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The Misleading Normal in an Unusual Case of Wiskott–Aldrich Syndrome: A Case Report with Review of Literature

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Abstract

Wiskott–Aldrich syndrome (WAS) is a rare X-linked disorder characterized by thrombocytopenia, eczema, and immunodeficiency. Mutations in the *WAS* gene disrupt hematopoietic cell actin cytoskeletal reorganization, often leading to classic small platelets, although variants exist. We present the case of a 2-year-old boy initially misdiagnosed with immune thrombocytopenia (ITP) and concurrent cytomegalovirus (CMV) infection, despite normal platelet volume. His clinical history included persistent thrombocytopenia, fever, hepatosplenomegaly, and recurrent bleeding episodes. The patient was initially treated for presumed ITP and meningitis without improvement in platelet count following standard therapies, including intravenous immunoglobulin (IVIG). Multiple hospitalizations and treatments failed to resolve his symptoms. Genetic testing later identified a hemizygous nonsense mutation in exon 1 of the *WAS* gene, confirming the diagnosis of WAS. The patient's treatment included several rounds of IVIG and antibiotics, with the consideration of alternative diagnoses such as autoimmune lymphoproliferative syndrome. After the genetic diagnosis, the patient was referred for hematopoietic stem cell transplantation. The delayed diagnosis of WAS due to initial misdiagnosis resulted in delayed appropriate interventions. Early genetic testing might have expedited the correct diagnosis and management. This case highlights the need to consider WAS in male infants with persistent thrombocytopenia, irrespective of platelet size, especially when standard treatments fail. Early genetic testing is crucial for timely diagnosis and appropriate management, potentially improving patient outcomes.

Keywords

- Wiskott–Aldrich syndrome
- immune thrombocytopenia
- normal platelet volume
- CMV infection
- hematology

Introduction

Wiskott–Aldrich syndrome (WAS) is an uncommon X-linked condition resulting from mutations in the *WAS* gene.[1] This condition affects 1 to 10 male infants per million.[2] *WAS* mutations lead to a spectrum of disorders, ranging from the severe, classic form to milder variants. The classic form of WAS is defined by a triad of symptoms: thrombocytopenia, recurrent infections, and eczema, accompanied by a heightened risk of autoimmune disorders and cancer. A milder variant, X-linked thrombocytopenia (XLT), presents with thrombocytopenia and little or no eczema/immunodeficiency.[1,2] Hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for WAS.[3,4]

The *WAS* gene encodes the Wiskott–Aldrich syndrome protein (WASp), a 502-amino acid protein crucial for actin

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cytoskeletal reorganization. WASp is broadly expressed in hematopoietic cells and plays a crucial role in essential cellular functions, including cell migration and the formation of immunological synapses.[5,6]

The primary diagnostic criteria for WAS include congenital thrombocytopenia and abnormally small platelets (mean platelet volume [MPV] of 5.0 fL in most cases).[7] In this report, we present a rare case of a 2-year-old boy with WAS who had normal platelet size and no history of eczema, initially diagnosed with immune thrombocytopenia (ITP) and concurrent cytomegalovirus (CMV) infection.[8]

Case Description

A 2-year-old boy was referred to our clinic for evaluation due to ongoing thrombocytopenia. He exhibited symptoms such as fever, loose stools, abnormal body movements, and bleeding from the ear. He was born weighing 2.75 kg through a normal vaginal delivery and was discharged in good health. His older sibling is healthy, and there is no family history of similar conditions.

At age 10 days, the child was hospitalized for suspected sepsis/meningitis. Despite a 21-day course of antibiotics and antifungals, his condition remained unstable, and his platelet count did not improve either. ►**Table 1** summarizes the complete blood count trends of the patient. Normal skull and head studies were performed, leading to a tentative diagnosis of ITP. Maternal blood work was normal. Initial treatment with intravenous immunoglobulin (IVIG) failed to improve platelet counts, and the child was discharged after stabilization.

