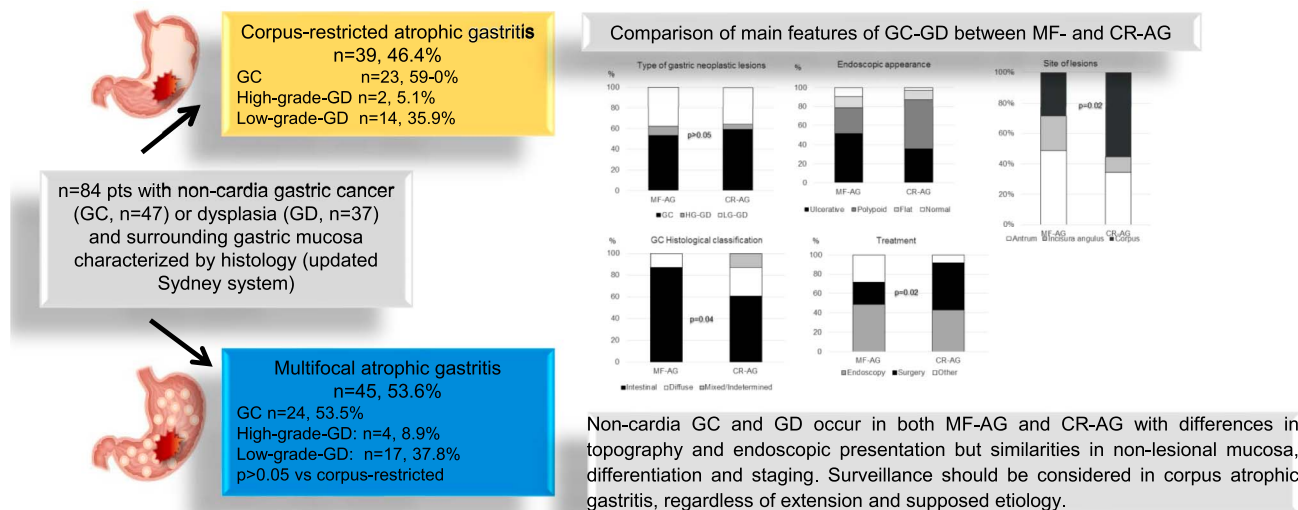


# Clinical and Endoscopic-Histological Features of Multifocal and Corpus-Restricted Atrophic Gastritis Patients With Non-Cardia Gastric Cancer or Dysplasia: A Multicenter, Cross-Sectional Study

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## Clinical and endoscopic-histological features of multifocal and corpus-restricted atrophic gastritis patients with non-cardia gastric cancer or dysplasia: a multicenter, cross-sectional study



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**INTRODUCTION:** *Helicobacter pylori* (Hp)-related atrophic gastritis (AG) affects corpus and antral mucosa, resulting in multifocal AG (MF-AG); autoimmunity-driven AG is corpus-restricted (CR-AG). AG carries increased gastric dysplasia (GD) and gastric cancer (GC) risk, well established in MF-AG, but debated in CR-AG. This study aimed to assess clinical, endoscopic-histological characteristics of GD-GC in patients with MF-AG and CR-AG.

**METHODS:** This was the multicenter cross-sectional study across 11 Italian gastroenterology centers on data of non-cardia GD-GC in adult patients with MF-AG or CR-AG based on clinical, endoscopic, and histological charts.

**RESULTS:** Eighty-four patients were included with MF-AG and CR-AG in 45 (53.6%) and 39 (46.4%), respectively. Low-grade GD, high-grade GD, and GC were diagnosed in 31 (36.9%), 6 (7.1%), and 47 (56.0%), respectively. GD-GC similarly occurred in patients with MF-AG and CR-AG: high-grade GD in 4 (8.9%) vs 2 (5.1%), low-grade GD in 17 (37.8%) vs 14 (35.9%), and GC in 24 (53.5%) vs 23 (59.0%) ( $P > 0.05$ ). Compared with MF-AG, in patients with CR-AG, GD-GC were more commonly polypoid (51.6% vs 27.3%,  $P = 0.048$ ) and more frequent in the corpus (55.3% vs 28.6%,  $P = 0.02$ ), but occurred also in the antrum (34.2%) and incisura (10.5%). Surgery was more frequent in CR-AG than in MF-AG (48.6% vs 23.1%,  $P = 0.02$ ). Corpus atrophy severity and intestinal metaplasia were not different ( $P > 0.05$ ), histological Hp positivity was low in both (2.3% vs 2.9%,  $P = 0.87$ ), but in Hp negatives, active inflammation was present in the antrum in 26.7% and 7.7% ( $P = 0.02$ ), and in the corpus in 31.1% and 21.5% ( $P = 0.27$ ).

**DISCUSSION:** Non-cardia GC and GD may occur in both MF-AG and CR-AG, displaying differences in topography and endoscopic presentation but similarities in nonlesional mucosa, differentiation, and staging. Surveillance should be considered in corpus AG, regardless of extension and supposed etiology.

**BACKGROUND:** La gastrite atrofica (AG) *Helicobacter pylori* (Hp)-relata interessa la mucosa dell'antro e del corpo-fondo dando luogo alla gastrite atrofica multifocale (MF-AG); la gastrite atrofica autoimmune invece è limitata al corpo-fondo risparmiando l'antro (CR-AG). L'AG è ad aumentato rischio per displasia (GD) e cancro gastrico (GC). Questo rischio è ben stabilito nella MF-AG, ma ancor adibattuto nella CR-AG. Questo studio ha come scopo di valutare le caratteristiche cliniche e endoscopico-istologiche di pazienti affetti da GD o GC in MF-AG e CR-AG.

