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SUPPLEMENT ARTICLE

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Activated phosphoinositide 3-dinase delta syndrome (APDS): An update

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Abstract

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a recently described form of inborn error of immunity (IEI) caused by heterozygous mutations in *PIK3CD* or *PIK3R1* genes, respectively, encoding leukocyte-restricted catalytic p110δ subunit and the ubiquitously expressed regulatory p85 α subunit of the phosphoinositide 3-kinase δ (PI3Kδ). The first described patients with respiratory infections, hypogammaglobulinemia with normal to elevated IgM serum levels, lymphopenia, and lymphoproliferation. Since the original description, it is becoming evident that the onset of disease may be somewhat variable over time, both in terms of age at presentation and in terms of clinical and immunological complications. In many cases, patients are referred to various specialists such as hematologists, rheumatologists, gastroenterologists, and others, before an immunological evaluation is performed, leading to delay

in diagnosis, which negatively affects their prognosis. The significant heterogeneity in the clinical and immunological features affecting APDS patients requires awareness among clinicians since good results with p110δ inhibitors have been reported, certainly ameliorating these patients' quality of life and prognosis.

KEYWORDS
activated phosphoinositide 3-kinase delta syndrome, clinical research, immune dysregulation, lymphoproliferation, p110δ, p85, primary combined immune deficiency

1 | INTRODUCTION

In 2013, two groups identified a small number of patients with monoallelic activating mutations in the *PIK3CD* gene encoding for the phosphoinositide 3-kinase (PI3K) catalytic subunit p110δ.[1,2] The peculiar features of this inborn error of immunity (IEI) led to its denomination of activated phosphoinositide 3-kinase delta syndrome-1 (APDS-1, OMIM #615513). Then, a similar phenotype was reported in 8 patients harboring a heterozygous splice site mutation in PIK3R1 encoding for the regulatory subunit p85 (APDS-2, OMIM #616005).[3,4]

Key Messages

APDS is a rare autosomal dominant form of inborn error of immunity (IEI) with a variable clinical and immunological presentation. Patients with APDS frequently show immune dysregulation as lymphoproliferation, cytopenia, arthritis, inflammatory bowel disease, and lymphoma. APDS is an IEI with a peculiar immunophenotype. However, APDS patients are frequently referred to various specialists such as hematologists, rheumatologists, gastroenterologists, and others, before an immunological evaluation is performed. APDS is an example of IEI for which tailored medicine different from HSCT is applicable.

2 | CLINICAL MANIFESTATIONS

Hallmarks of APDS in the described initial patients included lymphopenia, variable hypogammaglobulinemia, CD8 T-cell senescence, and lymphoproliferation, together with an increased risk for lymphomas, mainly B-cell ones. Following the first description, additional clinical and immunological features emerged. An increased susceptibility to viral infections, mainly EBV, leading to chronic viremia has become a frequent finding among affected patients.[5,6] It may depend on CD8 senescence, and CD19 and natural killer (NK) cell impairment and partly explain the high incidence of lymphoproliferation and malignancy described in these patients. Immune dysregulation manifestations, including cytopenia, arthritis, and gastrointestinal involvement with inflammatory bowel disease and nodular lymphoid hyperplasia (NLH) as the main hallmark, are frequent findings among affected and maybe the clinical manifestation onset. Frequent sinus and lung infections, in particular by encapsulated bacteria, lead to the development of bronchiectasis with ensuing implications for prognosis and patients' quality of life.[5,6] Pulmonary infection and obstruction by lymphadenopathy and focal nodular hyperplasia, and hyperinflammation resulting from PI3Kδ hyperactivation play a crucial role in the genesis of bronchiectasis. A higher incidence of neurologic/learning disorders, failure to thrive, and lymphoproliferation, especially tonsillar hypertrophy, is described in APDS-2 patients. Furthermore, a heterozygous nonsynonymous germline mutation located at the C-terminal part of p85 α results in a particular association of short stature, partial lipodystrophy, and insulin resistance (SHORT syndrome).[5,6]

Although most manifestations occurred in the pediatric age, the diagnosis could be delayed in the adult age with a potential increased risk of complications.

In literature, a limited number of patients underwent HSCT due to lack of response to medical treatment, most of which before the molecular diagnosis was achieved. Possibly due to the compromised conditions of affected patients undergoing HSCT, the outcome was not as good as expected with a 2 year overall and graft failure-free survival probabilities, respectively, of 86% and 68%.[7]

