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Linfoproliferación e hiper-IgM como manifestación inicial del síndrome de la cinasa 3-fosfoinosítida activada (APSD 2): reporte de caso

Lymphoproliferation and hyper-IgM as the first manifestation of activated phosphoinositide 3-kinase δ syndrome (APSD 2): case report

Linfoproliferación en APSD2

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Author contribution:

Mónica Fernandes-Pineda: design the paper, analyzed the clinical history, and drafted the manuscript.

Andrés F. Zea-Vera: recruited the patient, conceived and designed the report, analyzed the data, and revised the manuscript.

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Activated phosphoinositide 3-kinase δ syndrome (APDS) stands as an inborn error of immunity arising from mutations within the genes responsible for encoding PI3Kδ subunits. This results in an excessive activation of the PI3K signaling pathway. Gain-of-function mutations in PIK3R1 (encoding p85α, p55α, and p50α) lead to the development of APDS2. Notably, the clinical presentations of this syndrome often closely resemble those of other primary immunodeficiencies.

We present a case involving a 15-year-old male who displayed an immunological phenotype that bore a striking resemblance to hyper IgM syndrome. To pinpoint the underlying genetic mutation, comprehensive whole exome sequencing was undertaken.

Our investigation successfully identified a heterozygous splice site mutation, previously reported within the well-established hotspot of the PIK3R1 gene (GRCh37, c.1425+1 G>T). The diverse spectrum of inborn errors of immunity underscores the pivotal role of identifying gene mutations, particularly in patients who present with clinical manifestations spanning autoimmune disorders, lymphoproliferative conditions, and antibody deficiencies. Such precise genetic diagnoses hold significant potential for improving patient care and management.

Keywords: Immune system diseases; phosphatidylinositol 3-kinase; Hyper-IgM immunodeficiency syndrome; autoimmunity; human genetics; genetic testing.

El síndrome de fosfoinositida 3-quinasa delta activada (APDS) se presenta como un Error Innato de la Inmunidad (EII) derivado de mutaciones dentro de los genes responsables de codificar las subunidades de PI3Kδ, esto resulta en una activación excesiva de la vía de señalización de PI3K. Las mutaciones de ganancia de función en PIK3R1 (codificando p85α, p55α y p50α) conducen al desarrollo de APDS2. Notablemente, las presentaciones clínicas de este síndrome a menudo se asemejan a las de otras inmunodeficiencias primarias.

Presentamos el caso de un paciente de sexo masculino de 15 años que mostró un fenotipo inmunológico que se asemejaba al síndrome de hiper IgM. Para determinar la mutación genética subyacente, se llevó a cabo un análisis exhaustivo de secuenciación de exoma completo.

Nuestra investigación identificó con éxito una mutación in situ heterocigota, reportada previamente dentro del hotspot bien establecido del gen PIK3R1 (GRCh37, c.1425+1 G>T). El diverso espectro de errores innatos de la inmunidad resalta el papel crucial de identificar mutaciones génicas, particularmente en pacientes que presentan manifestaciones clínicas que abarcan trastornos autoinmunes, condiciones linfoproliferativas y deficiencias de anticuerpos. Dichos diagnósticos genéticos precisos tienen un potencial significativo para mejorar la atención y el manejo del paciente.

Palabras clave: enfermedades del sistema immune; fosfatidilinositol 3-quinasa; síndrome de inmunodeficiencia con hiper-IgM; autoinmunidad; genética humana; pruebas genéticas.