At 2.5 months, he was readmitted with fever, rapid breathing, and blood in his stools. He presented with pallor and hepatosplenomegaly. Direct Coombs test (DCT) was positive, though the peripheral smear showed no signs of hemolysis. A TORCH screen (for Toxoplasma gondii, other viruses, rubella, cytomegalovirus, and herpes simplex) indicated CMV IgG positivity (0.92). Urine polymerase chain reaction (PCR) for CMV and reverse transcription PCR (RT-PCR) for parvovirus were also positive, with viral loads of 2.5×10^7 and 4.8×10^9 copies/mL, respectively. Treatment with valganciclovir improved his platelet count. At 6 months, he was readmitted with severe pallor and petechial rashes and was treated with a short course of oral prednisolone $(2 + 2)$ without improvement.

An immunodeficiency workup showed elevated levels of IgG (2,957 mg/dL), IgA (468 mg/dL), and slightly elevated IgE (220 IU/mL). The T-cell, B-cell, and NK-cell distributions, as well as neutrophil function, were within normal limits, and repeat RT-PCR for parvovirus was negative. Bone marrow examination revealed a mild preponderance of pronormoblasts, some giant myelocytes and metamyelocytes, an adequate number of megakaryocytes, and a relatively increased plasma cell count.

At 2 years, the child presented with fever, loose stools, abnormal body movements, and ear bleeding. He was pale with petechial rashes across his body. Hepatosplenomegaly

Table 1 Complete blood count and immunoglobulin E trends of the patient

Age	10 d	2.5 mo			6 mo			2 y					
Hemoglobin (g/dL)	10.2	5.2	6.8	8.4	4.8	5.7	7.5	3.2	4.8	5.9	6.8	5.4	
Total leukocyte count	5,600	4,800	4,638	4,587	3,268	2,890	2,356	1,265	1,178	980	1,080	880	
Absolute lymphocyte count	1,400	1,200	1,365	1,500	980	1000	965	450	380	300	346	290	
Platelet count	30,000	25,000	32,000	56,000	15,000	23,000	40,000	7,000	14,000	22,000	28,000	18,000	
Mean platelet volume (fL)	7.6	7.4	7.2	7.3	7.9	7.8	7.4	7.4	8	7.8	7.6	7.4	
Immunoglobulin E (IU/mL)		Normal			Normal			220					

was noted (on the liver 4 cm below the right costal margin and on the spleen 3 cm below the left costal margin). A noncontrast CT (NCCT) scan of the head showed intraparenchymal hemorrhages (bilateral frontal and left temporal lobes) with surrounding edema and cerebral atrophy. Blood tests indicated anemia, leukopenia, and thrombocytopenia. The peripheral smear showed normocytic normochromic anemia with neutropenia and thrombocytopenia, without atypical cells. Despite continuing antibiotics, antiepileptics, and valganciclovir, the pancytopenia persisted.

A bone marrow examination was unremarkable, and DCT was negative. Immunoglobulin profiles showed elevated IgG and IgA levels (1,310 and 263 mg/dL, respectively).

MPV was consistently within normal limits (6.3–9.3 μm^3). A trial of IVIG failed to improve platelet counts. The possibility of autoimmune lymphoproliferative syndrome (ALPS) was considered, and flow cytometry revealed that double-negative T cells (DNT) comprised 40% of CD3 cells. An ALPS workup showed normal levels of vitamin B12, folate, and plasma soluble FAS ligand, with no history of nonmalignant/noninfectious lymphoproliferation. A temporary rise in platelet count was observed following an injection of methylprednisolone. We planned to consider mycophenolate mofetil and conduct a clinical exome analysis to rule out congenital disorders due to the refractory nature of his condition. The child stabilized hemodynamically and was discharged with follow-up recommendations, pending MRI, and clinical exome results.

Unfortunately, he missed the scheduled follow-up, and we later learned from his mother that he had passed away at home. The cause of death remains unknown, and no autopsy was performed. ►**Table 2** outlines the patient's clinical profile.

Genetic testing revealed a hemizygous nonsense mutation in exon 1 of the *WAS* gene (chrX:g.48683890C > T; Depth: 87x), leading to a premature stop codon and truncated protein at codon 13 (p.Arg13Ter; ENST00000376701.5). Testing of the mother and sibling was not performed.

