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Systemic Lupus Erythematosus- A Hematological Problem

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Abstract

An observational study conducted on patients with Systemic Lupus Erythematosus (SLE) at a tertiary referral centre of Northern Kerala in South India had shown that hematological manifestations as the most common initial presentation of the disease. It was observed that 82% of the patients had hematological manifestations either alone or with another problem at presentation. If we consider the organ or tissues initially affected as the seat of the disease, SLE is a Hematological disorder because it can present more often with hematological manifestations alone. Even in those who present with features of musculoskeletal, skin or other system involvement, many have coexisting hematological problems. In cases with hematological abnormalities as the predominant or only manifestation of the disease, the diagnosis may be delayed or missed at the time of presentation, if the index of suspicion is low or if there is improper and inadequate follow up. One of the common coexisting abnormalities in patients with initial hematological presentation was autoimmune hypothyroidism, which is not included in the American College of Rheumatology (ACR) criteria for diagnosis of SLE. The most prevalent hematological abnormality was anemia which was due to multiple mechanisms. There was an inverse association of arthritis with hematological manifestations. A significant number of patients did not satisfy the ACR criteria at the time of diagnosis but did so on follow up. ACR criteria are weak to diagnose such patients and therefore needs revision. We also propose an alternative to ACR criteria as "The Kozhikode Criteria for SLE".

Keywords: SLE; Anemia; Thrombocytopenia; ITP; Leucopenia; APLA; ACR; Kozhikode criteria

Introduction

Systemic Lupus Erythematosus (SLE) is prototype of an autoimmune disorder and may manifest initially by involving one or more organ systems and overtime additional manifestations appear after a variable period. Any tissue in the body could be involved in SLE like musculoskeletal, cutaneous, renal, neurological, hematological, vascular, pulmonary, gastrointestinal and ocular. It is observed that hematological manifestations (abnormalities of the formed elements of the blood, of the clotting and fibrinolytic factors and related systems) of SLE are diverse and often they are the only presenting manifestations of the disease [1-4]. The major hematologic manifestations of SLE are anemia, leukopenia, thrombocytopenia, and the antiphospholipid antibody syndrome (APLAS).

The hematological abnormalities though more commonly seen are not properly evaluated or estimated and are not given enough representation in the American College of Rheumatology (ACR) criteria for diagnosis of SLE. Since blood and blood vessels together contain more diverse number of antigens than any other organ in the body, it is only natural to expect hematological manifestations more often than others. It has been our observation since the last two decades that many cases of SLE present with hematological abnormalities alone, without features of musculoskeletal, skin or other system involvement [1,4]. In some of these cases presenting with anemia, thrombocytopenia, pancytopenia or thrombotic episodes, especially so in young females, the diagnosis may be delayed or initially missed if the index of suspicion is low or if there is improper and inadequate follow up [1,4]. Many cases which present initially with involvement of any one tissue or organ alone (autoimmune hemolytic anemia, thrombocytopenia etc.) and which are ANA negative did not satisfy the ACR criteria initially but did so on follow up. In most of these cases, if we have an alternative and more sensitive criteria, appropriate treatment could be started, to the advantage of the patient.

This study was conducted to estimate the proportion of patients with hematological abnormalities as the initial manifestation of SLE and to study the nature of these various hematological problems.

Materials and Methods

Hematological manifestations at presentation in patients with SLE were evaluated by an observational study design. All newly diagnosed cases of SLE and those previously diagnosed cases that came for follow up during the study period were included in the study. The period of study was for 12 months (April 2009-March 2010) and patients were pooled from the departments of General Medicine, Hematology, Rheumatology, Nephrology and Dermatology of Calicut Medical College (which is the chief referral centre of Northern Kerala). Data were collected by a structured personal interview and detailed clinical examination. Basic investigations consisting of complete blood counts including red cell indices and ESR, renal and liver function tests, urine routine, peripheral smear, ANA and Anti-dsDNA were done in all cases. Other relevant investigations like reticulocyte count, Coomb's test, ANA profile, radiological tests, tissue biopsy or cytology and bone marrow examination were done as and when indicated.

