Immunology and Genetics Journal

Review Article

Received: 13 July 2020
Accepted: 28 August 2020
Published online: 22 September 2020
Doi:10.22034/igj.2020.247410.1049

Activated PI3K-Delta Syndrome: Pathogenesis, Clinical Manifestations, Diagnosis, Classification and Management

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Abstract

Activated PI3 kinase delta syndrome (APDS) is a newly recognized primary immunodeficiency that was firstly discovered in 2013. APDS can be resulted from gain-of-function mutations in PI3Kδ catalytic p110δ (*PIK3CD* known as APDS1) and regulatory p85α (*PIK3R1* known as APDS2). Patients with APDS syndrome mostly present some major manifestations such as lymphadenopathy and autoimmune diseases like cytopenia and Immune thrombocytopenic purpura (ITP). Distinguishing APDS from the other antibody deficiencies such as the common variable immunodeficiency (CVID) and hyper IgM disorders is very important to use appropriate and targeted treatment strategies. In this review article, we attempted to discuss the pathogenesis, cell abnormality, clinical manifestations, diagnosis, and treatment of APDS disorder.

Keywords: Activated PI3 kinase delta syndrome (APDS), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD), phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1)

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1. Introduction

Activated phosphoinositide 3kinase-δ (PI3Kδ) syndrome (APDS), also called PASLI, is a primary immunodeficiency (PID), which was firstly described in 2013 (1). Accordingly, this disease is caused by autosomal dominant gain of function (GOF) mutations in *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta* (*PIK3CD)* gene that can consequently result in APDS1 and *phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1)* gene mutation leading to APDS2. Moreover, these mutations lead to hyper-activation of the PI3Kδ (1). Also, catalytic subunit p110δ along with regulatory subunit p85α form the heterodimeric lipid kinase PI3Kδ, which is expressed in leukocytes involving in various cell processes such as cell growth, survival, function, and proliferation through the phosphoinositide 3-kinase (PI3K)-AKT-mammalian signaling pathway (2, 3).

APDS is known as a complex of cellular and humoral deficiencies as well as a clinical heterogeneity. Patients with APDS manifest some symptoms such as recurrent respiratory tract infections, benign lymphoproliferation, herpes virus infections, autoimmunity, and thw increased risk of lymphomas. The immunological phenotype of APDS includes impaired maturation of B cell and T cell, augmented transitional B cells, reduced class-switch-recombination in memory B cells, and increased secretion of T cell cytokines. Moreover, the increased IgM level and decreased IgG2, IgG4, IgA levels are mostly presented in affected patients (4, 5).

In this review, we focused on the pathogenesis, clinical manifestations, diagnosis, and management of APDS syndrome.

2. Pathogenesis

PI3Kδ is known as a class IA lipid kinase that belongs to the family of kinases, and has involvement in immune cell function and development. In addition, PI3K δ is composed of three variants including p110 catalytic subunit (p110α, p110β, and p110 δ) as well as five associated variants of Src homology 2 (SH2), which contain regulatory subunits (p85α, p55α, p50α, p85β, and p55γ). Accordingly, regulatory subunits can prevent proteasomal degradation and stabilize catalytic subunit, as well as inhibiting the recruitment of p110 δ to plasma membrane. However, the inhibitory property of p85 is released by its sh2 domain binding to the phosphorylated tyrosine residue of the receptor (1, 5).

Somatic mutations in genes that are involved in PI3K δ pathway (*PIK3CD* or *PIK3R1*) lead to GOF, LOF *PIK3CD,* and *PIK3R1,* respectively. Also, these could_subsequently manifest immune dysregulation, immunodeficiency, autoimmunity, and malignancy (6). So far, 10 different missense mutations have been identified by *PIK3CD* mutations in APDS1, either in the C-terminal lobe (E1021K, H1047R, and R929C) or in the other functional domains (N334K, E525A, C416R, R405C, G124D, E525K, and E81K), which may have some effects on the interaction between p110δ and p85α. Accordingly, this interaction subsequently leads to hyper-activation of PIK3 δ and senescence of $CD8^+$ T cells, lymphoproliferation, and autoimmunity. In this regard, hyper IgM syndrome-like phenotype and the increased vulnerability to cancer could be related to these mutations (3, 7).

