Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.10.676 2020;(27)2:538-44

Original Article

Relationship between T regulatory cell levels (CD4 + CD25 + CD127- T cells) and the presence of autoantibodies in adult patients with selective IgA deficiency

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Abstract

Aim: Selective immunoglobulin A (sIgA) deficiency is the most common primary immunodeficiency. Individuals with selective IgA deficiency are generally considered to be asymptomatic. In some patients, autoimmune diseases have been reported. Regulatory T cells (T reg) are a group of cells that play a key role in preventing autoimmunity.

Material and Methods: 28 patients with selective IgA deficiency and a control group consisting of 15 individuals of similar age and sex were included in the study.

Results: Serum IgA levels were lower in patients with sIgA deficiency ($p < 0.001$). There was no difference between the two groups in term of the rate of Treg cells (p: 0.562 and p: 0.873). There was at least one autoantibody positivity in 19 (67.8%) patients with sIgA deficiency and 4 (26.7%) in the control group. The most common positive autoantibody was ANA in both groups. Serum IgG and IgG1 levels were significantly higher in sIgA deficiency patients with autoantibody than in the other group (p: 0.004 and p: 0.004) The relationship between presence of autoantibodies and Treg cell levels in patients with sIgA deficiency was not statistically significant (p: 0.199). The regression analysis showed that the IgG level (OR: 1.594, 95% CI: 1.096-2.319, p: 0.015) was an independent predictor for the presence of autoantibodies.

Conclusion: The findings of our study are important as they are the first evaluation in adult sIgA deficient patients. Further studies are required to shed light on this issue in order to evaluate more patients with sIgA deficiency with autoimmunity.

Keywords: Selective IgA deficiency; T regulatory cells; autoantibodies

INTRODUCTION

Selective immunoglobulin A (sIgA) deficiency is the most common primary immunodeficiency (1). Individuals with selective IgA deficiency are generally considered to be asymptomatic. In some patients, recurrent sinopulmonary infections (2), autoimmune diseases (3), gastrointestinal (GI) infections (4), GI inflammatory diseases (5), allergic diseases (6), and anaphylactic transfusion reactions (7) have been reported.

Autoimmunity is a relatively common clinical problem in the patients with selective IgA deficiency. Autoimmune diseases, such as systemic lupus erythematosus (SLE), Graves' disease, Type I Diabetes Mellitus (DM), juvenile and adult-onset rheumatoid arthritis, immune thrombocytopenia and myasthenia gravis develop in 20-30% of the patients (3,8-13). Autoantibodies may be positive even before symptoms of autoimmune disease occur in these patients (14,15).

Received: 28.10.2019 **Accepted:** 17.12.2019 **Available online:** 10.03.2020
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Regulatory T cells (T reg) are a group of cells that enables immune hemostasis and play a key role in preventing autoimmunity and controlling inflammation, and modulating the immune response during infection and cancer development (16,17). Although Tregs constitute approximately 1-2% of the CD4+ T cell population, they provide immune suppression either by inhibiting the interaction of antigen-presenting cells with CD4+ T cells and effector T cells or by direct cytotoxicity. Treg development is mediated by the transcription factor Forkhead Box P3 (FoxP3) and often expresses CD25, CD27, CD134, CD152, CD62-L on their surface (18).

In only a study in pediatric age group, showed that Treg cell ratio is lower in patients with selective IgA deficiency compared to healthy children (19). However, there are no studies on adult sIgA deficient patients with a higher presence of autoantibodies, autoimmune complications and comorbidities.

The aim of this study was to investigate the relationship between Treg cell levels and presence of autoantibodies in adult patients with sIgA deficiency and to compare them with a healthy control group.

MATERIAL and METHODS

Study population

A total of 43 individuals; 28 patients with selective IgA deficiency and followed up at the Immunology and Allergic Diseases Clinic of the Department of Internal Diseases of the Meram Faculty of Medicine at Necmettin Erbakan University and a control group consisting of 15 individuals of similar age and sex who visited the Internal Diseases Outpatient Clinic with normal IgA levels and no organic pathology were included in the study. The patients with selective IgA deficiency and the control group were completely asymptomatic. There was no one in the study group with autoimmune disease. Written informed consent was obtained from the participants before the study. European Society for Immunodeficiencies (ESID) criteria was used for diagnosis of sIgA deficiency (20).