**METODI:** E' stato condotto uno studio trasversale multicentrico in 11 centri gastroenterologici italiani su dati di pazienti adulti con GD o GC non cardiaci in MF-AG o CR-AG basati su schede cliniche e referti endoscopici e istologici.

**RISULTATI:** Sono stati inclusi 84 pazienti, di cui 45 (53.6%) con MF-AG e 39 (46.4%) con CR-AG. GD di basso (LG-GD) e di alto grado (HG-GD) e GC sono stati diagnosticati in 31 (36.9%), 6 (7.1%), and 47 (56.0%) pazienti, rispettivamente. GD e GC sono stati riscontrati con frequenza simile in pazienti con MF-AG e CR-AG: HG-GD in 4 (8.9%) vs 2 (5.1%), LG-GD in 17 (37.8%) vs 14 (35.9%), e GC in 24 (53.5%) vs 23 (59.0%) ( $p > 0.05$ ). Rispetto ai pazienti con MF-AG, nei pazienti con CR-AG GD e GC erano più frequentemente di aspetto polipoide (51.6% vs 27.3%,  $p = 0.048$ ) e più frequentemente localizzati nel corpo-fondo (55.3% vs 28.6%,  $p = 0.02$ ), ma venivano riscontrati anche nell'antro (34.2%) e a livello dell'incisura (10.5%). Il trattamento chirurgico era più frequente nei pazienti con CR-AG rispetto a coloro con MF-AG (48.6% vs 23.1%,  $p = 0.02$ ). La severità dell'atrofia del corpo-fondo e la presenza di metaplasia intestinale non erano differenti ( $p > 0.05$ ), mentre la positività istologica per l'Hp era bassa in ambedue i gruppi ((2.3% vs 2.9%,  $p = 0.87$ ), ma nei Hp negativi l'attività infiammatoria era presente nell'antro nel 26.7% e 7.7% ( $p = 0.02$ ), e nel corpo-fondo nel 31.1% e 21.5% ( $p = 0.027$ ).

**CONCLUSIONI:** GD e i GC non cardiaci possono sviluppare sia in pazienti con MF-AG che con CR-AG, con differenze nella topografia e nella presentazione endoscopica ma con similitudini nella mucosa non lesionale circostante, nella differenziazione e nella stadiazione. Pertanto, la sorveglianza dovrebbe essere considerata in tutti i pazienti con AG del corpo, a prescindere dall'estensione e dalla presunta eziologia.

**KEYWORDS:** atrophic gastritis; autoimmune gastritis; gastric cancer; gastric dysplasia; *Helicobacter pylori*; multicenter study

**ABBREVIATIONS:** AG, atrophic gastritis; AJCC, American Joint Committee on Cancer; CR-AG, corpus-restricted atrophic gastritis; GD, gastric dysplasia; GC, gastric cancer; Hp, *Helicobacter pylori*; HG, high-grade; LG, low-grade; MF-AG, multifocal atrophic gastritis; OLGA, operative link on gastritis assessment; WHO, World Health Organization

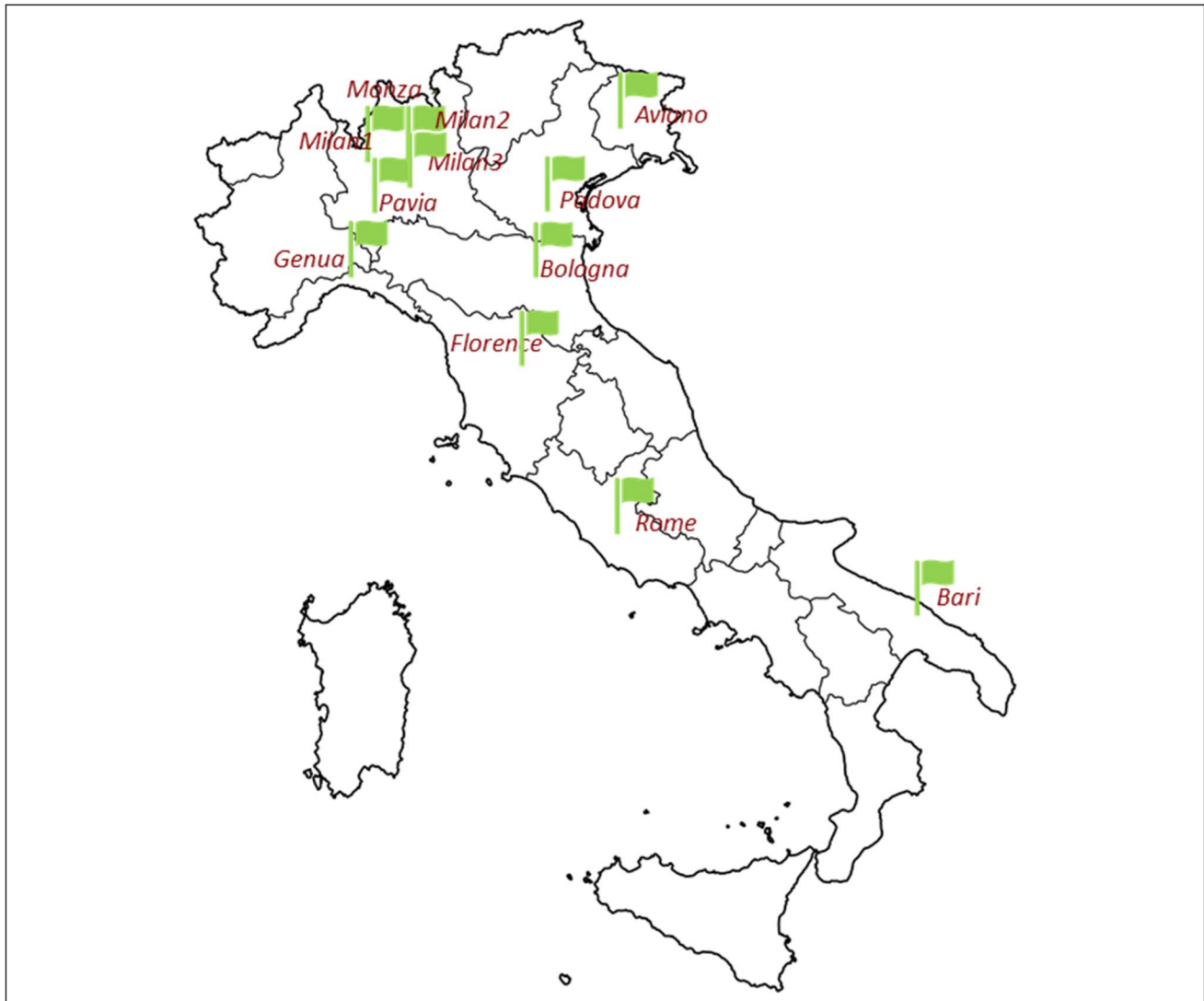
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## INTRODUCTION

