ORIGINAL ARTICLE

Antibodies involved in the development of pernicious anemia and other autoimmune diseases

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KEY WORDS

antibodies, autoimmunity, intrinsic factor, parietal cell, pernicious anemia

ABSTRACT

INTRODUCTION Pernicious anemia (PA) is an autoimmune hematopoietic disease.

OBJECTIVES The aim of the study was to determine autoantibodies involved in the pathogenesis of PA and the development of other autoimmune disorders such as connective tissue diseases and celiac disease. We also aimed to assess the potential usefulness of the specific diagnostic and screening tests in patients with PA.

PATIENTS AND METHODS The study group comprised 124 women and men with newly diagnosed PA and 41 healthy controls. Intrinsic factor (IF) antibodies, gastric parietal cell (GPC) antibodies, endomysium antibodies (EmAs), and antinuclear antibodies (ANAs) were determined in blood samples.

RESULTS IF or GPC antibodies were present in 61.3% of patients, GPC antibodies, in 46%, IF antibodies, in 30.6%, IF and GPC antibodies, in 15.3%. There was no difference in the occurrence of ANAs and EmAs between the PA and control groups. However, ANAs were found in 16.1% of patients with PA and in 4.9% of controls. The occurrence of EmAs in both groups was similar (3.2% vs 2.4%); however, it has been shown that patients with IF or GPC antibodies are more prone to be EmA positive ($P = 0.009$).

CONCLUSIONS Simultaneous determination of IF and GPC antibodies increases the chances of confirming the diagnosis of PA. Also, screening for connective tissue diseases and celiac disease may be considered in patients with PA, due to the presence of ANAs and EmAs in that population.

INTRODUCTION Pernicious anemia (PA; also known as Biermer disease, Addisonian anemia) is an autoimmune disease, the pathogenesis of which involves intrinsic factor (IF) antibodies and gastric parietal cell (GPC) antibodies.[1-16] While IF antibodies interfere with the absorption of intrinsic factor–vitamin B_{12} complex in the terminal ileum, GPC antibodies are directed against gastric enzyme H^+/K^+-ATPase (the proton pump).[5,9,17] In patients with diagnosed autoimmune disease, other disorders of the kind may develop over time or simultaneously, most likely as a result of general immune disturbances as well as cross-reactions between antibodies.[1,14,16,18-26] The aforementioned pathophysiological mechanism would justify expanding the diagnostic workup in order to detect the possible dysfunction of other organs. This seems to be of importance considering that treatment of the primary disease may interfere with the diagnosis of the subsequent disorder. In this context, the coexistence of immune abnormalities of the hematopoietic system and other autoimmune disorders could justify implementation of a wider diagnostic panel at the onset of the initial symptoms of the above-mentioned diseases.[1]

The aim of the study was to determine the occurrence of IF and GPC antibodies in patients diagnosed with PA, as well as the co-occurrence of IF and GPC antibodies with antibodies involved in pathological mechanism of some other (nonhematological) autoimmune diseases. There is a concept of an autoimmune alert, that is, predisposition of various autoimmune diseases to coexist in spite of their different pathological mechanisms

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Received: October 27, 2019.
Revision accepted: December 5, 2019.
Published online: December 9, 2019.
Pol Arch Intern Med. 2020; 130 (1): 31-37
doi:10.20452/pamw.15094

WHAT'S NEW?

Pernicious anemia (PA) is an autoimmune disease in the pathogenesis of which intrinsic factor (IF) antibodies and gastric parietal cell (GPC) antibodies are involved. In this study, the occurrence of IF and GPC antibodies in patients with newly diagnosed PA, as well as their co-occurrence with antibodies involved in the pathomechanism of some other (nonhematological) autoimmune diseases has been evaluated. An interesting concept of autoimmune alert have been introduced, that is, predisposition of various autoimmune diseases to coexist, despite their different pathomechanisms and various tissues and organs being affected. The study has shown that simultaneous determination of IF and GPC antibodies in blood increases the possibility of the PA diagnosis. Also, screening assessment for connective tissue diseases and celiac disease may be considered in patients with PA, as it was found that autoantibodies against nuclear components are present in 16.1% of patients with PA. Moreover, presence of IF or GPC antibodies increases the risk of the occurrence of antiendomysial antibodies.

and various tissues, organs, and systems being affected. The assessed antibodies include those participating in the pathogenesis of PA as well as the development of other autoimmune disorders—connective tissue diseases (CTDs) and celiac disease (CD). We have also aimed to document the potential usefulness of the specific diagnostic and screening tests in patients with PA.

