Hematological aspects of systemic lupus erytematosus (SLE) – A peripheral blood and bone marrow study.

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with a multiorgan involvement. Hematological system is frequently affected in the setting of the disease. The study aims to find out the peripheral blood and bone marrow changes in SLE.

Materials and Methods: This study was carried out in the Department of pathology in collaboration with the department of medicine ,, Regional Institute of Medical Scinces , Imphal , Manipur . A total of 25 diagnosed cases of systemic lupus erythematosus (SLE) attending the out patient department and those admitted in the ward were chosen for the study . A detailed history along with a clinical general examination was followed by peripheral blood examination and bone marrow aspiration to find out the effect of the disease on the haematological system. Other test including routine urine examination , kidney function test ,ANA (Antinuclear antibodies) test and Anti –ds DNA screening method were performed to correlate the findings along with the haematological findings.

Results: Majority of the cases were in the age group of 21 - 30 years and 21 patients were of the female gender . The major findings included anemia , leucopenia , lymphopenia and thrombocytopenia . Bone marrow was normocellular in the majority of the cases and some other abnormal findings included megablastoid erythropoiesis, suppressed megakaryopoiesis and plasmacytosis in 17 of the total cases studied . Anti-nuclear antibody (ANA) was found to be positive in 21 cases and high titres of double standard DNA (dsDNA)were found in patients with anemia of chronic disease (ACD) and nutritional anemia .

Conclusion: Systemic lupus erythematosus (SLE) commonly affects women of child bearing age and these patients frequently suffer from one or the other of the hematogical complications associated with it. There maybe a distinct link between the haematological findings and the serological abnormalities found in SLE. **Keywords:** Systemic lupus erythematosus, hematological changes, peripheral blood, bone marrow.

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I. Introduction

Systemic lupus erythematosis (SLE) is a multisystem disease of autoimmune origin in which organs and cells undergo damage , mediated by tissues binding auto – antibodies and immune complexes¹ Many of the clinical manifestations of SLE are secondary to the trapping of antigen- antibody complexes in capillaries of visceral structures or to auto antibodies mediated destruction of host cells .The disease is marked by spontaneous remission and relapses and the severity may vary from mild episodic to a rapidly fulminant , life threatening illness²

SLE primarily affects women of childbearing age . The median age of onset of Indian SLE is 24 -25 years and the sex ratio 11 : 1 (F: M). A prevalence study in india found a point prevalence of 3 / 100000. This is a lower figure than reported from the west³. The auto antibodies produced in SLE recognise diverse nuclear and cytoplasmic components of the cell including auto antibodies directed against cell surface antigens of blood cells such as the red cells , platelets and lymphocytes¹. ANA II(immunoflurescence) is an effective screening assay in patients with clinical features of SLE. Most patients with ANA do not have SLE but most people with SLE have ANA. False positives are common and higher titres (> 1 / 160) are more likely to be important . Patterns might suggest antibody specificities but are not diagnostic . ANA positive samples should be subjected to more specific and precise tests for the diagnosis of SLE⁴. Double stranded DNA antibodies are associated with systemic lupus and nephritis but not sub acute cutaneous lupus or discoid lupus .dsDNA antibody assays can be negative early in disease , after treatment or when patient is in remission ; therefore , not all patients with SLE are sero – positive at any one time⁴. Antihistone antibodies (IgG and IgM) are present in 50 -80 % of patients with SLE . Titres of antihistone antibody might reflect disease activity but are not specific for SLE and

