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Case Report

Autoimmune Lymphoproliferative Syndrome Misdiagnosed as Hemophagocytic Lymphohistiocytosis; A Case Report

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ABSTRACT

Autoimmune lymphoproliferative Syndrome (ALPS) is a rare inherited disorder of apoptosis. It usually presents with chronic lymphadenopathy, splenomegaly, and symptomatic cytopenia in a child. Herein, we report a 14-year-old boy with symptoms misdiagnosed as hemophagocytic lymphohistiocytosis who was treated before ALPS was diagnosed for the patient. This case should alert pediatricians to consider ALPS in differential diagnosis of a child with lymphadenopathy, splenomegaly, and cytopenia.

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Introduction

Autoimmune lymphoproliferative syndrome (ALPS) is a rare disease leading to cytopenia. Lymphoproliferative disorders, such as ALPS and hemophagocytic lymphohistiocytosis (HLH) both could be considered as differential diagnosis for lymphadenopathy, splenomegaly, and pancytopenia. Tables 1 and 2 show the diagnostic criteria for ALPS and HLH, respectively.[1,2]

Patients with ALPS have nonmalignant lymphadenopathy with/without splenomegaly associated with an increased $CD3^+$, TCR α/β^+ lymphocytes that do not express CD4 or CD8, referred to as double-negative T cells (DNTs). Patients may also have elevated levels of vitamin B-12.[1]

Herein, we describe a 14-year-old boy who was diagnosed with ALPS following a presumptive diagnosis of HLH.

Case Presentation

A 14-year-old boy was admitted with a history of seven months of abdominal pain and persistent fever. His medical history was unremarkable. Vital signs at admission were: temperature 38.8 °C, pulse rate: 90 beats per minute and blood pressure 123/70 mmHg. Palpable cervical and axillary lymphadenopathy was noted on physical examination. The patient's abdomen was diffusely tender to palpation mainly on the left upper quadrant. The spleen and liver were palpable 5 cm and 4 cm below costal margin, respectively.

Laboratory tests revealed WBC: 1300/mm^3, 40% polymorphonuclear leukocytes, 43.6% lymphocytes, Hb: 6.9 g/dl, Hct: 28%, Platelet: 57000 /mm^3. All biochemistry tests were within normal range. LDH: 712 IU/l (normal: 207 - 414 IU/l), Direct bilirubin: 0.9 mg/dl.

Wright agglutination test, coombs test, Rheumatoid

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Table 1: Diagnostic Criteria for ALPS

Required criteria
Chronic (>6mo), nonmalignant, noninfectious lymphadenopathy and/or splenomegaly
Elevated $CD3^+TCRab^+CD4^-CD8^-$ DNTs (>1.5% of total lymphocytes or >2.5% of CD3+ lymphocytes) in the setting of normal or elevated lymphocyte counts
Accessory criteria
Primary
Defective lymphocyte apoptosis
Somatic or germ-line pathogenic mutation in FAS, FASLG, or CASP10
Secondary
Elevated plasma sFASL levels (>200 pg/mL), plasma interleukin (IL) -10 levels (>20 pg/mL)
Serum or plasma vitamin B-12 levels (>1500 pg/mL) or plasma IL-18 levels >500 pg/mL
Typical immunohistologic findings
Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia)
Elevated IgG levels (polyclonal hypergammaglobulinemia)
Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity
Definitive diagnosis: both required criteria plus 1 primary accessory criterion
Probable diagnosis: both required criteria plus 1 secondary accessory criterion

Reprinted with permission from Oliveira JB, Bleesing JJ, Dianzani U, et al. Blood. 2010;116(14):e35–e40. IgG, immunoglobulin G; sFASL, Souble FasLigand.

Table 2: Diagnostic Criteria for HLH

(A) A molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 Or (B) If 5 of the 8 criteria listed below are fulfilled:
1. Fever>38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood) Hemoglobin <9 g/dL (in infants <4 weeks: hemoglobin <0 g/dL) Platelets $<100 \times 10^3$ per mL Neutrophils $<1\times10^3$ per mL
4. Hypertriglyceridemia (fasting: >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin >500 ng/mL
8. Elevated sCD25 (a-chain of sIL-2 receptor)

Reprinted with permission from Jordan MB, Allen CE, Weitzman Sheila, et al. Blood. 2011;118:4041–4052. NK, natural killer; sCD25, Soluble CD25 (a term sometimes used for alpha- chain of soluble IL-2 receptor).

