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Alimentary Tract

Antral mucosa healing at long-term follow-up in patients with corpus atrophic gastirits and concomitant antral gastritis may mimick autoimmune gastritis

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ABSTRACT

Background and aim: Corpus atrophic gastritis (CAG) is defined as autoimmune when the antrum is spared, representing this element a crucial diagnostic criterium of autoimmune gastritis. In contrast, CAG with concomitant antral gastritis (AG), atrophic or non-atrophic, is generally attributed to *H. pylori* infection. During the natural history of CAG, possible antrum healing has been supposed. The current study aimed to assess the antral mucosa histopathological changes at long-term follow-up (FU) with respect to baseline in patients with CAG and concomitant atrophic or non-atrophic gastritis AG.

Methods: Retrospective study on 130 patients with histologically diagnosed CAG with atrophic or non-atrophic AG. Mean FU gastroscopy was at 40.6 (range 4–192) months. Patients with confirmed CAG (n = 117; median age 66, range 20–87 years; 67.5 % F) were finally included. At baseline, 47 (40.2 %) had non-atrophic and 70 (59.8 %) atrophic AG. *Helicobacter pylori* (*Hp*) infection was present at histology in 27.3 % of patients, all treated.

Results: At FU, 30/117(25.6 %) patients showed a complete antral healing; 11/29(37.9 %) were *Hp* positive at baseline, cured in all but one. Atrophic AG regressed in 16/70(22.8 %) patients. Both, antral healing and regression of antral AG, were found to be similar in *Hp*-cured and not-cured/ naïve-negatives patients ($p > 0.05$).

Conclusion: In a subset of CAG patients, AG may regress at long-term FU irrespective of Hp cure, thus mimicking autoimmune atrophic gastritis and raising concerns about its current histopathological diagnostic criteria.

1. Background

Corpus atrophic gastritis (CAG) is an inflammatory condition characterized by the disappearance of oxyntic glands and their replacement by fibrosis or metaplasia (intestinal or pseudopyloric; IM, PPM). Traditionally, CAG is divided into two types: A) the autoimmune type, when atrophy is limited to the corpus, sparing the antrum ("corpus-restricted"), often characterized by the presence of anti-parietal cell antibodies (PCA), and B) the multifocal or extensive type, when both, the corpus and antrum mucosa are involved, caused by environmental factors mainly consisting of *Helicobacter pylori (Hp)* infection [1].

In *Hp* gastritis, previous studies postulated the possibility that antral mucosa might progressively heal and the atrophy border may progressively move up to the corpus mucosa; this was linked to the progressive shift of the bacterium colonization from the antrum to the corpus, where the bacterium gradually disappear and a complete heal is achieved [2]. Antral healing in *Hp* gastritis was also proved in case of eradication: Arkklia et al. showed how *Hp* eradication may not only delay antral atrophy progression but may even induce a complete atrophy disappearance in the antrum [3]. A trend towards healing of antral atrophy was also observed in first-degree relatives of patients with pernicious anaemia (PA) without a history of *Hp* infection [4], suggesting that antral atrophy regression may be possible even in patients with atrophy of other etiology.

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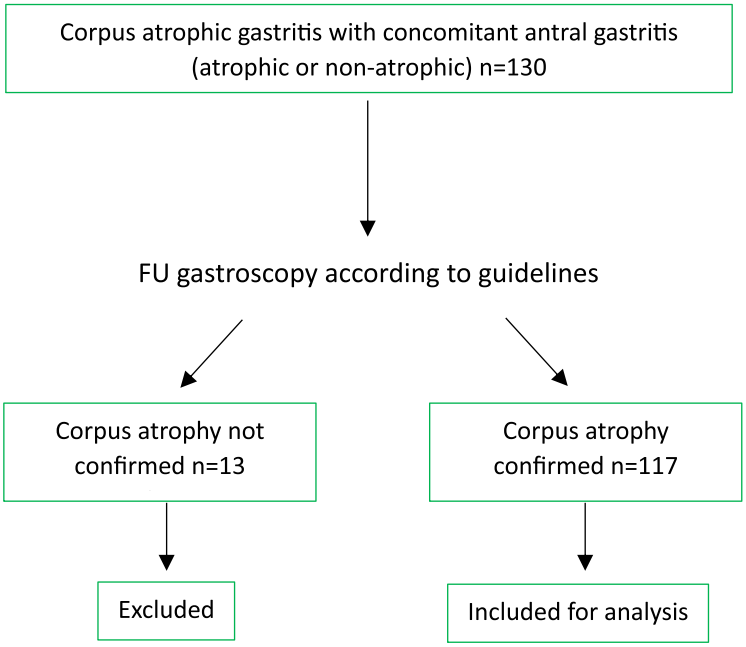


