

“Haematological Manifestations In Systemic Lupus Erythematosus”

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I. Introduction

Systemic lupus erythematosus (SLE) is a disease of autoimmune etiology affecting multiple systems involving most commonly females of the reproductive age group. “It is also a major cause of mortality and morbidity in the young population.”

The prevalence of SLE varies throughout the world. In the western world, it is around 40 for every lakh persons. It is found to be more common in blacks and Hispanics as compared to others. More than 80 % of cases occur in women in their reproductive years.

The overall outcome in the western countries showed dramatic improvement in the last couple of decades, from a survival rate at the end of 5 years of 50% in 1950s to 90% 10 year survival in 1990s. However, a poor survival of SLE is still reported in certain ethnic groups such as Indians, Black Caribbeans and Hispanics. Complications due to infection or the end organ damage due to SLE per se are the chief reasons for mortality.

Haematological abnormalities are frequently encountered in patients with SLE and are part of the American Rheumatic Association criteria for classifying the disease. But there is a relative paucity of information on the significance of these abnormalities in the course of the condition.

Anemia is the most common haematologic abnormality seen in SLE. The incidence of Autoimmune haemolytic anemia is around 5-10% of SLE and it responds well to corticosteroid treatment. Neutropenia is relatively common and has been related to an increased risk of infection in them. Although, thrombocytopenia due to breakdown of platelets by antibodies is frequent (about 20-40% extreme low platelet counts are relatively rare. It is now found that lymphopenia is also a more frequent manifestation of SLE.

Antiphospholipid antibodies frequently found in SLE are a group of self reactive antibodies characterized by a wide spectrum of target activities, identifying different mixture of membrane lipids like phospholipids or phospholipid binding proteins. The name "antiphospholipid antibody syndrome" implies the clinical union of antiphospholipid antibodies and of hypercoagulable state.

Though the haematological abnormalities encountered in SLE have been well documented in literature, there are very few studies done in India addressing this issue, hence this study is undertaken to establish the frequency and severity of haematologic abnormalities in patients of SLE in our geographic area.

II. Aims And Objectives

- To find out the prevalence of hematologic abnormalities in patients diagnosed with Systemic Lupus Erythematosus.

III. Materials And Methods

Study population :

This study is to be conducted among 50 patients who are admitted/attending Rheumatology Outpatient department in Govt. Rajaji hospital, Madurai diagnosed with Systemic Lupus Erythematosus

Inclusion criteria :

- All patients age > 16 years, both sexes with a diagnosis of SLE
 - Both inpatient and outpatients were included in the study
 - Both new and previously diagnosed cases were included in the study
 - The diagnosis of SLE was made on the basis of the 1982 American College of Rheumatologic revised criteria updated 1997, 4 out of the following criteria were satisfied for diagnosing SLE
1. Malar Rash- Fixed erythema, flat or raised over the malar eminence
 2. Discoid Rash-erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur.
 3. Photosensitivity- Exposure to ultraviolet rays causes rash

4. Oral ulcers-includes oral and nasopharyngeal ulcers observed by physician
5. Arthritis- Non erosive arthritis involving two or more peripheral joints characterised by tenderness, swelling and effusion
6. Serositis- Pleuritis, pericarditis documented by ECG, rub or evidence of pericardial effusion
7. Renal Disorder- Proteinuria>0.5g/dl or 3+ or cellular cast
8. Neurological disorder-Seizures or psychosis without other causes
9. Hematological disorder- Hemolytic anemia or leucopenia(<4000 cells/dl), lymphopenia(<1500 cells/dl), thrombocytopenia(<1,00,000 cells/dl) in the absence of offending drugs.
10. Immunological disorder- anti dsDNA, anti sm, antiphospholipid antibodies
11. Antinuclear antibody- Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point of time in the absence of drugs known to induce ANA

Exclusion criteria :

- Those who were not willing for the study
- Those who have known primary haematological diseases

Data collection :

A previously designed proforma will be used to collect the demographic and clinical details of the patients. A thorough clinical examination will be done and hematological investigations will be done.

