



**HAL**  
open science

## Development of Type I Gastric Carcinoid in patients with Chronic atrophic gastritis

Lucy Vannella, Andrea Sbrozzi-Vanni, Edith Lahner, Cesare Bordi, Emanuela Pilozzi, Vito Domenico Corleto, John Frederick Osborn, Gianfranco Delle Fave, Bruno None Annibale

► **To cite this version:**

Lucy Vannella, Andrea Sbrozzi-Vanni, Edith Lahner, Cesare Bordi, Emanuela Pilozzi, et al.. Development of Type I Gastric Carcinoid in patients with Chronic atrophic gastritis. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (12), pp.1361. 10.1111/j.1365-2036.2011.04659.x . hal-00632733

**HAL Id: hal-00632733**

**<https://hal.science/hal-00632733>**

Submitted on 15 Oct 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Development of Type I Gastric Carcinoid in patients with  
Chronic atrophic gastritis**

Journal:	<i>Alimentary Pharmacology &amp; Therapeutics</i>
Manuscript ID:	APT-1121-2010.R1
Wiley - Manuscript type:	Original Scientific Paper
Date Submitted by the Author:	11-Mar-2011
Complete List of Authors:	Vannella, Lucy Sbrozzi-Vanni, Andrea Lahner, Edith Bordi, Cesare Pilozi, Emanuela Corleto, Vito osborn, john; La Sapienza University of Rome, Public Health Science Delle Fave, Gianfranco Annibale, Bruno; University, Clinical Science
Keywords:	Stomach and duodenum < Organ-based, Gastritis < Topics, Gastric cancer < Disease-based, Endoscopy < Topics

## DEVELOPMENT OF TYPE I GASTRIC CARCINOID IN PATIENTS WITH CHRONIC ATROPHIC GASTRITIS

**Running Head :** Type I Gastric Carcinoids in atrophic gastritis

Lucy Vannella, M.D., Andrea Sbrozzi-Vanni, M.D., Edith Lahner, M.D., Cesare Bordi\*, M.D., Emanuela Pilozzi#, M.D., Vito Domenico Corleto<sup>^</sup>, M.D., John Osborn<sup>o</sup>, Gianfranco Delle Fave, M.D., Bruno Annibale, M.D.

Dipartimento Medico-chirurgico di Scienze cliniche, tecnobiomediche e medicina traslazionale, Sant'Andrea Hospital, School of Medicine, University Sapienza of Rome, Italy; \*Department of Pathology, University of Parma, Italy; #Department of Pathology, Sant'Andrea Hospital, School of Medicine, University Sapienza of Rome, Italy; <sup>^</sup>Centro Ricerche "Fate Bene Fratelli", San Pietro Hospital, Roma, Italy; <sup>o</sup>Department of Public Health Sciences, University Sapienza of Rome, Italy.

**Key Words:** chronic atrophic gastritis, type I gastric carcinoid, incidence, prevalence

**Word Count:** 3156

### ADDRESS for Correspondence:

Bruno Annibale,

Dipartimento Medico-Chirurgico di Scienze Cliniche,

Tecnobiomediche e Medicina Traslazionale,

Sant'Andrea Hospital, School of Medicine, University Sapienza of Rome, Italy

Via di Grottarossa 1035, 00189 Rome (Italy)

Fax number +39 06 4455292 e-mail: [bruno.annibale@uniroma1.it](mailto:bruno.annibale@uniroma1.it)

## ABSTRACT

**Background:** Long-term observational studies assessing the incidence of Type I Gastric Carcinoid (GC) in patients with chronic atrophic gastritis are **few**. The aim of the present study was to evaluate the occurrence at diagnosis and during follow-up and to identify patient features associated with the presence of TypeIGC in a cohort of chronic atrophic gastritis patients.

**Methods:** 367 chronic atrophic gastritis patients (245 females, age 54[18-79]years) underwent regular follow-up by gastroscopy. The incidence of TypeIGC was determined in chronic atrophic gastritis patients with at least 2 years of follow-up (n=214). Baseline clinical and histological features were analysed as **factors associated** with the presence of TypeIGC by **univariate analysis**.

**Results:** TypeIGC was diagnosed in **9(2.4%)** patients at the moment when chronic atrophic gastritis was diagnosed. After 1463 person-years, 6 patients developed TypeIGC with an annual incidence rate (person-year) of 0.4 %. Patients with TypeIGC had significantly higher levels of gastrin, chromogranin A and more frequently the presence of body polyps and ECL-dysplasia **compared** with chronic atrophic gastritis patients without TypeIGC.

**Conclusion:** This cohort study shows that TypeIGC is a rare complication in patients with chronic atrophic gastritis and the presence of body polyps and ECL-dysplasia at gastroscopic/histologic evaluation are strongly associated with the presence of TypeIGC.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Gastric carcinoids (GC) or gastric neuroendocrine tumors are tumors derived from enterochromaffin-like (ECL) cells which are localized in the gastric fundus and corpus. The main role of ECL-cells is the secretion of histamine that, in turn, stimulates acid secretion by parietal cells (1). GC were classified in three subgroups, Type I to Type III, with different pathogenic causes and outcomes (2-4). Type I lesions are more frequent, up to 80% of the total, and are gastrin-dependent tumors which are associated with atrophic gastritis (5). Gastrin, released by G-cells in the gastric antrum, is the main factor that regulates the release of histamine and produces trophic effects upon ECL-cells (6). In chronic atrophic gastritis (CAG), the loss of appropriate glands in the body leads to achlorhydria, and consequently, hypergastrinaemia. The chronic elevation of gastrin stimulates ECL- hyperplasia and sometimes the development of Type I GC (7-8). Given that only a small group of CAG patients develop Type I GC, factors other than gastrin are necessary for the progression of ECL-cells to Type I GC.

