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Adult-onset activated PI3Kδ syndrome presenting with HLH-like hyperinflammation, autoimmunity, and thrombosis: an underrecognized inborn error of immunity

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Running Head: APDS mimicking HLH with autoimmune overlap

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Keywords: Hemophagocytic lymphohistiocytic syndrome; Activated PI3K delta syndrome; PIK3R1 gene; autoimmune; thrombosis

Key points

1. Young adults presenting with secondary HLH and autoimmune or thrombotic manifestations may harbor underrecognized inborn errors of immunity.
2. Germline diagnosis of APDS enabled targeted PI3Kδ inhibition with leniolisib and sustained clinical remission.

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AUTHORSHIP CONTRIBUTIONS

JHY and JHL designed the analysis; JHY and JHL acquired data and contributed to the writing and editing of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY

The data supporting the findings of this study are not publicly available due to participant privacy concerns but are available from the corresponding author, JHY, upon reasonable request and with approval from the Institutional Review Board of The Catholic University of Korea.

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Activated phosphoinositide 3-kinase δ syndrome (APDS) is a primary immunodeficiency caused by gain-of-function mutations in the PI3K signaling pathway, most commonly involving *PIK3CD* (APDS1) or *PIK3R1* (APDS2). This pathway plays a central role in lymphocyte activation, differentiation, and survival, and its dysregulation leads to a complex phenotype characterized by recurrent infections, lymphoproliferation, and immune dysregulation.[1-3] Although APDS is typically diagnosed in childhood, an increasing number of adult-onset or delayed-diagnosis cases have been reported, often presenting with atypical features that overlap with autoimmune or inflammatory disorders.[4] In particular, APDS has been associated with autoimmune cytopenias, including autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and immune complex–mediated phenomena.[5]

Recent clinical observations further suggest that inborn errors of immunity (IEI) are increasingly recognized in young adults presenting with atypical or treatment-refractory immune manifestations. An educational case presented at the 2025 American Society of Hematology (ASH) meeting described a young adult initially diagnosed with refractory ITP who was subsequently found to harbor a *PIK3CD* mutation after additional evaluation revealed splenomegaly and lymphadenopathy. These findings highlight an emerging paradigm in which monogenic immune dysregulation disorders may remain unrecognized into adulthood and initially masquerade as isolated hematologic or autoimmune diseases.[6]

In parallel, hyperinflammatory syndromes such as hemophagocytic lymphohistiocytosis (HLH) represent a clinical phenotype characterized by excessive immune activation rather than a single disease entity.[7, 8] Several primary immunodeficiencies, including APDS, may manifest with HLH-like features, especially in the setting of viral triggers such as Epstein–Barr virus (EBV).[9] However, distinguishing between primary HLH and immune dysregulation syndromes remains clinically challenging. Furthermore, emerging evidence suggests that immune dysregulation syndromes may also be associated with thrombo-inflammatory complications through mechanisms involving complement activation, endothelial dysfunction, and autoantibody production.[10] Nevertheless, thrombotic manifestations in APDS remain poorly characterized.

Here, we report a case of adult-onset APDS type 2 caused by a pathogenic *PIK3R1* mutation, presenting with secondary HLH fulfilling HLH-2004 criteria, systemic autoimmune features resembling

systemic lupus erythematosus (SLE), and APS–associated thrombotic complications. Importantly, the patient demonstrated sustained clinical remission following targeted PI3Kδ inhibition with leniolisib, highlighting the importance of precision diagnosis in complex immune dysregulation syndromes. This study was approved by the Institutional Review Board of The Catholic University of Korea (IRB No. KC26ZISI0322). The requirement for written informed consent was waived due to the retrospective nature of the case study involving only de-identified data and procedures that were conducted in accordance with the Declaration of Helsinki.

A previously healthy 20-year-old male presented with fever, cytopenia, and progressive anemia. Initial laboratory evaluation revealed hemoglobin 7.4 g/dL, platelet count 54 $\times 10^9$/L, elevated lactate dehydrogenase (2033 U/L), indirect hyperbilirubinemia, and undetectable haptoglobin, consistent with hemolysis. Direct antiglobulin testing was strongly positive for IgG, IgA, IgM, and complement components. Further evaluation demonstrated hypocomplementemia (C3 49 mg/dL, C4 2.6 mg/dL), elevated ferritin (963.7 ng/mL), and multiple autoantibodies including ANA, anti-Sm, and antiphospholipid antibodies. Imaging revealed splenomegaly with multiple splenic infarctions and partial splenic vein thrombosis, along with generalized lymphadenopathy.

