Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study

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Background: Activated phosphoinositide 3-kinase δ syndrome (APDS) is a recently described combined immunodeficiency resulting from gain-of-function mutations in *PIK3CD*, the gene encoding the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ).

Objective: We sought to review the clinical, immunologic, histopathologic, and radiologic features of APDS in a large genetically defined international cohort.

Methods: We applied a clinical questionnaire and performed review of medical notes, radiology, histopathology, and laboratory investigations of 53 patients with APDS.

Results: Recurrent sinopulmonary infections (98%) and nonneoplastic lymphoproliferation (75%) were common, often from childhood. Other significant complications included herpesvirus infections (49%), autoinflammatory disease (34%),

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and lymphoma (13%). Unexpectedly, neurodevelopmental delay occurred in 19% of the cohort, suggesting a role for PI3Kδ in the central nervous system; consistent with this, PI3Kδ is broadly expressed in the developing murine central nervous system. Thoracic imaging revealed high rates of mosaic attenuation (90%) and bronchiectasis (60%). Increased IgM levels (78%), IgG deficiency (43%), and CD4 lymphopenia (84%) were significant immunologic features. No immunologic marker reliably predicted clinical severity, which ranged from asymptomatic to death in early childhood. The majority of patients received immunoglobulin replacement and antibiotic prophylaxis, and 5 patients underwent hematopoietic stem cell transplantation. Five patients died from complications of APDS. Conclusion: APDS is a combined immunodeficiency with multiple clinical manifestations, many with incomplete penetrance and others with variable expressivity. The severity of complications in some patients supports consideration of hematopoietic stem cell transplantation for severe childhood disease. Clinical trials of selective PI3Kδ inhibitors offer new prospects for APDS treatment. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Activated phosphoinositide 3-kinase δ syndrome, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency, phosphoinositide 3-kinase δ,* PIK3CD *gene, bronchiectasis, immunodeficiency, hematopoietic stem cell transplantation, phosphoinositide 3-kinase inhibitor*

Activated phosphoinositide 3-kinase δ syndrome (APDS) is an autosomal dominant primary immunodeficiency caused by gain-of-function (GOF) mutations in *PIK3CD*,[1,2] which encodes the p110δ catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ). PI3Kδ, a class 1 PI3K isoform generating phosphatidylinositol 3,4,5-trisphosphate, is a heterodimer comprising p110δ and a p85 family regulatory subunit. PI3Kδ is expressed predominantly in leukocytes and plays an important role in their proliferation, survival, and activation.[3-5]

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