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CLINICAL CASE

Case report on activated PI3K-delta syndrome

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Abstract

Background: *Activated phosphoinositide 3-kinase delta syndrome (APDS) [OMIM 615513] is an inborn error of immunity with autosomal dominant inheritance caused by a pathogenic variant in the PIK3CD gene. The prevalence ratio of APDS is < 1: 1,000,000 newborns. The main clinical features of APDS are sinopulmonary infections, benign lymphoproliferation, autoinflammatory disease, and a major risk of lymphoid neoplasms.* **Clinical case:** *A 17-year-old female with a history of pneumonia at 9 months of age subsequently developed recurrent respiratory tract infections, bronchiectasis, perforated otitis media, unilateral tonsillar lymphoid hyperplasia, pansinusitis, recurrent oral candidiasis, and chronic rhinitis. Laboratory studies reported persistent leukopenia and lymphopenia, low CD4 lymphocyte subpopulation, and persistently elevated immunoglobulin M immunoglobulin studies with values up to 692 mg/dL. An inborn error of immunity next-generation sequencing and multiplex ligation-dependent probe amplification analysis detected a heterozygous pathogenic variant in the PIK3CD gene, compatible with APDS. Treatment with monthly injectable gamma globulin and prophylactic antibiotics was started, allowing better control of the infectious processes.* **Conclusion:** *This is the second case of APDS reported in Mexico in the literature. It is important to be aware of this condition to make a timely diagnosis, which requires a high clinical suspicion and immunological and genetic studies to provide adequate treatment and prevent complications.*

Keywords: *Activated phosphoinositide 3-kinase δ syndrome. Gain of function mutation. Primary immunodeficiency disease. Inborn errors of immunity. Case report.*

Caso clínico de síndrome de PI3K-delta activada

Resumen

Introducción: *El síndrome de la Fosfoinositida 3-cinasa delta activado (Activated Phosphoinositide 3-kinase δ síndrome, APDS) [OMIM 615513] es un error innato de la inmunidad con patrón de herencia autosómica dominante causada por una variante patogénica heterocigota del gen PIK3CD. Su prevalencia es < 1: 1,000,000 nacidos vivos. Las principales manifestaciones clínicas son infecciones sinopulmonares, linfoproliferación benigna, autoinmunidad y aumento del riesgo de malignización linfoide.* **Caso clínico:** *Femenino de 17 años de vida con antecedentes de neumonía a los 9 meses de edad, posteriormente infecciones de vías respiratorias recurrentes, bronquiectasias, otitis media perforada, hiperplasia linfoide de amigdala unilateral, pansinusitis, candidiasis oral recurrente y rinitis crónica. Los estudios de laboratorio reportaron leuco*

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linfopenia persistente, subpoblación linfocitaria con CD4 baja y estudios de inmunoglobulinas con IgM persistentemente elevada con valor de hasta 692 mg/dl. Se realizó estudio molecular de secuenciación de siguiente generación (NGS por sus siglas en inglés Next-Generation Sequencing) y amplificación de sondas dependientes de ligandos múltiples (MLPA por sus siglas en inglés Multiplex Ligation-dependent Probe Amplification) dirigido a errores innatos de la inmunidad que detectó una variante patogénica en estado heterocigoto en el gen PIK3CD, compatible con APDS. Se inició tratamiento con gammaglobulina intravenosa mensual y antibiótico profiláctico, permitiendo mejor control de los procesos infecciosos. **Conclusiones:** *Este es el segundo caso reportado en la literatura de APDS en México, por lo que es importante su conocimiento para poder realizar un diagnóstico oportuno, para el cual se requiere una alta sospecha clínica, además de estudios inmunológicos y genéticos, con la finalidad de otorgar el tratamiento adecuado y prevenir complicaciones.*

Palabras clave: *Síndrome de la fosfoinositida 3-cinasa delta activado. Mutación de ganancia de función. Inmunodeficiencia primaria. Errores innatos de la inmunidad. Reporte de caso.*

Introduction

The activated phosphoinositide 3-kinase δ syndrome (APDS) [OMIM 615513] is an inborn error of immunity with an autosomal dominant inheritance pattern caused by a heterozygous pathogenic variant of the *PIK3CD* gene on chromosome 1p36, with a gain of function on its encoded product[1,2]. Its prevalence is estimated to be < 1: 1,000,000 live births[3]. The *PIK3CD* gene encodes the p110 delta isoform of the catalytic subunit of the activated phosphoinositide 3-kinase (PI3K) and is expressed in hematopoietic cells, participating in T and B lymphocyte homeostasis processes[4-6].