Fig. 1. Flow-chart of the included study population
FU = follow-up.

Thus, progressive antral healing and corpus atrophy development may occur in both: *Hp*-gastritis and non-*Hp* gastritis. This implies that corpus-restricted atrophy may be present in patients with or without a previous *Hp* history. Given that nowadays autoimmune atrophic gastritis (AAG) is defined on the basis of a "corpus-restricted" atrophy, understanding if antral healing reassembling corpus-restricted CAG may be part of the natural history of chronic gastritis and whether this could be independent from *Hp* eradication is of interest because the actual diagnostic criteria and classification of CAG are mainly based on the presence or not of antral gastritis (AG). For this reason, the current study aimed to assess changes of the histopathological pattern of the antral mucosa in a cohort of patients with CAG and concomitant atrophic or non-atrophic AG at long-term follow-up (FU) with respect to baseline.

2. Material and methods

2.1. Study population and design

A cohort of 130 patients with CAG and concomitant atrophic or non-atrophic AG, diagnosed and followed up in our teaching hospital, a referral center for gastric autoimmunity and atrophic gastritis, was retrospectively analyzed. This cohort was extrapolated from a prospective database where patients with CAG in FU for gastric cancer risk have been consecutively collected since 2001. Patients were followed up with annual clinical and serological evaluation and endoscopic FU every two or three years according to guidelines [5], except for cases requiring anticipated gastroscopy due to clinical or biochemical indications.

Data of histological findings at baseline gastroscopy and at the longest FU available were analyzed, including histological *Hp* status. PCA positivity at baseline was also assessed. Histologic assessment was performed according to the updated Sydney System [6]. Median time of FU gastroscopy was 36 (range 12–192; IQR 48) months.

Of these 130 patients, 13 were excluded because corpus atrophy was not confirmed at FU. Thus, 117 patients were finally included for further analyses (Fig. 1).

According to baseline antral histology, two groups were considered: (i) CAG patients with non-atrophic AG (n = 47) and (ii) CAG patients with atrophic AG (n = 70). For both groups, baseline and FU antral histopathology was compared and the Chi-squared-test was used to assess for differences between histological antral changes in patients with or without history of *Hp* infection. All patients were free from PPI use since CAG diagnosis.

2.2. Endoscopy

Baseline and FU gastroscopies were performed in our gastrointestinal endoscopy unit, in dedicated slots for patients with CAG by expert endoscopists. All gastroscopies followed the updated Sydney System protocol for biopsies [6], taking two biopsies from the antrum, one from the *incisura angularis*, and two from the corpus. Biopsies were sent for histopathological evaluation in two different vials: one for the antrum and *incisura angularis* and one for the corpus. After their availability in 2014, gastroscopes equipped with the electronic chromoendoscopy (Narrow Band Imaging, NBI, and/or Blue Light Imaging, BLI) device were used, allowing the endoscopic assessment of the presence and extension of IM and targeted biopsies, thus limiting sampling error being IM a valid predictor of mucosal atrophy. The endoscopic evaluation of IM was performed according to the endoscopic grading of gastric intestinal metaplasia (EGGIM) score, which considers a grade of 0, 1, or 2 respectively for no IM, $\leq$30 %, or >30 % of the mucosa in five areas (lesser and greater curvature of both antrum and corpus, and *incisura angularis*) [7].

