AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: A CASE REPORT

SÍNDROME LINFOPROLIFERATIVA AUTOIMUNE: RELATO DE CASO

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ABSTRACT

Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disease caused by mutations in the genes of the Fas pathway, resulting in impairments in lymphocyte apoptosis. ALPS leads to autoimmune hemolytic anemia, lymphadenomegaly, splenomegaly, hypergammaglobulinemia, an exaggerated elevation of vitamin B12, and a propensity for lymphomatous transformation. A five-month-old female, admitted with anemia, splenomegaly, and repetitive episodes of infection. Laboratory tests showed autoimmune hemolytic anemia, hypergammaglobulinemia, and serum elevation of vitamin B12. Flow cytometry revealed abnormal values of T lymphocytes: TCR-αβ C3+ CD4- CD8. The histopathological study of the lymph node revealed paracortical hyperplasia with T-transformed cells, characterized by CD3 + CD4- CD8-. G-banding cytogenetic analysis in the bone marrow showed a normal karyotype (46, XX), and the FISH technique in the interphase nucleus removed the occurrence of chromosome 7. Sequencing of the FAS gene revealed the presence of a pathogenic variant in the heterozygote form, at the intron four splicing site (IVS4 + 1G > A). The patient was diagnosed with ALPS and treated with corticosteroids; a significant regression of splenomegaly and stabilization of hemolytic anemia were observed, with a negative Coombs test. The patient is currently stable under low doses of corticosteroid. The authors highlight the importance of investigating ALPS in children with hemolytic anemia, splenomegaly, and recurrent infections.

Keywords: Autoimmune lymphoproliferative syndrome; Splenomegaly; FAS route genes

RESUMO

Introdução: A síndrome linfoproliferativa autoimune (ALPS) é uma doença rara, genética, decorrente de mutações nos genes da via FAS que ocasionam defeitos na apoptose linfocitária, levando a anemia hemolítica autoimune, linfoadenomegalia, esplenomegalia, hipergamaglobulinemia, elevação exagerada da vitamina B12 e propensão para transformação linfomatosa. **Relato do caso:** Lactente com cinco meses, gênero feminino, admitida para investigar anemia, esplenomegalia e episódios repetitivos de infecções. Exames laboratoriais mostraram anemia hemolítica autoimune, hipergamaglobulinemia e elevação sérica da vitamina B12. A citometria de fluxo evidenciou população de linfócitos T anormal: TCR-αβ/C3+/CD4-/CD8-. O estudo histopatológico do linfonodo revelou hiperplasia paracortical com células T transformadas, CD3+/CD4-/CD8-. A análise citogenética por bandeamento G na medula óssea mostrou cariótipo normal (46,XX) e a técnica de FISH em núcleos interfásicos afastou a ocorrência da monossomia do cromossomo 7. O sequenciamento do gene FAS revelou presença da variante patogênica de substituição em heterozigose, no sítio de *splicing* do íntron 4 (IVS4+1G>A). A paciente foi diagnosticada como ALPS e tratada com corticosteroide. Houve regressão significativa da esplenomegalia e estabilização da anemia hemolítica; o teste de Coombs deu negativo. Atualmente, a paciente está estável, usando doses baixas de corticosteroide. **Comentários:** Mostra-se necessária a investigação da ALPS em pacientes pediátricos que cursam com anemia hemolítica, esplenomegalia e infecções de repetição.

Palavras-chave: Síndrome linfoproliferativa autoimune; Esplenomegalia; Genes da via FAS

INTRODUCTION

The Autoimmune lymphoproliferative syndrome (ALPS) is a rare disease caused by defective homeostasis of lymphocytes associated with pathogenic variants of heterozygous germline in Fas pathway genes, causing impairments in lymphocytic apoptosis[1]. ALPS is characterized by autoimmune cytopenia, splenomegaly, lymphadenomegaly and increased polyclonal lymphocytes in peripheral blood and tissues. Also, individuals with ALPS are more susceptible to lymphoid infections and malignancies 2-5.

The ALPS should be considered as a differential diagnosis for several diseases due to clinical manifestations that overlap with hematological and autoimmune lymphoproliferative disorders[6]. The diagnosis considers clinical-laboratory data combined with detecting increased percentage of double-negative T cells (TCRαβ+ CD4- CD8-)[7]and a pathogenic variant in genes of the apoptosis Fas pathway (FAS, FASLG, CASP10)[8].

This report presents the differential diagnosis of ALPS based on an unprecedented clinical case in Pernambuco, Brazil. This study was approved by the Research Ethics Committee of the HUOC/PROCAPE Hospital Complex.