Laboratory investigations:

Complete haemogram with peripheral smear
Coombs test- direct and indirect
Renal function Tests

Design Of Study: Analytical Study

Period Of Study: July 2014 to September 2014

Study protocol:

All patients with a diagnosis of SLE were evaluated as per the proforma. The data collected included a detailed history, clinical examination and investigations with particular reference to the haematological abnormalities. The history includes amongst other details symptoms pertaining to SLE, haematological manifestations past treatment history and history of abortion and arterial or venous thrombosis. A detailed physical examination was carried out with particular reference to features of SLE and its complications.

The haematological investigations included haemoglobin, total WBC counts, differential counts, platelet count, peripheral smear examination, direct coomb's test, reticulocyte count. This is in addition to the relevant investigations needed for a complete evaluation of SLE.

Consent: Individual written and informed consent obtained from patients

Definitions

- Anemia - Haemoglobin < 12 g%
- Severe anemia - < 8g%
- Haemolytic anemia - Anemia + DCT positivity + Reticulocytosis (corrected reticulocyte count>2.0%)
- Anemia of chronic disease (ACD) - DCT negative and normocytic and normochromic anemia
- Iron deficiency anemia (IDA) - Hypochromicity on peripheral smear
- Leucopenia - Total WBC count < 4000/ mm³
- Lymphopenia - Total lymphocyte count < 1500/mm³
- Thrombocytopenia - platelet count < 100,000/mm³

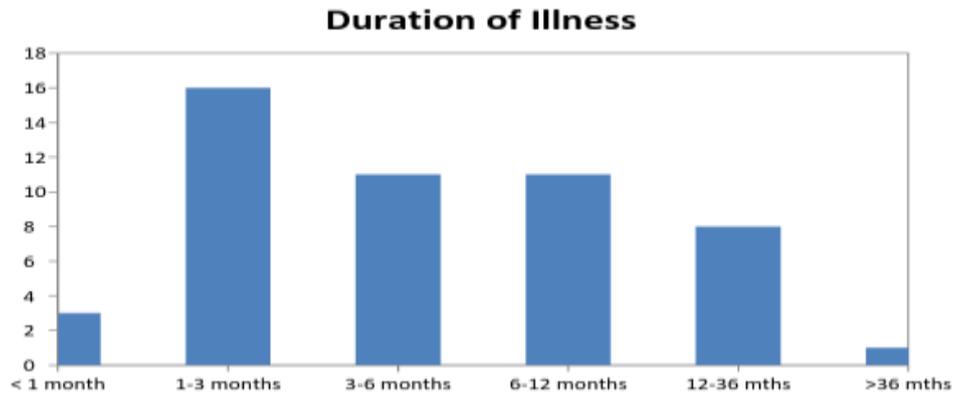
IV. Results

1. Sex

There were 50 patients in the study among which 46 (92%) were females and 4(8%) were males with a male:female ratio of 1:11.5.

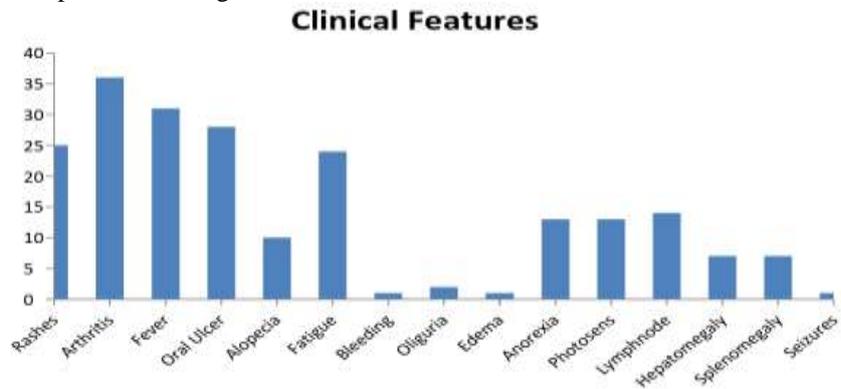
2. Age

The age of the patients ranged from 16 years to 48 years with a mean age of 27.6 years. The mean age in females was 27.6 years and that of males is 27.5 years.