Gastric cancer (GC) is still the fifth most frequent cancer in the world and the third leading cause of cancer-related death. Most GC cases are diagnosed at advanced or metastatic stages, limiting treatment options to palliative systemic therapies (1,2). Despite a decline in incidence over recent decades, GC represents a relevant economic and social burden on human health (3,4). Most commonly (90%–95%), GCs are adenocarcinomas originating from the innermost gastric mucosal glands and may be distinguished into 2 subtypes, namely, the intestinal type with a slightly more favorable prognosis and the diffuse type with a generally rapid spread representing a worse prognosis (2,3). Albeit one of the leading causes of GC is represented by *Helicobacter pylori* (Hp) infection, the carcinogenesis process is highly complex and

multifactorial, involving many factors related to the bacterium itself, the environment, and the host, possibly including gastric autoimmunity (5,6).

The most frequent clinical-histological background on which GC of the intestinal type develops is gastric atrophy extended to the corpus mucosa with intestinal metaplasia, according to the multistep cascade proposed by Correa on theoretical grounds, afterward confirmed by longitudinal studies (7,8). Atrophic gastritis (AG) is a chronic inflammatory condition mainly due to Hp infection or autoimmunity. Hp-related AG involves both the corpus and antral mucosa, giving rise to multifocal AG (MF-AG); AG driven by autoimmunity is restricted to the corpus mucosa only (CR-AG), sparing the antrum (9). According to the World Health Organization (WHO), Hp is a well-established type 1



**Figure 1.** Flags mark participating centers across Italy.

carcinogen, its role as a trigger of gastric autoimmunity has been proposed, although definitive evidence is lacking (6,10). Although GC risk is well-established in Hp-related MF-AG, its association with autoimmune CR-AG remains debated (6,11–14).

Current guidelines recommend endoscopic surveillance in patients with extensive, MF-AG at 3-year intervals, in CR-AG at 3–5 year intervals for early diagnosis of gastric neoplastic lesions to implement timely treatment and improve outcomes (15–18).

GC in AG may arise in the antrum, *incisura angularis* or, less frequently, the corpus. In some patients, diagnosis of GC is preceded by gastric dysplasia (GD), which sometimes occurs years earlier. Data on characteristics and potential differences of GD-GC lesions between extensive, MF AG and CR AG are lacking. Based on this background, this study aimed to assess the clinical, endoscopic, and histological characteristics of GD and GC in patients with MF-AG and CR-AG.

## METHODS

A multicenter, cross-sectional study was conducted across 11 Italian Gastroenterology centers (Figure 1). Participating centers were recruited by a call published online on the official website of the Italian Society of Gastroenterology.

### Working definitions

MF-AG and CR-AG were defined by histopathology assessed on gastric biopsies according to the updated Sydney system (9). MF-AG was diagnosed when gastric mucosal atrophy with or without intestinal metaplasia was present in both, the corpus and antral mucosa; instead, CR-AG was diagnosed when gastric mucosa atrophy with or without intestinal metaplasia was limited to the corpus mucosa with a spared antral mucosa (13).

### Data collection and analysis

Data on patients with MF-AG or CR-AG who had GD-GC (2001–2023) were retrospectively collected in an *ad hoc* database sheet based on clinical, endoscopic, and histological charts: site, dimension, endoscopic, and histologic features of GD-GC, perilesional gastric antral and corpus mucosa (updated Sydney system), and patients' clinical data (age, sex, outcome after GD-GC diagnosis, Hp infection, parietal cell autoantibodies, and family history for GC). Inclusion criteria were patients with MF-AG or CR-AG who had non-cardia GD or GC, aged >18 years, availability of endoscopic and histological description of GD-GC and the surrounding, not lesional gastric mucosa, and completeness of clinical data. Exclusion criteria were absence of gastric atrophy in the corpus or presence of gastric atrophy in the antrum only, presence of cardia GC or GD, absence of histological data regarding the surrounding, not lesional gastric mucosa, and previous endoscopic or surgical resection of gastric neoplastic lesions.