Class IA phosphatidylinositol 3-kinases (PI3K) constitute a vital family of heterodimeric enzymes, consisting of a 110-kDa catalytic subunit (p110α, β, or δ) paired with a regulatory subunit (p85α, p85β, p55α, p50α, or p55γ). These PI3K enzymes play a pivotal role in the activation of immune cells, orchestrating a spectrum of essential functions such as cell growth, proliferation, survival, migration, and differentiation (1). Genetic mutations in the genes encoding these PI3K subunits can lead to various immune-related disorders, exerting a profound impact on the immune system. Specifically, mutations in the PIK3R1 gene, responsible for encoding phosphatidylinositol 3-kinase (PI3K) regulatory subunits, underlie the condition known as Activated Phosphoinositide 3-Kinase δ Syndrome 2 (APDS2), while mutations in PIK3CD are associated with APDS1 (2). The clinical manifestations of these syndromes encompass symptoms akin to other inborn errors of immunity, including recurrent bacterial respiratory infections, heightened susceptibility to herpes virus infections, lymphoproliferation, autoimmunity, enteropathy, and lymphoma (3). In this case report, we present the clinical profile of a male patient harboring a PIK3R1 mutation, which has led to the manifestation of Activated Phosphoinositide 3-Kinase δ Syndrome 2 (APDS2), characterized by Hyper-IgM and lymphoproliferation that has been evident since childhood.

Case report

A 15-year-old Colombian boy, born to non-consanguineous healthy parents, was the first child in the family with one unaffected sibling. His medical history revealed an uneventful BCG vaccination at birth. At 5 months of age, he began experiencing recurrent upper respiratory tract infections. A subsequent episode of gastroenteritis at 6 months necessitated oral antibiotic treatment. At 2 years old, the patient was

admitted to the emergency room due to the bronchoaspiration of a peanut, requiring bronchoscopy for removal.

During a routine physical examination, visible tonsils, and bilateral submandibular and cervical lymphadenopathies (greater than 2cm in diameter) were noted. However, other physical findings were unremarkable, with no abnormalities detected in the lungs, heart, abdomen, or nervous system. Upon reassessment, the patient's mother reported persistent high fever (>38.5°C), night sweats, and a chronic cough over the previous 6 months. Subsequently, the patient was admitted to the pediatric infectious disease service, where tuberculosis was ruled out, and additional investigations were conducted.

Serological testing revealed positive Cytomegalovirus (CMV) IgM with negative IgG, while tests for Epstein-Barr (EBV) mononucleosis were negative. Viral load assessments for EBV or CMV were not available (table 1). A lymph node biopsy demonstrated lymphoid hyperplasia without evidence of malignancy. Infectious complications were considered, and due to suspected acute CMV infection and potential exposure to pets, cat scratch disease was suspected, leading to the prescription of oral antibiotics (azithromycin).

At 3 years of age, the patient was readmitted with suspected lymphoproliferative disease, attributed to the enlargement of cervical nodules. Physical examination revealed persistent submandibular and cervical lymphadenopathy, but no signs of hepatosplenomegaly. Bone marrow aspirate analysis showed a cellular composition comprising 5% megakaryocytic lineage, 61% myeloid lineage, 31% lymphoid lineage, and 3% eosinophils, with no evidence of tumorous growth.

Persistent serological assessments indicated persistently negative EBV and CMV IgG, yet CMV IgM remained consistently positive, with escalating titers. Serum immunoglobulin levels revealed elevated IgM (1290 mg/dL) with undetectable IgG and IgA, leading to the diagnosis of Hyper IgM immunodeficiency (HIGM) in 2012, according to ESID criteria. Consequently, the initiation of monthly intravenous immunoglobulin (IVIG) treatment (400-600mg/Kg) was recommended, along with the prophylactic use of macrolides (azithromycin) as needed. Despite these measures, lymphadenopathies persisted.

In 2019, targeted gene panel sequencing for AICDA, CD40, CD40L and UNG genes yielded negative results, failing to establish a molecular diagnosis at the time of clinical evaluation and follow-up. A renewed genetic evaluation in 2022, when he was 14 years old, employing a comprehensive whole-exome sequencing (WES) approach, revealed a heterozygous pathogenic variant GRCh37 (c.1425+1 G>T) in the *PIK3R1* gene, confirming the diagnosis of APDS2 (figure 1).