The patient fulfilled 5 of 8 HLH-2004 criteria, including fever (peak 39.6°C), cytopenia involving two lineages (minimum hemoglobin 6.0 g/dL and platelet count 42 $\times 10^9$/L), splenomegaly (16.5 cm), ferritin elevation (peak 1320 ng/mL), and decreased NK-cell cytotoxicity (14.3%; institutional lower limit of normal, 26.8%) measured using a CFSE-labelled K562 cell cytotoxicity assay. Hypertriglyceridemia was absent (150 mg/dL), fibrinogen was elevated (>500 mg/dL), and bone marrow examination showed increased histiocytosis without definite hemophagocytosis. Soluble IL-2 receptor and CXCL9 were not clinically available at our institution at the time of presentation. Based on these findings, the patient was initially diagnosed and managed as secondary HLH with concurrent autoimmune hemolytic anemia.

The patient was initially managed with corticosteroids for clinically diagnosed secondary HLH and autoimmune hemolytic anemia, resulting in hematological improvement. However, persistent lymphoproliferation and recurrent respiratory infections were noted. Immunologic profiling revealed IgA deficiency (7 mg/dL), elevated IgM, decreased B-cell fraction, and reduced CD4+ T cells. Given the constellation of findings, an underlying inborn error of immunity was suspected. Genetic testing

identified a pathogenic heterozygous splice-site mutation in *PIK3R1* (c.1425+1G>A), confirming APDS type 2. Prior to targeted therapy, the patient continued to exhibit recurrent infections and persistent splenomegaly. Leniolisib was initiated through an expanded access program, resulting in marked clinical improvement, normalization of hematologic parameters, and resolution of lymphadenopathy. The patient currently remains in sustained remission. Complement levels, which were markedly decreased at presentation (C3 49 mg/dL and C4 2.6 mg/dL), partially recovered after initial immunosuppressive treatment and remained stable during long-term follow-up (C3 60–75 mg/dL and C4 8.5–10.5 mg/dL). After initiation of leniolisib, complement levels showed further improvement, with recent C3 values of 81–85 mg/dL and C4 values of 11.5–12.5 mg/dL.

Lupus anticoagulant, anticardiolipin IgG, and anti-β2-glycoprotein I antibodies were all positive at presentation and remained persistently positive during follow-up for more than 1 year. Given the presence of splenic infarctions and partial splenic vein thrombosis, warfarin anticoagulation was initiated at diagnosis and has been continued. Follow-up abdominal CT demonstrated regression of the splenic vein thrombus and improvement of splenic abnormalities.

This case illustrates several important and clinically relevant aspects of APDS that extend beyond its classical presentation. Notably, compared with an educational case of APDS initially presenting as refractory ITP reported at the 2025 ASH Annual Meeting,[6] our patient exhibited a substantially broader phenotype encompassing HLH-like hyperinflammation, multisystem autoimmunity, and antiphospholipid antibody-associated thrombotic complications, further expanding the spectrum of adult APDS manifestations.

First, this case highlights that APDS can be present as secondary HLH in adulthood. Although the ferritin elevation was modest compared with that observed in fulminant HLH, the patient fulfilled 5 HLH-2004 diagnostic criteria, including fever, bicytopenia, splenomegaly, ferritin elevation, and impaired NK-cell cytotoxicity. In addition, active EBV infection was documented by positive EBV VCA-IgM and EA-DR IgM serologies together with detectable EBV viremia, providing a plausible inflammatory trigger. While contemporary adult HLH diagnostic frameworks remain heterogeneous and the clinical significance of individual criteria continues to be debated,[7, 8] this case illustrates how clinically diagnosed secondary HLH may represent the initial manifestation of an underlying inborn error of immunity rather than an isolated acquired inflammatory disorder. In APDS, constitutive

activation of the PI3Kδ pathway leads to impaired immune regulation, including defective cytotoxic function and chronic immune activation.[4, 5] These abnormalities may predispose patients to exaggerated inflammatory responses, especially in the context of viral infections such as EBV.[9] Therefore, the subsequent identification of APDS suggests that the HLH episode reflected immune dysregulation driven by an underlying monogenic disorder, with EBV acting as a triggering event. This case supports the concept that HLH should be regarded as an inflammatory syndrome requiring etiologic investigation rather than a final diagnosis, particularly in young adults presenting with recurrent infections, lymphoproliferation, or autoimmune manifestations. Together with prior reports summarized in Table 2, our case supports the concept that HLH in adolescents and adults may represent a shared inflammatory endpoint of diverse IEIs rather than a purely acquired disorder.

