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Research Article
Lupus

A study on hematological and immunological profile of patients with systemic Lupus Erythematosus

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Background: Systemic lupus erythematosus (SLE) is a chronic, relapsing, inflammatory and often febrile multisystem disorder of the connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes. Hematological findings may be present at the onset of the disease or can develop during the course of the disease. Since blood and blood vessels together contain more diverse number of antigens than any other organ in the body, it is only natural to expect hematological manifestations more often than the other systems. **Objectives:** To study the haematological and immunological Profile of Patients with Systemic Lupus Erythematosis. **Methodology:** An Ambispective study was conducted at Kasturba Medical College and hospital, Manipal from January 2011 to December 2013. A total of One hundred twenty seven cases of SLE were classified as having SLE according to the revised American College of Rheumatology (ACR) classification criteria (1997). **Results:** Hematological manifestations were frequently seen in the cases studied, which included anemia, neutropenia, lymphopenia, thrombocytopenia, pancytopenia, increased Erythrocyte sedimentation rate (ESR), presence of spherocytes, DCT positivity etc.Anemia was the most common hematological abnormality observed in the patients accounting to 87.4% (111/127) of cases. Hemoglobin of patients varied from a minimum of 3.8g/dl up to 13.5g/dl (Median = 9.6±2.2). The erythrocyte sedimentation rate (ESR) was assessed in all except one.The PCNA (Anti proliferating cell nuclear antigen) antibodies were positive in 44% of the cases. **Conclusion:** Hematological abnormalities are the commonest among all other manifestations in SLE, and their treatment is challenging. Bone marrow examination should be considered in all cases of severe or persistent leukopenia or thrombocytopenia in SLE, to exclude dug-induced myelotoxicity in susceptible patients.

Keywords: SLE, Haematological, Serological, Anca, Esr

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, relapsing, inflammatory and often febrile multisystem disorder of the connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes. [1]. The clinical course of SLE is diverse. Being a primary disease of young women, with a peak incidence between the ages of 15-40 years, it affects approximately one in every 200 individuals.

[2] The prevalence also varies with various factors like race, ethnicity and socioeconomic status.Hematological findings may be present at the onset of the disease or can develop during the course of the disease. Since blood and blood vessels together contain more diverse number of antigens than any other organ in the body, it

Is only natural to expect hematological manifestations more often than the other systems. All the cellular elements of the blood & coagulation pathway can be affected in SLE patients. Peripheral blood cytopenias are commonly seen in patients with SLE. Leukopenia, and more specifically lymphopenia, is common, and when accompanied by hypocomplementemia, it predisposes to frequent infections.

Anemia is a common manifestation in SLE accounting for about 50% of SLE patients[5]. Various mechanisms lead to the development of anemia, some of them being chronic inflammation, renal insufficiency, blood loss, dietary insufficiency, medications, hemolysis, infection, hypersplenism, myelofibrosis, myelodysplasia, and aplastic anemia [6]. Leukopenia in SLE and usually reflects disease activity. A low white blood cell count is common finding in patients with active disease while Leukocytosis (mostly granulocytes) can occur in SLE usually due to infection or the use of high dose of glucocorticoid therapy. Thrombocytopenia can be observed in two forms in SLE, either chronic form generally associated with mild disease or acute form similar to idiopathic autoimmune thrombocytopenia. While Thrombocytosis is a less frequent finding in patients with SLE, it might occur as an acute phase reactant and a sign of active disease.

Due to its major significance, the hematological manifestations have been added by the American Rheumatic Association as a criterion for the diagnosis and classification of SLE [2,3].

In previous studies, hematological involvement has been reported to range between 34% and 79% and it has been observed since the past two decades that it can often be the presenting manifestation of the disease [4, 5, 6]. SLE cases can present with hematological abnormalities alone, without any features of musculoskeletal, skin or other system involvement hence having significant importance in terms of morbidity and mortality. The major hematological manifestations include anemia, leukopenia, thrombo-cytopenia and the antiphospholipid antibody syndrome. Anemia especially Coomb positive hemolytic anemia is one of the most common hematological finding encountered.