Recently, several large studies in different countries have reported an increasing incidence of all gastric neuroendocrine tumors (9, 10). Although older studies reported a prevalence rate of Type I GC between 1 to 12.5% in patients with CAG (11-13), an estimate of Type I GC incidence in patients with this specific condition is unknown. In fact, long-term observational studies assessing the incidence of Type I GC in CAG patients are few (13-15). For this reason, the aim of the present study was to evaluate the occurrence of Type I GC at diagnosis and during follow-up and to identify patient features associated with the presence of Type I GC in a cohort of CAG patients.

## METHODS

### Patients and Study Design

Between 1992 and 2008, we diagnosed the presence of CAG in 367 (245 females, median age 54 years, range 18-79 years) patients referred to our Unit for unexplained anaemia or long-standing dyspepsia, as described in detail elsewhere (16). Patients underwent gastroscopy with biopsies and those with proven histological diagnosis of CAG were informed about the increased risk of gastric neoplasia associated with CAG and **about the need for regular follow-up by gastroscopy**. Personal and clinical data, family history for gastric neoplasia and smoking habit were recorded for all patients during a clinical interview. **Of the initial population, 102 patients dropped-out because 4 patients died from causes not-related to CAG and 98 patients refused to participate in further follow-up**. Thus the study population included 265 patients (177 females, median age 54 years, range 20-79 years) (see Figure 1). **The incidence of Type I GC was determined in CAG patients with at least 2 years of follow-up (n=214; median follow-up 6.3 [2-17]years), after the exclusion of prevalent Type I GC, because this interval of time was considered sufficient for the development of a new lesion of Type I GC. Regarding demographic (gender and age) and clinical features (severity of atrophy), there were no significant differences between patients of the initial CAG group (n=367), of the baseline population (n=265) and of follow-up population.** Diagnosis of CAG was based on the presence of fasting gastrin above upper normal values and the histological confirmation of gastric body (corpus and fundus) atrophy based on three biopsies taken from the gastric antrum (within 3 cm of the pyloric ring, lesser and greater curve, anterior or posterior wall) and three biopsies from the body along the greater curve (16-17). The degree of gastritis was assessed according to the updated Sydney System (18). Atrophy of the gastric body mucosa was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands. Atrophy of the antral mucosa was defined as focal or

1  
2 complete disappearance of antral glands or their replacement by intestinal metaplastic epithelium  
3  
4 (16).  
5

6  
7 The ECL-cell status was assessed according to the Solcia classification (19). Hyperplasia was  
8  
9 defined by ECL cells proliferation  $< 150 \mu\text{m}$  and classified as: normal pattern, simple, linear,  
10  
11 micronodular and adenomatoid. The diagnosis of dysplasia was based on ECL proliferation  
12  
13 between 150 and 500  $\mu\text{m}$ , while that of carcinoid on ECL proliferation  $>500 \mu\text{m}$ . MEN-I  
14  
15 diagnosis was excluded (20-21). In case of a visible lesion, additional biopsies were obtained.  
16  
17

18  
19 All biopsies were examined independently by two experienced pathologists (CB, EP), unaware  
20  
21 of the clinical data of the patients. In the event of disagreement, the biopsies were re-examined  
22  
23 simultaneously by both pathologists until agreement was reached (16).  
24

25  
26 Pernicious anaemia was defined as low hemoglobin concentration,  $\text{MCV} > 100 \text{ fl}$  together with  
27  
28 low B12 vitamin levels, responding to intramuscular B12 vitamin treatment (22). Iron  
29  
30 deficiency anaemia was defined as low hemoglobin concentration,  $\text{MCV} < 80 \text{ fl}$  and ferritin  $< 30$   
31  
32  $\text{ng/ml}$  (22). The diagnosis of autoimmune thyroid disease (AITD) was based on the presence of  
33  
34 thyroid autoantibodies and thyroiditis signs at ultrasound evaluation irrespective of thyroid  
35  
36 function as previously described (23).  
37  
38

39  
40 Plasma gastrin levels were determined by radioimmunoassay using antiserum 4562, kindly  
41  
42 supplied by Prof. J.F. Rehfeld, Copenhagen, Denmark, as previously described (gastrin normal  
43  
44 values  $\leq 40 \text{ pg/ml}$ ) (13). Chromogranin A (CgA) levels was assessed by ELISA kit (Dako A/S,  
45  
46 Glostrup, Denmark) (CgA normal values  $\leq 98 \text{ ng/ml}$ ); Pepsinogen I was measured using a  
47  
48 commercial RIA kit (Pepsik; Sorin, Saluggia, Italy; normal values 20-80  $\text{ng/ml}$ ); Parietal cell  
49  
50 antibodies (PCA) were measured by immunofluorescence and *H pylori* IgG antibodies using an  
51  
52 ELISA commercial kit (GAP test IgG, Biorad, Milan, Italy) (16). *H pylori* infection was  
53  
54 considered positive when the bacterium (Giemsa stain) was detected at histology and/or on the  
55  
56 basis of a positive IgG titre for *H pylori* (17). Bismuth-based triple regimen eradication therapy  
57  
58 was prescribed in the case of *H pylori* positivity and, after 6 months, the absence of *H pylori* at  
59  
60