Data were stratified for MF-AG and CR-AG, and the GD-GC lesions, the not lesional mucosa, and the clinical characteristics between groups were compared by univariate analysis ( $\chi^2$  test or Mann-Whitney test, as appropriate).

All participants provided informed consent, and the ethical committee was approved (No. CEUR-2024-Os99).

### Endoscopy and histopathology of GD-GC lesions

GD and GC lesions were characterized by localization (antrum, *incisura angularis*, and corpus), whereas lesions localized at the cardia were excluded. They were further characterized by size

and endoscopic appearance (ulcerative, polypoid, flat, and normal mucosa). Histopathology distinguished the gastric lesions in low-grade (LG) and high-grade (HG) GD according to the WHO classification of digestive tumors (19) and GC according to the Lauren classification in intestinal, diffuse, mixed, and undetermined type (20,21). The GC differentiation grade was expressed as G1, G2, and G3, and the GC staging follows the American Joint Committee on Cancer (AJCC) TNM (tumor-node-metastasis) staging system in stages from 0 to 4 considering the local gastric spread, the nodes, and distal involvement (22).

Concerning GD-GC treatment, data on endoscopic, surgical, chemotherapy, palliative, or combined treatment were collected, and patients' outcomes were binarily classified according to whether patients were alive or dead at the moment of data collection.

### Histopathology of the surrounding nonlesional gastric mucosa

Gastrosopies were performed by fully trained gastroenterologists and endoscopists. All patients underwent pharyngeal anesthesia (xylocaine spray puffs) and conscious intravenous sedation (midazolam 3–5 mg). Gastrosopies were performed using white light mode and, when available, using electronic chromoendoscopy (narrow band imaging). Biopsies were collected according to the updated Sydney system (9): 2 biopsies from the antrum, 1 from the *incisura angularis*, and 2 from the corpus, and sent for histopathological assessment in different vials.

Expert pathologists of upper-gastrointestinal pathology performed histopathological assessments in every single center. The histopathological report was redacted according to the criteria of the updated Sydney system (9). Gastric atrophy was graded on a four-grade scale: absence of replacement (score 0), replacement to a mild (score 1), moderate (score 3), or severe degree (score 3). Based on a morphological-histopathological assessment, intestinal metaplasia was defined as the substitution of normal gastric glands with intestinalized glands. Pseudopyloric metaplasia was defined as the replacement of the oxyntic glands resembling the mucosa-secreting cell-lined glands ordinarily present in the antral region.

Hp infection was considered present when the bacterium was retrieved by morphological evaluation at hematoxylin and eosin stain, in cases of doubt, specific stains (modified Giemsa stain, Warthin-Starry, or immunohistochemistry) were used, as well (23). The presence of active inflammatory infiltrate (polymorphonuclear cells) as an indirect sign of likely Hp infection was assessed as well.

### Statistical analyses

Statistical analyses were performed with MedCalc Statistical Software 22.009 (MedCalc Software, Ostend, Belgium; <http://www.medcalc.org>; 2023). Descriptive statistics were performed using mean, SD, median, and range for quantitative variables. The frequencies and percentages were computed for qualitative variables. To compare quantitative variables between groups, the Student *t*-test or Mann-Whitney test was used, as appropriate. To compare qualitative (dichotomous) variables between groups, the Fisher exact test or  $\chi^2$  test was used, as applicable. A *P*-value of <0.05 was considered statistically significant.

**Table 1.** Main features of the included study population: n = 84 patients with GD or GC arisen in a histopathological background of MF-AG or CR-AG

	All patients MF-AG and CR-AG n = 84 (100%)	MF-AG n = 45 (53.6%)	CR-AG n = 39 (46.4%)	P
Age at AG diagnosis				
Median, range	70.0, 33–90	70.0, 33–90	70.0, 48–86	0.46
Mean, SD	69.3, 10.6	70.0, 10.8	68.5, 10.4	0.50
Females, n (%)	54.8	42.2	69.2	0.01
GD-GC diagnosis concomitant to AG diagnosis	35.7	33.3	38.5	0.63
AG diagnosis >1 yr regarding GD-GC diagnosis median, range	4, 1–17	4, 1–12	5, 1–17	0.90
Mean, SD	5.5, 4.0	5.1, 3.2	6.0, 4.8	0.54
Hp eradication treatment before diagnosis of GD-GC	16.7	20.0	12.8	0.30
Positivity toward parietal cell autoantibodies	60.0	51.5	69.7	0.13
First-degree family history for GC	15.2	14.7	15.6	0.92
Active or previous use of proton pump inhibitors	56.4	56.2	56.5	0.98
Active or previous smoking habit	30.4	9/30 (30.0)	30.8	0.95
Type of anemia			n = 31	
Iron-deficiency	25.8	30.3	19.4	0.31
Pernicious	18.8	9.1	29.0	0.04
Mixed	9.4	12.1	6.5	0.44
None	46.9	48.5	45.2	0.79

Data expressed as % when not otherwise indicated.  
AG, atrophic gastritis; CR, corpus-restricted; GC, gastric cancer; GD, gastric dysplasia; Hp, *Helicobacter pylori*; MF, multifocal.

