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EDITORIAL

Risk for gastric neoplasias in patients with chronic atrophic gastritis: A critical reappraisal

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Abstract

Chronic atrophic gastritis (CAG) is an inflammatory condition characterized by the loss of gastric glandular structures which are replaced by connective tissue (non-metaplastic atrophy) or by glandular structures inappropriate for location (metaplastic atrophy). Epidemiological data suggest that CAG is associated with two different types of tumors: Intestinal-type gastric cancer (GC) and type I gastric carcinoid (T I GC). The pathophysiological mechanisms which lead to the development of these gastric tumors are different. It is accepted that a multistep process initiating from *Helicobacter pylori*-related chronic inflammation of the gastric mucosa progresses to CAG, intestinal metaplasia, dysplasia and, finally, leads to the development of GC. The T I GC is a gastrin-dependent tumor and the chronic elevation of gastrin, which is associated with CAG, stimulates the growth of enterochromaffin-like cells with their hyperplasia leading to the development of T I GC. Thus, several events occur in the gastric mucosa before the development of intestinal-type GC and/or T I GC and these take several years. Knowledge of CAG incidence from superficial gastritis, its prevalence in different clinical settings and possible risk factors associated with the progression of this condition to gastric neoplasias are important issues. This editorial intends to provide a brief review of the main studies regarding incidence and prevalence of CAG and risk factors for the development of gastric neoplasias.

Key words: Chronic atrophic gastritis; Gastric neoplasia; Intestinal-type gastric cancer; Type I gastric carcinoid; Prevalence; Incidence; Risk factors

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INTRODUCTION

Chronic atrophic gastritis (CAG) is an inflammatory condition characterized by the loss of gastric glandular structures which are replaced by connective tissue (non-metaplastic atrophy) or by glandular structures inappropriate for location (metaplastic atrophy)[1]. Epidemiological data suggest that CAG is associated with two different types of tumors: Intestinal-type gastric cancer (GC) and type I gastric carcinoid (T I GC). The pathophysiological mechanisms which lead to the development of these gastric tumors are different. It is accepted that a multistep process initiating from *Helicobacter pylori (H. pylori)*-related chronic inflammation of the gastric mucosa progresses to CAG, intestinal metaplasia, dysplasia, and finally leads to

the development of GC[2]. T I GC is a gastrin-dependent tumor and the chronic elevation of gastrin, which is associated with CAG, stimulates the growth of enterochromaffin-like (ECL) cells with their hyperplasia leading to the development of T I GC[3-5].

Considering that several events occur in the gastric mucosa before the development of GC and/or of T I GC, and that these events take several years, the knowledge of CAG incidence from superficial gastritis, its prevalence in different clinical settings and possible risk factors associated with the progression of this condition to gastric neoplasias are important issues.

EPIDEMIOLOGY OF CHRONIC ATROPHIC GASTRITIS

A recent systematic review was performed with the aim of evaluating the CAG incidence in patients free of CAG at moment of inclusion in the study[6]. From published studies, the authors selected only 14 follow-up studies in which CAG diagnosis was carefully made by histology (12 studies) or by serum pepsinogen (PG) levels (2 studies). The CAG incidence rates ranged from 0% to 10.9% per year. This wide CAG incidence range is explained by the particular settings in which the CAG diagnoses were made. In fact, the lowest incidence rates (0%) were found in patients with reflux esophagitis[7] and in patients successfully treated for *H. pylori* infection[8]. The highest incidence rate was observed in an older study conducted on patients who underwent vagotomy because of ulcer disease[9]. Regarding *H. pylori* infection, the CAG incidence rate was higher in *H. pylori*-positive patients than in *H. pylori*-negative ones[7,10-13] and the meta-analysis on the association between *H. pylori* infection and CAG incidence presented a rate ratio of 5 (95% CI: 3.1-8.3).

The prevalence of CAG was evaluated by serological screening using surrogate markers of gastric function (PG I or PG I/PG Ⅱ ratio) or by gastroscopy/histology. In the vast majority of cases, the serological and histological screenings were both made in a general population. Serological studies reported CAG prevalence rates between 3% and 7%, which were lower than those reported by histological ones. Studies on CAG prevalence subdivided on the basis of diagnostic tools used for CAG diagnosis (histology or serology) are shown in Table 1[14-23]. The observed differences between serological and histological studies could be explained by the fact that it is likely that symptomatic patients accepted more easily to undergo gastroscopy. Higher rates of CAG prevalence found in the Asian countries may be justified by the fact that these areas are at higher risk of GC and by the fact that the definition of CAG diagnosis may be different between Western and Asian countries. In studies reporting from Asian countries, CAG diagnosis included all atrophic lesions irrespective of the atrophy localization in the gastric mucosa (antrum and/or corpus); in the vast majority of the studies conducted in Western countries, CAG diagnosis included only patients with a corpus atrophic involvement such as corpus-atrophic gastritis or a multifocal atrophic gastritis (i.e., patchy areas of atrophic-metaplastic changes in the antral and corpus mucosa), because it is maintained that only corpus atrophic changes can lead to the development of gastric cancer.