3. Duration of Illness

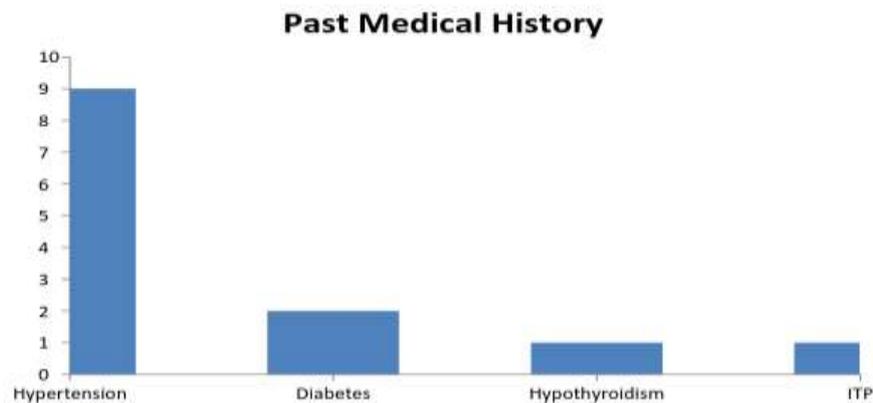
The duration of illness prior to the diagnosis of SLE was 8.5 months.



4. Clinical Features

The most presenting complaint was arthritis in 36 patients (72%) followed by fever in 31 patients (62%) and oral ulcers in 28 patients (56%). Fatigue and rash were present in 24 (48%) and 25 (50%) of patients respectively. Photosensitivity and anorexia were present in 13 (26%) patients each.

Clinical findings elicited at the time of examination include Lymphadenopathy in 14 (28%) and hepatosplenomegaly in 7 (14%) of patients. Seizures were present 1 patients.



5. Past Medical History

Out of the 50 patients interviewed, 9 (18%) were hypertensive at presentation, while 2 had diabetes and one had hypothyroidism.

6. Marital History

30 (60%) patients were married at the time of diagnosis. Among them three had a history of abortions, out of which two were found to have APS.

7. Diagnostic Criteria

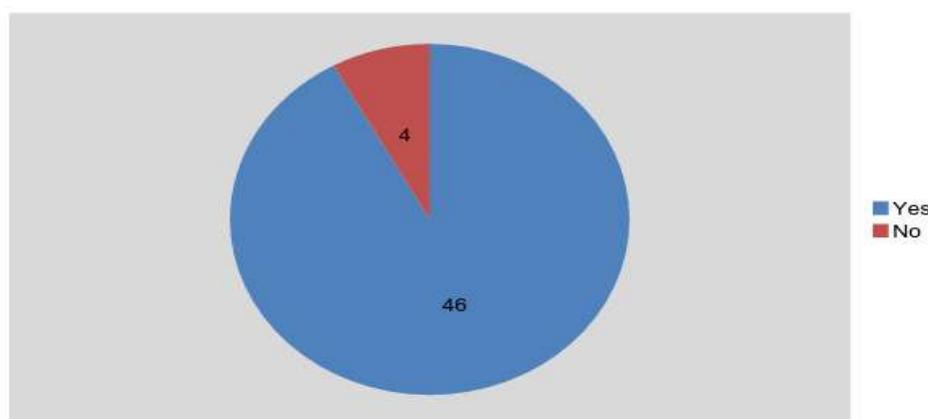
Diagnosis was based on the American college of Rheumatology revised criteria updated 1997. All the patients satisfied at least 4 criteria needed for the diagnosis of SLE as per recommendations. Among the ACR criteria, ANA was positive in all the patients, while diagnostic hematological criteria were present in 29 (58%) of the patients.

8. Antinuclear antibodies

ANA was positive in all the patients studied. Anti double stranded DNA (dsDNA) was positive in 30 patients (60%). The patterns of immunofluorescence seen are:

Pattern	Frequency	Percentage
Homogenous	26	52
Speckled	21	42
Rim pattern	2	4
Nucleolar	1	2

Haematological Abnormalities-I



9. Hematological abnormalities

Haematological abnormalities were detected in 46 (92%) patients. The various abnormalities include Anemia, Neutropenia, Thrombocytopenia, Pancytopenia, DCT positivity.

