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LETTER TO THE EDITOR

Coexistence of Autoimmune Lymphoproliferative Syndrome and Familial Mediterranean Fever

Sultan Aydin Koker[1*], Nesrin Gulez[2], Frederic Rieux-Laucat[3,4], Ferah Genel[2], Canan Vergin[1], Capucine Picard[5,6]

To The Editor

Autoimmune Lymphoproliferative Syndrome (ALPS), was first described in the early 1990s (1), is defined as immune system failure due to insufficiency to control lymphocyte homeostasis by activity of lymphocyte apoptosis. ALPS represents a chronic non-malignant lymphadenopathy, hepatomegaly, splenomegaly, and increased risk of lymphoma, as well as the autoimmune syndrome, typically affecting blood cells (2). According to the 2009 NIH International Workshop report, ALPS's is diagnosed by two required and six accessory criteria. Required criteria are the appearance of lymphadenopathy and/or splenomegaly, and elevated TCRαβ+-DNT cells (3) (Table 1). ALPS is commonly caused by an inherited germline or somatic heterozygous mutation in the *FAS (TNFRSF6)* gene, which is known as ALPS-*FAS type 1A*. A 12 years boy was admitted to our hospital with bicytopenia, hepatosplenomegaly, and lymphadenomegaly. First screening was performed for the metabolic disease at 18 months old. He had fever attacks lasting several days once every 2-3 months, and he was attended to our hospital due to developing a flat red rash on the body in this period at three years old. As he had growth retardation, hepatosplenomegaly, and elevated acute phase reactants, the metabolic diseases were excluded as a result of tests and liver biopsy. At seven years old, he developed self-healing wounds like an abscess on the face and fingers in 4-5 days, along with fever. MEFV gene analysis was identified as V726A heterozygous mutation. The patient received 1 mg/day colchicine treatment by rheumatologist collaborator. The fever attacks relapsed despite of colchicine treatment after two months. The patient developed mild neutropenia associated with colchicine treatment. However, periodic wounds like abscess occurred again. Because of the lymphopenia and neutropenia, axillary and cervical lymphadenopathy over 2 cm in addition to hepatosplenomegaly were again appeared at 12 years old, the patient was immunologically assessed which showed elevated DNT TCR alpha-beta on lymphocyte subgroup tests. The direct anti-globulin test was negative (IgG3+; C3d1+).

*Corresponding author: Dr. Sultan Aydin Koker, Department of Pediatric, Hematology and Oncology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey, e-mail: drsultanaydin@hotmail.com

Table 1. Autoimmune lymphoproliferative syndrome (ALPS) diagnostic criteria based on the first international workshop of ALPS 2009 (3).

Required criteria

- Chronic (>6 months) non-malignant, noninfectious lymphadenopathy and/or splenomegaly
- Elevated α/β-DNT cells with normal or elevated lymphocyte counts

Primary accessory criteria

- Defective lymphocyte apoptosis (repeated at least once)
- Germline or somatic pathogenic pathogenic variants in *FAS*, *FASLG*, or *CASP10*

Secondary accessory criteria

- Elevated levels of one of the following:
  - Plasma soluble FASL (>200 pg/mL),
  - Plasma interleukin-10(>20 pg/mL)
  - Serum vitamin B_{12}(>1500 ng/L)
  - Plasma interleukin-18(>500 pg/mL)
- Typical immunohistological findings as determined by an experienced hematopathologist
- Autoimmune cytopenia with elevated (polyclonal) immunoglobulin G levels
- Positive family history

Definitive diagnosis: Both required criteria plus one primary accessory criterion.

Probable diagnosis: Both required criteria plus one secondary accessory criterion.

Immunoglobulin (Ig) A, G, M, and E were 655, 2180, 85, and 1194, respectively. IgD levels were examined normal for hyperimmune globulin D. Serum amyloid A (SAA) was normal. Celiac antibodies (anti-endomysium, anti-gliadin, and anti-tissue glutaminase) were normal. HLA B5 and HLA B51 were negative. At this stage the patient was negative for hepatitis, HIV, parvovirus, cytomegalovirus, toxoplasmosis, brucella, and tuberculosis. In immunohistochemical staining, BOB-1, CD138, TCR Beta F1, PAX5, OCT-2, Ki67, CD20, CD3, kappa, and CD4 were highly positive, but the expression of CD25, CD57, perforin, Granzyme B, CD8, CD30, and TIA-1 were low. Therefore, lymph node biopsy was detected to be compatible with the autoimmune lymphoproliferative syndrome. Flow cytometry of peripheral blood reported that 9.6% of the lymphocytes were DNT cells, CD19 was lower than the five percentile, and the CD4/CD8 ratio was mildly low. Heterozygous *FAS* mutation was detected on p.E261K (c.781G>A). It has been found that about 66% of the ALPS cases have known genetic defect (4). Most of the cases with ALPS have a germline mutation in the *FAS* gene. In uncommon cases, homozygous or compound heterozygous mutations lead to ALPS's severe pattern (5,6). Germline mutations in the genes encoding *FAS ligand* (7) and *caspase-10* (8) are rarely published in cases with ALPS who do not have a *FAS* mutation (*ALPS-FASLG and ALPS-CASP10*, respectively). In most affected patients, heterozygous *FAS* mutations cause ALPS-FAS by the mechanism of dominant-negative interference. Although our patient had heterozygous FAS mutation, he had the clinical findings of ALPS, such as autoimmune cytopenia, hepatosplenomegaly, and lymphadenopathy.

Keywords: Autoimmune, Familial Mediterranean Fever, Hepatosplenomegaly, Lymphadenopathy

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Author Details

[1]Department of Pediatric Hematology, [2]Department of Pediatric Immunology, Dr. Behçet Uz Children's Hospital, Izmir, Turkey, [3]Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, [4]Imagine Institute, Paris Descartes-Sorbonne Paris Cité University, [5]Paris University, Necker Medical School, Paris, France. Study Center for Primary Immunodeficiencies, Necker-Enfants Malades Hospital,APHP, Paris, France

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