Haematological abnormalities in systemic lupus erythematosus

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ABSTRACT

Objectives: This study was conducted to evaluate the frequency and pattern of haematological abnormalities (HA) in SLE patients at the time of diagnosis and last follow-up, and their relationship with organ involvement.
Patients and methods: This retrospective study included patients who were diagnosed and treated for SLE from 1982 to 2008 at King Khalid University hospital, Riyadh. Demographic and haematological parameters at diagnosis and the last follow-up, disease manifestations, organ involvement and clinical haematological complications were recorded. Association of HA with organ involvement was explored by multivariate analysis.
Results: A total of 624 patients (90.7% females, mean age 34.3±11.9 years) were studied. HA were present in 516 (82.7 %) patients at the time of diagnosis. Anaemia was the most frequent HA in 63.0% patients followed by lymphopenia in 40.3%, leukopenia in 30.0%, thrombocytopenia in 10.9% and autoimmune haemolytic anaemia (AIHA) in 4.6% patients. Deep vein thrombosis and pulmonary embolism were diagnosed in 7.4% and 2.6% patients respectively. After a mean follow-up of 9.3±5.3 years, 329/491 (67%) patients still had some HA present. Anaemia remained the most common abnormality (51.7% patients) followed by lymphopenia in 33.1%, and thrombocytopenia in 4.8% patients. Leukopenia was associated with oral ulcers (p=0.021) and alopecia (p=0.031), anaemia with renal disease (p=0.017), AIHA with neurological involvement (p=0.003), elevated IgG with malar rash (p=0.027), and low C3 with serositis (p=0.026).
Conclusion: HA are very common at the time of diagnosis and during follow-up in SLE, and some of these abnormalities are associated with organ damage. This information may help in better management planning of SLE patients.

Keywords: Systemic lupus erythematosus; SLE; Haematological abnormalities; Follow-up; Organ involvement.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder which can involve many organ systems of the body. It has an unpredictable course and a wide spectrum of disease manifestations, with remissions and relapses occurring over time. Most of the patients with SLE develop some haematological abnormalities or clinical complications at some point during the course of the disease. The Hopkins lupus cohort study, a prospective longitudinal study on SLE outcomes, showed that race is a major factor in predicting clinical and laboratory features of SLE[1]. This implies that presentation and course of this disease is likely to be variable in different populations due to significant genetic and environmental influences[2-4]. Although haematological abnormalities are common in SLE, their frequency varies in different populations[5]. Previous studies have concentrated on haematological abnormalities at the time of presentation or diagnosis of SLE and little is known about the prevalence of these changes after treatment and during the course of follow-up. In addition, the relationship of haematological abnormalities with various organ system involvement has not been widely studied in Arab populations. We studied the haematological abnormalities and their relationship with organ involvement in a large cohort of SLE patients and present our findings here.

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METHODS

PATIENTS AND DEFINITIONS

All patients who were diagnosed and treated for SLE in Rheumatology clinics at King Khalid University hospital (KKUH), Riyadh, Saudi Arabia, were enrolled in the study. All patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE[6,7]. This retrospective study covered a 27 year period from 1982 to 2008. Data were collected from patients' case notes and hospital electronic records. Data retrieved included haematological parameters along with demographic features, disease manifestations, organ involvement and clinical complications related to the haematological system. Clinical features, laboratory values and organ involvement were defined according to ACR classification criteria for SLE[4,6-7]. Anaemia was defined as a hemoglobin of less than 12.0 g/dl, leukopenia was defined as a white blood cell (WBC) count of less than 4×10^9/l and lymphopenia as a count of less than 1.5×10^9/l. Neutrophilia was defined as a count more than 7.5×10^9/l. Thrombocytopenia in lupus patients was defined as a platelet count of less than 100×10^9/l. Other parameters were defined according to the reference population values and are given in Table I. Haematological parameters were required to be abnormal at least on two different occasions to be included. Anaemia was grouped into all types of anaemia and AIHA separately, for comparison purposes.

