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Original Article

Detailed features of hematological involvement and medication-induced cytopenia in systemic lupus erythematosus patients: single center results of 221 patients

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Abstract

Objective: Systemic lupus erythematosus (SLE) may affect a number of systems, with the hematological system being one of the most common. Our aim is to determine the existence of cytopenia at diagnosis or during follow-up of our SLE patients as well as the associated factors.

Material and Methods: A cohort of SLE patients that had been followed-up in the Department of Rheumotology from 1998 to 2015 was retrospectively assessed. Clinical and laboratory findings about the patients were recorded.

Results: Out of 221 patients composing the cohort, cytopenia was already present in 83.3% (n=184) at the time of diagnosis. Anemia was detected in 56.1% (n=124), leukopenia in 28.9% (n=64), lymphopenia in 76% (n=168), neutropenia in 4.5% (n=10), and thrombocytopenia in 17.2% (n=38) of patients. The proportion of patients with cumulative cytopenia was 90% (n=199). Cumulative cytopenia was disease-related in 83.4% (n=166) and medication-related in 16.6% (n=33) of the patients. In cases of drug-induced cytopenia, azathioprine was the most frequently prescribed drug. In patients with cytopenia at the time of diagnosis, erythrocyte sedimentation rates (ESR) were higher, C3 and C4 hypocomplementemia was more prevalent, and they were positive for anti-ds-DNA at a greater proportion ($p<0.001$, $p=0.015$, $p=0.028$, and $p=0.019$, respectively). Moreover, photosensitivity, renal involvement, and antiphospholipid syndrome (APS) were detected more frequently in patients with cytopenia at the time of diagnosis. There was no difference between the two patient sets in terms of other organ involvement ($p>0.05$).

Conclusion: The most common hematological disorders in SLE patients are lymphopenia and anemia, and patients must be further examined for APS and renal involvement if they suffer cytopenia.

Keywords: Anemia, blood cells, leukopenia, lupus erythematosus, systemic, thrombocytopenia

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease mostly affecting young women with several manifestations on the human body including skin, joints, kidneys, nervous system, and serous membranes (1). In a majority of SLE patients, hematological abnormalities including anemia, thrombocytopenia, and leukopenia may develop during the course of the disease with varying incidence rates among societies. Hematological involvement can already exist at the time of diagnosis or it may occur afterwards, induced by the disease or medication (2-4).

Our aim was to determine the incidence and causes of cytopenia that occur at diagnosis or during follow-up of SLE, and to reveal any correlation of cytopenia with clinical findings and abnormal laboratory test results related to the disease.

Material and Methods

This study enrolled a SLE cohort composed of patients who were followed-up at the Rheumotology Department from January 1998 to December 2015. Patients were retrospectively assessed as they were diagnosed with SLE based on the 1997 revised American College of Rheumatology (ACR) criteria (5). Demographic data, clinical findings, organ involvement, serological test results (for ANA, anti-ds-DNA, anti-Sm, anti-RNP, anti-Ro, and anti-La), complement levels, antiphospholipid antibodies (IgG and IgM anticardiolipin, lupus anticoagulant) detailed hematological testing, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels at the time of diagnosis, immunosuppressive agents including corticosteroids that patients

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may have taken during the entire follow-up, and presence of cumulative antiphospholipid syndrome (APS) (as diagnosed according to the 2006 Sapporo criteria) (6) were recorded as obtained from the patient files and electronic registry system.

Hematological involvement was classified such that a hemoglobin count of <13gr/dL in males and <12gr/dL in females was considered as anemia, and likewise, a leukocyte count of <4000/mm^3 as leukopenia, an absolute lymphocyte count of <1500/mm^3 as lymphopenia, an absolute neutrophil count of <1500/mm^3 as neutropenia, and a platelet count of <100000/mm^3 as thrombocytopenia. In a separate assessment, thrombocytopenia was also assumed for a platelet count of <150000/mm^3. Results of ferritin and direct Coombs' tests are saved for anemic patients. Either anemia, leukopenia, lymphopenia, neutropenia, or thrombocytopenia, if present, were considered as cytopenia. Our cohort was evaluated in terms of cytopenia in 2 different ways: existence of cytopenia at the time of diagnosis (d-cytopenia); and existence of cytopenia at diagnosis or at any time thereafter during follow-up (cumulative cytopenia, i.e., c-cytopenia). Drug- or disease-induced cytopenia were differentiated based on bone marrow aspiration/biopsy and on whether there was a response or not to the change of medication. Organ involvement was assessed based on the ACR classification criteria.

