Clinical characteristics and laboratory profile of childhood systemic lupus erythematosus in a tertiary care center

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Received - 15 November 2015 Initial Review - 12 December 2015 Published Online - 13 February 2016

Abstract

Objectives: To study the clinical characteristics and laboratory profile of systemic lupus erythematosus (SLE) in children in a tertiary care center. **Methods:** Children presenting to our tertiary care center with suspected SLE, fulfilling at least 4 out of 11 American College of Rheumatology (ACR) criteria for the diagnosis of SLE were reviewed retrospectively. The study period was from June 2012 to May 2015. The clinical presentation and laboratory parameters were analyzed. **Results:** A total of 14 patients fulfilled the ACR criteria; there were 12 girls and 2 boys with a sex ratio of 1:6 favoring girls. The mean age on presentation was 9.8 years with a range of 3-15 years. At presentation, 70% of the children had features not suggestive of SLE. The most common symptom was fever seen in 100% of the patients, followed by hematological abnormalities in 78%, and renal involvement in 57% patients. Arthritis, skin lesions, and pulmonary involvement were seen in 42% of the patients. The gastrointestinal presentation was seen in 21% of the patients. **Conclusion:** SLE has a varied clinical presentation depending on the predominant organ involved. A high index of suspicion is required for the early diagnosis of SLE in children.

Key words: *Anemia, American College of Rheumatology, Antinuclear antibodies, Arthralgia, Lupus nephritis, Systemic lupus erythematosus*

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. The pathogenesis is complex with immunological, genetic, hormonal, and environmental factors contributing to it. It is characterized by damage to various cells through pathogenic autoantibodies and immune complexes. It has diverse clinical features with remissions and relapses affecting the diagnosis and treatment strategies [1]. In the past, it was suggested that SLE is a rare disease in children. This was largely because of mild and early cases were being missed until end organ damage made the diagnosis evident. The clinical characteristics appear to be similar to adults but, lymphadenopathy and early renal and nervous system involvement are common in childhood SLE [1,2]. Furthermore, children tend to have more severe and more aggressive disease compared to adults [2,3].

SLE can also present with some unusual presentations initially which will make the clinical diagnosis difficult unless the clinician has a high index of suspicion [4-7]. There are reports of geographical variations in the clinical presentation of childhood SLE in different areas in India itself [2]. As there is a paucity of data in the childhood SLE, the present study was undertaken to evaluate the profile of pediatric patients presenting to our tertiary care hospital with SLE.

METHODS

This retrospective study was conducted in a tertiary care teaching hospital from June 2012 to May 2015. After obtaining clearance from the College Ethical Committee, retrospective review of medical records of patients admitted with SLE was done. Children with multisystemic involvement with the atypical course and high erythrocyte sedimentation rate (ESR) prompted for evaluation and diagnosis for SLE. Children found to have antinuclear antibodies (ANA) positivity and fulfilling at least 4 out of 11 American College of Rheumatology (ACR) criteria for the classification of SLE (Table 1) at the time of presentation or subsequently were included in the study [8]. Children with clinically suspected SLE but not fulfilling ACR criteria were excluded from the study. Their age, sex, demography, clinical and laboratory parameters including complete blood counts, platelet count, ESR, peripheral smears, urine routine, urinary protein excretion, renal functions, and ANA profile were entered in a predesigned format. The data collected were analyzed using SPSS software version 20.

RESULTS

Total 14 patients fulfilled the ACR criteria during the study period; out of which, 12 were girls and 2 were boys with a sex

Table 1: Revised ACR classification criteria for SLE [8]