9.1 Anaemia

Anaemia was found to be the most common haematological abnormality in 43 (86%) of patients. Autoimmune haemolytic anaemia was diagnosed in 7 (16.27%) of patients. About 36 (83.7%) patients had aemia due to various causes like iron deficiency anaemia (32.55%) and anaemia of chronic disease (22.2%).

9.2 Severe Anaemia

Twenty one (48.8%) patients among anaemia presented with severe anaemia. The mean Haemoglobin in this group was 6.4 gm%.

9.3 Autoimmune Haemolytic Anaemia

Seven (16.27%) had autoimmune haemolytic anaemia.

9.4 Iron Deficiency anaemia

Iron deficiency anaemia suggested by hypochromic cells on peripheral smear was present in 14 (32.55%) patients. The mean hemoglobin was 7.3gm%.

9.5 Anaemia of chronic disease

Anaemia of chronic disease was found in 9 (20.93%) patients with anaemia. the mean haemoglobin was 7.9gm%.ACD was not associated with any major organ involvement.

9.6 Peripheral blood Smear Examination

Normocytic normochromic picture was the most common finding on PS examination. It was found in 35 (70%) of the patients.

10. White blood cell abnormalities

The white blood cell abnormalities found were leucopenia, Lymphopenia. The mean Total WBC count was 5812 cells/cmm at presentation. Lymphocytopenia was the most common abnormality which was present in 33 (66%) patients. Leucopenia was seen in 18 (36%) patients.

11. Thrombocytopenia

Thrombocytopenia was present in 9 (18%) patients out of which 2 patients had very low platelet count of less than 20000 cells/cmm.

12. Direct coombs test

A positive direct coombs test was found in 37 (74%) of patients. There was no association between DCT positivity and any organ system involvement or age or sex of the patient.

13. Antiphospholipid antibodies

Antiphospholipid antibodies were found to be positive in 4 patients. Lupus anticoagulant and anticardiolipin antibodies was positive in 2 patients. APS patients were found to have low complements in serum. One of these patients presented with primary neurological involvement and the other with bad obstetric history.

Clinical parameters	Frequency
Cortical vein thrombosis	1
Recurrant abortions	1

14. Lupus Nephritis

Renal involvement was present in 21 patients. Proteinuria is the most common urinary abnormality detected in 17 patients. Microscopic hematuria was present in 5 patients and pyuria in 5 patients.

Urinary abnormalities	Frequency	Percentage
Proteinuria	21	42
Pyuria	5	10
Microscopic hematuria	5	10

15. Neurological Manifestations

Neurological manifestations were present in 8 patients. 3 patients had meningitis. 1 patient had Cortical venous thrombosis. One patient had peripheral neuropathy, 1 patient had seizures, one patient had chorea.

V. Discussion

This is a prospective study of hematological manifestations in 50 patients with Systemic Lupus Erythematosus at our hospital.

1. Demographic parameters

A. Sex Distribution

There was a predominant involvement of females in our study, 46 females (92%) and 4 males (8%). The ratio of males to females was 1:11.5. This result is similar to most of the studies. Cameron SJ et al⁶⁰ has reported an average female to male ratio of 8:1 to 12:1 in a study. An Indian study Malaviya et al⁶⁴ reports a female to male ratio of 8:1. In a south Indian study, Sasidharan et al⁸⁴ reported a female to male ratio of 10:1.

B. Age Distribution

The mean age of patients in our study was 27.6 years with a mean age of 27.5 in males and 27.6 in females. SLE is a disease affecting the reproductive age group.⁹ The mean age of onset of SLE in a series by Malaviya AN⁶⁴ was 24.5 years. In a study by Sasidharan PK⁸⁴ the mean age of onset in females was 30 and that of males was 34.5 years. The mean age of onset in males was reported as 40.4 years in Hochbery et al⁷⁰. In contrast an Indian study by Panda I⁶⁵ showed an earlier onset of disease in males. The mean age group affected by SLE in our study was similar in both males and females.

