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Prevalence of Autoimmune-phenomena behind Chronic Gastritis of Unknown Origin, and their Role in the Poor Histological Outcome of the Stomach: A Single-centre, Retrospective Cross-sectional Study

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ABSTRACT

Background & Aims: The underlying aetiology of chronic gastritis (CG) often remains unknown due to its underrated significance in clinical practice. However, the role of chronic inflammation of the stomach in the development of atrophy, intestinal metaplasia (IM) and eventually of gastric cancer is well documented. We aimed to explore the possible aetiological factors of CG, determine the prevalence of systemic autoimmune disorders in patients with CG of unknown aetiology, and clarify the role of autoantibodies in the development of precancerous lesions in the stomach.

Methods: This is a retrospective, cross-sectional study, conducted from January 2016 to January 2020, including data from 175 patients with CG. Exclusion criteria were: (1) acute gastritis; (2) reactive gastropathy; (3) gastric cancer; (4) subjects without any serology testing results; and (5) *Helicobacter pylori* positivity. The primary endpoint was a composite endpoint involving gastric atrophy and IM.

Results: Fifty-five per cent of patients with CG had autoantibodies. Systemic lupus erythematosus (SLE)-related antibodies were positive in most of the cases, including antinuclear antibody (ANA) positivity, which was found in 19.13% of the patients. Autoimmune positivity was shown to be associated with precancerous lesions in the stomach ($p<0.001$): IM, atrophy and IM with atrophy. Anti-parietal cell antibody positivity seems to be a significant risk factor for IM and IM with atrophy. Autoimmune thyroiditis-related antibodies and ANA positivity by itself were only associated with atrophy; SLE-related antibodies and inflammatory bowel diseases related antibodies (ASCA and ANCA) correlated either with IM or with atrophy. No significant relationship was found between any other investigated autoimmune disease-related antibodies and precancerous lesions.

Conclusions: Autoimmune positivity often underlies gastritis of unknown aetiology and predisposes to precancerous lesions in the stomach. These antibodies can serve as non-invasive markers for the of optimal timing of an endoscopic follow-up strategy. Furthermore, CG can be an early symptom of a systemic autoimmune disorder.

Key words: chronic gastritis – autoimmunity – autoantibodies – intestinal metaplasia – gastric atrophy – gastric cancer.

Abbreviations: AIG: autoimmune gastritis; AIN: autoantibody negative test; AIP: autoantibody positivity test; ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: antibodies against the yeast *Saccharomyces cerevisiae* (ASCA); CI: confidence interval; *H. pylori*: *Helicobacter pylori*; IBD: inflammatory bowel disease; IM: intestinal metaplasia; SLE: systemic lupus erythematosus; SSA: anti-Sjögren's syndrome-related antigen A; SSB: anti-Sjögren's syndrome-related antigen B.

INTRODUCTION

Chronic gastritis is a long-lasting inflammatory condition of the gastric mucosa without specific treatment. Mucosal atrophy with intestinal metaplasia (IM) is the result of a long-lasting inflammation independent of the aetiology [1, 2]. The significance of chronic gastritis is underrated in clinical practice, even though its role in the pathogenesis of gastric cancer is well documented: carcinoma develops in the milieu of mucosal atrophy and IM [3-6], with an estimated annual cancer rate of 0.1% within five years after diagnosis [7].

It is proven by several studies and as suggested by the Maastricht V and Kyoto consensus, the measurement of serum pepsinogen level is the most reliable non-invasive marker

for screening of chronic atrophic gastritis [8]. Screening of serum pepsinogen level in the diagnosis of chronic atrophic gastritis may improve compliance of the population and the cost-effectiveness of screening of gastric tumours, thereby improving mortality [9].

The two most common causes of chronic gastritis are *Helicobacter pylori* (*H. pylori*) infection in one-third of the cases and autoimmune gastritis (AIG) in 7.8–19.5% of the cases [10]. *Helicobacter pylori* was supposed to be the most common cause of chronic atrophic gastritis based on its high prevalence and has been listed as a class I carcinogen in the past three decades [11, 12]. Although the prevalence of *H. pylori* has been declining [13, 14], gastric cancer is still the fifth most common cancer worldwide [15], implying the role of other aetiological factors. Due to the overwhelming attention given to *H. pylori* infection, the relevance of AIG and other possible causative factors has faded.

