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Prevalence of selected organ-specific autoantibodies in rheumatoid arthritis and primary Sjögren's syndrome patients

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Abstract

Objectives: The aim of the study was to investigate the prevalence of selected organ-specific autoantibodies in rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) patients, and discuss their clinical significance.

Material and methods: The study included 121 RA and 30 pSS patients. Sera were tested for the presence of autoantibodies to thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG), TSH receptor (TRAbs), mitochondrial antigen M2 (AMA-M2-3E) and gliadin-analogous fusion peptides (anti-GAF(3X)) using the ELISA method. Non-organ-specific antibodies were determined: rheumatoid factor in IgM class, anti-citrullinated peptide antibodies and antinuclear antibodies. The occurrence of antibodies was also examined with regards to RA activity.

Results: The following autoantibodies were detected in RA patients: anti-TPO – 13 (10.7%), anti-TG – 6 (5%), AMA-M2-3E – 3 (2.5%), anti-GAF(3X) – 5 (4.1%). The respective levels of these autoantibodies in pSS patients were 3 (10%), 2 (6.7%), 4 (13.3%) and 2 (6.7%). Polyautoimmunity was confirmed in 34 RA patients (including 20 cases of autoimmune thyroid disease [AITD]) and in 6 pSS patients (6 cases of AITD). When RA patients were divided into anti-TPO positive and anti-TPO negative groups, we found a statistically significant relationship between groups regarding age and hemoglobin concentration. In pSS patients the anti-TPO positive group was less likely to use immunosuppressive drugs as compared with the anti-TPO negative group. Anti-TPO was significantly more frequently detected in RA + AITD vs. RA, RA + SS + AITD vs. RA and in pSS + AITD vs. pSS patients.

Conclusions: Organ-specific autoantibodies are relatively frequently observed in patients with RA and pSS. Their presence is connected with the clinical picture of the diseases.

Key words: rheumatoid arthritis, primary Sjögren's syndrome, antibodies.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic connective tissue disease of an autoimmune nature. It affects about 1–1.5% of the general population. The disease is characterized by the presence of non-organ-specific antibodies, including the marker antibodies rheumatoid factor in IgM class (IgM RF) and anti-citrullinated peptide antibodies (ACPA), as well as organ-specific ones.

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease of an unknown etiology that is characterized by the formation of lymphocytic infiltration in the exocrine glands and impairment of their function leading to changes in many organs and systems. It is the second most prevalent autoimmune rheumatic disease. The estimated prevalence of pSS is 0.5–5% of the general population, depending on the diagnostic criteria used [1]. The presence of antinuclear antibodies (ANA), of which anti-SSA and anti-SSB are marker antibodies, is listed among key classification criteria for the diagnosis of the disease [2, 3].

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Rheumatoid arthritis and pSS are the most common systemic diseases of the connective tissue. Both are associated with higher titers of organ-specific antibodies, including those characteristic of autoimmune thyroid disease (AITD), primary biliary cirrhosis (PBC) and celiac disease (CD). The clinical relevance of organ-specific antibodies is still debated. Systemic and organ-specific autoimmune diseases are often comorbid, and their clinical symptoms may overlap. In addition, increased prevalence of autoimmune diseases is found not only in patients with rheumatic diseases, but also in their relatives.

Autoimmune thyroid disease is characterized by the presence of specific autoantibodies against one or more thyroid antigens. It is one of the most common autoimmune diseases, as it affects about 1.5% of the population; 2–3% (up to 5%) according to other sources. Antithyroid peroxidase antibodies (anti-TPO) and antithyroglobulin antibodies (anti-TG) are considered to be markers for AITD. Antibodies against the TSH receptor (TRAbs) are associated with the pathogenesis of Graves' disease and are found in nearly all cases of it [4]. Recently, anti-livin antibodies have been described, which, in addition to being useful markers in the diagnosis of malignancies of the gastrointestinal tract, are also found in Hashimoto thyroiditis patients [5]. Antithyroid antibodies can be detected in up to 32–37% of patients with rheumatoid arthritis [6, 7].