C. Duration of Illness

The mean duration of illness prior to the diagnosis of SLE in our study was 8.5 months. “In a survey of 464 patients’ analysed between 1980-1989, the mean duration was 2.1 years⁷⁰.” “In a study by Malaviya et al⁶⁴ the duration of illness was 17 months.” The earlier diagnosis probably is attributed to the newer diagnostic serological tests. This is evidenced by a study which showed a mean duration to diagnosis of 3 months⁷⁰. Lack of awareness among patients, their financial difficulties and poor availability of newer diagnostic tests in rural areas would have contributed to the late diagnosis in patients of our hospital

2. Clinical Features

The most common presenting clinical complaint in our study was arthralgia and arthritis, present in 72% of our patients at the time of diagnosis. In an analysis of 520 cases by Wallace DJ⁷⁰ patients presenting with arthralgias constituted 92%. Analyzing various studies from all regions of India, Kumar A⁶¹ reports a proportion of patients reporting with the above complaints were 57% in North India, 68% in South India, 75% in east India.

The second most common presenting complaint was fever present in 62% of our patients. This result is similar to other studies. Paul BJ⁶⁷ reports an incidence of 50.6% in a series. Wallace DJ described an incidence of 84% in a study. In most of the patients the fever was related to the disease activity.

Oral ulcers were the next most frequent complaint present in 56% of patients. Malaviya⁶⁴ reports an incidence of 50% in a study conducted in eastern India. In a study conducted by Madhavan⁶³ in madras reported 64% patients presenting with oral ulcers. Our study has documented a higher incidence of oral ulcers compared

Malar rash was present in 40% of our patients. This finding is similar to that of a study by Wallace DJ⁷⁰ where an incidence of 10-61% was documented. In a study conducted in western India Vaidya⁸³ reported 53.1% of patients with oral ulcers.

Photosensitivity was found in 26% of our patients. This observation is found to be 37% in a series described by Wallace DJ⁷⁰. In a study by Binoy in south india, an incidence of 32% was reported.

Overall, the frequency of the common complaints at presentation was similar to that of other studies documented in various studies except a much higher incidence of oral ulcers in Indian patients.

3. Past medical History

Hypertension was the most common past medical history elicited in our patients which was 18% . In an analysis of various published series, a prevalence of 12-49% has been reported.

There is increased association of hypertension and renal disease.⁷¹ Our study could not find any statistical significance of such association between renal disease and hypertension. The small numbers studied could be the probable reason for not being able to bring out any significant association. However, it was found that 5 out of nine patients with hypertension had lupus nephritis.

Our study has two patients with history of diabetes mellitus and one patient had hypothyroidism and one patient had a history of Immune thrombocytopenic purpura. SLE is associated with other autoimmune disorders like thyroiditis. However the numbers are too small to bring out any significant association.

4. Drug History

NSAIDs and glucocorticoids were the most common drug history elicited in our patients. This was expected as the most common complaint in our patients was arthritis and arthralgia

5. Diagnostic Criteria

The most common criteria satisfied was ANA positivity which was found in all patients. This is in accordance as ANA negative lupus is a rare entity in our setting. ANA is the most sensitive parameter for the diagnosis of SLE. ANA positivity was reported to be positive in 90-95% of cases.

The most common pattern of immunofluorescence for ANA in our study was a homogenous pattern, seen in 52% of our patients. This pattern is the most common reported in literature.⁷

6. Anti double stranded DNA

Anti dsDNA antibodies are specific for the diagnosis of SLE. It was positive in 60% of our patients. This observation is in concordance with literature.

7. Haematological Abnormalities

In this study 92% of the patients studied had haematological abnormalities. In a study in China by Xu XM et al. 86% of the patients examined had haematological abnormalities⁸⁰. Though there were high incidence of hematological abnormalities at presentation, only 4 patients presented with symptoms related to hematological problems.

7.1 Anaemia

The most common hematologic abnormality was anaemia found in 86% of patients. In a study by Budman R³⁴ analysis of various studies were done and published that anaemia occurred in 57-78% of patients with SLE. In the Chinese study anaemia was noted in 70.7% of cases. In a study by Sasidharan PK, anaemia was detected in 62.9% being the most common haematological problem. The higher number of anaemia in India may be because of the high prevalence of iron deficiency anaemia.

Iron deficiency anaemia, anaemia of chronic disease, autoimmune hemolytic anaemia are the common causes of anaemia in Systemic lupus erythematosus patients. Iron deficiency has been diagnosed based on hypochromic picture on peripheral smear examination while anaemia of chronic disease on the basis of normocytic and normochromic picture in the presence of negative direct coombs and AIHA with a positive DCT and reticulocytosis. Further evaluation of anaemia like Iron studies, folate levels and bone marrow examination were not done due to financial constraints.

