patients were neither removed nor treated in any other way, also in these two patients, the coexistence of the gastric cancer and the neuroendocrine tumor cannot be excluded.

Discussion

The main finding of this case series is that gastric cancer occurred in 4 (23.5 %) out of 17 T1-GC patients. All these lesions occurred at long-term follow-up, the earlier two 5 years, the other two 6.7 years and even 13 years after diagnosis of T1-GC.

This relatively high frequency of gastric cancer in patients with T1-GCs is surprising. One possible explanation may be historical reasons regarding the changed treatment of T1-GCs. Albeit the management of T1-GCs has not yet been codified and several approaches have been suggested, in the past, mainly gastric surgery was proposed in order to definitively stop hypergastrinemia by antrectomy or radically remove the carcinoid by total gastrectomy [33–35]. In the last decade, as a valid alternative to gastric surgery, conservative management by serial endoscopic controls and endoscopic lesion removal has been proposed, and a recent single-center prospective study showed that endoscopic follow-up with lesion resection is a safe and effective management for T1-GCs [36]. The fact that in the past patients with T1-GCs underwent total gastrectomy or antrectomy preserved them from the occurrence of gastric cancer, and this may be one of the reasons why the high frequency of gastric cancer in patients with T1-GCs has never been observed before.

Another possible explanation for why patients with T1-GCs might more frequently develop gastric cancer may be the effects of long-standing hypergastrinemia in these patients. Hypergastrinemia has been proposed in many models of gastric carcinogenesis and seems to be a common causative factor in otherwise different circumstances; in all species where long-term hypergastrinemia has been induced, an increased risk of gastric malignancy, with adenocarcinoma phenotype and even the signet-ring cells phenotype, was observed [37, 38].

In any case, the long-term conservative management of T1-GCs exposes these patients to the development of gastric cancer. This risk is basically present in ABG because of the pathophysiological changes related to gastric body atrophy, such as increased pH, reduced ascorbic acid and scavenging of nitrites and other potential carcinogenic substances [14, 39]. Patients with ABG are at higher risk for gastric cancer, and progression rates of ABG to gastric cancer of up to 2 % per year [16–19] have been reported. In a recent cohort study on ABG patients with a median follow-up of 4.3 years, an annual incidence rate (person-years) of 0.2 % for gastric cancer was observed [18].

However, this new finding of the apparently high occurrence of gastric cancer in T1-GCs patients should not necessarily be interpreted as a causal association between the two gastric tumors, which may occur in the same patient at different time points of the natural history of ABG.

In patients with T1-GCs, because of the high recurrence rate an endoscopic follow-up, including an accurate bioptic

mapping of the gastric body and fundus to identify intramucosal carcinoids, every 6–12 months after diagnosis is suggested; this approach seems safe for T1-GCs [1, 9, 36].

Our results show that in patients with T1-GCs also gastric cancer may frequently occur. These patients should therefore be monitored also for this neoplasia by using a standardized biopsy protocol including the sampling of the gastric body and antral mucosa [18, 40]. Indeed, in our case series three out of the four gastric cancers were localized in the gastric antrum. The application of this standard biopsy control led to the diagnosis of one intestinal-type adenocarcinoma and one signet-ring diffuse gastric cancer on random biopsies in the gastric antrum. The case of one signet-ring diffuse gastric cancer in a patient with T1-GCs raises the possibility of a mere association by chance of two neoplasias in the same patients and thus not to be related to ABG gastric cancer risk.

The observation that three out of the four gastric cancers arose in the gastric antrum seems peculiar. In a previous study on ABG patients without T1-GCs at a median follow-up of 4.3 years, three intestinal-type adenocarcinomas occurred, which were all located in the gastric antrum [18]. With regard to biopsy locations, pre-malignant gastric lesions associated with *H. pylori* infection have been shown to occur most commonly in the antrum and incisura angularis [41]. Unfortunately, data about the topography of gastric cancer in ABG are scanty [16, 42].

Synchronous gastric adenocarcinoma and carcinoid have been reported in single cases or small case series [20–25]. Three of the four T1-GC cases with gastric cancer in this study had intramucosal T1-GCs without endoscopic changes, which were neither removed nor pharmacologically treated. Only in one of these T1-GC cases, at the moment of diagnosis of gastric cancer, did a concomitant T1-GC recur at random biopsies of the apparently normal gastric mucosa, but also in the other two cases with intramucosal T1-GCs the coexistence with gastric cancer could not be excluded. Thus, it is possible that at least in some of the described cases of synchronous gastric cancer and carcinoids the diagnosis of an underlying ABG predisposing to both tumor types was missed.

Another observation emerging from this case series is that all four patients with gastric cancer had well-known features of autoimmune gastritis [29, 30], that is, a spared antrum, associated pernicious anemia and autoimmune thyroid disease, while in the group of patients without gastric cancer, about half had antral gastritis and autoimmune thyroid disease, and pernicious anemia was present in slightly more than 75 %. These findings raise the question of the role of autoimmune gastritis in patients with T1-GCs and gastric cancer. A recent systematic review shows a pooled gastric cancer incidence rate in pernicious anemia of 0.27 % per person-years and an estimated nearly sevenfold relative risk of gastric cancer in pernicious anemia patients, thus strengthening the associated risk of gastric cancer in patients with autoimmune gastritis [43].

The present study has some strengths, such as the prospective inclusion of patients with standardized diagnostic criteria for ABG as well as for T1-GCs, the single referral center, the follow-up protocol and long-term cohort study, but we are aware of some limitations, such as the small sample size, which strongly limits the statistical analyses, and the long inclusion period. These limits are due to the overall low prevalence of T1-GCs and might be overcome by well-designed multicenter studies. To better evaluate the real occurrence of gastric cancer in these patients, in particular with regard to autoimmune gastritis, further studies are needed.

In conclusion, this case series shows that in T1-GC patients, gastric cancer may frequently occur at long-term follow-up. Thus, these patients should be monitored by a long-term surveillance program, including an accurate bioptic sampling of the antral mucosa.

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