Refractory Thrombocytopenia in Children: A Case Report

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Abstract

Pediatric systemic lupus erythematosus is a rare autoimmune disease that accounts for 10% of all cases of systemic lupus erythematosus. Isolated cytopenia as the only presentation of systemic lupus erythematosus is rare in children. An 8-year-old female with an unremarkable personal and family history was admitted to our pediatric rheumatology department due to refractory chronic thrombocytopenia after having received pulses of methylprednisolone, polyvalent immune globulin, anti-D immune globulin and eltrombopag. Laboratory tests revealed thrombocytopenia (< 10 x 10^9 cells/L), positive antinuclear antibodies and anti-double stranded DNA antibodies, consumption of complement and a positive Coombs test, allowing us to establish the diagnosis of systemic lupus erythematosus. She received pulses of methylprednisolone for three days, followed by oral corticoid, associated with azathioprine, with clinical and laboratorial improvement. The presence of refractory thrombocytopenia highlights the possibility of systemic lupus erythematosus when other diseases, mainly infectious or hemato-oncological diseases, are excluded.

Keywords: Child; Lupus Erythematosus, Systemic/complications; Lupus Erythematosus, Systemic/diagnosis; Thrombocytopenia/diagnosis; Thrombocytopenia/therapy

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease,[1-3] which can affect several organs and systems. It is more common among women of childbearing age.[1-3] Only 10%-20% of the reported cases develop during childhood.[4] Clinical manifestations may vary and are nonspecific, with hematological abnormalities (anemia, leukopenia, and thrombocytopenia) being described in more than half of the patients.[1,2] Isolated thrombocytopenia is relatively rare as the initial presentation of a child with SLE. Therefore, the diagnosis of immune thrombocytopenia is common and, thereby, delayed diagnosis and inappropriate therapy may occur.[5]

Case Report

An 8-year-old female, with unremarkable past medical and family history, was admitted to the rheumatology department because of a persistent decreased platelet count.

She reported easy bruising for 10 months, initially involving the lower limbs with progression to the abdomen. No gross bleeding was reported, such as gingival bleeding, epistaxis, hematuria, or rectal bleeding. There was no recent history of infections, vaccinations, or traveling, and she denied the use of any new drugs. Six months later, she was evaluated at the emergency department because of bruising and petechiae, with predominant involvement of the lower limbs. No other relevant abnormalities were present on physical examination. Laboratory tests showed thrombocytopenia (platelets 21 x 10^9 cells/L), without any other hematological abnormality. She was hospitalized and received intravenous methylprednisolone at a dose of 30 mg/kg/day for three consecutive days, followed by oral prednisolone at a dose of 1 mg/kg/day. A slight improvement of thrombocytopenia (platelets 34 x 10^9 cells/L) was documented. A direct Coombs test was positive and antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) were negative. Bone marrow examination was consistent with immune thrombocytopenia. She completed 15 days of oral prednisolone with tapering.

At the hematology department, due to the worsening of thrombocytopenia (platelets 10 x 10^9 cells/L), she received polyvalent immunoglobulin, with a partial but not sustained improvement. Fifteen days later, she received another administration, associated with anti-D immunoglobulin. Consequently to persistent severe thrombocytopenia, with no response to different treat-

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ments, eltrombopag was started (at a dose of 25 mg/day for eight weeks), without any improvement.

The patient was then admitted to rheumatology department. She maintained bruises of the lower limbs, but denied any other complaints, especially photosensitivity, rash, oral or genital ulcers, thrombotic events, alopecia, arthritis, or cardiorespiratory complaints. Physical examination showed bruises of the lower limbs bilaterally. Blood pressure was normal, and no other relevant abnormalities were present. She was medicated with oral prednisolone at a dose of 1 mg/kg/day. She repeated laboratorial tests, shown in Table 1, that allowed us to establish the diagnosis of juvenile SLE. Urinalysis and abdominal and pelvic ultrasound were also performed, and did not show any abnormality. She was hospitalized and received intravenous methylprednisolone at a dose of 13.5 mg/kg/day for three consecutive days, followed by oral corticoid at a dose of 1 mg/kg/day, associated with azathioprine at a dose of 1.5 mg/kg/day. She had a rapid improvement of the symptoms and laboratorial abnormalities. She continued her follow-up in our department, remained asymptomatic with a platelet count of 146 x 10^9 cells/L. Prednisolone was progressively reduced, maintaining immunosuppressive treatment with azathioprine.

