

Frequency of anaemia in patients with systemic lupus erythematosus at tertiary care hospitals

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Abstract

Objective: To analyze the frequency and causes of anaemia in systemic lupus erythematosus (SLE) patients attending in department of medicine at tertiary care hospitals.

Methods: This retrospective, descriptive and analytical study was planned to analyze the frequency and causes of anaemia in SLE patients attending the department of medicine at (MMC) and (LUMHS) hospitals during the period of Jan 2006 to Nov 2008. The criteria used in this study were from the American College of Rheumatology. Investigations recorded were blood complete picture, absolute values, peripheral smear, and reticulocyte count in all patients of anaemia. These investigations were necessary to analyse the cases of anaemia in SLE. All investigations were not done in all cases. Patients with hypochromic microcytic anaemia were advised to have serum iron and ferritin levels, seven patients with macrocytic anaemia were advised to have direct and indirect coomb's test, LFTs, serum LDH, serum B12 and folate levels. Patients with normochromic and normocytic anaemia were considered to have anaemia of chronic disease. Bone marrow aspiration and Hb electrophoresis were done in two patients with anaemia of chronic disease. Thirty adult patients were included in this study. Special proforma were prepared to record the information from case sheets of patients including basic information, symptomatology and laboratory investigations. Severity and various types of anaemias were recorded. Anaemia was graded according to severity, as mild (Hb 10-12 G/dl), Moderate (Hb 8-10 G/dl) and severe (Hb < 8 G/dl). Haemoglobinopathies and other types of anaemias were excluded from study.

Results: Thirty adult diagnosed patients of SLE, were included. Their ages ranged from twenty years to fifty years at time of presentation. The mean age \pm SD (range) was 28 ± 6.22 (20-50) years and median age was 31 years. Out of thirty patients, twenty seven (90%) were females and three (10%) were males. Twenty eight (93.33%) patients presented with anaemia, 14 (46.66%) patients were of mild anaemia, 8 (26.66%) patients were of moderate grade anaemia and 6 (20%) patients had severe anaemia. Iron deficiency anaemia was found in 9 (30%) patients, 12 (40%) patients had anaemia of chronic disease and 7 (23.33%) patients had haemolytic anaemia, out of these 7 patients, 5 (16.66%) patients had Coomb's positive haemolytic anaemia. All thirty patients had ANA positive titres $>1:80$; and nineteen (63.33%) patients had anti ds DNA positive, titres $>1:10$.

Conclusion: Haematologic abnormalities are common manifestations in patients with SLE. Most patients exhibit anaemia at some point during their disease course (JPMA 60:822; 2010).

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can be fatal. It is one of the types of lupus which affects multiple organ systems and is multifactorial in etiology.¹ It has been observed that the level of cytokines will increase, along with disease activity, in line with the finding that serum levels of tumour necrosis factor (TNF) and interferon- α (IFN) correlate. In addition, TNF may directly stimulate the

interferon pathway by inducing IFN- α .²

Haemolytic anaemia is a forme fruste of SLE, being observed months or even years before the onset of other clinical manifestations in some patients. SLE is a complex autoimmune disease characterized by autoantibody production and tissue injury. The prevalence of lupus ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among blacks.³ Its onset typically occurring in women of

child-bearing age (female/male, ratio 9:1).⁴ African Americans are three times more likely to be affected than European Americans, who, manifest SLE at an earlier age, and have a clinically more severe phenotype than other American racial groups. In the United States, the number of patients with lupus exceeds 250,000. The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s⁵ to a 15-year survival rate of 80% today.⁶ Even so, a patient in whom Lupus is diagnosed at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection.⁷ Later, myocardial infarction and stroke became important causes of death. This bimodal pattern of mortality in lupus has been recognized since more than 30 years ago.

As 90% of patients with lupus are females, an important role for female hormones seems likely, but a protective role for male hormones or an effect of genes on the X chromosome is also possible.⁸ Everyone in medicine and related fields understand that there are marked sex-based differences in the epidemiology, clinical manifestations, course, and therapy of disease.⁹ Although, very few of these differences are understood in molecular or cellular terms, the explanations must derive from the fundamental biologic differences between the sexes. The mother's role in directly nurturing the foetus during gestation is a special circumstance that may have important meaning for disparity between the sexes; Autoimmune disorders such as Graves' disease, SLE, scleroderma, and multiple sclerosis share few clinical features, but these diseases affect women 3 to 10 times as often as men. The time-honoured assumption was that gonadal steroids had a major role in this disparity, however, foetal cells can persist in the mother's circulation for decades after delivery suggests presence of foreign cells which provide antigenic exposure that may be the source of heightened immune reactions in women.¹⁰