APDS was first described in 2013[7]. It has been reported to have incomplete penetrance and variable expressivity among patients, ranging from asymptomatic cases to cases with severe immunodeficiency[8].

The diagnosis of APDS is suspected in patients with recurrent sinopulmonary infections, mainly bacterial and viral pneumonia, upper respiratory tract infections, rhinosinusitis, otitis, herpesvirus-associated infections, gastroenteritis, ocular infections, benign lymphoproliferation, and is confirmed by the detection of a pathogenic variant in the *PIK3CD* gene sequence[9]. The proposed treatment aims to prevent infections, limit lymphoproliferation, and control autoimmunity[10].

The objective of this case report is to report the second case of APDS in Mexico. The information, figures, and biological samples presented were collected with the parents' and patient's previous written informed consent.

Clinical case

The case is a 17-year-old female with a family history of consanguinity between parents, systemic lupus erythematosus on both sides, and a healthy brother and sister.

At 9 months of age, she required hospitalization for pneumonia and presented with recurrent respiratory tract infections from the age of 4. From the age of 8, she had prolonged cough and purulent rhinorrhea and was diagnosed with bronchiectasis by computed tomography (CT) of the chest at 11 years old, which persisted in the most recent CT (Fig. 1).

At 12 years old, she presented with perforated otitis media requiring ventilation tube placement. At 16 years old, she underwent tonsillectomy and adenoidectomy due to the presence of unilateral tonsillar lymphoid hyperplasia, also presenting with pansinusitis, recurrent oral candidiasis, and chronic rhinitis (Fig. 2).

Physical examination revealed a weight of 56.9 kg (50th percentile), height of 1.65 m (65th percentile), non-obstructive septal deviation, turbinates with partial edema predominantly on the right, hypertrophy of lingual papillae, small, non-painful cervical lymphadenopathy, chest with generalized bilateral hypoventilated areas, and clubbing in upper and lower extremities.

Cystic fibrosis, immotile cilia syndrome, and autoimmunity were investigated and ruled out. In the presence of leukopenia, lymphopenia, low CD4 lymphocyte subpopulation, and immunoglobulin studies with persistently elevated immunoglobulin M (IgM) and normal levels of other immunoglobulins (Table 1), a probable Hyper IgM syndrome was suspected, and the patient was referred to the genetics department.

Next-generation sequencing and multiplex ligation-dependent probe amplification studies targeting inborn errors of immunity were performed, which reported a heterozygous pathogenic variant in the *PIK3CD* gene c.3061G>A (p.Glu1021Lys), confirming an autosomal dominant inborn error of immunity known as APDS. Treatment was initiated by the Immunology department with monthly intravenous immunoglobulin at a dose of 500 mg/kg of body weight, plus prophylactic antibiotics, with favorable evolution and better

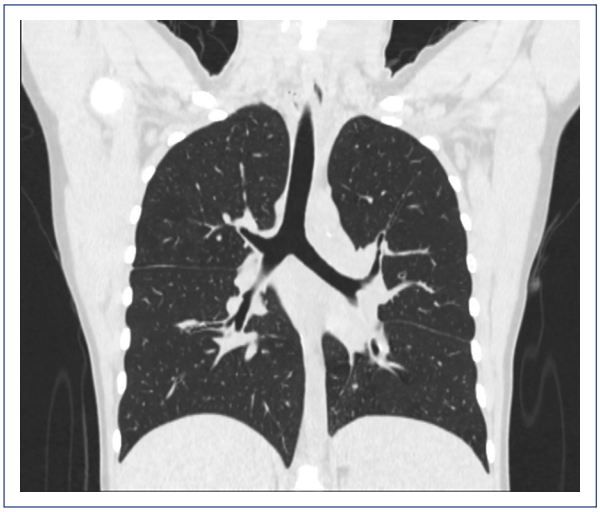

Figure 1. Computerized axial tomography at 17 years old, showing right upper solitary nodule, bilateral cylindrical lamellar atelectasis and bronchiectasis, left septal thickening, and axillary nodal hypertrophy.