Characteristics of the assessed antibodies Intrinsic factor antibodies are specific for PA (98.6%–100%),[9,14] and their sensitivity of 37% to 70%[9,14,18,27-30] increasing up to 80% over the course of the disease[27] was reported. However, these antibodies are not present in all patients with PA.[12] Antibodies targeting IF are immunoglobulin G (IgG) isotype.[14,27] On the other hand, the diagnostic sensitivity of GPC antibodies for PA is very high (80%–97%), although their specificity (50%–90.3%) is limited due to the number of other diseases in which these antibodies are present. Gastric parietal cell antibodies are detected in almost every case of PA but often also in the course of gastritis without anemia as well as in various autoimmune disorders.[1,4,5,9,10,14-18,20,24,27-31] These antibodies can appear even years before the onset of the clinical symptoms of PA[9,12,22] and subsequently decline over time,[12,22,28] possibly due to the loss of their target, that is, the GPCs, along with the progression of autoimmune gastritis,[1,4,5,9,10,14-16,22,24,27-29,31] which could explain why some of the patients with PA are GPC-antibody negative. Also, their prevalence in the general population rises with age.[32,33] Most sources indicate that GPC antibodies do not occur in healthy people,[4,5,9,10,14-16,24,27-29,31] although some studies report that GPC antibodies are present in 2.5% to 9% of the healthy population.[34]

Antinuclear antibodies (ANAs) play a role in the development and pathophysiology of CTDs, and their clinical utility is well established. For instance, they are relevant in the diagnostic workup of systemic lupus erythematosus, Sjögren syndrome, scleroderma, dermatomyositis, rheumatoid arthritis, CREST syndrome, or mixed CTD.

Among several antibodies known to participate in the development of CD, the role of antiendomysium antibodies (EmAs) is of particular interest. In children with suspicion of CD, the presence of certain autoantibodies plays a role in the diagnostic workup. First of all, the presence of tissue transglutaminase antibodies (tTGAs) is assessed. In some cases, sufficiently high concentrations of tTGAs associated with the presence of EmAs allow to avoid biopsy. Assessing antibodies to deamidated gliadin peptides might also be of use.[35] Diagnostic criteria for adults include several more possible antibodies.[36,37] However, also in this case, serological testing for CD relies on tTGAs as the first step. Endomysium antibodies may be used as a confirmatory test, particularly in low tTGA titers. Transglutaminase antibodies are the most sensitive for CD, whereas EmAs are the most specific.[36,37] The above-mentioned antibodies are regularly detected in the serum of patients with CD,[38] and EmAs are often detected even in the inactive stage of the autoimmune process and indicate a predisposition to the disease.

PATIENTS AND METHODS The study was approved by the bioethical committee of the Medical University of Silesia (no. KNW/0022/KB1/84/10). All patients gave informed consent to participate in the study. The study group (PA) included 124 people with a newly diagnosed autoimmune disease of the hematopoietic system, that is, PA. The group comprised 85 women and 39 men. The group was divided by age into the following categories: 30 to 39 years (6.5%), 40 to 49 years (12.1%), 50 to 59 years (20.2%), and 60 years or older (61.3%). The inclusion criteria were age over 18 years; the diagnosis of PA based on a typical clinical picture, as well as fulfillment of at least 2 of the following 3 diagnostic criteria: 1) reduced serum B_{12} levels (below 200 pg/ml); 2) positive results for one or both IF and GPC antibodies antibodies; 3) a positive therapeutic test. The following responses in laboratory parameters to a single parenteral administration of 1000 μg of vitamin B_{12}: an increase in the reticulocytes count after 5 to 10 days (reticulocytic break), 50% reduction of blood iron or lactate dehydrogenase concentrations as compared with baseline, remission of thrombocytopenia or / and neutropenia within 2 weeks, regression of anemia and hypersegmentation of granulocyte nuclei after 2 to 4 weeks. Exclusion criteria were: malignancy; renal failure (eGFR <30 ml/min/1.73 m^2); liver failure (bilirubin >34.2 μmol/l); symptomatic heart failure; symptomatic respiratory failure; severe neurological diseases and mental disorders. There were no participants with eGFR concentrations lower than 45 ml/min/1.73 m^2. The control group included 41 people, 30 women and 11 men, matched for age. The control group was created in order to compare the prevalence of ANAs and EmAs with the PA group. Criteria for inclusion

