ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME IN A PORTUGUESE TEENAGER WITH PIK3R1 VARIANT, A CASE REPORT

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ABSTRACT Activated phosphoinositide 3-kinase delta syndrome (APDS) is a recently described combined primary immunodeficiency caused by mutations that increase the activity of the phosphoinositide-3-kinase δ (PI3Kδ) pathway. APDS is characterized by the early onset of upper respiratory tract infections, benign chronic lymphoproliferative disorders and other signs of immune dysregulation, including gastrointestinal manifestations, autoimmunity and increased risk of malignancy. Here we describe a 12-year-old girl with a history of chronic diarrhoea, three hospitalizations for sepsis and recurrent respiratory infections. She also presented episcleritis at 4 years of age and exuberant periungual and perioral warts at the age of 5. Her physical examination was relevant for short stature, low weight for age and scoliosis.

Immunophenotyping revealed reduced IgG and IgA; no response to immunization was reported. The cellular immunity studies showed an important reduction of T CD4+ lymphocytes, CD4+/CD8+ ratio inversion, reduction of recent thymic emigrants, and increased activated TCD4+ and CD8+. Moreover, reduced switched memory B cells and low NKs levels were reported. She carried a heterozygous mutation of the PIK3R1 gene (c.1305A>C) not previously described in the literature. The initial management included vaccine boosters, anti-microbial prophylaxis and immunoglobulin replacement, resulting in significant improvement of weight gain and growth and reduction in the incidence of respiratory tract infections. The growing number of patients with APDS since the condition was first described in 2013 indicates that it should be considered in diagnosing patients with immunodeficiency, lymphoproliferation, autoimmunity and developmental delay.

KEYWORDS APDS, PIK3R1 gene, primary immunodeficiency, recurrent respiratory tract infection

Introduction

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a recently described combined primary immunodeficiency (PID) caused by autosomal dominant mutations that increase the activity of the phosphoinositide-3-kinase δ (PI3Kδ) pathway [1-4]. APDS can be caused by mutations in the PIK3CD gene encoding the p110δ catalytic subunit of PI3Kδ (APDS1, OMIM #615513) or the PIK3R1 gene that encodes the p85α regulatory subunit of PI3Kδ (APDS2, OMIM #616005) [1-3, 5-7]. APDS shows clinical heterogeneity and is characterized by the

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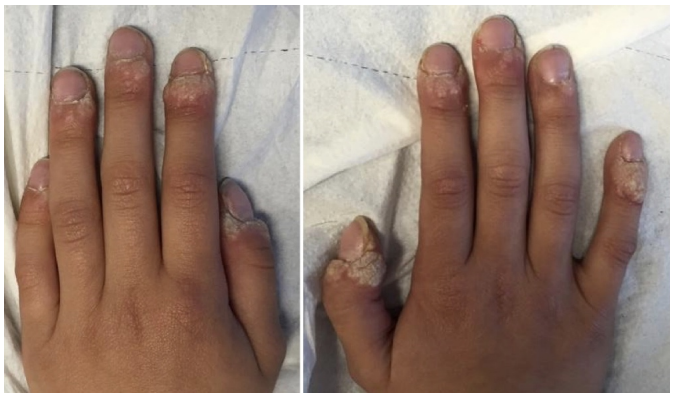

Figure 1: Exuberant periungual warts.

early onset of upper respiratory tract infections followed by the development of benign chronic lymphoproliferative disorders (lymphadenopathy, hepatosplenomegaly and focal nodular lymphoid hyperplasia) and other signs of immune dysregulation including gastrointestinal manifestations, autoimmunity and increased risk of malignancy. Severe, recurrent or persistent infection by herpesviridae – chronic Epstein-Barr (EBV) and cytomegalovirus (CMV) viremia in particular – is common [4, 8, 9].

Although most manifestations occur in individuals aged 15 years or less, cases of adult-onset and asymptomatic disease were also reported [4, 9]. The immunological phenotypes of APDS patients are also heterogeneous with both B and T cell abnormalities. B cell compartment abnormalities consist of mild B cell lymphopenia, increased transitional B cells, decreased class switched memory B cells and class-switch-recombination defects (CSR-D). Elevated IgM levels have been reported in most of the patients while total IgG and IgA levels can be either normal or markedly decreased. A reduction of naive CD4+ and CD8+ T cell numbers with increased frequency of effector memory CD8+ T cells and inverted CD4+/CD8+ T cell ratio was also reported [4, 10].