Discussion

Systemic lupus erythematosus is a chronic, autoimmune, inflammatory disease of unknown etiology. It is considered to result from the interaction between genetic susceptibility and environmental, hormonal, and infectious factors.[6-8] It is an autoimmune disorder, characterized by the loss of self-tolerance, leading to aberrant immune responses and a high production of autoantibodies.[3,6-8] These antibodies may bind directly to target cell antigens or may form circulating immune complexes and deposit in various tissues and organs, inducing an inflammatory response (with the recruitment of complement and inflammatory cells and production of cytokines).[4] In both situations, the result will be cellular damage, especially affecting the central nervous system, kidneys, joints, and hematopoietic system.[4] The diagnosis of SLE in children may be a challenge because it is a rare disorder with heterogeneous clinical manifestations.[5] The most common clinical presentation is the gradual onset of fever, malaise, fatigue, arthritis of the small joints, and mucocutaneous involvement.[5] Although hematologic abnormalities, especially cytopenia, are common in these patients, they are

Table 1. Results of the complementary investigation of the patient

Laboratory test	Patient values (reference values)
Hemoglobin (g/dL)	12.7 (12.0-16.0)
White blood cell (x 10^9 cells/L)	6.67 (4.70-12.70)
Neutrófilos (%) / Linfócitos (%)	64% (32-62%) / 25% (27-55%)
Platelet (x10^9 cells/L)	< 10 (250-500)
Erythrocyte sedimentation rate (mm 1st hour)	10 (4-20)
C-reactive protein (mg/dL)	2.5 (<3.0)
Aspartate aminotransferase (U/L)	20 (< 47)
Alanine aminotransferase (U/L)	26 (< 39)
Gama glutamyl transferase (U/L)	20 (< 32)
Lactate dehydrogenase (U/L)	275 (< 300)
Urea (mg/dL)	29 (10-34)
Creatinine (mg/dL)	0.38 (0.26-0.77)
Direct Coombs test	Positive
Complement C3c (mg/dL)	150 (83-177)
Complement C4 (mg/dL)	35 (12-36)
Complement CH50 (mg/dL)	24
Antinuclear antibodies	> 1/1000 (mottled pattern)
Anti-double stranded DNA antibodies	305.4 (< 100.0)
Rheumatoid factor	Negative
Anti-extractable nuclear antigens antibodies	Negative
Anti-cardiolipin antibodies	Negative
Anti-beta2-glycoprotein	Negative
Lupus anticoagulant	Negative

usually accompanied by other symptoms.[5] Isolated cytopenia as the only presentation of SLE is rare.[5] Cytopenia is defined as an abnormal reduction in the number of one or more mature blood cells.[9] Peripheral cytopenia, including anemia, leukopenia, and thrombocytopenia, are SLE classification criteria proposed by the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC), as shown in Table 2.[10-12] Thrombocytopenia is defined as a platelet count lower than 100 x 10^9 cells/L and may occur in 25%-50% of patients with SLE.[12] Severe thrombocytopenia (platelets < 50 x 10^9 cells/L) is less common, appearing in only 10% of all cases.[12]

Table 2. Classification criteria for systemic lupus erythematosus

ACR (Four of 11 criteria)
Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis
Serositis
Renal disorder
Neurologic disorder
Hematologic disorder
Immunologic disorder (anti-dsDNA, anti-Sm or lupus anticoagulant)
ANA
SLICC (Four of 17 criteria, including at least one clinical criterion and one immunologic criterion; or biopsy-proven lupus nephritis)
CLINICAL CRITERIA
Acute cutaneous lupus 64% (32-62%) / 25% (27-55%)
Chronic cutaneous lupus
Oral and nasal ulcers
Nonscarring alopecia
Joint disease
Serositis
Renal disorder
Neurologic disorder
Hemolytic anemia
Leukopenia or lymphopenia
Thrombocytopenia
IMMUNOLOGIC CRITERIA
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid
Low complement
Direct Coombs test

ACR - American College of Rheumatology; ANA - antinuclear antibodies; Anti-dsDNA - Anti-double stranded DNA antibodies; Anti-SM - anti-Smith antibodies; SLICC - Systemic Lupus International Collaborating Clinics.