cannot distinguish between drug induced SLE from idiopathic SLE⁴. Antibodies to ENA like Antibodies to Ro (SS – A) and La (SS – B) are found in SLE and Sjorens syndrome. Neither is specipic but both are very useful when anti dsDNA is absent. Anti –Ro is associated with cutaneous involvement in sub –acute cutaneous lupus erythematosis and with congenital heart disease. High titres of Antibodies to Sm/ RNP constitute an American college of rheumatology criterion for SLE and are highly SLE – specific⁴. Anticardiolipin antibodies (ACA) of all isotopes are seen in 16- 60 % of patients with SLE. IgG ACA,s are a risk factor for thrombosis and antiphospholipid syndrome, but are controversial risk factors for renovascular events, ACA,s might be an additional risk factor for pregnancy outcome in SLE . Additional lupus anticoagulant testing is essential because lupus anticoagulant might predispose to thrombosis and might occur without ACA⁴. Complement assays are occasionally useful in SLE. A single C4 elevation is not informative and serial monitoring is necessary because C4 null alleles are common in SLE, so that the baseline C4 maybe chronically low . Persistently low C3 is associated with chronic renal disease⁴. Other antibodies detectable in SLE include anti - ribosomal antibodies, anti Clq antibodies , anti –endothelial antibodies and anti neutrophil cytoplasmic antibodies .

Haematological complications constitute a common feature of systemic lupus erythematosis (SLE). The erythrocyte sedimentation rate is a sensitive but non specific indicator of activity in SLE, and is slow to reflect changes in disease activity .Although ESR is elevated , CRP is unusualy normal unless there is serositis or infectio⁵. Anemia is common and affects most SLE patients at some time during the course of their disease. The mechanism of anemia in SLE include anemia of chronic disease, hemolysis (immune or microangiopathic) , blood loss , renal insufficiency , medications , inflammation . Overt haemolytic anemia has been reported in 10 % of patients with SLE. SLE patients may have a positive Coombs s test without overt hemolysis⁶. Leocopenia can be presenting symptom in SLE and is usually associated with disease activity. A white blood count of less than 4500/ UI has been reported in approximately 50 % of patients, especially in patients with active disease. Lymphocytopenia (Lymphocyte count < 1500/ u L) occurs in approximately 20 % of SLE patients. Proposed mechanism of lymphocytopenia include presence of cytotoxic lymphocyte antibodies in the serum of SLE patients and increased apoptosis secondary to increased Fas antigen expression on the peripheral T cells in patients with SLE. Leucocytosis can occur inSLE and reflects an infection or the use of high - dose corticosteroids⁶. Thrombocytopenia is a major complication in patients with SLE. The pathogenesis of thrombocytopenia in SLE is heterogenous but the most common mechanism is believed to be increased platelet clearance mediated by anti platelet autoantibodies, which is analogous to the mechanism seen in patients with thrombocytopenia purpura (ITP). Other potential mechanism include thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, haemophagocytic syndrome, antiphospholipin syndrome and impaired thrombopoiesis. A recent study showed that anti GPIIb /IIIa and anti thrombopoietin receptor (TPOR), antibodies are major contributory factors to SLE associated thrombocytopenia⁷.

In a study of 21 bone marrow specimens from 21 patients with SLE and peripheral cytopenias, Pereira $\rm RM^8\,$ et al found global hypocellularity in 47.6 % increased reticulin proliferation in 76.2 % with myelofibrosis in one patient and necrosis in 9 %. Plasmacytosis was present in 26.7 % of cases and in one there was a serum monoclonal component (igG Kappa). Iron stores were normal or increased in 26.7% and decreased or absent in 73.3% of the specimens. The most frequent abnormality was leucopenia in 90.4% and granulocytic hypoplasia was observed in 47.3% of these patients .The authors observed that the bone marrow maybe target organ in SLE with cytopenias .

II. Aims And Objective

To determine the peripheral blood and bone marrow changes in systemic lupus erythematosus (SLE)).
 To find out the relationship of the various haematological changes in SLE patients with the demographic variables namely age, sex, family history and the serological parameters.

III. Materials And Methods

This study was carried out in the department of pathology in collaboration with the department of Medicine , Regional Institute of Medical Sciences ,Imphal , Manipur . The materials for this study were collected from patients attending the rheumatology OPD (out patient department) and admitted in the ward during the period between October 2011 and September 2013 . The present study was based on the study of 25 cases of SLE patients. The diagnosis of SLE was done according to the 1997 update of the 1982 Revised American College pf Rheumatology (ACR), classification criteria. All the patients were subjected to peripheral blood examination and bone marrow aspiration. Some of the other test performed were routine urine examination, kidney function test ,Anti- ds DNA screening , ANA (Antinuclear antibodies) test . Reticulocyte count and perls stain were done whenever indicated.