Primary biliary cirrhosis is a chronic progressive autoimmune disease of the liver that leads to cholestasis caused by destruction of the epithelium of small intrahepatic bile ducts. Antibodies characteristic of PBC are antimitochondrial antibodies (AMA). The prevalence of PBC is 100–400/million cases [8]. Primary biliary cirrhosis is often associated with other autoimmune diseases, especially Sjögren's syndrome (SS), AITD, RA, scleroderma, and CD.

Celiac disease is an inflammatory enteropathy of the small intestine. It is a disorder of an autoimmune origin, but without an established etiology, caused by gluten intolerance. It ranges from 0.7% to 3% [9]. In the pathogenesis of CD, anti-gliadin analogous fusion peptide (anti-GAF), anti-tissue transglutaminase and anti-endomysium antibodies play a role [10]. Celiac disease is comorbid with other autoimmune diseases, in particular autoimmune hepatitis (AIH) and AITD.

The aim of the present study was to determine the prevalence of anti-thyroid antibodies (anti-TPO, anti-TG, TRAbs), some other organ-specific autoantibodies (AMA-M2, anti-GAF) and, additionally, non-organ-specific antibodies (IgM RF, ACPA, ANA) in RA and pSS in the context of polyautoimmunity. At the same time, an attempt was made to demonstrate the relationship between the presence of the investigated organ-specific autoantibodies, especially anti-thyroid antibodies, and selected clinical and immunological parameters.

Material and methods

Patients

The analysis involved 121 patients with RA diagnosed according to the 1987 American College of Rheumatology (ACR) criteria [11] and 30 patients with pSS diagnosed according to the criteria established in 2002 by the American-European Consensus Group [2]. The patients were selected from the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland. The diagnosis of AITD was based on laboratory markers, including thyroid stimulating hormone (TSH), thyroid hormone levels and antithyroid antibodies, as well as ultrasound examination and/or biopsy of the thyroid. Patients with an additional connective tissue disease other than secondary SS (sSS), with active infection or with a neoplasm were excluded from the study. The patients were divided into groups based on the presence or absence of specific antibodies, especially antithyroid antibodies, and taking into account the concomitant AITD. The analysis involved clinical features: gender, age, disease duration, associated autoimmune diseases, history of treatment, including history of treatment with disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GCS), biologic agents (infliximab, etanercept, adalimumab and rituximab), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, hemoglobin (Hgb) concentration, and additionally, in RA patients, disease activity score in 28 joints (DAS28-ESR version with four variables) and duration of morning stiffness. Written informed consent was obtained from all patients and ethical committee approval was obtained.

Measurements

Blood was drawn between 7:00 and 9:00 AM. Blood for the detection of antithyroid antibodies was centrifuged, and serum was stored at –80°C. The organ-specific autoantibodies were determined using commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (Euroimmun, Lübeck, Germany). Serum samples were tested for anti-TPO, anti-TG, TRAbs, AMA-M2-3E and anti-GAF(3X)). The cut-off values were 50 IU/ml, 100 IU/ml, 2 IU/ml, 20 IU/ml and 25 IU/ml respectively. Serum levels of CRP and Hgb and ESR were determined in a local laboratory. IgM RF was determined by the ELISA method, ACPA by a third generation ELISA assay and ANA was detected by indirect immunofluorescence with Hep-2 cell substrate. All parameters were collected at the same time and by a single investigator.

Table I. Basic characteristics of patients included in the study

Variable	RA (n = 121)	pSS (n = 30)
Sex female/male	106 (87.6)/15 (12.4)	30 (100)/0 (0)
Age [years]	56.1 ±11.62 (22–79; 54.02–58.2; 58)	52.5 ±10.12 (23–71; 48.72–56.28; 52.5)
Disease duration [years]	11.89 ±9.26 (0–40; 10.22–13.56; 9)	3.6 ±3.18 (1–10; 2.41–4.79; 2)
Associated SS	14 (11.6)	not applicable
Associated AITD	20 (16.5)	6 (20)
Associated SS + AITD	2 (1.7)	not applicable
Polyautoimmunity	34 (28.1)	6 (20)

Data are presented as mean ± SD (range; 95% CI, Me) or proportion (%); AITD – autoimmune thyroid disease; pSS – primary Sjögren's syndrome; RA – rheumatoid arthritis; SS – Sjögren's syndrome.