2.3. Histopathology

Histopathological evaluation was performed by an expert pathologist (EP) following the criteria of the updated Sydney System [6]. CAG was defined as the disappearance of native oxyntic glands and replacement by fibrosis or metaplasia (IM or PPM). Atrophic AG was defined as the disappearance of native antral glands and replacement by fibrosis or IM. Atrophy was graded from 0 to 4: 0- no atrophy, 1- mild atrophy, 3- moderate atrophy, 4- severe atrophy. Non-atrophic AG was defined as the presence of increased

Hp, Helicobacter pylori

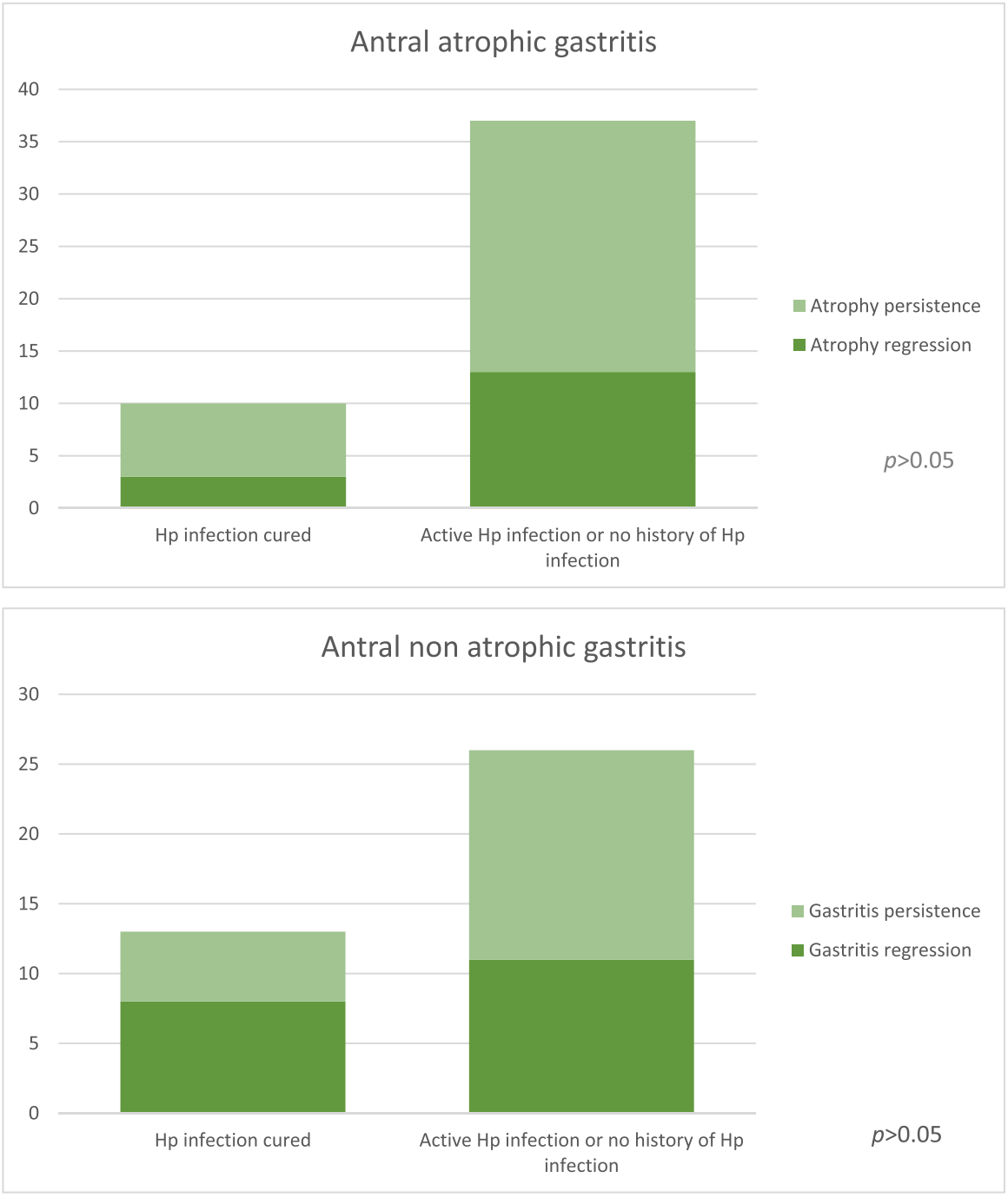


Fig. 2. Antral mucosal healing at follow-up and *Hp* infection in patients with corpus atrophic gastritis and concomitant antral gastritis (atrophic or non-atrophic) at baseline *Hp*, Helicobacter pylori.

inflammatory infiltrate without the disappearance of native gastric glands and, thus, without IM [6].

