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Demographic, hematologic, and endoscopic differences between predominant corporeal and antral atrophic gastritis

A STROBE-Compliant study

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Abstract

The study aimed to assess demographic, clinical, and endoscopic parameters in patients with predominant corporeal atrophic gastritis (CAG) and enterochromaffin-like cell hyperplasia suggestive for autoimmune etiology in comparison with patients presenting *Helicobacter pylori* atrophic gastritis limited to the gastric antrum (AAG).

Demographical, clinical, and pathological data of consecutive patients who underwent an upper digestive endoscopy for bleeding screening risk, symptoms, or anemia in a single endoscopy unit were retrieved. The final study group included 63 patients with CAG and enterochromaffin-like cell hyperplasia on histology and a control group of 142 patients with AAG.

Female patients were predominant in the group with CAG versus AAG (69.8% vs 46.4%, $P = .002$). Microcytic anemia ($P < .001$), but not macrocytic anemia ($P = .14$) was associated with CAG, the mean corpuscular volume of erythrocyte (MCV) (82.5 vs 86.5 fl, $P = .01$), the mean value of serum iron (11.8 vs 14.3 μmol/L, $P = .02$), and hemoglobin level (11.0 vs 12.7 g/dL $P < .01$) being significantly lower in patients with CAG versus AAG. Upper digestive endoscopies with no visible mucosal lesions ($P = .01$) were also more frequent in the patients with CAG, but there were not differences regarding digestive symptoms between groups. The linear regression models revealed that the low hemoglobin ($P < .001$) and low MCV ($P = .03$) are the independent variables that can predict CAG on histology, but not the serum iron level ($P = .77$)

Consecutive patients investigated on endoscopy with CAG in comparison with those having AAG are more frequent female, they have microcytic anemia, and no mucosal lesions on endoscopy. The decreased hemoglobin level and low MCV, rather than the serum iron level are predictors for CAG versus AAG on histology in endoscopic population.

Abbreviations: AAG = antrum atrophic gastritis, CAG = corporeal atrophic gastritis, CI = confidence interval, MCV = mean corpuscular volume of erythrocyte, NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, PPI = proton pump inhibitors, SPEM = spasmolytic polypeptide-expressing metaplasia.

Keywords: atrophic gastritis, intestinal metaplasia, iron deficiency anemia, macrocytic anemia

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OC and AN equally contributed to this work.

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The authors report no conflict of interest.

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1. Introduction

Chronic atrophic gastritis is a progressive inflammatory condition, which induces atrophic changes of gastric mucosa leading to the disappearance of normal antral and/or corpus glands.[1,2]

Despite the lack of the largely accepted definition or diagnosis of the condition,[2,3] there are 2 etiologies currently accepted: *Helicobacter pylori (H. pylori*) infection evolving for many years, usually multifocal, but affecting in the beginning mainly the antrum, and autoimmune etiology, usually limited to the gastric corpus and fundus, due to the autoantibody which targets the parietal gastric cells.[4]

H. pylori infection leading to environmental multifocal atrophic gastritis or type B gastritis involves predominantly the antrum with a combination of superficial plasmocytic inflammation and lymphoid aggregates, leading to early antral atrophy and metaplasia and late onset of corporeal lesions.[5]