All patients included in the study satisfied either the American College of Rheumatology criteria for the definition of SLE or the new criteria evolved by us (based on our own observations of SLE over last two decades) and were utilized for the purpose of the study (Kozhikode Criteria). The new criteria were essential to include some of those patients who did not initially satisfy the ACR criteria at the time of inclusion but did so on follow up [1].

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The Kozhikode Criteria for Diagnosis of SLE

Two essential/Major criteria

- Presence of an active or unresolved autoimmune disorder which is known to occur with SLE (eg:- Chronic ITP, autoimmune hemolytic anemia, skin lesions, Antiphospholipid antibody syndrome (APLAS), autoimmune hypothyroidism, autoimmune hepatitis).
- No other cause other than autoimmunity for the said clinical problem: by clinical reasoning, a reasonable period of observation less than six months and investigations.

Minor criteria

- Positive ANA
- Positive Anti-ds DNA
- Another coexisting autoimmune disorder/any other additional evidence of autoimmunity
- Sustained and definite response to treatment with steroids and immunosuppressant even after six months of follow up.

The diagnosis of SLE was made if the patient satisfies the presence of two essential criteria along with any two of the four minor criteria given above. We have been using these criteria for the last two decades and the follow up had proved that they were all SLE and subsequently satisfied the ACR criteria as well. But it was not validated by any organized study protocol.

Data entry was done by using Epi info software and Microsoft excel. Data was analyzed by standard statistical techniques with SPSS.

Results

One hundred and eight patients satisfied the inclusion criteria and were included in the study. 53 patients were newly diagnosed and the rest 55 were previously diagnosed cases who came for follow up during the study period. Male: female ratio in the whole of the study subjects was 1:10. The mean age of females was 30 (SD -10) and that of males was 34.5 (SD-18.5). Majority of the females were in the age group of 16-35 years, while the male subjects were distributed in the various age groups. Five patients (4.6%) were aged more than 50 years. There was male predominance in this group with a male: female ratio of 4:1.

Eighty nine patients (82%) had hematological manifestations at presentation out of which thirty eight had only hematological abnormality as the first manifestation (Figure 1). The next common presentations in the whole study subjects were arthralgia or arthritis in 44 cases (40.7%) followed by lupus nephritis in 25 cases (23%) (Table 1).

Among those subjects presenting with hematological abnormality, coexisting renal involvement was present in 19 patients and musculoskeletal involvement in the form of arthritis or arthralgia was seen in 12 only. On statistical analysis, a significant inverse association was found between the presence of musculoskeletal and hematological manifestations (p value- <0.001). Autoimmune hypothyroidism (n=10) and autoimmune hepatitis (n=6) were the next common associated manifestations in patients with initial hematological presentation but both of them are not included in the ACR criteria for diagnosis of SLE.

The most common hematological abnormality was anemia, present in 62.9% of the patients in the study group with a mean hemoglobin value of 9.5 mg/dl (hemoglobin level<12.5 mg/dl in males and <11.5 mg/dl in females was taken an anemia). Morphologically normocytic normochromic anemia was the most common type (53%). Anemia was multi-factorial in etiology, like autoimmune haemolysis, iron deficiency, folic acid deficiency, anemia of chronic inflammation etc. Autoimmune hemolytic anemia was seen in 27.9% of them. Thrombocytopenia was present in 39.8% and leukopenia in 15.7%.

The most common hematologic problem at presentation was immune thrombocytopenia (27 cases) followed by autoimmune hemolytic anemia and anti-phospholipid antibody syndrome (19 cases each) (Figure 1). Those with antiphospholipid antibody syndrome (APLAS) as the initial hematological manifestation presented with cerebral venous thrombosis and recurrent abortions as its most common presenting features (Figure 2). Coexisting thrombocytopenia was present in 37% of patients with APLA syndrome and one patient had associated autoimmune hemolytic anemia. Thrombocytopenia associated with APLAS was mild and benign and was not associated with bleeding; these patients did not require treatment for thrombocytopenia. There were two cases (1.8%) with thrombocytosis at presentation; one of them had APLAS also.