2.4. Diagnosis of Hp infection and treatment Hp infection

Hp infection was defined based on a positive histology, which is still the gold standard method for its diagnosis [8]. All patients with *Hp* infection underwent treatment using quadruple eradication therapy. The efficacy of eradication treatment was histologically assessed with gastroscopy with biopsies not earlier than six months after the end of treatment [8,9].

2.5. Statistical analyses

Data were expressed as mean ± SD or median (range) and as percentage of the total (%).

Histopathological characteristics at baseline and FU for both patients' groups, with atrophic and non-atrophic AG, were compared. To understand if changes were imputable to *Hp* infection present at baseline and then eradicated, the Chi-square test was used to assess in both groups, histological differences between patients with a history of *Hp* infection successfully cured and patients with failed eradication or without a history of *Hp*, to evaluate whether *Hp*

Table 1
Changes of antral histology at follow-up in patients with corpus atrophic gastritis and concomitant antral gastritis (atrophic or non-atrophic) at baseline
Hp, Helicobacter pylori.

	Antral mucosal healing n (%)	*Hp*+ at baseline n (%)	*Hp* cured n/tot
All-type antrum gastritis, $n = 117$	30 (25.6)	11 (36.7)	10/11
Antral non-atrophic gastritis, $n = 47$	19 (40.4)	9 (47.4)	9/9
Antral atrophic gastritis, $n = 70$	11 (15.7)	2 (18.2)	2/2

In 16 (22.8 %) patients with antral atrophy at baseline, at follow-up regression of atrophy with residual superficial chronic gastritis; 3 of these patients were *Hp*+ at baseline and successfully cured after eradication treatment.

eradication may have a role in antral healing. Further, changes between FU and baseline of updated Sydney scores of corpus and antral mucosa were compared by Student's *t*-test.

3. Results

3.1. Study population

Of the 117 included patients, 79 (67.5 %) were female, the median age was 66 (20–87) years.

At baseline, 47 patients (40.2 %) showed non-atrophic AG, while 70 (59.8 %) showed atrophic AG with IM in 84.3 % of cases. Even if the gastritis pattern of CAG with AG is typical of *Hp* infection, histologically diagnosed *Hp* was present only in 32 (27.3 %) of patients, all receiving eradication therapy. PCA positivity was present in 63 (53.8 %) of patients.

3.2. Follow-up histology data

At FU, of the 117 patients with concomitant AG, 30 (25.6 %) showed complete antral mucosal healing. In Fig. 2, an example of histological images of antral mucosa with atrophic AG at baseline and complete antral mucosal healing of patient with baseline CAG and AG are shown.

Among the 47 patients with non-atrophic AG, 19 (40.4 %) showed complete antral mucosal healing. Of these patients, 14 (77.7 %) were *Hp* positive at baseline and all were successfully cured of infection; two patients developed antral atrophy at FU.

Among the 70 patients with atrophic AG, 11 (15.7 %) showed complete antral mucosal healing. Of these patients, 7 (63.6 %) were *Hp* positive and all were successfully treated, 11 had severe, 22 had moderate and 37 had mild atrophy at baseline. Regression of atrophic AG with residual inflammatory infiltrate was observed in 16 (22 %) patients: of these 2 were *Hp* positive at baseline, and one was successfully cured of infection (Table 1), 5 had moderate and 11 had mild atrophy at baseline. Three patients with non-metaplastic atrophic AG at baseline developed metaplastic atrophic AG at FU. Both antral healing and atrophy regression were found to be similar in patients successfully cured of *Hp* infection and those with persistently active infection and/or naïve *Hp* negatives ($p > 0.05$) (Fig. 3). Corpus and antrum mucosa histopathological changes at baseline and follow-up are shown in Table 2.