On the contrary, autoimmune metaplastic atrophic gastritis or type A gastritis, characteristically presents body/fundus predominant injuries, showing combinations of different morphologic features: basal lymphocytes and profound lymphoid aggregates, restricted atrophy with intestinal and pseudo-pyloric metaplasia of oxyntic mucosa.[4] The onset of autoimmune gastritis is an aggressive immune mediated process developed against gastric parietal cells[2] that produces hydrochloric acid and intrinsic factor. The destruction of the native cells by inflammatory cells will develop in the deficiency of both.[3] The glandular cells are replaced by fibrosis and inflammation, or by a metaplastic epithelium. Different types of metaplasia may occur and they are subdivided mainly into 2 major phenotypes: intestinal metaplasia and pseudo-pyloric metaplasia.[4] Rarely, pancreatic metaplasia can occur. Enterochromaffin-like cell hyperplasia is also found and it is very characteristic for autoimmune gastritis due to the high level of gastrin that stimulates proliferation.[5,6] It only occurs in severe body/fundus atrophy, increased in parallel with the degree of the glandular destruction and it may not be present in the early stages of the disease. The hyperplasia can be simple, linear, and nodular, while in advanced stages, it can be dysplastic or even neoplastic as in the case of type I carcinoid tumors, associated with autoimmune metaplastic atrophic gastritis.[4,5] Enterochromaffin-like cells are involved in secreting molecules responsible for histamine processing and histamine secretion trying to increase acid secretion of adjacent parietal cells.[6]

Due to the lack of symptoms, atrophic gastritis of the corpus is usually found by chance, in patients who have undergone gastrointestinal check-up for anemia, who have unspecific symptoms or in patients with other confirmed autoimmune diseases who are investigated for the possibility of autoimmune gastritis.[7,8]

The present observational retrospective study aims to compare the most important demographical and laboratory parameters, symptoms, and endoscopic lesions in patients with predominant corporeal atrophic gastritis (CAG) and enterochromaffin-like cell hyperplasia on histology in comparison with patients presenting *H. pylori* associated antral atrophic gastritis (AAG).

2. Methods

Patients admitted to the Internal Medicine Clinic II from the Emergency County Hospital of Târgu Mureş during the last 6 years, from January 2014 until November 2019, and who had had an upper digestive endoscopy with a complete set of gastric biopsies, were screened for inclusion in the study. Gastroscopies were performed for symptoms, anemia, or to evaluate the risk of gastrointestinal bleeding.

Five biopsy specimens (1 from incisura, 2 from the antrum, and 2 from the corpus including the lesser and greater curvature), according to the Sydney protocol were examined in every patient. All specimens were sent in different containers and marked accordingly to identify the place of origin of the biopsies. All specimens were routinely processed, after fixation in 10% buffered formaline and for each biopsy 3 stainings were performed: Hematoxiline Eosine, Pas- alcian blue (for intestinal metaplasia), and Giemsa (for *H. pylori*). In selected cases, immunohistochemically examination for *H. pylori* infection was performed. Also, enterocromafin-like cell hyperplasia was evaluated with Chromogranin and Synaptophysin immunostanins.

Pseudo-pyloric metaplasia (mucous metaplasia) or spasmolytic polypeptide-expressing metaplasia (SPEM) was diagnosed when an antralization of the oxyntic mucosa was found.[4] The pseudo-pyloric metaplastic epithelium was revealed by immunostaining for pepsinogen I (which is only present in the oxyntic mucosa), while the absence of immunostained gastrin secreting cells (present only in the antrum) confirmed the body/fundus origin of the specimens. Intestinal metaplasia occurring in the oxyntic mucosa, represents the replacement of the normal gland with cells, which are normal in the bowel epithelium. Different types of intestinal metaplasia are classified based on the resemblance of the changed epithelium with the colon (type II and III, incomplete type) or small intestine (type I, complete type).

Patients with atrophic gastric changes described only at the level of the corpus, suggesting the autoimmune etiology of the gastritis were included in the study group (CAG, 63 cases). Patients with atrophic changes of the gastric glands limited at the level of the antrum, with no changes into the gastric corpus comprised the control group (AAG, 142 cases).

We collected data reviewing the medical records of each patient. Age, gender, symptoms, endoscopic aspects of the mucosa, histopathological characteristics, and biological parameters were collected and analyzed. We followed visible modifications described at upper digestive endoscopy: submucosal hemorrhages, erosions (mucosal defect of less than 5 mm), and ulcers (defects larger than 5 mm, extended into the deeper layer).

