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Prevalence, Clinical Profile, and Outcome of Autoimmune HemolyticAnemia in Patients with Systemic Lupus Erythematosus

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ABSTRACT
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. This is an observational and prospective study was carried out at Dept. of Medicine, (Medicine), 250 Beded Mohammad Ali Hospital, Bogura, Bangladesh from January to December 2023. 120 SLE patients were included in this study and investigated for anemia. 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.In study of total 120 SLE patients, 110 (91.6%) patients were females and 10(8.4%) patient was male. Maximum, 68(56.6%) patients were in the age group 20-30 years, followed by 28 (23.4%) 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.The most common clinical manifestations, in chronological orders were, musculoskeletal 66 (55%), followed by, mucocutaneous 51(42.5%), renal symptoms 50(41.6%), constitutional 48(40%), hematological 31 (25.8%), neuropsychiatric 15(12.5%), then, followed by cardiac 5 (4.2%) in SLE out of total 120 SLE patients.Out of 25 patients of SLE with AIHA, SLEDAI score was > 20 in 10 (40.0%) patients and had severe anemia ($p<0.04$) which is statistically significant**.** SLE with AIHA with thrombocytopenia was in 3 (12.0%) patients out of 120 SLE patients.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, 28.0% patients had mild anemia and 36.0% had normal Hb level ($P < 0.001$).

Keywords: Systemic Lupus Erythematous (SLE), autoimmune hemolytic anemia (AIHA), SLEDAI (SLE Disease Activity Index), SLICC-SLE International Collaboration Clinics.

I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical features.[1] Clinical manifestations are associated with many autoantibodies, ensuing immune complex formation and deposition, and other immune processes.[2,3] Hematological abnormalities are common in children with SLE, with an incidence of 34% to 82.7%.[4] Anemia, thrombocytopenia, and leucopenia are common hematological manifestations in pediatric SLE patients.[4] Hematological involvement may result from bone marrow failure or excessive peripheral cell destruction, both of which may be immune-mediated.[5] Hematological abnormalities develop at the time of diagnosis and throughout the course of the disease. Knowledge and awareness of patients with hematological involvement are essential for making an appropriate diagnosis and management.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 [6-8].Autoimmune hemolyticanemia (AIHA) a classification criteria for SLE.[2] The mechanism is thought to be caused by the

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destruction of red blood cells through warm or cold antibodies.[9] Patients with AIHA may present with symptoms of anemia or hemolysis or symptoms of an underlying disorder. Severe hemolysis may lead to hepatosplenomegaly, hemoglobinuria, and signs of heart failure.[10] Managing patients with AIHA may be challenging because specific therapy should be individualized in accordance with the disease manifestations and its severity.[11]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 Haemolyticanaemia in systemic lupus erythematosus and its Clinical profile by study of immunological and clinical parameters and to study correlation between severity of Autoimmune HaemolyticAnaemia and disease activity by (SLEDAI) score [12].

II. MATERIAL AND METHODS

This is an observational and prospective study was carried out at Dept. of Medicine, (Medicine), 250 Beded Mohammad Ali Hospital, Bogura, Bangladesh from January to December 2023. 120 SLE patients were included in this study and investigated for anemia. 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 12 months. Comprehensive clinical examination including brief physical examination and systemic examination was done. 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.

All data collected was presented in mean and percentages. Data of immunological parameters, SLED and SLIC C/ACRSLE damage index were analyzed using Cho square test. A p value of <0.05 was considered significant.

III. RESULTS

In study of total 120 SLE patients, 110 (91.6%) patients were females and 10(8.4%) patient was male. Maximum, 68(56.6%) patients were in the age group 20-30 years, followed by 28 (23.4%) 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 (Table-1).

Table-1: Association between Age and SLE patients

Age	No of patients (N=120)(M-10,F-110)	%
<20	12	10
20-30	68	56.6
30-40	28	23.4
40-50	7	5.8
50-60	5	4.2

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

Symptoms	SLE patients(N=80)	SLEwithAIHA(N=25)
Constitutional	48(40%)	11(44.0%)
Musculoskeletal	66(55%)	6(24.0%)
Renal	50(41.6%)	11(44.0%)
Cardiac	5 (4.2%)	5(20.0%)
Neuropsychiatric	15(12.5%)	6(24.0%)

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Mucocutaneous	51(42.5%)	9(36.0%)
Hematological	31(25.8%)	25(100%)

The most common clinical manifestations, in chronological orders were, musculoskeletal 66 (55%), followed by, mucocutaneous51(42.5%), renal symptoms 50(41.6%), constitutional 48(40%), hematological 31 (25.8%), neuropsychiatric 15(12.5%), then, followed by cardiac 5 (4.2%) in SLE out of total 120 SLE patients (Table 2).