Although chronic gastritis is one of the most common findings with upper gastrointestinal endoscopy, the underlying aetiology often remains unknown [16]. If the results of *H. pylori* tests and antibodies related to AIG are negative, diagnostic measures for other autoinflammatory diseases are not carried out routinely. However, clarification of the underlying aetiology might be beneficial in the prevention of gastric neoplasm.

In this study, we aimed to explore the possible causes of chronic gastritis in south-western Hungary and to assess the possible relationship between these factors and IM and atrophy. We also aimed to determine the prevalence of systemic autoimmune disorder-related autoantibody positivity in chronic gastritis in our region and to investigate a possible relationship between these conditions in a retrospective study. Furthermore, we aimed to revise the current clinical practice in the diagnosis and management of chronic gastritis.

METHODS

This retrospective study was conducted from January 2016 to January 2020. All patients who were admitted to gastroscopy, and were diagnosed with chronic gastritis, and who underwent any serology testing were included in the analysis consecutively. A diagnosis of gastritis was established based on histologic findings from patients undergoing upper gastrointestinal endoscopy. Multiple biopsy samples (no less than five) were taken from pre-defined sites of the stomach according to the updated Sydney system [2]. Additional biopsy samples were obtained from any detected focal lesion. All included patients were managed by the same medical team (patients, with regular care from one, single examining endoscopic specialist were only considered for enrolment; one pathologist, who specialized in gastrointestinal pathology, reviewed all the histological findings) to avoid performance bias.

The exclusion criteria were: (1) acute gastritis; (2) reactive gastropathy; (3) gastric cancer; and (4) subjects without any serology testing results; (5) *H. pylori* positivity. Reactive gastropathy is also called reflux gastritis or type C gastritis and was identified based on the existence of certain histological criteria [17], determined by the pathologist. *Helicobacter pylori* infection status was assessed by histological assessment, serological tests and urea-breath test as well. Given that the connection between chronic atrophic gastritis and *H. pylori* infection has been shown, it can be considered as a confounding factor. Therefore, to examine the role of autoimmune markers in the development of precancerous lesions of the stomach, *H. pylori* positive patients were excluded from the study in order to minimize bias.

Patients were identified using an electronic database. The following data were collected: baseline characteristics of the analysed population (age, gender and their correlation to the outcome measures), histological findings (localisation of the inflammation; OLGA score; and the presence of atrophy, IM), gastroesophageal reflux disease, ulcer or cancer, autoantibody positivity, *H. pylori* infection status (histology, results of the urea breath test and/or serology), the presence and type of symptoms (key symptoms and presence of dyspepsia-like symptoms) and data regarding other risk factors [body mass index (BMI), alcohol consumption and smoking]. We split the identified patients into those with any autoantibody positivity (AIP) and those with negative autoimmune tests (AIN) for comparison.

Autoantibody positivity was considered using the threshold for the laboratory at our centre in line with the European standard laboratory criteria. Autoantibodies were separated into groups according to the autoimmune diseases of which they are characteristic. These findings are shown in Table I.

Table I. Grouping autoantibodies according to the specific autoimmune disorders in our study

Disease	Attributed antibodies
Celiac disease	Anti-gliadin, anti-endomysium, tissue transglutaminase antibody IgA and/or IgG
Sjögren's syndrome	Anti-Sjögren's syndrome-related antigen A (SSA), anti-Sjögren's syndrome-related antigen B (SSB)
Systemic lupus erythematosus (SLE)	Anti-nuclear antibodies (ANA), anti-nucleosome antibodies, anti-cardiolipin, anti-centromere, anti-C1q, anti-b2 glycoprotein, anti-double-stranded DNA (ds-DNA)
Autoimmune hepatitis	Anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal antibodies (LKM-1, LKM-2, LKM-3), anti-soluble liver antigens (SLA), liver–pancreas antigens (LP), anti-mitochondrial antibodies (AMA), anti-filamentous actin 1 antibodies (F1 actin)
Rheumatoid arthritis (RA)	Anti-cyclic citrullinated peptide antibodies (CCP), anti-rheumatoid factor (RF) antibodies
Systemic sclerosis (Ssc)	Anti-Scl-70 antibodies, anti-centromere antibodies
Polymyositis/ dermatomyositis	Anti-Jo-1 antibodies
Inflammatory bowel disease (IBD)	Anti-yeast *Saccharomyces cerevisiae* (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA)
Autoimmune thyroiditis	Anti-thyroid peroxidase (TPO), anti-TSH receptor antibodies (TRAb), anti-thyroglobulin antibodies (Tg)
Autoimmune gastritis	Anti-parietal cell antibodies, anti-intrinsic factor antibody