Statistical analysis

Statistical analyses were performed using STATISTICA 10.0 PL software (StatSoft Inc.). The descriptive statistics were shown as: mean values ± standard deviation (SD), 95% confidence interval of mean value (95% CI), median value (Me), and minimal and maximal values. For qualitative variables the numbers and percentages are given. Distribution of variables was checked using the Lilliefors test and Shapiro-Wilk W test. Due to non-Gaussian distribution of variables the non-parametric Mann-Whitney U test was used for analysis of differences. For analysis of qualitative variables we used χ^2 tests: the Pearson test for theoretical frequencies > 10, the V^2 test for theoretical frequencies < 10 and > 5, Yates' test for theoretical frequencies < 5. A p value < 0.05 was considered statistically significant for all analyses.

Results

The basic characteristics of the patients are presented in Table I. The prevalence of detected autoantibodies is presented in Table II: there are statistically significant differences in the frequency of IgM RF, ACPA, ANA and AMA-M2 between RA and pSS patients. Polyautoimmunity was confirmed in 34 (28.1%) RA patients (20 cases of AITD, 14 SS, 2 AITD + SS, 1 psoriasis, 1 recurrent uveitis) and in 6 pSS patients (6 cases of AITD, 1 AITD + AH). All patients with diagnosed AITD suffer from Hashimoto's thyroiditis. The distribution of DMARDs was similar among the patients in each group. When RA patients were divided into anti-TPO positive and anti-TPO negative groups, we found a statistically significant relationship between them. The anti-TPO positive group was significantly younger (p = 0.0001) and patients had a significantly lower Hgb concentration (p = 0.022) compared with the anti-TPO negative group (Figs. 1 and 2). Patients in the anti-TPO positive group with pSS had lower total use of DMARDs compared with the anti-TPO negative group (p = 0.023) (Fig. 3). Anti-TPO was significantly more frequently detected in RA + AITD patients (p < 0.0001), RA + SS + AITD (p = 0.0004) patients and in pSS + AITD (p = 0.004) patients than in patients without polyautoimmunity. There is no correlation between presence of organ-specific antibodies tested in the study and parameters of RA activity (presented in Table III).

Discussion

Rheumatoid arthritis and SS are among the most prevalent systemic diseases of connective tissue. Sicca symptoms in RA patients are quite common, and in the

Table II. Prevalence of detected autoantibodies in the study group

Variable	RA (n = 121)	pSS (n = 30)	p
IgM RF	89 (73.6%)	13 (43.3%)	0.002
ACPA	105 (86.8%)	3 (10%)	0
ANA	28 (23.1%)	29 (96.7%)	0
Anti-TPO	13 (10.7%)	3 (10%)	0.91
Anti-TG	6 (5%)	2 (6.7%)	0.71
Anti-TPO and/or anti-TG	17 (14%)	5 (16.7%)	0.71
TRAbs	0	0	1
AMA-M2-3E	3 (2.5%)	4 (13.3%)	0.012
Anti-GAF/3X/	5 (4.1%)	2 (6.7%)	0.54

ACPA – anti-citrullinated peptide antibodies; AMA-M2-3E – antimitochondrial antigen M2 antibodies; ANA – antinuclear antibodies; anti-GAF/3X/ – anti-gliadin analogous fusion peptide antibodies; anti-TG – antithyroglobulin antibodies; anti-TPO – antithyroid peroxidase antibodies; IgM RF – immunoglobulin M rheumatoid factor; pSS – primary Sjögren's syndrome; RA – rheumatoid arthritis; TRAbs – antibodies against the TSH receptor