were age over 18 years; exclusion of an autoimmune disease based on the interview and available test results; negative titers of IF and GPC antibodies; no clinical signs of organ dysfunction; no abnormalities in blood count or blood smear; no aberrations in basic laboratory parameters (listed below), including serum vitamin B_{12} concentration; exclusion of long-term pharmacotherapy; no history of autoimmune diseases in the family. In both groups (PA and control), blood samples of up to 20 ml for testing were collected in the morning in a fasting state from the antecubital vein. Serum and plasma were stored at –75°C until antibody determination.

Antibodies against IF (IgG) were determined by enzyme-linked immunosorbent assay (ELISA) and quantified. A test result of less than 20 RU/ml was considered negative and of 20 RU/ml or higher, positive. An ELISA kit from EUROIMMUN Medizinische Labordiagnostika AG (Lübeck, Germany) was used. The upper cutoff limit recommended by the kit manufacturer was 20 RU/ml. Since there is no international reference serum or plasma for the assessment of IF antibodies, the calibration is performed in RU/ml. The manufacturer evaluated the level of IF antibodies in 351 healthy blood donors using an EUROIMMUN ELISA test and showed that all blood donors were negative at a cutoff point of 20 RU/ml (reference group). The linearity of the applied test was within the measurement range of 0.2 to 200 RU/ml. The lower detection limit of the test used is 1 RU/ml (analytical sensitivity). This limit was defined as 3 times the standard deviation of the blind test and was the lowest value of the determined IF antibodies titer. The test kit does not show cross-reactions (analytical specificity) and also does not interfere with hemolytic, lipemic, and hyperbilirubinemia sera (up to 10 mg/ml hemoglobin, 20 mg/ml triglycerides, 0.4 mg/ml bilirubin). The coefficient of variations (CV) for intra- and inter-assay–variation measurements in various ranges, evaluated in order to control the repeatability, in the standard curve are 4% to 5.1% and 3.7% to 7.8%, respectively.

The levels of GPC antibodies (IgG) were determined by an ELISA kit (EUROIMMUN). The test results were interpreted either as positive or negative. The results were evaluated semiquantitatively by calculating the ratio of the extinction value of the control or the patient sample to the extinction value of the appropriate calibrator. The upper cutoff limit recommended by the kit manufacturer is 20 RU/ml. Since there is no international reference serum or plasma for the assessment of GPC antibodies, the calibration is carried out in RU/ml. The EUROIMMUN recommends the following interpretation of the test results: ratio of less than 1.0, negative; ratio of 1.0 or higher, positive result; in the quantitative assessment, less than 20 RU/ml, negative result; 20 RU/ml or higher, positive result. The manufacturer evaluated the level of GPC antibodies (IgG) in 200 healthy blood donors using the EUROIMMUN ELISA test and showed that at a cutoff point of 20 RU/ml, 4.5% of blood donors were GPC antibody–positive (reference group). The linearity of the applied test was within the measurement range of 2 to 200 RU/ml. The lower detection limit of the test used is 1 RU/ml. This limit of detection was defined as 3 times the standard deviation of the blind test and was the lowest value of the GPC-antibody titer determined. The test kit does not show cross-reactions and does not interfere with hemolytic, lipemic, and hyperbilirubinemia sera (up to 10 mg/ml hemoglobin, 20 mg/ml triglycerides, 0.4 mg/ml bilirubin). The CVs for intra- and inter-assay–variation measurements in various ranges of the standard curve are 2.5% to 4.8% and 3.1% to 4.4%, respectively. The sensitivity and specificity of the ELISA used for the indirect immunofluorescent antibody test (IIFT) considered to be the reference method are 97.3% and 94%, respectively.

