Case Report

# Childhood-onset systemic lupus erythematosus in the first year of life with joint involvement: A case report and mini-review

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## Abstract

Systemic Lupus Erythematosus (SLE) is a multisystem disorder that can affect any organ system. It can have varied presentations, and often early disease is challenging to pick up due to the absence of classical features. Pediatric systemic lupus erythematosus is rare before five years of age. We report a seventeen-month-old female child who came to us with a long-standing non-specific febrile illness. She was eventually diagnosed with childhood-onset systemic lupus erythematosus and treated with prednisolone and hydroxychloroquine with vitamin D and calcium supplements.

**Keywords:** Autoimmune, childhood SLE, dsDNA, hydroxychloroquine, non-erosive arthritis

## Introduction

Systemic Lupus Erythematosus (SLE) can affect both children and adults with a specific predilection for adolescent females. Multiple factors like genetic susceptibility, hormonal milieu, and environmental triggers cause the generation of autoantibodies against the self which leads to this multisystem chronic inflammatory condition. Childhood SLE (cSLE) is thought to affect 10-20% of all SLE patients. cSLE has been reported to be having more severe disease course, and a worse prognosis[1] Therefore, it has to be important to diagnose it early so that morbidity associated with it can be minimized and the quality of life of children can be improved. We, hereby, report a 17-month-old girl with cSLE who was diagnosed and treated with steroid and hydroxychloroquine and is now in our pediatric rheumatology clinic follow-up and doing well.

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## Case History

A seventeen-month-old female child presented to our outpatient department with a history of on and off fever, for the past 20 days. One to two fever spikes occurred every day, and this was relieved with oral antipyretics. The child appeared well in between febrile episodes. There was a long-standing loss of appetite, lethargy, irritability, and history of visible weight loss.

She was born full-term after normal delivery in the hospital to non-consanguineous parents. There were no perinatal concerns, and the child was discharged home. There was no history suggestive of systemic lupus erythematosus (SLE) in the mother. She remained well till two months of age, after which there was an episode of generalized seizure. She was treated for acute encephalitis at a primary health care facility, with antiepileptics, and antibiotics. Cerebrospinal fluid analysis was reported normal, and antiepileptics were discontinued before discharge after three days. There had been no recurrence of seizures since then. She had age-appropriate neuro-developmental milestones at the time of presentation. She developed a fever at three-and-half months



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of age, for which she required a long course of intravenous antibiotics. Since then, she has had multiple admissions in view of repeated febrile episodes and had received multiple courses of intravenous antibiotics. At fourteen months of age, she developed painful bilateral knee swellings with fever. Blood culture grew coagulase-positive staphylococcus, and antibiotics were given according to the sensitivity. Bilateral knee aspiration was done, which was unremarkable on analysis, however, the swelling persisted. She was discharged on oral linezolid with the diagnosis of septic arthritis.

When she presented to us, she was an anxious child with failure to thrive with marked pallor, bilateral knee swellings which were non-erosive, non-erythematous, but with tenderness and limiting joint movement due to pain [Figure 1 and 2]. She had a distended abdomen with moderate hepatosplenomegaly (Liver enlarged 2-3 centimeters below the right costal margin, spleen palpable 1-2 centimeters before left costal margin along its axis), generalized lymphadenopathy, with the largest palpable lymph node in the left axilla, measuring 3 cm X 1.5 cm, mobile and non-tender. Additionally, she also had thin friable, discoloured hair with a firm, non-tender, non-erythematous swelling measuring 1 cm X 1 cm in the left parietal area of the scalp, likely an old healing abscess.