Autoantibodies

Clinical and demographic data, autoantibodies and other laboratory parameters of the patients were obtained from their records. The following were assessed as autoantibodies in patients with selective IgA deficiency: antinuclear antibodies (ANA), anticardiolipin antibodies Immunoglobulin (Ig) M and IgG, anti-smooth muscle antibody (ASMA), liver-kidney microsomal antibodies (LKM), antimicrosomal antibodies (AMA), rheumatoid factor (RF), extractable nuclear antigen (ENA) panel, anti-double stranded DNA (anti-dsDNA), anti-cyclic citrullinated peptide (Anti-CCP), thyroid microsome antibody (Tmab), anti-thyroglobulin (Anti-Tg), tissue transglutaminase (tTG) antibodies IgA and IgG, pancreatic islet-cell antibody, antigliadin IgA, antigliadin panel, haptoglobin, direct and indirect Coombs.

T regulatory cells phenotyping

Although CD4+ Tregs are the most well-known suppressor cell population, the specific markers for identifying Treg phenotype remain variable. CD4+ CD25+ T cells, CD4+ FoxP3+ T cells and CD4+ CD127- CD25+ T cells are all recommended by different groups for Treg phenotyping. In current study, we determined Treg cells by 3 methods; similar to Yu et al. (21). Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque centrifugation (Amersham-Pharmacia-Biotech) from whole-blood samples obtained from healthy volunteers and patients. Folllowing anbibodies were used for Treg analysis; CD3 (SK1), CD4 (SK3), CD25 (M-A251), CD127 (HL-7R-M21), FoxP3 (236A-E7) (Figure 1). Cells were fixed and permeabilized with a fixation/permeabilization kit (eBioscience) after extracellular staining, for intracellular staining. Samples were analyzed with a FACS CANTOII cytometer machine. Data were then analyzed with FlowJo 10.1r5 software.

Statistics

IBM SPSS Version 25.0 software package was used for statistical analysis. The One-Sample Kolmogorov-Smirnov test was used to determine whether the numerical values showed normal distribution. Parametrically distributed data from numerical variables were expressed as mean ± standard deviation, and non-parametrically distributed parameters were expressed as median (minimum-maximum). Categorical variables were expressed as numbers and percentages. The Chi-square test and Fisher's exact test were used to compare categorical data between the groups. The independent Student's t test was used in the comparison of numerical data with normal distribution, and the Mann-Whitney U test was used for numerical data without normal distribution. The significance level was considered $p < 0.05$.

RESULTS

Comparison of selective IgA deficiency patients and the control group

The demographic characteristics of the patients are summarized in Table 1. There was no difference between the control and patient groups in terms of age and sex distribution ($p = 0.532$ and $p = 0.512$, respectively). Upon comparison of the immunological parameters of the two groups, serum IgA levels were significantly lower in patients with sIgA deficiency as expected ($p < 0.001$). There was no difference between the two groups in terms of the rate and absolute number of Treg cells (p: 0.562 and p: 0.873) (Figure 2 and Table 1).

There was at least one autoantibody positivity in 19 (67.8%) patients with sIgA deficiency and 4 (26.7%) in the control group. The presence of autoantibodies was significantly higher in patients with sIgA deficiency than the control group (p: 0.01). The most common positive autoantibody was ANA in both groups. ANA was found to be positive in 16 (57.1%) patients and in 3 (20%) in the control group ($p = 0.019$). The second most common autoantibody was Tmab ($n = 10$; 35.7%) in patients. Table 2 shows the number and percentage of individuals tested positive for autoantibodies, as well as the comparison of the two groups.

Table 1. Comparison of demographic and immunological parameters of patients with selective IgA Deficiency with the control group