Second, this case demonstrates a striking overlap between APDS and systemic autoimmune disease. The patient showed strong serologic evidence of autoimmunity, including ANA, anti-Sm antibodies, hypocomplementemia, and immune complex–mediated hemolysis. These findings closely resemble systemic lupus erythematosus (SLE), raising important diagnostic challenges. Autoimmune cytopenias are well-recognized complications of APDS, occurring in up to one-third of patients [5]. The underlying mechanism is thought to involve dysregulated B-cell maturation, impaired tolerance, and expansion of autoreactive lymphocyte populations.[2] In particular, the combination of IgA deficiency, elevated IgM, and reduced B-cell fraction observed in this case is consistent with the immunologic phenotype of APDS.[3] Importantly, this case underscores that autoimmune manifestations in APDS may be severe and multisystemic, mimicking classical rheumatologic diseases. Failure to recognize the underlying immunodeficiency may lead to suboptimal management focused solely on immunosuppression rather than targeted therapy.

Third, this case reveals a unique thrombo-inflammatory phenotype, including splenic infarctions and splenic vein thrombosis representing APS-associated thrombotic manifestations. While thrombotic complications are not traditionally emphasized in APDS, emerging evidence suggests that immune dysregulation and chronic inflammation can promote a prothrombotic state.[10] Several mechanisms may contribute to thrombosis in this context: (1) autoantibody-mediated endothelial activation, (2) complement activation and consumption, (3) systemic inflammation, and (4) direct effects of PI3K pathway dysregulation on immune and vascular cells. The coexistence of

antiphospholipid antibodies in this patient suggests an overlap with APS-like pathology, further supporting the concept of a unified “thrombo-inflammatory” spectrum in immune dysregulation disorders. To our knowledge, the combination of APDS with both autoimmune and APS–associated thrombotic features has been rarely described, representing a potentially underrecognized phenotype.

Finally, this case highlights the critical role of genetic testing in patients with atypical immune dysregulation. This case also illustrates when adult hematologists should suspect an underlying IEI in patients presenting with secondary HLH. Practical red flags include young age, recurrent or unusual infections, persistent lymphadenopathy or splenomegaly, autoimmune cytopenias, dysgammaglobulinemia, EBV susceptibility, recurrent inflammatory episodes, family history, or treatment-refractory immune manifestations. In addition, hypomorphic variants in classical HLH-associated genes or pathogenic variants in immune-dysregulation genes may present beyond childhood and mimic acquired secondary HLH. Therefore, selected adults with atypical or unexplained HLH should undergo germline genetic evaluation, as molecular diagnosis may directly guide therapy. Identification of a pathogenic *PIK3R1* splice-site mutation confirmed the diagnosis of APDS type 2, allowing for a shift from nonspecific immunosuppression to targeted therapy. Leniolisib, a selective PI3Kδ inhibitor, directly targets the underlying molecular defect in APDS and has demonstrated efficacy in reducing lymphoproliferation and improving immune function.[11] In our patient, initiation of leniolisib led to sustained clinical remission, normalization of hematologic parameters, and resolution of lymphadenopathy. This outcome underscores the importance of recognizing APDS as a treatable condition when appropriately diagnosed. Early identification may prevent disease progression and reduce reliance on prolonged immunosuppressive therapy.

A limitation of this report is that serial reassessment of immunologic biomarkers, including DAT status, ANA, anti-Sm antibodies, and other serologic autoimmune markers, was not performed systematically following leniolisib initiation. Although antiphospholipid antibodies had remained persistently positive for more than 1 year before leniolisib treatment, whether PI3Kδ inhibition can attenuate or eliminate these antibodies over time remains unknown and will require continued longitudinal monitoring. Therefore, the impact of PI3Kδ inhibition on serologic autoimmune markers could not be formally evaluated. Nevertheless, complement levels demonstrated sustained

improvement over time, and the marked clinical, hematologic, infectious, and radiologic responses observed after leniolisib support APDS as the principal driver of the patient's immune dysregulation.

In summary, this case expands the clinical spectrum of APDS by demonstrating that it may present in adulthood as a complex syndrome and also emphasizes the need for heightened clinical suspicion for inborn errors of immunity and early incorporation of genetic evaluation in young adults presenting with unexplained immune dysregulation, particularly in the presence of lymphoproliferation, recurrent infections, autoimmune cytopenias, or hyperinflammatory manifestations.