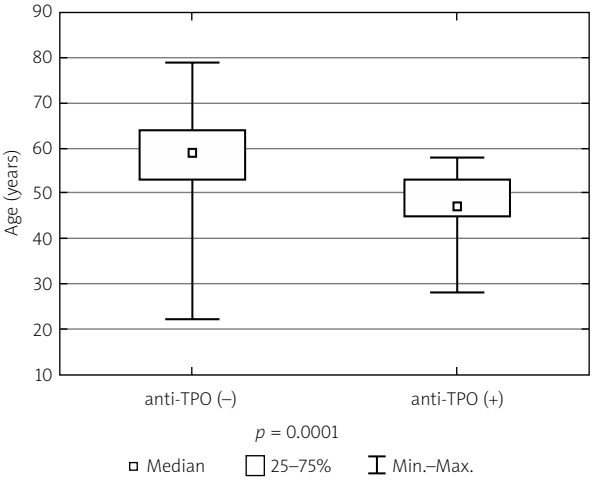

Fig. 1. Comparison of age in anti-TPO negative RA vs. anti-TPO positive RA patients.

anti-TPO – antithyroid peroxidase antibodies; RA – rheumatoid arthritis

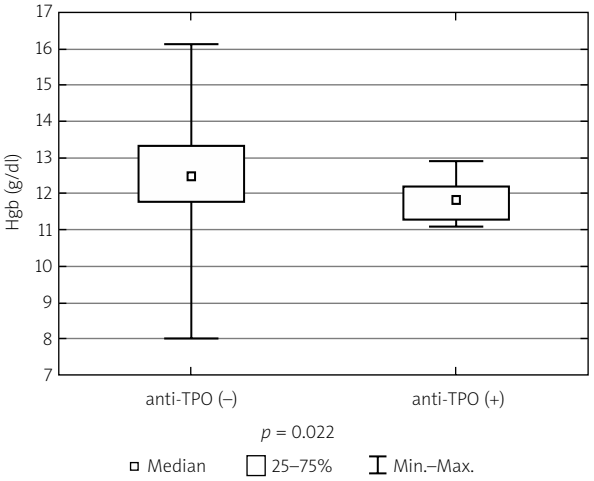

Fig. 2. Comparison of Hgb in anti-TPO negative RA vs. anti-TPO positive RA patients.

anti-TPO – antithyroid peroxidase antibodies; Hgb – hemoglobin; RA – rheumatoid arthritis

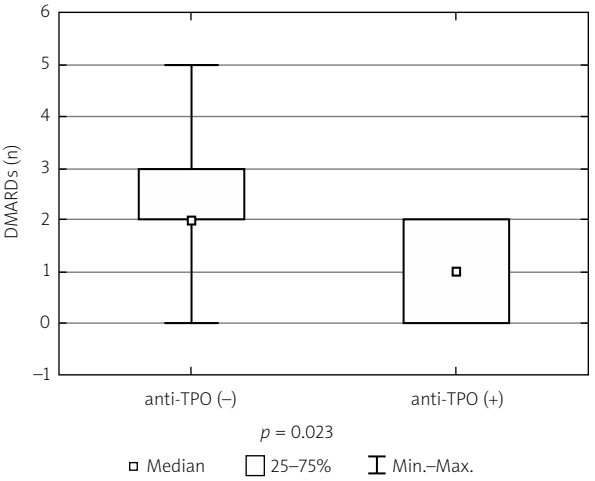

Fig. 3. Comparison of total use DMARDs in anti-TPO negative RA vs. anti-TPO positive pSS patients.

anti-TPO – antithyroid peroxidase antibodies; DMARDs – disease-modifying antirheumatic drugs; pSS – primary Sjögren's syndrome

present study group, 14 (11.6%) patients with RA were diagnosed with sSS. Polyautoimmunity is the subject of an animated debate in the literature. Amador-Patarroyo et al., in a study of 410 pSS patients, not only showed increased comorbidity with other autoimmune disorders, of which the most common was AITD (21.5%), but also defined the risk factors for such comorbidities [12]. The group analyzed in the present study consisted of 30 pSS patients, which may limit the possibility of obtaining statistically significant results allowing separation of the patients into subgroups based on test results for the presence of relatively rare autoantibodies. When identifying subgroups positive for the investigated autoantibodies, an inherent statistical analysis was performed in the search for new aspects of autoimmunity in primary rheumatologic diseases.