The spectrum of hematological findings varies in SLE and has a large impact not only on the quality of life of the patient but also on survival. Hence it is important to be aware of the different types of involvement since their treatment requires prompt recognition of the problem and the treatment of each abnormality may be different. Hence the present study is designed to evaluate and assess the various clinical and hematological manifestations of SLE.

Objective

To study the haematological and immunological Profile of Patients with Systemic Lupus Erythematosis.

Materials and Methods

Methodology

Study setting: Kasturba Medical College and hospital, Manipal.

Study duration: January 2011 to December 2013

Type of study: Ambispective Study

Sample size: A total of One hundred twenty seven cases of SLE were classified as having SLE according to the revised American College of Rheumatology (ACR) classification criteria (1997)

Sampling technique: Convenient Sampling

Inclusion criteria

01. All cases diagnosed and proved to be SLE for the first time at our institution in various departments of the hospital during the study period.
02. Patients of all ages were included in the study.

03. Patients were included in the study irrespective of the co morbidities present.

04. Both inpatients and outpatients were included in the study.

Exclusion criteria

1. All cases that were suspicious of SLE but did not satisfy the revised American College of Rheumatology (ACR) classification criteria[5].

Data collection and analysis: The details of the history of presenting complaints, associated symptoms, past medical history, findings on physical examination, reports of the various investigations done and procedures performed along with the follow up information were obtained from the files of the patients in the medical records department.

Hematological and biochemical data was retrieved by using hospital and laboratory information system.

All patients with a diagnosis of SLE were evaluated as per the proforma that was submitted and accepted by the Ethical Committee.

Along with the details of history, physical examination and clinical examination was performed. Based on the findings of the initial investigations, patients were worked up further with specific investigations like bone marrow aspiration and biopsy, renal biopsy or skin biopsy, APLA work up, CT, MRI etc. All the information were entered in excel sheet and then analyzed using SPSS v 20.

Criteria

Anemia: Hemoglobin <12g/dl for females and < 13g/dl for males.

Hemolytic anemia: Anemia + DCT positivity

Leucopenia : Total WBC count < 4×109/l,

Thrombocytopenia: Platelet count 150×109/l

All the information were entered in excel sheet and then analyzed using SPSS v 20.

Results

A total number of 127 cases of SLE were included in the present study. Their serological and hematological manifestations were evaluated in detail by studying the ANA profile, peripheral smears, complete blood counts, bone marrows, renal biopsies etc.

The age of the patients in the present study ranged from 6 to 63 yrs (median age = 29.85 ± 12.61yrs). The male to female ratio was 1:11.7, showing a female predominance (117/127 i.e. 92%).

Hematological manifestations were frequently seen in the cases studied, which included anemia, neutropenia, lymphopenia, thrombocytopenia, pancytopenia, increased Erythrocyte sedimentation rate (ESR), presence of spherocytes, DCT positivity etc.

Table-1: Hemoglobin values of the patients

Gender	Reduced (M<13g/dl; F<12g/dl)	Normal M : 13-17g/dl F : 12-15g/dl
Males (n = 10)	9	1
Females (n = 117)	102	15

Anemia was the most common hematological abnormality observed in the patients accounting to 87.4% (111/127) of cases. Hemoglobin of patients varied from a minimum of 3.8g/dl up to 13.5g/dl (Median = 9.6±2.2). The frequency of anemia seen in male (9/10 = 90%) and female (102/117=87%) patients.

Table-2: COOMB test of the study subjects

	Direct Coomb test	Indirect coombs test
Positive	34	13
Negative	5	26

The anemia was multi-factorial in etiology. Morphologically, normocytic normochromic and microcytic hypochromic anemia were the most common types observed.

Autoimmune hemolytic anemia seen in 34 cases out of the 111 cases with anemia (34.66%), which were direct coomb test (DCT) positive Other causes for anemia included iron deficiency anemia and vitamin B12 deficiency

Table-3: RBC indices of the study subjects.

