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Study of Prevalence, Clinical Profile and Outcome of Autoimmune Haemolytic Anaemia in Patients with Systemic Lupus Erythematosus

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Abstract **Original Research Article**

Systemic Lupus Erythematous is a multisystem autoimmune connective tissue disorder. Hematological manifestations of SLE are diverse and mostly are the presenting manifestations of the disease. Many SLE cases present with anemia, leucopenia and thrombocytopenia mainly in young females, diagnosed with high index of suspicion and after regular follow up. In the present article we have studied, prevalence of autoimmune hemolytic anemia in Systemic Lupus Erythematous patients and outcome, in teaching medical institute attached to tertiary referral centre.

Key words: Systemic Lupus Erythematous (SLE), autoimmune hemolytic anemia (AIHA), DCT & ICT (Direct & Indirect Coomb's Test). SLEDAI (SLE Disease Activity Index), SLICC-SLE International Collaboration Clinics.

INTRODUCTION

SLE is a multisystem autoimmune connective tissue disorder with variable clinical presentations. The disease course is unpredictable, with flares alternating with remissions. SLE is also known as "the great imitators" because it often mimics other illnesses. SLE is a classical disease in many differential diagnoses. The systems involved in SLE are musculoskeletal, cutaneous, renal, nervous system, hematological, vascular, pulmonary, gastrointestinal and ocular. Hematological manifestations of SLE are diverse and mostly are the presenting manifestations of the disease [1-3]. The major hematologic manifestations of SLE are anemia, leucopenia, thrombocytopenia, and the anti-phospholipid antibody syndrome (APLAs). It has been observed since the last two decades many cases of SLE present with hematological abnormalities alone or with other system involvement. Some of these cases present with anemia, thrombocytopenia, pancytopenia, or thrombotic episodes, especially in young females.

Hematological manifestations affecting one or more blood cell lineage are frequent in SLE and anemia is most common finding. This study was conducted to estimate the proportion of patients with prevalence of Autoimmune Haemolytic anaemia in systemic lupus erythematosus and its Clinical profile by study of immunological and clinical parameters and to study correlation between severity of Autoimmune Haemolytic Anaemia and disease activity by (SLEDAI) score[4].

MATERIAL AND METHOD

This is an observational and prospective study. After obtaining institutional review board permission and written informed consent of patient (or guardian) who fulfill inclusion and exclusion criteria, subjects were recruited over the period of one year. Study conducted over a period of 18 months. 80 subjects were enrolled in study. Comprehensive clinical examination including brief physical examination and systemic examination was done. 80 SLE patients were included in this study and investigated for anemia. Patients with hemoglobinopathies and other connective tissue disorders were excluded. A questionnaire was used to gather data prospectively. Demographic data on age, sex, age of onset of symptoms of SLE and anemia were recorded. Patients were enrolled as per ACR 2010 EULAR criteria for SLE. Laboratory data including complete blood count, erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), liver function test, Anti-nuclear antibody (ANA), Anti Ds DNA, Anti SM, C3,C4,urine R/M, 2DEcho,Direct and Indirect Coomb's test were recorded in case record form. Clinical profile of AIHA in SLE patients was studied according to SLICC criteria and disease activity was measured by SLEDAI score. SLEDAI was calculated at the beginning and at the end of 3 months of study to evaluate treatment response to AIHA in a tertiary care centre.

RESULTS

In study of total 80 SLE patients, 79 (98.7%) patients were females and 1(1.25%) patient was male. Maximum, 45(56.25%) patients were in the age group 20-30 years, followed by 19 (23.75%) were of age group 30-40 years. Most of the patients were in the age group between 20-40 years accounting 80% and a mean of 29.01± 8.28 (SD) years in females and 20 years in males (Table1).

The most common clinical manifestations, in chronological orders were, musculoskeletal 44(55%), followed by, mucocutaneous 34(42.5%), renal symptoms 33(41.25%), constitutional 32(40%), hematological 21(26.25%), neuropsychiatric 10(12.5%), then, followed by cardiac 3(3.75%) in SLE out of total 80 SLE patients (Table 2).

Out of 80 patients, 45 patients had anemia (56.25%). 17(21.25%) had autoimmune hemolytic anemia and 28(35%) had other causes for anemia out of 80 SLE patients. 24 (30%) patients were Coomb's test positive out of total 80 SLE patients.Out of 17 patients of SLE with AIHA, SLEDAI score was > 20 in 7(41.17%) patients and had severe anemia ($p<0.04$) which is statistically significant**.** SLE with AIHA with thrombocytopenia was in 10(12.5%) patients out of 80 SLE patients (Table 3).

