Association between Lymphopenia and Systemic Lupus Erythematosus in Iraqi Patients

Najlaa B. Al-Awadi Sabah J. Al-Rubiae Ali S. Biae

College of Medicine- University of Babylon- Hilla- P.O. Box 473
E-mail : alyasiri1973@yahoo.com

Abstract

Aim: To determine if there is any association between lymphopenia and clinical features, disease activity and damage in systemic lupus Erythematosus (SLE).

Methods: The study group consists of 50 Iraqi patients with SLE mostly from Babylon Governorate who were diagnosed depending on the American College of Rheumatology revised criteria (ACR) for SLE; they were attending Marjan Teaching Hospital during the period from 1st Jan. 2007 to 1st Jul. 2008.

The clinical manifestations were obtained by detailed medical history and physical examination.

The disease activity was assessed with the systemic lupus erythematosus disease activity index (SLEDAI) and the Physician's Global Assessment (PGA).

The disease damage was determined with the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI).

Lymphocytes count was expressed in two categories: normal (more than 1500/cmm) and lymphopenia (less than 1500/cmm); the count of less than 500/cmm was considered as marked lymphopenia.

The relationship of lymphopenia with clinical, pharmacologic treatment variables, SLEDAI, PGA and SLICC-DI scores was examined.

Results: Lymphopenia was found to be positively associated with skin manifestations, renal involvement, serositis and the use of steroids.

Marked lymphopenia was associated with even higher SLEDAI, PGA and SLICC-DI scores.

Conclusion: Lymphopenia was associated with some clinical manifestations of SLE and with more disease activity and damage. Marked lymphopenia was associated with even higher disease activity and damage .

العلاقة بين قلة كريات الدم اللمفاوية وداء الذئب الاحمراري لدى المرضى العراقيين

الخلاصة

الهدف: دراسة العلاقة بين قلة كريات الدم اللمفاوية والسمات السريرية وفعالية المرض والضرر الناتج عنه لدى مرضى داء الذئب الاحمراري

طريقة العمل والأدوات: لقد تمت دراسة ٥٠ مريضا من العراق – محافظة بابل مصابين بداء الذئب الاحمراري ، علما أن تشخيص المرض قد تم اعتمادا على الخصائص الأحدى عشرة المعتمدة لدى الكلية الأمريكية لأمراض الروماتزم .

تم أخذ التاريخ المرضي لكل مريض بصورة مفصلة مع فحص سريري دقيق ثم تم تقييم فعالية المرض باستخدام مؤشر فعالية داء الذئب الاحمراري والتقييم الطبي الشامل ومدى الضرر الناتج عن المرض باستخدام مؤشر الضرر العالمي لعيادات داء الذئب العالمية المشتركة.

كما تم حساب عدد الكريات اللمفاوية وتصنيفها في مجموعتين ؛ الأولى تشمل المرضى الذين تزيد كرياتهم اللمفاوية على ١٥٠٠/ملم^3 أما الثانية فقد شملت المرضى الذين تقل كرياتهم عن ١٥٠٠ /ملم^3 ، علما أنه قد تم اعتبار نقص الكريات عن ٥٠٠/ملم^3 نقصا شديدا .

النتائج: تم اكتشاف علاقة مهمة بين قلة الكريات اللمفاوية والأعراض الجلدية والكلوية والتهاب الأغشية المصلية واستعمال الأدوية الستيرويدية .

كما تم اكتشاف ان هناك علاقة بين قلة الكريات اللمفاوية وزيادة فعالية المرض والضرر الناتج عنه؛ والعلاقة تكون أكبر عند المرضى ذوي النقص الشديد في الكريات اللمفاوية .

الاستنتاج: ترتبط قلة الكريات اللمفاوية ببعض السمات السريرية لداء الذئب الاحمراري وبزيادة فعالية المرض والضرر الناتج عنه.

Introduction

Lymphopenia is one of the most common clinical manifestations of SLE. Some studies had found lymphopenia in 75 % of SLE patients with active and untreated SLE and an additional 15 % of patients developed lymphopenia during the course of disease[1].

Lymphopenia occurs more frequently with increasing age and appears to be more common in men than in women[2,3].

