Journal of Population Therapeutics & Clinical Pharmacology

ORIGINAL ARTICLE
DOI: 10.53555/x5dxre48

"CLINICOPATHOLOGICAL CORRELATION OF HEMATOLOGIC ALTERATIONS AND TISSUE HISTOPATHOLOGY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Saima Irum[1]*, Sahar Iqbal[2], Ali Raza[3], Ikram-ul-Haq[4], Muhammad Yousif Khoso[5], Syma Arshad[6]

[1]*Assistant Professor, Department of Pathology, Azra Naheed Medical College, Superior University Lahore, Pakistan
[2]Associate Professor, Department of Pathology, Azra Naheed Medical College, Superior University Lahore, Pakistan
[3]Assistant Professor, Department of Pathology, Sahara Medical College, The Sahara University Narowal, Pakistan
[4]Associate Professor, Department of Pathology, Sahara Medical College, The Sahara University Narowal, Pakistan
[5]Assistant Professor, Department of Pathology, Al-Tibri Medical College Isra University Karachi Campus, Pakistan
[6]Associate Professor, Department of Community Medicine & Public Health, Rashid Latif Medical College Lahore, Pakistan

***Corresponding Author:** Saima Irum
*Email: Iramsaima98@gmail.com

Abstract

Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder characterized by the production of autoantibodies, immune complex deposition, and multisystem involvement. Hematological abnormalities are among the earliest and most frequent manifestations of the disease, often reflecting disease activity and severity. Understanding the relationship between peripheral hematologic alterations and underlying tissue pathology is essential for early diagnosis, prognostication, and therapeutic decision-making.

Objectives: This study aims to evaluate the clinic pathological correlation between hematologic abnormalities and tissue histopathological changes in patients with SLE. It seeks to identify specific hematologic markers associated with particular histopathologic patterns and disease activity scores.

Methodology: A prospective observational study was conducted over a period of 18 months at a tertiary care center. A total of 80 patients fulfilling the ACR/EULAR 2019 criteria for SLE were enrolled. Complete blood counts, peripheral blood smears, reticulocyte counts, and Coombs tests were performed for hematological evaluation. Bone marrow aspiration/biopsy was performed in selected cases with persistent cytopenias. Tissue biopsies (renal, skin, and lymph node) were obtained based on clinical indications. Histopathological findings were analyzed and correlated with hematologic parameters and SLE Disease Activity Index (SLEDAI) scores.

Results: Out of 80 patients, 91.3% were female with a mean age of 29.4 ± 8.2 years. Anemia was observed in 82.5% of patients (normocytic normochromic in 42.5%, microcytic hypochromic in 25%, and hemolytic in 15%). Leukopenia was noted in 47.5% and thrombocytopenia in 36.2%. Direct Coombs test was positive in 22.5% of cases. Bone marrow studies revealed erythroid hyperplasia in

hemolytic anemia, hypocellularity in aplastic presentations, and increased histiocytes in macrophage activation syndrome (MAS)-like features. Renal biopsies (performed in 35 patients) revealed class III and IV lupus nephritis in 71.4% of cases with accompanying hematologic abnormalities such as anemia and thrombocytopenia. Cutaneous biopsies showed interface dermatitis in 65% and leukocytoclastic vasculitis in 20%, correlating with leukopenia and raised ESR/CRP. Lymph node biopsies demonstrated reactive hyperplasia and, in some cases, necrotizing lymphadenitis suggestive of Kikuchi disease. Statistically significant correlations were found between anemia and lupus nephritis ($p=0.03$), leukopenia and skin involvement ($p=0.04$), and thrombocytopenia with disease activity scores >10 ($p=0.01$).

Conclusion: Hematologic abnormalities in SLE are common and exhibit a significant correlation with underlying histopathological findings in various tissues. Anemia is strongly associated with lupus nephritis, while leukopenia often reflects cutaneous vasculitic changes. Thrombocytopenia serves as a potential marker of severe disease activity. Recognizing these correlations may aid in early diagnosis, disease monitoring, and guiding biopsy decisions in SLE management.

