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Haematological Manifestations of Systemic Lupus Erythematosus at a Tertiary Rheumatology Clinic

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Abstract: Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease with variable multisystem involvement and heterogeneous clinical features. Haematological abnormalities were common findings in patients with SLE. Sometimes, haematological abnormalities can be caused by the pathophysiology of SLE itself, but at other times the anaemia may not be directly related to the SLE. This retrospective study included patients who were diagnosed according to the American college of rheumatology criteria and treated for SLE from April 2015 to March 2018 at Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, Nigeria. The Demographic and haematological parameters at diagnosis were recorded. A total of 26 SLE patients were seen. All the cases were females and the mean age was 33.3± 8.9 years. Twenty-two (84.6%) had haematological abnormalities. Anaemia was present in 20 (76.9%) patients with a mean hemoglobin value of 8.6 mg/dl at the time of first presentation. Leukopenia was seen in 6 (23.1%), lymphopenia in 17 (65.4%), thrombocytopenia in 8 (30.8%) and 2 (7.7%) patients presented with anti-phospholipid antibody syndrome. The most common hematological abnormality among our patients was anemia which has a multifactorial aetiology. Lymphopenia was far more common than leucopenia.

Keywords: Rheumatology, SLE, Haematology, Anaemia, multi-factorial.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic auto-immune connective tissue disease. The disease is characterized by a wide variety of clinical features and presence of numerous auto-antibodies [1]. The disease course is unpredictable and has a wide spectrum of disease manifestations, with episodes of remissions and relapses occurring over time [1].

Virtually all the tissues in the body could be affected by SLE. The hematological manifestations of SLE are diverse and often may be the first presenting manifestations of the disease. All the cellular elements of the blood and coagulation pathway can be affected in SLE patients [2].

The major haematological manifestations are anemia, leucopenia, thrombocytopenia, and antiphospholipid syndrome (APS). The frequency of haematological abnormalities are however varies in different populations [3].

The pathogenesis of hematologic disturbance has been attributed to the presence of autoreactive lymphocytes, autoantibodies, and the action of proinflammatory cytokines that act against the bone marrow progenitor cells as well as peripheral blood cells [4]. Sometimes the haematological abnormalities can be caused by the pathophysiology of SLE itself, but at other times anaemia can be found in patients with SLE but not be a manifestation of SLE [5].

Drug treatment and secondary infections also contribute to the development of haematologic problems in SLE. Hematological abnormalities in patients with this disease require careful long-term monitoring and prompt therapeutic intervention.

This study was conducted to estimate the proportion of patients with hematological abnormalities at first contact in the rheumatology clinic of a teaching hospital.

METHODOLOGY

Patients, methods and definitions of terms

All consecutive patients who were diagnosed and treated for SLE at the Rheumatology clinic of Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State were enrolled in the study. All the included patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE [6]. This was a retrospective study that spanned over 3 years from April 2015 to March 2018. Patients

with unclassified and inconclusive diagnosis were excluded from the study. Data were collected from patients' case notes that were retrieved from the medical record department of the hospital. Ethical clearance was obtained from the ethical committee of the institution.

Clinical and laboratory data collection

Data extracted from the case notes included the demographic and haematological parameters of the patients.

The haematological parameters including Haemoglobin, total white cell count (WBC), neutrophil count, lymphocyte count, platelet count, erythrocyte sedimentation rate (ESR), were recorded, at the time of initial presentation. The laboratory results for packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC) were noted and analyzed.

Disease definition

The definition of the disease was in accordance with the ACR classification criteria for SLE. Anaemia was defined as a hemoglobin of less than 10.0 g/dl, leukopenia was defined as a white blood cell (WBC) count of less than 4×10^9/l and lymphopenia as a count of less than 1.5×10^9/l. Neutrophilia was defined as a count more than 10.0×10^9/l. Thrombocytopenia in lupus patients was defined as a platelet count of less than 100×10^9/l. Patients with normal MCV and MCHC were classified as having anaemia of chronic disease since the two red cell indices, MCV and MCHC, tend to be normal in anaemia of chronic disease (ie, normocytic and normochromic).

Patients with microcytic hypochromic picture (low MCV and MCHC) are classified as having iron deficiency anaemia. Patients with Coomb positive results are classified as haemolytic anaemia

Statistical analysis- Data were analyzed with statistical software SPSS version 20. The results are presented as frequency, percentages and means ± SD.

RESULTS

A total of 1,280 rheumatology patients were seen over the study period that spanned between April 2015 and March 2018. 26 patients satisfied the inclusion criteria of the American college of rheumatology and were included in the study. During the study period, 17 patients were newly diagnosed while 9 were previously diagnosed at other facilities but referred for follow up.

All the 26 SLE patients were females. The mean age of the cohort of SLE patients was 33.3± 8.9 years. The duration of disease at diagnosis ranged between 2 - 8.5 years, and the mean duration of diagnosis of SLE was 4.3 ± 2.3 years.