## RESULTS

The original database of collected data included 112 patients; 28 patients were excluded (because of the absence of corpus AG, n = 18; the presence of cardia cancer, n = 6; or lack of complete histological data of surrounding nonlesional gastric mucosa, n = 4). The final cohort included 84 patients with non-cardia GD-GC arising in the context of corpus-involving AG (females n = 46, 54.8%; median age 70, range 33–90, mean age 69.3, SD 10.6 years). These patients were derived from a total pool of n = 2,714 patients with corpus-involving AG diagnosis in all participating centers.

Among the 84 included patients, MF-AG was observed in 45 (53.6%), while CR-AG was in 39 (46.4%) patients. Women were more frequent in CR-AG than in MF-AG (69.2% vs 42.2%,  $P = 0.01$ ). In addition, pernicious anemia was more frequently associated with CR-AG than MF-AG (29% vs 9.1%,  $P = 0.04$ ), while iron-deficiency anemia showed a nonsignificant difference between the 2 groups (19.4% in CR-AG vs 30.3% in MF-AG,  $P = 0.31$ ); interestingly, 30 (46.9%) patients did not have any type of anemia, 14 (45.2%) and 16 (48.5%) in the CR-AG and MF-AG groups, respectively.

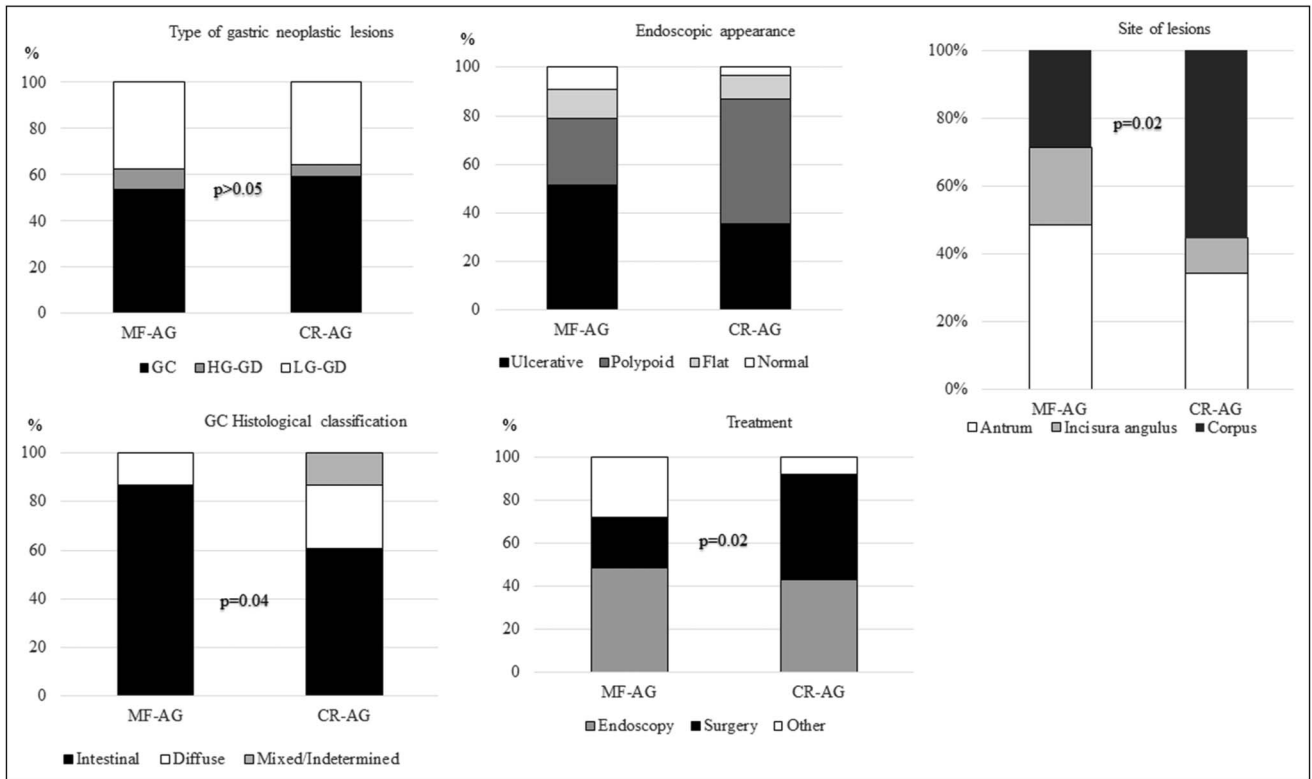
Other clinical features such as age, family history of GC, smoking habit, previous use of proton pump inhibitors, and parietal cell autoantibodies positivity were not statistically different

between patients with MF-AG and CR-AG. Hp eradication treatment was previously performed in 9 (20%) patients with MF-AG and 5 (12.8%) patients with CR-AG ( $P = 0.30$ ). Table 1 presents the main features of patients with MF-AG and CR-AG.

### GD and GC lesions

Among the 84 included patients, 31 (36.9%) had LG GD, 6 (7.1%) HG GD, and 47 (56.0%) GC. The occurrence of GD or GC was not statistically different between patients with MF-AG and CR-AG: HG-GD was present in 4 (8.9%) vs 2 (5.1%), LG-GD in 17 (37.8%) vs 14 (35.9%), and GC in 24 (53.5%) vs 2 (59.0%) patients ( $P > 0.05$ ). In 15 (33.3%) patients with MF-AG and 15 (38.5%) patients with CR-AG, the GD-GC diagnosis was attendant to the diagnosis of AG. In others, GD-GC was diagnosed later, with a median delay of 4 years (range 1–12, mean  $5.1 \pm 3.2$ ,  $P = 0.90$ ) in MF-AG and 5 years (range 1–17, mean  $6.0 \pm 4.8$ ) in CR-AG ( $P = 0.54$ ).