Keywords: Systemic Lupus Erythematosus, Hematologic Abnormalities, Histopathology, Anemia, Lupus Nephritis, Clinicopathological Correlation, SLEDAI, Tissue Biopsy

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, inflammatory disease that can affect virtually any organ system in the body. Characterized by the production of a wide array of autoantibodies, particularly antinuclear antibodies (ANAs), SLE leads to immune complex deposition and subsequent tissue inflammation and damage. It is a prototypical autoimmune disease, representing a complex interaction of genetic, environmental, hormonal, and immunological factors. The disease is notable not only for its clinical heterogeneity but also for the significant burden it imposes on patients' quality of life and long-term health outcomes.[1, 2].

Globally, the prevalence of SLE varies widely by geographic region and ethnicity, with estimates ranging from 20 to 150 cases per 100,000 individuals. It disproportionately affects women, with a female-to-male ratio of approximately 9:1, particularly during the reproductive years. The disease is more prevalent and often more severe among individuals of African, Asian, Hispanic, and Indigenous descent. This demographic predilection suggests a potential genetic susceptibility, which has been increasingly supported by genome-wide association studies (GWAS) identifying multiple susceptibility loci associated with immune function, including genes involved in antigen presentation, T- and B-cell signaling, and cytokine production.

The pathogenesis of SLE is multifactorial and remains incompletely understood. Central to the disease is a breakdown of immune tolerance to self-antigens, leading to autoantibody production. These autoantibodies, particularly those directed against double-stranded DNA (dsDNA), Sm antigen, and ribonucleoproteins, form immune complexes that deposit in tissues and activate complement pathways, initiating a cascade of inflammation. A dysregulated type I interferon (IFN) response is another key feature, with elevated IFN-α levels correlating with disease activity and severity. Environmental factors such as ultraviolet radiation, infections (particularly Epstein-Barr virus), and certain medications have been implicated as triggers in genetically susceptible individuals. Hormonal influences, particularly estrogen, also play a role, potentially explaining the female predominance.

SLE is often referred to as "the great imitator" due to its broad spectrum of clinical presentations. The disease may present acutely or insidiously, and its course can vary between periods of flares and remission. Common manifestations include constitutional symptoms (fever, fatigue, weight loss), malar rash, photosensitivity, oral ulcers, arthritis, and serositis. More severe complications can affect the kidneys (lupus nephritis), central nervous system (neuropsychiatric lupus), cardiovascular system (accelerated atherosclerosis), hematologic system (anemia, leukopenia, thrombocytopenia), and pulmonary system (pleuritis, interstitial lung disease). Lupus nephritis, in particular, is a major cause

of morbidity and mortality and is associated with poor long-term outcomes if not promptly treated[3, 4].

This study aims to evaluate the clinicopathological correlation between hematologic abnormalities and tissue histopathological changes in patients with SLE. By identifying specific hematologic markers associated with particular histopathologic patterns and disease activity scores, we hope to enhance the understanding of SLE pathogenesis and improve patient management strategies[5, 6].

Methodology

Study Design and Setting

A prospective observational study was conducted over 18 months (January 2023 to June 2024) at tertiary care Hospital. The study was approved by the Institutional Review Board, and informed consent was obtained from all participants.

Inclusion Criteria

- Patients aged 18 years and above.
- Diagnosed with SLE based on the 2019 ACR/EULAR classification criteria.
- Presence of hematological abnormalities (anemia, leukopenia, thrombocytopenia).
- Willingness to undergo tissue biopsy (renal, skin, or lymph node) as clinically indicated.

Exclusion Criteria

- Patients with overlapping autoimmune disorders.
- Pregnant or lactating women.
- Patients on immunosuppressive therapy for more than six months prior to enrollment.
- Individuals with known hematological malignancies or chronic infections.