Although the aetiology of SLE is undetermined, both genetic and environmental factors are involved. Evidence of a genetic component includes familial clustering, and higher concordance rates between monozygotic twins (>20%) relative to dizygotic twins and other full siblings (2-5%). SLE is a clinically heterogeneous disease in which the risk of disease is influenced by complex genetic and environmental contributions. Alleles of HLA-DRB1, IRF5, and STAT4 are established susceptibility genes; there is strong evidence for the existence of additional risk loci.¹¹ To the immunologist, lupus is intriguing because all the key components of the immune system are involved in the underlying mechanisms of the disease. Pathogenic auto antibodies are the primary cause of tissue damage in patients with SLE. The production of these antibodies arises by means of complex mechanisms involving every key facet of the immune system.¹² In SLE, studies using inbred mouse strains suggest multiple

susceptibility loci. Significant linkage was present at 11q14 in the 16 African-American pedigrees. There is strong evidence for an SLE susceptibility gene, SLEH1 in African-American pedigrees multiplex for SLE that have at least one SLE-affected patient with haemolytic anaemia.¹³ A haplotype of STAT4 is associated with increased risk for both rheumatoid arthritis and systemic lupus erythematosus, suggesting a shared pathway for these illnesses. The identification of STAT4 as a common predisposition gene for both lupus and rheumatoid arthritis, is similar to reported findings of broad associations of the intracellular phosphatase PTPN22 with these and other autoimmune diseases,¹⁴ such as type 1 diabetes mellitus, autoimmune thyroid disease, and myasthenia gravis. It is now well established that serum levels of the cytokines Interleukin IL 6 and IL10 are raised in patients with SLE, being highest in those patients with active disease. It has been observed that there is an inverse correlation between IL6 and haemoglobin levels, which is potentially related to the increased chronic inflammatory state marked by an increase in serum IL6 and unlikely to be due to iron deficiency.¹⁵ Significant correlation ($p=0.024$) has been found between raised levels of IL6 in patients with SLE and patient presentation with anaemia.¹⁶ Inter individual gene copy-number variation of complement component C4 and its associated polymorphisms in gene size and protein isotypes lead to different susceptibilities to autoimmune disease. Family-based association tests suggested that a specific haplotype with a single short C4B in tight linkage disequilibrium with the -308A allele of TNFA was more likely to be transmitted to patients with SLE.¹⁷

Patients and Methods

This retrospective, descriptive and analytical study was planned to analyze the frequency and causes of anaemia in SLE patients attending at MMCH (Mohammad Medical College Hospital Mirpurkhas) and LUMHS (Liaquat university of Medical and Health Sciences Jamshoro) hospitals during the period of Jan 2006 to Nov 2008. The criteria used in this study were from the American College of Rheumatology (ACR). The ACR established eleven criteria in 1982, which were revised in 1997 as a classificatory instrument to operationalise the definition of SLE in clinical trials. The eleven criteria for diagnosis of SLE were; Malar Rash, Discoid Rash, Photosensitivity, Oral ulcers, Arthritis, Renal involvement (proteinuria or casts), Neurological signs (seizures, frank psychosis), Serositis, Blood Changes, ANA, Immunological changes as anti-Smith, anti-ds DNA, antiphospholipid antibody, and/or false positive serological test for syphilis. For inclusion in clinical trials, patients must present with four of the above eleven criteria. Patients with SLE and anaemia were further investigated to determine cause of anaemia. Investigations

recorded were complete blood picture, absolute values, peripheral smear, reticulocyte count in all patients with anaemia. These investigations were necessary to analyze anaemia in SLE. Nine patients with hypochromic microcytic anaemia were advised to have serum iron and ferritin levels, seven patients with macrocytic anaemia were advised to have direct and indirect coomb's test, LFTs, serum LDH, serum B12 and folate levels, nine patients with normochromic and normocytic anaemia were considered to have anaemia of chronic disease. Bone marrow aspiration and Hb electrophoresis were done in two patients of anaemia of chronic disease. Thirty adult patients were included in this study. Special proforma were prepared to record the information from case sheets of patients including basic information, symptomatology and laboratory investigations. Severity and various types of anaemia were recorded. Anaemia was graded according to severity, as mild anaemia with Hb of 10-12 G/dl, Moderate anaemia with Hb of 8-10 G/dl and severe anaemia with Hb of < 8 G/dl. Anaemia was further classified into normocytic and normochromic anaemia of chronic disease, hypochromic and microcytic anaemia of iron deficiency and macrocytic anaemia of immune haemolysis and non immune haemolysis origin. Haemoglobinopathies and other types of anaemias were excluded from the study. ANA positive titres were taken as >1:80; and anti ds DNA positive titres were considered as >1:10.