Autoimmune thyroid disease is one of the most common autoimmune diseases, and it is comorbid with systemic connective tissue diseases, especially RA, SS and systemic lupus erythematosus (SLE), but also with CD.

Table III. Parameters of disease activity in RA study group

Variable	Mean (range)	SD	95% CI	Me
ESR [mm/h]	35.81 (5–112)	25.36	31.24–40.38	28
CRP [mg/l]	20.75 (0.09–142.7)	25.75	16.12–25.39	10.79
Hgb [g/dl]	12.4 (8–16.1)	1.34	12.16–12.64	12.3
Morning stiffness [min]	87.77 (0–240)	45.85	79.52–96.02	60
DAS28	4.41 (1.35–8.01)	1.28	4.18–4.64	4.3

CI – confidence interval; CRP – C-reactive protein; DAS28 – disease activity score with 28-joint count; ESR – erythrocyte sedimentation rate; Hgb – hemoglobin; Me – median; RA – rheumatoid arthritis; SD – standard deviation.

Reports in the literature describe mutual relationships between AITD and the presence of organ-specific autoantibodies against other diseases; one exception is the relationship between AITD and ANA, which has not been fully explained yet [13]. Previous studies demonstrate that AITD is the most prevalent comorbid autoimmune disease in RA, followed by SS and SLE. These data are confirmed by the characteristics of the patients investigated in the present study. In the analyzed group of RA patients, 20 (16.5%) had been diagnosed with AITD. Altogether, 12/20 patients (60%) had antithyroid antibodies. In 8/20 patients (40%) with AITD, no antibodies were found, but it should be remembered that there are many factors affecting the titer of particular antibodies at a given time of the disease in a particular individual, among others, the variable nature of the autoimmune disease or previous disease-modifying treatment, including biological treatment. Such a hypothesis seems to be supported by one of the results of this study concerning pSS patients: patients in the anti-TPO positive group were found to have used statistically significantly lower amounts of DMARDs in comparison with anti-TPO negative patients. We realize it is not appropriate to study traditional DMARDs alongside biologic DMARDs, but it is important to note that we observed such a dependence. Biological treatment is not without an effect on the titer of previously detected autoantibodies or the emergence of new ones [14]. In patients treated with adalimumab, during a 6-month follow-up, Dutch researchers obtained a statistically significant reduction in the titer of anti-TPO and an improvement in the function of the thyroid, as confirmed by the normalization of TSH levels [15]. In the course of immunosuppressive therapy, including treatment with GCS, antibodies specific to CD may disappear, as shown by Diamanti et al. in a follow-up study of CD patients treated with immunosuppressants due to a liver disease [16]. A similar explanation can be given for the existence of potential relationships between the parameters of activity of the primary disease and the presence of autoantibodies in different groups of patients and at different periods of disease activity. In this study, no statistically significant relationships were found between the parameters of inflammation or DAS28 (also divided into groups of patients in remission, or with low, moderate and high RA activity) and the presence of antithyroid antibodies in patients with RA. In 2013, an article was published summarizing the results of our preliminary research, which demonstrated the existence of potential relationships between antithyroid antibodies and RA activity. That study, however, was conducted on patients who at the time of the study had decidedly less often and for shorter periods been treated with biological drugs [17]. A study by Choe et al. showed a relationship between the titer of marker antibodies for RA and the activity of the disease [18].