ANA testing was conducted by the indirect immunofluorescence method, and a result >1/160 was taken as positive. Immunoblotting assay was performed to detect anti-Sm, anti-RNP, anti-Ro, and anti-La antibodies. Anti-ds-DNA, and IgM and IgG anticardiolipin immunoglobulins were tested by the ELISA method, lupus anticoagulant was screened by functional coagulation test and complement levels were tested by the nephelometric method. Patients were assessed every 2-4 weeks if they suffered any serious organ involvement and every 1-3 months in there was no serious involvement. Anti-ds-DNA and complement levels were determined at the time of diagnosis, in the event of a suspected exacerbation, and every 6 months if the patient reported no problems. The approval of the local ethics committee was obtained for the study. Written informed consent was obtained from the patients who participated in this study.

Statistical Analysis

Statistical Packages for Social Sciences (SPSS) for Windows version 22.0 (IBM Corp.; Armonk, NY, USA) was used for the statistical analysis of the results. Within a confidence interval of 95%, a value of $p<0.05$ was accepted as statistically significant. Measurement variables are presented as mean±SD (standard deviation). Normality assumptions were evaluated by the Shapiro Wilk test. Parametric tests were conducted for normally distributed data, and non-parametric tests were conducted for non-normally distributed data. Non-normally distributed data is presented as the median and the 25-75th percentile. Independent samples t test and Mann Whitney U test were used for the comparison of two independent groups. Chi-square test was employed to conduct analyses of cross tables. The binary logistic regression model was applied in order to identify multiple independent risk factors for the dependent variables d-cytopenia, c-cytopenia, anemia at the time of diagnosis, leukopenia, lymphopenia, neutropenia, and thrombocytopenia.

Results

Out of 221 patients included in this study, 95.5% (n=211) were female, and the average age of the patient group was 41.7±13.5 (18-73) years. Most common symptoms at admission were arthralgia in 22.1% (n=49) and malar rash in 12.7% (n=28). Cytopenia was diagnosed on 16.2% (n=32) of the patients, and 33% (n=12) of the cytopenia cases were due to immune thrombocytopenia (ITP). Demographic features and organ involvement in the patients are given in Table 1 and their hematological and immunological data are shown in Table 2.

Table 1. Demographic features and organ involvements of SLE patients

	All patients
N	221
Age, mean±SD, year	41.7±13.5 (18-73)
Sex, female, n,%	211 (95.5)
Age at onset disease, mean±SD, year (range)	32.7±12.9 (10-70)
Age at the diagnosis of SLE, mean±SD, year (range)	32.5±13.1 (10-70)
Follow-up period, mean±SD, year (range)	7.01±5.3 (1-31)
Disease duration, mean±SD, year (range)	8.1±6.2 (1-33)
Antiphospholipid syndrome,n,%	57 (25.8)
Organ involvements, n, (%)	
Hematological involvement	184 (83,2)
Malar rash	74 (33.5)
Discoid rash	13 (5.9)
Alopecia	16 (7.2)
Oral ulcers	34 (15.4)
Photosensitivity	84 (38)
Joint involvement	68 (30.8)
Serositis	21 (9.5)
Pericarditis	12 (5.4)
Pleuritis	11 (5)
Fever	10 (4.5)
Neurologic involvement	20, %9
Cutaneous vasculitis	11 (5)
Renal involvement	55 (24.9)

SD: standard deviation

d-Cytopenia Features

Cytopenia was already present in 83.3% (n=184) of patients at the time of diagnosis. Among them, anemia was detected in 56.1% (n=124), leukopenia in 28.9% (n=64), lymphopenia in 76% (n=168), neutropenia in 4.5% (n=10), and thrombocytopenia with <100000/mm^3 in 17.2% (n=38) of patients. Our search for the etiology of anemia revealed that 60.5% of the anemic patients suffered anemia of chronic disease (A-CD), while 29% had hemolytic anemia and were positive for the direct Coombs' test. In terms of morphology, 35.5% (n=44) had hypochromic microcytic anemia, 62.1% (n=77) had normochromic normocytic anemia, and 2.4% (n=3) had macrocytic anemia. Table 3 shows the characteristics of the SLE patients who presented cytopenia at diagnosis.