TABLE I. HAEMATOLOGICAL FINDINGS AT DIAGNOSIS AND FOLLOW-UP IN 624 SLE PATIENTS

Parameter	At diagnosis No (%) (n=624)	At the last follow-up No (%) (n=491)
Anaemia	393 (63.0)	254 (51.7)§
Thrombocytopenia	68 (10.9)	23 (4.8)§
Leukopenia	188 (30.0)	80 (16.8)§
Neutrophilia	103 (16.5)‡	70 (26.9)†
Lymphopenia	141 (40.3)‡	86 (33.1)†
Raised ESR (>17)	495 (79.3)	300 (77.1)£
Low C3 (<0.83 g/l)	283 (45.4)	48 (34.5)Ψ
Low C4 (0.15 g/l)	263 (42.2)	49 (35.3)Ψ
AIHA	29 (4.6)	0 (0)
Coombs test (n=223)		
Direct +ve	80 (35.9)	13 (2.6)
Indirect +ve	6 (2.7)	
Direct & indirect +ve	13 (5.8)	
Negative	124 (55.6)	
APTT (n=408)		
Normal (<39)	256 (62.7)	
Prolonged (≥40)	152 (37.3)	
Positive ACA		
IgG	116 (49.7)¥	19 (38.8)¶
IgM	78 (33.5)¥	14 (28.6)¶
LAC (n=248)	67 (27.0)	

n=624 where not indicated in brackets, leukopenia WBC <4, anemia Hb <12, thrombocytopenia PLT <100; § = n is 476; ‡= n is 350; †= n is 260; £ n is 389; Ψ n is 139; ¥ n is 233; ¶ n is 49

CLINICAL AND LABORATORY DATA COLLECTION

The haematological parameters including Hb, total white cell count (WBC), lymphocyte count, platelet count, erythrocyte sedimentation rate (ESR), C3 and C4 complement levels along with anticardiolipin antibodies (ACA), IgG and IgM level were recorded, both at the time of initial presentation and at the time of last follow-up. Direct and indirect Coombs' test, activated partial thromboplastin time (APTT) and lupus anticoagulant (LAC) test results were also noted and were available only at the time of diagnosis.

Development of any of the clinical complications related to the haematological system during the study period were also recorded and include; deep vein thrombosis (DVT), pulmonary embolism (PE), antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura (TTP), Evans syndrome (AIHA+ITP) and Budd-Chiari syndrome.

STATISTICAL ANALYSIS

Data were analyzed by statistical software SPSS version 15. The results are presented as frequency, percentages and means ± SD. Chi square test was used to compute association(s) between haematological abnormalities and organ involvement. Haematological abnormalities present at the time of diagnosis were compared with organ involvement present either at diagnosis or developing at any time during the course of follow-up. Haematological parameters significantly associated with organ involvement in univariate analysis were further explored in multivariate analysis. A p-value of ≤ 0.05 was considered significant.