The clinical usefulness of lymphopenia in SLE includes:

1. Lymphopenia aids the diagnosis of SLE as it is one of the hematological criteria according to the American College of Rheumatology (ACR) classification[4].
2. Lymphopenia is one of the clinical parameters to assess disease activity in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[5,6].
3. Lymphopenia may be associated with some clinical manifestations of SLE such as arthritis and neurological involvement[1].

There are some theories to explain the association between lymphopenia and SLE activity and damage:

1. T-cell apoptosis is increased in active SLE with high expression of both membrane bound and soluble Fas[7].
2. CD4+ and CD8+ T-cells that carry the CD28 molecule (the potent signal for T-cell activation) are decreased in SLE[8].
3. High titer of anti-T cells Ab are found in patients with SLE and active nephritis, especially proliferative glomeriolonephritis; specifically anti CD4 Ab is frequently found in SLE[9].
4. Anti-ribosomal protein Ab induces apoptosis of Jurkat T-cells suggesting that anti-ribosomal Ab might have a role in the pathogenesis of lymphopenia in SLE[10].
5. Another important clinical implication of lymphopenia is the possibility of predisposing to infections that are the major cause of morbidity and mortality in SLE[11,12].
6. Decreased number of T and B cells, especially CD4+ T cells and naïve B cells[13].
7. Lower levels of plasma cells free FC gamma receptor III than those with normal lymphocytes count[14].
8. Decreased number of peripheral blood dendritic cells in SLE is more common in patients with lymphopenia[15].

To further ascertain the role of lymphopenia in terms of disease manifestations, disease activity, and damage occurrence in patients with SLE we decided to carryout this study.

Methods

50 patients with SLE were taken, they were mostly from Babylon Governorate and had the diagnosis of SLE depending on the American College of Rheumatology (ACR) revised criteria for SLE classification. Those patients were attending Marjan Teaching Hospital during their first diagnosis or for follow up from 1st January 2007 to 1st July 2008.

For all patients, full medical history and thorough physical examination were done looking for signs and

symptoms of SLE or its complications (this was done by the physician); then routine laboratory tests were done [including complete blood count and film using electronic counter and Leishman's stain, blood urea and serum creatinine, total serum bilirubin and SGPT/SGOT/serum alkaline phosphatase, antinuclear antibody(ANA by agglutination test) and anti-ds DNA antibody (by agglutination test) and general urine exam for albumin and casts].

The disease activity was assessed with SLEDAI and PGA (using the attached format).

The disease damage was assessed with SLICC-DI (using the attached format).

Lymphocytes count was expressed in two groups:

1. Normal: count 1500/cmm or more.
2. Lymphopenia: count less than 1500/cmm.

Lymphocytes count less than 500 was considered as marked lymphopenia.

Results

Lymphopenia was found positively associated with skin manifestations (malar rash and photosensitivity), renal manifestations, serositis, anti–ds DNA antibodies and the use of steroids. (Table 1)

Table 1 Lymphopenia with different SLE features and therapies

The clinical feature or therapy	No. of patients having that feature	No. Of patients with lymphopenia	Normal lymphocytes count	P-value
Malar rash	15	12	3	< 0.001
Photosensitivity	10	8	2	< 0.001
Discoid rash	0	0	0	--------
Arthritis	13	7	6	0.547
Oral ulcers	4	2	2	0.794
Serositis	8	7	1	< 0.001
Neurological	5	3	2	0.204
Renal	21	16	5	< 0.001
Hemolysis	3	2	1	0.0251
Leucopenia	2	1	1	0.624
ANA	14	8	6	0.442
Anti-dsDNA Ab	10	8	2	< 0.001
Steroids	34	25	9	< 0.001
Imuran	10	6	4	0.0912
Chloroquin	4	2	2	0.794

N.B. : Significant P-value if less than 0.001

Lymphopenia was found positively associated with high SLEDAI , PGA and SLICC-DI scores. (Table 2)

Marked lymphopenia was associated with even higher SLEDAI, PGA and SLICC-DI scores. (Table 2)

Table 2 Lymphopenia with disease activity and damage .