c-Cytopenia Features

Cytopenia also developed in our SLE patients after the time of diagnosis, i.e., during the follow-up period, reaching up to a cumulative incidence of 90% (n=199). Cumulatively, anemia was detected in 66.5% (n=147), leukopenia in 48% (n=106), lymphopenia in 79.2% (n=175), neutropenia in 10% (n=22), and thrombocytopenia with <100000/mm^3 in 34% (n=76) of patients. Cumulative cytopenia was disease-related in 83.4% (n=166) and drug-related in 16.6% (n=33) of the patients. In drug-induced cytopenia, the drugs prescribed were azathioprine in 66.7% (n=22), methotrexate in 15.2% (n=5), cyclophosphamide in 9.1% (n=3), and mycophenolate mofetil in 9.1% (n=3) of patients.

The most common involvement in SLE patients was hematological, in 83.2% (n=184) of patients, followed by photosensitivity in 38% (n=84) of patients. Furthermore, renal involvement was detected in 24.9% (n=55) of patients.

In order to understand any differences, we assessed patients according to presentation of cytopenia at diagnosis, and patients who

Table 2. Hematological and immunological laboratory findings of SLE patients at the time of diagnosis

	All patients
N	221
At diagnosis Hb g/dL	11.3±1.9 (5.5-16)
MCV mean±SD/fL	84±6.8 (62-102)
WBC mean±SD/mm^3	5601±2280 (700-12500)
ALC mean±SD/mm^3	1310±916 (100-8800)
ANC mean±SD/mm^3	3703±1899 (200-10500)
Plt mean±SD/mm^3	212000±103933 (3000-659000)
CRP mean±SD, mg/dL	0.973±2.03 (0.04-15.2)
ESR mean±SD, mm/h	47.6±33.4 (2-140)
ANA positivity, n,%	220 (99.5)
Anti-ds-DNA positivity, n,%	191 (86.4)
Sm positivity, n,%	21 (9.5)
Anti-Ro positivity, n,%	31 (14)
Anti-La positivity, n,%	20 (9)
Anti-RNP positivity, n,%	24 (10.9)
C3 hypocopmlementemia,n,%	109 (49.3)
C4 hypocomplementemia,n,%	105 (47.5)
LA positivity n,%	43 (19.5)
ACA-IgG positivity, n,%	34 (15.4)
ACA-IgM positivity, n,%	13 (5.9)

Hb: hemoglobin; MCV: mean corpuscular volume; WBC: white blood cell; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; Plt: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: anti-nuclear antibody; Sm: smith antbody; ACA: anticardiolipin; LA. lupus anticoagulant

Table 3. Features of cytopenia in SLE patient with cytopenia at diagnosis

Cytopenia at the time of diagnosis	n, (%)
Cytopenia	184 (83.2)
Anemia	124 (56.1)
ACD	75 (60.5)
AIHA	36 (29)
DC negative HA	1 (0.8)
IDA	11 (8.9)
Thalasemi minor	1 (0.8)
Leukopenia <4000/mm^3	64 (28.9)
Lymphopenia <1500/mm^3	168 (76)
Neutropenia <1500/mm^3	10 (4.5)
Thrombocytopenia <150000/mm3	58 (26.2)
Thrombocytopenia <100000/mm3	38 (17.2)

ACD: anemia of chronic disease; AIHA: autoimmune hemolytic anemia; DC: direct coombs; HA: hemolytic anemia; IDA: iron deficiency anemia

Table 4. Variances in laboratory results between patients with and without cytopenia at the time of diagnosis