Antinuclear antibodies were determined by indirect IIFT and qualitatively assessed. The test results were interpreted either as positive or negative. The assays were made using a test kit from BioSystems (Barcelona, Spain), which is intended for in vitro testing of human serum ANA concentrations. Human epithelial cells were incubated with patient samples. In positive cases, ANA binds to the relevant antigens present in human epithelial cells. The resulting antigen-antibody complexes were detected with the goat antihuman IgG labeled with fluorescein isothiocyanate and visualized using a fluorescence microscope equipped with an excitation filter with a wavelength of 495 nm and an emission filter with a wavelength of 525 nm. The presence of specific fluorescence at the recommended dilution was regarded as a positive result. There are different patterns of fluorescent taints that can be found in the same serum. The pattern can be homogeneous, peripheral, speckle, nucleolar, centromeric. If one of these specific taints does not occur, the result is negative for these autoantibodies. Sensitivity and diagnostic specificity are 98.3% and 93%, respectively.

Endomysium antibodies (IgG) were determined by an ELISA kit (Eagle Biosciences, Nashua, New Hampshire, United States). The test results were interpreted either as positive or negative. The results were evaluated semiquantitatively by calculating the ratio of the extinction value of the control or the patient sample to the extinction value of the appropriate calibrator. The manufacturer recommends the following interpretation of the test results: ratio of less than 1.0, negative; ratio of 1.0 or higher, positive; in the quantitative assessment, less than 20 U/ml, negative, 20 U/ml or higher, positive. The lower detection limit of the assay is 3 U/ml. The CV for intra- and inter-assay–variation measurements in different ranges of the standard curve are 2.4% to 6% and 6.1% to 7.9%, respectively. The sensitivity and specificity of the ELISA used for the IIFT test considered as the reference method are 97.3% and 94%, respectively.

TABLE 1 Intrinsic factor antibodies and gastric parietal cell antibodies in patients with pernicious anemia

Antibody	Proportion, %
IF or GPC antibodies	61.3
GPC antibodies	46.0
IF antibodies	30.6
IF and GPC antibodies	15.3

Abbreviations: GPC, gastric parietal cell; IF, intrinsic factor

TABLE 2 Prevalence of antibodies involved in the development of connective tissue disease and celiac disease, that is, antinuclear and antiendomysium antibodies in patients with pernicious anemia and the control group

Antibodies	Result	Pernicious anemia	Control	*P* value[a]
ANA	Negative	104 (83.9)	39 (95.1)	0.07
	Positive	20 (16.1)	2 (4.9)	
EmA	Negative	120 (96.8)	40 (97.6)	0.80
	Positive	4 (3.2)	1 (2.4)	
ANA and EmA	Negative	124 (100)	41 (100)	–
	Positive	0	0	

Data are presented as number (percentage).

a Fisher exact test

Abbreviations: ANA, antinuclear antibody; EmA, antiendomysium antibody

The following were determined using routine laboratory methods with biochemical analyzers: serum concentration of vitamin B_{12}, iron, ferritin, folic acid; peripheral blood smear, manual platelet count, international normalized ratio, activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimers; proteinogram, total protein concentration; basic biochemical tests (creatinine, glucose, bilirubin, alanine aminotransferase, electrolytes, lipid profile, uric acid, C-reactive protein), thyroid-stimulating hormone, free thyroxine, free triiodothyronine.