Parameters	sIgA deficiency n: 28	Control n: 15	P
Age, year, (min-max)	32 (18-64)	28 (22-49)	0.532
Gender (F/M)	16/12	7/8	0.512
IgG (g/L)	11.8±3.1	11.1±2	0.496
IgA (g/L)	0.258 (0.16-0.8)	1.62 (0.79-3.24)	**<0.001**
IgM (g/L)	1.1±0.7	1.4±0.7	0.201
IgG_1 (g/L)	8.1±1.8	7.2±1.3	0.145
IgG_2 (g/L)	2.47 (0.35-6.5)	3.24 (1.69-6.74)	0.268
IgG_3 (g/L)	0.5±0.1	0.4±0.1	0.163
IgG_4 (g/L)	0.27 (0.03-2.37)	0.52 (0.1-1.53)	0.058
Lymphocyte (/mm^3)	2160.7±662.4	2346.7±585.4	0.392
$CD3^+$ T cells, %	69.5±10.1	68.4±5.5	0.686
$CD4^+$ T cells, %	39.7±10.7	40.1±4.8	0.914
$CD8^+$ T cells, %	25.2±9.6	24.9±4.5	0.912
$CD19^+$ B cells, %	10.6±5.4	12.6±4.4	0.232
$CD16/56^+$ NKs, %	7.5±4.6	7±2.8	0.689
$CD4^+$ $CD25^+$ T cells, %	3.23±1.39	2.96±1.26	0.532
$CD4^+$ $CD25^+$ T cells (absolute count)	60.62 (32.4-132.02)	60.27 (29.21-141.90)	0.899
$CD4^+$ $FoxP3^+$ T cells, %	3.90±1.50	3.34±1.19	0.220
$CD4^+$ $FoxP3^+$ T cells, (absolute count)	83.98±41.06	76.06±26.74	0.505
$CD4^+$ CD127- $CD25^+$ T cells, %	3.67±1.40	3.37±1.86	0.562
$CD4^+$ CD127- $CD25^+$ T cells, (absolute count)	75.87±27.80	74.27±36.47	0.873

Table 2. Comparison of patients with selective IgA deficiency and the control group in terms of autoantibodies

Autoantibody	sIgA deficiency (n, %)	Control (n, %)	P
ANA	16 (57.1)	0	**<0.001**
Anti-ds DNA	1 (3.6)	0	0.459
Anticardiolipin IgM	1 (3.6)	0	0.459
Anticardiolipin IgG	0	0	-
ASMA	1 (3.6)	0	0.459
Anti-LKM	0	0	-
AMA	0	0	-
RF	1 (3.6)	0	0.459
ENA panel	2 (7.2)	0	0.289
Anti-CCP	0	0	-
Tmab	10 (35.7)	1 (6.7)	0.065
Anti-Tg ab	1 (3.6)	0	0.459
tTG IgA	1 (3.6)	0	0.459
tTG IgG	1 (3.6)	0	0.459
Pancreatic islet antibody	0	0	-
Antigliadin IgA	0	0	-
Antigliadin panel	1 (3.6)	0	0.459
Haptoglobulin	0	0	-
Direct coombs	1 (3.6)	0	0.459
Indirect coombs	0	0	-

ANA: anti-nuclear antibody, ASMA: anti smooth muscle antibody, LKM: liver kidney microsomal, AMA: anti microsomal antibody, RF: rheumatoid factor, anti-CCP: anti Cyclic citrullinated peptide, Tmab: thyroid microsomal antibody, anti-Tg ab: anti-thyroglobulin antibody, tTG: tissue trans-glutaminase,

Comparison of sIgA deficiency patients with and without autoantibodies

Patients with selective IgA deficiency were divided into two groups as autoantibody-positive and autoantibody-negative. In the group with autoantibodies, the female to male ratio was higher than the other group, but the difference was not statistically significant (2.1 vs. 0.5, p = 0.09).

Upon comparison of the immunological parameters of sIgA deficiency patients with and without autoantibodies, serum IgG and IgG1 levels were significantly higher in the autoantibody group than in the other group (p = 0.004 and p = 0.004, respectively). When we evaluated the relationship between presence of autoantibodies and Treg cell levels in patients with sIgA deficiency, the difference was not statistically significant, although both the rate and absolute number of Treg cells were lower in the autoantibody group (3.57±1.14 % vs. 3.87±1.91 %, p = 0.199 and 76.43±28.38/mm^3 vs. 74.69±28.19/mm^3, p = 0.880) (Table 3).

