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CASE REPORT

3-kinase-d phosphoinositide syndrome activated - PIK3CD mutation: case report

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Abstract

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a primary dominant autosomal immunodeficiency caused by a gain of function mutation in gene PIK3CD encoding catalytic subunit p110d of phosphoinositide 3-kinase delta (PI3Kd). This primary immunodeficiency is characterized by the early onset of upper respiratory tract infection, development of benign chronic lymphoproliferative disorders and other signs of immune dysregulation, including gastrointestinal manifestations and autoimmune cytopenias. A 14-year-old male followed at the Teaching Hospital of the Federal University of Paraná (HC-UFPR) since the age of six had a history of three hospitalizations for pneumonia, an episode of meningitis by Listeria monocytogenes, five episodes of otitis media with effusion, EBV infection, and ulcerative colitis (UC). He carried a heterozygous mutation in the PIK3CD gene (c.3061G> A) confirmed by genetic tests performed at the Seattle Children's Hospital. Immunophenotyping revealed he had B-cell and CD4+ lymphopenia. Chest CT scans showed bronchiectasis in the right lower third of the lungs. The patient was asymptomatic and had been on azathioprine continuously for two years for UC, on intravenous immunoglobulin 400mg/kg/month, and on antifungal prophylaxis for Pneumocystis jirovecii. APDS is a combined immunodeficiency with different phenotypes. The growing number of patients with APDS since the condition was first described in 2013 indicates it should be considered in the diagnosis of patients with antibody deficiency, bronchiectasis, severe herpes virus infection, and lymphoma. The severe complications and high death rates connected to APDS have supported the prescription of bone marrow transplantation to young patients and the organization of clinical trials on selective PI3K delta inhibitors.

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INTRODUCTION

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a primary dominant autosomal immunodeficiency caused by a gain of function mutation in gene PIK3CD encoding catalytic subunit p110d of phosphoinositide 3-kinase delta (PI3Kd)[2] found in B and T cells. Mutations may also occur in the PIK3CD (APDS1) and PIK3R1 (APDS2) genes. Four heterozygous PIK3CDn gain of function mutations have been described (E1021K, N334K, E525K, and C416R), the most common being E1021K.[2]

This primary immunodeficiency is characterized by the early onset of upper respiratory tract infection followed by the development of benign chronic lymphoproliferative disorders and other signs of immune dysregulation, including gastrointestinal manifestations and autoimmune cytopenias.[1] Although most manifestations occur in individuals aged 15 years or less, cases of adult-onset and asymptomatic disease have been documented. Maccari et al. reported bronchiectasis in 24/40 patients with APDS1 examined with computed tomography versus 4/15 patients with APDS2. At the age of 20 years, half of the patients had been prescribed at least one immunosuppressive agent, although prescription of second and third line immunosuppressive therapy is not uncommon in patients aged less than 10 years.[1]

Severe, recurrent, or persistent infection by herpesviridae – chronic Epstein-Barr (EBV) and cytomegalovirus (CMV) viremia in particular – is common. Benign lymphoproliferative disorders (lymphadenopathy, hepatosplenomegaly, and focal nodular lymphoid hyperplasia) have been often seen in studied cohorts with APDS.[3,4]

Immunophenotyping findings include low CD4 and CD8 cell counts, increased CD8 cell counts, and transitional B cell expansion. Serial B cell counts have shown that B cell levels decrease more quickly in patients with the condition than in age-matched controls.[2]

CASE REPORT

A 14-year-old male had been followed since the age of six at the immunology ward of the Pediatric Allergy and Immunology Service of the Teaching Hospital of the Federal University of Paraná (HC-UFPR). The patient had a history of three episodes of pneumonia, all requiring hospitalization for at least seven days; one episode of meningitis by *Listeria monocytogenes* that progressed to hydrocephalus and resolved after specific therapy; five episodes of unilateral otitis media with effusion; infection by the *Epstein-Barr Vírus* (EBV) at the age of six with a now resolved residual hepatomegaly; ulcerative colitis treated by a specialist physician with continuous administration of azathioprine for two years.

The patient had been diagnosed for eight months after a genetic test was performed at the Seattle Children's Hospital to confirm a heterozygous mutation of gene PIK3CD (c.3061G> A) encoding catalytic subunit p110d of phosphoinositide 3-kinase delta (PI3Kd).