Homozygous mutation in *PIK3R1* (known as APDS2) was firstly described in 2012 in a patient with agammaglobulinemia and B cell lymphopenia. Notably, several mutations such as missense and splice sites exon-11 mutations could lead to the manifestation of APDS1 phenotype. Also, deletion in N-terminal of the iSH2 domain is considered as a result of these mutations. Moreover, SHORT syndrome and agammaglobulinemia were shown to be associated with the mutation in *PIK3R1* (1, 8, 9).

3. Cell abnormalities

3.1 B cell

The peripheral blood B cell compartment showed a significant increase in the proportions of transi-

tional CD10+ B cells (4, 10). These phenomena have been resulted from GOF in *PIK3CD* that impedes human B cell development and differentiation in bone marrow (BM). Of note, a defect in B cell maturation could lead to the accumulation of peripheral immature transitional B cells (11-13).

Generally, the reduced B cell is seen in APDS patients and B-cell counts have decreased with aging in APDS disorder. Accordingly, in these patients, the numbers of immature B and pre B cells have increased in BM, while the number of mature recirculating B cells (CD19+CD20+CD10−) has dramatically decreased (8, 11, 14).

It has been reported that *PIK3CD* GOF mutations could not only perturbed B cell differentiation and development, but also impede generation of normal memory (CD10−CD27+) B cells. Although IgG and IgA expressions and secretions as well as the frequencies of class-switched IgG^+ and IgA^+ cells have decreased in these patients, secretion of IgM was normal (5, 11, 14). In addition, it has been observed that secretion of IgG and switched plasma blasts count have reduced and a defect was also observed in the secretion of class-switched immunoglobulin isotypes in APDS patients (15-17).

3.2 T cell

The majority of APDS patients presented normal to decreased $CD3^+$ and $CD4^+$ T cell counts, the increased $CD8^+$ T cell counts of an effector/effector memory cells, and the elevated granzyme B and degranulation (18, 19). CTL from APDS patients also exhibit exhaustion markers such as PD1 and 2B4 (15). However, a mild increase in naïve T cells has been observed have decreased in these patients. Indeed, in 80% of patients, an inverted CD4/CD8 ratio was observed (4, 10, 20). Subsequently, PI3K/AKT pathway signaling inhibited peripheral induced Treg (iTreg) generation that resulted in a reduction in Treg proportion (13, 15). Notably, Hyperproliferation, differentiation, and T cell senescence (CD57+, CD3+) are often investigated in APDS patients. Increase in circulating T_{FH} cell (cT_{FH}) have been also observed, but they were not fully functional (5, 18)

4. Clinical manifestations

4.1. Infections

Recurrent respiratory tract infections are considered as the most common clinical manifestations in APDS patients with early-onset at their pediatric ages. Upper respiratory tract infections (sinusitis and otitis) and lower respiratory tract infections (bronchitis and pneumonitis) are also present in about 65-95% of the affected patients (10). Patients with APDS1 are often suffering from sinusitis, while pneumonitis is more common among APDS2 patients (4). In addition, bronchiectasis is the most common consequence of recurrent respiratory tract infection that increase susceptibility to further infections and also promote colonization of bacterial pathogens, which consequently lead to progressive airway damage. Correspondingly, this complication is more common among APDS1 patients (14, 21).

Haemophilus influenza and *Streptococcus pneumonia* are known as the most common pathogens that cause bacterial infections. In this regard, some other less common pathogens such as *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa* and *Klebsiella sp* have also been observed (5). Notably, invasive bacterial infections are not frequent; however, non-respiratory tract bacterial infections including ocular infections (conjunctivitis, orbital cellulitis, and dacryocystitis) and abscesses (skin, salivary glands, and dental abscesses) have also been reported (12). Although mycobacterial infections have not been reported in APDS patients, persistent granulomatous skin lesions have been documented at Bacillus Calmette–Guérin (BCG) vaccination injection sites (6, 12).

In addition, viral infections particularly herpes viruses e.g. *EpsteineBarr virus (EBV), herpes simplex virus (HSV), and cytomegalovirus (CMV)* are well-documented. Herpes viruses express several proteins that can target PI3K/AKT pathway sig-

naling to maintain their latency and promote their reactivation and replication. Moreover, inefficient antibody production and dysregulation in B cell function increase susceptibility to systemic infection among APDS patients (5). Several other common viruses including adenovirus infections (respiratory syncytial virus (RSV), coxsackie viruses, and parainfluenza virus) were also identified during progressive airway damage (5, 11). Regarding fungal infections, out of APDS1 patients, only 2 patients have been reported with Aspergillus species pneumonia (6).