3.3. Electronic chromoendoscopy evaluation of intestinal metaplasia in CAG patients with atrophic AG at baseline

Of the 70 CAG patients with atrophic AG, electronic chromoendoscopy (EC) was available at FU gastroscopy in 43 (61.4 %). Median EGGIM score was 3 [2-10] and endoscopic IM was observed in 14 (32.5 %). Of the 16 patients with complete regression of atrophic AG, EC was available in 14: in two (14.3 %) cases, endoscopic IM was observed, while at histopathology of target biopsies of these areas nor IM neither atrophy were detected, thus suggesting an endoscopic overestimation of IM. Of the 31 patients with persistence of atrophic AG at FU, EC was available in 22 patients, and endoscopic IM was observed in 13 (59.1 %) cases, thus being in accordance with histopathology on targeted biopsies. On the contrary, in 9 (40.9 %) patients endoscopic IM was not observed underestimating its histopathological presence or indicating non-metaplastic atrophic AG (Fig. 4).

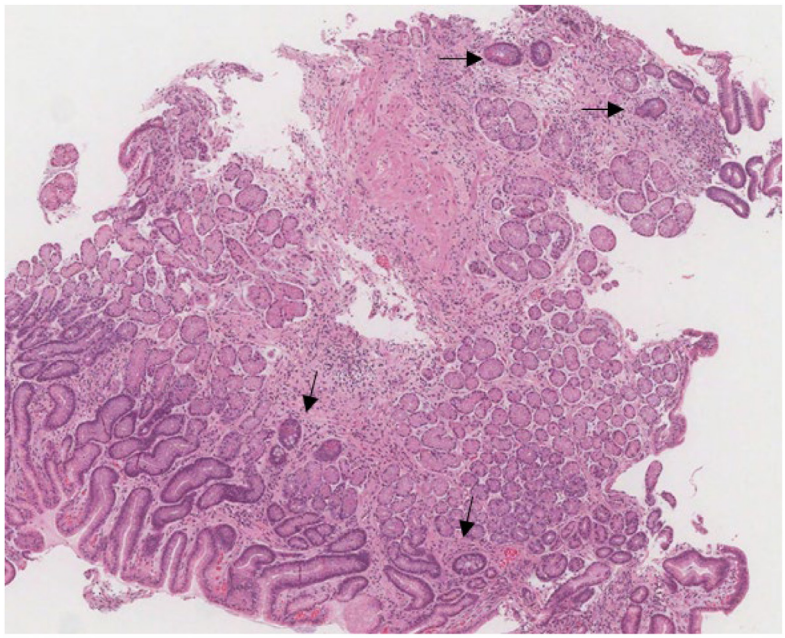
Table 2
Corpus and antrum mucosa histopathological changes at baseline and follow-up according to updated Sydney system in patients with corpus atrophic gastritis and concomitant antral gastritis at baseline.

	Corpus baseline Mean ± SD	Corpus follow-up Mean ± SD	*p*
Inflammation	1.85 ± 0.8	1.7 ± 0.65	0.113
Neutrophil activation	0.84 ± 0.9	0.13 ± 0.3	<0.001
Atrophy	2.1 ± 0.7	2.37 ± 0.7	<0.001
Intestinal Metaplasia	1.15 ± 0.9	1.43 ± 0.9	0.012
	Antrum baseline Mean ± SD	**Antrum follow-up Mean ± SD**	
Inflammation	1.13 ± 0.7	0.63 ± 0.6	<0.001
Neutrophil activation	0.45 ± 0.7	0.06 ± 0.3	<0.001
Atrophy	0.92 ± 0.9	0.68 ± 0.9	0.009
Intestinal Metaplasia	0.76 ± 0.9	0.64 ± 0.1	0.15