Anti nuclear antibody test was negative or ACR criteria was not satisfied at the time of presentation in 12 patients (11%) (Table 2). The maximum latency for developing ANA positivity or the time taken to

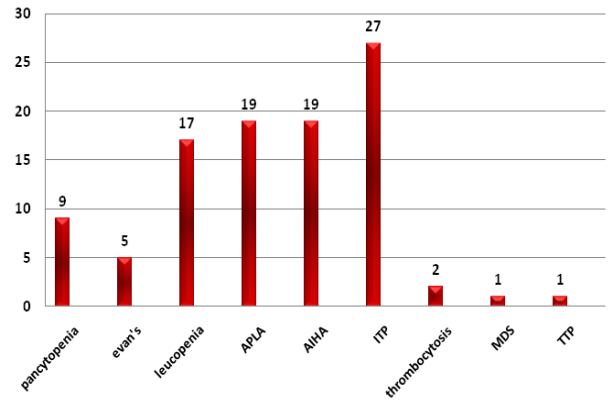

Figure 1: The hematological manifestations at presentation.

Manifestations	number	percentage
Hematological		
Anemia	68	63
Thrombocytopenia	43	40
APLAS	19	17.5
Leukopenia	17	16
Others		
Arthrthralgia/arthritis	44	31
Renal (lupus nephritis-20/renal tubular acidosis-5)	25	23
Dermatological	20	18.5
Fever	9	8
Neurological	8	4
Ocular(episcleritis)	3	3
Pulmonary	3	3
Endocrine Hypothyroidism(13) Addison (1) Graves (1)	15	14

Table 1: Clinical features at the onset of systemic lupus erythematosus.

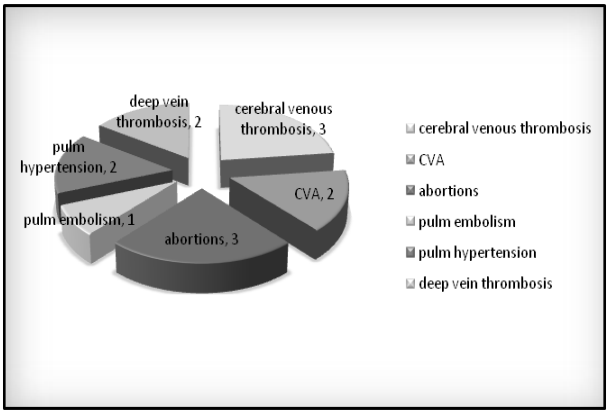

Figure 2: Presentation of Anti phospholipid antibody syndrome.

Case No.	Diagnosis	App.time to ANA positivity or satisfying ACR criteria
1.	Immune thrombocytopenia(ITP)	32 months
2.	Immune thrombocytopenia	22 months
3.	Immune thrombocytopenia, hypothyroidism	40 months
4.	Autoimmune hemolytic anemia	7 months
5.	Autoimmune hemolytic anemia, hepatosplenomegaly, nephrotic syndrome.	11 months
6.	ITP,APLA, severe PAH, high ESR	144 months
7.	APLA, high ESR	8 months
8.	Anemia, splenomegaly, Sjogren	6months
9.	Secondary sjogren	4 months
10.	Thyrotoxicosis, (ITP)	11 months
11.	Polyarthralgia	8 months
12.	Polyarthralgea, elevated ESR, anemia	4 months

Table 2: Cases which were initially ANA negative, with the time period to subsequent positivity on prospective and retrospective follow up.

satisfy the ACR criteria was 12 years, in a patient of SLE with APLA syndrome. This was a young female who initially presented with isolated thrombocytopenia 12 years back and was ANA negative, recently presented as cerebrovascular accident with multiple infarcts due to APLAS and was found ANA positive. The time taken to evolve the complete picture and satisfying ACR criteria can be pretty long as illustrated by this patient.