4.2. Non neoplastic lymphoproliferation

Nonmalignant lymphoproliferation such as chronic lymphadenopathy, splenomegaly, and/or hepatomegaly were mostly observed in APDS patients. Hepatomegaly and Lymphadenopathy typically manifest during childhood, which were also commonly seen in APDS1 and APDS2 patients, respectively (4, 6, 12). Benign lymphoid proliferations including nodular lymphoid hyperplasia of mucosal surfaces and lymphadenitis, have been identified in the gastrointestinal and respiratory tract. Accordingly, these conditions were commonly observed in APDS1 patients, but tonsillar and adenoidal hypertrophy were frequently seen among APDS2 patients, as some of them required multiple surgical excisions (4, 6). Nodular lymphoid hyperplasia and infiltration of the gut can consequently result in chronic diarrhea, malabsorption, bleeding, obstruction, and rectal prolapse (6, 12). Histological examination of lymph nodes revealed a small germinal center with an absence or attenuation of follicular mantle zones, which were shown to very rare IgD mantle cells. Hyperplasia of PD1+ T cells has been also observed in extra follicular areas and germinal centers, and the latter was disrupted by T follicular helpers (5, 10, 11).

4.3. Autoimmune and inflammatory disease

Various autoimmune disorders have been reported in APDS patients. It is noteworthy that autoimmunity mostly present after the age of 10 years old. Cytopenias (coombs-positive hemolytic anemia and immune thrombocytopenic purpura (ITP)) as well as glomerulonephritis are known as the most frequent autoimmune complications among the reported APDS patients (4, 5, 12, 22). The other autoimmune/inflammatory conditions including rheumatologic, endocrine (e.g. Insulin-dependent diabetes and exocrine pancreatic insufficiency), gastrointestinal, nephrotic syndrome, autoimmune thyroiditis and hepatitis, Sjogren syndrome, pericarditis, and dermatologic disorders (e.g. chronic eczema) have been also reported in these affected patients (4, 6, 10).

4.4. Malignancies

As it was shown, APDS patients are susceptible to malignancies and this susceptibility is associated with a history of chronic viral infections, as the lymphoma risk is significantly higher in cases with a previous EBV infection compared to those without a history of any previous EBV infection (4, 6). Lymphoma including diffuse large B cell lymphoma, classical Hodgkin lymphoma (CHL), and marginal zone B cell lymphoma, has been identified as a frequent complication in both APDS1 and APDS2 patients. Moreover, some of these patients had multiple lymphomas (4, 10, 11). The activation of the PI3K pathway was also indicated to be associated with malignant transformations. Aerobic glycolysis has been increased in lymphocytes during malignant transformation and this metabolic reprogramming is mostly used to differentiate benign lymphoproliferation from malignant disease (11, 14).

4.5. Other Complications

Apart from benign and malignant blood disorders, autoimmune disorders, and inflammation, other complications are also seen in APDS patients, and the important classification of which in APDS is recognized to be neurologic/learning disorders such as speech and global developmental delays (4-6). The other complications such as pervasive developmental (e.g. growth retardation), adenoid, ear, nose, and throat problems (e.g.

tonsillar hypertrophy, otitis, hearing impairment, and parotitis) have been reported in patients with APDS, as well (5, 23).

5. Diagnosis

Given various clinical manifestations and immunological features of APDS, genetic analysis along with immunological findings are important for the diagnosis and distinguishing APDS patients. Regarding immunoglobulin phenotypes, APDS patients mostly manifest hyper IgM (HIGM) or CVID phenotypes (24, 25). The whole-exome sequencing showed that all patients carry a heterozygous point mutations in *PIK3CD* and *PIK3R1* along with the increased senescent T-cells and lymphoma susceptibility (2, 24).

Paraclinically, patients with APDS demonstrate the decreased serum IgG and IgA levels, but the increased level of IgM (26). Also, Hyperactive PI3K signaling in mature B cells disrupts antibody class switching from IgM to IgG/IgA (20). This HIGM is more prevalent among APDS2 patients compared to patients with APDS1 (23).