Lymphocytes count	SLEDAI	P-value	PGA	P-value	SLICC-DI	P-value
> 1500/cmm	16.1 ± 3.8	< 0.001	0.9 ± 0.2	< 0.001	2.7 ± 0.55	< 0.001
< 1500/cmm	25.5 ± 4.9	< 0.001	1.9 ± 0.3	< 0.001	6.8 ± 0.92	< 0.001
< 500/cmm	43.4 ± 6.5	< 0.001	2.2 ± 0.6	< 0.001	8.3 ± 1.15	< 0.001

N.B. : Significant P-value of less than 0.001

Discussion

This study has shown that lymphopenia is significantly associated with renal and dermatologic manifestations and serositis.

More importantly; we found that marked lymphopenia is strongly associated with disease activity and damage .

Few studies have found similar association between clinical manifestations of SLE and lymphopenioa; in contrast, other studies have found association with arthritis, neurological manifestations and vasculitis[1,16]. Like our study; some studies have reported association with anti-dsDNA antibodies[17-19].

The association of lymphopenia with anti dsDNA antibody is particularly interesting because these autoantibodies may be lymphotoxic due to possible cross-reactivity between nuclear material and the lymphocytes membrane[20].

The association between lymphopenia and disease activity has been reported previously[9,17,21] and lymphopenia was used as a marker of SLE activity and disease flare within a year of follow up[9].

The association between lymphopenia and damage occurrence is expected for reasons :

- Lymphopenia was associated with major organ involvement e.g. renal disease .
- Lymphopenia was associated with the use of steroids and cytotoxic drugs
- Marked lymphopenia was associated with disease activity that in turn is an important predictor of damage occurrence[22].

Damage occurrence in SLE is a predictor of mortality in lupus so lymphopenia will be a predictor of decreased survival in SLE[23].

On the other hand, some limitations for our study are still present and they include:

1. Small number of patients; so larger study group is needed for future studies.
2. Lymphopenia may be secondary to drug therapy as most of our patients were previously diagnosed with SLE and on treatment; however, the use of steroids and cytotoxics is a reflection of more aggressive disease course.

References

1. Rivero S. J., Diaz-Jouanen E, Alarcon-Segovia D. Lymphopenia in systemic lupus erythematosus: clinical, diagnostic, and prognostic significance. Arthritis Rheum 1987: 21: 295-305.

2. Ward MM, Studenski S. Age associated clinical manifestations of systemic lupus erythematosus: a multivariate regression analysis. J Rheumatol 1990;17:476-81.
3. Cooper GS, Parks CG. Treadwell EL, St Clair EW, Gilkeson GS, et al. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. Lupus 2002;11:161-7.
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
5. Socher SA, Larson MG, Schur PH. Reliability and sensitivity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 2004;2;1107-18.
6. Fortin PR, Isenberg DA, Snaith L. Quantitative clinical assessment of disease activity in systemic lupus erythematosus : progress report and research agenda. Rheumatol int. 1991;11:133-6.
7. Silvestris F, Grinello D, Tucci M, Cafforio P. Enhancement of T cell apoptosis correlates with increased serum levels of soluble Fas in active lupus. Lupus 2003;12:8-14.
8. Kaneko H, Saito K, Hashimoto H. Preferential elimination of CD28+ T cells in systemic lupus erythematosus and the relation with activation-induced apoptosis. Clin Exp Immunol 1996;106:218-29.
9. Lenert G, Senecal JL. CD4-reactive antibodies in systemic lupus erythematosus. Hum Immunol 1996;49:38-48.
10. Sun KH, Tang SJ, Lin ML, Wang YS, Sun GH. Monoclonal antibodies against human ribosomal P proteins penetrates into living cells and cause apoptosis of Jurkat T cells in culture. Rheumatology 2001;40:750-6.
11. Cervera R, Khamashta MA, Font J. Morbidity and mortality in systemic lupus erythematosus during a 10 year period. Medicine 2003;82:299-308.
12. Edwards CJ, Lian TY. Hospitalization of individuals with systemic lupus erythematosus; characteristics and prediction of outcome. Lupus 2003;12:672-6.
13. Scheinberg MA, Cathcart ES. B cell and T cell lymphopenia in systemic lupus erythematosus. Cell Immunol 1974;12:309-14.
14. Hutin P, Lamour A, Pennec YL. Cell free Fc-gamma receptor III in sera from patients with systemic lupus erythematosus: correlation with clinical and pathological features. Int Arch Allergy Immunol 1994;103:23-7.
15. Robak E, Smolewski P, Wozniacka A. Clinical significance of circulating dendritic cells in patients with systemic lupus erythematosus. Mediator Inflamm 2004;13:171-80.
16. Drenkard C, Villa AR, Reyes E, Abello M, Alarcon-Segovia D. Vasculitis in systemic lupus erythematosus. Lupus 1997;6:235-42.
17. Utsinger PD. Relationship of lymphocytotoxic antibodies to lymphopenia and parameters of disease activity in systemic lupus erythematosus. J Rheumatol 1976; 3: 175-85.
18. Wenzel J, Gerdsen R, Uerlich M, Bauer R. Lymphocytopenia in lupus erythematosus: close in vivo association to autoantibodies targeting nuclear antigen. Br. J. Dermatol 2004;150:994-8.
19. Harley JB, Sestak AL, Willis LG. A model for disease heterogeneity in systemic lupus erythematosus: relationships between histocompatibility antigens, autoantibodies, and lymphopenia or renal disease. Arthritis Rheum 1989;32:826-36.