Data Collection

A total of 80 patients fulfilling the inclusion criteria were enrolled. Demographic data, clinical features, and laboratory parameters were recorded. Hematological evaluations included complete blood counts, peripheral blood smears, reticulocyte counts, and Coombs tests. Bone marrow aspiration and biopsy were performed in cases with persistent cytopenias. Tissue biopsies (renal, skin, and lymph node) were obtained based on clinical indications.

Histopathological Analysis

Biopsy specimens were processed and stained using standard hematoxylin and eosin techniques. Renal biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Skin and lymph node biopsies were evaluated for features such as vasculitis, interface dermatitis, and reactive hyperplasia.

Statistical Analysis

Data were analyzed using SPSS version 25. Descriptive statistics were used to summarize demographic and clinical characteristics. Chi-square tests and Pearson correlation coefficients were employed to assess associations between hematological abnormalities and histopathological findings. A p-value of <0.05 was considered statistically significant.

Results

1. Demographic and Clinical Characteristics

A total of 80 patients diagnosed with systemic lupus erythematosus (SLE) were included in the study. The majority were female (n = 73, 91.3%), with only 7 (8.7%) males, reflecting the well-established female predominance of the disease. The mean age was 29.4 ± 8.2 years, and the mean duration of illness was 3.2 ± 1.5 years, indicating that most patients were in the early to mid-phase of the disease course.

Clinically, arthritis was the most frequently reported manifestation, present in 85% of the patients, followed by malar rash (70%), photosensitivity (65%), and oral ulcers (60%). These features align with common mucocutaneous and musculoskeletal involvement typical of SLE.

2. Hematological Abnormalities

Hematologic involvement was prevalent, affecting a significant proportion of patients:

- Anemia was observed in 66 patients (82.5%), making it the most common hematological abnormality. Among these, the distribution was:
  - Normocytic normochromic anemia in 34 patients (42.5%)
  - Microcytic hypochromic anemia in 20 patients (25%)
  - Hemolytic anemia in 12 patients (15%)
- Leukopenia was detected in 38 patients (47.5%), and thrombocytopenia in 29 patients (36.2%).
- Coombs test was positive in 18 patients (22.5%), indicating autoimmune hemolysis in a subset.

These abnormalities reflect both direct autoimmune destruction and bone marrow suppression mechanisms common in SLE.

Hematological Abnormality	Number of Patients	Percentage (%)
Anemia	66	82.5%
Leukopenia	38	47.5%
Thrombocytopenia	29	36.2%
Positive Coombs Test	18	22.5%

Table 1: Prevalence of Hematological Abnormalities (n = 80)

3. Bone Marrow Findings

Bone marrow examinations were performed in 20 patients with persistent cytopenias to determine the underlying cause. The following patterns were observed:

- Erythroid hyperplasia in 6 patients, predominantly those with hemolytic anemia, indicating compensatory marrow response.
- Hypocellularity in 5 patients, suggestive of aplastic anemia or marrow suppression, possibly secondary to medications or autoimmunity.
- Hemophagocytosis and increased histiocytes in 3 patients, consistent with macrophage activation syndrome (MAS).

These findings underscore the diverse mechanisms by which hematologic alterations occur in SLE.

Histopathological Finding	Number of Patients	Clinical Correlation
Erythroid Hyperplasia	6	Hemolytic Anemia
Hypocellularity	5	Aplastic Features
Hemophagocytosis with Histiocytosis	3	Macrophage Activation Syndrome
Normal/Non-specific Findings	6	-

Table 2: Bone Marrow Examination Findings (n = 20)

4. Tissue Histopathology

Renal Biopsies (n = 35):

Lupus nephritis was subclassified based on the ISN/RPS classification:

- Class IV (diffuse proliferative) lupus nephritis was the most common (n = 13, 37.1%)
- Followed by Class III (focal proliferative) in 12 (34.3%)
- Class V (membranous) and Class II (mesangial) were less frequent, each in 5 (14.3%)

Skin Biopsies (n = 20):
- Interface dermatitis was the predominant finding (n = 13, 65%), typical of cutaneous lupus.
- Leukocytoclastic vasculitis was observed in 4 (20%) and non-specific dermatitis in 3 (15%).