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight by history or on physical exam
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Non-erosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis/pericarditis	a. Pleuritis - convincing h/o pleuritic pain or rub or pleural effusion on physical examination OR b. Pericarditis - documented by ECG, rub or e/o effusion
Renal disorder	a. Persistent proteinuria >0.5 g/day or >+++, OR b. Cellular casts - May be red cell, Hb, granular, tubular or mixed
Neurological disorder	a. Seizures - in the absence of offending drugs, or known metabolic derangement, e.g., uremia, ketoacidosis or electrolyte imbalance, OR b. Psychosis - in the absence of offending drugs, or known metabolic derangement, e.g., uremia, ketoacidosis or electrolyte imbalance
Hematological disorder	a. Hemolytic anemia with reticulocytosis, OR b. Leukopenia <4000/cumm on two or more occasions, OR c. Lymphocytopenia <1500 on two or more occasions, OR d. Thrombocytopenia <100,000/cu mm in the absence of offending drugs.
Immunological	a. Anti-DNA: Antibody to native DNA in abnormal titer, OR disorder b. Anti-Sm: Presence of antibody to Sm nuclear antigen, OR c. Positive finding of aPL antibodies based on: (1) ↑ Serum level of IgG or IgM aCL or (2) a positive test result for lupus anticoagulant, using a standard method, or (3) a false-positive test for syphilis for at least 6 months and confirmed by TPI or FTA-abs test
Positive ANA	An abnormal titer of ANA by immune-fluorescence or an equivalent assay at any point in time in the absence of drug

FTA: Fluorescent treponemal antibody, ACR: American College of Rheumatology, SLE: Systemic lupus erythematosus, aCL: Anticardiolipin, IgM: Immunoglobulin-M, ANA: Antinuclear antibodies, FTA-abs: Fluorescent treponemal antibody absorption

ratio of 1:6 favoring girls. The mean age on presentation was 9.8 years with a range of 3-15 years.

Clinical features of the study population are presented in Table 2. The initial presentation varied from pyrexia of unknown origin (PUO), anemia, pneumonia, and seizure disorder. Non-specific constitutional symptoms were the most common presenting feature and fever was present in all 14 (100%) of the patients. Lupus nephritis was seen in 8 (57%) cases on the renal biopsy. Renal involvement was seen in 8 (57%) of patients in the form of asymptomatic proteinuria, nephrotic syndrome, and nephritis, one patient had presented with acute renal failure (Fig. 1).

Musculoskeletal symptoms varying from 6 to 12 weeks of duration were seen in 6 (42%) of the cases, they included on and off arthralgias and myalgias in 4 cases, and 2 cases had presented with frank arthritis. Serositis was seen in 7 (50%) cases. 6 (42%) cases had pulmonary involvement including two cases of pleural effusion with lupus pneumonia and 4 (28%) cases of pulmonary hemorrhage with pulmonary hemosiderosis.

Table 2: Clinical features seen in the childhood SLE

Features	Number of children	Percentage
Fever	14	100
Renal involvement	8	57
Serositis	7	50
Musculoskeletal	6	42
Skin lesions	6	42
Pulmonary	6	42
Neuropsychiatric	5	35
Oral ulcers	4	28
Cardiac	4	28
Lymphadenopathy	4	28
Gastrointestinal	3	21

SLE: Systemic lupus erythematosus

Neuropsychiatric features including seizure disorder and chronic headache were seen in 5 (35%) cases. Skin lesions were seen in 6 (42%), and oral ulcers, cardiac involvement, and lymphadenopathy were seen in 4 (28%) patients (Figs. 2-5).

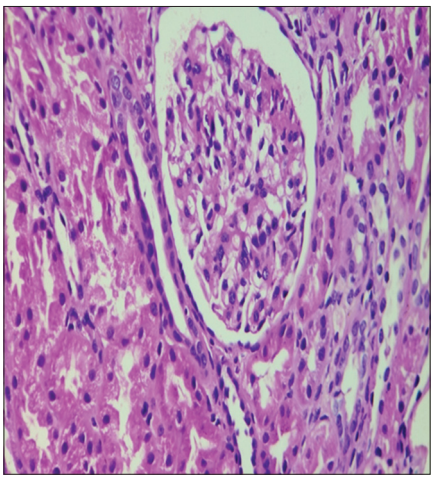

Figure 1: Focal proliferative lupus nephritis International Society of Nephrology/Renal Pathology Society Class III-(A)