Statistical analysis The SPSS software (IBM, Armonk, New York, United States) was used for the analysis. Variables were available in the qualitative form (IF antibodies, GPC antibodies, ANAs, EmAs), and one parameter was available on the quantitative scale (IF antibodies). A *P* value of less than 0.05 was considered significant. The Pearson χ^2 test was used for nominal values. For small sample sizes, the Fisher exact test was used. We analyzed the study group with respect to the risk of the appearance of the antibodies. In order to achieve this, the probability maximizing approach was used, with the probability of the response being taken into consideration. A multiple correspondence analysis (MCA) was used for the occurrence of certain groups of antibodies in the study population. This analysis allowed to select groups of clusters of certain measured parameters, for example, antibodies and diseases caused by them.

RESULTS Intrinsic factor or GPC antibodies were present in 76 patients (61.3%) who fulfilled the criteria for the diagnosis of PA (n = 124). Gastric parietal cell antibodies were found more often than IF antibodies (57 vs 38 patients, respectively), and both antibodies simultaneously were present in 19 patients (15%) (TABLE 1). For the quantified IF antibodies, descriptive statistics were calculated: mean (SD), 40.71 (71.08) RU/ml; minimum, 0 RU/ml; maximum, 329.1 RU/ml; median 5.4 RU/ml. There were no differences in the occurrence of ANAs and EmAs between the PA and control groups. However, ANAs were found in 16.1% of patients with PA and in 4.9% of controls, and the occurrence of EmAs in both groups was at a similar level of around 2% to 3% (TABLE 2). No association between the occurrence of antibodies involved in the development of CTD and CD with antibodies involved in the pathogenesis of PA has been found in patients with PA. In 7.9% of the patients diagnosed with IF antibodies, EmAs were positive as compared to 1.2% among those without IF antibodies ($P = 0.050$) (TABLE 3). The analysis of the associations has been extended with the MCA for the occurrence of certain groups of antibodies, which allowed to create a statistically significant ($\chi^2 = 4584.51$; $P = 0.009$) model (distribution of factors and their clusters on the Burt matrix). Based on this, it was shown that patients with PA with IF or GPC antibodies present have high probability of being EmA positive (FIGURE 1).

DISCUSSION The presence of either IF antibodies, or GPC antibodies, or, subsequently, both, constitutes one of the diagnostic criteria of PA. Thus, in the clinical context, the category IF antibody or GPC antibody has been introduced to encompass the whole study population of patients with PA. The aim of our study was to define the group of patients at higher risk for other autoimmune diseases (ie, autoimmune alert would be the most evident). Accordingly, in order to distinguish the group of patients in whom both antibodies are present, the IF antibody and GPC antibody category was introduced. Introducing separate categories—IF antibody, GPC antibody—allowed us to determine the occurrence of each antibody in patients with PA. Gastric parietal cell antibodies occurred more often than IF antibodies, and the concomitant occurrence of both antibodies was observed least often. This remains in line with data from the literature. For instance, in patients with PA who underwent gastroscopy (n = 34), IF antibodies were present in 52%, GPC antibodies, in 97%,[15] and the combination of both antibodies for PA yields 73% sensitivity (and 100% specificity).[18] Intrinsic factor antibodies were positive in 38% and GPC antibodies in 56% of 50 patients as shown by Divate and Patanwala.[39] On the other hand, in a study in the Korean population (n = 83), IF antibodies or GPC antibodies were present in 85.5% of patients with PA, which agrees with our findings. However, in contrast to our results, in this population,

TABLE 3 Various antibodies in patients with pernicious anemia

Antibodies		IF antibodies			GPC antibodies			IF or GPC antibodies			IF and GPC antibodies		
		Negative	Positive	*P* value[a]	Negative	Positive	*P* value[a]	Negative	Positive	*P* value[a]	Negative	Positive	*P* value[a]
ANA	Negative	73 (84.9)	31 (81.6)	0.65	56 (83.6)	48 (84.2)	0.92	42 (87.5)	62 (81.6)	0.38	87 (82.9)	17 (89.5)	0.47
	Positive	13 (15.1)	7 (18.4)		11 (16.4)	9 (15.8)		6 (12.5)	14 (18.4)		18 (17.1)	2 (10.5)	
EmA	Negative	85 (98.8)	35 (92.1)	0.05	65 (97)	55 (96.5)	0.87	48 (100)	72 (94.7)	0.11	102 (97.1)	18 (94.7)	0.59
	Positive	1 (1.2)	3 (7.9)		2 (3)	2 (3.5)		0	4 (5.3)		3 (2.9)	1 (5.3)	

