International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 5, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I5/050

"PI3K delta syndrome associated with systemic lupus erythematosus"

Elias A Alraqibah

Department of Medicine, College of Medicine, Qassim University, Qassim, Saudi Arabia

Received: 18.09.2024 Revised: 22.10.2024 Accepted: 09.11.2024

ABSTRACT
Background: Activated PI3K delta syndrome (APDS) is an uncommon primary immunodeficiency that arises from gain-of-function mutations in the PIK3CD gene. Clinical features of APDS include immune dysregulation, which leads to recurrent infections, lymphoproliferation, and autoimmune manifestations. SLE is a chronic autoimmune disease wherein pathogenic autoantibodies are produced and manifest multisystem inflammation. The concomitance of APDS and SLE is rare and presents considerable challenges in diagnosis and treatment because of the contradictory coexistence of immune deficiency and autoimmunity.
Case Presentation: The patient was a 6-year-old Saudi girl who presented with recurrent pneumonia, lymphadenopathy, hepatosplenomegaly, and bronchiectasis and had received an initial diagnosis of dysgammaglobulinemia that subsequently progressed towards common variable immunodeficiency. SLE developed features of autoimmune disease over time, including elevated anti-double-stranded DNA, polyarthritis, and, finally, pancytopenia. Mutations in the PIK3CD gene were identified using whole-exome sequencing, where the patient was heterozygous. Clinical outcomes improved due to a multidisciplinary approach that included various medications targeting recurrent infections and autoimmune complications.
Conclusion: The clinical dilemmas and therapeutic challenges regarding the coexistence of the two disease entities are brought to light. Their coexistence warrants genetic testing in patients who exhibit overlapping immunodeficiency and features of an autoimmune disease. Early diagnosis combined with a personalized treatment plan is pivotal in optimizing outcomes in cases with such rare and complex pathology.

Keywords: Activated PI3K delta syndrome, systemic lupus erythematosus, primary immunodeficiency, autoimmunity, PIK3CD mutation, recurrent infections, pediatric lupus.

INTRODUCTION

Activated PI3K delta syndrome (APDS) is a rare genetic disorder. disorder of the immune deficiency type characterized by a gain-of-function mutation in the PIK3CD gene, which encodes the p110δ subunit of phosphoinositide 3-kinase (PI3K) [1–3]. This kinase is pivotal in regulating multiple facets of immune cell signalling, proliferation, survival, and differentiation [3]. The hyperactivation of this PI3Kδ by mutations produces extreme immune dysregulations, marked by recurrent infections, lymphoproliferation, autoimmune diseases, and an increased disposition towards a range of malignancies [4,5]. Described for the first time in 2013, APDS has recently been recognized as a disorder that displays a great range of clinical phenotypes across the spectrum of immunodeficiency and autoimmunity [6]. Most patients have recurrent sinopulmonary infections, bronchiectasis, poor vaccine responses, and autoimmune complications, including cytopenia and inflammatory arthritis [7]. It is considered rare but may be missed due to variable presentations as well as overlapping features with other immunological disorders [7].
Systemic lupus erythematosus (SLE) is a long-lasting autoimmune disorder marked by multisystem involvement and the production of pathogenic autoantibodies, chiefly anti-double-stranded DNA (anti-dsDNA) antibodies [8]. The disease engages various organs, including the skin, kidneys, joints, and central nervous system, causing significant morbidity [9]. The pathogenesis of SLE involves a complicated interaction of genetic susceptibility, environmental triggers, and immune dysregulation, which leads to the breakdown of self-tolerance and persistent inflammation [10]. SLE is most observed in females between the teenage and reproductive age group, and it may occur in children and teenagers, where it has a rapidly progressive course [11].
The combination of an immunodeficiency disease, such as APDS, and an autoimmune disease like systemic lupus erythematosus (SLE) presents a unique phenomenon in clinical medicine. This interplay highlights the different paradigms that exist between immune deficiency and autoimmunity. Altered PI3Kδ signalling in APDS results in poor pathogen defence and aberrant immune activation and sets the stage for the generation of

autoantibodies and the setting of systemic inflammation [13]. The incidence of autoimmune manifestations is a little greater than 30% among the population of patients affected by APDS, including symptoms very much in tune with SLE, lupus nephritis, and autoimmune cytopenia [8]. Although these diseases commonly coexist in the patient population, the exact molecular and immunological mechanisms driving the coexistence of APDS and SLE are only incompletely understood.