The presence of heartburn, abdominal pain, flatulence, nausea, and vomiting was recorded for each patient. The smoking and number of cigarettes daily were quantified referring to the habit in the month before investigations. We recorded the values of hemoglobin, mean corpuscular volume and serum iron level. Normal range of values were defined by the laboratory reference interval. Normal range for hemoglobin value was defined by gender, 12 to 17 g/dL for women and 13 to 17 g/dL for men. MCV was for both genders, 78 to 95 fl. For female gender, serum iron was considered normal if was between 9.0 and 30.4 μmol/L and for male gender between 11 and 28 μmol/L. Macrocytic anemia was defined as a low value of hemoglobin and a high value of MCV. Microcytic anemia was defined as a decreased value of both, hemoglobin and MCV.

Patients with any type of other neoplasia, active bleeding during endoscopy, lacking clinical or pathological data were excluded.

We registered the proton pump inhibitor (PPI) consumption before endoscopy as a gastroprotective drug (pantoprazole, esomeprazole, omeprazole) and non-steroidal anti-inflammatory drugs (NSAIDs) consumption (diclofenac, ibuprofen as the main gastrotoxic drugs, based on patient medical records.

Table 1

Demographical and clinical characteristics in the studied groups.

	Patients with CAG		Patients with AAG			
	N	%	N	%	*P* /OR	95% CI
Total cases	63	–	142	–	–/–	–
Female	44	69.84	66	46.48	**.002/2.667**	**1.419 – 5.013**
Male	19	30.16	76	53.52	–/–	–
Mean age	66.73	–	65.61	–	.28/–	–
Abdominal pain	18	28.57	47	33.10	.63/0.890	0.458 – 1.614
Heartburn	12	19.05	30	21.13	.77/0.898	0.434 – 1.860
Meteorism	6	9.52	20	14.08	.60/0.711	0.285 – 1.776
Nausea and vomiting	7	11.11	14	9.86	.59/1.419	0.580 – 3.466
Smoking*	10	15.87	21	14.79	.97/1.011	0.446 – 2.287
PPI consumption†	29	46.03	71	50.00	.76/0.914	0.511 – 1.635
NAIDs consumption‡	18	28.57	43	30.28	.94/0.979	0.519 – 1.847

AAG = antrum atrophic gastritis, CAG = corpus atrophic gastritis, CI = confidence interval: [lower limit, upper limit], NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, PPI = proton pomp inhibitor.

* > 5 cigarettes/day including quitters during the past 5 years.

† > 20 mg/day in the last 2 weeks.

‡ > 5 days with > 1 NAIDs/day in the past 2 weeks.

Values in bold indicate statistically significant results.

2.1. Statistical analysis

Nominal variables were presented using absolute (number of cases) and relative frequencies (percentage, %). Statistical analysis was performed using OpenEpi (version 7) and GraphPad and SPSS (Statistical Package for Social Science, version 23.0). Chi-square or Fisher's exact tests were performed for the analysis of associations between the 2 groups. The Student *t* test and analysis of variance (ANOVA) were performed for means and variance comparison between groups for the numerical/quantitative variables of the study. The linear regression model was used for predictors analysis for CAG. Statistical significance for all tests was accomplished when the estimated significance level *P* was lower than .05. The size effect for statistically significant associations was expressed as an odds ratio (OR) with a 95% confidence interval (CI) associated.

3. Results

Analyzing the distribution by gender in patients with CAG, a predominance of female gender 69.84% (44), with a sex ratio F:M = 2.3:1was evidenced, the association being statistically highly significant ($P = .002$, OR: 2.667, 95% CI: 1.419–5.013) (Table 1).

Abdominal pain, heartburn, bloating, nausea, and vomiting were present more frequently in patients with predominant AAG, but the differences were not statistically significant (Table 1).