Patients' body weight and height were measured during the gastroenterological consultation. Following the international standards, patients were divided into two groups based on BMI: those with high BMI ≥ 25 kg/m^2 and those below [18].

The primary endpoint was a composite endpoint which included gastric atrophy and IM. Secondary endpoints were the prevalence of each antibody positivity and the stage of the atrophy based on the OLGA score. All parameters were assessed at the level of autoimmune disease groups and in autoantibody-positive and negative groups. Assessment of the individual level of each autoantibody was carried out if the sample size reached at least eight patients. Furthermore, we evaluated whether simultaneous positivity to 2 or more autoimmune diseases is related with an even higher risk of precancerous lesions.

The study was approved by the Director of the Clinical Centre and the Director of the First Department of Medicine at the University of Pécs (Institutional Review Board; case number: KK/999-1/2020). The data collection and analysis were carried out in compliance with the current laws and regulations and according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19]. All recruited cases received a numeric code to ensure privacy and personal data protection. No informed consent was required for the study, as the University of Pécs obtains automatically a general allowance for scientific purpose data usage from all patients. Therefore, we have not included data from patients who refused scientific purpose handling of their data at the time of admission.

Statistical Analysis

Data were analysed using SPSS 25.0 software. Mean, standard deviation, and minimum and maximum values were calculated for descriptive statistics. Univariate and multivariate analyses (adjusted for gender and age) were performed. Two-sided Pearson Chi-square was counted to compare dichotomous variables for patient frequencies. Odds ratios (OR) with 95% confidence interval (CI) were used for other analyses. In the case of significant differences, standardized residuals were also observed to arrive at the exact results. Multinominal logistic regression was performed when co-factors were also considered. In the case of continuous variables, an independent sample t-test was used. We observed the distribution on a Q-Q plot. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

A total of 285 patients with histologically proved chronic gastritis were assessed in the time period noted above. Three patients were excluded due to gastric cancer, 56 due to *H. pylori* positivity, 42 due to reactive gastropathy and 9 because of a lack of serology testing. 175 patients were included in the final analysis (52 men and 123 women). The mean age of the analysed population was 61.6 years (±15.13 years), ranging from 21 to 89, and most patients were female (70.29%). The age distribution as regards AIP and AIN can be seen in Fig. 1.

Significant differences were not seen in the baseline characteristics between the AIP and AIN groups. The mean

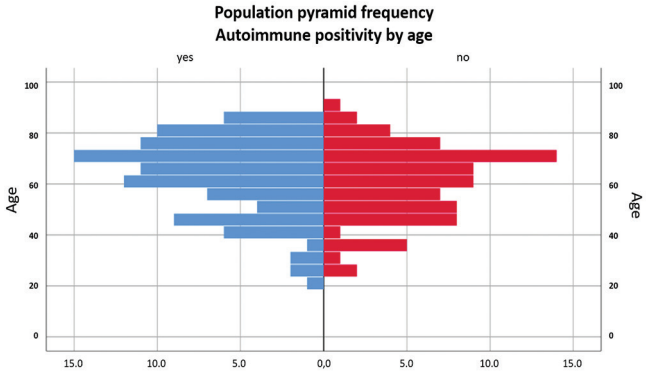

Fig. 1. Population distribution by age and AI positivity. Blue columns represent the age distribution of the autoimmune-positive patients, while red columns represent the autoimmune-negative patients.

BMI of the patients was 25.89 kg/m^2 (±5.42 kg/m^2). There was no significant relation between gender and autoimmune positivity (p=0.641). As regards risk factors, alcohol consumption was present in 39.20% of the cases (29/74), while 17.39% of the patients smoked (20/115). Eighty-one patients suffered from GERD.