Inclusion criteria

All patients presenting with four or more of the revised ACR criteria for the diagnosis of SLE belonging to all age groups, both the genders and economic strata were included in the study.

Exclusion criteria

SLE patients suffering from acute infection and patients receiving immunosuppressive drugs within six months prior to the bone marrow aspiration and pregnant female patients were excluded from the study.

Table 1 - Age distribution in 25 diagnosed cases of SLE.								
Sl No	Age range	No of cases	Percentage(%)					
1	1-0	1	4.0					
2	11-20	3	12.0					
3	21-30	9	36.0					
4	31-40	1	4.0					
5	41-50	8	32.0					
6	51-60	2	8.0					
7	61-70	1	4.0					
Total		25	100					

IV. Results And Observation

Out of the total 25 cases studied , the majority of the patients 36 % were in the age range of 21 - 30 years . The youngesst patient was 8 years and the oldest was 65 years old . The mean age of the patients in the study was 40.4 years .



Out of the total patients, 84 % were females and 16 % were males with a female male ratio of 5.3; 1.

Asso. BM Findings	0-10	11-20	21-30	31-40	41-50	51-60	61-70	Total
NRM	0	2	5	0	2	2	0	11
ACD	1	0	3	0	2	0	0	6
Mixed deff	0	0	0	0	1	0	0	1
MA	0	0	1	0	2	0	0	3
HA	0	1	0	0	1	0	0	2
IDA	0	0	0	1	0	0	1	2
Total	1	3	3	1	8	2	1	25

Table 2 -	Distribution	of associated	bone marro	ow findings v	with age .
				Age(Year	·s)

The commonest bone marrow finding was that of a normal reacting marrow which occured in a majority of patients in the age group of 21 - 30 years which comprised 20 % of the cases followed by ACD which was seen to be common in the age group of 21- 30 years in 12 % of the cases . Megaloblastic anemia occured in 8 % of cases in the age group of 41 - 50 years . Hypoplastic anemia was seen in 2 cases each in the age group of 11-20 years and 41-50 years . Mixed deficiency was seen in a single case in the age group of 41 - 50 years while IDA was observed in 2 cases each in the age group of 31-40 years and 61-70 years.

Table 3 – Distribution of hematological parameters .

Parameters	Range	No of cases (%)		
Hemoglobin (gm/dl)	4.4 - 5	2(8%)		
	5.1 - 6	4 (16%)		

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	6.1 – 7	2(8%)
	7.1-8	4 (16 %)
	8.1 -9	4 (16 %)
	9.1 - 10	3 (12 %)
	10.1 - 11	3 (12%)
	11.1 – 12	3 (12%)
Total laucocyte count (/cumm.)	3000 4000	11(44.94)
	4001 - 5000	11 (44 70)
	5001 - 6000	2 (8%)
	6001 - 7000	5 (20%)
	7001 - 8000	3 (12%)
	8001 - 9000	1 (14%)
	9001 - 10000	2 (8%)
Platelet count (/cumm)	1 - 50000	3(12%)
	50001 - 100000	7 (28%)
	10001 - 150000	2 (8%)
	150001 - 200000	10 (40%)
	200001 - 250000	3 (12%)
ESP(mm/1 hr)	50	6(245)
	51 - 100	$\frac{0(2+3)}{14(56\%)}$
	101 - 150	5 (20%)

In this study, the haemoglobin percentage varied from 5 - 12 gm/dl. The least haemoglobin level recorded was 5 gms/dl in a case of hypoplastic anemia and the highest haemoglobin recorded was 12 gms/dl seen in a case of SLE with normal reacting marrow. The total leucocytec count in the maximum number of patients 11 (44 %) were seen in the range of 3000 - 5000/ cumm. The lowest TLC recorded was 2000 / cumm in a case of megaloblastic anemia and the highest TLC recorded 9700 /cumm was seen in a case of normal reacting marrow (NRM) . The majority of the cases 40 % had platelet count in the range of 150001 - 200000 / cumm followed by 28 % of cases having platelet count in the range of 50001 - 100000 / cumm. ESR ranged from $20 - 120 \text{ mm} / 1^{st}$ hr . Majority of cases(56 %) had ESR in the range of 51 - 100 mm / hr.