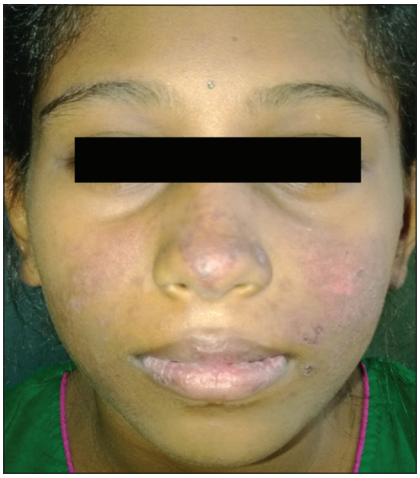

Figure 2: Classical butterfly rash of systemic lupus erythematosus

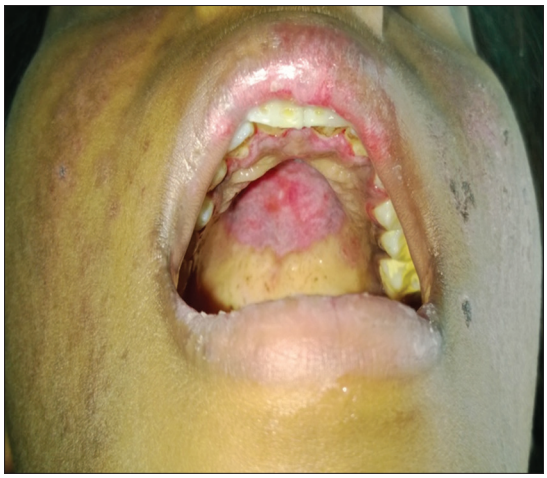

Figure 3: Painless mouth ulcer involving the hard palate

Laboratory investigations of the studied patients showed raised ESR in 12 (85%) cases. Anemia was seen in 10 (71%) children, thrombocytopenia in 6 (42%), leukopenia in 5 (35%), and hemolytic anemia was seen in 4 (28%) patients. Renal

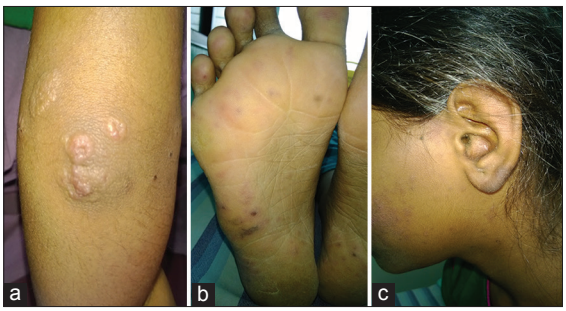

Figure 4: (a-c) Skin lesions in systemic lupus erythematosus. Cutaneous vasculitis of foot and ear lobule in adolescent girl

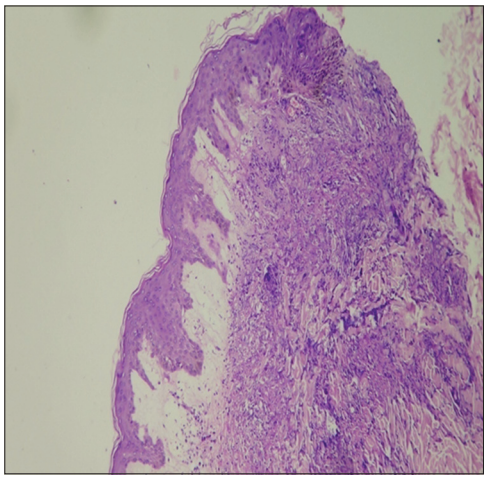

Figure 5: Edema and lymphocytic infiltrate of superficial dermis along with focal vacuolar degeneration of basal cell layer. Endothelial destruction, extravasation of RBCs are also seen suggesting severe leukocytoclastic vasculitis

involvement in the form of proteinuria in 4 (28%), and hematuria in 3 (21%) cases was observed. Results of immunological studies are given in Table 3. ANA was positive in all 14 (100%) patients while anti-dsDNA was positive in 12 (85%) children and anti-Smith antibody in 3 (21%) cases. Low C3 and C4 were found in 7 (50%) patients.

DISCUSSION

SLE is a rare disease in children with 15-20% of adult SLEs presenting in childhood or in adolescence. The male:female ratio is 3:4 before puberty and increases to 1:4, more in females in older age groups [1]. However, the median age of SLE onset in a study by Malaviya et al. was 24.5 years with a female preponderance of 11:1 [3]. In the present study, the mean age of presentation was 9.8 years with a male: female ratio of 1:6 which is also comparable with other studies from India [1,3,5].