1  
2 histology and a decrease by at least 50% in the initial titre of *H pylori* IgG was the criterion for  
3  
4 the successful cure of infection (17).  
5  
6  
7

### 8 9 **Follow-up Protocol**

10 The first follow-up gastroscopy was scheduled at intervals between 2 and 4 years after diagnosis  
11  
12 of CAG and the same baseline bioptic sampling was repeated (24).  
13

14  
15 If Type I GC was detected, an extensive bioptic sampling of at least ten biopsies (2 biopsies in  
16  
17 antrum, 4 in gastric body and 4 in the fundus) of the gastric mucosa was taken after 6 and 12  
18  
19 months (13). If Type I GC was not confirmed at two following gastroscopies, patients were  
20  
21 followed by the general follow-up protocol. Polypoid lesions up to 5 mm were removed by  
22  
23 forceps, otherwise an electrocautery snare was used. All patients with a diagnosis of Type I GC  
24  
25 underwent at least one imaging procedure for the tumor staging (Octreoscan, CT-scan,  
26  
27 Magnetic Resonance Imaging).  
28  
29  
30  
31

### 32 33 **Data Analysis and Statistical Evaluation**

34  
35 Type I GC at diagnosis and during follow-up in CAG patients was evaluated and prevalence and  
36  
37 incidence rates (person-year) were calculated. Quantitative data are presented as medians and  
38  
39 ranges or, absolute counts and percentages. Mann-Whitney and Fisher exact test were used when  
40  
41 appropriate.  
42

43  
44 Univariate analysis was performed to identify patient features associated with the presence of  
45  
46 Type I GC. The following baseline patient characteristics were analysed: age at CAG diagnosis,  
47  
48 gender, presence of atrophic pangastritis defined as the concomitant presence of atrophy in the  
49  
50 gastric antrum and body, presence of pernicious anaemia, gastrin, pepsinogen I, CgA, presence  
51  
52 of PCA, presence of dyspepsia, presence of gastric polyp, presence of ECL-dysplasia, smoking  
53  
54 habits, presence of *H.pylori*, family history for gastric cancer and presence of AITD. A p value  
55  
56 of less than 0.05 was considered statistically significant.  
57  
58  
59  
60



## RESULTS

### Occurrence of Type I GC

Type I GC were diagnosed in 9 out of 367 (2.4%) patients at the moment of the initial diagnosis of CAG (6 female, median age 59 [range 40-72] years). As shown in **Table 1**, all Type I GC patients but one presented polyps of the body with a diameter between 0.3 and 3 cm at gastroscopy. In 6 out of 9 (66.7%) patients with Type I GC, the body gastric mucosa presented a severe atrophy, in the remaining cases the atrophy was moderate. The alterations of ECL-pattern associated with Type I GC were micronodular hyperplasia (n=4; 44.5%) and dysplasia (n=5; 55.5%). Further details of CAG patients with Type I GC such as the presence of pernicious anemia, the levels of gastrin and CgA, the degree of body atrophy are summarized in the **Table1**.

Of the initial population, after the exclusion of 102 patients who dropped-out, 265 patients remained in the study and of these, 214 patients had at least 2-years follow-up (see Figure1). After 1463 person-years, 6 patients developed Type I GC with an annual incidence rate (person-year) of 0.4 % (3 female, median age 57 [range 23-69] years) (Table 1). Two out of 6 patients with incident Type I GC presented ECL dysplastic lesions at first diagnosis of CAG. Observed ECL-pattern alterations associated with Type I GC were linear (n=1; 16.7%), micronodular (n=2; 33.3%), adenomatoid (n=1; 16.7%) hyperplasia and dysplasia (n=2; 33.3%).

### Patient Features associated with Type I GC

To identify patient features associated with the presence of Type I GC, we compared baseline clinical, biochemical and histological characteristics between CAG patients without (n=199) and with Type I GC (n=15). As shown in **Table 2**, patients with Type I GC presented significantly higher levels of gastrin and CgA with respect to the other group. At the moment of the diagnosis of Type I GC, 7 out of 15 Type I GC patients (46.6%) had a diagnosis of ECL-dysplasia with

1  
2 respect to none of the other group ( $p < 0.000001$ ). Other analyzed features were similar between  
3  
4 the two groups.

5  
6 Regarding the features of gastric polyps, the gastric location, the numbers and the endoscopic  
7  
8 appearance (sessile or pedunculated) of the polyps were not significantly different between CAG  
9  
10 patients with and without Type I GC (see **Table 3**). Body polyps were more frequently found in  
11  
12 patients with Type I GC with respect to the other group ( $p = 0.000001$ ). Twelve out of 15 (80%)  
13  
14 polyps diagnosed in CAG patients without Type I GC were hyperplastic while the remaining  
15  
16 were adenomas (3/15, 20%).  
17  
18  
19

### 20 21 22 23 Management and Follow-up of Type I GC

24  
25 All polypoid lesions up to 12 mm underwent endoscopic polypectomy. Endoscopic polypectomy  
26  
27 failed on the polyp of 3 cm because of its hard consistency. The patient, a man aged 55,  
28  
29 underwent total gastrectomy. At histological evaluation, the tumor extended from the mucosa to  
30  
31 the submucosa and infiltrated the muscularis propria. Immunohistochemistry showed positivity  
32  
33 for CgA and VMAT-2 with Ki67 proliferation index lower of 1%. In three out of 19 local lymph  
34  
35 nodes removed during the surgery a metastatic endocrine tumor was found. When Type I GC  
36  
37 was diagnosed, CT-scan and Octreoscan were performed and resulted negative.  
38  
39  
40  
41