We initially started the child on intravenous piperacillin-tazobactam and amikacin, considering an infectious etiology as a differential while we evaluated her for additional causes of such a presentation. A complete hemogram showed anemia, with leukocytosis, and thrombocytosis. Since the child has had multiple febrile episodes with failure to thrive, we kept immunodeficiency particularly T-cell defect, as one of the differentials, however, the absolute lymphocyte count was within the normal range for age, and thymic shadow on chest x-ray was also normal. The corrected reticulocyte count was 2.13%, and lactate dehydrogenase was raised. Direct Coombs' test was positive. X-ray of the bilateral knee joint only showed soft tissue swelling with no erosion of the knee joint. Ultrasound of knee joint showed thick synovium with mild effusion, suggestive of synovitis. This effusion, however, could not be aspirated due to scanty content. We ruled out common infective etiologies and in the face of ongoing fever, lethargy, failure to localize a source of infection, laboratory markers of inflammation, and associated knee swelling, we narrowed our differentials to malignancy and rheumatological disease. ANA (Antinuclear Antibody) profile came out to be positive for anti-double-stranded DNA. Rheumatoid factor and anti-CCP (anti-cyclic citrullinated peptide) were negative. Bone marrow aspiration ruled out malignancy, and there were hematological findings consistent with SLE in view of the clinical description of the patient [Table 1].

Considering the ongoing fever, and raised ferritin levels in the setting of diagnosis of SLE, markers for MAS (macrophage activation syndrome) were sent which revealed hypertriglyceridemia. However, no hemophagocytes were present on bone marrow aspirate, and the child did not meet five out of eight criteria for MAS.

The signs, symptoms, and clinical findings were matched with the established diagnostic criteria as per the 2012Systemic Lupus International Collaborating Clinics (SLICC) and 2019 European League Against Rheumatism (EULAR), and the diagnosis was confirmed. We started the child on oral prednisolone at 2mg/kg/day along with hydroxychloroquine (4mg/kg/day) following ophthalmic evaluation to rule out maculopathy, retinal deposits, and any color vision defects. She showed some clinical improvement in the first week after starting therapy. The size of enlarged lymph nodes decreased, knee pain improved, and the child became more active and started taking interest in the surroundings. For renal involvement, the urine protein: creatinine ratio came out to be high (523mg/gm). The renal function test was normal. Subsequent proteinuria was monitored using urine dipsticks. It decreased from 3 + proteinuria to 1+ on the day of discharge. There was also associated hypertension and she was started on oral enalapril at 0.1mg/kg/day. Renal biopsy was advised to identify and if present, classify lupus nephritis, but the procedure could not be done in the current admission due to personal reasons of the parents. Electrocardiogram and echocardiography were done to rule out pericarditis. The patient