PPIs and NSAIDs consumptions were similar in patients with different localizations of atrophic gastritis ($P = .76$, respectively, $P = .94$).

CAG was not statistically associated with erythematous appearance of mucosa ($P = .10$), erosive gastritis ($P = .26$), hemorrhagic gastritis ($P = .43$), or ulcers ($P = .31$). Even more, atrophic gastritis was statistically correlated with no visible lesions at the upper digestive endoscopy ($P = .01$, OR = 2.175, 95% CI: 1.175–4.027) (Table 2).

Microcytic anemia was significant more frequent in patients with predominant CAG ($P < .001$, OR = 3.667, 95% CI: 1.653–8.000), as well as the low level of serum iron ($P = .01$, OR = 2.208, 95% CI: 1.181–4.131). The average values of hemoglobin were 11.0 g/dL in the study group and 12.72 g/dL in the control

Table 2

Hematologic parameters, endoscopic findings and active *H. pylori* infection in the studied groups.

	Patients with CAG		Patients with AAG			
	N	%	N	%	*P* /OR	95% CI
Anemia*	42	66.67	48	33.80	**< .001/3.817**	**2. 088 – 7.346**
Microcytic anemia†	17	26.98	13	9.15	**< .001/3.667**	**1.653 – 8.000**
Macrocytic anemia‡	8	12.70	8	5.63	.14/2.436	0.8704 – 6.819
Low level of serum iron§	27	42.86	36	32.39	**.01/1.565**	**0.850 – 2.882**
Erythematous gastritis	22	34.92	67	47.18	.10/0.600	0.325 – 1.110
Erosive gastritis	10	15.87	34	23.94	.26/0.599	0.275 – 1.305
Hemorrhagic gastritis	1	1.59	7	43.66	.43/0.311	0.037 – 2.584
Ulcer	4	6.35	16	41.55	.31/0.533	0.171 – 1.667
No endoscopic lesions	29	46.03	40	28.17	**.01/2.175**	**1.175 – 4.027**
Active gastritis	8	12.70	75	52.82	**< .001/0.129**	**0.057 – 0.292**

AAG = antrum atrophic gastritis, CAG = corpus atrophic gastritis.

CI = confidence level: [lower limit, upper limit], OR = odds ratio.

* Hemoglobin < 12 – 17 g/dL for women and Hemoglobin < 13 – 17 g/dL for men.

† Anemia and mean corpuscular volume < 78 fl.

‡ Anemia and mean corpuscular volume > 95 fl.

§ Serum iron < 9.0 μmol/L for female and < 11 μmol/L for male.

Values in bold indicate statistically significant results.

Table 3

Comparison of the hematologic parameters means in patients with predominant corporeal atrophic gastritis (CAG) vs antral atrophic gastritis (AAG).

						95% Confidence interval of the difference	
	t - value	df	Mean difference	Std. error difference	*p*	Lower	Upper
Serum iron	−2.349	203	−2.447	1.042	**.020**	−4.502	−.393
Hemoglobin	−5.071	203	−1.6791	.3311	**.000**	−2.3320	−1.0263
MCV	−2.463	203	−4.0887	1.6599	**.015**	−7.3616	−.8158

df = degrees of freedom; MCV = mean corpuscular volume of erythrocyte, *t* – value = result of Student *t* test, indicating the difference between the 2 sample sets.
P = level of significance <.05, calculated with Student *t* test.

group, while the mean serum iron level was 11.88 μmol/L in the study group and 14.33 μmol/L in the patients with AAG. The average MCV was 82.50 fl in patients with CAG, lower than that in patients with AAG (86.55 fl). The Student *t* test showed significant differences between groups regarding the mean value of the haemoglobin ($P \leq .001$), serum iron level ($P = .020$), and MCV ($P = .015$) (Table 3).

