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Autoimmune Lymphoproliferative Syndrome: Meticulous Care for Diagnosis

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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[3] 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 al[4] 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, TNFSF6 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 accumulation of non-malignant lymphoid cells, manifested as lymphadenopathy and/or hepatosplenomegaly, defective in vitro Fas-mediated lymphocyte apoptosis and ≥ 1% α/β-double negative T cells (α/β-DNT cells) in peripheral blood, or lymphoid tissues.[5] Autoimmunity and a family history of ALPS are considered as supporting features which are not included in the NIH criteria.

Alavi et al[3] have employed the increase in DNT cells as a clue for diagnosis of ALPS in their patient. DNT cells consist of γ/δ and α/β subsets. In healthy human most of the circulating DNT cells are of γ/δ subset.[6] γ/δ-DNT cells have a role in mucosal immunity and their number increases in some viral infections and malignant processes.[6] To evaluate a patient suspected to have ALPS, it is essential to enumerate circulating α/β-DNT cells, whereas total DNT cells could mostly represent γ/δ-DNT cells.[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 Ib, there are other patients with an ALPS phenotype who also have a normal Fas-mediated apoptosis in vitro.[7] Recently Holzelova et al[8] and Rössler et al[9] 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 germline 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;[8] "m" points out a mosaic pattern (Table 1). Defective Fas-mediated apoptosis can not 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 al[8] and Rössler et al[9] 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.[4,9]

ALPS Classification	Gene Mutated
Ia	Fas (TNFRSF6)
Ib	FasL (TNFSF6)
Im	Fas somatic mutation in DNT cells
II	CASP 8, 10
III	Molecularly undefined

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REFERENCES

1. Bleesing JJ, Straus SE, Fleisher TA, Autoimmune lymphoproliferative syndrome. A human disorder of abnormal lymphocyte survival. Pediatr Clin North Am 2000; 47(6):1291-310.
2. Rieux-Laucat F, Fischer A, Deist FL. Cell-death signaling and human disease. Curr Opin Immunol 2003; 15(3):325-31.
3. Alavi S, Arzanian MT, Chavoshzadeh Z, Esteghamati M. Autoimmune lymphoproliferative syndrome: A Case Report. Iran J Allergy Asthma Immunol 2005; 4(3):149-52.
4. Sneller MC, Dale JK, Straus SE. Autoimmune lymphoproliferative syndrome. Curr Opinion Rheum 2003; 15(4):417-421.
5. Bleesing JJ. Autoimmune lymphoproliferative syndrome (ALPS). Curr Pharm Des 2003; 9(3):265-78.
6. Carding SR, Egan PJ. Gammadelta T cells: functional plasticity and heterogeneity. Nat Rev Immunol 2002; 2(5):336-45.
7. Lenardo M, Chan KM, Hornung F, McFarland H, Siegel R, Wang J, et al. Mature T lymphocyte apoptosis--immune regulation in a dynamic and unpredictable antigenic environment. Annu Rev Immunol 1999; 17:221-53.
8. Holzelova E, Vonarbourg C, Stolzenberg MC, Arkwright PD, Selz F, Prieur AM, et al. Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med 2004; 351(14):1409-18.
9. Rossler J, Enders A, Lahr G, Heitger A, Winkler K, Fuchs H, et al. Identical phenotype in patients with somatic and germ line CD95 mutations requires a new diagnostic approach to autoimmune lymphoproliferative syndrome. J Pediatr 2005; 147(5):691-4.