The presence of anemia, arthritis, and seizures at the time of presentation results in the increased chances of severe disease with the attendant poor outcome as outlined in other studies [9,10]. In the present study, the majority of the children (71%) had presenting symptoms of a single system initially, and the initial provisional diagnosis and primary treatment offered

was aimed at the predominant symptom and system involved. SLE was thought of as a possible diagnosis only when the child had an atypical course or an obvious laboratory abnormality which in turn delayed the final diagnosis. These initial provisional diagnoses varied from viral hemorrhagic fever, nutritional anemia, PUO, seizure disorder, and pneumonia to acute glomerulonephritis.

In our study, a final diagnosis of SLE was made on the basis of multisystemic involvement, atypical course of the initial primary disease and laboratory abnormalities. Hematological manifestations were very common (78%) with raised ESR seen in 85% of cases and anemia in 71%. Some of the children with anemia were treated unsuccessfully with hematinics initially. Immunological abnormalities (Table 3) were seen in all patients with 100% ANA positivity. This is probably because the diagnosis of SLE was suspected in most children when they were admitted to our hospital with acute flares. One of our male patients was even confused with child abuse as he was unwell for 2-3 months with abdominal pain and on and off diarrhea secondary to colitis (Fig. 6).

Pulmonary involvement in childhood SLE includes pleuritis, lupus pneumonia, chronic interstitial lung disease, alveolar hemorrhage, and pulmonary fibrosis. It can also cause respiratory muscle myopathy and pulmonary hypertension [11-13]. In our study, 42% of children had pulmonary involvement with many being initially treated for pneumonia without relief and some undergoing prolonged admissions for PUO. Subsequently, we found 6 cases (including 2 cases of pleural effusion) with lupus pneumonia and 4 (28%) with pulmonary hemorrhage and pulmonary hemosiderosis. Nervous system manifestations including organic brain syndrome, seizures, psychosis, chorea, cerebrovascular accident, neuropathy, cranial nerve palsy, benign intracranial hypertension, anxiety, and depression have been reported in childhood SLE [14]. In our series, 35% of children had nervous system involvement in the form of seizures, chorea, psychosis, and stroke.

Table 3: Prevalence of autoantibodies in the children with SLE

Autoantibody	Number N=14	Percentage
ANA	14	100
Anti-dsDNA	12	85
Anti-Sm	3	21
Anti-RNP	1	7
Anti-La	1	7
Low C3 and C4	7	50

SLE: Systemic lupus erythematosus,
RNP: Ribonucleoprotein

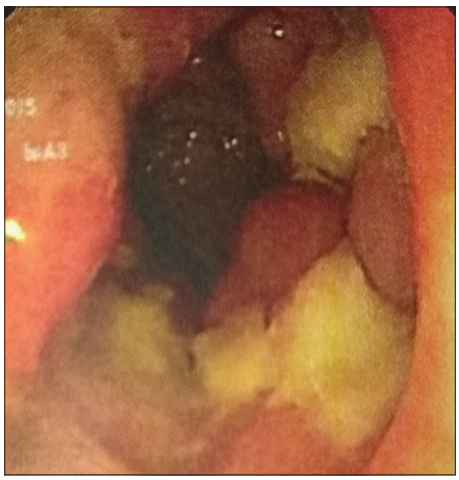

Figure 6: Non-specific colitis in systemic lupus erythematosus on colonoscopy

The diagnosis of SLE should be suspected in children, especially adolescent girls, who present with vague musculoskeletal symptoms such as myalgias, arthralgias, fatigue, and fever. No or poor response to treatment of initially diagnosed disease with varied and atypical clinical features involving multiple systems or an unexplained multisystem disease with or without typical skin rash can help in early recognition of the illness. Studies such as this present the varied manifestations of the illness in a wide spectrum of the regional childhood population and highlight this very aspect of the disease in this country.

The major limitation of our study was that it's a retrospective analysis of records of SLE cases after the diagnosis and management. Further large scale, multicentric studies involving large sample size will throw more light on the overall disease, the outcome of each case, factors affecting the treatment and their prognosis.

CONCLUSION

SLE in children has varied clinical and laboratory presentations depending on the major organs involved. Any child with multisystem involvement, prolonged unexplained fever and atypical clinical manifestations should be evaluated for SLE. A high index of suspicion is needed for the early diagnosis of SLE in children.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kumar BMS, Rau ATK, Rao C. Clinical characteristics and laboratory profile of childhood systemic lupus erythematosus in a tertiary care center. Indian J Child Health. 2016;3(1):39-43.