	MCV	MCH	MCHC	RBC Count	RDW
Reduced	41	41	40	40	0
Increased	3	0	0	0	50
Normal	40	42	43	43	33

The RBC indices were done in 84 patients.Among the 84 patients, 41 patients (47%) showed microcytosis and 40 patients (47%) showed a decreased RBC count.

Peripheral blood smears were done in 98 patients of whom 38 patients (39%) showed presence of spherocytes indicating hemolysisOf these 38 c

Coomb test was done in 29 cases of which 24 cases showed a positive direct coomb test.

A complete blood count was done in all the 127 patients. Among the 127 patients, total WBC count of the patients ranged from 1.5 – 18.5 x 103/µl (median = 4.6 x 103/µl), of whom 36 patients (28.3%) showed leucopenia and 11 patients (8.7%) showed leucocytosis.

Neutropenia was seen in 20 patients (15.7%) and neutrophilia in 19/127 patients (15%). Lymphopenia was seen in 38/127 patients (29.9%) and lymphocytosis in 9/127 patients (7.1%).

Table-4: Complete blood count of the patients

	Reduced	Increased	Normal
Total count 4-11 x 103/µl	36	11	80
ANC 2-7 x 103/µl	20	19	88
ALC 1-3 x 103/µl	38	9	80
Platelets 150-400 x 103/µl	53	6	66

Thrombocytopenia was a common finding and was observed in 53/127 patients (41.7%) at the time of presentation, of which 7cases were later proved to be ITP. Thrombocytosis was seen in 7 patients (5.5%) of who two patients had bleeding manifestations, two patients had infection and one patient was diagnosed with malignancy (Infiltrating ductal carcinoma of the breast)

Pancytopenia accounted to 28/127 (22%) of the cases. The erythrocyte sedimentation rate (ESR) was assessed in all except one patient and their results are displayed in chart 9. A value of >20mm/hr was taken as elevated ESR. The ESR of the patients ranged from 3 to >140mm/hr, of who 118/126 patients (94%) showed an elevated ESR while only 8/126 patients (6%) showed the ESR within the normal range.

Thrombotic events were noted in 4 cases, two of who had cerebrovascular accident (CVA), one case had CRAO, while one case had right ventricular thrombus. Coagulation studies like Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) were done in 92 patients and 90 patients respectively

The normal range of PT was taken as 13.4-16.6 seconds and aPTT was 25.2-39.2 seconds. PT of the patients ranged from 14.3 – 31.4 seconds (median = 16.32 seconds). PT was prolonged in 8/92 patients (9.7%) while it was within the normal range in the rest. The aPTT in the patients ranged from 22.1-58.4 of seconds (median = 32.3 Seconds), it was prolonged in 22/90 cases (22.22%) and reduced in 2/90 cases (2.22%). Bone marrow aspiration and biopsy was done in 14 cases, the most common indication being pancytopenia. The bone marrow was observed to be hypercellular in 5 of the 14 cases (35%), while hypocellular in 2 cases (14.28%).

Erythroid hyperplasia was seen in 5 cases. Erythroid dyspoiesis was seen in 11 cases, including bi nucleation, multinucleation and nuclear budding; myeloid dyspoiesis in 4 cases and megakaryocytic dyspoiesis was seen in all the cases, with frequent micro megakaryocytes and immature megakaryocytes (10/15 i.e. 66%). The megakaryocytes showed abnormal localization (paratrabecular) in all the cases.

Complement levels, which included the C3 and C4 levels, were assessed in 88/127 cases (69%), the results of which are displayed in chart 12. The normal range of complements was taken as 90-150mg/dl for C3 and 15-50mg/dl for C4. The values of C3 and C4 of the patients ranged from 3 – 32 mg/dl (median = 12mg/dl) for C3 levels and 12 to 88mg/dl (median = 23mg/dl) for C4 levels. Of the 88 cases, 77 cases (87.5%) showed a decreased C3 level and 80 cases (90.9%) showed a reduced C4 levels.