CASE REPORT

LMS patient, female, five-month-old, born in Cupira-PE, admitted to the Pediatric Oncology Center of the Oswaldo Cruz University Hospital to investigate anemia and increased abdominal volume. The mother reported increased abdominal volume since the child was four months old, frequent episodes of diarrhea, and fever. The mother also reported difficulty in getting pregnant and underwent several treatments over seven years, culminating in the success of artificial insemination. Family history was negative for consanguinity, cancer, or rheumatological diseases. On physical examination, the patient had a protruding abdomen, with giant splenomegaly that reached the left iliac fossa, occupying the entire hemiabdomen, exceeding the midline, and a four-centimeter lymph node enlargement in the left cervical region without phlogistic signs. Laboratory tests were requested to investigate the disease. The blood count showed severe anemia, thrombocytopenia, lymphocytosis with lymphocytic atypia, and high erythrocyte sedimentation rate (Hb: 6.6g/dL; Hct: 23.8%; MCV: 75.1; leukocytes: 5,600/mm3; platelets: 91,000/mm3). Except for the elevation of vitamin B12 (2000 pg/ml), other biochemical tests showed no significant changes. The coproparasitological and urine summary showed no abnormalities. The proteinogram showed hypergammaglobulinemia with an IgG level of 3137mg/dL. The cryoagglutinins test, Coombs test, and antinuclear antibody were negative and the purified protein derivative test (or Mantoux test) was non-reactive. Serology was negative for EBV, CMV, HAV, HBV, and toxoplasmosis. Computed tomography of the upper abdomen confirmed homogeneous splenomegaly (Figure 1), and a computed tomography scan of the chest showed no abnormalities. Ultrasonography of the cervical region showed a pattern of nonspecific cervical lymphadenitis.

Aspiration puncture and bone marrow biopsy showed hypercellularity of the myeloid series with eosinophilia, discrete signs of megaloblastosis, and histiocytes with hemophagocytosis. Examination revealed neither parasites nor metastatic malignant infiltration. The conclusion was reactive bone marrow. Flow cytometry immunophenotyping of peripheral blood revealed that 10% of lymphocytes were TCR αβ CD3+ CD4- CD8-, and 10% of T cells were gamma/delta (Figure 2).

The histopathological study of the left cervical lymph node showed hyperplasia in the interfollicular and paracortical regions, with areas of numerous lymphoid cells, transformed (CD3+), polymorphous and a high number of mitosis figures, many of them without CD4 or CD8 expression in whose immunohistochemical analysis negativity for CD1a, CD30 and TdT and cell reactivity for CD20, CD3, CD4, CD8, Ki-67 (70%), and S-100 (Figure 3).

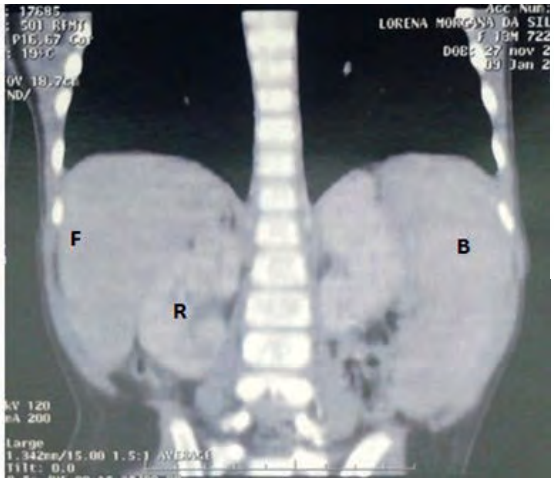

Figure 1. Abdominal tomography with contrast of the patient LMS showing Hepatosplenomegaly: (F) liver; (R) kidneys; and (B)

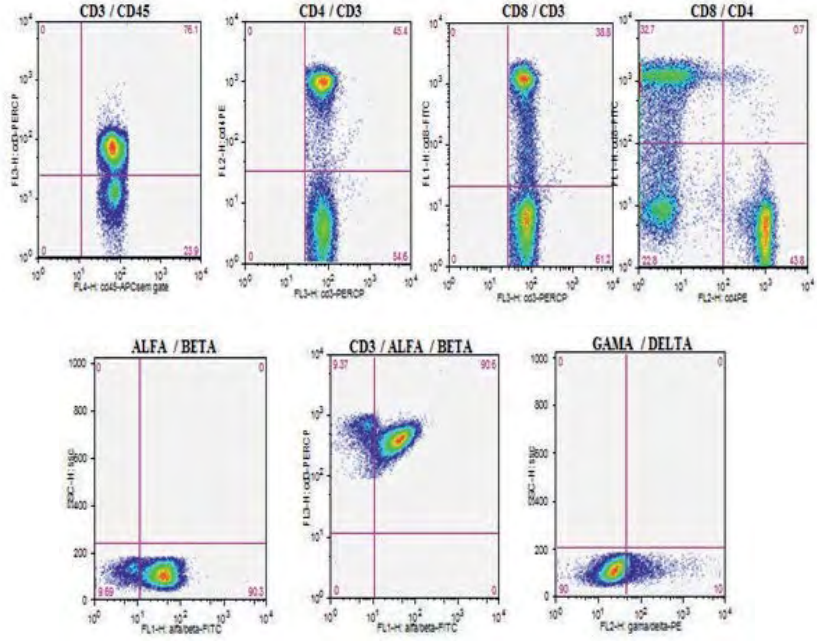

Figure 2. Histograms of blood immunophenotyping peripheral, showing CD3+ CD4- lymphocyte population CD8-.

