Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Activated phosphoinositide 3-kinase delta syndrome 2 associated with Kikuchi–Fujimoto disease: a rare Palestinian case report

Karim J. Abulaila, MD[a], Mosa A. Sabha, MD[b], Momin R. Misk, MD[a], Amr A. Alhalabeye, MD[a], Afnan W.M. Jobran, MD[a,*], Fawzy M. Abunejma, MD[c], Izzeddin A. Bakri, MD[d]

Introduction: Histiocytic necrotic lymphadenitis (HNL), also known as Kikuchi–Fujimoto disease (KFD), is a rare local lymphadenopathy with a benign course and clinical manifestations such as fever, lymphadenopathy, rash, hepatosplenomegaly, central nervous system (CNS) symptoms, and hemophilic cell syndrome. It was first identified by Japanese pathologists Kikuchi and Fujimoto. KFD damages the meninges, the brain parenchyma, and peripheral nerves in addition to the CNS. Neurological symptoms may even be the most obvious clinical manifestations or initial symptoms of the disease.

Case presentation: We present a unique case of a 7-year-old male patient who was diagnosed with activated phosphoinositide 3-kinase delta syndrome 2 (APDS 2) associated with KFD, a HNL during a workup for fever without a focus and cervical lymphadenopathy.

Conclusion: Highlighted the unique relationship between two uncommon conditions and stressed the significance of adding KFD to the list of possible diagnoses for lymphadenopathy in APDS 2. Furthermore, we demonstrate that patients with APDS 2 may exhibit low immunoglobulin M levels.

Keywords: histiocytic necrotic lymphadenitis, Kikuchi–Fujimoto disease, lymphadenopathy

Introduction

Primary immunodeficiency, also called Human Inborn Errors of Immunity, is a group of disorders caused by mutations in single genes. They present clinically with increased susceptibility to infectious agents, allergy, autoimmunity, and/or malignancy[1].

Phosphoinositide 3-kinases are enzymes expressed mainly in the lymphocytes and play a crucial role in the lymphocytes' activation, proliferation, function, and survival[2]. Activated phosphoinositide 3-kinase delta syndrome (APDS) is an inborn error of immunity that was first described in 2013–2014[3]. It is caused by a heterozygous gain of function and autosomal dominant mutation in phosphoinositide 3-kinase (PI3K) genes. APDS 1 is a result of a mutation in the *PI3KCD* gene, whereas APDS 2 is the phenotypic presentation of the mutation in the *PI3KR1* gene[4].

HIGHLIGHTS

- This case report highlighted a unique association between activated phosphoinositide 3-kinase delta syndrome 2 (APDS 2) and Kikuchi–Fujimoto disease (KFD), both are rare disorders.
- Emphasize the importance of expanding the differential diagnosis of lymphadenopathy in APDS 2 to include KFD.
- Moreover, the patients of APDS 2 may present with low levels of immunoglobulin M.

APDS is characterized by combined immunodeficiency and altered B-cell and T-cell responses. APDS is associated with recurrent respiratory infections such as tonsillitis, acute otitis media, and pneumonia, typically with encapsulated bacteria like *Haemophilus influenzae* and *Streptococcus pneumoniae*, which indicate an altered antibody response[3]. In addition to that, the patient may suffer from lymphadenopathy, lymphopenia, and an increased risk for lymphoma and malignancy[3]. APDS patients may exhibit chronic viral infection, mainly with cytomegalovirus (CMV) and Epstein–Barr virus (EBV)[5]. However, the clinical presentation shows complex variable manifestations suggesting incomplete penetrance[6]. To our knowledge, there are less than 100 APDS cases reported, but the exact number is still unknown[7].

In this paper, we present a unique case of a 7-year-old male patient who was diagnosed with APDS 2 associated with Kikuchi–Fujimoto disease (KFD), a histiocytic necrotizing lymphadenitis (HNL) during a workup for fever without focus and cervical lymphadenopathy.

[a]Faculty of Medicine, Al-Quds University, Jerusalem, [b]Faculty of Medicine, Al-Quds University, Jerusalem, [c]Alahli Hospital, Hebron Private Clinics, Hebron and [d]Alahli Hospital, Hebron, Palestine

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

*Corresponding author. Address: Faculty of Medicine, Al-Quds University, Jerusalem 9160401, Palestine. E-mail address: afnanjobran26@gmail.com (A.W.M. Jobran).

