LETTER TO THE EDITOR
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Autoimmune Lymphoproliferative Syndrome: Meticulous Care for Diagnosis

Nima Parvaneh1, Mehdi Veganeh1, and Ashgar Aghamohammadi1,2

1 Children's Medical Center, Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
2 Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Autoimmune lymphoproliferative syndrome (ALPS) is a prototypic disorder of abnormal lymphocyte homeostasis. In the September 2005 issue of The Iranian Journal of Allergy, Asthma and Immunology, a patient with clinical features consistent with ALPS was described. Although the clinical presentation was in favor of ALPS, a precise diagnosis needed more laboratory evaluations.

Key words: Autoimmune lymphoproliferative syndrome; Diagnosis; Fas pathway

LETTER

Autoimmune lymphoproliferative syndrome (ALPS) is a prototypic disorder of abnormal lymphocyte homeostasis.1 Defective programmed cell death of lymphocytes (apoptosis) through the Fas (CD95) pathway dwells a central role in the pathogenesis of ALPS.2 In the September 2005 issue of The Iranian Journal of Allergy, Asthma and Immunology (Vol. 4, No 3, Pages 149-152), Alavi et al described a patient with clinical features consistent with ALPS. Although the clinical presentation is in favor of ALPS, more laboratory evaluations were needed for a precise diagnosis. Current knowledge on molecular pathogenesis of ALPS has remarkably grown in recent years. 

Sneller et al3 have proposed a classification scheme, based on the genetic defects causing ALPS (Table 1). Patients with the mutations in the TNFRSF6 gene are classified as type Ia, TNF6SF6 as type Ib, CASP 8 or 10 as type II and patients without known mutation are classified provisionally as type III. Criteria that are currently used by the National Institute of Health (NIH) ALPS group to identify patients include chronic lymphadenopathy and/or hepatosplenomegaly, defective in vitro Fas-mediated lymphocyte apoptosis and ≥ 1% α/β-/DNT cells. In healthy human most of the γ/δ-/DNT cells are of γ/δ/β- subsets.2,5 In keeping with the criteria developed by the NIH group, patients with ALPS must have defective Fas-mediated apoptosis of lymphocytes, but this criterion is somewhat debatable.

In addition to patients in group Ia, there are other patients with an ALPS phenotype who also have a normal Fas-mediated apoptosis in vitro.7 Recently Holzelova et al8 and Rössler et al9 described several patients with a typical presentation of ALPS, who were found to have somatic mutations in TNFRSF6 in their sorted α/β-DNT cells with no germ line mutations. The Fas-mediated apoptosis assays were normal for all of these patients. These patients stand for a new group of ALPS designated as Im; "m" points out a mosaic pattern (Table 1). Defective Fas-mediated apoptosis cannot authenticate the diagnosis of patients with somatic mutations in TNFRSF6, hence is no longer considered as the gold standard for diagnosis of ALPS.8

Fortunately, all patients described by Holzelova et al8 and Rössler et al9 showed an expansion of α/β-DNT cells. The analysis of α/β-DNT cells is the central laboratory test for diagnosis of a patient with presumed ALPS.

Table 1. Molecular classification of autoimmune lymphoproliferative syndrome.

<table>
<thead>
<tr>
<th>ALPS Classification</th>
<th>Gene Mutated</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Fas (TNFRSF6)</td>
</tr>
<tr>
<td>Ib</td>
<td>Fasl (TNFSF6)</td>
</tr>
<tr>
<td>Im</td>
<td>Fas somatic mutation in DNT cells</td>
</tr>
<tr>
<td>II</td>
<td>CASP 8, 10</td>
</tr>
<tr>
<td>III</td>
<td>Molecularly undefined</td>
</tr>
</tbody>
</table>

REFERENCES


Corresponding Author: Nima Parvaneh, MD; Children's Medical Center, Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran. Tel: (+98 21) 6693 5855, Fax: (+98 21) 6642 8995, E-mail: nparvaneh@razi.tums.ac.ir