RESULTS

PATIENTS' CHARACTERISTICS AND HAEMATOLOGICAL ABNORMALITIES AT DIAGNOSIS

A total of 624 patients, 566 (90.7%) females, were

diagnosed to have SLE during the study period. The mean age of the cohort of SLE patients was 34.3±11.9 years, and the mean duration of SLE was 9.3 ± 5.3 years (range 0.3-30 years) at the time of data collection. Out of these 624 SLE patients, 516 (82.7 %) had haematological abnormalities present at the time of diagnosis (Table I). Briefly, anaemia was the most frequent of all the haematological abnormalities occurring in 393 (63.0%) patients. Leukopenia was observed in 188 (30%) patients, lymphopenia in 141 (40.3%) and thrombocytopenia in 68 (10.9%) patients. C3 and C4 hypocomplementemia was seen in 283 (45.4%) and 263 (42.2%) patients respectively. A positive Coombs' test was found in 80 (35.9%) of the 223 patients tested, and 29/624 (4.6%) patients developed autoimmune hemolytic anaemia (AIHA). APTT was prolonged in 152 (37.3%) patients, anticardiolipin antibodies ACA-IgG was elevated in 116 (49.7%) and ACA-IgM in 78 (33.5%) of the 233 SLE patients tested for this antibody. LAC was positive in 67 (27.0 %) of the 248 patients tested. DVT developed in 46 (7.4%) patients, PE in 16 (2.6%) and APS was diagnosed in 257 (41.2%) among the 624 SLE patients. Ten (1.6%) patients developed TTP, 3 (0.5%) had Evans syndrome and 3 (0.5%) patients were diagnosed to have Budd-Chiari syndrome.

FINDINGS AT FOLLOW-UP

After a mean follow-up of 9.3±5.3 years (range 0.3-30 years), 491 patients had follow-up haematological data available and 329 (67%) patients still had some haematological abnormalities present. Not all the parameter data were available at the time of last follow-up. Haematological abnormalities present at the time of last follow-up are shown in Table I. Briefly, anaemia remained the most common abnormality present in 254 (51.7%) patients. Lymphopenia was present in 80 (33.1%) patients, thrombocytopenia in 23 (4.8%) and a low C3 and C4 in 35% of patients each.

ORGAN INVOLVEMENT

Different organ system involvement is presented in Table II. Of all the SLE disease manifestations summarized in this table, haematological abnormalities were the most frequent, present in 516 (82.7%) patients, followed by arthritis in 502 (80.4%) and muco-cutaneous symptoms in 401 (64.3%) patients. Lupus nephritis occurred in 299 (47.9%) patients.

ASSOCIATION OF HAEMATOLOGICAL ABNORMALITIES WITH ORGAN INVOLVEMENT

The associations between different haematological abnormalities and various organ involvement in SLE patients are given in Table III. Only those associations which were found to be significant in univariate analysis ($p < 0.05$) are shown in Table III. APS was found

TABLE II. ORGAN INVOLVEMENT IN 624 PATIENTS WITH SLE

Manifestations of SLE and organs involved	No. of patients (%)
Haematological	516 (82.7)
Malar rash	299 (47.9)
Discoid rash	110 (17.6)
Alopecia	297 (47.6)
Oral ulcer	244 (39.1)
Arthritis	502 (80.4)
Serositis	171 (27.4)
Pleuritis	99 (15.9)
Pericarditis	130 (20.8)
Renal Involvement	299 (47.9)
Neurological	172 (27.6)

TABLE III. ASSOCIATION OF HAEMATOLOGICAL ABNORMALITIES WITH ORGAN INVOLVEMENT IN UNIVARIATE ANALYSIS

Haematological abnormality	Organ involvement	P-Values
Leukopenia	Oral ulcers	0.014
	Serositis	0.028
	Alopecia	0.044
Anaemia (all types)	Renal disease	<0.001
	Serositis	0.001
	Neurological disorder	0.045
Thrombocytopenia	Arthritis	0.004
	Serositis	0.029
	Neurological disorder	0.007
Coombs' positive haemolytic anaemia	Serositis	0.010
	Neurological disorder	0.002
C3 hypocomplimentemia	Serositis	<0.001
	Renal disease	0.008
Elevated IgG	Malar rash	0.030
	Renal disease	0.001
	Photosensitivity	0.045

TABLE IV. MULTIVARIATE ANALYSIS OF ASSOCIATION BETWEEN HAEMATOLOGICAL ABNORMALITIES AND ORGAN INVOLVEMENT IN SLE PATIENTS