Out of these 26 SLE patients, 22 (84.6%) had haematological abnormalities present at the time of consultation at the teaching hospital. Anaemia was the most frequent of all the haematological abnormalities occurring in 20 (76.9%) patients with a mean hemoglobin value of 8.6 mg/dl**.** Out of the people with anaemia, morphologically, normocytic normochromic anemia was seen in 13 (65%) patients, iron deficiency seen in 5 (25%) and autoimmune haemolytic anemia seen in 2 (10%). Leukopenia was observed in 6 (23.1%) patients, lymphopenia in 17 (65.4%) and thrombocytopenia in 8 (30.8%) patients, and 4 (15.4%) patients had leucocytosis with neutrophilia. Two (7.7%) patients presented with anti-phospholipid antibody syndrome.

Detailed laboratory findings are as shown in table-2. Table-1 depict the socio-demographic parameters of the patients, while figure 1 shows the Percentage of haematological abnormalities in our SLE patients.

Table-1: Socio-demographic characteristics of the 26 SLE patients

Parameter	Result
Females	26
Male	0
Age range	22-46 years
Mean age	33 ± 8.9 years
Duration of disease	2-8 years
Mean duration of disease	4 ± 2 years
Education	
Primary school	6 (23.1%)
Secondary school	16 (61.5%)
Post secondary	4 (15.4%)
Employment	
Self employed	18 (69.2%)
Civil servants	8 (30.8%)

Table-2: Laboratory findings among the SLE patients

Parameter	(n= 26) %
Anaemia -	20 (76.9%)
- of chronic disease	13 (65%)
- Iron deficiency	5 (25%)
- Haemolytic	2 (10%)
Thrombocytopenia	8 (30.7%)
Leucopenia	6 (23.1%)
Leucocytosis with neutrophilia	4 (15.4%)
Lymphopenia	17 (65.4%)
Coomb's positive	2 (7.7%)
Increase activated partial thromboplastin time	2 (7.7%)
Positive anti-cardiolipin antibody	2 (7.7%)
Increase erythrocyte sedimentation rate	26 (100%)
Erythrocyte sedimentation rate range	45-105mm/hr

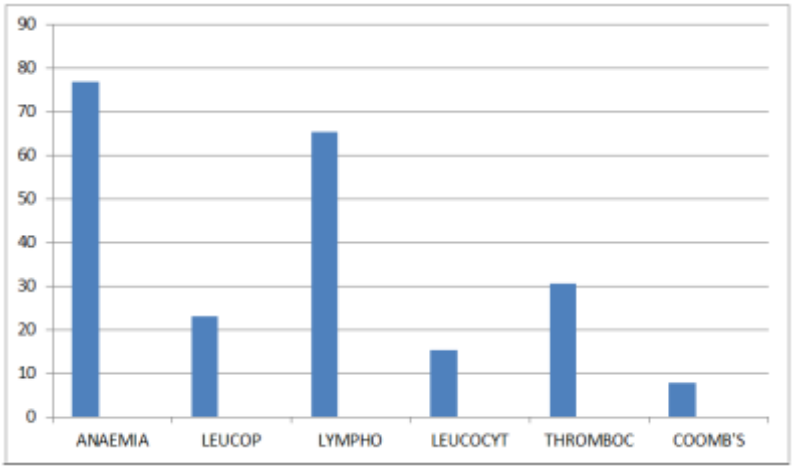

Fig-1: Percentage of haematological abnormalities in our SLE patients

Leucop- leucopenia, Lympho- Lymphopenia, Leucocyt- Leucocytosis, Thromboc-Thrombocytopenia, Coomb's positive.

DISCUSSION

This study shows that haematological abnormalities are common at the time of diagnosis among our SLE population.

Most of the patients with SLE develop some haematological abnormalities or clinical complications at some point during the course of the disease. The frequency of haematological abnormalities are however differs in different populations [3]. The Hopkins lupus cohort study, a prospective longitudinal study on SLE outcomes, showed that race is a major factor in predicting clinical and laboratory features of SLE [7]. This implies that presentation and course of this disease is likely to be variable in different populations due to significant genetic and environmental influences.

Anaemia was the most common disorder present in 20 (76.9%) of our patients. The aetiology of anaemia in SLE is heterogeneous and may result from immune or non-immune causes [8]. Some of the common causes of anaemia in SLE include anaemia of chronic disease (ACD), iron deficiency anaemia (IDA), autoimmune haemolytic anaemia (AIHA) and drug-induced myelotoxicity [9, 10], while some of the less common or rare causes include aplastic anaemia [11] thrombotic thrombocytopenic purpura (TTP), pure red cell aplasia, pernicious anaemia, myelofibrosis and sideroblastic anaemia [12, 13]. Other mechanisms that contribute to the development of anemia include inflammatory process, renal insufficiency, dietary insufficiency, infection and hypersplenism [14, 15].

It is noteworthy that ACD often coexists with anaemia caused by other mechanisms. Iron deficiency is common in patients with SLE as a result of menorrhagia and increased gastrointestinal blood loss caused by the use of non-steroidal anti-inflammatory drugs, aspirin, and oral anticoagulants [11].

