Childhood-onset systemic lupus erythematosus associated with inborn errors of immunity: One or several conditions?

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ABSTRACT

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem disease; its severity depends on the organs involved. Monogenic diseases have been described as predisposing to the onset of cSLE.

Analytical and immunological tests are used for diagnostic confirmation. The main goal of treatment is remission and flare prevention.

Here we describe the clinical case of a patient with prolonged febrile syndrome, arthralgias, and anemia, positive analytical tests for antinuclear antibodies and anti-DNA antibodies and low values of complement C3, C4, and C1q; so the patient was diagnosed with cSLE associated with C1q deficiency.

Patients with C1q deficiency present with early onset of disease and significant target organ damage with nephritis. An early diagnosis of cSLE is important to ensure an early and appropriate treatment. Treatment may be personalized depending on the underlying defect that generates the subtype of lupus.

Keywords: *systemic lupus erythematosus; primary immunodeficiency disease; complement C1q, deficiency.*

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INTRODUCTION

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem disease; its severity depends on the organs involved. Patients with symptom onset before 5 years of age develop more severe clinical forms, with a higher incidence of proteinuria, malar rash, arthritis, anemia, and leukopenia.

The presence of autoantibodies (antinuclear antibodies [ANA], anti-DNA antibodies, anti-Sm antibodies, etc.) is one of the characteristics of SLE; they are partially responsible for the inflammation and damage through the formation of immune complexes. There is an association between cSLE and the presence of inborn errors of immunity.[1]

The severity of the clinical manifestations is variable. Throughout the course of the disease, any organ or system may be affected; skin, joint, renal, hematological, cardiorespiratory, and neurological involvement are the most frequent. Renal involvement is one of the most severe manifestations in cSLE (50–80%),[2] so active follow-up is recommended.

Several analytical tests are done to reach a diagnosis: ANA, anti-DNA antibodies, anti-extractable nuclear antigen (ENA) antibodies —including anti-Sm, anti-RNP, anti-Ro/SS-A, and anti-La/SS-B antibodies—, anti-phospholipid (APL) antibodies, complement (C3, C4), immunoglobulins, acute phase reactants (APR). There is no single diagnostic test, which means that the diagnosis is based on classification criteria.

The main goal of treatment is remission or low disease activity, and the prevention of flares and accumulated systemic damage.

Here we describe the clinical case of a patient diagnosed with cSLE associated with complement C1q deficiency with pulmonary, joint, and renal involvement.

CASE REPORT

A 2-year-old patient consulted due to pain in both lower limbs and slow gait for the past 3 weeks, which progressed to difficulties in standing and decreased strength in both upper limbs. She had weight faltering. On physical examination, she presented generalized hypotonia, predominantly in the lower limbs, and generalized essential tremor. She was malnourished and had polyneuropathy. Vitamin deficiency, heavy metal poisoning, and a neurological condition were proposed as differential diagnoses.

The computed tomography (CT) of the brain and the magnetic resonance imaging (MRI) of the brain and spine were normal; the blood tests showed mild anemia and were negative for heavy metals, arsenic, and mercury; the total and active vitamin B12 results were below the normal limit, so a diagnosis of neuropathy due to vitamin deficiency was assumed. Intravenous vitamin B12 supplementation was started. During the course of her condition, a slight clinical improvement was observed.

During hospitalization, the patient began with prolonged febrile syndrome and arthralgia in the left tibia-ankle joint and left knee. Systemic involvement due to infectious and/or immune causes was suggested as a differential diagnosis. The blood cultures did not show microorganism rescue; the bone x-ray was unremarkable; the chest x-ray showed bilateral peribronchovascular (interstitial) infiltrate; the chest CT scan found bilateral ground-glass opacities, predominantly on the left, with nodular images. Abundant axillary lymph nodes were observed. Due to the patient's pulmonary involvement, samples of respiratory secretions, gastric lavage, and bronchoalveolar lavage were performed; no microorganisms were found. She had high APR levels; her rheumatology profile screen showed positive anti-nuclear factor 1/1280, hypocomplementemia with C3 at 48 mg/dL, C4 at 3 mg/dL, and anti-DNA antibodies 1/640. A 24-hour urine sample was collected, which showed significant proteinuria. The patient met the classification criteria for cSLE, so she started immunosuppressive therapy with meprednisone at 2 mg/kg/day, which resulted in clinical resolution of joint symptoms, without improvement of renal involvement. Two months later, a gastric lavage culture was positive for *Mycobacterium avium*, so she started treatment with ethambutol and azithromycin.