Normocytic hypochromic anaemia was the most common cause of anaemia and was seen in 32.55% of patients with anaemia. The finding is similar to that of a study by Voulgarelis et al⁷⁷ who reports 35.6% cases of iron deficiency anaemia. Anaemic of chronic disease was the second most common cause of anaemia according to our definition and constituted 20.9% of anaemic patients. This observation was 37.1% in Voulgarelis et al.

A positive direct Coombs test was observed in 74% of patients but autoimmune haemolytic anaemia was diagnosed only in 6 patients (14%). Budman R³⁴ in a study of series of various studies found 18-65% DCT positivity in patients with SLE. However, the AIHA was detected in less than 10%.

Reticulocytosis is a diagnostic criteria for the diagnosis of AIHA. The bone marrow response to haemolysis in the form of reticulocytosis may be depressed due to coexistence of iron or folate deficiency or an associated bone marrow suppression of chronic disease is present. This could be the reason for the discrepancy between DCT positivity and AIHA.

Anaemia was found to be associated with Lupus nephritis. Prior studies in patients with SLE reported an association between anaemia and lupus nephritis⁶⁰ and a poor survival in patients having anaemia and lupus nephritis.

7.2 White blood cell abnormalities

Lymphopenia was found to be the most common white cell abnormality in our study (66%). In a study by Debarre et al³² lymphopenia was detected in 84% cases and was found to be independent of leucopenia. However, only 20% patients had lymphopenia in Nossent JC⁴⁴ study. Indian studies also showed an incidence of 20% and 7.5% in North and South India respectively. This discrepancy may be due to differences in spectrum of disease severity and use of glucocorticoid or immunosuppressant drug use. Neutropenia was found in 7 patients and can be due to drug induced.

7.3 Thrombocytopenia

Thrombocytopenia was detected in 18% of our patients but only 2 patients had severe thrombocytopenia (platelet count <20000/cmm³). 1 of them presented with bleeding manifestation (bleeding gums). Budman R³⁴ reports 14-26% frequency of thrombocytopenia in multiple studies. Nossent⁴⁴ detected a 27% incidence of thrombocytopenia. The incidence in our study is similar to that of other studies and likewise bleeding manifestations secondary to thrombocytopenia is unusual. Low platelet count is described to be associated with renal involvement, serositis, neurological involvement in different studies^{69,76}. Nossent⁴⁴ described reduced survival in patients with thrombocytopenia.

7.4 Antiphospholipid antibodies

Antiphospholipid antibodies were found in 8 patients among whom anticardiolipin antibodies and lupus anticoagulant were present 5 patients. Antiphospholipid antibodies were detected in 12-30% of cases and lupus anticoagulant in 15-34% cases of SLE⁴⁷. The incidence in our study was similar. Antiphospholipid antibody syndrome was diagnosed in 3 patients. APS can develop in 50-70% of patients with SLE⁸⁴.

VI. Conclusion

- This was a prospective study of haematological manifestations in 50 patients with features consistent with SLE.
- Most patients were females in the reproductive age group
- The most common presenting complaint was arthritis with a mean duration of disease prior to diagnosis was 8.5 months
- Haematological manifestations were detected in 92% of the patients
- Anaemia was the most common abnormality detected. Iron deficiency anaemia was the most common cause among them followed by anaemia of chronic disease and autoimmune haemolytic anaemia.
- Anaemia was significantly associated with renal involvement.
- A normochromic normocytic picture on peripheral smear was the most common blood picture.
- Lymphopenia was the most common white blood cell abnormality.
- Thrombocytopenia was also a frequent finding (18%) and was associated with presence of lupus anticoagulant.
- Direct coombs test was positive in 74% of the patients.
- Antiphospholipid antibody syndrome was diagnosed in 3 patients.
- Renal involvement was present in 42% patients with proteinuria being the most common urinary abnormality. Lupus nephritis was the most common indication for high dose glucocorticoids and immunosuppressants.
- Neurological manifestations were detected in 6 patients.

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