This study presents the case of a 6-year-old girl with a confirmed diagnosis of APDS and coexisting SLE, characterized by recurrent infections, lymphadenopathy, bronchiectasis, and autoimmune features including arthritis and pancytopenia. Through a detailed exploration of her clinical course, genetic findings, and therapeutic response, this case report aims to clarify the complex relationship between primary immunodeficiency and autoimmunity. Understanding the mechanisms underlying their coexistence may inform diagnostic approaches and optimize therapeutic strategies for patients with overlapping immunological disorders.

Case presentation

A 6-year-old Saudi girl was referred to the Allergy/Immunology Unit in January 2003 due to a history of recurrent pneumonia that began at the age of 1 year. Upon evaluation, she exhibited lymphadenopathy, clubbing of fingers, hepatosplenomegaly, and bronchiectasis. Laboratory investigations revealed normal levels of serum IgG (14.1 g/L, Normal range= 6.1 to 15.7 g/l), IgA (1.39 g/L, Normal range= 0.5 to 2 g/l), and high IgM (3.55 g/L, Normal range= 0.5 to 2 g/l), with a low IgE level (<2 KU/L, Normal range= 5 to 500 KU/l). Functional antibody production tests showed no increase in specific antibody titres four weeks after administering pneumococcal vaccine and tetanus toxoid.

Sweat chloride test was normal, and serology for hepatitis C, hepatitis B, and human immunodeficiency virus (HIV) RNA were negative. T-cell proliferation studies in response to mitogens, adenosine deaminase levels, and nitro blue tetrazolium (NBT) test results were all normal. Lymphocyte subset analysis indicated reduced absolute CD3 T lymphocytes (1082 mm^3, Normal range= 1700–1900 mm3), CD4 T lymphocytes (298 mm^3, Normal range= 800 to 1700 mm3), CD8 T lymphocytes (595 mm^3, Normal range= 700 to 1000 mm3), and B cells (108 mm^3, Normal range= 400 to 800 mm3), and CD4/CD8 ratio (0.9-1.4).

Diagnosing the patient's condition was not without its challenges. A diagnosis of dysgammaglobulinemia with poor antibody response and possible progression to common variable immunodeficiency (CVID) was considered. Intravenous immunoglobulin (IVIG) therapy was initiated. However, in 2005, after being off IVIG for five months, the patient developed persistent fever, cough, and shortness of breath that did not respond to systemic antibiotics. Despite extensive cultures and serology, no clear source of infection was identified. This prompted us to consider an autoimmune cause. which was supported by autoimmune studies suggestive of systemic lupus erythematosus (SLE).

An assessment of antibody production in response to pneumococcal vaccine and tetanus toxoid was repeated, showing a continued inadequate specific antibody response to vaccines, similar to the previous test, even though the patient can produce autoantibodies. The patient received treatment with prednisone and hydroxychloroquine. but IVIG was withheld. While this led to temporary clinical improvement, she developed pneumonia caused by Haemophilus influenzae one year later, requiring hospitalization and resumption of IVIG therapy. The patient remained stable for a year. In July 2008, she was presented with fever, pancytopenia, and significantly elevated anti-dsDNA titres (4700 U/ml). Prednisone was increased, and mycophenolate mofetil (MMF) was initiated, but therapy was complicated by multiple skin abscesses caused by methicillin-sensitive Staphylococcus aureus, requiring systemic antibiotics and abscess drainage. IVIG was restarted, and MMF was discontinued, leading to stabilization of her complete blood count and clinical status and prednisone dose was gradually tapered off.

