ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Double Negative (DN) αβ T Cells for the diagnosis of ALPS and ALPS-like – are the 2010 ALPS diagnostic criteria values adequate?

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Dear editor,

Autoimmune lymphoproliferative syndrome, known as ALPS (Autoimmune Lymphoproliferative Syndrome), is part of the group of inborn errors of immunity with immune dysregulation, and is characterized by autoimmunity (especially cytopenias), chronic lymphoproliferation and increased risk for lymphoma. It occurs by mutations in genes (FAS, FASL and CASP10) that encode molecules of the FAS-FAS-L signaling pathway, compromising lymphocyte apoptosis.[1,2]

Mutations in 24 other genes unrelated to the FAS-FASL apoptosis pathway were identified in patients with a clinical picture similar to ALPS (ALPS-like).[2]

CTLA-4 haploinsufficiency (CHAI), LRBA deficiency (LATAIE), RAS-associated autoimmune lymphoproliferative disease (RALD), activated p110 delta syndromes 1 and 2 (APDS 1 and 2), BENTA disease (CARD11 mutation), STAT1 and STAT3 gain-of-function defects, adenosine deaminase 2 (DADA2) deficiency, and type 1 and 2 X-linked lymphoproliferative syndromes are examples of diseases that are part of the ALPS-like group, mutations in CTLA4 and LRBA correspond to approximately 50% of this group.[1,2]

In common, non-malignant lymphoproliferation (splenomegaly and adenomegaly) and autoimmune cytopenias occur in patients with ALPS, as well as in those with ALPS-like.[3] However, the clinical manifestations observed are heterogeneous and other clinical and laboratory data may lead to suspicion. For example, contrary to what is described in ALPS, organ-specific autoimmune diseases, such as type 1 diabetes mellitus, thyroiditis, enteropathy and hepatitis, are described in patients with diseases of the ALPS-like group. Recurrent infections, hypogammaglobulinemia and lymphocytic infiltrate in some organs occur in most patients with ALPS-like diseases.[2,3] Among the most frequent infections, those of the upper and lower respiratory tract, both viral and bacterial, stand out. In some diseases of the ALPS-like group, other infections such as mucocutaneous candidiasis, herpes zoster, mycobacteriosis or diseases caused by other intracellular pathogens occur.[2,3]

The criteria in use for the diagnosis of ALPS are those proposed by Oliveira in 2010.[4] The presence of lymphadenopathy and/or splenomegaly lasting more than 6 months is considered mandatory for a definitive or probable diagnosis (excluding infectious causes and malignancy), and levels high levels of double negative T lymphocytes (TDN) (≥ 1.5% of total lymphocytes or ≥ 2.5% of total $CD3^+$ lymphocytes), these cells being defined as $CD3^+$ $TCR\alpha\beta^+$ $CD4^-CD8^-$, in a lymphocyte scenario at normal or increased values. The association of these two necessary criteria with a primary accessory criterion (identification of pathogenic mutation in FAS, FASL or CASP-10 or identification of lymphocyte apoptosis defect in at least two functional assays) allows the definitive diagnosis of ALPS, while association with one secondary accessory criterion makes the diagnosis likely. The following are listed as secondary accessory criteria: autoimmune cytopenias and polyclonal hypergammaglobulinemia; typical immunohistochemical findings in biopsy material; increased plasma levels of FAS-ligand, or IL-10 or IL-18 or increased serum/plasma levels of vitamin B12.[4]

Diagnostic criteria for ALPS-like diseases, including TDN cells and other biomarkers, are not yet defined.

In patients with ALPS-like diseases with mutations in the PRKCD, MAGT1, RASGRP1 and TPP2 genes, elevated levels of TDN lymphocytes were not observed. However, recently, patients with ALPS-like diseases related to mutations in the PIK3CD, ITK, STK4, STAT3 GOF, CTLA4, LRBA, IL2RA, TET2, IL12RB1, ADA2, TNFAIP3, NRAS/KRAS and CARD11 GOF genes have also been reported. they present levels of TDN lymphocytes greater than 2.5% in relation to the total value of $CD3^+$ cells. This study demonstrated that among patients with ALPS-like diseases, 14 also met criteria regarding vitamin B12, soluble FASL

and IL-10, which would have diagnosed them as ALPS.[2] On the other hand, normal levels of TDN, especially in the face of an important clinical suspicion, do not rule out the diagnosis of diseases of the ALPS-like group.

Genetic testing is not always readily available, and many of the secondary accessory criteria are not available in our daily practice. Thus, considering that TDN cell levels ≥ 6% (in relation to $CD3^+$ lymphocytes) are rarely observed in patients with defects included in the ALPS-like group, this cut-off point was proposed by the European Society for Immunodeficiencies (ESID) in 2019 as a criterion to be used in the registration of patients with ALPS without a genetic diagnosis.[5,6]

It is important to point out that it is essential to dose TDN cells by flow cytometry properly, marking T cell receptors (TCR) with alpha and beta chains. The $CD3^+$ cell population includes cells with TCRs composed of alpha-beta chains and gamma-delta chains. Cells with gamma-delta chains are constitutively $CD4^-CD8^-$ (double negative). There are several clinical conditions of an infectious, inflammatory or malignant nature that promote an increase in $CD3^+TCR\lambda\delta$ cells.[7] Therefore, the strategy of inferring the value of TDN$\alpha\beta$ cells by means of subtraction between total $CD3^+$ cells and $CD4^+$ and $CD8^+$ cells is inappropriate, as it can, in many cases, overestimate the TDN value, wrongly leading to a diagnosis of ALPS or ALPS-like.

In view of a suggestive clinical picture (lymphoproliferation and cytopenias, in particular) with inconclusive or unavailable genetic examination and/or unavailability of flow cytometry and/or functional assays that allow an accurate diagnosis, we suggest that the diagnosis of ALPS should be considered in light of the criteria 2010, however, using values ≥ 6% of TDN cells with TCR$\alpha\beta$ among $CD3^+$ lymphocytes. Patients with TDN TCR cells between 2.5 and 6% of $CD3^+$ lymphocytes may have one of the ALPS-like defects, which may require specific and different therapeutic measures in patients with ALPS.

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