Compared with MF-AG, in patients with CR-AG, GD-GC were more commonly polypoid lesions (51.6% vs 27.3%,  $P = 0.048$ ), but less frequently ulcerative without reaching statistical significance (35.5% vs 51.5%,  $P = 0.199$ ); furthermore, they were localized more frequently in the corpus than in the antrum (55.3% vs 28.6%,  $P = 0.02$ ), occurring in the antrum (34.2%) and at the *incisura angularis* (10.5%) less commonly.



**Figure 2.** Main features of non-cardia GD and GC in 84 patients with a histopathological background of MF-AG or CR-AG. AG, atrophic gastritis, CR, corpus-restricted; GC, gastric cancer; GD, gastric dysplasia; HG, high-grade; LG, low-grade; MF, multifocal.

The intestinal-type GC was most prevalent and more frequent in MF-AG than CR-AG (87% vs 60.9%,  $P < 0.046$ ), while diffuse GC was twice as frequent in CR-AG than in MF-AG (26.1% vs

13%,  $P = 0.27$ ) without reaching statistical significance. No significant differences were observed in GC differentiation grade or TNM staging between groups.

**Table 2.** Characteristics of the nonlesional gastric mucosa of 84 patients with GD or GC arising in the histopathological background of MF-AG or CR-AG

	All patients MF-AG and CR-AG n = 84 (100%)	MF-AG n = 45 (53.6%)	CR-AG n = 39 (46.4%)	<i>P</i>
<b>Antral mucosa</b>				
Acute inflammation	19.0	28.9	7.7	0.0142
Chronic inflammation	57.1	80.0	30.8	<0.0001
Atrophy	50.0	93.3 <sup>a</sup>	0.0	<0.0001
Intestinal metaplasia	41.0	75.6	0.0	<0.0001
Presence of Hp	1.3	2.3	0.0	0.3657
<b>Corpus mucosa</b>				
Acute inflammation	28.6	33.3	23.1	0.3023
Chronic inflammation	94.0	91.1	97.4	0.2245
Severe corpus atrophy	51.2	48.9	46.4	0.6523
Intestinal metaplasia	82.9	84.4	81.1	0.6889
Pseudopyloric metaplasia	47.8	46.2	50.0	0.7530
Presence of Hp	2.5	2.3	2.9	0.8703

Data expressed as % when not otherwise indicated.

AG, atrophic gastritis, CR, corpus-restricted; GC, gastric cancer; GD, gastric dysplasia; Hp, *Helicobacter pylori*; MF, multifocal.

<sup>a</sup>3 (6.7%) of the 45 MF-AG patients without antral atrophy had antral intestinal metaplasia.

Endoscopic treatment of GD-GC was similar in both groups. Patients with CR-AG underwent surgery more frequently than MF-AG (48.6% vs 23.1%,  $P = 0.0207$ ), while other treatments (such as chemotherapy, palliative treatment or both, 8.1% vs 28.2%,  $P = 0.0248$ ) were prescribed more frequently in patients with MF-AG. In patients with CR-AG treated with surgery, tumor size was significantly higher than in those treated with endoscopy (mean  $\pm$  SEM:  $37.4 \pm 5.9$  mm vs  $15.9 \pm 3.8$  mm,  $P = 0.018$ ); also in patients with MF-AG treated with surgery, tumor size was higher, but statistical significance was missed ( $38.0 \pm 8.9$  mm vs  $19.8 \pm 5.2$  mm,  $P = 0.084$ ).

Figure 2 and Table 1 detail the main GD-GC-related differences between the CR-AG and MF-AG groups.

### Histopathological features of the not lesional gastric mucosa

The histopathological features of the corpus mucosa (acute and chronic inflammation, corpus atrophy severity, and presence of pseudopyloric/intestinal metaplasia) were not statistically different between patients with MF-AG and CR-AG ( $P > 0.05$ ). By contrast, compared with CR-AG, in patients with MF-AG, acute inflammation was more prevalent (28.9% vs 7.7%,  $P = 0.01$ ) as was chronic inflammation in the antrum (80% vs 30.8%,  $<0.0001$ ) (Table 2).

### Role of Hp infection in MF-AG and CR-AG patients with GD or GC

Histological Hp positivity was low in both groups and not statistically different (2.3% vs 2.9%,  $P = 0.87$ ). In the MF-AG group, 1 patient (2.3%) had histological Hp positivity in both, corpus and antral mucosa; in the CR-AG group, 1 patient (2.9%) had histological Hp positivity only in the corpus mucosa.

Among histologically Hp-negative patients, active inflammatory infiltrate in the antral mucosa was present in 26.7% ( $n = 12$ ) patients with MF-AG and 7.7% ( $n = 3$ ) patients with CR-AG ( $P = 0.02$ ) and in the corpus mucosa in 31.1% ( $n = 14$ ) patients with MF-AG and in 21.5% ( $n = 8$ ) ( $P = 0.27$ ) patients with CR-AG, likely indirectly suggesting the presence of active Hp infection.

Hp IgG serology (ELISA) was available from 29 CR-AG patients (74.3%) with histological Hp negativity and without previous history of Hp infection and was positive in 9 (31%) documenting previous Hp exposure.