control of infectious processes. The pathogenic variant was screened for in the siblings using the same study but was not identified; the parents did not wish to know if either of them carried the variant.

Discussion

Our patient presented with pneumonia, recurrent respiratory tract infections, bronchiectasis, chronic rhinosinusitis, recurrent otitis media, tonsillitis requiring tonsillectomy, leukopenia, lymphopenia with low CD4 count, and persistently elevated IgM levels, which are clinical findings compatible with APDS[10], confirmed by the identification of a heterozygous pathogenic variant in the *PIK3CD* gene c.3061G>A (p.Glu1021Lys). In this variant, there is a change from guanine to adenine at nucleotide 3061 of the coding DNA, which at the protein level generates a change from glutamic acid to lysine at amino acid 1021. This change causes a gain of function of the p110 delta catalytic subunit of the PI3K enzyme and corresponds to the most commonly reported variant in the literature[11]. The gain of function of the PIK3CD gene allows the coexistence of a state of immunodeficiency and autoimmunity[12,13].

The PI3K protein family is formed by a heterodimeric protein with subunits p110-alpha (encoded by the *PIK3CA* gene), p110-beta (encoded by the *PIK3CB* gene), and p-110-delta (encoded by the *PIK3CD* gene), the latter associated with APDS1[14,15]. In APDS, the gain of function of *PIK3CD* produces hyperactivity of p-110-delta, which hyperphosphorylates downstream mediators of mammalian target of rapamycin (mTOR), resulting in hyperactivation of the mTOR pathway. This alters B cell maturation and differentiation and increases the senescence of effector CD8 T cells, which are important for antiviral and antitumor functions. It also decreases the population of CD4 T cells and natural killer cells[13,16,17], as well as causes dysgammaglobulinemia with increased serum IgM and deficiency of IgG and IgA[17]. Furthermore, it stimulates the proliferation of lymphocytes in lymph nodes, leading to lymphadenopathy[7,18].

Due to the alterations in immune homeostasis described above, patients have increased susceptibility to infections by encapsulated bacteria, which affect up to 96% of patients with otitis media or rhinosinusitis[7,9,19]. About 80% of cases of pneumonia are bacterial, mainly caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*; bronchiectasis occurs in 60% of cases; about 50% of patients present with chronic viral infections, mainly by Epstein-Barr virus and cytomegalovirus; fungal and parasitic infections are less frequent[20]. Up to 30% of patients with APDS develop autoimmune cytopenias[21].

The treatment in these patients should be individualized, ranging from surveillance in asymptomatic cases to the use of prophylactic antimicrobials, immunoglobulin replacement, and even mTOR pathway inhibitors or haploidentical hematopoietic stem cell transplantation, which has been described to produce a reversal of the post-transplant phenotype[22,23]. At present, the use of selective PI3K-delta inhibitors is being studied, which is reported to have greater efficacy and fewer adverse effects, mainly in patients with lymphoproliferation[23,24].

This case is the second reported in Mexico, as only one previous case was reported with the pathogenic variant PIK3CD c.3061G>A (p.Glu1021Lys) with de novo gain of function. This suggests that this change arises as a response to the presence of HIV in the parents to inactivate viral genes, and therefore, a probable relationship between infectious processes, immune response, and genetic changes should be studied[25].