42 In 6 out of 15 (40%) patients with Type I GC, there was a recurrence of the tumor, but all lesions  
43  
44 were small (up to 1 cm) and underwent endoscopic polypectomy (see **Table 1**). At the end of the  
45  
46 study, all the patients were alive and in good health.  
47  
48  
49

### 50 51 52 Concomitant GI Findings

53  
54 During an overall median follow-up of 6.3 [2-17] years, three intestinal-type adenocarcinomas  
55  
56 were diagnosed [2 female; median age 51 (51-77) years]. All three were located in the gastric  
57  
58 antrum and were diagnosed 8, 5 and 1 years after diagnosis of CAG. The stage of the gastric  
59  
60 cancer was T2N1M0 in the male patient, and T1N0M0 in the two female patients. After

1  
2       gastrectomy, two patients died, one for neoplastic disease progression and the other for  
3  
4       complications after surgery. At the end of the study, one female patient was alive and free of  
5  
6       neoplasia.  
7  
8

## 11       **DISCUSSION**

13  
14       In the present work, we followed-up a cohort of CAG patients for 1463 person-years and found  
15  
16       an annual incidence rate (person-year) for the Type I GC of 0.4%. Recently, large studies on  
17  
18       population-based data in different countries have reported an increasing incidence of GC among  
19  
20       all gastric malignancies and an increase of these among all gastrointestinal carcinoid lesions (9-  
21  
22       10). This increase could be partially explained by the increased diffusion of diagnostic  
23  
24       gastroscopy (25) and correlates temporally with the increasing use of proton pump inhibitors  
25  
26       (26). To our knowledge, few studies evaluated the real incidence of Type I GC in patients with  
27  
28       CAG because the surveillance of CAG was not recommended (27). An old study by Kokkola et  
29  
30       al described 8 new cases of Type I GC in 416 patient-years which corresponds to an annual  
31  
32       incidence of 2% (14). Sjoblom et al studied 196 patients with pernicious anemia, but gastroscopy  
33  
34       was performed only in 70 of these patients (15). After 1397 patient-years, 2 new cases of Type I  
35  
36       GC were reported on hospital registries among the initial group of 196 patients. This figure  
37  
38       should correspond to an annual incidence rate of 0.1%, but in this study not all patients  
39  
40       underwent gastroscopy and the incidence rate can only be obtained indirectly. These differences  
41  
42       in the Type I GC incidence rates could be explained by the patient selection. CAG can have a  
43  
44       wide range of clinical presentations as already reported (28). Patients included in our series had  
45  
46       dyspepsia, iron deficiency anemia or pernicious anemia. In particular, the latter was present in  
47  
48       almost 50% of our patients, while previous studies included exclusively patients with pernicious  
49  
50       anemia. In our previous study, we diagnosed 1 new case of Type I GC in a smaller sample of  
51  
52       CAG patients (n=96) for a shorter period of observation (median time of 2.5 years) which  
53  
54       corresponds to an annual incidence of 0.4% (13). Thus, in the present study, increasing both the  
55  
56  
57  
58  
59  
60

1 cohort of CAG patients and follow-up period (median time of 6,3 years) the annual incidence  
2 rate remained constant.  
3  
4

5  
6 **At initial diagnosis of CAG, we observed 9 cases of Type I GC which is 2.4% of all patients.**

7  
8  
9 Previous studies reported a rate between 1% and 12.5% of Type I GC (11,13- 15,29-30). The  
10 wide range of the prevalence rates of Type I GC among several studies could be explained by  
11 different settings where patients were selected, such as type of hospital (secondary, tertiary  
12 center), symptoms/signs of presentation, type of patient (in-patient, out-patient).  
13  
14  
15  
16  
17

18 In order to identify patient features associated with the presence of Type I GC, we compared the  
19 baseline features between CAG patients with and without Type I GC. **Higher levels of gastrin  
20 and CgA were associated with the presence of Type I GC by univariate analysis. A recent  
21 review has confirmed that the CgA is the most sensitive biomarker in neuroendocrine tumors  
22 and it is more frequently elevated in well-differentiated tumors compared to poorly differentiated  
23 ones (31). However, patients with atrophic gastritis present high values of CgA (32) and the  
24 low specificity of the CgA assay does not identify those with Type I GC among CAG patients as  
25 already reported (33). For the same reasons, gastrin does not detect patients with Type I GC as  
26 it is increased in all CAG patients. In fact, as shown in Table 2, although patients Type I GC had  
27 a median value of gastrin higher than the other CAG patients, the ranges of gastrin overlapped  
28 widely between the two groups. We retain that these assays are clinically useful for identifying  
29 patients with CAG diagnosis or to exclude those from patients with Type III GC, but they cannot  
30 be considered as markers of the presence of Type I GC.**  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49 The presence of ECL-dysplasia was associated more frequently with Type I GC. This pattern of  
50 ECL-cells is considered to be the true gastric carcinoid precursor lesion and it can represent the  
51 sign of a concomitant carcinoid lesion (19). Our previous study showed that this lesion also  
52 carries an increased risk for the development of Type I GC during the follow-up (13). Thus,  
53 CAG patients with a diagnosis of ECL-cell dysplasia could benefit from a shorter endoscopic  
54  
55  
56  
57  
58  
59  
60