Table 3. Comparison of demographic and laboratory parameters of patients with selective IgA deficiency with and without autoantibody positivity

Parameter	Autoantibody (+) n: 19	Autoantibody (-) n: 9	P
Age, year, (min-max)	35.5±13.9	31.7±7.1	0.451
Gender (F/M)	13/6	3/6	0.090
IgG (g/L)	12.9±2.7	9.3±2.6	0.004
IgA (g/L)	0.33±0.15	0.36±0.18	0.563
IgM (g/L)	1.1±0.5	0.9±1.1	0.519
IgG1(g/L)	8.7±1.5	6.7±1.7	0.004
IgG2 (g/L)	3.6±2.1	2.3±0.8	0.089
IgG3 (g/L)	0.5±0.2	0.4±0.1	0.572
IgG4 (g/L)	0.5±0.6	0.2±0.1	0.238
Lymphocyte (/mm^3)	2210.5±732.4	2055.5±505.2	0.573
CD3$^+$ T cells, %	70.3±10	67.9±10.6	0.572
CD4$^+$ T cells, %	38.7±11.5	42±9.1	0.461
CD8$^+$ T cells, %	26.6±9.7	22.2±9.2	0.263
CD19$^+$ B cells, %	9.9±4.3	12.1±7.3	0.346
CD16/56$^+$ NKs, %	7.1±4.1	8.5±5.7	0.462
CD4$^+$ CD25$^+$ T cells, %	2.98±1.01	3.77±1.94	0.168
CD4$^+$ CD25$^+$ T cells (absolute count)	60.60 (32.4-132.02)	62.89 (38.08-107.12)	0.438
CD4$^+$ FoxP3$^+$ T cells, %	3.64±1.20	4.44±1.98	0.607
CD4$^+$ FoxP3$^+$ T cells, (absolute count)	83.25±47.64	85.53±24.04	0.894
CD4$^+$ CD127- CD25$^+$ T cells, %	3.57±1.14	3.87±1.91	0.199
CD4$^+$ CD127- CD25$^+$ T cells, (absolute count)	76.43±28.38	74.69±28.19	0.880

Ig: İmmunoglobulin, CD: cluster of differentiation, NK: Natural Killer Cells, FoxP3: Forkhead box P3

Table 4. Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and presence of autoantibody

Variables	Univariants		Multivariants	
	OR (95% CI)	P value	OR (95% CI)	P value
IgG, at diagnosis, (g/dl)	1.594 (1.096-2.319)	**0.015**	1.594 (1.096-2.319)	**0.015**
IgG1, at diagnosis, (g/dl)	2.028 (1.161-3.542)	**0.013**	0.082 (0.001-4.809)	0.229
IgG3, at diagnosis, (g/dl)	3.512 (0.053-231.711)	0.557	0.001 (0.001-35.400)	0.126
CD19$^+$ B cells, %	0.930 (0.801-1.080)	0.340	0.905 (0.757-1.082)	0.273
CD4$^+$CD25$^+$T cells, %	0.653 (0.344-1.242)	0.194	0.547 (0.215-1.395)	0.207
CD4$^+$ FoxP3$^+$ T cells, %	0.699 (0.398-1.228)	0.213	0.208 (0.032-1.340)	0.099

Ig: İmmunoglobulin, CD: cluster of differentiation, NK: Natural Killer Cells, FoxP3: Forkhead box P3