In 2009, the patient developed polyarthritis +acute joint pain+ of the Wrist joints, intermediate interphalangeal joints, metacarpophalangeal joints, and knee joints. accompanied by morning stiffness, fatigue, fever, and elevated anti-dsDNA levels. She was treated with a combination of prednisone, hydroxychloroquine, and monthly IVIG. Azathioprine was added to her regimen but was discontinued after she developed methicillin-resistant Staphylococcus aureus (MRSA) abscesses. Her prednisone dose gradually diminished to 7.5 mg daily. Beginning in June 2010, she experienced recurrent episodes of fever, arthritis, and pancytopenia, due to which she needed to be admitted repeatedly. Investigations, including computed tomography (CT) scans of the chest and abdomen, positron emission tomography (PET) scans, and echocardiography, were unremarkable. Laboratory tests showed white blood cells (WBCs) ranged between 1.06 to 1.2, haemoglobin 6–8 g/l, platelet count 90–100, and septic work-up has always been negative. Despite high-dose prednisone therapy, her anti-dsDNA titres continued to rise (>8000 U/ml). She was treated with pulse methylprednisolone and broad-spectrum antibiotics with only temporary improvement.

After consultation with the Allergy/Immunology team, rituximab therapy was initiated at a dose of 375 mg/m^2 weekly for four doses. The patient remained on IVIG, hydroxychloroquine, and a tapering dose of prednisone. She gradually showed improvement, with resolution of fever, reduced arthritis symptoms, increased appetite,

and overall better well-being. Her laboratory findings also improved, including an increase in CD4 T lymphocyte counts.

Later on, whole exome sequencing (WES) identified a heterozygous pathogenic variant in PIK3CD (c.3061G>A, p.E1022K), consistent with a diagnosis of activated PI3K delta syndrome (APDS). This immunodeficiency, characterized by immune dysregulation and susceptibility to autoimmunity, provided an explanation for her complex clinical presentation. WES analysis confirmed that this was a known Saudi mutation.

With the confirmation of APDS, the therapeutic approach was refined. The patient continued IVIG, hydroxychloroquine, and tapering doses of prednisone. Rituximab was effective in managing her autoimmune features, including arthritis and pancytopenia, although recurrent infections and complications persisted. Nevertheless, her condition stabilized under coordinated multidisciplinary care.

DISCUSSION

APDS is a rare primary immunodeficiency arising due to gain of function mutations occurring in PIK3CD, a gene that encodes the p110δ subunit of the phosphoinositide 3-kinase [1]. This is a class of lipids that primarily expresses itself inside leukocyte cells and plays an important role in signalling, development, and functions of an immune response [14]. The hyperactivity in PI3K signalling results in immune imbalance, which causes predisposition to infections, lymphoproliferative disorders, and autoimmune diseases [15]. APDS illustrates an immunological paradox as it presents both features of immunodeficiency and autoimmunity [3], as observed in this case.

SLE refers to an autoimmune disease in which pathogenic autoantibodies are produced, and immune complex deposition causes systemic inflammation [8]. Although rare, the combination of APDS with SLE underscores the delicate interplay between immune dysregulation and autoimmunity [16]. Autoimmune disorders arise to the tune of approximately 30% of APDS, including frequently noted cytopenia, inflammatory bowel disease, and lupus-like nephritis [17]. The immune dysregulation in APDS, particularly due to PI3K independence by atypical activation of T and B cells, is conceived to have contributed to the production of autoantibodies and the development of autoimmunity in this patient [18].