Low platelet counts may result from the phagocytosis of platelet-bound antiplatelet antibodies by splenic macrophages (like immune thrombocytopenia), increased consumption of platelets in situations of hypersplenism, or abnormalities in platelet production secondary to pharmacological treatment.[1]

Patients may present several clinical scenarios, ranging from mild and asymptomatic, requiring observation only, to severe and life-threatening, demanding aggressive immunological and surgical treatments (splenectomy).[13] Moreover, thrombocytopenia is an independent risk factor for early mortality in SLE.[13] In fact, these patients are more likely to present increased disease activity and organ damage, especially renal disease, neuropsychiatric involvement, and hemorrhage.[13,14]

In our case, it was possible to establish the diagnosis of SLE, considering the following clinical and immunological abnormalities: thrombocytopenia, presence of ANA and anti-dsDNA antibodies, consumption of complement (CH50), and positive direct Coombs test and absence of hemolytic anemia, fulfilling four of the SLICC systemic lupus erythematosus classification criteria. Considering the criteria proposed by the ACR, the patient only fulfills three of them (hematologic disorder, immunologic disorder, and positive ANA). However, during follow-up, the patient may develop other criteria (mainly clinical criteria). In fact, although it is rare, patients with SLE may not present all four classification criteria simultaneously, especially when they present SLE-specific antibodies (as anti-dsDNA antibodies).[15]

As in other cases described in the literature,[5,16-17] the presence of isolated thrombocytopenia leads to the diagnosis of immune thrombocytopenia, with the use of multiple therapies, without an effective response. In fact, the absence of improvement should raise the suspicion of SLE, when other diseases, mainly infectious or hemato-oncological disorders (including Evans syndrome, characterized by thrombocytopenia associated with hemolytic anemia) are excluded.[1] The absence of SLE-specific antibodies, such anti-dsDNA, may also have been responsible for the delay in the diagnosis (usually their presence precedes the diagnosis of SLE). In SLE, its titer varies according to the degree of disease activity, with an increase during the inflammatory process and a decrease with an effective treatment. Therefore, the periodic evaluation of these antibodies is important and should be performed not only in the diagnosis, but also as a marker of disease activity.[8,11,18] In our case, the absence of these antibodies may have been the result of using a

less sensitive and more specific method, with the detection of antibodies with high avidity. However, we should remember that anti-dsDNA antibodies are positive in 70%-98% of patients with SLE and that there is a small, but real number of patients in whom these antibodies are negative (it is more common in patients with serositis).[19] Regarding the treatment, we emphasize the importance of immunosuppressive drugs due to their steroid-sparing effect and their role in severe or refractory patients.[4,5]

WHAT THIS CASE REPORT ADDS

- Isolated thrombocytopenia is rare as the initial manifestation in children with systemic lupus erythematosus, and the initial diagnosis of immune thrombocytopenia is common.
- Hematologic abnormalities (anemia, leukopenia, and thrombocytopenia) are described in more than half of the patients and are immune thrombocytopenia classification criteria (American College of Rheumatology and Systemic Lupus International Collaborating Clinics).
- The presence of refractory thrombocytopenia is an alert for the diagnosis of immune thrombocytopenia when other diseases, mainly infectious or hemato-oncological, are excluded in this population.
- It is important to use immunosuppressive drugs due to their steroid-sparing effect or in severe or refractory patients.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Trombocitopenia Refratária na Criança: A Propósito de um Caso Clínico

Resumo:
O lúpus eritematoso sistémico pediátrico é uma doença autoimune rara, correspondendo a 10% do total de casos de lúpus eritematoso sistémico. As citopenias isoladas são raras na apresentação inicial da criança com lúpus eritematoso sistémico, condicionando frequentemente um atraso no diagnóstico. Uma criança de 8 anos, sexo feminino, sem antecedentes pessoais ou familiares relevantes, foi orientada para reumatologia pediátrica por trombocitopenia crónica refratária à terapêutica com corticoides em alta dose, imunoglobulina polivalente, imunoglobulina anti-D e eltrombopag e estudo imunológico inicial sem alterações. Na nossa investigação, realizamos um estudo analítico, que mostrou trombocitopenia (< 10 x 10^9 células/L), anticorpos antinucleares e anti-dsDNA positivos, consumo de complemento e prova de Coombs direta positiva, permitindo estabelecer o diagnóstico de lúpus eritematoso sistémico. Efetuou pulsos de metilprednisolona durante três dias, seguindo-se corticoide oral, associado a azatioprina, com melhoria clínica e analítica. A trombocitopenia refratária constitui um alerta para a possibilidade de lúpus eritematoso sistémico, quando excluídas outras doenças, sobretudo infeciosas ou hemato-oncológicas.

Palavras-Chave: Criança; Lúpus Eritematoso Sistémico/complicações; Lúpus Eritematoso Sistémico/diagnóstico; Trombocitopenia/diagnóstico; Trombocitopenia/tratamento