Table-5: Profile of autoimmune serology

	Positive	Negative
P ANCA	18	27
ANA Global	80	4
ANA Profile	104	3
An Ds DNA Ab	9	14

Autoimmune Serology was done in all the 127 cases. p-ANCA was done in 45 cases, of whom 18 cases were positive (46.15%). Among the 18 positive cases, 9 of them (50%) were diagnosed with cutaneous vasculitis proved by skin biopsy. ANA Global was done in 84 of the 127 cases, of which 80 cases (95.2%) were positive. The remaining 4 negative patients had a positive ANA profile.

ANA Profile was done in a total of 108 cases, of which 105 cases (97.22%) showed positivity. All the three cases which were negative showed ANA global positivity. Two of the three cases showed lupus nephritis, while one case showed significant proteinuria and grade one renal parenchymal changes on ultrasound.

Among the 104 positive cases, majority of the cases showed positivity to Sm (51.4%) and RNP Sm (32%). The Sm proteins, being the RNA binding proteins, are found in every cellular organism, hence is less sensitive and very specific to SLE.

The SS-A and the Ro-52 are the ribonucleoprotiens which can cross the maternal placenta hence causing neonatal lupus erythematosus (NLE). These were seen positive in 31.4% (SS-A) and 8.5% (RO-52) of the cases.

The PCNA (Anti proliferating cell nuclear antigen) antibodies were positive in 44% of the cases. PCNA are the auxiliary proteins for DNA polymerase delta and their expression are usually increased proportionally to the DNA synthesis and cell growth. They are known to be expressed in <10% of the SLE cases.

The Anti dsDNA was seen to be positive in 46.6% of the cases. This antibody has a pathogenetic role in SLE. It was observed that the presence of dsDNA positivity was correlated directly with the disease activity in the patients. The presence of strong positive ds DNA cases had a higher grade of lupus nephritis. The anti-dsDNA immune complexes deposits in the mesangial matrix and leads to complement activation hence causing inflammation and mesangial nephritis. It can also directly bind to the exposed chromatin fragments in the glomerular basement membrane hence contributing to end stage lupus nephritis.

Similar to dsDNA, the anti nucelosome and anti histone antibodies are also of a high value as diagnostic predictors of SLE. The anti nucleosome antibody is more specific and sensitive than the anti histone antibody. These antibodies were positive in 42.8% and 34.25% of the cases respectively.

The Ribosomal P antibodies are known to have neuropathogenic potential and are of prognostic importance. Thirty one out of the total 127 cases showed positivity for this antibody of who five cases were diagnosed with CNS lupus.

Discussion

Hematological manifestations were most commonly encountered in our study accounting to 87.4% of the cases, which included hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia, which were also seen as the most common manifestation in the studies by Aleem et al [5], Hu et al [6] and Sasidhar et al [7] accounting to 82.7%, 86.2% and 82% respectively. It was observed in our study that anemia was a very frequent finding among the patients accounting to 111 cases (87.4%), as against other studies by Aleem et al [5] (63%), Fathi et al [8] (43.24%), Sasidhar et al [7] (63%) andPaudyal et al [8] (28%) who reported a lesser frequency of anemia in their studies. Among the anemias, hemolytic anemia confirmed by Coomb test was commonly encountered, accounting to 34 cases(34.66%), which was high in comparison with the studies by Agarwal et al [9], Aleem et al [5], Hu et al [6] and Paudyal et al [9] who reported 8.1%, 4.6%, 12% and 1% respectively.

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Among the anemias, hemolytic anemia confirmed by Coomb test was commonly encountered, accounting to 34 cases (34.66%), which was high in comparison with the studies by Agarwal et al [10], Aleem et al [5], Beyan et al[12], Sasidhar et al[7], Chen et al[11], Hu et al[6] and Paudyal et al[9] who reported 8.1%, 4.6%, 28%, 17.5%, 14.6%, 12% and 1% respectively.