In this case, the clinical presentations of recurrent infections, lymphadenopathy, bronchiectasis, and poor responses to vaccines characterized the initial expression of primary immunodeficiency. Although these clinical features were consistent with a diagnosis of dysgammaglobulinemia, there were progressive features consistent with common variable immunodeficiency (CVID). Yet, features of autoimmunity were discovered: polyarthritis, reactive pancytopenia, high levels of anti-double-stranded DNA (anti-dsDNA) antibodies, and levels of IgG subclasses that were far from normal-lending credibility to the complex immunophenotype being offered. This syndrome ultimately led to the diagnosis of APDS after a modal-like approach ruled in the heterozygous pathogenic variant in PIK3CD (c.3061G>A, p.E1022K), a mutation known to exist within the Saudi population.

The pathophysiology of APDS implicates the hyperactive evolution of PI3K signalling, which affects the function of T and B lymphocytes [4]. However, patients with APDS have been documented to show low CD4 T-cell numbers, vaccine responses, and impedance to the balance among T-helper cell subsectors [1]. On the other hand, hyperactive signalling of B cells has been implicated in antibody production mis regulation that, through its poor responses to vaccine and pathogenic autoantibody generation, explains the recurrent infections and autoimmune manifestations existing together in APDS [1].

The overlapping appearance of APDS and SLE in this patient makes therapeutics challenging to begin with. Reaching out for balanced immune suppression without recognizing that this control may lead to massive immunosuppression and thus aggravate the existing immunodeficiency called for caution. Treatments such as intravenous immunoglobulin, corticosteroids, hydroxychloroquine, and rituximab were initiated concurrently with the management of infectious susceptibility and autoimmune complications [19]. Rituximab is a monoclonal antibody that effectively reduces B-cell-mediated autoimmune processes, such as arthritis and pancytopenia, with good reduction of anti-dsDNA titres [19].

Recurrent infections were associated with clinical advances in this patient, including methicillin-sensitive Staphylococcus aureus and methicillin-resistant Staphylococcus aureus abscesses; these revealed the weaknesses of patients with APDS against opportunistic microorganisms, which is one of the hallmarks of primary immunodeficiencies [3–5]. While it brought in more challenges, confirmation of APDS through whole exome sequencing made targeted therapeutic approaches possible, including continued use of IVIG, judicious immunosuppressive therapies, and immune reconstitution.

This case demonstrates the necessity to appreciate the overlap between immunodeficiency and autoimmunity among patients with complex clinical presentations. Recognizing genetic aetiologies, such as APDS, positioning guides to diagnostic and therapeutic strategies are crucial. Whole exome sequencing has emerged as a valuable tool in uncovering more profound knowledge on autosomal recessive conditions, primarily in consanguineous prevailing backgrounds [20].

In conclusion, this case underscores the intricate relationship between genetic mutations in immune signalling pathways and their clinical manifestations, spanning immunodeficiency and autoimmunity. The coexistence of APDS and SLE exemplifies the challenges in managing such patients, requiring coordinated multidisciplinary care and a personalized therapeutic approach. Further studies are needed to better understand the mechanisms underlying autoimmunity in APDS and optimize treatment strategies for affected individuals.