Anemia was observed in the majority of cases (76%) in the study and was found to be absent in 24 % of the cases. The majority of the cases presenting with anemia were females (78.6%) and males comprised only 21.1 % of cases presenting with anemia.



Leucopenia which was categorised as those cases with a total leucocyte count of < 4000 uLl was found to be present in 40 % of the cases and absent in 60 % of the cases . Leucopenia was found in 90 % of females and 10 % of males .



Fig 4 . Distribution of thrombocytopenia .

Thrombocytopenia was found to be positive in 40 % of the cses and it was found to be negative in 60 % of the cases . The distribution of thrombocytopenia with sex revealed that it was found in increased frequency in case of female patients accounting for 80 % of the cases with thrombocytopenia . Males had a decreased frequency of thrombocytopenia compared to the females occuring only in 20 % of the cases .



Lymphopenia defined as total lymphocyte count < 1500uL was present in 32 % of the cases and absent in 68% of the cases .The majority of cases presenting with lymphopenia were females accounting for 87.5 % and only 12.5 % of cases males presented with lymphopenia.

					0.0	
			RBC Morphol	ogy		
Assoc BM	Normocytic	Microcytic	Macro -	Dimorphic	Findings	Normochromic
Hypochromic	Ovalocutes					

Table 4 – Distribution of RBC morphology with bone marrow findings.	
RBC Morphology	

NRM	11	0	0	0	11
ACD	6	0	0	0	6
Mixed deff	0	0	0	1	1
MA	0	0	3	0	3
HA	2	0	0	0	2
IDA	0	2	0	0	2
Total	19	2	3	1	25

As shown in table 6 ,normocytic, normochromic RBCs was present in majority of cases with NRM occuring in 44% of the cases followed by 24% of cses with ACD. Macro-ovalocytes were seen in 12% of the cases of megaloblastic anemia . Microcytic hypochromic RBCs was seen in 4 % of the cases with IDA . Dimorphic blood picture was seen in a single case of mixed deficiency. Hypoplastic anemia was observed in 4 % of the cases with normocytic normochromic RBC s.

Bone marrow findings Cellularity :



Bone marrow was norm ocellular in 76 % of the cases and hypercellular in 12 % of the cases . Hypocellular marrow was encountered in 12 % of the cases studied.

Associated Bone Marrow Findings								
Parameters	NRM	AC	D Mixed	Deff	M	A	HA	IDA
Erythropoiesis								
Normoblastic	10	4	0	0	2	0		
Megaloblastoid	0	0	0	3	0	0		
Dyspoietic	1	2	0	0	0	0		
Micronormoblastic&								
Megaloblastoid	0	0	1	0	0	0		
Micronormoblastic	0	0	0	0	0	2		
Mylopoiesis								
Wnl	11	6	1	3	2	2		
Megakaryopoiesis								
Adequate	9	5	1	2	0	2		
Suppressed	1	0	0	1	2	0		
Increased	1	0	0	0	0	0		
Dyspoietic	0	1	0	0	0	0		

 Table 5 – Distribution of the various bone marrow parameters with the associated bone marrow findings .

 Associated Bone Marrow Findings

Erythropoiesis was predominantly normoblastic in maximum of the cases (40%) with a normal reacting marrow. Megaloblastoid erythropoiesis was seen in 12 % of the cses. Dyspoietic erythropoiesis was seen in 8 % of cases with ACD. 8% of the cases of IDA showed micronormoblastic erythropoiesis. A single case of mixed deficiency was also encountered. Myelopoiesis was within normal limits in all the cases studied. Megakaropoiesis was adequate with active platelet formation in a majority of cases with NRM comprising 36 % of cases. Suppresed megakaryopoiesis was seen in 8 % of cases with anemia. Increased megakaryopoiesis was observed in 4 % case of NRM and dyspoietic megakaryopoiesis was seen in 14 % of the cases with ACD.