In clinical practice, particular attention should be paid to cases of RA with the presence of antithyroid antibodies and without previously diagnosed AITD. In the present study, 3 (3/13; 23%) cases of RA with the presence of anti-TPO and 4 (4/5; 80%) cases with the presence of anti-TG were reported – all patients should be further screened for AITD. We believe that all patients with RA and pSS should have their thyroid function tested for a comorbid thyroid disease, not necessarily AITD. Such screening in patients with RA is also recommended by Raterman et al. [19], who draw attention to the fact that cardiovascular diseases are more prevalent in female RA patients with hypothyroidism than in those with normal thyroid function. Currently, based on the scientific evidence, it is believed that RA and associated inflammation is associated with cardiovascular risk [20, 21]. On the other hand, Carvalho et al. [22], in an endocrinologically oriented summary of guidelines for testing antithyroid antibodies, recommend that autoantibody tests should be performed when AITD is suspected but do not mention the need for screening in other autoimmune diseases. Nevertheless, they do make the reservation that clinicians should test patients for thyroid disorders in individual cases [22].

During the analysis of RA patients, a statistically significant difference in Hgb concentrations was found between anti-TPO positive patients and patients with no anti-TPO antibodies as well as between anti-TPO and/or anti-TG positive patients as compared to patients who were negative for antithyroid antibodies. Differential diagnosis of anemia should primarily take into account the anemia of chronic disease, iron-deficiency anemia caused by various factors, erythroid hypoplasia and pernicious anemia. An analysis of the previously demonstrated statistically significant relationship between anti-TPO and Hgb in the aspect of anemia in patients with RA or SS shows that AITD is particularly frequent in patients with pernicious anemia: in a study of 22 patients conducted by Ottesen et al., 50% had anti-TPO and 13.6% had anti-TG, i.e. 2–3 times more than in the control group [23]. Möller et al. stated that anemia may serve as a predictor of worse outcome independently of common disease activity factors in RA patients [24]. In conclusion, as in the case of AITD, studies confirm the need for earlier testing of organ-specific antibodies.

Rheumatoid arthritis patients with positive anti-TPO as well as those with anti-TPO and/or anti-TG were statistically significantly younger than patients in whom these antibodies were not found. Also, RA patients with positive anti-TG and pSS patients with positive anti-TPO

were younger, though not in a statistically significant way. Similar relationships between patients' age and the presence of antithyroid antibodies were described by Kerimovic-Morin [25] in a group of patients with various autoimmune diseases. Patients with systemic scleroderma and thyroid disease were significantly younger than those with negative antithyroid autoantibodies. Thyroid dysfunction was three times more prevalent in women with RA than in women with non-inflammatory rheumatic disease, and the diagnosis of the dysfunction correlated with a shorter duration of arthritis at the time of the study [25]. Anti-TPO positive patients with RA and SLE were characterized by a younger mean age at diagnosis of hypothyroidism than anti-TPO negative patients [26]. In a study by Lazúrová et al. [13], AITD patients with positive ANA were statistically significantly younger than ANA negative patients with AITD. These reports provide a basis for a discussion on the existence of a genetic predisposition to autoimmunity and symptomatic autoimmune diseases. Our findings may speak in favor of the existence of a subtype of RA which presents at a younger age and is characterized by greater activity of the primary disease; patients with this subtype of RA should be screened for comorbid AITD. In the case of SLE, subphenotypes of the disease were announced by exploring epigenetic mechanisms [27]. In addition, patients described above are more likely to be hospitalized. It should be remembered that screening of thyroid dysfunction that consists of the TSH test alone may be inadequate, especially in patients treated with GCS, as pointed out by some researchers [28]. In such cases, testing of thyroid antibodies may gain in importance.

No statistically significant differences were found in the prevalence of IgM RF, ACPA or ANA between RA patients with positive thyroid antibodies (anti-TPO, anti-TG) and patients in whom no such antibodies were detected. The literature available focuses on the discussion of the recommendations for testing autoantibodies, such as RF, in patients with AITD, emphasizing the well-established increased prevalence of AITD, anti-TPO and anti-TG in patients with RA [29]. ANA antibodies, on the other hand, are specific to SLE, which is why it would be purposeful to study the potential correlations between ANA and anti-TPO or anti-TG in patients with SLE, the more so that some reports indicate the probable existence of higher comorbidity between SLE and AITD than between RA and AITD [29]. A comparison of the presence of non-organ-specific antibodies in patients with RA and pSS shows that a fairly high percentage of pSS patients have IgM RF (43.3%). This result confirms that the presence of IgM RF in patients with pSS is quite common and that high-positive RF was justifiably included in the new criteria for SS proposed by the ACR in 2012 [3].