factor and CRP were negative. Immunoelectrophoresis demonstrated Ig M: 290 mg/dl (normal : 40-230 mg/dl) and Ig G: 3300 mg/dl (normal : 700-1600 mg/dl). ANA, Anti double-stranded DNA (anti-dsDNA), Anti-citrulline antibodies, CH_{50}, C-ANCA, P-ANCA, Anti Toxoplasma (IgM and IgG), Anti Brucella (Ig M and Ig G), IFA for visceral leishmaniasis, Anti body for Borrellia and plasmodium malaria, viral hepatitis and HIV serology tests were negative. Flowcytometry revealed CD_3: 185mg/dl (normal: 90-180 mg/dl), CD_4: 35 mg/dl (normal: 10-40 mg/dl) and CD_8: 0. Anti EBV-VCA Ig M was 16 U/ml(normal<20 U/ml).

Double negative (DN) T cells were positive. He also showed hypofibrinogenemia with plasma fibrinogen of 150 mg/dl (normal: 180-540 mg/dl). Serum vitamin B12 level was in normal range. PCR for Cytomegalovirus (CMV)-DNA and Herpes simplex virus (HSV)-DNA was negative. A diagnosis of HLH was considered since he met four of 8 criteria including pancytopenia, >38.5 °C fever, splenomegaly and hypofibrinogenemia. Notably, he had normal ferritin levels.

One month later, a repeated ferritin measurement was 876 ng/ml, providing the fifth criterion for the diagnosis of HLH. Treatment of HLH was initiated according to the HLH-2004 protocol.[3] Because of huge splenomegaly and discomfort of the patient, splenectomy was performed for therapeutic and diagnostic purposes where the spleen was found to have diameters of 28×17×5 cm and weight of 1900 gr. Histopathology revealed hypersplenism with widened splenic cords and rare to absent hemophagocytosis. It was also noted that the spleen had atypical T-cell hyperplasia with DNTs, consistent with the diagnosis of ALPS.

He was then treated with prednisone 15 mg once daily and azathioprine 150 mg per day accordingly. Clinical and hematologic remission was ensued so that treatment was continued while tapering off the immunosuppressives. The patient is in good clinical conditions seven months after treatment.

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Discussion

ALPS and HLH are both considered in differential diagnosis of lymphadenopathy, splenomegaly, and pancytopenia and have many clinical and laboratory features in common which could be overlapping. Spergel and colleagues reported a 6-year-old girl with ALPS after initial diagnosis of HLH.[4] Both present in childhood and are characterized by lymphadenopathy, splenomegaly along with evidence of immune dysregulation such as cytopenia.[5] However, distinguishing between ALPS and HLH is vital because of different therapeutic measures.

Patients with ALPS often require long-term immunosuppressive therapies with corticosteroids and also steroid-sparing measures.[6] They also need to be taken care of for development of possible hematologic malignancies specially Hodgkin and non-Hodgkin's lymphoma.[7] Splenectomy is not necessary either for diagnosis or management in most of the cases.[6,8,9]

In contrast, the standard treatment of HLH is chemotherapy, including dexamethasone and cyclosporine with or without etoposide and if the patient has a family history of HLH and/or has central nervous system disease, allogeneic bone marrow transplantation is indicated.[2] Considering that none of these circumstances existed in our patient, bone marrow transplantation was not considered for our patient.

In this case, the initial diagnosis of HLH caused a delay in identification of the actual diagnosis for almost one month. He underwent splenectomy before a definitive diagnosis of ALPS was established, that might be an additional risk factor in the future for mounting probable infections in a patient who is also receiving immunosuppressive treatments. As a result, there is a need to carefully monitor the patient in the long term for the risk of pneumococcal sepsis secondary to splenectomy.[10]

In order to differentiate ALPS from HLH, it is important to be careful about diagnostic criteria of both conditions. Elevated serum biomarkers (vitamin B-12, sFASL, IL-10, IL-18) with evidence of autoimmune cytopenia can point toward a diagnosis of ALPS. The level of serum vitamin B12 >1.5 picograms/L bears important diagnostic significance.[5] However, our case had normal level of vitamin B12. Some recent studies have shown elevated IL-10 levels in HLH patients.[11,12]

Serum ferritin level could be of help to differentiate ALPS from HLH. Its level in ALPS is generally lower than 3000 ng/mL, which is reportedly specific for HLH.[13]

Conclusion

We have highlighted this case to emphasize the necessity of considering rare disorders, particularly ALPS in differential diagnosis of patients presenting with lymphadenopathy, splenomegaly and cytopenia.

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Conflict of Interest: None declared.

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