Haematological abnormality	Organ involvement	Odds ratio	95% Confidence interval	P-value
Leukopenia	Oral ulcers	2.035	1.111-3.726	0.021
	Alopecia	1.899	1.060-3.401	0.031
Anaemia (all types)	Renal disorder	3.282	1.237-8.705	0.017
Coombs' positive haemolytic anaemia	Neurological involvement	6.162	1.989-19.093	0.003
Low C3	Serositis	2.631	1.123-6.163	0.026
Elevated IgG	Malar rash	1.949	1.078-3.523	0.027

to be associated with adverse pregnancy outcome. There were 77 (37.5%) fetal losses (includes miscarriages, stillbirths and neonatal deaths) among 205 SLE pregnancies with APS, as compared to 37 (20.7%) pregnancy losses among 178 SLE pregnancies without APS (p= 0.0003). In multivariate analysis leukopenia was associated with oral ulcers (p=0.021) and alopecia (p=0.031), anaemia was associated with renal disease (p=0.017), AIHA with neurological involvement (p=0.003), elevated IgG with malar rash (p=0.027) and low C3 with serositis (p=0.026). Haematological abnormalities significantly associated with organ involvement in multivariate analysis along with odds ratios, 95% confidence intervals and p-values are shown in Table IV.

DISCUSSION

This study shows that haematological abnormalities are extremely common at the time of diagnosis and during the course of follow-up in our SLE population. Anaemia was the most common disorder present in 63% of patients. The etiology of anaemia in SLE is heterogeneous and may result from immune or non-immune causes[8-12]. Some of the common causes of anaemia in SLE include anaemia of chronic disease (ACD), iron deficiency anaemia (IDA), autoimmune haemolytic anaemia (AIHA) and drug-induced myelotoxicity[8-10], while some of the less common or rare causes include aplastic anaemia[13,14], TTP[15], pure red cell aplasia, pernicious anaemia, myelofibrosis and sideroblastic anaemia[16-19]. It is noteworthy that ACD often coexists with anaemia caused by other mechanisms. Iron deficiency is common in patients with SLE as a result of menorrhagia and increased gastrointestinal blood loss caused by the use of non-steroidal anti-inflammatory drugs, aspirin, and oral anticoagulants[8,9].

Among the white cell abnormalities, lymphopenia was the most common occurring in 40.3% of patients, followed by leukopenia in around 30% of patients. Thrombocytopenia, a comparatively less common occurrence in SLE, was present in around 11% of our patients. The causes of thrombocytopenia and white cell abnormalities are usually immune in nature and result from destruction of antibody coated cells[8,9,20]. Thrombocytopenia in SLE may also be due to drugs, infection and bone marrow suppression, and may be closely associated with hemolytic anaemia or a manifestation of APS[10,21,22].

Presence of haematological abnormalities during the follow-up has not been studied well. This study shows that haematological abnormalities continue to be present in a substantial number of SLE patients, even years after the diagnosis. Anaemia remained the most common disorder followed by white cell abnormalities. The most common causes of cytopenias during the course of SLE include drugs, infections and immune mediated[20]. Drugs like cyclophosphamide and azathioprine were considered to be the cause of cytopenias in a substantial number of cases in our series. Polymorphonuclear leukocytosis was also commonly found at the time of follow-up, usually related to steroid administration or infection. Hypocomplementemia also continued to be present in a significant number of patients and both C3 and C4 were found to be low in around 35 % of patients. ESR was raised in a high percentage of patients (77%) during the follow-up but it was thought to be associated with causes other than the disease activity in many of these patients.