Data are presented as number (percentage).

a χ^2 test or the Fisher exact test as appropriate

Abbreviations: see TABLES 1 and 2

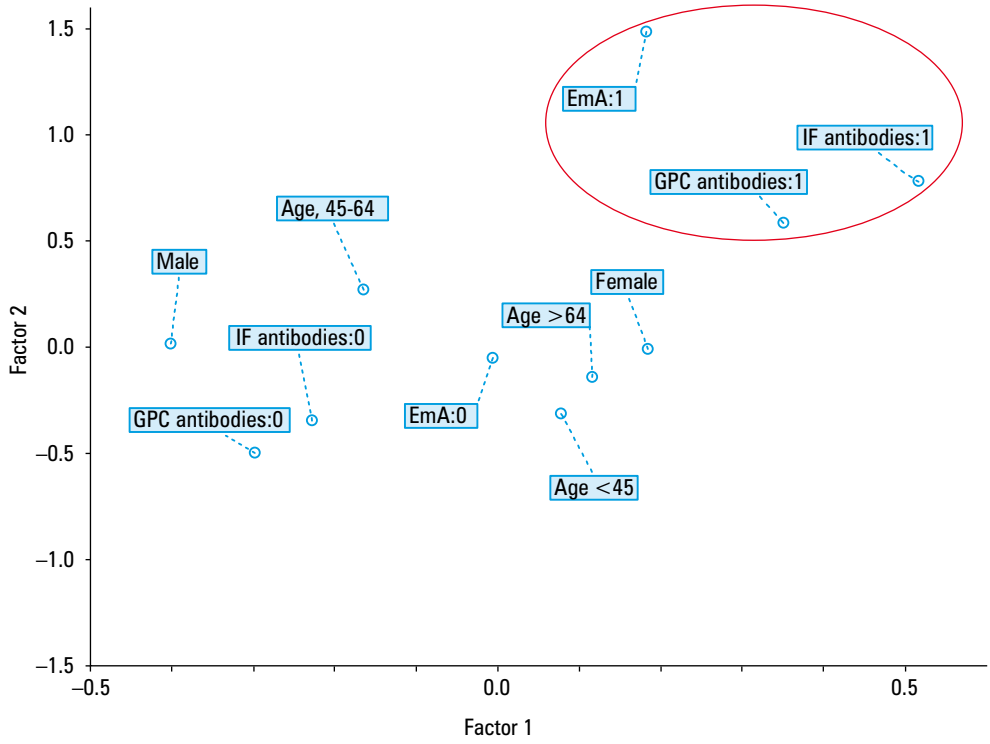

FIGURE 1 Coexistence of antibodies involved in the development of celiac disease with antibodies involved in the pathogenesis of pernicious anemia; 1, study group; 0, control group;
Abbreviations: see TABLES 1 and 2

IF antibodies were present more often (77.5%) than GPC antibodies (43.2%), and the concomitant presence of both antibodies was observed in 34.6% of patients.[7] The highest prevalence of PA is seen in the United Kingdom and Scandinavia.[9] This raises the question whether this epidemiological diversity can be related to a different constellation of the prevalence of IF and GPC antibodies.