At present, the individual is receiving monthly IVIG substitution replacement and is being closely observed for any changes in lung function. Recent scans showed no evidence of bronchiectasis or new masses. It is worth mentioning that the patient was last hospitalized at the age of 11 due to pansinusitis. Since then, there has been no additional decline in their health condition, although they still have persistent splenomegaly and adenomegaly.

Right to privacy and informed consent

The authors have obtained the written informed consent from the mother and the assent from the patient mentioned in the article. The corresponding author is in possession of this document.

Discussion

In this case report, we present the first published case of Activated Phosphoinositide 3-Kinase δ Syndrome 2 (APDS2) in Colombia, involving a young boy with a heterozygous splice site mutation in the *PIK3R1* gene. The patient's clinical presentation was characterized by chronic lymphadenopathy, recurrent viral and bacterial infections, and hepatosplenomegaly. This case underscores the diagnostic complexities often encountered in patients with APDS1/2, as the initial diagnosis of hyper IgM syndrome gave way to a genetic diagnosis obtained through subsequent WES.

Phosphoinositide 3-kinases (PI3Ks) are integral enzymes within the PI3K-AKT-mTOR signaling pathway, playing a crucial role in the metabolism, differentiation, proliferation, growth, survival, and migration of immune cells (4). Mutations affecting the regulatory subunit PI3Kδ lead to the constant hyperactivation of the Akt-mTOR pathway in B and T lymphocytes. This hyperactivation, stemming from mutations in the PIK3R1 regulatory subunit, results in APDS2 (Activated PI3K Delta Syndrome 2), marked by progressive lymphopenia and compromised differentiation and function of T and B cells (5).

APDS2 patients frequently suffer from multiple infectious complications, including recurrent upper respiratory tract (URT) and lower respiratory tract (LRT) infections, such as sinusitis, otitis media, and pneumonia (6). These complications arise due to defects in antibody and cytokine production. Our patient experienced multiple hospitalizations for otitis media and sinusitis, which responded well to antibiotic therapy. Despite these recurrent respiratory infections, our patient did not exhibit

bronchiectasis in the follow-up thorax CT scan, which can develop in some APDS2 patients following multiple respiratory infections (7).

Notably, our patient initially presented with CMV infections, ultimately leading to the diagnosis of the Hyper IgM (HIGM) phenotype. The literature has reported that APDS2 patients may experience recurrent infections caused by herpes family viruses, including EBV, CMV, herpes simplex virus (HSV), and varicella-zoster virus (VZV)(6).

Beyond infectious complications, APDS2 patients can encounter non-infectious issues, including lymphadenopathy, hepatosplenomegaly, autoimmune and autoinflammatory disorders, malignancies, and growth problems. In our case, recurrent hospitalizations were attributed to cervical and submandibular lymphadenopathy, often linked to overactive proliferation in lymph node germinal centers, frequently triggered by EBV infections (3). Hepatosplenomegaly, observed in other APDS2 cases, was also evident in our patient (8). Moreover, the lymph nodes exhibited hyperplasia, and bone marrow biopsies ruled out hematological malignancies.

The common occurrence of the Hyper IgM (HIGM) phenotype in APDS2 patients may be a consequence of the dysregulation of PI3K signaling and class-switching recombination (CSR) in developing B lymphocytes (9). Our patient's immunoglobulin profile strongly suggested HIGM syndrome, despite negative results on molecular diagnostic tests for the AICDA, CD40, and UNG genes. Consequently, the patient was managed as if they had HIGM syndrome.

Notably, the mutations localized at c.1425 of the PIK3R1 gene are considered hotspot mutations. These mutations affect the donor splice site [c.1425+1G>(A, C,

T), c.1425+2T>(G, A), c.1425+2,3delTG] and the acceptor splice site [c.1300-1G>C] of intron 10.(4) Consequently, exon 10 is skipped, leading to the truncation of the regulatory subunit (p85α) and the activation of PI3K signaling activity in APDS (10). Our patient harbored a previously reported heterozygous pathogenic variant GRCh37 (c.1425+1 G>T) in the *PIK3R1* gene (6,11).

