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Conceptual Paper

SLE- As A Haematological Problem and the Kozhikode Criteria for Diagnosis

Sasidharan PK*, Arathi N and Bindiya M

Professor of Medicine and Former Head, Department of Medicine and Division of Hematology, Calicut Govt. Medical College, Presently Senior Consultant Aster MIMS Kozhikode, Calicut, Kerala, India

***Corresponding Author:** Sasidharan PK, Professor of Medicine and Former Head, Department of Medicine and Division of Hematology, Calicut Govt. Medical College, Presently Senior Consultant Aster MIMS Kozhikode, Calicut, Kerala, India.

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Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disorder, which is difficult to diagnose as there is no single diagnostic marker. Tissue binding autoantibodies are responsible for the damage to organs and tissues. It may affect any one organ or tissue in isolation or more than one organ sequentially or simultaneously. Diagnosis is made using criteria developed using clinical and laboratory features. Early and correct diagnosis is important because early and appropriate treatment gives excellent outcomes. This article gives some new observations on SLE, after studying more than 300 cases in three separate studies at a referral center. These patients were having diagnostic problems and were not initially diagnosed as SLE. In general, autoimmune disorders are diagnosed by good clinical evaluation and clinical judgement, supported by carefully chosen laboratory tests to exclude other causes for the presenting symptoms. The purpose of clinical and laboratory evaluation in any autoimmune disorder, or in SLE, is to look for supportive evidences for it and to exclude other conditions which come in the differential diagnosis. After this step a prompt clinical response and sustained remission with immunosuppressants confirms the diagnosis in all cases.

Hematological manifestations as the commonest at initial presentation in SLE was proven beyond doubt by our studies and observations [1-6]. Our observations also confirmed that rheumatologic manifestations are rather late. Most patients we studied were diagnostic problems rather than fully established cases and early diagnosis could be made only with high index of suspicion. To label a clinical problem as SLE we still depend on the American College of Rheumatology (ACR) Criteria but it does not really help us for early diagnosis. Most patients do not satisfy the ACR criteria and the duration needed to satisfy 4 out of the 11 criteria is variable and long. Therefore, if we depend on the ACR criteria, it would take several years sometimes to confirm the diagnosis as SLE. This unacceptable delay in diagnosis of this potential life-threatening, but easily manageable disorder, would lead to poorer outcomes in the patients. One more bigger shortcoming of the ACR criteria is ignoring the commonest presentation, that is hematological, which is not given adequate representation leading to missing the diagnosis of SLE [6,7]. It appears illogical to consider SLE as a rheumatologic disorder, since the manifestations are more often hematological. It is because blood and blood vessels together contain more numbers and variety of antigens than all the other organs put together, and hence it is only natural to expect hematological presentations to dominate.

Based on our observations, the first author of this article proposed the need for a practical guideline to diagnose SLE and framed a new criterion and named it "The Kozhikode Criteria". We were diagnosing and managing these patients based on this new criterion for the last two decades and we want to share this information with others who are involved in management of SLE, especially when they come with hematological problems.

The Kozhikode criteria [5]

Major/Essential criteria:

- Presence of an unresolved autoimmune disorder, which is known to occur with SLE. (Chronic ITP, autoimmune hemolytic anemia, autoimmune hypothyroidism, autoimmune hepatitis/cholangitis/IBD/vasculitis/)

- No other causes other than autoimmunity for the identified clinical problems by clinical reasoning and investigations.

Minor criteria

- Another coexisting autoimmune disorder/any other evidence of autoimmunity
- Positive ANA
- Positive Anti Ds DNA
- Sustained and definitive response to steroid and immunosuppressant even after six months of follow up.

If the patient has two essential and two or more minor criteria, it can be diagnosed as a systemic autoimmune disorder or even as SLE.

We conducted two landmark studies including all diagnosed cases on follow up and the new cases. The first study was in 2012 which clearly documented that hematological manifestations are the commonest and the second study could validate the new criteria [6,7]. The clinical possibility of SLE was considered in those patients presenting with unsettled clinical problems, supposed to be autoimmune in nature or in those patients with other identified autoimmune disorders with clinical and laboratory evidence of autoimmunity. The hematological manifestations found in the patients in the two studies were Chronic ITP, autoimmune haemolysis, autoimmune B12 deficiency, iron deficiency anemia, Evan's syndrome, pancytopenia, refractory anemia, pure red cell aplasia, leukopenia, antiphospholipid antibody syndrome, lymphadenopathy with or without hepatosplenomegaly, acquired clotting factor deficiencies, HELLP syndrome, TTP, MDS, HLH etc [6].

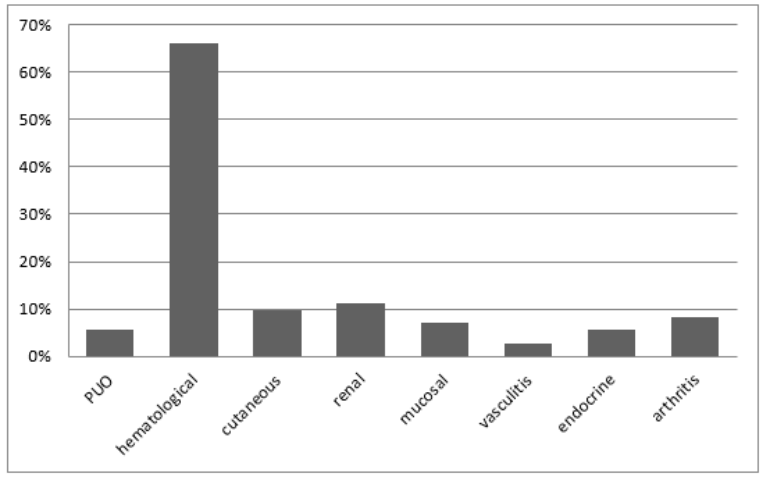

Figure 1: *Clinical manifestations in patients with SLE [6].*

After the observations and the first study, it became essential to validate the Kozhikode criteria and hence another study was undertaken for this.[7] The study for validation of the new criteria included 71 patients out of which 41 patients were already under follow up and 30 were newly diagnosed and it was published in 2017. The male to female ratio was 1: 9 with majority of them belonging to the age group of 20 - 40 years. At the time of recruiting the subjects into the study, 67 out of 71 satisfied the Kozhikode criteria, but only 22 subjects

satisfied the ACR criteria. Among the thirty new cases 26 subjects satisfied the Kozhikode criteria but only six of them could be diagnosed as SLE with the ACR criteria. There were 4 patients with an autoimmune disorder suspected to be SLE, but did not satisfy either criterion. But there was a more striking observation among the 67 subjects finally diagnosed as SLE, there was no patient who satisfied the ACR criteria alone. Among the four suspected SLE, who did not satisfy either criterion, two on follow up, after six months, were satisfying the Kozhikode criteria. We had also observed that several of these patients were ANA negative at the time of diagnosis and they became ANA positive only during the follow up. All these patients could be diagnosed as SLE or evolving SLE only with the Kozhikode Criteria and not with the ACR criteria, highlighting the usefulness of this for early diagnosis. Based on our observations it was also found that if they presented with anyone autoimmune disorder, it could be SLE in evolution, even if the tests for SLE are negative at first evaluation. If there are two or more autoimmune disorders coexisting, it is almost always a systemic autoimmune disorder and could be SLE irrespective of the age. Etiology of this disorder is not clear-cut but our observation is that it could be due to improper diet and lifetsyle. Even the name SLE need to be changed, into Systemic Autoimmune Disorder (SAID), to make it more appropriate and to avoid the stigma attached to SLE.

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