An added interesting finding in the study was that of bone marrow plasmacytosis which was defined as plasma cells more than 5% was observed to be present in 68% of the cases studied .



The distribution of anti nuclear antibody (ANA) was found to be variable in all the cases studied . ANA was found to be positive in a total of 84 % of cases .Cases with NRM showed a positivity in 8 cases (32 %) followed by positivity in 6 cases (24 %) with ACD .Megaloblastic anemia had a positive ANA in 3 (12%) cases whereas it was positive in 1 (4 %) case each of nutritional anemia and hypoplastic anemia.



The commonest frequency of the ds DNA titre observed in the patients studied were in the range of 101- 200 IU / ml in 44 % of the cases , folloed by 24 5 of cases having the titre in the range of 0 – 100 IU / ml and 20 % having the titre in the range of 201 -300 IU/ ml .There were 12 % with a ds DNA titre in the range of 301 – 400 IU /ml . The highest titre of ds DNA recorded was 400 IU /ml seen in 8 % of the cases which included 1 case each with ACD and nutritional anemia and the lowest titre was 40 IU / ml recorded in a patient of NRM .





Fig10(b)



Fig10(c)

Fig10(d)

Fig10(a): Photomicrograph of bone marrow aspirate smear showing a hypocellular marrow in case of hypoplastic anemia. Leishman's stain. X 100.

Fig 10(b): Photomicrograph of bone marrow aspirate smear showing megaloblastoid erythropoiesis with features of dyserythropoiesis. Leishman's stain. X 1000.

Fig10(c): Photomicrograph of bone marrow aspirate smear showing a increased plasma cells. . Leishman's stain. X 1000.

Fig10(d): Photomicrograph of bone marrow aspirate smear showing increased iron stores(Grade-3)Perl's stain. X 100.

V. Discussion

SLE is a fairy common disease with prevalence rate that maybe as high as 1 in 2500 in certain populations⁹.Prevalence rate s in SLE are estimated to be 51 per 100000 in the united states , the highest prevalence amongst the ethnic groups⁹. The present study of 25 cases with SLE shows that there were 21 (81 %) females and 4 (16 %) males with a female male ratio of 5.3 :1 The majority of the patients 9 (36 %) were in the age group of 41- 50 years . This finding correlates with the findings reported by Lahita RG¹⁰

In the present study ANA was found to be positive in 21 (84%) of the cases. Cases with normal reacting marrow (NRM) showed a positivity in 8 cases (24%) followed by positivity in 6 (16%) of cases with anemia of chronic disease (ACD). The test is a sensitive one because 90% of patients with SLE are ANA positive. Although a small group of patients seem to have persistently ANA negative SLE¹¹.

All the patients in this study had a positive Anti ds DNA titre . The highest titre of anti dsDNA recorded in the study was 400IU/ml seen in 2 cases , 1 each in patients with ACD and nutritional anemia. The Anti ds DNA result is quantified and this value is often a measure of the activity of the disease, but there is a group of patients who have a persistently high anti ds DNA antibody level but no clinically active disease¹¹.