4. Discussion

The current study was performed to verify the hypothesis of possible antral mucosal healing in the course of CAG with concomitant atrophic or non-atrophic AG, both in cases with and without *Hp* infection. In the case of *Hp* infection, it has been argued that the bacterium colonization spontaneously tends to migrate from the antrum to the corpus along with the duration of infection [2,10]. In chronic gastritis, the involvement of the corpus mucosa leads to its progressive damage and consequently to hypoachlorhydria which in turn favors the bacterium shift in a pylorocardial direction [11,12]. On the other hand, several studies showed how *Hp* eradication might provide a mucosal injury improvement or regression, probably triggered by chronic inflammation [13,3]. Annibale et al. reported that *Hp* eradication does not reverse atrophy, even if it may improve damage severity [13]. Arkkila et al. showed how antral atrophy healing is more marked and frequent in *Hp*-positive patients receiving successful eradication than in patients who do not achieve eradication: in their prospective study on 92 patients with *Hp* infection and atrophic gastritis, the eradicated group showed a higher reduction of the antral atrophy score with respect to the non-eradicated group (1.5 to 0.7 vs 1.5 to 1.3, $p < 0.05$), showing possible regression of antral atrophy even at 1-year FU [3]. Similarly, also Ito et al. found that *Hp* eradication may lead to atrophy reversal at long-term FU (5 years) [14].

In our study, at a medium FU of slightly more than three years, but up to 16 years, antral atrophy regressed in 16 patients (22.8 %),



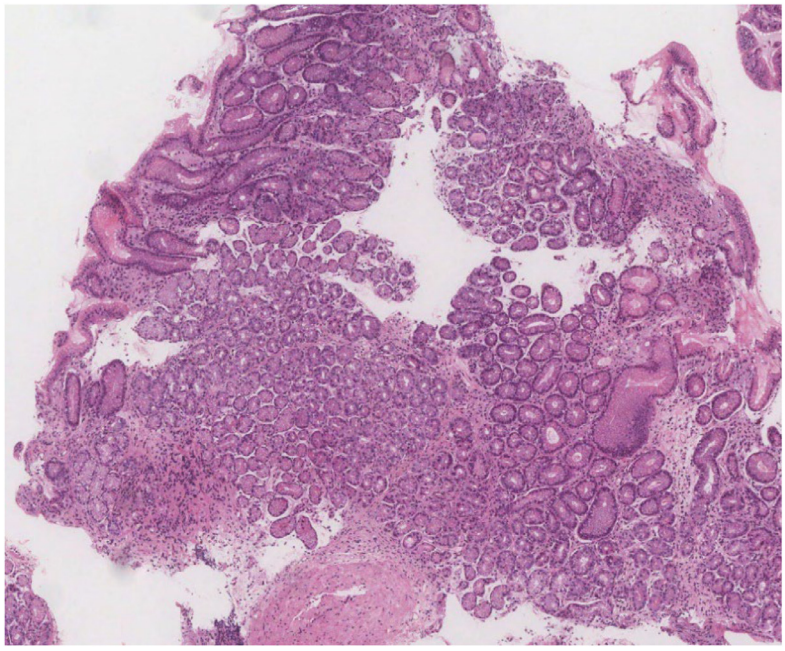


Fig. 3. Histological images of antral mucosa in eosin-hematoxylin staining (6x) showing A) atrophy of antral glands with intestinal metaplasia and inflammatory infiltrate at baseline and B) complete antral healing as shown by clearly visible antral gland at follow-up (4 years). In this patient, the histological samples of corpus mucosa showed concomitant severe atrophy with mild intestinal metaplasia at baseline, and these histological changes were persistent at follow-up.

among these, only 3 (18.7 %) were *Hp* positive and all of them were cured of infection. This may lead to the consideration that *Hp* eradication may be a responsible factor for atrophy healing. Conversely, there was no significative difference between patients who were cured and those who had persistent active infection or were *Hp* naïve negatives ($p < 0.05$). This result shows how antral healing is possible at long-term FU in patients with CAG and atrophic AG irrespective of *Hp*. A similar finding was previously reported by Kekki et al. who found that antral atrophy in first-degree relatives of PA patients tends to improve with possible healing of antral gastritis, more evident for superficial gastritis [4]. However, histology detects active infection only, therefore we cannot exclude possible previous exposure to *Hp* in a higher proportion of these patients with a typical *Hp*-related gastritis pattern involving the antral mucosa.