Annals of Medicine & Surgery (2023) 85:2064–2067

Received 11 January 2023; Accepted 18 March 2023

Published online 7 April 2023

http://dx.doi.org/10.1097/MS9.0000000000000476

Case presentation

A 7-year-old male patient was born at term following a complicated pregnancy with placental inefficiency and intrauterine growth restriction. He was delivered via cesarean section, with a birth weight of 1400 g; thus, he was admitted to the neonatal intensive care unit for 26 days, during which he did not need supplemental oxygen. The family history was unremarkable. He has three healthy siblings, no history of miscarriages or deaths at young ages, and the parents are nonconsanguineous.

During early childhood, the patient had repeated hospitalizations for fever events due to tonsillitis, acute otitis media, and pneumonia every 2–3 months, as well as cervical lymphadenopathy. He suffered from a fever without focus for 20 days that was recorded at 39°C axillary; he was treated with antibiotics and antipyretics without significant improvement. Later on, he developed bilateral cervical lymphadenopathy associated with hypoactivity, poor feeding, night sweating, intermittent abdominal pain and abdominal distention, and epistaxis during fever, so he was admitted to the pediatric department.

Physical examination revealed a weight of 18 kg (10th percentile), distinct facial features (small eyes, mild hypertelorism, short philtrum, low set ears), high pitch sound, intellectual disability, and bilateral neck swelling measuring 5 cm in diameter. The computed tomography scan was done and showed multiple enlarged lymph nodes in the neck and upper mediastinum. The abdominal ultrasonography showed a homogenous spleen enlarged to 12 cm and a homogenous liver measuring 11.6 cm at the mid-clavicular line.

The blood surface showed microcytic hypochromic anemia with anisopoikilocytosis, neutrophils with left shift, and no blasts.

The patient underwent cervical lymph node excision and biopsy that was compatible with HNL (KFD).

Histology sections showed lymph node effacement and involvement by irregularly shaped, pale areas composed of histiocytes, plasmacytoid dendritic cells, eosinophilic granular material, and abundant karyorrhectic debris (nuclear dust) surrounding a central zone of necrosis. Karyorrhectic areas extend beyond the nodal capsule. Regions between pale areas exhibit a mottled/starry sky appearance. Histiocytes include phagocytic cells with eosinophilic cytoplasm and crescent-shaped nuclei (crescentic histiocytes) and nonphagocytic cells with twisted or reniform nuclei (Figure 1).

The infectious workup was negative for blood culture, *CMV* serology, *EBV* serology, acid-fast stain, and PCR for *Mycobacterium tuberculosis*. The immunological analysis showed low levels of immunoglobulin (Ig)G, IgM, and IgA. The flow cytometry showed the absence of B-cell (CD19 and CD20) and an increase in T-cells (CD3 and CD8) (see Table 1). The antinuclear antibody (ANA) test was negative.

The result of the bone marrow biopsy showed hypercellular for age, with bone marrow showing megakaryocytic hyperplasia with occasional atypical forms and bone marrow neutrophilia and eosinophilia. There are no granulomas or other signs of lymphoma, so the morphologic findings are most likely reactive.

The patient was referred for genetic testing that revealed a mutation in the *PIK3R1* gene, and the diagnosis of APDS 2 was made. The patient started on immunoglobulin replacement and sirolimus. The recommendation was to continue on his medication; if there is no response, he will be referred for bone marrow transplantation after checking *PIK3R1* in his sister.

Discussion

We describe a case of a 7-year-old child who was diagnosed with KFD in the background of APDS 2. KFD is a rare, benign, self-limiting entity that is also called HNL. KFD patients are most commonly present with cervical lymphadenopathy, which may be accompanied by fever, nausea and vomiting, weight loss, upper respiratory symptoms, sore throat, chills, myalgia, arthralgia, skin rash, and hepatosplenomegaly. Laboratory findings are commonly normal, but there are some patients who may have anemia, leukopenia, elevated serum transaminase and serum lactate dehydrogenase (LDH), and elevated C-reactive protein. These clinical manifestations can be suggestive of an autoimmune disorder; Imamura *et al*. suggested that KFD is a lupus-like autoimmune disorder following a viral infection, and Yilmaz *et al*. suggested that KFD and systemic lupus erythematosus (SLE) have in common a hyperimmune reaction, which later is expressed as two different manifestations: one compromising lymph nodes (KFD), and the other manifesting as SLE.