Lymph Node Biopsies (n = 10):
- Reactive hyperplasia was seen in 6 patients (60%)
- Necrotizing lymphadenitis, consistent with Kikuchi disease, was noted in 3 patients (30%)
- One patient (10%) showed non-specific findings

These results emphasize the systemic nature of SLE and its multi-organ pathology.

Tissue Type	Histopathological Finding	Number of Patients	Percentage (%)
Renal (n = 35)	Class III Lupus Nephritis	12	34.3%
	Class IV Lupus Nephritis	13	37.1%
	Class V Lupus Nephritis	5	14.3%
	Class II Lupus Nephritis	5	14.3%
Skin (n = 20)	Interface Dermatitis	13	65%
	Leukocytoclastic Vasculitis	4	20%
	Non-specific Dermatitis	3	15%
Lymph Node (n = 10)	Reactive Hyperplasia	6	60%
	Necrotizing Lymphadenitis (Kikuchi)	3	30%
	Non-specific Findings	1	10%

Table 3: Histopathological Findings in Tissue Biopsies

5. Correlation Between Hematologic Abnormalities and Histopathological Findings

Statistical analysis revealed several significant associations:
- Anemia was significantly associated with Class III and IV lupus nephritis ($p = 0.03$), suggesting renal involvement as a contributor to anemia, possibly via chronic inflammation or loss of erythropoietin.
- Leukopenia was significantly correlated with interface dermatitis in skin biopsies ($p = 0.04$), possibly reflecting concurrent immunological activity in skin and bone marrow.
- Thrombocytopenia was significantly associated with high SLEDAI scores (>10) ($p = 0.01$), indicating its role as a marker of disease severity.

These correlations highlight how specific hematologic alterations can reflect the underlying systemic disease activity and organ involvement.

Parameter	Correlated Histopathology	p-value
Anemia	Class III & IV Lupus Nephritis	0.03
Leukopenia	Interface Dermatitis in Skin Biopsy	0.04
Thrombocytopenia	High Disease Activity (SLEDAI >10)	0.01

Table 4: Statistically Significant Clinico-pathological Correlation

Discussion

This study highlights the significant prevalence of hematological abnormalities in SLE patients and their correlation with specific tissue histopathological changes. Anemia was the most common hematological abnormality, observed in 82.5% of patients, aligning with previous studies reporting anemia in up to 98% of SLE cases. The association between anemia and Class III/IV lupus nephritis suggests that anemia could serve as a marker for renal involvement in SLE[7, 8].

Leukopenia, present in 47.5% of patients, showed a significant correlation with skin involvement, particularly interface dermatitis. This finding supports the notion that leukopenia may reflect active cutaneous disease in SLE. Thrombocytopenia was associated with higher disease activity scores, indicating its potential as a marker for disease severity[9, 10].

Bone marrow examinations revealed diverse findings, including erythroid hyperplasia, hypocellularity, and hemophagocytosis, reflecting the multifactorial nature of hematological abnormalities in SLE. These findings underscore the importance of bone marrow evaluation in patients with persistent cytopenias to elucidate underlying mechanisms and guide management[11, 12].

The study's limitations include its single-center design and relatively small sample size, which may affect the generalizability of the findings. Additionally, the cross-sectional nature of the study limits the ability to establish causal relationships between hematological abnormalities and histopathological changes[13, 14].

Conclusion

Hematological abnormalities are common in SLE and exhibit significant correlations with tissue histopathological findings. Anemia is strongly associated with lupus nephritis, leukopenia reflects cutaneous involvement, and thrombocytopenia correlates with disease activity. Recognizing these correlations can aid in early diagnosis, disease monitoring, and guiding biopsy decisions in SLE management.

Implications

Understanding the clinic pathological correlations in SLE can enhance diagnostic accuracy and inform treatment strategies. Hematological abnormalities may serve as non-invasive markers for organ involvement, reducing the need for invasive biopsies in certain cases. Incorporating routine hematological assessments into SLE management protocols can facilitate early detection of organ involvement and prompt intervention.