There is variable association of haematological

abnormalities with different organ system involvement reported in the literature, likely to be due to differences in disease pattern in various ethnic groups and populations[2-4]. We chose to correlate haematological abnormalities at the time of presentation with organ involvement instead of disease activity as it is likely to be more relevant for the clinicians and easier to follow in the clinical practice. We found that patients with leukopenia were more likely to develop oral ulcers and alopecia. Anaemia predicted renal disease and AIHA was associated with neurological involvement. Patients with elevated IgG were more likely to have malar rash and low C3 was associated with serositis. Thrombocytopenia was associated with arthritis, serositis and neurological involvement in univariate analysis but no significant association was found in multivariate analysis. In some studies thrombocytopenia in SLE, particularly severe thrombocytopenia, was related to higher disease activity, end organ damage and a poorer prognosis[22-24]. Sultan *et al* found that SLE patients with severe haematological involvement were more likely to have significant disease in the renal, central nervous and general systems, but not in the other systems[25]. Jeffries *et al* reported that presence of haemolytic anaemia was associated with a subset of lupus patients characterized by more severe disease, younger age, and a higher likelihood of renal involvement, seizures, serositis and lymphopenia[26]. In our cohort, anaemia was the only factor in multivariate analysis associated with renal disease, and AIHA was not associated with renal disease but predicted neurological involvement. In contrast to other studies, Nossent and Swaak did not find any association of haemolytic anaemia with other organ involvement and these patients were also less likely to have serositis[27].

Venous thromboembolism (VTE) is one of the most common clinical complications of SLE related to the haematological system. This is usually a manifestation of antiphospholipid syndrome and important risk factors for VTE in SLE include presence of lupus anticoagulant, anticardiolipin antibodies, hereditary thrombophilia, smoking, disease activity, older age and high triglycerides[28-30]. The risk of VTE differs in SLE patients from various ethnic groups, and risk factors for VTE in SLE need to be studied in different populations[30]. As VTE is associated with a significant morbidity and mortality, it is important to evaluate the risk factors for VTE in SLE so the patients at high risk can be identified and considered for thrombo-prophylaxis.

This is one of the largest studies to report on the haematological abnormalities and their relationship with organ involvement in SLE patients. This study derives its strength from a large number of patients, long follow-up, and being the first to report on haematological abnormalities in SLE patients during the course of the disease. There are also certain limitations of this study. Apart from being retrospective in nature, some of factors influencing the haematological parameters like the effect of therapy and infections during the follow up could be recorded only in a limited manner. Further studies are needed to address these issues in a prospective manner to better define the etiology of these abnormalities.

CONCLUSION

Haematological abnormalities are present in the majority of SLE patients at the time of diagnosis and continue to be present in a substantial number of patients during the follow-up even after many years. Some of the abnormalities like anaemia, leukopenia, AIHA, elevated IgG and low C3 are associated with certain disease manifestations and organ involvement. This information may help in better management planning of SLE patients.

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REFERENCES

1. Petri M. The effect of race on incidence and clinical course in systemic lupus erythematosus: The Hopkins Lupus Cohort. J Am Med Womens Assoc 1998;53:9-12.
2. Tsao BP, Grossman JM. Genetics and systemic lupus erythematosus. Curr Rheumatol Rep 2001;3:183-190.
3. Fernández M, Alarcón GS, Calvo-Alén J, Andrade R, McGwin G Jr, Vilá LM, Reveille JD; LUMINA Study Group. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Rheum 2007;57:576-584.
4. Al Arfaj AS, Khalil N. Clinical and immunological manifestations in 624 SLE patients in Saudi Arabia. Lupus 2009;18:465--473.
5. Alarcon GS, McGwin GJr, Roseman JM, et al. Systemic lupus erythematosus in three ethnic groups. XIX. Natural history of