In ten cases (out of 167 patients) anaemia was observed (5.99%), from which eight patients had AIP: three patients had AIP for AIG, one for celiac disease, one for inflammatory bowel disease (IBD), and three patients for systemic lupus erythematosus (SLE).

Out of 175 patients with chronic gastritis, 53 (30.29%) had atrophy with fibrosis, and 49 (28%) had atrophy with IM. A detailed description of the baseline characteristics of the patients is presented in Table II.

Prevalence of Autoantibody Positivity

Fifty-five per cent (97/175) of patients with chronic gastritis had AIP. The prevalence of AIG was 21.71% (38/175), of whom 35 (20%) had serum antibodies to parietal cell, and three patients (1.71%) had them to both parietal cell and intrinsic factor. Antibodies related to celiac disease were found in 8% (14/175) of the patients; anti-gliadin was observed in all 14 patients (100%), anti-endomysium in two patients (1.14%), and tissue transglutaminase antibody IgA and/or IgG in six patients (3.43%). Autoimmune thyroiditis was observed in 17.54% (20/114) of the patients examined. 11.90% of the subjects (15/126) had antibodies against the yeast *Saccharomyces cerevisiae* (ASCA).

As regards systemic AI disorder-related serology, the most common antibody was the antinuclear antibody (ANA), found in 19.13% of the patients (22/115). Antibodies were also found against nucleosome (8.7% of chronic gastritis patients), rheumatic factor (7.34% of the analysed population) and double-strand DNA (6.07% of the patients). Autoimmune hepatitis-related serology was positive in 9.52% (6/63) of the examined cases. In 3.48% of the analysed population (4/115), the anti-b2 glycoprotein titre was high. Three individuals out of 126 (2.38%) had elevated titres to antineutrophil cytoplasmic antibodies (ANCA), and three out of 111 (2.70%) showed high titres to anti-Sjögren's syndrome-related antigen A (SSA). Anti-cardiolipin, anti-centromere, anti-C1q and

Table II. Patients' baseline characteristics

Parameter	Overall (n=175)	AIP (n=97)	AIN (n=78)	p
Age (mean, SD)	61.66; 15.13	62.68; 15.03	60.40; 15.13	0.321
Female n, (%)	123 (70.29)	64 (65.98)	59 (75.64)	0.641
BMI (mean, SD)	25.89, 5.42	25.81, 5.44	25.81, 5.51	1.000
Alcohol consumption n, (%)*	29/74 (39.19)	16/41 (39.02)	13/33 (39.39)	0.946
Smoking n, (%)*	20/115 (17.39)	11/58 (18.97)	9/57 (15.79)	0.238
GERD n, (%)	81 (46.29)	40 (41.24)	41 (52.56)	0.888
Anaemia n, (%)*	10/167 (5.99)	8 (8.25)	2 (2.56)	0.188
Precancerous lesion				
Atrophy with intestinal metaplasia n (%)	49 (28.00)	33 (34.02)	16 (20.51)	<0.001
Atrophy with fibrosis without intestinal metaplasia n (%)	53 (30.29)	37 (38.14)	16 (20.51)	<0.001

AIP: autoimmune antibodies positive; AIN: autoimmune negative; BMI: body mass index; SD: standard deviation; GERD: gastroesophageal reflux disease; *indicates missing data. The total number of patients with information on smoking status is 115, of whom 20 are smokers; in the case of alcohol consumption, the total number is 74, of whom 29 are regular alcohol consumers (on a daily basis).

anti-Sjögren's syndrome-related antigen B (SSB) and myositis-specific antibodies were also observed in a low number of cases (<1%) (Table III). There was no significant difference between females and males in the prevalence of each antibody positivity (p>0.05).

Poor Histological Outcomes and Autoimmune Antibodies Positivity

As regards precancerous lesions, the AIP group was associated with a significantly higher rate of atrophy alone (37 vs 16 patients, p<0.001). Atrophy with IM was found in 33 (34.02%) and 16 (20.51%) subjects in the AIP and AIN groups, respectively (p<0.001) (Table II).

Univariate Analyses

With regard to the univariate analyses of the relationship between histological outcomes and autoimmune positivity, it was found that there is a significant correlation between autoimmune positivity and precancerous lesions. Among patients with AIP, atrophy (p=0.015) was presented more frequently. The co-occurrence of atrophy and IM was also associated with AIP (p=0.039).