1  
2 follow-up to exclude concomitant Type I GC lesions or to identify new lesions in the gastric  
3  
4 mucosa.  
5

6  
7 Another finding of the present study was that the presence of body polyps increases the risk of a  
8  
9 Type I GC in CAG patients. Unfortunately, no features of endoscopic appearance of the gastric  
10  
11 polyps (size, number, sessile/penduculated presentation) permitted a differential diagnosis  
12  
13 between patients with and without Type I GC. In the group of CAG patients without Type I GC,  
14  
15 almost three-fourth of all polyps were hyperplastic and the remaining were adenomas.  
16  
17 Hyperplastic polyps are very common among all benign epithelial gastric polyps (42,43) and  
18  
19 more frequently associated with CAG (44,45). Importantly, some authors have reported an  
20  
21 increased risk of neoplastic progression also for this type of lesions. Moreover, CAG has an  
22  
23 increased risk of gastric adenocarcinoma (14,15). As a consequence, each polyp found at  
24  
25 gastroscopy should be removed and histologically examined.  
26  
27  
28  
29

30  
31 Different approaches were proposed for the management of Type I GC such as surgery (34),  
32  
33 endoscopic polypectomy (1,4,12), somatostatin analogs (35,36) and an endoscopic follow-up  
34  
35 without any specific treatment (37,38). We used a conservative management by endoscopic  
36  
37 follow-up and performing polypectomy of all visible polypoid lesions. Only one patient, in  
38  
39 which the endoscopic approach failed, underwent gastrectomy. This patient had a deeper  
40  
41 neoplastic lesion in the gastric wall, extended to muscularis propria and metastatic involvement  
42  
43 of three lymph nodes. Thus, the surgery in this particular case was appropriate. After surgery,  
44  
45 imaging procedures (CT-scan and Octreoscan) for the staging did not reveal metastatic  
46  
47 involvement of the other organs. The possibility of more invasive lesions among Type I GC is  
48  
49 already described in the literature (39,40) and for patients with larger polyps, local surgical  
50  
51 tumor resection is recommended (41).  
52  
53  
54  
55

56  
57 Finally, in our study, the rate of recurrence of the Type I GC during follow-up was almost of  
58  
59 40%. This high recurrence rate could be explained by Type I GC misdiagnosis during the  
60  
previous gastroscopy, by bioptic sampling errors or the continuous trophic effect of

1  
2 hypergastrinemia on the gastric mucosa. Endoscopic follow-up every 6-12 months, as suggested  
3  
4 also by ENETS guidelines, allowed us to identify recurrent lesions or new lesions (incidence-  
5  
6 cases) when they had a small size and were easily removable by polypectomy without  
7  
8 complications (46). This approach was safe, and the 100% survival of all Type I GC within the  
9  
10 study period is in keeping with previous works (37,40).  
11  
12

13  
14 Our study has some limitations. The first is the high number of CAG patients who dropped-out  
15  
16 during the follow-up, almost 27%. We do not know the clinical outcomes of these CAG patients  
17  
18 and, as a consequence, the incidence rate could be underestimated. However, we know that this  
19  
20 group of patients did not present demographic or baseline clinical features different from the  
21  
22 CAG patients who remained in the study and we retain that the main findings of this study  
23  
24 remain generally valid.  
25  
26

27  
28 Moreover, the power of the statistical analysis was limited by the small numbers of case-  
29  
30 findings of Type I GC. However, larger number of case-findings could be obtained only  
31  
32 performing studies with larger cohorts and longer period of observation.  
33  
34

35  
36 In conclusion, this cohort study implies that Type I GC is a rare complication in patients with  
37  
38 CAG and the presence of body polyps at gastroscopy and ECL-dysplasia at histological  
39  
40 evaluation are strongly associated with the presence of Type I GC.  
41  
42

43  
44 **Financial disclosure:** None of the authors had potential conflicts of interest in the present work.  
45

46  
47 **Grants Supports:** This work was supported by grants from the Italian Ministry for University  
48  
49 and Research, PRIN, COFIN 2007 and University Sapienza Roma 2007-2009, Italy.  
50

51  
52 **Conflict of Interest:** None  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES:

- 1) Burkitt MD, Pritchard DM. Review article: Pathogenesis and management of gastric carcinoid tumours. *Aliment Pharmacol Ther.* 2006;24(9):1305-20.
- 2) Rindi G, Bordi C, Rappel S, et al. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg.* 1996;20(2):168-72.
- 3) Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993;104(4):994-1006.
- 4) Mulkeen A, Cha C. Gastric carcinoid. *Curr Opin Oncol.* 2005 Jan;17(1):1-6.
- 5) Bordi C, D'Adda T, Azzoni C, et al. Pathogenesis of ECL cell tumors in humans. *Yale J Biol Med* 1998;71(3-4):273-84.
- 6) Dockray GJ, VarroA, Dimaline R, et al. The gastrins:their production and biological activities. *Annu Rev Physiol* 2001;63:119-39
- 7) Creutzfeldt W. The achlorhydria-carcinoid sequence: role of gastrin. *Digestion.* 1988;39(2):61-79.
- 8) Bordi C, D'Adda T, Azzoni C, et al. Hypergastrinemia and gastric enterochromaffin-like cells. *Am J Surg Pathol.* 1995;19 Suppl 1:S8-19.
- 9) Modlin IM, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol* 2004;99(1):23-32.
- 10) Ellis L, Shale MJ, Coleman MP. Carcinoid Tumors of the Gastrointestinal Tract: Trends in Incidence in England Since 1971. *Am J Gastroenterol* 2010 Sep7.[Epub ahead of print]