	Patients with cytopenia	Patients without cytopenia	p
N	184	37	
Age	41 (31-51)*	42 (32-51)*	0.647
Sex, female	178, 96.7%	33, 89.2%	0.06
Diagnosis age	30 (21-41)*	33 (24-43)*	0.301
At diagnosis Hb g/dl	11.3±1.9 (10-12.3)*	12.8 (12.1-13.4)*	<0.001
MCV/fL	84.2±6.8 (78.9-88.6)	85.9 (82.1-88.5)*	0.139
WBC/mm^3	5000 (3637-6400)*	6800 (5850-8050)*	<0.001
ALC/mm^3	1000 (800-1300)*	2000 (1800-2150)*	<0.001
ANC/mm^3	3200 (2100-4450)*	4000 (3100-4950)*	0.04
Plt/mm^3	205500 (135000-272000)*	271000 (237000-316500)*	<0.001
CRP mg/dL	0.319 (0.20-0.70)*	0.319 (0.10-1.02)*	0.770
ESR mm/h	45 (21-77)*	21 (9-44.5)*	<0.001
C3 hypocomplementemia, %	98, 53.3%	11, 29.7%	0.015
C4 hypocomplementemia %	94, 51.1%	11, 29.7%	0.028
Anemia, n,%	124, 56.1%	-	
Leukopenia, n, %	64, 28.9%	-	
Lymphopenia,n, %<1500/mm^3	168, 76%	-	
Neutropenia, n, %, <1500/mm^3	10, 4.5%	-	
Thrombocytopenia, n, %, <150000/mm^3	58, 26.2%	-	
Thrombocytopenia, n, %, <100000/mm^3	38, 17.2%	-	
ANA positivity	183, 99.5%	37, 100%	>0.05
Anti-ds-DNA positivity	164, 89.1%	27, 73%	0.019
Sm positivity	20, 10.9%	1, 2.7%	0.214
Anti-Ro positivity	26, 14.1%	5, 13.5%	>0.05
Anti-La positivity	17, 9.2%	3, 8.1%	>0.05
Anti-RNP positivity	21, 11.4%	3, 8.1%	0.774
LA positivity	39, 21.2%	4, 10.8%	0.219
ACA-IgG positivity	33, 17.9%	1, 2.7%	0.036
ACA-IgM positivity	13, 7.1%	0	0.132

Hb: hemoglobin; MCV: mean corpuscular volume; WBC: white blood cell; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; Plt: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: anti-nuclear antibody; Sm: smith antbody; ACA: anticardiolipin

were cytopenic at the time of diagnosis (Table 4) showed a significantly higher ESR (p<0.001), significantly more C3 and C4 hypocomplementemia (p=0.015 and p=0.028), significantly greater number of positive anti-ds-DNA tests (p=0.019), and significantly higher ACA-IgG (p=0.036).

Upon comparison of patients with and without cytopenia at the time of diagnosis, it was observed a significantly higher incidence of photosensitivity, renal involvement and APS in patients with cytopenia at diagnosis (p=0.039, p=0.017, and p=0.007, respectively). There was no difference between the two patient sets in terms of other organ involvements (p>0.05).

After evaluating the patients regarding the medical treatment they had received throughout the follow-up, it was found that the most frequently used drugs by the 221 patients were: hydrochloroquine, the most prescribed, with a proportion of 97.3% (n=215); steroids, which were used by 70.6% (n=156); azathioprine, used by 49.3% (n=109); cyclophosphamide, used by 21.7% (n=48); mycophenolate mofetil, used by 9% (n=20); and lastly, methotrexate, used by 7.2% (n=16).

When cumulative cytopenia periods of our patients have been reviewed 128 patients with autoimmune hemolytic anemia (AIHA), thrombocytopenia, leukopenia, or neutrope-

Table 5. Independent risk factors for cytopenia (anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia) at diagnosis and for c-cytopenia

Hematological abnormality	Laboratory findings and organ involvement	OR	95% CI	p*
Cytopenia at the time of diagnosis	Female sex	6.15	1.22-30.79	0.027
	APS	6.87	1.72-27.37	0.006
	Photosensitivity	2.55	1.03-6.34	0.043
	Renal involvement	4.83	1.30-17.96	0.019
	ESR at the time of diagnosis	1.02	1.00-1.03	0.004
Anemia at the time of diagnosis	ESR at the time of diagnosis	1.03	1.02-1.04	<0.001
	C3 hypocomplementemia	2.05	1.92-9.44	0.028
	Leukopenia at the time of diagnosis	4.26	1.07-3.92	<0.001
Leukopenia at the time of diagnosis	Anemia at the time of diagnosis	4.65	2.23-9.71	<0.001
	C4 hypocomplementemia	2.34	1.22-4.47	0.010
Lymphopenia at the time of diagnosis	Anti-ds-DNA	2.68	1.10-6.55	0.030
	Leukopenia at the time of diagnosis	8.7	1.97-38.34	0.004
	C3 hypocomplementemia	2.24	1.08-4.67	0.030
	Anemia at the time of diagnosis	2.78	1.34-5.78	0.006
Thrombocytoepnia at the time of diagnosis	ESR at the time of diagnosis	1.02	1.01-1.03	<0.001
Cumulative cytopenia	APS	8.60	1.06-69.69	0.044
	Photosensitivity	4.84	1.23-19.05	0.024
	ESR at the time of diagnosis	1.02	1.00-1.05	0.015
	C4 hypocomplementemia	5.41	1.41-20.66	0.015
	Anti-ds-DNA	4.70	1.53-14.35	0.007