In our study, complete antral mucosal healing, with disappearance of all-type histopathological changes of antral mucosa was found in 25.6 % of patients. In the case of superficial, non-atrophic AG, the percentage of mucosal healing reached the greatest value, up to 40.4 % without a significant difference between patients with and without *Hp* cure ($p < 0.05$). This may be a manifestation of the tendency of antral mucosa to heal, especially when IM and atrophy are not yet established. While in *Hp* gastritis this may be due to the progressive disappearance of the bacterium from the antrum during the natural history or consequent to eradication leading to the cessation of inflammation [12], in non-*Hp* gastritis the mecha-

IM, intestinal metaplasia

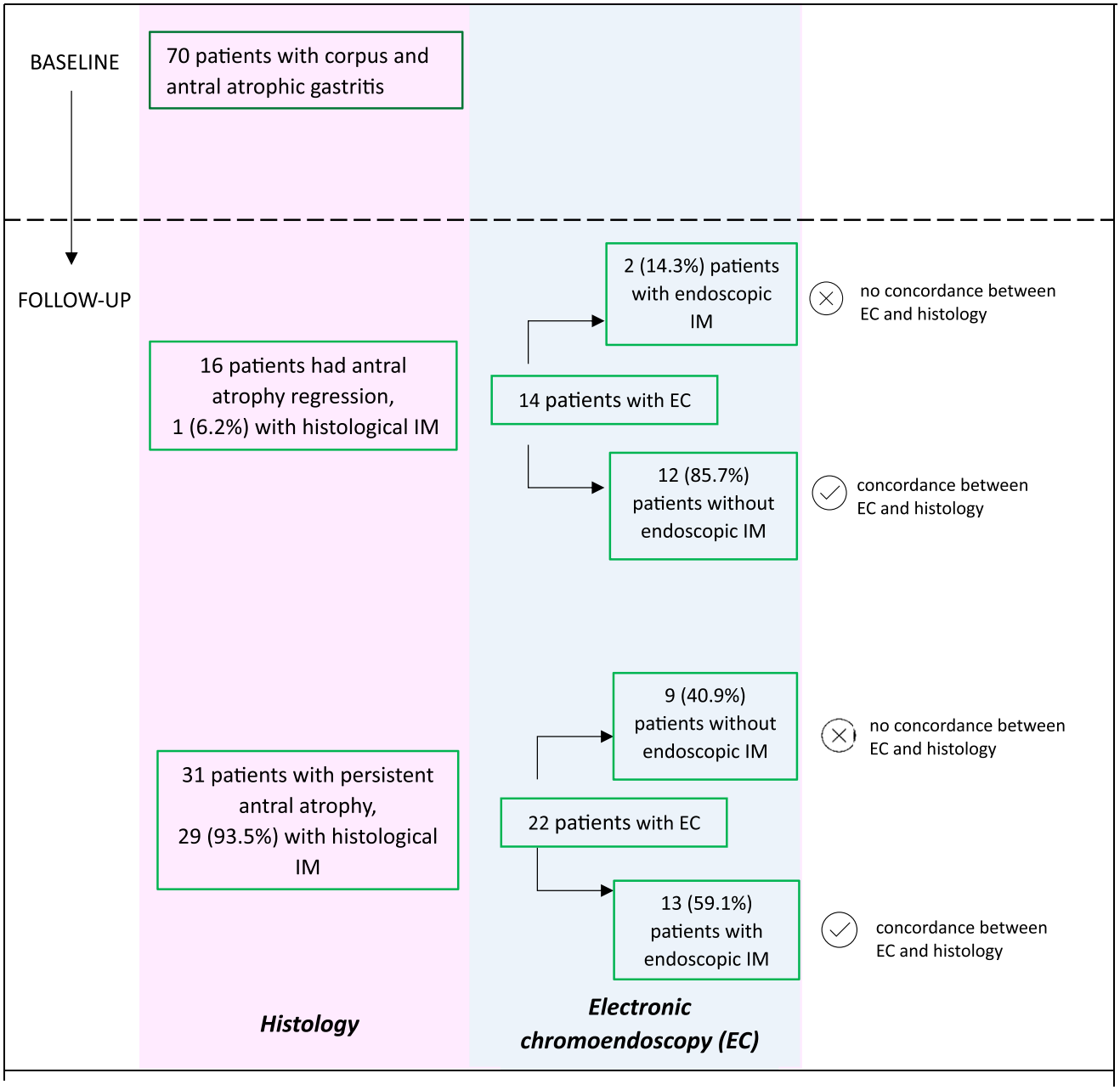


Fig. 4. Electronic chromoendoscopy (EC) in patients with corpus and antral atrophic gastritis at baseline and antral atrophy regression at follow-up
IM, intestinal metaplasia.