- 1  
2 11) Lehtola J, Karttunen T, Krekelä I, et al. Gastric carcinoids with minimal or no macroscopic  
3  
4 lesion in patients with pernicious anemia. *Hepatogastroenterology* 1985;32(2):72-6.  
5  
6  
7  
8 12) Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. *Surg Oncol*. 2003  
9  
10 Aug;12(2):153-72.  
11  
12  
13  
14 13) Annibale B, Azzoni C, Corleto VD, et al. Atrophic body gastritis patients with  
15  
16 enterochromaffin-like cell dysplasia are at increased risk for the development of type I gastric  
17  
18 carcinoid. *Eur J Gastroenterol Hepatol*. 2001;13(12):1449-56.  
19  
20  
21  
22 14) Kokkola A, Sjöblom SM, Haapiainen R, et al. The risk of gastric carcinoma and carcinoid  
23  
24 tumours in patients with pernicious anaemia. A prospective follow-up study. *Scand J*  
25  
26 *Gastroenterol* 1998;33(1):88-92.  
27  
28  
29  
30 15) Sjöblom SM, Sipponen P, Miettinen M, et al. Gastroscopic screening for gastric carcinoids  
31  
32 and carcinoma in pernicious anemia. *Endoscopy* 1988;20(2):52-6.  
33  
34  
35  
36 16) Annibale B, Marignani M, Azzoni C, et al. Atrophic body gastritis: distinct features  
37  
38 associated with *Helicobacter pylori* infection. *Helicobacter* 1997;2(2):57-64.  
39  
40  
41  
42 17) Lahner E, Bordi C, Di Giulio E, et al. Role of *Helicobacter pylori* serology in atrophic body  
43  
44 gastritis after eradication treatment. *Aliment Pharmacol Ther* 2002;16(3):507-14.  
45  
46  
47  
48 18) Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated  
49  
50 Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J*  
51  
52 *Surg Pathol* 1996;20(10):1161-81.  
53  
54  
55  
56 19) Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of nonantral gastric  
57  
58 endocrine growths in man. *Digestion*. 1988;41(4):185-200.  
59  
60



- 1  
2 20) Berna MJ, Annibale B, Marignani M, et al. A prospective study of gastric carcinoids and  
3  
4 enterochromaffin-like cell changes in multiple endocrine neoplasia type 1 and Zollinger-Ellison  
5  
6 syndrome: identification of risk factors. *J Clin Endocrinol Metab* 2008;93(5):1582-91.  
7  
8  
9  
10 21) Bordi C, Corleto VD, Azzoni C, et al. The antral mucosa as a new site for endocrine tumors  
11  
12 in multiple endocrine neoplasia type 1 and Zollinger-Ellison syndromes. *J Clin Endocrinol*  
13  
14 *Metab* 2001;86(5):2236-42.  
15  
16  
17  
18 22) Lahner E, Norman GL, Severi C, et al. Reassessment of intrinsic factor and parietal cell  
19  
20 autoantibodies in atrophic gastritis with respect to cobalamin deficiency. *Am J Gastroenterol*  
21  
22 2009;104(8):2071-9.  
23  
24  
25  
26 23) Lahner E, Centanni M, Agnello G, et al. Occurrence and risk factors for autoimmune thyroid  
27  
28 disease in patients with atrophic body gastritis. *Am J Med* 2008;121(2):136-41.  
29  
30  
31  
32 24) Lahner E, Caruana P, D'Ambra G, et al. First endoscopic-histologic follow-up in patients  
33  
34 with body-predominant atrophic gastritis: when should it be done? *Gastrointest Endosc*  
35  
36 2001;53(4):443-8.  
37  
38  
39  
40 25) Modlin IM, Sandor A, Tang LH, et al. A 40-year analysis of 265 gastric carcinoids. *Am J*  
41  
42 *Gastroenterol* 1997;92(4):633-8.  
43  
44  
45  
46 26) Hodgson N, Koniaris LG, Livingstone AS, et al. Gastric carcinoids: a temporal increase with  
47  
48 proton pump introduction. *Surg Endosc* 2005;19(12):1610-2.  
49  
50  
51  
52 27) Hirota WK, Zuckerman MJ, Adler DG, et al. Standards of Practice Committee, American  
53  
54 Society for Gastrointestinal Endoscopy. ASGE guideline: the role of endoscopy in the  
55  
56 surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc*  
57  
58 2006;63(4):570-80.  
59  
60