*Binary logistic regression
APS: antiphospholipid syndrome; ESR: erythrocyte sedimentation rate

nia received treatment for cytopenia, except patients with isolated lymphopenia as its own existance did not constitute an indication for treatment. Persistent hematological abnormalities required treatment. Consequently, the following treatments were administered and the corresponding responses were obtained: recovery was achieved by corticosteroids in 16.4% (n=21) of patients, by corticosteroids plus azathioprine and cyclophosphamide in 35.9% (n=46) of patients, by reduction of the immunosuppressive dosage in 18.8% (n=24), and by rituximab in 1.6% (n=2); discontinuation of drugs in 5.5% (n=7), and splenectomy in 3.1% (n=4) of patients were required for recovery. Finally, 14.8% (n=19) of patients recovered spontaneously, whereas no recovery was attained in 3.9% (n=5) of the patients despite the administered treatment.

Anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia at the time of diagnosis were not found to be related to other organ involvement by SLE. Regarding the presence of cytopenia at the time of diagnosis, independent risk factors were identified as being female, elevated ESR and existence of APS, photosensitivity, renal involvement; anemia and decreased C4 were identified as independent risk factors for leukopenia at the time of diagnosis; independent risk factors for lymphopenia at diagnosis were being positive for anti-ds-DNA, reduced C3 levels, and existence of anemia and leukopenia; for anemia, independent risk factors were elevated ESR, decreased C3 levels, and presentation of leukopenia; finally, the only independent risk factor for thrombocytopenia was elevated ESR. No independent risk factors were identified for neutropenia at the time of diagnosis. APS presentation, photosensitivity and elevated ESR at the time of diagnosis, as well as decreased C4 levels and being positive for anti-ds-DNA were identified as independent risk factors for cumulative cytopenia. (Independent risk factors for each of the dependent variables are given in Table 5).

Discussion

Hematological involvement may already exist at the time of SLE diagnosis or it may develop subsequently induced by the disease or drugs (2-4). The most frequent hematological involvement suffered by the patients at the time of diagnosis were lymphopenia and anemia.

Leukopenia has been reported in the literature in about 22%-41.8% of SLE patients, oftentimes at the time of diagnosis and in treatment-naïve patients. Leukopenia may be triggered by either or both lymphopenia and neutropenia. Lymphopenia and neutropenia occur with a prevalence of approximately 15%-82% and 20%-40%, respectively (7, 8). Although thrombocytopenia with < of 100000/mm^3 may appear in 10%-25% of SLE patients, thrombocytopenia may, like anemia, result from a number of immune (antiplatelet antibodies, anti-thrombopoietin antibodies, antiphospholipid antibodies, etc.) and non-immune (drug-induced bone marrow suppression, infection, etc.) causes (7, 9). Among the patients composing our SLE cohort, we determined the proportion of leukopenia at diagnosis as 28.9%, a figure remaining within the range described in the literature, and the proportion of leukopenia when the cumulative cytopenia period is taken into account was 48%. Lymphopenia was present in 76% of our patients when they were diagnosed with SLE. Thrombocytopenia at diagnosis was comparable to the figure mentioned in the literature, existing in 17.2% of patients. The frequency of neutropenia at diagnosis, on the other hand, was 4.5% and lower than in other studies. The discrepancy may arise from the racial difference of our study population compared to the population of other studies.

There are a plethora of diverse causes underpinning anemia development in SLE patients, including non-immune and immune causes (AIHA, pure red cell aplasia, etc.). ACD and anemia related to chronic renal failure stand for the most common non-immune etiologies (7). SLE patients may already have anemia at the time of diagnosis at varying proportions from 63% to 89% (10-14). In our SLE patients, anemia was present in 56.1% at the time of diagnosis and the most frequent cause was inflammation-related ACD in 60.5%, followed by hemolytic anemia (detected by a positive direct Coombs' test) and iron deficiency anemia. In line with literature data, the most common reason for anemia in our cohort was ACD, a non-immune cause. The percentage of AIHA reported in the literature ranges around 10%-28% (11, 13), and 29% of our patients was affected by AIHA, in a similar manner to the available data.