Diagnosing inborn errors of immunity, such as activated PI3K-delta syndrome, represents a challenge for current medicine due to the lack of recognition of the clinical data presented by patients and the low availability of molecular diagnostic studies. The patient's diagnosis in this case was prolonged, as it was not suspected during the years she remained under study. In particular, diagnosing activated PI3K-delta syndrome

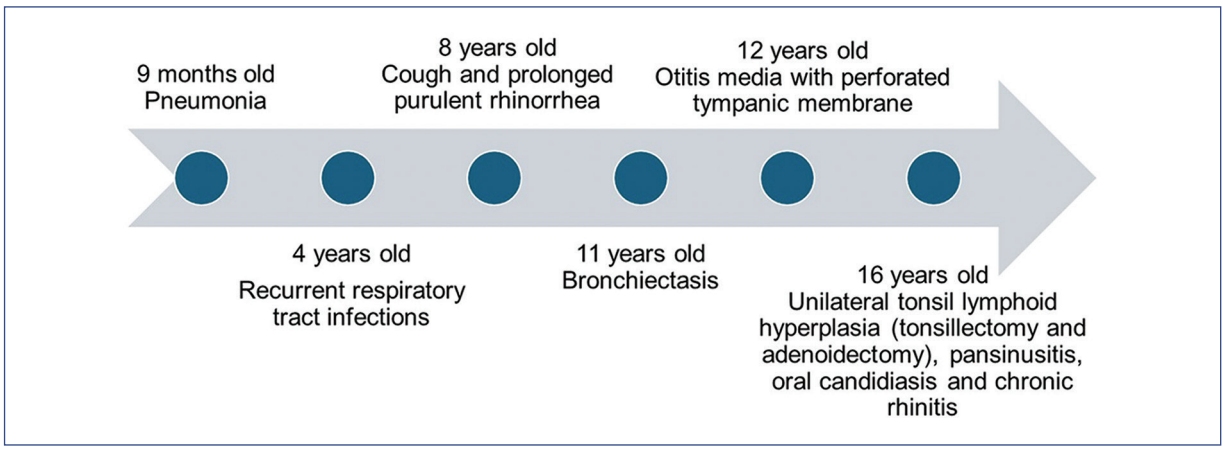

Figure 2. Clinical evolution with the most relevant findings that required medical attention throughout the patient's growth.

Table 1. Laboratory results

Item	24 October 2018	25 April 2019	17 June 2019	09 October 2022
Leucocytes Patient value RR	 5000-10000 cel/µL	5770 cel/µL	**4497 cel/µL**	**4480 cel/µL**
Total lymphocytes Patient value RR	1080 cel/µL 1000-3400 cel/µL	**732.7 cel/µL**	**776 cel/µL**	**770 cel/µL**
Immunoglobulin M Patient value RR	**297 mg/dL** 29-200 mg/dL	**362 mg/dL**	**3.140 mg/dL** 0.40-2.30 mg/dl	**692 mg/dL** 40-280 mg/dl
C3 Patient value RR	112 90-180	123	-	**36.7**
C4 Patient value RR	16.3 16-389	17.9	-	**6.39**
Total CD3 cells Patient value RR	-	-	**526 cel/µL** 600-3100 cel/µL	-
Total CD4 cells Patient value RR	**365 cel/µL** 404-1612 cel/µL	385 cel/µL 134-3061 cel/µL	**226 cel/µL** 428-2020 cel/µL	-
Total CD8 cells Patient value RR	554 259-1080	-	267 259-1080	-
CD4/CD8 Patient value RR	**0.66** 1-2.9	-	**0.85** > 1	-

The bold highlighted values are outside of reference range. RR: reference range; cel/µL=cells/µL.

requires demonstrating the pathogenic variant of the *PIK3CD* gene through molecular studies that require *per* se clinical suspicion. Thus, publishing this case report provides a guideline to broaden the clinical suspicion that allows the integration of a targeted diagnosis of inborn errors of immunity.

Conclusion

This is the second case reported in the literature of APDS in Mexico, so it is important to know about it in order to make a timely diagnosis, for which a high clinical suspicion is required, in addition to immunological and genetic studies, in order to provide appropriate treatment and prevent complications.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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