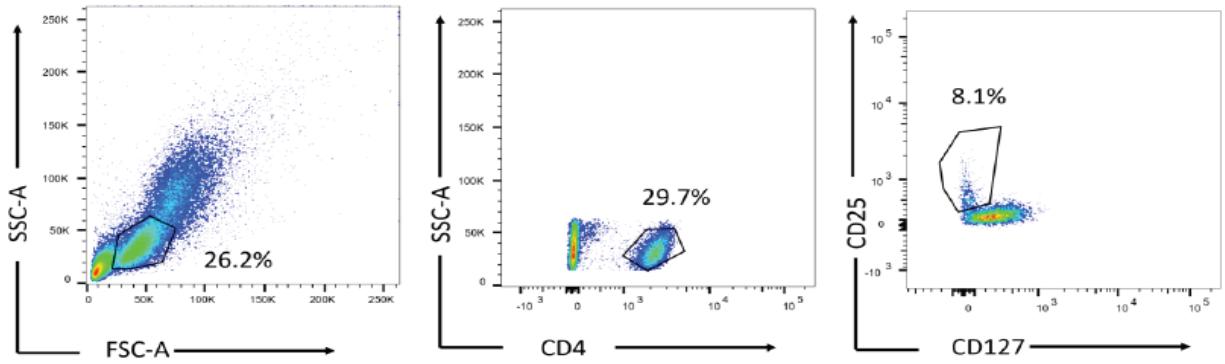

Figure 1. Gating of $CD4^+$ $CD127^-$ $CD25^+$ T cells

Factors affecting the presence of autoantibodies
A univariate regression analysis revealed that the IgG level (odds ratio, OR: 1.594, 95% confidence interval, CI: 1.096-2.319, P: 0.015) and IgG1 level (OR = 2.028, 95% CI: 1.161-3.542, P: 0.013) were significantly associated with the presence of autoantibodies (Table 4). A multivariate regression analysis showed that the IgG level (OR = 1.594, 95% CI: 1.096-2.319, P: 0.015) was also an independent predictor for the presence of autoantibodies (Table 4).

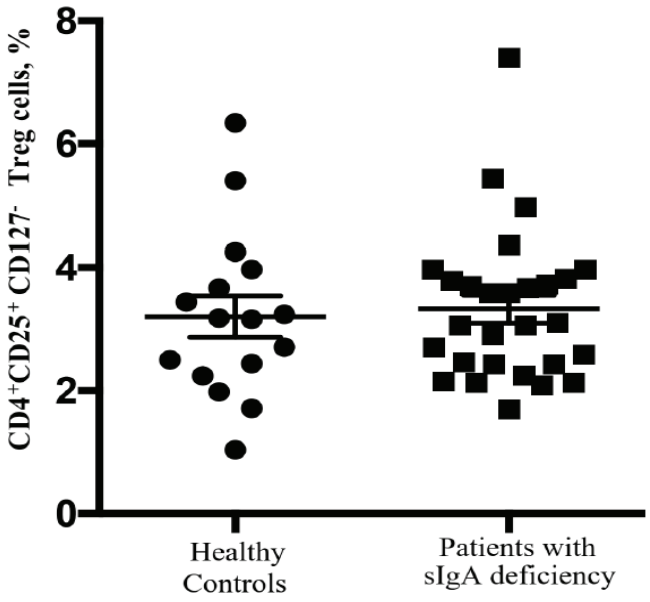

Figure 2. Comparison of $CD4^+$ $CD127^-$ $CD25^+$ T cells of patients with selective IgA deficiency and healty controls

DISCUSSION

In this study, we aimed to compare Treg cell levels in adult patients diagnosed with sIgA deficiency with healthy control group and to investigate the relationship between Treg ratio and presence of autoantibodies. There is only a study showing that Treg cell rates are lower in children with selective IgA deficiency than in healthy children (19). However, there are no studies in the literature on adult sIgA deficient patients diagnosed with more autoimmune complications and comorbidities. In this respect, this is the first study on this subject.

In current study, Treg cell ratio in the patients and the control group were similar. Although patients with positive autoantibodies tend to have higher lymphocyte counts, the ratio and absolute numbers of Treg cell were lower in the patients with autoantibodies than the patients without autoantibodies.

A strong correlation has been reported between autoimmune diseases and sIgA deficiency in several studies (3,22). Two thirds of our patients had tested for positivity of autoantibodies. It is not possible to predict how many of these patients will develop an autoimmune disease over time as an autoimmune disease cannot be diagnosed only with autoantibody positivity. Autoantibodies may also be positive before the onset of disease symptoms, but the clinical evidence of the presence of autoantibodies need to be monitored (14,15). In the literature, the rate of detection of autoimmunity in patients with sIgA deficiency is reported as 7-36% (23). In our study, at least one autoantibody was detected in 19 (67.8%) patients and 4 (26.7%) individuals in the control group.

A study by Soheili et al. is the most comprehensive study evaluating the Treg cells in pediatric sIgA deficient patients (19). In their study, 26 children with sIgA deficiency (age 4-17) were compared with 26 age matched healthy controls and 26 immune thrombocytopenia patients with normal immune systems. The ratio of Treg cells was found to be significantly lower in patients than controls (2.93±1.3 vs. 4.08±0.86, p: 0.003). Treg cell levels do not have an accepted standard value. Therefore, the authors regarded 2.36% as the limit, one of the two lower values of standard deviation of the mean Treg cell value in the control group, and divided the children with sIgA deficiency into two groups above and below this value to compare the two groups in terms of the frequency of autoimmunity (G1 group Treg < 2.36%, 16 patients; G2 group Treg > 2.36%, 10 patients). They detected autoimmunity in 9 (53.6%) patients in the G1 group and 1 patient in the G2 group (p: 0.034).(19) In our study, this method could not be applied

since there was no significant difference between the rate and level of Treg cells between control group and sIgA deficient patients.