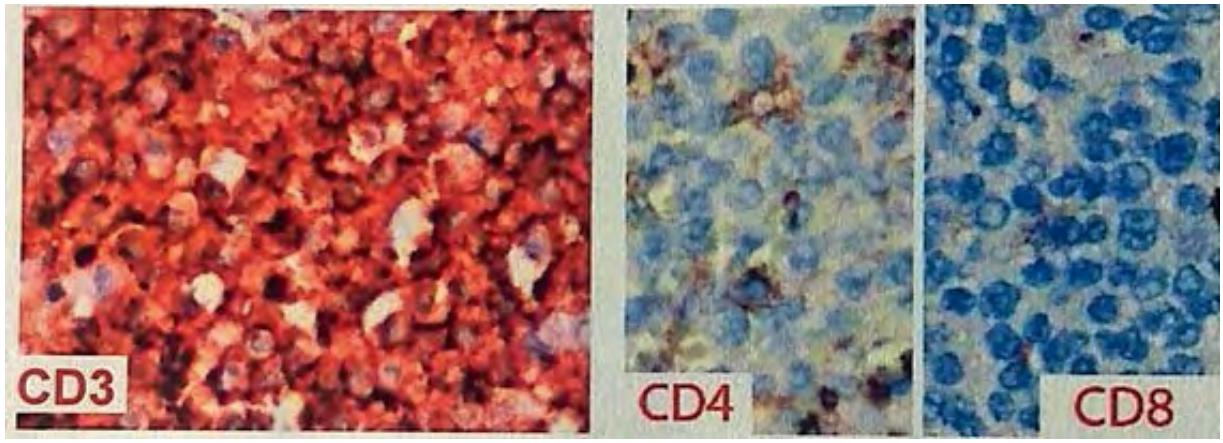

Figure 3. Lymph node immunohistochemistry showing CD3+ CD4- CD8- lymphocytes

Cytogenetic studies by G-banding showed normal karyotyping, 46, XX, and the FISH technique detected no monosomy[7]. Sequencing of the FAS gene revealed a heterozygous substitution at the intron four splicing site (IVS4+1G>A). Thus, the patient was diagnosed with ALPS and initially started treatment with high doses of corticosteroids for three months, achieving regression of splenomegaly and stabilization of anemia. After a slow reduction of this medication and due to the difficulty in acquiring other immunosuppressors, the patient was treated with low doses (2.5 mg) of prednisolone. Currently, at the age of five months, the patient is clinically stable with clinical follow-up and periodic exams to monitor the disease.

COMMENTS

The ALPS was initially described in 1967 and is considered a disease of lymphocyte homeostasis caused by defects in the apoptotic pathway of the FAS/CD95 genes. Different types of genetic mutations have been described in the literature and can be classified into subtypes Ia and Ia with somatic mutation, whose mutated protein is Fas, which is involved in apoptosis, in the major lymphocyte receptor; subtype Ib that affects the Fas ligand; type II that affects caspase-10, caspase-8 and the intracellular protease of the apoptotic cascade and type III whose protein is still unknown[9].

Individuals with ALPS have T and B cell lymphocytosis, which can reach five times the normal

value. Usually, these individuals have T cells that are TCR α/β+ CD4- CD8-, commonly present in a proportion of less than 1% in peripheral blood, with variations between 5% and 40%. These cells express CD45RA+, CD45RO-, CD57+, and HLA-DR10, which were found in our patient.

Although lymphoproliferation is initially benign, about 10% of individuals with type Ia ALPS develop B-cell lymphoma, with approximately 50 times more risk of developing Hodgkin and non-Hodgkin lymphoma. Monitoring these individuals throughout their lives proves prudent, justifying the importance of constant outpatient follow-up. ALPS evolution is variable; however, the disease usually improves over the years, with an average lifespan exceeding that of the normal population. The recurrence and severity of autoimmune episodes decrease with age, and an adequate response to therapy may suggest favorable outcomes.

ALPS is poorly understood, with approximately 300 cases reported in the literature[9]. Also, ALPS is an important differential diagnosis for other immunodeficiency disorders characterized or complicated by lymphoproliferation, autoimmune disease, and lymphoma, due to their heterogeneous phenotypes, which clinically overlap with other diseases[6,8]. This syndrome appears in childhood in the first years of life, with no predominance by sex or race[9,10]. The patient described in this case was a five-month-old female who presented clinical and laboratory findings compatible with ALPS, including autoimmune hemolytic anemia, lymph adenomegaly, splenomegaly, hypergammaglobulinemia, and an increased vitamin B12, along with an abnormal population of TCRαβ+ CD3+ CD4- CD8- T cells. Specific laboratory, biochemical, hematological, and genetic tests were necessary due to manifestations like those of other pediatric diseases, such as lymphoproliferative disorders, JML/Monosomy 7, autoimmune disorders, storage diseases, and infectious diseases, including visceral leishmaniasis (kala-azar).

The ALPS should be investigated in individuals and family members with non-malignant lymphoproliferation using laboratory tests. The test includes autoimmune anemia, gamma globulin dosage, vitamin B12 levels, and immunophenotyping by flow cytometry to search for the expansion of double-negative T cells (> 1%) and mutations in the FAS gene.

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