Using ANOVA tables to compare the variance of means of hemoglobin, serum iron level, and MCV between the study and control groups, we found that only the hemoglobin level was statistically different ($P = .003$). We questioned, using linear regression models, the association of abnormal hematologic parameters with the localization of atrophic gastritis on histology study (Table 4). Low hemoglobin level and low MCV are the independent variables, which can predict CAG, and also both microcytic and a macrocytic anemia.

We further stratified the patients with CAG (63 patients) according to the presence of active and inactive gastritis into 2 groups (55 inactive and 8 active gastritis). No significant differences were noticed among studied variables, except for microcytic anemia that was absent in the patients with active gastritis. The linear regression model to investigate the role of the studied independent variables showed that only MCV and microcytic anemia have a significant influence on the presence of active or inactive gastritis in the biopsies of patients with CAG. The validity of the obtained regression model is accepted only for 78.5% of cases into the studied population. The nonparametric Mann–Whitney test for independent groups demonstrated that there are differences between the 2 groups, regarding serum iron level ($P = .015$), hemoglobin ($P = .009$), and MCV ($P = .02$).

4. Discussion

Although the prevalence of autoimmune gastritis is increasing in European countries, there is little information concerning its pathobiology, natural evolution, and frequency.[9,10] The diagnosis of this condition might be challenging and the clinical presentation of the patient may not suggest the disease.[11] Iron deficiency anemia and pernicious anemia are the main clinical presentation of the condition worldwide, while symptoms are unspecific. The immune-mediated destruction of gastric parietal cells leads to a low level of gastric acidity, and furthermore to a high gastrin secretion. Hypergastrinemia induces proliferation of neuroendocrine cells in oxyntic glands mucosa, leading to enterochromaffin-like cells hyperplasia and an increased risk for polyps, adenocarcinoma and neuroendocrine tumors.[10]

The majority of studies revealed that autoimmune gastritis affects women more frequently than men,[12] as our study does, probably correlated with the estrogen level, accepted as a potent stimulator of autoimmunity.[13]

Studies showed that about 20% to 30% of patients with iron deficiency anemia without clinical evidence of gastrointestinal blood loss have autoimmune gastritis.[14] Iron deficiency anemia appears due to impaired gastric acid secretion that interferes with

Table 4

Linear regression models for predominant corpus atrophy (CAG) in biopsy samples.

Model 1	**B**	**SE**	**Beta**	***t***	***P***
Serum iron	−.001	.005	−.022	−.286	.775
Hemoglobin	.066	.014	.332	4.586	.000
MCV	.006	.003	.149	2.165	.032
Constant	.371	.285		1.300	.195
Model 2	**B**	**SE**	**Beta**	***t***	***P***
Low level of serum iron*	−.065	.078	−.065	−.832	.406
Microcytic anemia†	−.284	.103	−.218	−2.756	.006
Macrocytic anemia‡	−.254	.118	−148	−2.159	.032
Constant	2.377	.178		13.383	.000

MCV = mean corpuscular volume, SE = standard error.
B, Beta, *t* = coefficients.
P = level of significance, <.05.
* Serum iron < 9.0 μmol/L for female and < 11 μmol/L for male.
† Anemia and mean corpuscular volume < 78 fl.
‡ Anemia and mean corpuscular volume > 95 fl.

iron absorption. A case–control study of patients undergoing investigations for iron deficiency anemia found CAG in 25.6% of cases with refractory iron deficiency anemia.[14,15] Our study identified significantly more frequent microcytic anemia in patients with CAG in comparison with patients having *H. pylori* related AAG. *H. pylori* can be a cause of unknown or refractory iron deficiency anemia, due to the interference with iron uptake or due to increasing iron loss from bleeding lesions.[16] Also, *H. pylori* eradication therapy seems to improves iron absorption and a combined therapy with iron administration showed up to be more affective.[17] The mean serum iron level in our study was lower in patients with predominant CAG, but using the regression model, decreased MCV and low level hemoglobin, better predict CAG on histology.