**Figure 1:** Anxious child with failure to thrive

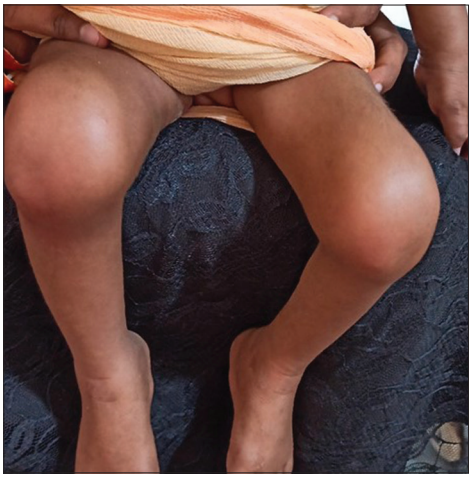

**Figure 2:** Bilateral knee joint swelling

**Table 1: Laboratory investigations**

| Investigation | Result | Normal value |
|---|---|---|
| Haemoglobin (g/dL) | 5.2 | 12.0-15.0 |
| Platelets (per cmm) | $700\times10^3$ | $150\text{-}450\times10^3$ |
| Leucocyte count (per cmm) | 12,100 | 4,000-11,000 |
| Differential leucocyte count (%): | | |
| Neutrophils | 50 | 40-80 |
| Lymphocytes | 47 | 20-40 |
| Monocytes | 2 | 2-10 |
| Eosinophils | 0 | 1-6 |
| Basophils | 0.8 | 0-1 |
| Corrected reticulocyte count (%) | 2.13 | |
| ESR (mm in first hour) | 120 | 0-10 |
| Serum bilirubin (total) (mg/dL) | 0.50 | 0.3-1.2 |
| Serum bilirubin (direct) (mg/dL) | 0.20 | <0.3 |
| Aspartate aminotransferase (IU/L) | 29 | <31 |
| Alanine aminotransferase (IU/L) | 25 | 10-28 |
| Alkaline phosphatase (IU/L) | 229 | 100-290 |
| Blood urea (mg/dL) | 20.3 | 13-43 |
| Serum creatinine (mg/dL) | 0.49 | 0.7-1.3 |
| Serum uric acid (mg/dL) | 4.13 | 3.5-7.2 |
| Serum sodium (mmol/L) | 137.2 | 135-145 |
| Serum potassium (mmol/L) | 4.1 | 3.5-5 |
| Lactate dehydrogenase (μ/L) | 1048.3 | 150-500 |
| C-reactive protein (mg/L) | 224 | 0.8-7.9 |
| Serum ferritin (ng/mL) | 1650 | 10-291 |
| Triglyceride (mg/dL) | 423.9 | 27-125 |
| Direct Coombs' test | Positive | |
| Anti-double-stranded DNA antibody | Positive | |
| Tuberculosis work-up (Mantoux, chest-X ray, gastric aspirate for acid-fast bacilli and CBNAAT) | Negative | |
| rK-39 for kala-azar | Negative | |
| Rapid antigen test for malaria and scrub typhus | Negative | |
| Dengue NS1 antigen and IgM negative | Negative | |
| TORCH profile | Negative | |
| HIV 1 & 2 serology | Negative | |
| HBsAg | Negative | |
| Hepatitis C antibody | Negative | |
| Blood culture | Sterile | |
| Urine culture | Sterile | |
| Lymph node aspirate | Hemorrhagic | |
| Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) | Negative | |
| Bone marrow aspirate | Not suggestive of malignancy, no hemophagocytes were seen | |
| Bilateral knee aspiration | Unremarkable | |

DNA=deoxyribonucleic acid, CBNAAT=Cartridge Based Nucleic Acid Amplification Test, IgM=immunoglobulin M, TORCH = (toxoplasma, others, rubella, cytomegalovirus, and herpes) virus, HIV=human immunodeficiency virus, HBsAg=hepatitis B surface antigen

was discharged on request on prednisolone at 1.5mg/kg/day, hydroxychloroquine, vitamin D, and calcium supplements.

## Discussion

Childhood-onset SLE constitutes 10-20% of all diagnosed cases. It is generally agreed that childhood-onset SLE is a more severe disease with accelerated organ damage over time when compared to its adult counterpart.[1] As in adult-onset, female affection is disproportionately higher than males. Females constitute approximately 80% of the patient burden.[2] The median age of onset of cSLE reported in the majority of studies is between 11 to 12 years, and it is a rare disease in children younger than five years of age.[3] SLE is a disease that can affect any organ system and therefore could have myriad presentations. Particularly when the classical photosensitive rash is absent, as it is in many children at the time of presentation, the diagnosis could be challenging, as it was in our case. Children with SLE could present with non-specific complaints of fever, anorexia, weight loss, and arthralgia. Careful ruling out of alternative explanations for the constellation of symptoms before considering SLE, particularly in a young child less than two years of age (infantile-onset systemic lupus erythematosus) is crucial to a correct diagnosis. We evaluated our patient for chronic infectious illnesses, immunodeficiency, and malignancy before considering cSLE. The EULAR criteria for SLE also stress ruling out alternative explanations before considering the clinical feature as a potential diagnostic pointer to SLE.[4]

Studies from multiple countries have established those hematological abnormalities (anemia, leucopenia, and/or thrombocytopenia), lupus nephritis, fever, seizures, and lymphadenopathy are more common at presentation in childhood-onset SLE than adult-onset SLE.[5,6] Our patient also had anemia, proteinuria, and lymphadenopathy.