Immunophenotyping revealed the patient had B-cell and CD4+ lymphopenia (Table 1). Chest CT scans showed bronchiectasis predominantly in the right lower third of the lungs (Figure 1).

The patient had been on continuous treatment with azathioprine for inflammatory bowel disease (currently asymptomatic), prednisone for liver enzyme alterations, and immunoglobulin 400mg/kg/month since the time of diagnosis. His neck lymph nodes shrank since the start of therapy and the patient is asymptomatic.

DISCUSSION

Although APDS may manifest as a condition similar to common variable immunodeficiency, viral infection is one of its defining traits. Lymphocyte immunophenotyping has confirmed that APDS is a combined immunodeficiency.[2]

Recurrent infection in the lungs, ears, and sinuses (with encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*) is almost universal and has been associated with high incidence of target organ damage, including hearing loss and bronchiectasis (permanent airway scarring).[3]

In conclusion, APDS is a combined immunodeficiency with a varying phenotype complicated by recurrent sinus and lung infection caused by bacteria and herpesviridae, bronchiectasis, nodular lymphoid hyperplasia, and autoimmunity; cognitive impairment and lymphoma are observed less frequently. The growing number of patients with APDS since the condition was first described in 2013 indicates it is a clinically significant cause of primary immunodeficiency and should be considered in the diagnosis of patients with atypical primary and inherited antibody deficiency, bronchiectasis, severe herpes virus infection, and lymphoma. The severe complications and high death rates connected to APDS warrants the prescription of bone marrow transplantation to young patients and the organization of clinical trials on selective PI3K delta inhibitors.[2]

Table 1. Lymphocyte immunophenotyping (2017).

T cells	%	N	Reference Values
CD3 +	76.88	505.27	800-3500
CD3 + CD4 +	31.06	204.13	400-2100
CD3+ CD8++	41.27	271.23	200-1200
CD3 + 4 – 8	1.96	12.88	
CD3 +4+8	0.49	3.22	
CD3 +CD8	2.1	13.8	
B cells – CD19	0.43	2.82	200-600
NK cells	22.69	149.12	70-1200

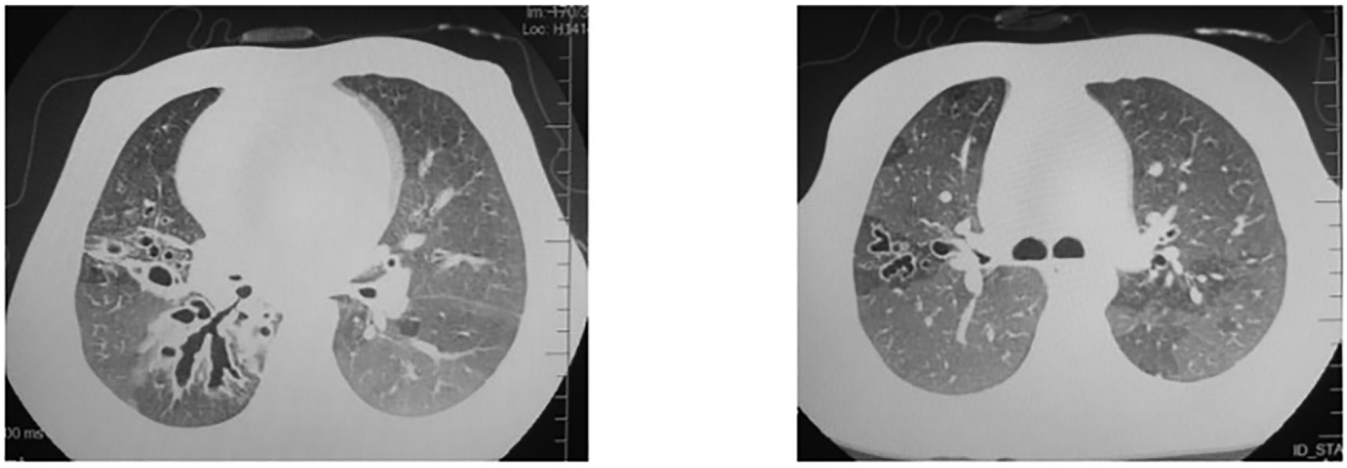


Figure 1. Chest computed tomography scans (2017).

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