Discussion

It is concluded that hematological manifestations were found to be the most common initial presentation of SLE and it was present in 82% of the subjects at the time of presentation. Besides, 35% had only hematological manifestation at the time of presentation. Therefore one should be on the lookout for SLE in all atypical hematological disorders. This observation was made in 108 patients both newly diagnosed and those who came for follow up during the study period of one year in a tertiary care centre in North Kerala. This observation is contradictory to the description of the disease in most Western and Indian text books [5,6] and majority of the previously conducted studies [7,8]. However a multicentre French study and a Turkish study on the initial presentation of childhood onset lupus showed that the most common initial manifestation was hematological [9,10]. This finding supports our observation and emphasizes the fact that hematological manifestations are a common presentation that may be missed if the index of suspicion is low.

Several studies conducted in different parts of the world have evaluated the hematological findings in SLE and the prevalence rates obtained in them are almost comparable with that of ours with anemia being the most common hematological manifestation [10-13]. But hematological manifestation as the initial presentation and its proper inclusion in the criteria for diagnosing SLE was not addressed in any of the studies.

A coexisting musculoskeletal manifestation was present in only 12 of the subjects who presented with a primary hematological problem and a significant inverse association was found between the presence of musculoskeletal and hematological manifestations. The commonly coexisting abnormality of autoimmune hypothyroidism in patients presenting with hematological manifestations is also not represented in the ACR criteria. In a study from Netherlands published in 1991, serositis was found to be less common with hemolytic anemias [10] while no studies comparing the coexistence of arthritis and hematological manifestations were found in literature.

Coexisting thrombocytopenia was present in 7 out of the total 19 patients (36.8%) with APLA syndrome. In a study conducted by Caudrado et al. approximately 25% of patients with antiphospholipid antibody syndrome (APLAS) were found to have thrombocytopenia [14].

Twelve patients (11%) were tested negative for ANA and did not satisfy the ACR criteria at the time of presentation but did so on follow up. Thus ANA negativity does not rule out SLE in its early stages. Since we maintained a high index of suspicion, they all had the clinical diagnosis of possible SLE or evolving SLE at the time of initial presentation itself. In 1982 McHardy et al., investigating a cohort of SLE patients in Aberdeenshire, had suggested a prevalence of 8.9% for ANA-negative SLE [15]. Gladman et al. and Ferreiro et al. in two separate studies found that 5% of the patients with SLE were ANA negative at the time of diagnosis [16,17]. This emphasizes the importance of relying on individualized clinical judgment for diagnosis rather than on the existing criteria alone. It also emphasizes the need for meticulous follow up of all suspected cases even if they are ANA negative initially. Needless to say that the criteria for diagnosis of SLE needs revision to make an early diagnosis in such patients for which we are proposing the new criteria (The Kozhikode Criteria) which was utilized in this study; currently we are doing another study for validation of this.

Conclusions

Hematological manifestation is the most common presenting manifestation of SLE in people of North Kerala, India. Thrombocytopenia, hemolytic anemia and antiphospholipid antibody syndrome (APLAS) were the most common hematologic presentations. The most common hematological abnormality over the entire course of the disease was anemia which was multifactorial. There was no significant association of arthritis with hematological manifestations. Thus SLE is a Heamtological disorder in all respects and the ACR criteria needs revision. Autoimmune hypothyroidism, which is not included in the ACR criteria, is a common coexisting abnormality in patients with initial hematological manifestations. A significant number of patients did not satisfy the ACR criteria at the time of diagnosis but did so on follow up. We are proposing a new criterion for early diagnosis of SLE which we would call as "The Kozhikode criteria" which is detailed before.

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