Thrombotic events were noted in 4 patients in our study accounting to 3.11%, while a study by Aleem et al [5] conducted among 624 SLE cases showed thrombotic events in 72 (10.2%) patients. On doing the coagulation studies PT was observed to be prolonged in 8/92 patients (9.7%) while it was within the normal range in the rest. The aPTT was prolonged in 22/90 cases (22.22%) and reduced in 2/90 cases (2.22%). In the study by Aleem et al the aPTT was prolonged in 152 patients accounting to 37.5%. DRVVT was done in 7 patients, of which 3 showed presence of lupus anticoagulant, in a similar study done by Aleem et al [5], 67 out of 624 cases showed lupus anticoagulant.

Antiphospholipid syndrome was diagnosed in 6 cases (5%) in our study based on clinical features along with DRVVT positivity or presence of anticardiolipin antibodies, while other studies by Beyan et al [12] and Sasidharan et al[7] showed a higher incidence of APLA in their study accounting to 11 cases (9.5%) and 19 (8.3%) cases respectively. As APLA is known to develop in patients with SLE usually at 20yr follow up, the shorter duration of follow up can be one of the causes for the lower incidence of APLA in the present study.

The bone marrow examination was done in 14 cases and was observed to be hypercellular in 5 of the 14 cases (35%), while hypocellular in 2 cases (14.28%) in our study, which is in concordance with a study of bone marrow aspiration and biopsy in 40 cases of SLE by Voulgaris et al [13] who reported normocellular marrow in 7 (17.5%), hypercellular in 10 (25%), and hypocellular in 23 (57.5%) cases.

Of the 88 cases whose complement levels were assessed, 77 cases (87.5%) showed a decreased C3 level and 80 cases (90.9%) showed a reduced C4 levels. This is in concordance with the studies by Fathi et al [8] and Beyan et al [12] who reported reduced complement levels in 119 (64.32%) and 100 (86%) respectively. Aleem et al5 reported a lesser incidence of hypocomplementemia accounting to 283(45.4%) cases.

The ANA positivity was the most common criterion satisfied in our study accounting to105/108 cases (97.22%). This is an expected finding as ANA is the most sensitive indicator of the presence of SLE and ANA negative lupus is a very rare entity.

This was in concordance with other studies by Agarwal et al [10], Sasidhar et al [7], Paudyal et al [9], Saigal et al [14] and Fathi et al [8].

Anti dsDNA was seen to be positive in 49 cases in our study accounting for 46.66% of the cases, which is relatively less frequent in comaprision with the other studies by Agarwal et al [10], Paudyal et al [9], Binoy et al[15], Saigal et al [14]and Fathi et al [8]which were 94%, 88%, 76%, 65%, 71.89% respectively.

Limitation of Study: Many patients were lost to follow up, hence we were unable to know the outcome and prognosis of the disease in them.

Studies like Bone Marrow aspiration and Biopsy was done in only few cases, hence the data available was very limited.

Conclusion

Haematological abnormalities are common findings in patients with SLE. It is important to distinguish haematological abnormalities as either manifestation of SLE, consequence of SLE treatment or as a part of another blood dyscrasia.

Hematological abnormalities are the commonest among all other manifestations in SLE, and their treatment is challenging.Bone marrow examination should be considered in all cases of severe or persistent leukopenia or thrombocytopenia in SLE, to exclude drug-induced myelotoxicity in susceptible patients.

What the study adds in the existing knowledge?

The commonest manifestation that is encountered in patients with SLE is Hematological manifestations. The patients can have a large spectrum of presentations including hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia etc.

A serious coexisting syndrome that should be evaluated is APLA, which can be confirmed by DRVVT positivity. A thorough workup, including Bone Marrow Analysis and Coagulation Profile should be done without fail in all patients with SLE as it will unmask an impending complication.

Author's contributions

The data collection and analysis was performed by **Dr. Akshatha N.,** The review of articles, introduction, references and Manuscript preparation was done by both **Dr. Akshatha N. and Dr. Shwetha Patil.** The final proof reading was done by **Dr. Shwetha Patil.**

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