A link was found between AIG-related antibody positivity, especially anti-parietal cell antibody positivity and atrophy with IM (p=0.033). No significant link was found between any other autoimmune disease-related antibodies and precancerous lesions.

No difference was found regarding the worse OLGA score (OLGA 3–4) and autoimmune positivity. Comparisons on the level of individual autoimmune bodies were not carried out due to the low number of cases.

Bivariate Analyses

Bivariate analyses adjusted for age found significant differences in the following relations: AIG-related antibodies with atrophy (OR=2.250; 95%CI: 1.945-5.357; p<0.001) and atrophy with IM (OR=2.229; 95%CI: 1.019-4.877; p<0.001); SLE-related antibodies and atrophy (OR=2.288; 95%CI: 1.523-3.176; p=0.002) and atrophy with IM (OR=2.340; 95%CI 1.375-5.841; p=0.006); IBD-related antibody (ASCA and ANCA) positivity with atrophy with IM (OR=2.760; 95%CI: 1.218 to 2.645; p=0.017) and atrophy without IM (OR=5.308; 95%CI: 1.480-19.036; p=0.001); anti-parietal cell antibody with atrophy with IM (OR=2.229; 95%CI: 1.019-4.877, p=0.006).

As regards the results of bivariate analyses adjusted for gender, AIG-related antibodies correlated with atrophy (OR=2.732; 95%CI: 1.350-2.349; p<0.001) and atrophy with IM (OR=2.222; 95%CI: 1.040-4.749; p<0.001). SLE-related antibody positivity was associated with atrophy (OR=2.766; 95%CI: 1.755-4.132; p<0.001) and atrophy with IM (OR=4.294; 95%CI: 1.313-14.043; p=0.001). Significant links were found between atrophy without IM and ASCA and ANCA positivity (OR=2.352; 95%CI: 1.032-6.645; p=0.007), ANA positivity (OR=2.044; 95%CI: 1.097-5.242; p=0.029) and autoimmune thyroiditis-related antibody positivity (OR=2.566; 95%CI: 1.574-4.274; p=0.048). Anti-parietal cell antibodies also correlated with worse histological outcome (OR=2.222; 95%CI: 1.040-4.749; p=0.038).

Sjögren's syndrome, autoimmune hepatitis, rheumatoid arthritis, systemic sclerosis and polymyositis/dermatomyositis-related antibody positivity did not show a statistically significant correlation with precancerous lesions. Detailed results of univariate and multivariate analyses are presented in Table IV.

The analysis regarding simultaneous AIP showed a higher risk for precancerous lesions in some cases: SLE related antibodies (OR=4.778; 95%CI: 1.945-2.089; p=0.058); AIG related antibodies (OR=3.182; 95%CI: 1.708-8.142).

DISCUSSION

This retrospective cross-sectional study with data from 175 patients was conducted to explore possible causes behind chronic gastritis of unknown origin and to understand the possible relationship between systemic autoimmune disorders and poor histological outcomes of chronic gastritis. Furthermore, we aimed to revise the current clinical practice in the diagnosis and management of chronic gastritis.

Table III. Prevalence of autoantibody positivity in patients with chronic gastritis