ATROPHIC GASTRITIS AND GASTRIC CANCER

Nowadays, GC represents one of the most challenging tumors due to the fact that its diagnosis is often late and, in the advanced stage, the therapeutic options are scarce with consequent high rate of mortality[24]. In fact, although a reduction of global incidence for this neoplasm is reported, it remains the second cause of cancer-related death. The knowledge of precursor lesions for the development of intestinal-type GC could contribute to anticipating GC diagnosis at an early stage when surgery or chemotherapy offers a better prognosis. Several studies have estimated the risk of GC in patients with CAG[25-33]. Although the vast majority of these were performed on small numbers of patients and were based on older histological classifications, the progression rate of CAG to GC fluctuates from 0% to 10% with annual incidence (person-year) lower than 1% (Table 2). It is interesting to observe that, although the incidence rate of CAG in patients with superficial gastritis is higher in populations with higher risk of GC (Table 1), the progression rate of CAG towards GC is similar irrespective of different geographic areas.

Some studies have attempted to identify risk factors linked with the progression of precancerous lesions (CAG or intestinal metaplasia) towards GC to select those patients who should undergo endoscopic surveillance.

Age

Age has been identified as a possible risk factor in several studies. In the study by Leung *et al*[40], *H. pylori*-positive patients with intestinal metaplasia were followed up for 5 years to evaluate the progression or the improvement of histological lesions after *H. pylori* eradication treatment compared with placebo. At multivariate analysis, the presence of age > 45 years showed an approximate two-fold increased risk of progression of intestinal metaplasia compared to younger subjects[40]. This same age limit had already been identified in a screening survey performed on 3386 subjects from a rural Chinese population that showed an approximate three-fold increased risk of progression to GC[28]. In a large cohort study, increasing age at initial diagnosis was associated with higher hazard ratio (HR) for the progression to GC (for age > 55 years, HR > 2.38)[32]. In a recent work, patients with CAG who were aged > 50 years at the moment of initial diagnosis presented HR = 8.8 for the progression to gastric neoplastic lesions[33].

Pernicious anemia

Although the vast majority of the older studies on CAG

Table 1 Prevalence of chronic atrophic gastritis

Author	Year	Country	Study type	Patients	Age (yr)	CAG (%)
Serology						
Sipponen *et al*[14]	2003	Finland	General population	12 252 (men)	51-65	5.2
Green *et al*[15]	2005	New Zealand	General population	466	> 65	6.7
Weck *et al*[16]	2007	Germany	General population	9444	50-74	6
Telaranta-Keerle *et al*[17]	2010	Finland	General population	4256	18-92	3.5
Histology						
Oksanen *et al*[18]	2000	Finland	Endoscopic cohort	207	19-83	13[1]
Borch *et al*[19]	2000	Sweden	General Population	501	35-85	9.4[2]
Asaka *et al*[20]	2001	Japan	General Population	2455	< 20 to > 70	55.5[3]
Redéen *et al*[21]	2003	Sweden	General Population	488	37-85	9
Storskrubb *et al*[22]	2008	Sweden	General Population	976	20-80	6.6[4]
Zou *et al*[23]	2011	China	General Population	1022	18-80	63.8[3]

[1]This percentage refers to patients (n = 27) with atrophic body gastritis; [2]this percentage refers to patients (n = 47) with atrophic pangastritis and corpus- predominant (gastritis; [3]these percentages included chronic atrophic gastritis (CAG) diagnosis irrespective of the atrophy localization in the gastric mucosa (antrum and/or corpus); [4]this percentage refers to patients (n = 54) with multifocal atrophic gastritis and atrophic corpus- limited gastritis.