Regarding B cell subsets, these patients demonstrate an abnormal circulating B cell distribution, the elevated proportions of T1 transitional B cells, and low class-switched memory B cells. On the other hand, T cell abnormalities such as reversed CD4/CD8 T cell ratio, increased effector memory CD8+ T cells, and senescent T-cells ($CD57^+$ $CD3^+$) have been also observed in these patients (27, 28). Notably, dysregulation in cytokine production and increase in sensitivity to apoptosis are the results of abnormality in terminal differentiation in effector T cells (20). PI3K activity can be detected by flow cytometry through intracellular staining of p-akt; therefore, phosphorylated AKT can be considered as a marker for functional studies in APDS patients (5).

6. Management

6.1. Anti-infection prophylaxis

The antibiotic prophylactic regimens used by patients with APDS are mainly Trimethoprim / Sulfamethoxazole or Azithromycin. In this regard, it was shown that, antibiotic prophylaxis alone may be effective for a few patients. Therefore, in most cases, immunoglobulin replacement therapy (IRT) is used in combination with antibiotics. The combined IRT and antibiotic prophylaxis can be beneficial on decreasing recurrent respiratory tract infections (10, 12, 17, 29). Also, some antiviral (such as Acyclovir/Valaciclovir or ganciclovir) and antifungal drugs can be used in antifungal and antiviral prophylaxis (12, 30, 31).

6.2. Immunoglobulin replacement

Most of APDS patients have multiple antibody defects (e.g. IgG subclass deficiencies) and ineffective vaccine responses, which are similar to CVID and HIGM disorders. One of the effective treatment methods on the treatment of these patients is IRT, which can be given either by intravenous immunoglobulin (IVIG) or by subcutaneous immunoglobulin (SCIG) infusions. IRT is also prescribed besides APDS for the other antibody deficiencies. IVIG is usually prescribed as a dose of dose 0.4 g/kg/month in patients without any symptom of bronchiectasis and increases to 0.6 g/kg/month in case of a patient with bronchiectasis (10, 12, 31-34). Correspondingly, this treatment has been shown to be effective on reducing respiratory tract infections; however, it has not been shown to be beneficial on preventing herpes infections, autoimmune disorders, and lymphoproliferation, yet (10, 13, 29, 32, 35, 36).

6.3. HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Hematopoietic stem cell transplantation (HSCT) is beneficial for APDS patients, so it can be considered as a treatment option, especially in young cases. As it was discussed earlier, life-threatening diseases such as infections and lymphoma are common among patients with APDS, so HSCT can be helpful in treating these kinds of disorders (10, 12, 37). However, data on long-term follow-up of patients who have been transplanted, is

not available yet (38).

6.4. Immunosuppression

Many APDS patients have various autoimmune disorders including cytopenia (as the most common one), inflammatory colitis, arthritis, renal disease, exocrine pancreatic failure, cirrhosis, and sclerosing cholangitis (10, 12, 13, 39). In this regard, various treatments are considered to control and manage these autoimmune manifestations. Splenectomy, rituximab, and steroids are frequently used to manage and treat cytopenia (29). Also, rituximab is prescribed for non-neoplastic lymphoproliferation in APDS1 patients (12). In a study by Elgizouli et al., the use of prednisolone and maintenance of mesalazine showed positive results in APDS1 patients who have suffered from inflammatory bowel disease (29).

6.5. SIROLIMUS (Rapamycin)

The serine/threonine kinase mechanistic/mammalian target of rapamycin (mTOR) is a downstream molecule of PIK3 and AKT, which plays an eminent role in T cell metabolism and is also known as a key regulator of immune responses and cell differentiation (17, 40). Rapamycin is beneficial on decreasing hepatosplenomegaly, lymphadenopathy, and in the treatment of non-neoplastic lymphoproliferation. Moreover, it also restitutes T cell proliferation and IL-2 secretion. However, Sirolimus is less beneficial for cytopenias and gastrointestinal symptoms. It should be noted that the benefits and risk of rapamycin therapy are not well-identified in the long run yet (17, 22, 31).

Conclusion

The present study reviewed molecular, immunological, and clinical manifestations in APDS patients. Accordingly, APDS is a combined immune deficiency that aberration in PI3K signaling may lead to susceptibility to infections, lymphoid malignancy, and a high incidence of inflammatory/autoimmune disease. Therefore, identifying the precise pathogenesis at the time of diagnosis is necessary for better management and treatment of this disease.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We highly appreciate the “Department of Immunology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran”.

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