Discussion

Children with WAS often face initial misdiagnosis, frequently being labeled as having ITP. This misidentification not only results in ineffective treatments but also causes delays in receiving crucial, potentially lifesaving interventions. Notably, WAS is eventually identified in 7% of patients who are initially misdiagnosed with ITP. In this case, the infant was diagnosed with thrombocytopenia, which was initially diagnosed as sepsis, and was treated with the necessary antibiotics and antifungals, but thrombocytopenia did not improve. Subsequent consideration of neonatal ITP led to IVIG administration, but platelet counts did not show significant rise. A TORCH profile at the previous hospital revealed positive CMV IgG, high CMV IgG avidity (0.92), and a urine CMV PCR count of 2.5×10^7 copies/mL.

Despite receiving valganciclovir and IVIG multiple times during hospitalizations, the patient's platelet count showed limited improvement.

The condition of WAS was not initially considered because of the atypical symptoms. The patient had normal platelet size despite having thrombocytopenia, which differs from the smaller platelets usually seen in WAS and helps distinguish it from ITP.[9] In WAS cases, the MPV typically falls below the standard lower limit of 7.1 fL, often ranging between 3.8 and 5.0 fL.[10] Instances of WAS patients with normal platelet sizes are rare. Patel et al describe the example of a youngster who had thrombocytopenia but normal platelet size in a previously published case report. Flow cytometry analysis of WASp expression revealed that he had lower expression than a healthy control. A c.862A > T mutation in exon 9 of the *WAS* gene was discovered by molecular analysis.[3] Mantadakis et al documented three examples in a more recent case report: a set of twins with a c.854_855insA mutation in exon 9 and a patient with a c.743 743 + 1delAG mutation in exon 7.[11]

A hemizygous nonsense variant in exon 1 of the WAS gene (chrX:g.48683890C > T; Depth: 87x) was discovered in this case, resulting in a stop codon and premature truncation of the protein at codon 13 (p.Arg13Ter; ENST 00000376701.5).

The clinical presentation of WAS is highly variable, and some patients have been found to have a normal MPV. The clinical features of WAS, including platelet size, are influenced by specific mutations in the WAS gene.[12]

Additionally, despite eczema being a common sign of WAS, this patient did not exhibit it. Cases of WAS without eczema have been reported previously.[13] In the initial 12 months, over half of WAS patients usually present with eczema, akin to atopic dermatitis, often complicated by infections and occasional bleeding into the lesions.[14]

Finally, our patient concurrently experienced CMV infection and thrombocytopenia. CMV, along with ITP, is a leading cause of thrombocytopenia. Consequently, his thrombocytopenia was attributed to the CMV infection, leading to a prior diagnosis of ITP associated with CMV infection in other health care settings.

Patients with WAS (without HSCT) have a dismally poor survival rate.[15] In previous studies, individuals with WAS had a median survival period of just 20 years. Contrastingly, patients with XLT have demonstrated a notably improved overall survival rate.[16] HSCT is the only available treatment for WAS currently. Younger WAS patients exhibit improved HSCT outcomes. Over time, HSCT outcomes have enhanced across all donor types. With human leukocyte antigen (HLA) identical sibling donors, an established overall survival rate exceeds 80%. In the absence of HLA-identical siblings, matched unrelated donor HSCT has proven effective. However, haplo-identical HSCT yields less favorable outcomes, with prominent studies reporting around a 50% survival rate.[15] New medicines are being developed, and gene therapy studies and trials are now underway.[17]

Supportive treatment serves as the cornerstone for patients awaiting HSCT, and particularly for those for whom HSCT is not a viable option. Supportive care entails paying great attention to infection prevention and treatment.