The prevalence of the assessed antibodies has also been described in other autoimmune diseases, such as autoimmune thyroid disease (AITD), including Hashimoto disease or Graves disease as well as type 1 diabetes, vitiligo, and CD.[12,14,18,24,26,40,41] Genetic susceptibility for PA is suggested by a specific human leukocyte antigen (HLA)-DR pattern, which is known to be associated with other autoimmune diseases.[9,12,18,21,42,43] It has been proved that the genotypes of HLA-DRB1*03 and HLA-DRB1*04, which are known to be associated with other autoimmune diseases such as type 1 diabetes and AITD,[21] are also associated with PA. This observation supports the role of autoimmunity in PA[18] (the majority of patients with CD is HLA-DQ2– and/or HLA-DQ8–positive)[35,37,44]. Antithyroid peroxidase antibodies or antithyroglobulin antibodies, typical of AITD, are more frequently present (mainly antithyroid peroxidase antibodies) in patients with PA who have IF antibodies or GPC antibodies. This correlation seems most evident in patients with concomitant occurrence of IF antibodies and GPC antibodies.[1] Our hypothesis that antiadrenal and antipituitary antibodies, involved accordingly in some cases of Addison disease and hypopituitarism, could be more frequent in patients with PA, have not been confirmed.[1] GPC antibodies are also more frequent in patients diagnosed with Graves disease and vitiligo.[5,14,22,26,31] The coexistence of endocrine disease with gastroenterological and rheumatic diseases is referred to as autoimmune polyendocrine syndrome. Patients with this syndrome had higher frequencies of the HLA-A24, -A31, -B8, -B51, -B62, -DR3, and -DR4.[45] In order to continue our previous research,[1] we tested patients with PA for biochemical screening indicators of CTD (ANAs) and CD

(EmAs). At first, we have also considered screening the study group for antibodies involved in latent autoimmune diabetes in adults. However, based on the available literature, in our opinion this possibility is unlikely.[46]

The co-occurrence of autoimmune diseases is such a well-known fact that it seems surprising that so few studies evaluated the usefulness of the so-called autoimmune alert, that is, the measurement of the clinically accepted diagnostic exponents of these processes. This could prove especially useful during the prodromal stage of the subsequent autoimmune disease. With regard to CTD, in the last 20 years, very little data other than case reports were described. Seven patients with an association of PA and Sjögren syndrome have been described[47] as well as a group of 74 patients with PA, among whom 7 had Sjögren syndrome, 5 were diagnosed with antiphospholipid syndrome, and 1 had systemic lupus erythematosus.[26] Gastric parietal cell antibodies and PA were found in 1 out of 194 patients with systemic lupus erythematosus.[48] In patients with CD, GPC antibodies occurred 3- to 10-fold more frequently.[14,31] Gastric parietal cell antibodies are also more common in first- and second-degree relatives of people with CD.[14,24] Celiac disease is associated with an increased risk of all malignancies, especially those affecting the gastrointestinal tract,[49] while PA is associated with increased risk of stomach cancer.[11,50] In this context, the assessment of the co-occurrence of CD and PA could be considered when oncological vigilance is discussed. The determination of the co-occurrence of only 2 nonhematological antibodies with IF antibodies or GPC antibodies can be seen as a limitation of our study. Even though we were not able to demonstrate a difference in the occurrence of ANAs and EmAs between the PA group and the control group, our analysis shows that patients with PA in whom IF antibodies or GPC antibodies are present have a higher risk of positive EmAs (FIGURE 1). Considering that 16.1% of patients with PA in our study were ANA positive, CTD screening could also be considered.

In conclusion, simultaneous determination of IF antibodies and GPC antibodies significantly increases the likelihood of confirming the diagnosis of PA. In patients with PA, screening for CTD and celiac disease may be considered.

ARTICLE INFORMATION

ACKNOWLEDGMENTS This work was supported by the Medical University of Silesia (grants no. KNW-1-135/N/3/0, KNW-1-056/N/4/0, KNW-1-158/K/5/0; to DK). DK was assigned a digital identifier (ORCID iD, https://orcid.org/0000-0002-5577-800X).

CONTRIBUTION STATEMENT EM-S and DK conceived the concept of the study. EM-S, DK, WF, BM, JG-S, BK-K contributed to the design of the research. EM-S, DK, and WF were involved in data collection. All authors analyzed the data, edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Morawiec-Szymonik E, Foltyn W, Marek B, et al. Antibodies involved in the development of pernicious anemia and other autoimmune diseases. Pol Arch Intern Med. 2020; 130: 31-37. doi:10.20452/pamw.15094

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