The commonest range of the erythrocyte sedimentation rate recorded in this study was 51- 100 mm/1st hr observed in 14 (56%) of the cases. The findings correlates with those recorded by Ahmed¹². Haematological abnormalities were found in 76% of the cases in this study which is comparable to the findings of 71.18 % reported by Chen JL¹³. Hematological abnormalities were found in 86 % of children with SLE in a study done by Gokce¹⁴. In the present study, anemia was found to be present in 19 (76%) cases out of which 15 (78.9%) were females and 4(21.1 %) males. Normocytic normochromic RBCs was seen in 11 (44%) cases of NRM, followed by 6 (24%) cases with ACD. Hypoplastic anemia found in 2 (8%) cases with normocytic normochromic RBCs. The above findings are comparable to the findings observed by Sashidharan P K 15 Leucopenia which was grouped as those cases having total leucocyte count < 4000ul was found to be present in 10 (40%) out of which 9(90%) were females and only 1(10%) was a male. These findings are similar to the findings observed by Michaeal et al¹⁶ which showed the presence of leucopenia in 47 (39.63%) of the 111 SLE patients studied . Thrombocytopenia was found in 10(40%) of the cases in this study which is similar to the findings of thrombocytopenia in a study conducted by Beyan¹⁷. The causes of thrombocytopenia which is a common finding in SLE patients include platelet destruction, ineffective hematopoiesis, abnormal platelet pooling, bone marrow hypoplasia and dilutional thrombocytopenia related to therapy. Lymphopenia was found in 8(32%) of the cases in this study out of which 7 (87.5%) of the cases were females .the commonest range of patients with lymphopenia was 41-50 years. The findings are comparable to the results observed by Rivero¹⁸.

Bone marrow aspiration was found to be normocellular in 76% of the cases followed by hypercellular and hypocellular marrow in 12% of the cases each . The findings are comparable to the results obtained by Michael SR (12). Voulgarelis M^{19} in their study of 40 SLE patients found that 7 (17.5%) cases has a normocellular marrow while hypercellularity of the marrow was seen in 10 (25%) and hypocellular in 23 (57.5%) of the cases . The decreased frequency of both hypercellular and hypocellular marrow in the present study could be due to a concurrent low frequency of megaloblastic anemia and hypoplastic marrow in the study as compared to the study done by other authors . Erythropoiesis was normoblastic in 16(64%), megaloblastoid in 3 (12%) and dyspoietic in 3 (12%). Clen JL¹³ observed similar findings where it was observed that bone marrow erythropoiesis was within normal limits except in 2 cases where erythropoiesis was decreased .

Myelopoiesis in the present study were within normal limits . However, in a study by Deleze M^{20} , revealed myeloid hyperplasia in 14.28 % of the cases. The probable reason for such a difference could be because this study included all the diagnosed case of SLE without any knowledge of the haematological status unlike in the other study which included only neutropenic patients suffering from SLE. Megakaryopoiesis in the present study was increased in 1(14 %) of the cases, suppressed in 4 (16 %) of the cases. This findings correlates with the finding in the study by Deleze M^{20} . Dyspoietic features were seen in 4 (16 %) of the cases which included 3 (12%) cases of dyserythropoiesis and 1 (4%) cases of dysmegakaryopoiesis . Myeloid lineage failed to show any dyspoietic change. The findings are similar to the findings of Voulgaraelis M¹⁹. Reactive plasmacytosis was observed in 8 (32%) of the cases studied which is comparable to the findings of Wanitpongpun C^{21} were plasmacytosis occurred in 35% of the cases with SLE and Feng CS²²). where plasmacytosis was reported in 2 (8.6 %) of the 23 lupus patients wit pancytopenia .During the course of the present study a single case of coombs positive haemolytic anemia was encountered in a 14 year old female patient. The occurrence of haemolytic anemina in association with SLE has been reported by various authors including Antolin JL²³ and Nossent JC^{24} . Beyan E^{17} reported haemolytic anemia in 28% of the total 115 cases of SLE patients studied .The low prevalence of haemolytic anemia in the present study could be attributed to the small sample size as compared to the other studies.

VI. Conclusion

Hematological complications constitute a common feature of systemic lupus erythromatosis (SLE). Anemia was a common feature of the cases at the time of presentation. Other haematological abnormalities included leucopenia , thrombocytopenia and lymphopenia. Bone marrow abnormalities include megaloblastoid changes, dysmegakaryopoiesis and plasmacytosis .Correlation between the haematological abnormalities like anemia and other cytopenias reveal a distinct relation between it and the abnormal serological titres also . We conclude that as distinct therapeutic approaches are required to treat the various causes of anemia in SLE patients, bone marrow aspiration if performed routinely may prove to an effective tool to reveal the cause of anemia in these patients and therefore augment improved management of SLE patients with haematological complications.

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