All CR-AG patients with GD-GC localized at the *incisura angularis* ( $n = 4$ , 10.2%) were Hp negative at both histology and serology, with no active inflammatory infiltrate; in the CR-AG patients with GD-GC localized in the antrum ( $n = 13$ , 33.3%), Hp was histologically negative, but active inflammatory infiltrate was present in 4 patients in the corpus mucosa, and serology was positive in 3 patients, suggesting a likely role of Hp infection in a subset of these patients.

## DISCUSSION

This Italian multicenter cross-sectional study focusing on GD and GC arising in the histological background of corpus-involving AG revealed that non-cardia GD and GC are both associated with MF-AG and CR-AG (53.6% vs 46.4%,  $P > 0.05$ ). These findings challenge the traditional understanding that GD-GC typically occur in the context of MF-AG, a well-known longstanding consequence of Hp infection (5,6,24,25), while the association of GD-GC with CR-AG, the typical histological pattern of autoimmune AG, is much more infrequent and even debated (25–28). Thus, the current data show that CR-AG might be

associated with GD-GC more frequently than expected, especially in a real-world setting. In front of a new endoscopic diagnosis highly suspicious for GD or GC, attention generally focuses on the histological characterization of the neoplastic lesion, shifting away the focus from obtaining biopsies of the nonlesional mucosa necessary to characterize the type of the associated AG; in this way, the underlying gastric condition unfortunately often remains misrecognized. In this study, only GD-GC lesions having a simultaneous characterization of the nonlesional neoplastic gastric mucosa were included, thus making it possible to shed light on this aspect. In this context, it should also be considered that CR-AG not in all cases is synonym of pure autoimmune AG. First, as recently stated, autoimmune AG may, in some cases, be triggered by Hp infection, giving rise to secondary autoimmune AG (25,29); additionally, antral mucosa may heal over time in patients formerly diagnosed as MF-AG irrespective of Hp eradication, possibly ending up at a later point of the natural history as CR-AG resembling autoimmune AG and leading to an overestimation of pure autoimmune CR-AG (30,31). Interestingly, the results of this study show further that GD-GC may develop in low-risk Operative Link on Gastritis Assessment (OLGA) stages (I–II) as in CR-AG, OLGA II represents the highest possible OLGA stage that can be reached because of the spared antrum (27), raising the question of endoscopic surveillance need mainly deserved for high-risk OLGA stages (III and IV) (12,15,16,23). As already postulated, in CR-AG, the OLGA staging system may therefore underperform (27,32).

In this study, the prevalence of histological Hp positivity was low in both GD-GC groups (2.5%), consistent with the difficulty of detecting Hp in advanced corpus atrophy due to an altered gastric microenvironment (11,25). Nonetheless, active inflammation (infiltrate of polymorphonuclear cells) and positive serology of Hp IgG antibodies may play a role in diagnosing active infection or in shedding light on previous exposure to infection (11,13). In this study, in histologically Hp-negative patients, acute inflammatory infiltrate was present in about 30% and 20% of patients with MF-AG and CR-AG, respectively, testifying the presence of active Hp infection, while positive Hp IgG serology in about 30% of patients with CR-AG showed previous Hp exposure, again proving that Hp infection likely plays a major role in GC-GD, irrespective of the associated pattern of corpus-involving AG.

However, it might be considered as well that the longstanding histological damage of AG and intestinal metaplasia may progress to neoplastic complications, irrespective of the initial trigger of gastric atrophy as observed in inflammatory cancers in other body districts, for example, the liver, the pancreas, or the lung in which chronic inflammation may over time progress to cancer, once a certain level of histological damage has been reached (33–35). Intestinal metaplasia has been reported to represent the condition *sine qua non* generating the histological background permitting the development of gastric intestinal adenocarcinoma (36–39); in this study, indeed, intestinal metaplasia was similarly present in the MF-AG and CR-AG patients with GD-GC.

In patients with CR-AG, as expected, the GD-GC lesions occurred more frequently in the corpus region, harboring the predisposing mucosal histopathological changes. However, in 10.2% of the patients with CR-AG, the neoplastic complications

occurred at the *incisura angularis*, and in 33.3%, even in the “spared” antral mucosa. The *incisura angularis* is an endoscopically defined region theoretically corresponding to the transition between the corpus and pyloric regions and is generally sent to the pathologist in the same vial of antral biopsies (9). Histologically, this region does not always correspond to transitional mucosa and may represent pure antral or even pure corpus mucosa, thus sometimes representing a confounding factor; for this reason, it has been proposed to waive the histological sampling of this region to reduce confounding (24,40). The accurate location of the *incisura angularis* in transitional corpus-pyloric mucosa is significantly influenced by the accurate endoscopic recognition of the topographical landmarks and by the topographical variability of the embryological pattern (25). This may explain the untypical GD-GC topographical localization in patients with CR-AG, even more so because these patients were all Hp negative at histology and serology and did not show active inflammation.