3 | PATHOPHYSIOLOGY

Class I PI3Ks are typically formed by heterodimers comprising a catalytic (p110α, β, or δ) and a regulatory subunit (p85α, p55α, p50α, p85β, and p55γ). The monoallelic mutations identified in APDS-1 patients involve the PIK3CD gene coding for the p110δ subunit, mainly expressed in leukocytes, particularly lymphocytes and myeloid cells. The most common variant reported in the literature is the c.3061 G > A (p. E1021K). Monoallelic mutations identified in APDS-2 involve the ubiquitously expressed regulatory subunit p85 α. The more frequently reported are splice donor site mutations causing a skipping of exon 11 encoding amino acids 434 to 475 of p85 α (c.1425+1 G> (A, C, T) (p.434–475del)). The p110δ catalyzes the phosphorylation of the phosphatidylinositol-4,5-bisphosphate to phosphatidylinositol-3,4,5-trisphosphate, which acts as a membrane tether for signaling proteins as PDK1 and AKT. Mutation of the p110δ causes hyperactivation of the AKT/pS6K/mammalian target of rapamycin (mTOR) signaling pathway, and thus, these mutations are considered gain-of-function mutations. Instead, the

mutations involving the p85 α subunit cause a loss of p85-mediated inhibition of p110 activity, leading to increased activity of PI3K. The mTOR pathway is involved in numerous cell functions such as cell growth, metabolism, proliferation, differentiation, motility, and survival, resulting in various alterations in the affected patients' immune system.[1-4] Hypogammaglobulinemia with typically conserved or increased IgM serum levels is rather frequent, although not constant, together with impaired antibody responses to vaccinations. Lymphopenia with significant reduction of all lymphocyte subsets is frequent. CD4 T-cell reduction is frequent, and CD8 T-cells present a peculiar phenotype independently of patients' age and infectious conditions with the expansion of the CD57+ senescent subset and the effector memory subset.[1-6] T follicular helper cells (Tfh) show a dysregulated phenotype with increased expression of PD1, CXCR3, and INFγ.[8] B cells, on the other hand, present variable maturation perturbations compatible in any case with the humoral defect, in particular an expansion of transitional B cell and CD21low B cells and decreases in naive B (CD19+CD27-IgM+IgD+), marginal zone-like B (CD19+CD27+IgM+IgD+), unswitched, and class-switched memory B cells (CD19 +CD27+ IgM+IgD+/IgD-).[1-6] Natural killer cells show impaired maturation and, most importantly, defective cytotoxicity that may be partially rescued by rapamycin, an mTOR inhibitor.

The impaired ability to control EBV infection is undoubtedly associated with the exhaustion of CD8 T-cells, which show an increased TCR restimulation-induced cell death and cannot clonally expand, associated with the NK cell inability in conjugation to target cells and inactivation and execution of the killing. Though CD8 and NK cells are the principal player in controlling virus infections, also CD19 and humoral immunity seem to play a role. The impaired antibody responses, unable to control the spread of the virus, and the expansion of transitional B cells that may act as a reservoir for EBV virus facilitate the infection persistence. Furthermore, the expression of viral proteins, as the latent membrane protein 1 (LMP1), can activate PI3K signaling and trigger B-cell proliferation, transformation, and/or EBV reactivation. However, the higher incidence of EBV-negative lymphomas compared with EBV-positive lymphomas indicates the oncogenic potential of hyperactivation of PI3K signaling.[9]

4 | TREATMENT

APDS patients were treated with Ig replacement therapy and antibiotic prophylaxis (trimethoprim/sulfamethoxazole and/or azithromycin) only. These therapies are ineffective in preventing herpes virus infection, immune dysregulation manifestations, and lung damage. Understanding the pathogenesis of APDS has paved the way for personalized treatment in IEI. Treatment with rapamycin, an mTOR inhibitor, has given good results in the control of lymphoproliferation and gastrointestinal manifestations, although less efficient in the control of cytopenias.[10] Recently, specific p110 δ inhibitors have been introduced in different clinical trials on small cohorts of affected patients with encouraging results, including reducing circulating transitional B cells and senescent CD57 + T-cells. Of note, nearly all patients showed amelioration of lymphoproliferation and autoimmune manifestation. These clinical studies underline the concrete possibility to target and pharmacologically modulate the driving cause of this disorder. Since PI3K hyperactivation has been shown to lead to B-cell lymphomas, the future utilization of oral p110 δ inhibitors may define the beginning of a novel era of personalized treatment for this IEI with improved prognosis and quality of life for affected patients.[9]

CONFLICT OF INTERESTS

Authors declared they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Vassilios Lougaris contributed to writing—original draft (equal). **Caterina Cancrini contributed to** writing—original draft (equal). **Beatrice Rivalta** contributed to writing—review and editing (equal). **Riccardo Castagnoli** contributed to writing—review and editing (equal). **Giuliana Giardino** contributed to writing—review and editing (equal). **Stefano Volpi** contributed to writing—review and editing (equal). **Lucia Leonardi** contributed to writing—review and editing (equal). **Francesco La Torre** contributed to writing—review and editing (equal). **Silvia Federici** contributed to writing—review and editing (equal). **Stefania Corrente** contributed to writing—review and editing (equal). **Bianca Laura Cinicola** contributed to writing—review and editing (equal). **Annarosa Soresina** contributed to writing—review and editing (equal). **Gian Luigi Marseglia** contributed to supervision (lead) and writing—review and editing (equal). **Fabio Cardinale** contributed to conceptualization (equal); supervision (lead); and writing—review and editing (equal).

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