the accrual of the American College of Rheumatology Criteria prior to the occurrence of criteria diagnosis. Arthritis Rheum 2004;51: 609-615.
6. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-1277.
7. Hochberg MC. For the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum [letter] 1997;40:1725.
8. Giannouli S, Voulgarelis M, Ziakas PD, Tzioufas AG. Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. Ann Rheum Dis 2006;65:144-148.
9. Voulgarelis M, Kokori SI, Ioannidis JP, Tzioufas AG, Kyriaki D, Moutsopoulos HM. Anaemia in systemic lupus erythematosus: aetiological profile and the role of erythropoietin. Ann Rheum Dis 2000;59:217-222.
10. Liu H, Ozaki K, Matsuzaki Y, Abe M, Kosaka M, Saito S. Suppression of haematopoiesis by IgG autoantibodies from patients with systemic lupus erythematosus (SLE). Clin Exp Immunol 1995;100:480-485.
11. Kokori SIG, Ioannidis JPA, Tzioufas AG, Voulgarelis M, Moutsopoulos HM. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus. Am J Med 2000;108:198-204.
12. Durán S, Apte M, Alarcón GS, et al. Lumina Study Group. Features associated with, and the impact of hemolytic anemia in patients with systemic lupus erythematosus: LX, results from a multiethnic cohort. Arthritis Rheum 2008;59:1332-1340.
13. Sumimoto S, Kawai M, Kasajima Y, Hamamoto T. Aplastic anemia associated with systemic lupus erythematosus. Am J Hematol 1991;38:329-331.
14. Bailey FA, Lilly M, Bertoli LF, Ball GV. An antibody that inhibits in vitro bone marrow proliferation in a patient with systemic lupus erythematosus and aplastic anemia. Arthritis Rheum 1989;32:901-905.
15. Aleem A, Alsugair S. Thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus. Acta Haematologica 2006;115:68-73.
16. Meyer RJ,Hoffman R, Zanjani ED. Autoimmune hemolytic anemia and periodic pure red cell aplasia in systemic lupus erythematosus. Am J Med 1978;65:342-345.
17. Junca J, Cuxart A, Tural C, Marti S. Systemic lupus eythematosus and pernicious anemia in an 82-year-old woman. J Rheumatol 1991;18:1924-1925.
18. Kaelin WGJr, Spivak JL: Systemic lupus erythematosus and myelofibrosis. Am J Med 1986;81:935-938.
19. Jimenez-Balderas FJ, Morales-Polanco MR, Gutierrez L. Acute sideroblastic anemia in active systemic lupus erythematosus. Lupus 1994;3:157-159.
20. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford) 2010; 49: 2243-2254.
21. Pujol M, Ribera A, Vilardell M, Ordi J, Feliu E. High prevalence of platelet autoantibodies in patients with systemic lupus erythematosus. Br J Haematol 1995;89:137-141.
22. Zhao H, Li S, Yang R. Thrombocytopenia in patients with systemic lupus erythematosus: significant in the clinical implication and prognosis. Platelets 2010;21:380-385.
23. Fernández M, Alarcón GS, Apte M, Andrade RM, Vilá LM, Reveille JD; LUMINA Study Group. Systemic lupus erythematosus in a multiethnic US cohort: XLIII. The significance of thrombocytopenia as a prognostic factor. Arthritis Rheum 2007;56:614-621.
24. Ziakas PD, Giannouli S, Zintzaras E, Tzioufas AG, Voulgarelis M. Lupus thrombocytopenia: clinical implications and prognostic significance. Ann Rheum Dis 2005;64:1366-1369.
25. Sultan SM, Begum S, Isenberg DA. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. Rheumatology (Oxford) 2003;42:230-234.
26. Jeffries M, Hamadeh F, Aberle T, et al. Haemolytic anaemia in a multi-ethnic cohort of lupus patients: a clinical and serological perspective. Lupus 2008;17:739-743.
27. Nossent JC, Swaak AJ. Prevalence and significance of haematological abnormalities in patients with systemic lupus erythematosus. Q J Med 1991;80:605-612.
28. Calvo-Alén J, Toloza SM, Fernández M, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXV. Smoking, older age, disease activity, lupus anticoagulant, and glucocorticoid dose as risk factors for the occurrence of venous thrombosis in lupus patients. Arthritis Rheum 2005;52:2060--2068.
29. Danowski A, de Azevedo MN, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol 2009;36:1195-1199.
30. Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. Arthritis Rheum 2005;52:2774--2782.