By contrast, it is challenging to explain the antral occurrence of GD-GC in CR-AG patients with a “spared” antrum by definition. A previous study investigating histopathological and molecular characteristics in GC associated with autoimmune AG showed that 11 (42.3%) of 26 GC specimens were localized in the antrum (39). At least in a subset of patients of this study, active inflammatory infiltrate in the corpus mucosa and positive Hp serology suggest a role of Hp infection even in the presence of a “spared” antral mucosa. However, as mentioned above, antral mucosa may have healed over time, resembling the “spared” antral mucosa typically associated with autoimmune CR-AG (29,30). In addition, the question of sampling error may be brought into play, questioning the reliability of CR-AG diagnosis with a spared antrum. However, about 50% of the included patients had electronic chromoendoscopy, which is able to endoscopically identify intestinal metaplasia (as a surrogate of atrophy), permitting target biopsies and thus reducing sampling error (41–43). Therefore, the presence of GD-GC lesions in the “spared” antral mucosa of patients with CR-AG is particularly intriguing and raises questions about the underlying mechanisms. Autoimmune corpus gastritis could induce not only local but also systemic alterations, modifying the gastric microenvironment in a way that predisposes or aggravates neoplastic risk, even in areas not directly involved in the autoimmune process. Hypoacidity, for example, could lead to compensatory hypergastrinemia, which has been implicated in promoting neoplastic changes (44,45). This systemic disruption may create a proneoplastic environment, potentially affecting also the antral mucosa.

It is well known that Hp infection is the primary etiological agent of GC, but Hp may not be detected anymore at the moment of GC diagnosis (46); in Japan, Sasaki A and colleagues showed a prevalence of 2.6% (54 of 2,112) Hp-negative GC (47), and GC may occur even many years after Hp eradication (47,48). This phenomenon led to the conclusion that Hp is necessary for the initial steps of gastric carcinogenesis, which are likely put forward and completed by other agents, probably related to gastric dysbiosis as a consequence of impaired gastric acid secretion (49–54).

From a histopathological point of view, the intestinal-type GC was the most frequently diagnosed type and more prevalent in the MR-AG than in the CR-AG group. This finding was unsurprising because the intestinal-type GC is the histological type

characteristically associated with Hp infection (2,3,25). On the other hand, the diffuse GC type was more frequent in CR-AG. This was an interesting finding because an increased association of this GC type with Hp-negative stomachs and autoimmune AG was reported (54).

The endoscopic appearance of GD-GC was different between patients with MF-AG and CR-AG because the lesions in the first group were more frequently ulcerative and the second more frequently elevated, while flat lesions were similarly represented. We cannot provide a plausible explanation for this difference; further studies are needed to verify whether the endoscopic appearance might predict the associated AG pattern.

Concerning treatment, although the endoscopic therapy of GD-GC was similar in patients with MF-AG and CR-AG, patients with CR-AG more often underwent surgery (48.6% vs 23.1%,  $P = 0.02$ ), while patients with MF-AG more frequently received chemotherapy or palliative care (8.1% vs 28.2%,  $P = 0.02$ ). Explaining the different treatments in the 2 groups of patients is challenging. Tumor size might have played a relevant role for surgery indication because patients with CR-AG treated with surgery had 2-fold larger tumors than those treated with endoscopy. Other reasons such as varying approaches in different centers, according to the availability of oncology units and gastrointestinal endoscopy units skilled in advanced endoscopic resection techniques might have influenced treatment decision.

This study has limitations. Local pathologists performed histopathology, and this might have led to inhomogeneities in histopathological assessment. The study may suffer from potential sources of selection bias. In the participating centers, a larger population of patients was possibly diagnosed with GC and GD than those patients included in this study, but without taking biopsies from the gastric mucosa able to identify atrophy and subclassify into MF and CR. For example, patients presenting with advanced age, large lesions, aggressive disease, active bleeding, or similar circumstances may have led physicians to not see additional benefit of biopsying the background mucosa and have been missed by the methodology of this study. This cross-sectional study was not designed to perform data on GD-GC incidence or prevalence in patients with MF-AG or CR-AG. Finally, Hp serology was only available in a subset of patients to provide clear information about previous Hp exposure.

Thus, the findings of this study permit the conclusion that non-cardia GD and GC may occur in both MF-AG and CR-AG, displaying differences in topography, endoscopic presentation, and treatment approach, but similarities in perilesional gastric corpus mucosa, differentiation, staging, and outcome. Endoscopic-histological surveillance should be deserved to patients with gastric corpus atrophy, irrespective of its extension, staging, and supposed etiology.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Edith Lahner, MD, PhD.

**Specific author contributions:** E.L., B.A., F.F.: planning and conducting the study, drafting the manuscript, and approving the final version; M.V.L., A.D. S., S.M., F.Z., M.M.D'E.: conducting the study, interpreting data, and drafting the manuscript; R.C., E.D., C.M.L., E.M., N.Z., S.R., G.L., A.V.B., E.M., E.G.G., A.P., F.C., L.M., R.E.R., V.S., A.C., A.P., A.D.R., M.S., G.G., C.D.B., D.M.: conducting

the study, collecting and interpreting data. Each author has approved the final draft submitted.

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## Study Highlights

### WHAT IS KNOWN

- ✓ *Helicobacter pylori*-related atrophic gastritis (AG) affects corpus and antral mucosa, resulting in multifocal (MF) AG.
- ✓ Autoimmunity-driven AG is corpus-restricted (CR), and the role of *H. pylori* in CR-AG is not clear.
- ✓ AG carries increased non-cardia gastric dysplasia (GD) and cancer risk.
- ✓ The GD-GC risk is well established in MF-AG, but debated in CR-AG.

### WHAT IS NEW HERE

- ✓ The occurrence of non-cardia GD-GC in patients with MF-AG or CR-AG was not different.
- ✓ Compared with MF-AG, in CR-AG, GD-GC were more frequent in the corpus than in the antrum or *incisura angularis* and presented more commonly as polypoid lesions; nonlesional mucosa, differentiation, and staging were similar between groups.
- ✓ Surveillance should be considered in corpus AG, regardless of extension and supposed etiology.

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