Case report

The patient was a 12-year-old girl, born to nonconsanguineous parents at 41 weeks gestational age to an uncomplicated pregnancy. Maternal history of recurrent respiratory infections in childhood was reported. In the first days of life the child suffered from severe sepsis, without pathogen isolation, requiring intensive care admission. At three months of age she started suffering from chronic diarrhea, requiring parenteral nutrition. At that time she had 3 episodes of sepsis, in the first Klebsiella Oxytoca was isolated and in the second Enterococcus faecalis. Afterwards, she had recurrent respiratory infections, most of them caused by Adenovirus. Her history of infections also includes recurrent episodes of otitis media, requiring placement of ear tubes, tonsillectomy and adenoidectomy. She also presented episcleritis at 4 years of age and then exuberant periungual and perioral warts at the age of 5 (Figure 1). Her physical examination was relevant for short stature, low weight for age and scoliosis. She has normal cognition. The initial basic immunologic screening identified a normal whole blood count, significantly reduced IgG and IgA, but IgM within the reference range. No response to immunization was reported. The cellular immunity studies showed an important reduction of T CD4+ lymphocytes, CD4+/CD8+ ratio inversion, reduction of recent thymic emigrants, and increased activated TCD4+ and CD8+. Moreover, reduced switched memory B cells were reported as well as low NKs levels. A genetic test revealed a heterozygous mutation of the PIK3R1 gene (c.1305A>C) with an autosomal dominant mode of inheritance in association with APDS2. This variant was not previously described in the literature. Her mother was also a carrier of the mutation. However, she had a normal immunologic study and did not present autoimmune manifestations or lymphoproliferative disorders, probably explained by incomplete penetrance and variable expressivity. The initial management included vaccine boosters, sulfamethoxazole/trimethoprim prophylaxis and intravenous immunoglobulin (IVIG) substitution resulting in significant improvement of weight gain and growth and reduction in the incidence of respiratory tract infections.

Discussion

APDS has been shown to produce a wide spectrum of disease phenotypes with varying degrees of immunodeficiency, lymphoproliferation, autoimmunity, and developmental delay [10]. From an infectious standpoint, patients with APDS frequently develop the classic respiratory infections of antibody-deficient subjects, often leading to long-term clinical implications such as bronchiectasis and lung scarring. Other described infec-tions are gastroenteritis, eye infections [5, 11] and recurrent herpes virus, in the set-ting of overactivation of the mTOR pathway [1, 8, 10].

The clinical spectrum is extremely variable, ranging from asymptomatic patients not requiring supplemental immunoglobulin replacement therapy to other subjects with the same gene mutation necessitating stem cell transplant and subsequently dying from overwhelming infections as a complication of diffuse large B-cell lymphoma [1].

This can explain that our patient's mother was also carrying the mutation, besides having a normal immune cell phenotype and not presenting autoimmune manifestations or lymphoproliferative events. Immunoglobulin replacement and prophylactic anti-microbial medications are common therapies used to treat the immune deficiency in most APDS patients [5]. Anti-infection prophylaxis medications include antibiotics such as trimethoprim/sulfamethoxazole and azithromycin, and anti-virals such as acyclovir and valaciclovir. Additionally, patients often require immune suppressive therapies for the inflammatory and autoimmune sequelae of the disease. As treatment for inflammatory disease in APDS, broad immunosuppressants such as corticosteroids and mycophenolate mofetil as well as B cell-depleting therapy such as rituximab have been used along with mTOR inhibition (rapamycin) and PI3Kd inhibition (e.g. oral leniolisib and inhaled nemiralisib tested).

Despite these treatments, about 13% of patients still need hematopoietic stem cell transplantation (HSCT) for persistent severe disease [5, 10].

Conclusion

APDS is a combined immunodeficiency resulting from gain-of-function (GOF) mutations in one of two genes encoding subunits of the phosphoinositide-3-kinase δ (PI3Kδ). There is a wide range of clinical phenotypes seen with APDS, including severe respiratory tract infections, diffuse lymphadenopathy, persistent herpes virus infections, and lymphoma. Apart from anti-microbial prophylaxis and immunoglobulin replacement, patients are treated with various immunomodulatory agents, and some need hematopoietic stem cell transplants [11].

The growing number of patients with APDS since the condition was first described in 2013 indicates that 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 [10].

Author contributions

All authors have contributed to this work: Lorena Stella was a major contributor in writing the manuscript, Mariana Pinto reviewed the manuscript, Eduarda Ferreira, João Parente Freixo, Isabel Carvalho, and Diana Moreira took part in the patients' medical approach, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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