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Table 1. Diagnostic red flags and immunologic features leading to identification of adult-on set APDS

Domain	Findings
Demographics	21-year-old male
Presenting symptoms	Fever, fatigue, dyspnea, cytopenia
HLH features (sIL-2R was unavailable)	Fever 39.6℃, Cytopenia (Minimum Hb 6.0 g/dL, platelet 42×10⁹/L), Ferritin 1320 ng/mL; splenomegaly (16.5 cm), Bone marrow histiocytosis (no hemophagocytosis), decreased NK cytotoxicity (14.3% by CFSE-labelling K562 cell cytotoxicity)
Trigger	EBV infection EBV (EA-DR) IgG Positive(1.93) EBV (EBNA) IgG Positive(1.33) EBV (VCA) IgG Positive(2.60) EBV (EA-DR) IgM Positive(2.04) EBV (VCA) IgM Positive(2.28) Max. RQ-PCR 3,564(3.55Log)(2,067 IU/ml)
Cytopenia / AIHA	Hemoglobin 7.4 g/dL; platelet 54×10⁹/L LDH 2033 U/L Haptoglobin <20 mg/dL; DAT pan-positive
Autoimmune findings	ANA 1:160 (speckled); anti-Sm positive Hypocomplementemia (C3 49 mg/dL, C4 2.6 mg/dL)
APS-associated findings	Anti-β2GP1 positive; anticardiolipin IgG positive; lupus anticoa gulant positive
Thrombo-inflammatory findings	Multiple splenic infarctions; splenic vein thrombosis
Lymphoproliferative findings	Splenomegaly; generalized lymphadenopathy
Immunologic profile	IgA deficiency (7 mg/dL); elevated IgM (377 mg/dL); reduced B-cell fraction (CD19 2.8%); CD4 reduction
Infectious history	Recurrent respiratory infections; EBV serologic activation
Initial diagnostic considerations	HLH; systemic lupus erythematosus-like syndrome; APS-like s yndrome
Genetic findings	Heterozygous pathogenic splice-site mutation in PIK3R1 (c.142 5+1G>A), confirming APDS type 2
Targeted therapy and outcome	Leniolisib under expanded access program → sustained clinical remission

Abbreviations: AIHA, autoimmune hemolytic anemia; ANA, Anti-nuclear antibody; APS, antiphospholipid-antibody syndrome; DAT, direct antiglobulin test; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis.

Table 2. Representative inborn errors of immunity presenting as HLH or HLH-like inflammatory syndromes in adolescents and adults

Syndrome / IEI	Gene	Representative report(s)	Typical age	HLH / HLH-like manifestations	Trigger(s)	Associated immune dysregulation	Precision therapy
Activated PI3Kδ syndrome (APDS1/2)	PIK3CD PIK3R1	Zhou et al., J Clin Immunol 2021[1]	Adolescence Young adult	Secondary HLH, hyperferritinemia, EBV-associated HLH	EBV infection Viral infection	Lymphadenopathy, splenomegaly, autoimmune cytopenias, hypogammaglobulinemia	PI3Kδ inhibitor (leniolisib), Sirolimus
CTLA4 haploinsufficiency	CTLA4	Kuehn et al., Science 2014 [2] Schubert et al., Nat Med 2014[3] Schwab et al., JACI 2018[4]	Childhood Adulthood	HLH-like inflammation, severe immune dysregulation	Infection Spontaneous	Autoimmune cytopenias, enteropathy, lymphoproliferation	Abatacept, HSCT
LRBA deficiency	LRBA	Ren et al., Exp Hematol Oncol 2021[5]	Adulthood	HLH fulfilling HLH-2004 criteria	Infection	CVID-like phenotype, recurrent infections, hypogammaglobulinemia	Abatacept, HSCT
STAT3 gain-of-function	STAT3	Milner et al., Blood 2015[6] Haapaniemi et al., NEJM 2015[7]	Childhood Adulthood	Recurrent HLH-like inflammation, cytopenias	Viral infection Immune activation	Autoimmunity, endocrinopathy, lymphoproliferation,	JAK inhibition, HSCT
XIAP (XLP2) deficiency	XIAP (BIRC4)	Speckmann et al., J Clin Immunol 2013[8] Marsh et al. Blood 2013[9]	Childhood Adulthood	Recurrent HLH, EBV-positive or -negative HLH	EBV and non-infectious triggers	IBD-like disease, splenomegaly, cytopenias	HLH therapy, HSCT
GATA2 deficiency	GATA2	Rukerd et al., BMC Infect Dis 2024[10]	Adolescence Adulthood	HLH associated with infection	EBV, CMV, Mycobacteria, Fungal infections	Monocytopenia, NK-cell deficiency, MDS predisposition	Infection control, HSCT
Hypomorphic HLH familial genes	PRF1 UNC13D, STX11, STXBP2	Zhang et al. Blood 2011[11]	Adolescence Adulthood	Delayed-onset familial HLH, recurrent HLH episodes	EBV, CMV, other infections	Defective cytotoxicity without classic pediatric presentation	HLH therapy, HSCT
DADA2	ADA2 (CECR1)	Zhou et al., NEJM 2014[12] Navon Elkan et al., NEJM 2014[13]	Childhood Adulthood	Secondary HLH, Systemic inflammation	Infection, Vasculitic flare	Vasculitis, cytopenias, thrombo-inflammatory manifestations	TNF inhibition, HSCT
CD27/CD70 deficiency	CD27 CD70	van Montfrans et al. JACI 2012[14] Abolhassani et al., J Exp Med 2017[15]	Childhood Adulthood	EBV-associated HLH and lymphoproliferation	EBV infection	Hypogammaglobulinemia, lymphoma predisposition	Rituximab, HSCT