Autoimmune disease (attributed antibodies)	Positive (n)	Total number of patients tested	%
AI gastritis (AIG)	38	175	21.71
Anti-parietal cell antibodies	35	175	20.00
Anti-intrinsic factor antibodies	3	175	1.71
Celiac disease	14	175	8.00
Anti-gliadin	14	175	8.00
Anti-endomysium	2	175	1.14
Tissue transglutaminase antibodies IgA	3	175	1.71
Tissue transglutaminase antibodies IgG	3	175	1.71
Sjögren's syndrome	3	111	2.70
Anti-Sjögren's syndrome-related antigen A (SSA)	3	111	2.70
Anti-Sjögren's syndrome-related antigen B (SSB)	0	111	0.00
Systemic lupus erythematosus (SLE)	31	115	26.96
Anti-nuclear antibodies (ANA)	22	115	19.13
Anti-nucleosome antibodies	10	115	8.70
Anti-cardiolipin	2	115	1.74
Anti-centromere	1	115	0.87
Anti-C1q	1	115	0.87
Anti-b2 glycoprotein	4	115	3.48
Anti-double-stranded DNA (ds-DNA)	7	115	6.07
Autoimmune hepatitis	6	63	9.52
Anti-smooth muscle antibodies (SMA)	1	63	1.59
Anti-liver/kidney microsomal antibodies (LKM-1, LKM-2, LKM-3)	0	63	0.00
Anti-soluble liver antigens (SLA)	0	63	0.00
Liver–pancreas antigens (LP)	0	63	0.00
Anti-mitochondrial antibodies (AMA)	3	63	4.76
Anti-filamentous actin 1 antibodies (F1 actin)	2	63	3.17
Rheumatoid arthritis	8	109	7.34
Anti-cyclic citrullinated peptide antibodies (CCP)	0	109	0.00
Anti-rheumatoid factor (RF) antibodies	8	109	7.34
Systemic sclerosis (Ssc)	1	96	1.04
Anti-Scl-70 antibodies	0	96	0.00
Anti-centromere antibodies	1	96	1.04
Polymyositis/dermatomyositis	0	99	0.00
Anti-Jo-1 antibody	0	99	0.00
Inflammatory bowel disease (IBD)	18	126	14.29
Anti-yeast *Saccharomyces cerevisiae* (ASCA)	15	126	11.9
Anti-neutrophil cytoplasmic antibodies (ANCA)	3	126	2.38
AI thyroiditis	20	114	17.54
Anti-thyroid peroxidase (TPO)	13	114	11.40
Anti-TSH receptor antibodies (TRAb)	2	114	1.75
Anti-thyroglobulin antibodies (Tg)	5	114	4.39

Patients were summarized in each autoimmune disorder group taking multiple autoantibody positivity into consideration to avoid duplication.

One of our major findings was that more than half of the patients with chronic gastritis had positive immunoserology. In line with previous results from other countries, in Hungary, the prevalence of AIG was about 20%, and anti-parietal cell antibodies are more common than anti-intrinsic factor antibodies [10]. The most frequently occurring antibodies in our patients with chronic gastritis besides AIG were SLE-related antibodies in one-quarter of

Table IV. Uni- and bivariate analyses

	Univariate analysis (p)	Bivariate analysis – age (p)	Odds ratio [95% CI]	Bivariate analysis – gender (p-value)	Odds ratio [95% CI]
			Atrophy with intestinal metaplasia		
Autoimmune gastritis	0.033	<0.001	2.229 [1,019-4,877]	<0.001	2.222 [1.040; 4.749]
Celiac disease	0.353	0.345	0.469 [0.98-2.240]	0.213	0.374 [0.080; 1.757]
Sjögren's syndrome	1.000	0.358	1.178 [0.101-13.729]	0.969	0.953 [0.083; 10.946]
Systemic lupus eritematous	0.433	0.006	2.340 [1.375-5.841]	0.001	4.294 [1.313; 14.043]
Autoimmune hepatitis	1.000	0.856	0.843 [0.134-5.316]	0.886	1.143 [0.186; 7.032]
Rheumatoid arthritis	1.000	0.124	1.175 [0.260;5.311]	0.909	1.092 [0.244; 4.889]
Systemic sclerosis	0.374	0.570	1.039 [1.006; 1.074]	0.241	0.594 [0.248; 1.420]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
Inflammatory bowel diseases	0.313	0.017	2.760 [1.218; 2.645]	0.083	1.134 [0.214; 2.324]
Autoimmune thyroiditis	0.935	0.814	0.882 [0.308; 2.522]	0.099	1.155 [0.408; 3.268]
Anti-parietal cell antibodies	0.033	0.006	2.229 [1.019; 4.877]	0.038	2.222 [1.040; 4.749]
Anti-gliadin antibodies	0.111	0.212	0.212 [0.260; 1.700]	0.200	0.185 [0.023; 1.475]
Antinuclear antibodies	0.333	0.413	1.221 [0.449; 3.323]	0.155	1.637 [0.626; 4.280]
Anti-dsDNA antibodies	0.683	0.486	1.218 [0.251; 5.914]	0.311	1.857 [0.382; 9.020]
Anti-nucleosome antibodies	0.728	0.484	1.152 [0.292; 4.541]	0.303	1.637 [0.626; 4.280]
Anti-rheumatoid factor	1.000	0.914	1.175 [0.260; 5.311]	0.966	1.092 [0.244; 4.889]
			Atrophy without intestinal metaplasia		
Autoimmune gastritis	0.374	<0.001	2.250 [1.945; 5.357]	<0.001	2.732 [1.350; 2.349]
Celiac disease	0.228	0.394	0.416 [0.087; 1.991]	0.848	0.343 [0.073; 1.600]
Sjögren's syndrome	0.551	n/a	n/a	n/a	n/a
Systemic lupus eritematous	0.168	0.002	2.288 [1.523; 3.176]	<0.001	2.766 [1.755; 4.132]
Autoimmune hepatitis	0.638	0.331	1.354 [0.172; 10.684]	0.160	1.509 [.227; 10.015]
Rheumatoid arthritis	1.000	0.096	1.137 [0.241; 5.638]	0.123	1.040 [0.234; 4.619]
Systemic sclerosis	0.378	0.559	1.068 [1.020; 1.097]	0.405	1.058 [1.020; 1.97]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
Inflammatory bowel diseases	0.099	0.001	5.308 [1.480; 19.036]	0.007	2.352 [1.032; 6.645]
Autoimmune thyroiditis	0.322	0.085	1.359 [0.473;3.909]	0.048	2.566 [1.574; 4.274]
Anti-parietal cell antibodies	0.374	0.174	1.350 [0.616; 2.958]	0.104	1.446 [0.675; 3.093]
Anti-gliadin antibodies	0.065	0.216	0.186 [0.023; 1.497]	0.182	0.168 [0.021; 1.328]
Antinuclear antibodies	0.126	0.110	1.522 [0.561; 4.128]	0.029	2.044 [1.097; 5.242]
Anti-dsDNA antibodies	1.000	0.924	0.531 [0.094; 2.987]	0.650	0.629 [0.114; 3.465]
Anti-nucleosome antibodies	0.317	0.215	1.646 [0.424; 6.386]	0.079	1.892 [0.510; 7.018]
Anti-rheumatoid factor	1.000	0.353	1.137 [0.241; 5.368]	0.257	1.040 [0.234; 4.619]