Table-3: Correlation between SLE with AIHA & SLEDAI

Characteristics	**%**
Totalno.ofpatients	120 (100%)
Anaemia	67(55.9%)
SLEwithAIHA	25 (20.8%)
DCT/ICTPositive	36 (30%)
DCT/ICTNegative	74 (61.6%)
Anaemiaduetoothercauses	42 (35%)
Leucopenia(<3000/cumm)	6 (24.0%)
Thrombocytopenia(<1L/cumm)	15 (60.0%)
SLEDAI<20	15 (6.0%)
MildAnaemia(Hb-11-12.9gm%)	0
Moderate(Hb-8-10.9gm%)	10(4.0%)
Severe(Hb-<8 gm%)	15(60%)
SLEDAI>20	10(40.0%)
MildAnaemia	0
Moderate	7(28.0%)
Severe	18(72.0%)
SLEwithAIHAwithThrombocytopenia	3 (12.0%)

Out of 80 patients, 65 patients had anemia (55.9%). 25 (20.8%) had autoimmune hemolytic anemia and 42 (35%) had other causes for anemia out of 120 SLE patients. 36 (30%) patients were Coomb's test positive out of total 120 SLE patients.Out of 25 patients of SLE with AIHA, SLEDAI score was > 20 in 10 (40.0%) patients and had severe anemia ($p<0.04$) which is statistically significant**.** SLE with AIHA with thrombocytopenia was in 3 (12.0%) patients out of 120 SLE patients (Table-3).

IV. DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic multi system autoimmune disorder mainly affecting young women.[13] While there has been a significant improvement in the survival of these patients over the past four decades, the incidence of SLE has nearly tripled in the same period.[14] The development of SLE is dependent on environmental and genetic factors, though, the mechanisms behind clinical findings and etiologic events remain largely unclear.[15] Prevalence rates and predominant symptoms differ in different ethnic populations.[16] Several studies have shown that SLE is more common among Asians when compared to Caucasians. **In this** present study, was to find prevalence, clinical profile and outcome of autoimmune hemolytic anemia in Systemic Lupus Erythematosus. 120 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 [6]. According to study done by Domiciano et al. AIHA in SLE mostly associated with thrombocytopenia [17]. 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 20.8%.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. About 50% of people with lupus will experience anemia. The most common form of anemia in people with lupus is anemia of chronic disease, a condition where inflammation stops the body from using iron stores. People with lupus also get other forms of anemia, such as iron-deficiency anemia. 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 is unable to suppress this self-reactive response, resulting in hemolysis. In IgG-mediated hemolysis, redblood cells are coated with IgG molecules, which mark the cells for uptake and destruction by macrophages in the spleen. Cold antibodies account for 13-15% of AIHA. In cold AIHA, IgM molecules fix complement to the surface of red blood cells, which can activate the complement cascade and cause red blood cell lysis. The process stops at the C3 stage, generating C3-coated red blood cells that are taken up by macrophages in the liver. AIHA occurs in 5-10% of SLE patients with anemia [18-21]. The direct Comb test is positive in 18-65% of SLE patients. AIHA is a marker for SLE.One proposed mechanism for anemia is decreased erythropoietin (EPO) levels and resistance to its action in several autoimmune diseases [22-24]. 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 [25]. Overproduction of these cytokines has been associated with primary resistance of haemopoietic progenitors to the action of EPO [26,27]. Steroids are the treatment of choice in AIHA with SLE [28]. 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 [29]. Azathioprine MycophenolateMofetil is also shown to induce remission [30,31].Other causes of anemia, other than AIHA, in our study contributes to 42(62.6%) out of 67 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 %) [32,33]. 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 [34].

V. CONCLUSION

In the present study the prevalence of AIHA in SLE is 20.8%. 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, 28.0% patients had mild anemia and 36.0% had normal Hb level ($P < 0.001$).

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