Table 2 Incidence of gastric cancer in patients with chronic atrophic gastritis or pernicious anemia

Author	Year	Country	Study type	Patients	Age, median or range (yr)	GC	Annual incidence of GC, person-year (%)
Patients with chronic atrophic gastritis							
Walker *et al*[25]	1971	Australia	Retrospective	40	40-64	4 (10)	0.6
Ectors *et al*[26]	1986	United Kingdom	Retrospective	225	-	3 (1.3)	0.1
Tatsuta *et al*[27]	1993	Japan	Retrospective	654	-	22 (3.4)	0.2
You *et al*[28]	1999	China	Prospective	2082[1]	35-64	19 (0.9)	0.2
Whiting *et al*[29]	2002	United Kingdom	Prospective	1042	> 40	12 (11.5)	1.1
Dinis-Ribeiro *et al*[30]	2004	Portugal	Retrospective	1771	-	4 (2.2)	0.7
Lahner *et al*[31]	2005	Italy	Prospective	106	22-74	1 (0.9)	0.1
de Vries *et al*[32]	2008	Netherlands	Retrospective	84 072[2]	65.7	1035 (1.2)	0.2
Vannella *et al*[33]	2010	Italy	Retrospective	300	18-78	3 (1)	0.2
Patients with pernicious anemia							
Borch *et al*[34]	1986	Sweden	Prospective	61	-	0	0
Kokkola *et al*[35]	1998	Finland	Prospective	62	20-73	2 (3.2)	1.10
Sjöblom *et al*[36]	1993	Finland	Prospective	56	27-78	2 (3.5)	1.20
Armbrecht *et al*[37]	1990	United Kingdom	Prospective	27	26-81	0	0
Bresky *et al*[38]	2003	Spain	Prospective	68	-	0	0
Ye *et al*[39]	2003	Sweden	Retrospective	21 265	74.3	177 (0.8)	0.10
Vannella *et al*[33]	2010	Italy	Retrospective	129	23-74	2 (1.5)	0.30

[1]This number refers to biopsies taken in 144 patients and includes chronic atrophic gastritis (CAG) with type Ⅰ, Ⅱ, Ⅲ intestinal metaplasia; [2]this number refers to CAG patients with or without intestinal metaplasia. GC: Gastric cancer.

included patients with pernicious anemia, the risk of GC in this particular clinical setting seems to be generally low (Table 2). In fact, this clinical condition is often associated with corpus-restricted gastritis and, as a consequence, with less extensive atrophy in the gastric mucosa. In a recent study, the presence of atrophic pangastritis increased the risk of progression to gastric neoplastic lesions by 4.5 times, in keeping with previous works[33,41,42]. The apparent contrast between older and more recent works about pernicious anemia can be explained by the difficulty in comparing studies with methodological differences linked to adopted gastritis classification or small number series. It is interesting to underline the fact that studies on the relationship between pernicious anemia and GC are lacking in Asian countries where the risk of GC is higher, thus it remains to be established whether pernicious anemia has low prevalence in the Asian geographic area or if this condition is overlooked.

Intestinal metaplasia

Parallel with more extensive atrophy in the gastric mucosa, the extensive replacement of this by intestinal metaplasia is considered a hallmark of severity of CAG. In the literature, the intestinal metaplasia extension was widely related to a higher risk of GC[32,33,40,42]. In particular, type Ⅲ intestinal metaplasia was associated with an increased risk of GC in some studies[43,44], but subsequent studies showed conflicting findings[45,46], thus the clinical utility of different subtyping of intestinal metaplasia is limited.

Helicobacter pylori

The role of *H. pylori* infection in progression from CAG

to GC is controversial. In the Leung study, *H. pylori*-positive patients who had not undergone eradication therapy had a progression rate of intestinal metaplasia higher than cured patients[40]. However, in this study, the vast majority of patients had only a superficial gastritis at baseline and, after 5 years of follow-up, the rate of patients with intestinal metaplasia increased significantly. It is maintained that the effect of eradication therapy on the progression to GC in patients with precancerous lesions is limited. A previous large prospective study demonstrated that *H. pylori* eradication may be beneficial in arresting the progression to GC only in patients without CAG or intestinal metaplasia[47]. Two recent meta-analyses showed a beneficial long-term effect of *H. pylori* eradication therapy on atrophic gastritis, but not on intestinal metaplasia[48,49]. Up till now, although the possibility of histological improvement of CAG is accepted after *H. pylori* cure, the efficacy of *H. pylori* eradication in reducing GC incidence needs to be demonstrated.

ATROPHIC GASTRITIS AND TYPE I GASTRIC NEUROENDOCRINE TUMOR

T I GC derives from ECL cells which are localized in the gastric fundus and corpus. ECL cells are specialized in the secretion of histamine that, in turn, stimulates acid secretion by parietal cells[50]. Gastric carcinoids have been classified into three subgroups, type I to type Ⅲ, with different outcomes[51-53]. Type I lesions are associated with atrophic gastritis and constitute up to 80% of all gastric carcinoids[54]. Gastrin, released by G-cells in the gastric antrum, stimulates the release of histamine and produces trophic effects upon ECL cells[3]. In CAG, the loss of appropriate glands in the body leads to achlorhydria, and the consequent chronic hypergastrinemia stimulates ECL hyperplasia and sometimes the development of T I GC[4,5].