- 1  
2 28) Marignani M, Delle Fave G, Mecarocci S, et al. High prevalence of atrophic body gastritis  
3  
4 in patients with unexplained microcytic and macrocytic anemia: a prospective screening study.  
5  
6 Am J Gastroenterol 1999;94:766-72.  
7  
8  
9  
10 29) Stockbrügger RW, Menon GG, Beilby JO, et al. Gastroscopic screening in 80 patients with  
11  
12 pernicious anaemia. Gut 1983;24(12):1141-7.  
13  
14  
15  
16 30) Borch K, Renvall H, Kullman E, et al. Gastric carcinoid associated with the syndrome of  
17  
18 hypergastrinemic atrophic gastritis. A prospective analysis of 11 cases. Am J Surg Pathol  
19  
20 1987;11(6):435-44.  
21  
22  
23  
24 31) Modlin IM, Gustafsson BI, Moss SF, et al. Chromogranin A--biological function and clinical  
25  
26 utility in neuro endocrine tumor disease. Ann Surg Oncol 2010;17(9):2427-43.  
27  
28  
29  
30 32) Borch K, Stridsberg M, Burman P, et al. Basal chromogranin A and gastrin concentrations in  
31  
32 circulation correlate to endocrine cell proliferation in type-A gastritis. Scand J Gastroenterol  
33  
34 1997;32(3):198-202.  
35  
36  
37 33) Peracchi M, Gebbia C, Basilisco G, et al. Plasma chromogranin A in patients with  
38  
39 autoimmune chronic atrophic gastritis, enterochromaffin-like cell lesions and gastric carcinoids.  
40  
41 Eur J Endocrinol 2005;152(3):443-8.  
42  
43  
44  
45 34) Dakin GF, Warner RR, Pomp A, et al. Presentation, treatment, and outcome of type 1 gastric  
46  
47 carcinoid tumors. J Surg Oncol 2006;93:368-72.  
48  
49  
50  
51 35) Manfredi S, Pagenault M, de Lajarte-Thirouard AS, et al. Type 1 and 2 gastric carcinoid  
52  
53 tumors: long-term follow-up of the efficacy of treatment with a slow-release somatostatin  
54  
55 analogue. Eur J Gastroenterol Hepatol 2007;19:1021-5.  
56  
57  
58  
59  
60

- 1  
2 36) Grozinsky-Glasberg S, Kaltsas G, Gur C, et al. Long-acting somatostatin analogues are an  
3  
4 effective treatment for type 1 gastric carcinoid tumours. *Eur J Endocrinol* 2008;159:475-82.  
5  
6  
7  
8 37) Hosokawa O, Kaizaki Y, Hattori M, et al. Long-term follow up of patients with multiple  
9  
10 gastric carcinoids associated with type A gastritis. *Gastric Cancer* 2005;8:42-6.  
11  
12  
13  
14 38) Ravizza D, Fiori G, Trovato C, Fazio N, Bonomo G, Luca F, Bodei L, Pelosi G, Tamayo D,  
15  
16 Crosta C. Long-term endoscopic and clinical follow-up of untreated type 1 gastric  
17  
18 neuroendocrine tumours. *Dig Liver Dis* 2007;39(6):537-43.  
19  
20  
21  
22 39) Granberg D, Wilander E, Stridsberg M, et al. Clinical symptoms, hormone profiles,  
23  
24 treatment, and prognosis in patients with gastric carcinoids. *Gut* 1998;24:223-8.  
25  
26  
27  
28 40) Borch K, Ahrén B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis  
29  
30 after differentiated treatment in relation to type. *Ann Surg* 2005;242:64-73.  
31  
32  
33  
34 41) Ruszniewski P, Delle Fave G, Cadiot G, et al. Frascati Consensus Conference; European  
35  
36 neuroendocrine Tumor Society. Well-differentiated gastric tumors/carcinomas.  
37  
38 *Neuroendocrinology* 2006;84(3):158-64.  
39  
40  
41  
42 42) Carmack SW, Genta RM, Graham DY, et al. Management of gastric polyps: a pathology-  
43  
44 based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 2009;6(6):331-41.  
45  
46  
47  
48 43) Goddard AF, Badreldin R, Pritchard DM, et al. British Society of Gastroenterology. The  
49  
50 management of gastric polyps. *Gut* 2010;59(9):1270-6.  
51  
52  
53  
54 44) Dirschmid K, Platz-Baudin C, Stolte M. Why is the hyperplastic polyp a marker for the  
55  
56 precancerous condition of the gastric mucosa? *Virchows Arch* 2006; 448: 80–84.  
57  
58  
59  
60

1  
2 45) Di Giulio E, Lahner E, Micheletti A, et al. Occurrence and risk factors for benign epithelial  
3  
4 gastric polyps in atrophic body gastritis on diagnosis and follow-up. Aliment Pharmacol Ther  
5  
6 2005;21(5):567-74.  
7  
8

9  
10 46) Arnold R, Chen Y, Costa F, et al .ENETS Consensus Guidelines for the Standards of Care  
11  
12 in Neuroendocrine Tumors: Follow-Up and Documentation. Neuroendocrinology 2009;  
13  
14 90:227–233.  
15  
16  
17  
18  
19  
20  
21  
22

### 23 **LEGEND TO FIGURES**

24  
25 **Figure 1:** Study population  
26  
27

28 **Figure 2:** Kaplan-Meier Analysis: Intervals between initial diagnosis of atrophic body gastritis  
29  
30 and diagnosis of Type I gastric carcinoids. Proportion of patients with atrophic body gastritis  
31  
32 who remained free of Type I gastric carcinoids.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