nisms underlying this kind of evolution are not known. The fact that possible antral healing may occur irrespective of *Hp* treatment, as shown from our data, strengthens the hypothesis that a long-standing *Hp* gastritis may evolve as a corpus-restricted type, perfectly resembling AAG. This finding sets doubts about its real etiology [15] and makes it difficult to distinguish between primary and secondary AAG, being in contrast with the idea that a normal antral mucosa would be the hallmark of an *H. pylori* "naïve" gastritis [16].

The eventuality of sampling error has already been advocated by Annibale et al. to explain atrophy and IM regression and this is an important issue to be taken into consideration [12]. In the current study, the use of chromoendoscopy and EGGIM score in large part of the FU gastroscopies (>60 %), allowing targeted biopsies highly reduces the possibility that biopsies were taken in an atrophy-spared site of mucosa erroneously diagnosing antral mucosal healing. Indeed, in 87.5 % of patients showing atrophy regression at FU, antral IM was detected not even by chromoendoscopy, increasing the reliability of our results. Previous studies showed how the use of chromoendoscopy increases the accuracy in detecting IM, which is directly correlated with the presence of atrophy at histology [17-19], allowing correct IM identification in patients that would not be diagnosed without chromoendoscopy [19]. A recent meta-analysis reports a very good diagnostic accuracy for NBI in detecting gastric IM, with an AUC of 0.93 % [20]; BLI technology showed a good diagnostic performance too, with 84 % of agree-

ment in EGGIM scoring between NBI and BLI-bright [21] and a diagnostic accuracy of 94 % for ME-BLI [22].

Currently, the presence of atrophic gastritis restricted to the corpus with a spared antrum is the main histopathological hallmark of AAG [23-26] and it is still the main criterium for the definitive diagnosis of AAG [1,24]. The main serological markers of AAG, namely PCA, may contribute to support the diagnosis of AAG. Unfortunately, they cannot be used as an indisputable criterium for autoimmune etiology as they can be found in up to 20 % of *Hp*-non-atrophic gastritis [27] and, importantly, 20 % of AAG patients are seronegative, typically in the elderly population [1,24,28,29].

Our result showing that in CAG patients 25.6 % of atrophic or non-atrophic AG gastritis may be completely healed in a mean time of 3.5 years, suggests the possibility facing in clinical practice patients with current corpus-restricted atrophy, whose possible previous antral involvement cannot be confidentially excluded. This may lead to misdiagnosis of AAG and misclassification of patients, with implications for gastric cancer risk estimation and clinical management, since cancer risk is different in autoimmune and non-autoimmune atrophic gastritis [1,15,24,26,30].

We are aware of some limits of this study. First of all, this is a retrospective, single-center study that can be influenced by operator-dependent procedures, both in bioptic sampling and in histopathological evaluation, even if this is reduced to a minimum thanks to the adherence to standardized protocols for each procedure and the high expertise of involved researchers. Secondly, a FU gastroscopy is not available for all included cases, due to loss of patients at FU. Moreover, EC was not available for all gastroscopies due to the timing of availability and technical problems in some endoscopic investigations.

Anyway, in conclusion, this study shows that in a subgroup of CAG patients, AG may regress at long-term FU, thus mimicking AAG. Antral mucosal healing is also observed in patients without *Hp* eradication. These data show that during the natural history of CAG with concomitant AG, antral healing may occur irrespective of *Hp* cure, raising concerns about the current histopathological diagnostic criteria of AAG based on the presence of antrum-spared CAG.

Conflict of interest

All the authors reported above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript entitled “Antral mucosa healing at long-term follow-up in patients with corpus atrophic gastrits and concomitant antral gastritis may mimick autoimmune gastritis”.

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