Contrary to the literature, we have determined no correlation beetwen the hematological alterations and the organ involvement in our patient with SLE. When the comparison was made for positive autoantibody results, anti-ds-DNA and ACA-IgG were significantly higher in cytopenic patients. We determined a significantly higher occurrence of photosensitivity, renal involvement, and APS in patients with cytopenia at diagnosis with respect to those with no cytopenia at that time. APS, photosensitivity, and elevated ESR at the time of diagnosis were independent factors for both cytopenia at the time of diagnosis and cumulative cytopenia, while being female and renal involvement were identified as independent risk factors for cytopenia at the time of diagnosis; C4 hypocomplementemia and being positive for anti-ds-DNA represent the independent risk factors for cumulative cytopenia. In SLE patients with cytopenia, a closer follow-up should be maintained regarding development of cytopenia and the frequency of complete blood count (CBC) testing should be improved in case they present with C3 and C4 hypocomplementemia, elevated ESR, positive anti-ds-DNA, photosensitivity, and APS.

Leukopenia may also be a predictor for being anti-ds-DNA positive, a component of the SLE diagnostic criteria (4). Similarly, our patients with cytopenia at diagnosis were significantly found to be positive for anti-ds-DNA more frequently. This result suggests the possibility to predict a positive result for anti-ds-DNA in SLE patients who were detected to be cytopenic at the time of diagnosis. Thus, ordering anti-ds-DNA testing together with ANA in patients who attend outpatient departments of internal diseases or hematology due to leukopenia and lymphopenia would be guiding in the diagnosis of SLE.

As well as it may exist at the time of diagnosis in SLE patients, cytopenia may also be related to the medications used during the follow-up or to the disease itself. In the study by Rabbani et al., including 198 SLE patients, the three most frequently used immunosuppressive agents were steroid, azathioprine, and cyclophosphamide with percentages of 90%, 41%, and 14%, respectively (2). Similarly, Pego-Reigosa et al. (3) have specified that among immunosuppressive drugs, they have used corticosteroids in 84.6% and azathioprine in 31.2% of 3658 SLE patients. The most widely used immunosuppressive medications in our study rank in a similar manner as the data in the literature, namely, corticosteroid in 70.6% followed by azathioprine in 49.3% of SLE patients.

Assessment of cytopenia in SLE patients requires repeated CBC tests. In the event that cytopenia is detected, a detailed anamnesis should be obtained for past medication history, particularly in patients who have been followed-up. In SLE, the drugs that most often cause drug-related cytopenia are cyclophosphamide, azathioprine, and methotrexate (7). Cytopenia also developed during the follow-up of our patients, and taken cumulatively, cytopenia was diagnosed in 90% of our cohort throughout the entire follow-up, including the diagnosis. Cumulative cytopenia was disease-related in 83.4% and drug-related in 16.6% of the patients. In cases of disease-related cytopenia, the most widely used and effective medications for the treatment of our cohort were combinations of corticosteroids with either azathioprine or cyclophosphamide. In drug-induced cases of cytopenia, on the other hand, azathioprine was the main drug to cause cytopenia, and methotrexate was at the second place, with proportions of 66.7% and 15.2%, respectively. The drugs that induce cytopenia in our study are included in the drug list reported in the literature as causes of drug-related cytopenia in SLE patients. However, the literature indicates that cyclophosphamide is the most frequent cause of drug-induced cytopenia, whereas in our study the drug which most frequently caused drug-induced cytopenia was azathioprine (7).

There are potential limitations to our study. We have conducted a retrospective study on the clinical and immunological characteristics of SLE patients. Differential diagnosis of leukopenia and/or thrombocytopenia were not done in all cases (peripheral blood smear, bone marrow examination, etc.).

Hematological abnormalities might be encountered in SLE patients at diagnosis or during the follow-up period. The most prevelant clinical involvement was the hematological involvement with lymphopenia and ACD being the most prominent hematological alterations. For cytopenia at the time of diagnosis, independent risk factors were identified as being female, APS, photosensitivity, renal involvement, and elevated ESR. On the other hand, APS, photosensitivity, and elevated ESR at the time of diagnosis, in addition to C4 hypocomplementemia and being positive for anti-ds-DNA represent the independent risk factors for cumulative cytopenia. In SLE patients with cytopenia, renal involvement and APS were more frequently detected as compared to non-cytopenic SLE patients, and therefore, in the event of cytopenia, affected patients should be examined for APS and be closely followed-up regarding renal involvement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Osmangazi University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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