The prevalence rate of T I GC in patients with CAG is reported to be between 1% and 12.5% in different studies[36,37,55-58]. The wide range of the prevalence rates of T I GC among several studies can be explained by different settings where patients were selected, such as type of hospital (secondary, tertiary center) or symptoms/signs of presentation. CAG can have a wide range of clinical presentations such as dyspepsia, iron deficiency anemia or pernicious anemia[59]. In particular, in a recent observational study in which the T I GC incidence and prevalence were evaluated, pernicious anemia was present in almost 50% of patients, while previous studies included exclusively patients with this condition[60].

Long-term observational studies assessing incidence of T I GC in CAG patients are scarce[35,56,61]. We recently followed up a cohort of CAG patients for 1463 person-years reporting an annual incidence rate (person-year) for T I GC of 0.4%[60]. An old study by Kokkola *et al*[35] reported an annual incidence of 2%, observing 8 new cases of T I GC in 416 patient-years. Sjöblom *et al*[61] studied 196 patients with pernicious anemia and after 1397 patient-years, 2 new cases of T I GC were reported in hospital registries among the initial group of patients. This figure should correspond to an annual incidence rate of 0.1%, but in this study only 70 patients (35.7%) underwent gastroscopy and the incidence rate can only be obtained indirectly. Furthermore, although there are small fluctuations in the reported incidence rates, only a small group of CAG patients develop T I GC showing that factors other than gastrin are necessary for the progression of ECL cells to T I GC.

Few studies have attempted to identify risk factors associated with the development of T I GC. In a recent work, we found higher baseline levels of gastrin and chromogranin A in CAG patients with T I GC compared to those without T I GC. However, all patients with CAG present high plasma values of chromogranin A[62] and gastrin, thus these markers have limited clinical utility because of low specificity[63].

An accepted risk factor for T I GC is the presence of ECL dysplasia, which is often associated with T I GC. This lesion is considered as the true gastric carcinoid precursor lesion and it can represent the sign of a concomitant carcinoid lesion[56,64]. CAG patients with a diagnosis of ECL cell dysplasia could benefit from a shorter endoscopic follow-up time to exclude concomitant T I GC lesions or to identify newly arisen lesions in the gastric mucosa.

Although T I GC lesions can also be present on flat mucosa, in the vast majority of cases they are associated with the presence of body polyps. In CAG patients, hyperplastic or adenomatous polyps are very common; however, the presence of body polyps increases the risk of having a T I GC[60]. Unfortunately, no feature of endoscopic appearance of the gastric polyps (size, number, sessile/pedunculated presentation) seems useful to differentiate histology of polyps, thus all polyps should be removed and histologically examined[65,66].

CONCLUSION

The risk of development of GC or T I GC appears higher in CAG patients with respect to the general population. In geographic areas with low risk of GC, a surveillance program for all CAG patients may be not cost-effective considering that the vast majority of CAG patients will not develop a gastric neoplasm[67]. A subset of CAG patients at higher risk for GC should be identified allowing the selection of those CAG patients in whom gastroscopic/histologic surveillance may be warranted. Recently, an international consensus developed evidence-based guidelines on the management of precancerous conditions and lesions of the stomach, recommending an endoscopic surveillance every 3 years after diagnosis in all patients with extensive atrophy and/or intestinal metaplasia in the antrum and corpus[68]. New systems for histopathological staging (OLGA, OLGIM) have been developed with the aim of combining pathological findings with the risk of GC for the patient and to iden-

tify a subgroup of those at higher risk[69,70]. The OLGA system includes gastritis grading and staging[69]. Grading measures the severity of acute and chronic inflammatory infiltrate in the antrum and body. Staging refers to the extent of atrophy with or without intestinal metaplasia. The OLGIM system is based on intestinal metaplasia which is considered a more reproducible histopathological diagnosis with respect to atrophy diagnosis. Further studies are necessary to validate these new classifications and to establish their real clinical value. Regarding T I GC, although risk factors for its development have not been identified, ENETS guidelines suggest an endoscopic follow-up every 6-12 mo after T I GC diagnosis. This interval allows the identification of recurrent lesions or new lesions (incidence-case) at an early stage when they can easily be removed by polypectomy without complications[71]. This approach seems safe for T I GC, a neoplasm with an excellent outcome[60,72].

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