n/a: not assessed.

the cases, followed by autoimmune thyroiditis, IBD, celiac disease and rheumatoid arthritis-related antibody positivity. Autoimmune positivity was shown to be associated with precancerous lesions in the stomach: atrophy, and atrophy with IM. AIG-related antibodies, especially anti-parietal cell antibody positivity, seem to be a significant risk factor for worse histological outcome. Autoimmune thyroiditis-related antibodies and ANA positivity by itself were associated with atrophy; SLE-related antibodies and IBD-related antibodies (ASCA and ANCA) correlated with atrophy and with atrophy with IM. Any other autoantibodies examined did not show any effect on the histological outcomes of chronic gastritis. No difference was found with regard to a worse OLGA score and autoimmune positivity.

Although these relationships were not examined in this context, gastrointestinal manifestations can occur in various autoimmune disorders. Frequent occurrence of gastritis has been described in patients with IBD and celiac disease [20-22]. Rheumatoid arthritis can affect both the gastrointestinal tract and the liver [23]; chronic superficial and chronic atrophic gastritis can be seen in 30 and 62.5% in patients with rheumatoid arthritis, respectively [24]. Systemic lupus erythematous may involve the gastrointestinal tract as well; however, according to the literature, manifest gastritis is rare in patients with SLE [25]. Lecouffe-Desprets et al. [26] reported that SLE, rheumatoid arthritis, systemic sclerosis, inflammatory myopathies, Sjögren's syndrome and scleromyositis or other overlapping connective tissue diseases (5% each) are related to eosinophilic gastrointestinal disorders [26].

Regarding the relationship between histological outcomes and autoimmunity, a recent meta-analysis has shown that a wide range of autoimmune diseases was associated with an increased risk of gastric cancer. It concluded that dermatomyositis, pernicious anaemia, Addison's disease, dermatitis herpetiformis, IgG4-related disease, primary biliary cirrhosis, diabetes mellitus type 1, systemic lupus erythematosus and Graves' disease were associated with a significantly increased gastric cancer risk [27].