Statistically significant differences were noted in the prevalence of antithyroid antibodies between RA patients with AITD and those without AITD, and between patients with AITD and sSS compared with patients without these autoimmune diseases. The results obtained in this study can be considered as being in line with expectations, since the presence of antithyroid antibodies determines the diagnosis of AITD, and the antibodies themselves usually do not disappear in the course of the disease, but show some fluctuations. Also in the group of RA patients with AITD and sSS, the statistically significant increased prevalence of antithyroid antibodies is not controversial when looked at from the point of view of polyautoimmunity and the fact that the pathogenic mechanisms and antigens in both AITD and SS may be similar. In the pSS group, statistical significance was demonstrated between the presence of anti-TPO and comorbid AITD. All anti-TPO positive patients had already had a diagnosis of AITD.

In our study, no statistically significant differences were found in the prevalence of antithyroid antibodies between RA patients with sSS (n = 14) and patients with pSS (n = 30), although the data we collected indicated a higher prevalence in the group of patients with RA and sSS. Both RA and SS patients were shown to have an increased prevalence of antithyroid antibodies, but the numerical advantage of the first group mentioned was supported by the clustering of two immune disorders and by phenotyping of autoimmunity phenomena.

In the group of patients with RA, 3 (2.8%) were AMA-M2 positive and one suffered from AITD. In patients with pSS, AMA-M2 was found in 4 (13.3%), and the difference was statistically significant, but it should be noted that in this group there was one patient with pSS + AIH. The considerably higher prevalence of AMA-M2 in patients with pSS can be explained by the fact that PBC, for which AMA are marker antibodies, is a disease that mainly affects middle-aged women [30], a population that is much more akin to the pSS group than to the RA group. The serological profile of patients with PBC in addition to AMA also includes ANA, and in our group of patients with pSS almost all were ANA positive (29/30, 96.7%). Antimitochondrial antibodies positivity may be a risk factor for the development of PBC [31].

In the investigated group of patients with RA, 5 (4.1%) were anti-GAF positive. In the pSS group, 2 (6.7%) patients had anti-GAF and both were diagnosed with AITD.

Our results allowed us to extract from the investigated population of patients with RA those suspected of having a comorbid autoimmune disease and a course

characterized by more severe anemia not associated with age as a risk factor. It is known that the effectiveness of RA treatment depends on the genetically determined form of the disease and thus on the immune mechanisms involved in the rheumatoid process. Recent research on RA focuses, on the one hand, on the genetic aspects promoting the development of an autoimmune disease, and, on the other hand, on immunotherapy aimed at the search for new drugs that can directly suppress autoimmune or autoinflammatory processes at different stages.

Conclusions

The following conclusions can be drawn from the study:

1. The presence of organ-specific autoantibodies which are not associated with the rheumatoid process is relatively frequently observed in patients with RA and pSS. Autoimmune thyroid disease is more common in patients with RA and pSS than in the general population.
2. There is no significant correlation between RA activity and the presence of the organ-specific antibodies tested in this study.
3. In RA patients with anti-TPO positivity, low Hgb concentration is more common, which may be due to the severity of non-specific inflammation.
4. The positivity of antithyroid antibodies is not correlated with the presence or absence of serological markers (IgM RF and ACPA) in RA or in pSS patients.
5. Thyroid antibodies in RA are more frequently observed in younger patients; therefore it may be concluded that younger RA patients are more likely to exhibit organ-specific autoimmunity.
6. In pSS patients the rare usage of DMARDs is associated with the presence of antithyroid antibodies.
7. The prevalence of antithyroid antibodies in patients with RA and sSS is comparable to the prevalence of these autoantibodies in patients with pSS.

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The authors declare no conflict of interest.

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