**TABLE 1: Baseline features of 15 CAG patients with prevalent and incident Type I GCs.**

<b>Patients</b>	<b>Gender</b>	<b>Age (years)</b>	<b>Gastrin (pg/ml)</b>	<b>CgA (ng/ml)</b>	<b>Body Atrophy *</b>	<b>Pernicious Anaemia</b>	<b>Endoscopic Findings</b>	<b>Detection of Type I GC</b>	<b>Recurrence</b>
<b>1</b>	F	45	305	60	2	No	Body polyp of 0.5 cm	At Diagnosis	No
<b>2</b>	M	67	975	175	3	Yes	Body polyp of 0.5 cm	At Diagnosis	At 4-month follow-up
<b>3</b>	F	40	975	150	3	No	Body polyp of 0.6 cm	At Diagnosis	No
<b>4</b>	F	40	570	140	3	No	Normal mucosa	At Diagnosis	At 6,15,32-month follow-up
<b>5</b>	F	66	690	245	3	No	Body polyp of 0.5 cm	At Diagnosis	No
<b>6</b>	F	72	680	250	3	Yes	Body polyp of 0.5 cm	At Diagnosis	At 3,5-month follow-up
<b>7</b>	M	59	2000	167	2	Yes	Body polyp of 0.3 cm	At Diagnosis	No
<b>8</b>	F	61	1150	150	3	Yes	Body polyp of 0.5 cm	At Diagnosis	No
<b>9</b>	M	55	1183	547	2	No	Body polyp of 3 cm	At Diagnosis	No metastasis after total gastrectomy
<b>10</b>	M	47	1090	150	3	Yes	Normal mucosa	At 31-month follow-up	At 35,46,64-month follow-up
<b>11</b>	M	67	500	405	2	No	Body polyp of 0.5 cm	At 31-month follow-up	No
<b>12</b>	M	69	220	120	3	No	Body polyp of 0.5 cm	At 41-month follow-up	No
<b>13</b>	F	65	2800	370	3	No	Normal mucosa	At 7-month	At 13,18,50-month

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

								follow-up	follow-up
<b>14</b>	F	23	565	230	3	Yes	Body polyp of 1.2 cm	At 59-month follow-up	No
<b>15</b>	F	49	1475	240	3	Yes	Body polyp of 0.4 cm	At 18-month follow-up	At 30,37,61-month follow-up

\* scored accordingly to the Sydney System.

For Peer Review

TABLE 2: Baseline clinical, biochemical and histological features of 214 CAG patients with and without Type I GC.

	Type I GC n=15	CAG n=199	<i>p</i>
Age, years (range)	59 (23-72)	54 (22-77)	0.39
Female gender, n (%)	9 (60)	137 (68.8)	0.7
Gastrin, pg/ml, median (range)	832.5 (220-2800)	500 (50-2700)	<b>0.01</b>
Pepsinogen I, ng/ml, median (range)	10 (3-28)	10 (3-79)	0.6
Chromogranin A, ng/ml, median (range)	171 (60-405)	100(30-280)	<b>0.0001</b>
Pernicious Anemia, n(%)	7 (46.6)	98 (49.2)	1
Family history for gastric cancer, n(%)	3 (20)	18 (9)	0.13
Smoking habit, n(%)	8 (53.3)	81 (40.7)	0.39
PCA, n(%)	14(93.3)	158(79.3)	0.3
<i>Hpylori</i> positivity , n(%)	7 (46.6)	84 (42.2)	0.79
Dyspepsia, n(%)	7(46.6)	43 (21.6)	0.05
AITD, n(%)	9(60)	91(46)	0.29
ECL-dysplasia*, n(%)	7 (46.6)	0	<b>&lt;0.000001</b>
Atrophic pangastritis, n(%)	2(13.3)	44(22.1)	0.5
Body Atrophy, n (%)	0	22(11.3)	0.37
Mild	4(26.6)	55(27.4)	1
Moderate	11(73.4)	122(61.3)	0.4
Severe			

PCA=parietal cell antibodies; CAG= chronic atrophic gastritis; AITD=autoimmune thyroid disease

\*ECL-dysplasia was concurrent at Type I GC in 5 prevalent and 2 incident cases.

Data are expressed as median(range). Mann-Whitney test or Fisher-test were used for the comparison of baseline features between two groups



**TABLE 3: Comparison of gastric polyps in CAG patients with and without Type I GC.**

<b>POLYPOID LESION</b>	<b>Type I GC§ n=15*</b>	<b>CAG# n=199</b>	<b><i>p</i></b>
<b>Gastric Location</b>			
Antrum	0	6(3)	ns
<b>Body</b>	<b>12(80)</b>	<b>7(3.5)</b>	<b>0.000001*</b>
Antrum and Body	0	2(1)	ns
<b>Size</b>			
<0.5 cm	9/12(75)	7/15(46.7)	ns
0.5-1 cm	2/12(16.7)	6/15(40)	ns
>1 cm	1/12(8.3)	2/15(13.3)	ns
<b>Numbers</b>			
Single	5/12(41.6)	8/15(53.3)	ns
Multiple	7/12(58.3)	7/15(46.7)	ns
<b>Endoscopic Appearance</b>			
Sessile	12/12(100)	12/15(80)	ns
Pedunculated	0	3/15(20)	ns

§ reported polypoid lesions refer to gastroscopy performed at the moment of type I GC diagnosis; # reported polypoid lesions refer to baseline gastroscopy; \*3patients had intramucosal carcinoids;

Data are expressed as proportions and Fisher-test was used for the comparison between the two groups.

1  
2  
3  
4  
5  
6  
7  
8 **n=367** patients with atrophic body gastritis referred to the  
9 Department of Digestive and Liver Diseases  
10 between January 1992 and June 2008  
11

12  
13  
14  
15  
16  
17 **Excluded Patient from the study because:**

- 18 • *n*=4 died for other causes
- 19 • *n*=98 lost at follow-up

20  
21  
22  
23  
24  
25  
26 **n=265** baseline population  
27

28  
29  
30  
31  
32  
33 **Excluded Patients from the incidence calculation:**

- 34 • *n*=51 follow-up < 2 years

35  
36  
37  
38  
39  
40  
41  
42 **n=214 (80.7%)** follow-up population  
43  
44  
45

46  
47 120x147mm (400 x 400 DPI)  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60