ACKNOWLEDGMENT
Dr. RK Arnaout , Dr. A Al Shaikh and Dr. H Al Hamzi

REFERENCES

1. Serra I, Manusama OR, Kaiser FMP, et al. Activated PI3Kδ syndrome, an immunodeficiency disorder, leads to sensorimotor deficits recapitulated in a murine model. Brain, Behav Immun - Heal. 2021;18:100377. doi:10.1016/j.bbih.2021.100377
2. Brodsky NN, Lucas CL. Infections in activated PI3K delta syndrome (APDS). Curr Opin Immunol. 2021;72:146-157. doi:10.1016/j.coi.2021.04.010
3. Singh A, Joshi V, Jindal AK, Mathew B, Rawat A. An updated review on activated PI3 kinase delta syndrome (APDS). Genes Dis. 2020;7(1):67-74. doi:10.1016/j.gendis.2019.09.015
4. Berglund LJ. Modulating the PI3K Signalling Pathway in Activated PI3K Delta Syndrome: a Clinical Perspective. J Clin Immunol. 2024;44(1):34. doi:10.1007/s10875-023-01626-0
5. IJspeert H, Dalm VASH, van Zelm MC, Edwards ESJ. Hyperactivation of the PI3K pathway in inborn errors of immunity: current understanding and therapeutic perspectives. Immunother Adv. 2024;4(1). doi:10.1093/immadv/ltae009
6. Vanselow S, Wahn V, Schuetz C. Activated PI3Kδ syndrome – reviewing challenges in diagnosis and treatment. Front Immunol. 2023;14. doi:10.3389/fimmu.2023.1208567
7. Cinetto F, Scarpa R, Rattazzi M, Agostini C. The broad spectrum of lung diseases in primary antibody deficiencies. Eur Respir Rev. 2018;27(149):180019. doi:10.1183/16000617.0019-2018
8. Ameer MA, Chaudhry H, Mushtaq J, et al. An Overview of Systemic Lupus Erythematosus (SLE) Pathogenesis, Classification, and Management. Cureus. Published online October 15, 2022. doi:10.7759/cureus.30330
9. Bai Y, Tong Y, Liu Y, Hu H. Self-dsDNA in the pathogenesis of systemic lupus erythematosus. Clin Exp Immunol. 2017;191(1):1-10. doi:10.1111/cei.13041
10. Moulton VR, Suarez-Fueyo A, Meidan E, Li H, Mizui M, Tsokos GC. Pathogenesis of Human Systemic Lupus Erythematosus: A Cellular Perspective. Trends Mol Med. 2017;23(7):615-635. doi:10.1016/j.molmed.2017.05.006
11. Levy DM, Kamphuis S. Systemic Lupus Erythematosus in Children and Adolescents. Pediatr Clin North Am. 2012;59(2):345-364. doi:10.1016/j.pcl.2012.03.007
12. Chan SCW, Lau CS. Systemic lupus erythematosus and immunodeficiency. Rheumatol Immunol Res. 2021;2(3):131-138. doi:10.2478/rir-2021-0019
13. Elworthy S, Rutherford HA, Prajsnar TK, et al. Activated PI3K delta syndrome 1 mutations cause neutrophilia in zebrafish larvae. Dis Model Mech. 2023;16(3). doi:10.1242/dmm.049841
14. Okkenhaug K. Signaling by the Phosphoinositide 3-Kinase Family in Immune Cells. Annu Rev Immunol. 2013;31(1):675-704. doi:10.1146/annurev-immunol-032712-095946
15. Durandy A, Kracker S. Increased activation of PI3 kinase-δ predisposes to B-cell lymphoma. Blood. 2020;135(9):638-643. doi:10.1182/blood.2019002072
16. Lucas CL, Lenardo MJ. Identifying genetic determinants of autoimmunity and immune dysregulation. Curr Opin Immunol. 2015;37:28-33. doi:10.1016/j.coi.2015.09.001
17. Zhou H, Balint D, Shi Q, Vartanian T, Kriegel MA, Brito I. Lupus and inflammatory bowel disease share a common set of microbiome features distinct from other autoimmune disorders. Ann Rheum Dis. Published online September 18, 2024:ard-2024-225829. doi:10.1136/ard-2024-225829
18. Sood AK, Francis O, Schworer SA, et al. ANCA vasculitis expands the spectrum of autoimmune manifestations of activated PI3 kinase δ syndrome. Front Pediatr. 2023;11. doi:10.3389/fped.2023.1179788
19. Ahmed AR, Kaveri S. Reversing Autoimmunity Combination of Rituximab and Intravenous Immunoglobulin. Front Immunol. 2018;9. doi:10.3389/fimmu.2018.01189
20. Tan JK, Awuah WA, Ahluwalia A, et al. Genes to therapy: a comprehensive literature review of whole-exome sequencing in neurology and neurosurgery. Eur J Med Res. 2024;29(1):538. doi:10.1186/s40001-024-02063-4