Normocytic normochromic anemia was seen in 13 (65%) of our patients. This type of anaemia is frequently due to suppression of erythropoiesis from chronic inflammation (anemia of chronic disease or anemia of chronic inflammation), and usually the commonest common form [16]. This type of anemia is normocytic and normochromic with a relatively low reticulocyte count. Although serum iron levels may be

reduced, bone marrow iron stores are adequate and the serum ferritin concentration is elevated [16].

Iron deficiency anaemia was seen in 5 (25%) of the patients. This type of anaemia may reflect acute or chronic blood loss from the gastrointestinal tract, usually secondary to medications [10] (nonsteroidal antiinflammatory drugs or steroids).

Autoimmune haemolytic anemia was seen in 2 (10%) of our patients. Autoimmune haemolytic anemia is usually characterized by an elevated reticulocyte count, low haptoglobin levels, increased indirect bilirubin concentration, and a positive direct Coomb's test [17]. The presence of hemolytic anemia may be associated with other manifestations of SLE such as renal disease, seizures, and serositis [18]. Other patients may have a positive Coomb's test without evidence of overt hemolysis [18]. Reports regarding its diverse clinical presentations and heterogenous association with other autoimmune manifestations make prompt attention essential. In this study, we defined haemolytic anaemia with positive Coomb's test.

Among the white cell abnormalities, lymphopenia was the commonest, seen in 17 (65.4%) of our patients, followed by leukopenia which was observed in 6 (23.1%) patients. Leukopenia is common in SLE and usually reflects disease activity [19]. Neutropenia, lymphocytopenia, and decreased circulating eosinophils and basophils may all contribute to leukopenia [19].

Lymphocytopenia (lymphocytes less than 1,500/microL), especially involving suppressor T cells, has been observed in 20 to 75 percent of patients, particularly during active disease [20]. Lymphopenia may occur by interplay of different mechanisms. Specific therapy for lymphopenia is not indicated in patients with SLE, but lymphopenia, and its degree, may be related to the disease activity [21]. Severely low lymphocyte count may predispose patients to opportunistic infections such that prophylactic therapy should be considered, especially in those patients on immunosuppressive therapy [22].

Neutropenia in patients with SLE can result from immune mechanisms, medications (eg, cyclophosphamide or azathioprine), bone marrow dysfunction, or hypersplenism [23]. Mild neutropenia is a common finding in SLE that requires no specific therapy. However, a small percentage of patients with SLE develop severe, even life-threatening, neutropenia. The patient with severe neutropenia with opportunistic infection or the risk of such infection can be successfully treated with granulocyte- colony stimulating factor) (G-CSF [24].

The definition of a low total white count or low neutrophil count is complicated by the presence of benign ethnic neutropenia in many (25–50%) persons of sub-Saharan African [25]. In individuals with this condition, an abnormally low neutrophil count is not easily definable.

Four (15.4%) patients had leucocytosis with neutrophilia. Leukocytosis in systemic lupus erythematosus, when present, is usually due to infection or the use of high doses of glucocorticoids [26], but may occur during acute exacerbations of SLE [26]. A shift of granulocytes to more immature forms (a "left" shift) suggests infection.

Thrombocytopenia was present in 8 (30.8%) patients. Mild thrombocytopenia (platelet counts between 100,000 and 150,000/microL) has been noted in 25 to 50 percent of patients; while counts of less than 50,000/microL occur in only about 10 percent [27]. There are several potential causes of thrombocytopenia in patients with SLE. Immune mediated platelet destruction is most often the cause, platelet consumption may also occur in association with microangiopathic hemolytic anaemia [28]. Thrombocytopenia in SLE may also be due to drugs, infection and bone marrow suppression or may be associated with a manifestation of anti-phospholipid syndrome (APS) [28].

Many patients with thrombocytopenia as a manifestation of SLE can be watched without specific treatment directed at the low platelet count, and the great majority of those requiring treatment can be successfully managed. For acute treatment, glucocorticoid is the mainstay of therapy [29]. There are emerging data that rituximab is an effective therapy in patients with refractory thrombocytopenia [29].

Although we did not correlate haematlogial abnormalities with organ involvement in our study. Study by Sultan et al found that SLE patients with severe haematological involvement were more likely to have significant disease in the renal, central nervous and general systems, but not in the other systems [30]. Jeffries *et al*., also reported that presence of haemolytic anaemia was associated with a subset of lupus patients characterized by more severe disease, younger age, and a higher likelihood of renal involvement, seizures, serositis and lymphopenia [17].

In conclusion, haematological abnormalities are common findings in patients with SLE at the time of diagnosis. Anaemia was the leading haematological abnormality in our SLE cohort. Neutrophilia in our patients was generally due to infection. It is therefore important to distinguish haematological abnormalities as either manifestation of SLE, consequence of SLE treatment or as a part of another blood abnormality or dyscrasia.

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