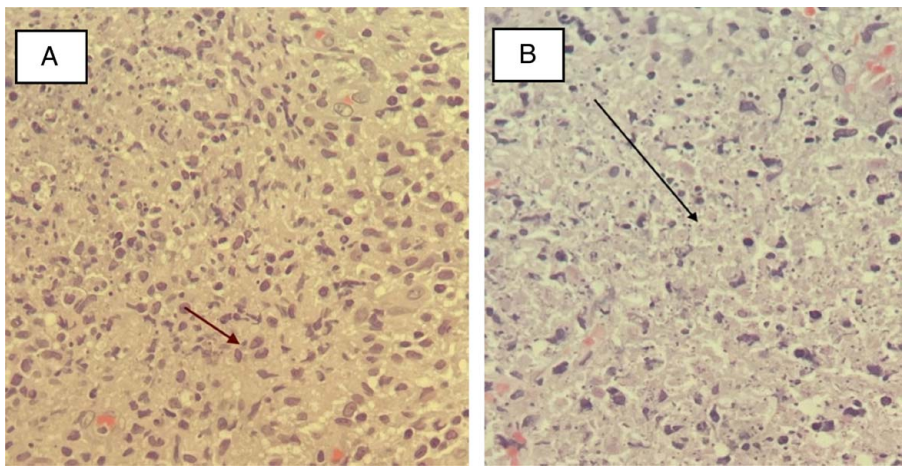

Figure 1. (A) Hematoxylin and eosin 40 × : histiocytic debris; some histiocytes have crescentic nuclei (arrow). (B) Hematoxylin and eosin 20 × : area of necrosis with karyorrhectic debris is present.

Table 1

Diagnostic data

Test	Reference range	Value	Unit
IgA	48–179	26.8	mg/dl
IgG	670–1530	522	mg/dl
IgM	52–274	32.7	mg/dl
Lymphocytes	25–40	21.6	%
CD3 (mature T-cell)	60–85	90	%
CD4 (T helper)	36–63	30	%
CD8	15–40	52	%
CD4/CD8 (ratio)	1.5–3.3	0.58	%
CD20 (mature B-cell)	5–25	0	%
CD19 (pan B-cell)	5–25	0	%
LDH	100–260	446	U/l

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase.

Thus, diagnosing KFD can be challenging given the similarities between KFD-lymphadenopathy and other autoimmune-lymphadenopathies and that KFD is not a well-known entity among clinicians and pathologists[8,9].

APDS is a newly discovered primary immunodeficiency disease with features of autoimmune inflammation[3]. It is a genetic disease following an autosomal dominant pattern of inheritance. Depending on the gene involved, ADPS has two types: APDS 1, in which the *PIK3CD* gene encodes for p110δ catalytic subunit of phosphoinositide 3-kinase delta (PI3Kδ) is affected, and APDS 2, in which *PIK3R1* gene that encodes for p85a regulatory subunit of PI3Kδ is affected. PI3Ks have an important role downstream of various receptors, including T-cell receptors, B-cell receptors, different cytokine receptors, and Toll-like receptors. In other words, PI3Ks are involved in intracellular signaling, proliferation, trafficking, differentiation, and survival[7].

Since APDS involves both cellular and humoral immunity, its clinical manifestations are bound to be heterogeneous. These manifestations can range from infections and lymphoproliferation in young patients to asymptomatic adult patients. Patients most commonly show up with recurrent respiratory infections (typically caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*), which may lead to bronchiectasis, followed by otitis media and rhinosinusitis. Viral [by human papillomavirus (HPV), CMV, EBV], fungal, and parasitic infections have also been reported[1]. Other manifestations include hepatosplenomegaly, enteropathy, and local and systemic lymphoproliferative disorders. APDS patients are at increased risk of neoplastic transformations (especially hematologic malignancies)[4].