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; IEI, inborn error of immunity; HSCT, hematopoietic stem cell transplantation; MAS, macrophage activation syndrome.

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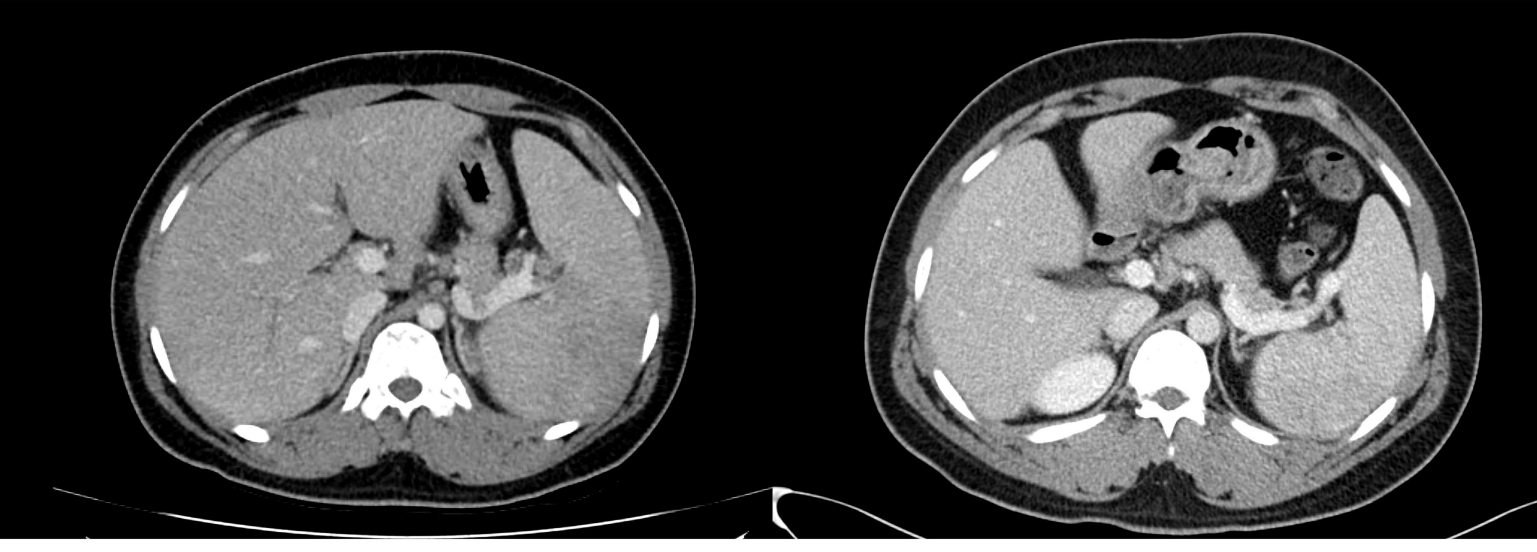
Figure legend

Figure 1. Radiologic findings before and after treatment. Contrast-enhanced abdominal CT at diagnosis demonstrated splenomegaly with splenic vein thrombosis and associated lymphoproliferative findings. Follow-up CT imaging obtained 24 months after treatment showed decreased splenic size and improvement of splenic vein abnormalities, accompanied by partial regression of lymphoproliferative features.



PRE-TREATMENT FINDINGS

- ✓ Marked splenomegaly (16.5 cm)
- ✓ Partial splenic vein thrombosis
- ✓ Splenic infarction
- ✓ Lymphoproliferative features

POST-TREATMENT FINDINGS

- ✓ Decreased liver and spleen size
- ✓ Resolution of splenic vein thrombus
- ✓ Decreased extent of splenic infarction
- ✓ Reduced lymphoproliferative features