Iron deficiency may appear several years before the complete depletion of vitamin B12 deposits due to gastric parietal cell destruction by the immune process.[18] Pernicious anemia is the most important clinical manifestation of CAG.[19] In our study, macrocytic anemia was not statistically significantly more frequent in patients with CAG. In our endoscopic population, using regression models, both microcytic and macrocytic anemia seem to predict CAG. The presence of macrocytic anemia in the group of patients with AAG (5.63%) may be probably explained by chronic alcohol consumption influencing the nutrients' abortion.[20]

H. pylori has been claimed to be implicated in the induction of autoimmune gastritis,[18] but literature data are conflicting: some of the studies reported a high prevalence of seropositivity in patients with CAG, while others found a negative association with autoimmune gastritis,[19,21,22] the host immune response being accepted to be modulated genetically.[23] Current data support that some of the autoimmune gastritis may develop as a sequelae of chronic *H. pylori* infections, proved by the presence of antibodies against *H. pylori*, reflecting prior or current infection. Although biopsies do not reveal mucosa colonization in the majority of the cases, the lack of the germ is due to the atrophy of oxyntic mucosa and clearing of the bacteria.[5] In our study, *H pylori* active gastritis on histology and immunohistochemistry study was identified in only 12.7% of patients with CAG and neuroendocrine cell hyperplasia, being negatively associated with microcytic anemia or abnormal value of MCV.

Comparing our data with parameters reported in patients with CAG based on the value of hypergastrinemia and antiparietal antibodies,[24] microcytic anemia was discovered more frequently than in our study (51.87% vs 26.9%), while macrocytic anemia was detected in 11.2% of the cases, similar to our findings (12.7%). The mean value of hemoglobin was also similar (11.0 vs 11.3 g/dL).[24]

Patients with atrophic gastritis may be asymptomatic for many years, the condition being discovered when the patient is investigated for unexplained anemia or for nonspecific digestive symptoms.[21,22] No differences were noticed regarding dyspeptic symptoms in patients with *H. pylori* related AAG in comparison with patients with predominant CAG. The results emphasized that dyspeptic symptoms are not good predictors for endoscopic lesions or histologic changes in gastric mucosa as previous our work done.[25,26]

The endoscopic appearance of atrophic gastritis may have no specific appearance during the early stages and without histology the diagnosis is missed.[19,22] There were not significant differences in endoscopic mucosal lesions in our studied groups, the decreased acid secretion probably leading to less mucosal changes in patients with CAG.

Our work has several limitations, being an observational study performed in an endoscopic population, which may limit generalizations. The retrospective design made it difficult to have a detailed history of the patients, such as diet or previous eradication therapies for *H. pylori* infection.

The putative effect of PPI drugs on gastric mucosa deserves commentaries. Indeed, PPI administration in experimental settings modifies gastric mucosa: atrophy, parietal cells enlargement, enterochromaffin-like cells enlargement, reduction in gastric chief cells.[27,28] Moreover, they may produce ultrastructural[29] and functional changes[30] of the intestinal mucosa, with possible interaction with the absorption of iron. These changes were not comprised in the aim of our study.

The observations of our work emphasize the importance of a histological study of gastric mucosa in patients with macrocytic or microcytic anemia without specific symptoms or obvious bleeding endoscopic lesions, as in daily practice, the iron replacement therapy is usually offered, while the risk for progression toward gastric cancer is not assessed.

In conclusion, microcytic anemia and low iron level, but not macrocytic anemia are significantly more frequent in patients with predominant CAG and neuroendocrine cell hyperplasia than in those with *H. pylori* related AAG. Decreased hemoglobin and low MCV, rather than a low iron serum level, are predictors for CAG on histology in an endoscopic population. There are not significant differences in dyspeptic symptoms in patients with different localization of atrophic gastritis, but patients with CAG are less frequent endoscopic lesions than patients with *H. pylori* related AAG.

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