Limitations

The study's limitations include its single-center design, which may limit the generalizability of the findings. The relatively small sample size may also affect the statistical power of the study. Future multicenter studies with larger cohorts are warranted to validate these findings and explore the underlying mechanisms linking hematological abnormalities to tissue histopathology in SLE.

References

1. Voulgarelis M, Giannouli S, Tasidou A, Anagnostou D, Ziakas P, Tzioufas A. Bone marrow histological findings in systemic lupus erythematosus with hematologic abnormalities: a clinicopathological study. American journal of hematology. 2006;81(8):590-7.
2. VIGUIER M, PINQUIER L, CAVELIER-BALLOY B, DE LA SALMONIÈRE P, CORDOLIANI F, FLAGEUL B, et al. Clinical and histopathologic features and immunologic variables in patients with severe chilblains: a study of the relationship to lupus erythematosus. Medicine. 2001;80(3):180-8.
3. Tiniakou E, Goldman D, Corse A, Mammen A, Petri MA. Clinical and histopathological features of myositis in systemic lupus erythematosus. Lupus Science & Medicine. 2022;9(1).
4. Velayutham B, Padhi S, Devi S, Patra S, Panigrahi C, Ramasubbu MK, et al. Immunohistochemical expression of perforin in adult systemic lupus erythematosus associated macrophage activation syndrome: Clinicohematological correlation and literature review. Lupus. 2024;33(1):26-39.
5. Saleh M, Eltoraby EE, Tharwat S, Nassar MK. Clinical and histopathological features and short-term outcomes of lupus nephritis: a prospective study of 100 Egyptian patients. Lupus. 2020;29(8):993-1001.

6. Khan ZA, Mushtaq S, Samreen S, Salim B, Ahmed SN, Zahid PM, et al. Clinico-Immunological Profile of Systemic Lupus Erythematosus Patients of Pakistan and Their Correlation. Pakistan Armed Forces Medical Journal. 2022;72(4).
7. Ranathunga U, Wijesinghe H, de Silva M. A study of clinicopathological features and selected laboratory parameters in a cohort of Sri Lankan patients with lupus nephritis. Journal of Diagnostic Pathology. 2023;18(1).
8. Anafi IYG. Haematological abnormalities in South Africans with systemic lupus erythematosus: University of the Witwatersrand, Johannesburg (South Africa); 2021.
9. Fresneda Alarcon M, McLaren Z, Wright HL. Neutrophils in the pathogenesis of rheumatoid arthritis and systemic lupus erythematosus: same foe different MO. Frontiers in immunology. 2021;12:649693.
10. Apalla Z, Papadimitriou I, Iordanidis D, Errichetti E, Kyrgidis A, Rakowska A, et al. The dermatoscopic spectrum of cutaneous lupus erythematosus: A retrospective analysis by clinical subtype with clinicopathological correlation. Dermatologic Therapy. 2020;33(6):e14514.
11. Mardia AI, Hamijoyo L, Susandi E, Prihatni D, Alisjahbana B, Oehadian A. The Potential Role of Neutrophil Reactivity Intensity and Reactive Lymphocytes as Extended Hematological Parameters to Detect Active Systemic Lupus Erythematosus. International Journal of Rheumatic Diseases. 2024;27(12):e15449.
12. Choi EW. Relationship between neutrophil gelatinase-associated lipocalin levels and disease parameters including clinicopathological parameters and various cytokine levels in systemic lupus erythematosus. Journal of Veterinary Medical Science. 2023;85(6):601-8.
13. Horisberger A, Griffith A, Keegan J, Arazi A, Pulford J, Murzin E, et al. Blood immunophenotyping identifies distinct kidney histopathology and outcomes in patients with lupus nephritis. bioRxiv. 2024:2024.01. 14.575609.
14. Al-Adhoubi NK, Bystrom J. Systemic lupus erythematosus and diffuse alveolar hemorrhage, etiology and novel treatment strategies. Lupus. 2020;29(4):355-63.