Given the early age of presentation, the renal and pulmonary impact at onset, and the isolation of an opportunistic infection, a test was done for monogenic causes of SLE and additional lab tests showed normal C2 and C1q at 17 mg/dL (normal value: 118–238 mg/dl); therefore, cSLE associated with C1q deficiency was diagnosed. The patient progressed with massive proteinuria, so a kidney biopsy was performed, which showed focal lupus nephritis (class III), so she started treatment associated with intravenous cyclophosphamide with poor response.

DISCUSSION

cSLE is an autoimmune disease with multisystem involvement that begins before 16 years of age; its prevalence is 3.3 to 8.8 per 100 000 children[3,4] and it has an estimated mortality of 3.8% in the pediatric population in Latin America.[4] The sex distribution varies according to the age at onset, being almost equal in cSLE with onset in children under 5 years of age. From a pathophysiological perspective, early disease onset may also indicate a stronger genetic contribution. Over the years, the identification of rare genetic variants that cause lupus-like phenotypes, so-called monogenic lupus, has in turn provided insight into the pathogenesis of lupus as a whole.[5]

Patients with deficiencies in the early stages of the complement pathways (C1q, C1r, C1s, C2, C3, C4A, and C4B) have an increased predisposition to develop autoimmune diseases. In fact, C1q deficiency and C2 fraction deficiency are considered to be the major genetic risk factor for the development of cSLE. Other defects associated with monogenic cSLE include DNASE1L3 deficiency, defects in *TREX1*, interferonopathies, and alterations in RAS/MAPK signaling pathways.[5]

There are several factors by which patients with complement deficiency develop more severe autoimmunity that could act alone or in combination; among these is the role of complement, particularly C1q, which, by acting on apoptotic cell clearance, allows greater exposure to autoantigens and may be causative of this earlier and more severe presentation.[5–7] Circulating autoantibodies against complement proteins, such as C1q and C3b, may be found deposited in the kidneys of patients with lupus nephritis and cause inflammation and tissue damage.[5,8]

Patients with cSLE associated with C1q deficiency develop clinical manifestations at early ages, severe skin involvement, glomerulonephritis with torpid and rapid course.[7,9] Renal involvement is one of the most important predictors of a poor prognosis in cSLE, which may progress to end-stage renal disease.[8,9]

cSLE is a syndrome with great clinical and analytical variability, making its diagnosis a challenge on many occasions. There is no single diagnostic test; therefore, the diagnosis is based on classification criteria. The most commonly used criteria in the medical bibliography are those established by the American College of Rheumatology (ACR), which were revised in 1997.[10,11] More recently, the European League Against Rheumatism (EULAR), in collaboration with the ACR, has proposed new classification criteria based on a score derived from both clinical and analytical criteria.[12]

The main goal of treatment is remission or low disease activity, and the prevention of flares and accumulated damage. Pharmacological treatments include first-line immunosuppressants, e.g., glucocorticoids (GC), classical disease-modifying drugs (methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide), and biologic disease-modifying drugs (rituximab, belimumab).[12,13]

The anti-C1q antibody titer correlates with disease activity in children with lupus nephritis. The use of fresh frozen plasma (FFP) to replenish complement components may be effective in patients with inherited complement deficiency. A recent case series described 3 children with C1q deficiency and severe SLE. In all 3 patients, treatment with FFP allowed a rapid recovery and the possibility of steroid discontinuation.[14]

cSLE, although it is often phenotypically similar to adult-onset SLE, may also present with particular or severe features. An early age at presentation or severe involvement at onset makes the healthcare team rule out associations with inborn errors of immunity. The molecular and immunological profile of SLE patients has also resulted in the development of novel biomarkers and therapeutic targets.

In this regard, our conclusion is that, the approach to patients with severe cSLE, especially those with early renal involvement, who develop recurrent or opportunistic infections associated with low complement levels, should be to rule out inborn errors of immunity, which is a conditioning factor of this disease. Thus, cSLE would not be considered a single disease, but a heterogeneous group of different monogenic defects with susceptibility to infection and organ involvement.[15] ■

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