We continued our analysis by dividing our patient group into two groups: those with and without autoantibodies. None of our patients had clinically diagnosed autoimmunity. Our hypothesis at the beginning of the study was to determine a lower level of Treg cells in patients with sIgA deficiency and autoantibody positivity since Treg cells are one of the most important inhibitors of autoreactivity (17). As expected, the Treg cell rate was found to be lower in sIgA deficient patients with autoantibodies compared to the group without autoantibodies, but the difference was not significant. This may be caused by our small number of patients. In addition, Treg levels may not be affected as these patients had not yet developed autoimmunity. Unlike children, environmental factors play a critical role in the development of autoimmunity in the adult group (24). In addition to the presence of autoantibodies, environmental factors are considered to affect Treg rates and autoimmunity. In order to shed light on this issue, further studies are required to evaluate more patients with sIgA deficiency who have been diagnosed with autoimmunity both clinically and in the laboratory.

Mean serum IgG and IgG1 values, which are among the other immunological parameters we evaluated, were higher in sIgA deficient patients with autoantibodies than those without autoantibodies. The high level of autoantibodies in autoimmune diseases is mainly found in the IgG structure (25). Four subgroups of IgG have been identified with different physical and biological properties (26). Among these, IgG4 has been associated more with autoimmune diseases and in 2010, a new clinical entity was identified under the title of IgG4-related diseases (27). The serum IgG1 level is one of the subgroups that constitutes total IgG and has the highest percentage (28). In our study, since there was no difference between the other subgroups (IgG2, G3 and G4), we can infer that IgG1 was the subgroup responsible for the difference between IgG levels. In a study of serum IgG and subgroups of autoimmune diseases, 102 Sjögren syndrome, 102 systemic sclerosis, 100 SLE and 59 primary biliary cirrhosis patients and 40 healthy controls were evaluated and serum IgG, IgG1 and IgG3 levels were significantly higher than control group (25). Similar to this study, in our study, serum IgG and IgG1 levels were higher in sIgA patients with autoantibodies compared to the group without autoantibodies; however, no difference was found between serum IgG4 levels.

Zhang et al. showed that IgG1 and IgG3 levels were elevated in patients with autoimmune disease compared to healthy individuals (25). In a similar study, Lin et al. showed that IgG1, IgG2 and IgG3 levels were elevated and IgG4 levels were similar in SLE patients compared to the control group (29). In the present study, only elevated IgG levels were found to be independent risk factors for the presence of autoantibodies in patients with selective IgA deficiency. Treg cell numbers and percentages were not risk factors for the presence of autoantibodies.

In our country, there is no large-scale study investigating ANA positivity in healthy individuals. In a population-based study with 3608 participants in the United States, ANA was positive in 15% of the participants (30).

In a study conducted in Turkey in 2009, in which autoantibody positivity was assessed in 60 children with sIgA deficiency, ANA was positive in 23.3% of the patients. In clinical and laboratory evaluations of these patients in terms of autoimmune diseases, none of the patients were diagnosed with autoimmune diseases (15). In our study, autoantibody positivity may have been higher since only adult patients were assessed and autoimmune diseases are more prevalent in adults. However, particularly patients in our study with autoantibody positivity should be clinically evaluated by relevant departments in accordance with their autoantibodies.

The number of control group caused by the small number and not equal to the number of patients. This may be a limitation of our study.

CONCLUSION

In conclusion, in this study, we compared the ratio and number of Treg cells in adult sIgA deficiency patients and the control group, and did not show a difference between the two groups. We found that the ratio and number of Treg cells were lower in adult sIgA patients with autoantibodies compared to those without autoantibodies, although not statistically significant. The findings of our study are important as they are the first evaluation in adult sIgA deficient patients. Further studies are required to shed light on this issue in order to evaluate more patients with sIgA deficiency with autoimmunity both clinically and in the laboratory.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: The study was approved by Necmettin Erbakan University, Scientific Research Projects Coordinator with project number 181518013.

Ethical approval: The study protocol was approved by the Ethics committee of the Necmettin Erbakan University, Faculty of Medicine.

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