It's worth noting that APDS was first described in 2014, and since then, between 47 and 100 new cases of APDS have been reported. Our patient exhibited symptoms in 2010, four years before the disease was even described (12) (figure 1). The field of inborn errors of immunity is rapidly evolving, with new genes reported and new diseases described annually (13). This necessitates ongoing assessment of patients being studied for primary immunodeficiency. The importance of characterizing such orphan diseases has led to the development of broad population registries, like the European registry, which includes 170 APDS patients and evaluates their heterogeneity (14).

At the Latin American level, increasing genetic diagnoses in patients presenting with common variable immunodeficiency or Hyper IgM syndrome, and whose etiology remains unknown, can potentially lead to therapeutic changes (15). Some inborn errors of immunity have specific treatments, such as leniolisib in APDS1 and APD2, which is currently in phase 3 clinical trials. Leniolisib, a PI3Kδ inhibitor, has the potential to mitigate long-term complications associated with lymphoproliferation and positively impact immune dysregulation in APDS patients (16). With this treatment decrease lymphadenopathy and splenomegaly, increase B lymphocyte counts, address cytopenias, and improve overall symptoms (17).

This underscores the need for greater awareness and genetic testing in the Latin American context to improve patient care and management (18).

Conclusion

Initially, our patient's clinical immunoglobulin profile suggested Hyper IgM (HIGM) syndrome. However, inborn errors of immunity (IEI) represent a dynamic field characterized by an ever-expanding array of newly described gene disorders. This evolving landscape underscores the importance of considering these novel gene disorders for patients who remain without a molecular diagnosis. Given the inherent heterogeneity within the spectrum of IEI, the identification of gene mutations becomes an invaluable tool in accurately diagnosing patients initially presenting with clinical manifestations resembling autoimmune disorders, lymphoproliferative conditions, and antibody deficiencies. As our understanding of these conditions continues to evolve, early genetic diagnoses can significantly enhance patient care and management.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

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Table 1. Results of laboratory tests in the here reported patient

Laboratory parameter	Date 2011 (3 yo)	Date 2012 (4 yo)	Date 2015 (7 yo)	Date 2019 (11 yo)	Date 2022 (14 yo)	Age-specific norm
Leukocyte count	7.030	15.700			7.310	
Neutrophil count	1.360	6.140			2.920	
Lymphocyte count	4.290	6.760			3.390	
Hemoglobin concentration	27.7%	30.7%			32.2%	
Platelet count	692.000	440.000			435.000	
IgG concentration		<320 mg/dL	787 mg/dL	415.34 mg/dL	480.51 mg/dL	700 - 1600 mg/dL
IgA concentration		<5 mg/dL	<33 mg/dL	<40 mg/dL	<40 mg/dL	70 - 400 mg/dL
IgM concentration		1290 mg/dL	879.1 mg/dL	468.5 mg/dL	651.32 mg/dL	40 - 230 mg/dL
IgE concentration		15.5 UI/mL	0 UI/mL	<0.100 UI/mL	<0.100 UI/mL	<200 UI/mL
B lymphocytes (CD 19+)					169 cel/uL (3.3%)	200-600 (8-24%)
T lymphocytes (CD 3+)					3775.5 cel/uL (80.5%)	1088.1-2087.9 (53.3-75.3%)
T-helper lymphocytes (CD3+CD4+)					963.0 cel/uL (20.5%)	639.5-1278.5 (30.7-46%)
T-cytotoxic lymphocytes (CD3+CD8+)						
NK cells (CD3-CD56+CD16+)					690 cel/ul (13.6%)	70-1200 (6-27%)
PPD					0 mm	>10 mm
Toxoplasma IgG	0					
Toxoplasma IgM	0.288					

Monotest	Negativo					
Citomegalovirus IgG	0	0				<15
Citomegalovirus IgM	1.307	1.976				<0.399
VIH	0.37					<1
AgSHBV	0.17	0.75				<1.2

Figure 1. Clinical history timeline