There was a history of seizures between 2-3 months of age which could be attributed to the neurological manifestation of SLE but this cannot be said with certainty. Two-thirds of patients with cSLE have neurological involvement, and this could be very variable, ranging from headache, and seizures to psychosis.[7] Both SLICC and EULAR classifications have retained seizures in their criteria.[4]Our patient had seizures at around three months of age, but this could not have been attributed to SLE at that time. As the clinical picture evolved, we were able to rule out more common causes and then consider the much rarer cSLE.

Once the mandatory immunological criteria for SLE diagnosis were established (ANA positivity), we evaluated our patient against the minimum set of required criteria for diagnosing SLE. It is worthwhile to note that such attribution should be done only in the face of no other likely diagnosis plus the presence of fever.[8] Non-scarring alopecia is defined as diffuse thinning of hair or visible friability, synovitis, proteinuria, seizures, positive Coombs' test without hemolytic anemia in addition to anti-double-stranded DNA (dsDNA) and ANA positivity fulfilled the SLICC criteria (minimum requirement: histology compatible with lupus nephritis and ANA or anti-dsDNA OR any four out of 17 with at least one immunological criteria). EULAR has a point-based system with a minimum requirement of 10 points in addition to ANA positivity. Our patient had non-scarring alopecia (2 points), joint effusion (5 points), proteinuria (4 points), seizure (5 points), anti dsDNA (6 points),

and fit well into this classification as well. While classification criteria could make a physician more confident in their suspicion of SLE, it must be remembered that diagnosis is not dependent on fulfilling these criteria, but rests with an appropriately trained physician.[9] Classification criteria must be not used for screening. These should be employed only when there are reasons to believe a patient could have SLE. Childhood SLE might not present fulfilling the criteria mentioned in these classifications. Since it is still an evolving illness at the time of early presentations, many features may come to the forefront over time.

Care of a child with SLE requires a multidisciplinary approach with the involvement of a pediatric rheumatologist, pediatric nephrologist, child psychologist, and physical and occupational therapist. Pharmacological therapy is tailored to the extent and severity of symptoms. Oral and/or injectable steroids remain the backbone of therapy and help achieve rapid disease control.[10] The duration depends upon the resolution of the active manifestation being treated. Children are routinely monitored for steroid toxicity, and when needed switched to steroid-sparing agents. Methotrexate and azathioprine are frequently prescribed for controlling persistent arthritis. Hydroxychloroquine remains the staple for managing extra-renal manifestations like rash and arthritis and is often used as maintenance therapy.[11] Hydroxychloroquine also prevents SLE flares and improves lipid profile. Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed primarily for musculoskeletal symptoms. Cyclophosphamide, an alkylating agent, is reserved for the most severe and life-threatening symptoms because of its risk for toxicities. Concomitant control of hypertension, proteinuria with fluid restriction, a low salt diet, and anti-hypertensives are important for a favorable outcome. Angiotensin-converting enzyme inhibitors are particularly effective for reducing proteinuria. There are no recommendations for the use of lipid-lowering statins in cSLE. Newer therapies including belimumab (a monoclonal antibody against B lymphocytes, also called B cell-activating factor) have been approved by FDA, but not yet studied in cSLE.

Children risk running a more severe course of this disease. Mortality in the first several years of disease is most commonly secondary to an infection, end-stage renal disease, or neuropsychiatric disease, while cardiovascular disease and malignancy play a significant role in late mortality. However, owing to advances in the diagnosis and treatment of childhood SLE, the current five-year survival for pediatric SLE is approximately 90%.[12] Given the complex and chronic nature of this disease, it is optimal for children with SLE to be treated in a multidisciplinary clinic.

## Conclusion

Childhood SLE is a rare occurrence in children younger than five years.SLE is a great mimicker and could present with long-standing non-specific features commonly attributed to infectious, malignant, and other autoimmune etiology in a child. It is imperative to rule out alternative diagnoses before considering childhood-onset SLE. Childhood SLE runs a more accelerated and severe course than adult SLE and needs close monitoring and multidisciplinary management. Therefore, it is important, especially for general primary care providers and family physicians to consider and timely refer children suspected to have cSLE, where common infective and neoplastic conditions have been ruled out.

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## Conflicts of interest

There are no conflicts of interest.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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