Chronic inflammation precedes the development of many types of cancer in time. Immune dysregulations, which play a pivotal role in autoimmunity, are thought to be important in malignancies as well. Moreover, autoimmune disorders have been observed in patients with neoplastic tumors [28]. Inversely, increased incidence of neoplasms has been described among patients with autoimmune diseases [29]. Rheumatoid arthritis, SLE, Sjögren's syndrome, celiac disease, idiopathic inflammatory myositis and systemic sclerosis were associated with various neoplasms, including gastrointestinal tumors [30-34].

Although these studies examined the relationship between autoimmune disorders and gastric cancer, it is well-known that chronic inflammation predisposes to atrophy and IM, which are the precancerous lesions in the stomach. Therefore, it can be assumed that, if an antibody is associated to the development of IM and/or atrophy, it is also indirectly related to gastric cancer. If some autoimmune disorders predispose to the development of gastric cancer, close monitoring may be recommended in those cases. Routine measurement of these immuno-serological markers may be useful in the evaluation of the etiology and follow-up of patients with chronic gastritis.

Given that our study population did not suffer from diagnosed manifest autoimmune disorders, it also raises the possibility that gastritis may predict the development of a later autoimmune disease. Thus, if there is no clear explanation for the etiology of chronic gastritis or if the symptoms persist after eradication of *H. pylori*, it is advisable to assess these patients for systemic autoimmune-related antibodies and, if positive, to involve an immunologist for a close follow-up.

To our knowledge, this is the first study to present epidemiological data on the prevalence of different autoantibody positivity in patients with chronic gastritis in south-western Hungary and to raise the possibility that it may be worthwhile to investigate the etiology of chronic gastritis further when *H. pylori* is negative or after successful *H. pylori* eradication therapy. The study was conducted following a rigorous, pre-defined methodology.

However, our research had several limitations, so our results should be interpreted with caution. First, these results are based on a single-center retrospective medical database analysis; therefore, the role of the confounder factors cannot be excluded (e.g. smoking, dietary habits, immunosuppressant/modulatory treatment). To minimize the role of confounders, we excluded patients with *H. pylori* positivity from the analysis. Moreover, chronic atrophic gastritis is a common age-related finding, and female gender is more often prone to autoimmunity. To address this problem, we performed multivariate analyses adjusted for age and gender. Due to the observational nature of our study, causality cannot be determined; therefore, we report only possible associations. Second, the number of enrolled patients is relatively low (or the event rate was rather low for some antibodies), which could be the reason for the insignificance in some cases. Since we examined the presence of autoimmune markers, the possibility of incidental positivity may also arise. Therefore, to confirm our results, we also evaluated simultaneous effects of two or more AIP for the outcome.

Our results raise interesting questions, and due to the limited information on this topic and the limitations of our research, it could serve as a subject for future studies. Prospective studies with long-term follow up and larger event rate are required for confirmation and could revise the current clinical practice in the diagnosis and management of chronic gastritis and offer a more thorough insight into this topic. Autoimmune antibodies can serve as non-invasive markers for the optimal timing of an endoscopic follow-up strategy. Furthermore, chronic gastritis can be the first sign of an incipient autoimmune disorder, and with proper diagnostic approaches, autoimmunity may be recognisable in the early stages of the disease. Therefore, these patients may also be worth following immunologically for the later development of a manifest autoimmune disorder.

CONCLUSION

Autoimmune positivity often underlies gastritis of unknown etiology and predisposes to precancerous lesions in the stomach. Thus, if a clear etiological factor cannot be identified in the cause of chronic gastritis, it may be worthwhile to look for autoimmunity in these patients. In the south-western Hungarian population, anti-parietal cell antibody, ANA, ANCA and ASCA positivity correlated with a worse histological outcome, such as atrophy with or without IM. Further prospective observational studies on this topic are required to confirm our findings.

Conflicts of intersest: None to declare.

Authors' contribution: N.Z. and J.C. designed the study. N.Z., N.V. and L.F. extracted the data. S.V., S.L. and D. validated the extracted data. D.N. did the statistical analysis. S.V., L.F and N.Z. prepared the tables. N.Z. and L.S. wrote the first draft of the manuscript. P.H., Z.S. and J.C. supervised the manuscript and approved the submitted draft. J.C. is the guarantor of this paper and managed the patients. All the authors critically revised and approved the final version of the manuscript.

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