Table 2 Case summary

Category	Description
Patient details	A 2-year-old boy
Initial presentation	Persistent thrombocytopenia, fever, loose stools, abnormal body movements, and bleeding from the ear
Birth details	Normal vaginal delivery, birth weight of 2.75 kg, discharged in good condition
Family history	Older sibling well, no family history of similar condition
Age 10 d	Hospitalized with meningitis, treated with 21-d antibiotics and antifungals; diagnosed with immune thrombocytopenia (ITP); maternal CBC normal; discharged after stabilization
Age 2.5 mo	Readmitted with fever, fast breathing, blood in stools; pallor and hepatosplenomegaly; positive DCT; CMV IgG positive, urine PCR for CMV (2.5×10^7 copies/mL), and RT-PCR for parvovirus (4.8×10^9 copies/mL); treated with valganciclovir, improved platelet count
Age 6 mo	Severe pallor, petechial rashes; treated with oral prednisolone, no response; immunodeficiency workup revealed high IgG (2957) and IgA (468); T cell, B cell, NK cell distribution, and neutrophil function normal; bone marrow showed mild preponderance of pronormoblasts, adequate megakaryocytes, increased plasma cells
Age 2 y	Fever, loose stools, abnormal body movements, bleeding from the ear; pallor, petechial rashes, hepatosplenomegaly; NCCT head scan showed intraparenchymal hemorrhages, cerebral atrophy; anemia, leukopenia, thrombocytopenia; peripheral smear: normocytic normochromic anemia, neutropenia, thrombocytopenia; treated with antibiotics and antiepileptics; valganciclovir continued, pancytopenia persisted; bone marrow insignificant, DCT negative; IgG and IgA elevated (1,310 mg/dL, 263 mg/dL); mean platelet volume normal; IVIG trial ineffective
Further investigation	Suspected autoimmune lymphoproliferative syndrome (ALPS); flow cytometry showed 40% double-negative T cells (DNT); ALPS workup normal; temporary rise in platelet counts with methylprednisolone
Outcome	Considered mycophenolate mofetil and clinical exome; child hemodynamically stable at discharge; missed follow-up; child passed away at home, cause unknown, no autopsy performed
Genetic Findings	Hemizygous nonsense variation in exon 1 of the *WAS* gene (chrX .48683890C > T) detected, resulting in stop codon and premature protein truncation at codon 13 (p.Arg13Ter; ENST00000376701.5); mother and sibling not tested
	Intraparenchymal hemorrhages, cerebral atrophy; anemia, leukopenia, thrombocytopenia; peripheral smear: normocytic normochromic anemia, neutropenia, thrombocytopenia; treated with antibiotics and antiepileptics; valganciclovir continued, pancytopenia persisted; bone marrow insignificant, DCT negative; IgG and IgA elevated (1,310 mg/dL, 263 mg/dL); mean platelet volume normal; IVIG trial ineffective
Further investigation	Suspected ALPS; flow cytometry showed 40% DNT; ALPS workup normal; temporary rise in platelet counts with methylprednisolone
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Abbreviations: CBC, complete blood count; CMV, cytomegalovirus; DCT, direct Coombs test; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; NCCT, noncontrast computed tomography; RT-PCR, reverse transcription polymerase chain reaction; WAS, Wiskott–Aldrich syndrome.

The strength of this report lies in its emphasis on the importance of considering WAS in cases of persistent thrombocytopenia, even when platelet size is normal, and the presence of concurrent infections like CMV further complicates the diagnosis.

However, this case also has limitations, including the delayed diagnosis due to the misattribution of symptoms to ITP and CMV infection, as well as the lack of access to early genetic testing in resource-limited settings. These factors contributed to the inability to initiate potentially curative treatments promptly.

Future perspectives should focus on increasing awareness and access to genetic testing for early diagnosis of WAS, particularly in atypical presentations. Additionally, the development of new treatments, including gene therapy, holds promise for improving outcomes in WAS patients.

Conclusion

This case highlights the diagnostic challenges associated with WAS, particularly when classic symptoms such as small platelets and eczema are absent.

In conclusion, persistent thrombocytopenia in male infants, especially in poor response to standard treatments, should prompt consideration of WAS. Early genetic testing is crucial for timely diagnosis and the initiation of appropriate management strategies, such as HSCT, which can be lifesaving and ensure improved prognosis.

This case points toward the necessity for heightened clinical vigilance and the integration of genetic testing in the diagnostic process, particularly in complex cases with atypical presentations.

Patient Consent

Informed consent was obtained from all participants involved in the study.

Authors' Contributions

All the authors were involved in patient management, planning of the study, and writing of the manuscript, and the final manuscript was approved by all the authors.

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None.

Conflict of Interest

None declared

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