Table-1: Association between Age and SLE patients

Age	No of patients (N=80) (M-1,F-79)	%
<20	8	10
20-30	45	56.25
30-40	19	23.75
40-50	5	6.25
50-60	3	3.75

Table-2: Clinical manifestations of study population of SLE patients and SLE with AIHA patients

Symptoms	SLE patients (N=80)	SLE with AIHA(N=17)
Constitutional	32(40%)	8(47.05%)
Musculoskeletal	44(55%)	4(23.52%)
Renal	33(41.25%)	8(47.05%)
Cardiac	3(3.75%)	3(17.64%)
Neuropsychiatric	10(12.5%)	4(23.52%)
Mucocutaneous	34(42.5%)	6(35.29%)
Hematological	21(26.25%)	17(100%)

Table-3: Correlation between SLE with AIHA & SLEDAI

SR NO.	Characteristics	%
1	Total no. of patients	80(100%)
2	Anaemia	45 (56.25%)
3	SLE with AIHA	17(21.25%)
4	DCT/ICT Positive	24(30%)
5	DCT/ICT Negative	56(61.75%)
6	Anaemia due to other causes	28(35%)
7	Leucopenia(<3000/cumm)	4(23.5%)
8	Thrombocytopenia(<1L/cumm)	10(58.8%)
9	SLEDAI<20	10(58.8%)
	Mild Anaemia (Hb-11-12.9gm %)	0
	Moderate (Hb-8-10.9gm %)	4(40%)
	Severe (Hb- <8 gm %)	6(60%)
10	SLEDAI >20	7(41.17%)
	Mild Anaemia	0
	Moderate	2(28.5%)
	Severe	5(71.42%)
11	SLE with AIHA with Thrombocytopenia	10(12.5%)

DISCUSSION

Aim of the present study, was to find prevalence, clinical profile and outcome of autoimmune hemolytic anemia in Systemic Lupus Erythematosus.80 diagnosed SLE patients were included in the study. P. K. Sashidharan *et al*. had studied SLE with all types of

anemia and has found most common anemia as AIHA in SLE [1]. According to study done by Domiciano *et al.* AIHA in SLE mostly associated with thrombocytopenia [5]. The prevalence of AIHA in SLE is 17.55% in P.K. Sashidharan *et al*. Study and 5-10% in Domiciano *et al*. study. In our study, prevalence of AIHA in SLE is 21.25%.

Immune hemolytic anemia is classified as autoimmune, alloimmune and drug induced based on the antigenic stimulus responsible for immune response. AIHA incidence is estimated as 1-3 per 1,00,000 general population. Warm antibodies are responsible for 40-70% of AIHA, the ultimate etiology is unknown. In warm AIHA, the target epitopes are Rh proteins. Initial immune response to a foreign antigen starts to cross react with the Rh proteins and the immune system fails to suppress this autoreactive response leading to hemolysis. In IgG –mediated hemolysis, the red cells get coated with IgG molecules, which mark the cells for uptake and destruction by splenic macrophages. Cold antibodies are responsible for 13-15% of AIHA.In cold AIHA, IgM molecules fix the complement to the surface of red blood cells. This can lead to activation on complement cascade resulting in red cells lysis, process stops at C3 stage, leading to C3 coated red cells, which are taken up by hepatic macrophages. AIHA is seen in 5-10% of SLE patients with anemia [6-9]. Positive direct combs' test is seen in 18 - 65% with SLE. AIHA is a marker of SLE.

Other causes of anemia, other than AIHA, in our study contributes to 28(62.22%) out of 45 anemia patients, which includes anemia of chronic disease, Iron deficiency anaemia, anemia due to renal insufficiency, red cell aplasia, Microangiopathic hemolytic anemia. Chronic inflammation causes suppression of erythropoiesis results in this type of anemia which is normocytic and normochromic with a relatively low reticulocyte count, being the most common form (60 to 80 %) [10, 11]. Hepcidin, a central regulator of iron homeostasis inhibits the release of iron from macrophages and iron absorption in the small intestine, results in reduced serum iron despite normal ferritin and bone marrow stores. The pathophysiologic mechanisms behind a mild to moderate normocytic-hypochromic anemia remains obscure [12].

One proposed mechanism for anemia is decreased erythropoietin (EPO) levels and resistance to its action in several autoimmune diseases 13-15. The impaired EPO levels and its resistance is the result of inhibitory action of inflammatory cytokines such as IL - 1, TNF – α, TNF- β and TGF- β [16]. Overproduction of these cytokines has been associated with primary resistance of haemopoietic progenitors to the action of EPO [17-18].

Steroids are the treatment of choice in AIHA with SLE [19]. Pulse therapy response is seen in one week as raised relic count with rise of Hb 2-3 gm per week. Blood transfusion along with steroids to maintain Hb at 10 gm%. Once Hb reaches 10 gm%, dose of steroids reduced by 50 % over 4 to 6 weeks and slow tapering over 4-6 months. Relapse occurs in 40 to 50% of patients requiring maintenance dose of more than 15 mg per day. Complete remission with steroids reported in only 16-35% of patients. IV Cyclophosphamide can be given. Second line treatment for refractory AIHA is IV Rituximab, splenectomy [20]. Azathioprine Mycophenolate Mofetil is also shown to induce remission [21, 22].

CONCLUSIONS

In the present study the prevalence of AIHA in SLE is 21.25%. In SLE with AIHA, patients with greater SLEDAI score (SLEDAI ≥ 20) have greater degrees of anemia and with significant p value of ($p < 0.04$). 70% of AIHA patients had severe anemia at presentation and after therapy at three months of follow up, 29.41% patients had mild anemia and 35.29% had normal Hb level ($P < 0.001$).

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