Our reported case has a typical presentation for APDS 2 with the exception of a low IgM level and negative CMV and EBV[1]. Table 2 summarizes the clinical manifestations of our patient compared with the literature. Lymphadenopathy is common in APDS patients and has a wide differential diagnosis; evaluation of lymphadenopathy in APDS patients is demanded since there is a vast difference in the management of each differential. The presence of worsening lymphadenopathy despite the treatment, especially if it is associated with night sweats and fever, should raise the suspicion of malignancy. Our case highlights the need to broaden the differential diagnosis to include KFD, in which histopathological examination is of utmost importance in distinguishing KFD from other causes of lymphadenopathy in APDS 2 patients. The work has been reported in line with the SCARE (Surgical CAse REport) criteria[10].

Table 2

The clinical presentation of our case compared with the literature[7]

Manifestations	APDS 2	Our patient
Recurrent respiratory infections	+	+
CMV	+	–
EBV	+	–
Parasitic and fungal infections		+
Gastrointestinal infections	–	–
Lymphadenopathy	+	+
Splenomegaly	+	+
Hepatomegaly	+	+
Dysmorphic face	+	+
Intellectual disability	+	+
Low IgG and IgA	+	+
Normal/elevated IgM	+	–
Low B-cell (CD20, CD19)	+	+
Increased T-cell (CD3, CD8)	+	+

APDS 2, activated phosphoinositide 3-kinase delta syndrome 2; CMV, cytomegalovirus; EBV, Epstein–Barr virus; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

Conclusion

This case report highlighted the unique association between two rare disorders and emphasized the importance of expanding the differential diagnosis of lymphadenopathy in APDS 2 to include KFD. Moreover, we show that the patients of APDS 2 may present with a low level of IgM.

Ethical approval

This study is exempt from ethical approval in our institution.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

The authors declare that writing and publishing this manuscript was not funded by any
organization.

Author contribution

M.A.S., K.J.A., M.R.M., and A.A.A.: writing the manuscript; F.M.A. and I.A.B.: imaging description; A.W.M.J.: reviewing and editing the manuscript.

Conflicts of interest disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Afnan W.M. Jobran.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Acknowledgments

None.

References

[1] Tangye SG, Al-Herz W, Bousfiha A, *et al*. Human Inborn Errors of Immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2022;42:1473–507.
[2] Pham MN, Cunningham-Rundles C. Evaluation of lymphoproliferative disease and increased risk of lymphoma in activated phosphoinositide 3 kinase delta syndrome: a case report with discussion. Front Pediatr 2018;6:402.
[3] Preite S, Gomez-Rodriguez J, Cannons JL, *et al*. T and B-cell signaling in activated PI3K delta syndrome: from immunodeficiency to autoimmunity. Immunol Rev 2019;291:154–73.
[4] Singh A, Joshi V, Jindal AK, *et al*. An updated review on activated PI3 kinase delta syndrome (APDS). Genes Dis 2020;7:67–74.
[5] Oh J, Garabedian E, Fuleihan R, *et al*. Clinical manifestations and outcomes of activated phosphoinositide 3-kinase δ syndrome from the USIDNET cohort. J Allergy Clin Immunol Pract 2021;9:4095–102.
[6] Lougaris V, Cancrini C, Rivalta B, *et al*. Activated phosphoinositide 3-kinase delta syndrome (APDS): an update. Pediatr Allergy Immunol 2022;33:69–72.
[7] Ewertowska M, Grześk E, Urbańczyk A, *et al*. Activated phosphoinositide 3-kinase delta syndrome 1 and 2 (APDS 1 and APDS 2): similarities and differences based on clinical presentation in two boys. Allergy Asthma Clin Immunol 2020;16:22.
[8] Perry AM, Choi SM. Kikuchi–Fujimoto disease: a review. Arch Pathol Lab Med 2018;142:1341–6.
[9] Lee CH, Cheng ST. Kikuchi–Fujimoto disease: a case report. Kaohsiung J Med Sci 2003;19:246–50.
[10] Agha RA, Franchi T, Sohrab C, *et al*. The CARE 2020 guideline: updating consensus surgical CAse REport (CARE) guidelines. Int J Surg 2020;84:226–303.