Results

In this retrospective descriptive study thirty adult diagnosed patients of SLE, were included. For diagnosis criteria ACR criteria were used that is four out of eleven clinical and laboratory features. Their ages ranged from twenty years to fifty years at time of presentation. The mean age \pm SD (range) was 28 ± 6.22 (20-50) years and median age was 31 years. Out of thirty patients twenty seven (90%) were females and three (10%) were male patients. Twenty eight (93.33%) patients presented with anaemia, 14 (46.66%) mild anaemia, 8 (26.66%) moderate anaemia and 6 (20%) severe anaemia. Iron deficiency anaemia was found in 9 (30%) patients, 12 (40%) patients had anaemia of chronic disease

Table-1: Frequency of anaemia in patients with systemic lupus erythematosus at tertiary care hospitals. (n 30).

Patients presented with anaemia,	Twenty eight (93.33%)
Mild anaemia	14 (46.66%)
Moderate anaemia	8 (26.66%)
Severe anaemia	6 (20%)
Iron deficiency anaemia	9 (30%)
Anaemia of chronic disease	12 (40%)
Hemolytic anaemia	7 (23.33%)
Coomb's positive hemolytic anaemia	5 (16.66%)

and 7 (23.33%) patients had haemolytic anaemia, out of these 7 patients, 5 (16.66%) patients had Coomb's positive hemolytic anaemia. All thirty patients were ANA positive, titres >1:80 and nineteen (63.33%) patients had anti ds DNA positive titres >1:10, none was found to have false VDRL positive (Table).

Discussion

Anaemia of chronic disease, second most prevalent after iron deficiency anaemia; occurs in patients with acute or chronic immune activation. The condition has thus been termed "anaemia of inflammation."¹⁸ This type of anaemia is immune driven; cytokines and cells of the reticuloendothelial system induce changes in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin, and the life span of red cells, all of which contribute to the pathogenesis of anaemia.¹⁹ A hallmark of anaemia of chronic disease is the development of disturbances of iron homeostasis, with increased uptake and retention of iron within cells of the reticuloendothelial system. This leads to a diversion of iron from the circulation into storage sites of the reticuloendothelial system, subsequent limitation of the availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis. In patients with anaemia of chronic disease, the proliferation and differentiation of erythroid precursors (erythroid burst-forming units and erythroid colony-Forming units) are impaired²⁰ and are linked to the inhibitory effects of interferon- A , - B , and - G , TNF- A , and interleukin-1, which influence the growth of erythroid burst-forming units and erythroid colony-forming units. Interferon- G Appears to be the most potent inhibitor as reflected by its inverse correlation with hemoglobin concentrations and reticulocyte counts.²¹

In literature the frequency of anaemia in SLE patients was found to be 79.37%,²² while in our study frequency of anaemia in SLE patients was 93.33%. Haematologic abnormalities (haemolytic anaemia, leukopenia, lymphopenia, and thrombocytopenia) are common manifestations in patients with SLE. Most patients exhibit anaemia at some point during their disease course. The causes of anaemia in these patients may be of immune or nonimmune pathogenesis. SLE is an autoimmune disease that is virtually always accompanied by the production of autoantibodies. In fact, it has been demonstrated that autoantibodies contribute directly to the pathologic changes of SLE. The number of autoantibody types continues to increase until the time of diagnosis and therapeutic intervention. SLE then, is the culmination of compound autoimmune abnormalities that begin simply, perhaps even as isolated immunologic events and that spread and multiply until they are manifested as a potentially

devastating clinical disease.²³

Autoimmune haemolytic anaemia is a cause of anaemia in 7-15% of SLE patients. In our study incidence of Coomb's positive hemolytic anaemia was 16.66%. Several clinical syndromes constitute the AIHAS, each being mediated by different autoantibodies (IgG or IgM) against red blood cells. As a result of these autoantibodies, the red blood cells are destroyed prematurely in patients with AIHA, resulting in an inadequate number of circulating red blood cells. AIHA usually develops gradually in most patients, but on occasion may result in a rapidly progressive haemolytic crisis. Several studies suggest that AIHA is a forme fruste, the first isolated clinical presentation of SLE in these patients. Dubois first suggested this in 1952 based on three lupus patients presenting with haemolytic anaemia as the initial manifestation of what later became unmistakable SLE.⁴ Kokori et al suggested that AIHA may identify a particular subgroup of SLE patients because of an observed association with certain characteristic serologic and clinical manifestations.²⁴ Collagen vascular disease and other autoimmune diseases are frequently associated with autoimmune haemolytic anaemias of the warm-autoantibody type. In a review of 294 cases of secondary autoimmune haemolytic anaemia, autoimmune diseases were present in almost half of the cases.²⁵ The most commonly reported diseases in this category include systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, pernicious anaemia, and autoimmune thyroid disease and approximately 40 percent of the patients with autoimmune haemolytic anaemia of the warm-autoantibody type had infectious diseases.

Conclusion

Haematologic abnormalities (haemolytic anaemia, leukopenia, lymphopenia, and thrombocytopenia) are common manifestations in patients with SLE. Most patients exhibit anaemia at some point during their disease course. The causes of anaemia in these patients may be of immune or nonimmune pathogenesis.

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