20. Shoenfeld Y, Zamir R, Joshua H. Human monoclonal anti-DNA antibodies react as lymphocytotoxic antibodies. Eur J Immunol 1985; 15:1024-8.
21. Schmidt RE, Witte T. Prognostic parameters for flare systemic lupus erythematosus. Rheumatology 2000; 39: 1316-9.
22. Alarcon GS, McGwin G Jr, Bartolucci AA, et al. Lupus in minority population, nature versus nature. Systemic lupus erythematosus in three ethnic groups. Differences in damage accrual. Arthritis Rheum 2001;44:2797-806.
23. Halberg P, Alsbjorn B, Balslev JT, et al. Systemic lupus erythematosus: follow-up study of 148 patients. Predictive factors of importance for course and outcome. Clin Rheumatol 1987;6:22-6.

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX
SELENA MODIFICATION

Physicians Global Assessment _____

0 None 1 Mild 2 Med 3 Severe

SLEDAI SCORE

Check box: If descriptor is present at the time of visit or in the proceeding 10 days

Wt	Present	Descriptor	Definition
8	□	Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8	□	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	□	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	□	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	□	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	□	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	□	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	□	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	□	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	□	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	□	Urinary Casts	Heme-granular or red blood cell casts
4	□	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	□	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	□	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	□	New Rash	New onset or recurrence of inflammatory type rash.
2	□	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	□	Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations

2	□	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	□	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	□	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	□	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	□	Fever	>38°C. Exclude infectious cause
1	□	Thrombocytopenia	<100,000 platelets/mm3
1	□	Leukopenia	<3,000 White blood cell/mm3. Exclude drug causes.

_____ TOTAL SCORE (Sum of weights next to descriptors marked present)

Mild or Moderate Flare □	**Severe Flare** □
□ Change in SLEDAI > 3 points	□ Change in SLEDAI > 12
□ New/worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ New/worse CNS-SLE Vasculius Nephritis Myositis Pk < 60.000 Home anemia: Hb <7% or decrease in Hb > 3% **Requiring:** double prednisone Prednisone>0.5 mg/kg/day hospitalization
□ Increase in Prednisone, but not to >0.5 mg/kg/day	□ Prednisone >0.5 mg/kg/day
□ Added NSAID or Plaquenil	□ New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)
□ ≥1.0 Increase in PGA, but not to more than 2.5	□ Increase in PGA to > 2.5

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus*

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 > 1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate<50%	1
Proteinuria ≥3.5 gm/24hours	1
Or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if > 1)	1(2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months, or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site)	1(2)
Venous thrombosis with swelling, ulceration, or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	1(2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if > 1)	1(2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for > 6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if > 1 site)	1(2)

*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice.