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Case Report

Clinical Manifestations of Wiskott-Aldrich Syndrome in an Iranian Patient

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Abstract

Wiskott-Aldrich Syndrome (WAS) is an immunodeficiency disorder resulting from genetic mutations in the WAS protein (*WASP*) gene in the X chromosome, characterized by thrombocytopenia, eczema, and infections. This case report focused on a 12-year-old Iranian male with WAS with a history of Crohn's disease, meningitis, and bilateral hernia. His WAS was diagnosed at age six with a hemizygous c.777+1 G>A mutation in the *WASP* gene. The patient was referred to our clinic with symptoms including fever, abdominal pain, thrombocytopenia, and elevated ESR. Clinical Imaging revealed a significant lung nodule align bronchiectasis, mild ascites, bilateral epididymitis, and lymphadenopathy. Nephrotic syndrome with proteinuria and low levels of albumin have been observed. After six months of receiving intravenous immunoglobulin (IVIG) therapy in addition to antibiotics and antivirals, the patient suffered from arthritis, edema, and fever. Our WAS patient presented the late comorbidity of renal involvement, which highlights the monitoring of this patient, such as those involved in chronic infections. Therefore, a precise treatment approach is needed to manage either the primary immunodeficiency or the late-discovered diseases.

Keywords: Wiskott-Aldrich Syndrome; X-Linked Recessive Immunodeficiency; Primary Immunodeficiency; Thrombocytopenia

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Introduction

Wiskott-Aldrich Syndrome (WAS) is an X-linked immunodeficiency disorder characterized by the Wiskott-Aldrich Syndrome Protein (WASP), encoded by the *WAS* gene with 12 exons on the X chromosome (1, 2). WASP engages in cytoskeletal reorganization and regulates signaling pathways; WASP is expressed in hematopoietic cells, including T cells, B cells, natural killer cells (NKs), and myeloid cell lineages (3). Mutations in the WASP protein may affect platelet production and innate and adaptive immunity (4). These defects lead to increased apoptosis, impaired activation, and diminished cellular re-

sponses to antigens in T lymphocytes and exhibit reduced proliferation and antibody production in B lymphocytes; however, B cells presented less dependence on WASp than T cells (5-7). NKs exhibit impaired cytotoxic function due to defective actin reorganization at the immunological synapse, which is crucial for effective target cell killing (8). Various functional deficiencies demonstrate the significance of WASP protein dysfunction for preserving immune regulation and the variety of immune responses (9). For example, while the classic WAS phenotype typically involves complete loss of WASP function, partial mutations may cause milder forms like X-linked thrombocytopenia (XLT) or X-linked neutropenia (XLN) (10). There is a complicated and diverse range of expressions in the relationship between certain mutations in the *WASP* gene and clinical ramifications. Several studies focus on finding novel mutations in the *WASP* gene among WAS patients that cause clinical presentations such as severe immune dysfunction or affect platelet counts and help to clarify the intricate link between genotype and phenotype (11, 12). Mutations may predispose individuals to severe autoimmune disorders or malignancies, suggesting comprehensive genetic or molecular testing could provide valuable insights into these risks (13, 14). *WASP* gene mutations can cause renal diseases (15), while studies demonstrated autoimmune manifestations in XLT patients include hemolytic anemia, vasculitis, arthritis, neutropenia, inflammatory bowel disease, and IgA nephropathy (16, 17). These studies indicate despite genetic and molecular advancements WAS still presents significant challenges. Research must continue since therapeutic approaches must be customized for each patient's severity and comorbidities.

Case Presentation

Here we present a 12-year-old male patient with no family record of immunodeficiency diseases in his non-consanguineous parents. In addition, his mother had records of multiple sclerosis, his father had polio records, and he underwent strabismus surgery on his right eye in his early years. At 1.5 months of age, he was first taken to the hospital for hypertrophic pyloric stenosis, and before surgery, the laboratory tests revealed a low level of platelets and immune thrombocytopenia diagnosed (ITP). He managed with standard treatments for ITP. However, later he experienced infections, meningitis, and Crohn's disease. He was first admitted to our hospital with Wiskott-Aldrich syndrome at age 5 following exhibiting symptoms of mild eczema and complication of epistaxis with thrombocytopenia. Also, the initial laboratory tests indicated a low level of platelet count, which prompted further genetic testing.

A hemizygous mutation of the WAS gene, as c.777+1 G>A in the exon 8, was discovered through gene sequencing of the patient's DNA. Mutation analysis confirmed a pathogenic variant in the WAS gene, establishing the diagnosis of Wiskott-Aldrich Syndrome. Also, the patient's symptoms, particularly the eczema in **Figure 1**, are likely due to a mutation disrupting the normal function of the WASP. After diagnosis of WAS, the patient underwent supportive care to address any problems or related symptoms.

The previous examination reported After the hospitalizion at the age of eight due to the activation of characteristic symptoms of WAS, he has been receiving IVIG therapy regularly. Two years later, an IVIG dose of 25 grams was given regularly every three to four weeks. His general quality of life was enhanced by this medication, which dramatically decreased the frequency and severity of illnesses.

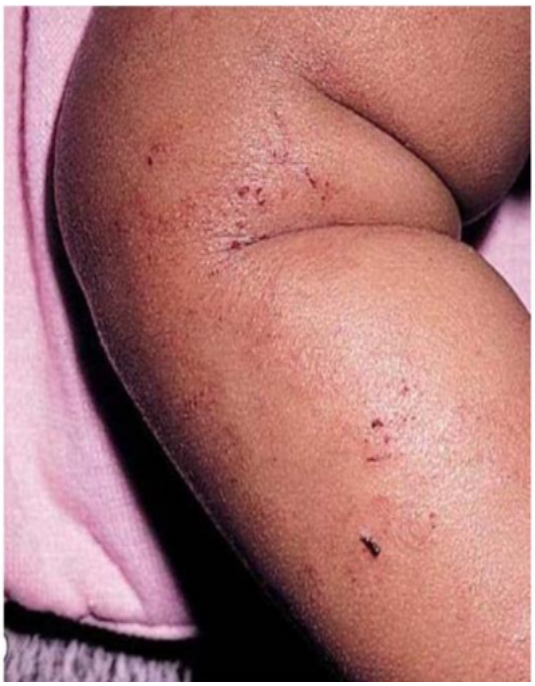

Figure 1. Clinical presentation of eczema on the patient's skin.

The patient complained of fever, vomiting, abdominal pain, thrombocytopenia, and epistaxis, the patient was referred to the hospital. The comprehensive examination includes blood tests, urine protein tracer, and bone marrow (BM) immunophenotyping were performed, and the results are summarized in **Table 1**. Results of blood tests were as follows: white blood cell (WBC) 8.93 × 10^3/ul, hemoglobin (HGB) 12.5 g/ul, platelet (PLT) 15 × 10^3/ ul, ESR 116 mm/hr, and also high levels of triglycerides (TG), cholesterol (Chol), and lactate dehydrogenase (LDH) detected as follows: TG 226 mg/dL, Chol 322 mg/dL, LDH 378 U/L. BM immunophenotyping revealed a precursor B-cell population (hematogones) comprising approximately 5.1% of the total cell count. The BM smear's morphology showed myeloid and erythroid series at different phases of development, with an about 4:1 myeloid-to-erythroid (M/E) ratio. Monocyte counts were somewhat elevated, and 12–14% of the lymphoid cells were varied in size. There were a few smudge cells, but there was no discernible rise in blasts. Additionally, megakaryocytes were found.

Table 1. The laboratory data of patient

Blood Tests					
Parameter	**Patient data**	**Normal range**	**Parameter**	**Patient data**	**Normal range**
WBC	8.93 10^3/ul	4.5-13.5x10^3/µL	INR	1.03	0.8 - 1.1
RBC	3.73 10^6/ul	4.0-5.5x 10^6/µL	IgG	650	700-1400
Hb	12.5 g/dL.	12.0 - 15.5 g/dL	C3	197 mg/dL	90-180
Plt	15 10^3/ul	150-400x10^3/µL	C4	23 mg/dL	10-40
PT	12.8	11.0 - 14.0 seconds	CH50	>90 U	60 - 140 U
PTT	32	30 - 45 seconds	EBV IgM	0.02	
TG	226	<150 mg/dL	Anti CMV IgM	0.03	
Chol	322	<200 mg/dL	HIV Ag/Ab	Negative	
LDH	378	120 - 250 U/L	Alb	1.8	3.5 - 5.0 g/dL
ALT	10	7 - 56 U/L	Total protein	3.5	6.0 - 8.0 g/dL
AST	20	10 - 40 U/L	Amylase	43	30 - 110 U/L
ALP	278	150-500 U/L	Lipase	23	10 - 140 U/L
Na	132	135 - 145 mmol/L	Gamma GT	13	7 - 30 U/L
K	3.3	3.5 - 5.0 mmol/L	Protein Urine	162.9	
Ca	7.3	8.5 - 10.5 mg/dL	Urea Urine	114	
Mg	2.2	1.7 - 2.2 mg/dL	Creatinine Urine	11.8	
CRP	46 mg/L	Up to 8.0	ESR	116	0 - 10 mm/hr
BM Flow Cytometry Immunophenotyping Analysis					
CD3	18.4 %	56-84	HLA DR	59.1 %	
CD4	6.3%	31-52	CD13	29.7 %	
CD8	10.1 %	18-35	CD33	33.5 %	
CD19	30.5 %	13-29	CD45	78.9%	
CD20	24.9 %	11-29	CD117	5.6%	
CD10	23.6%		CD34	6.7%	<1%
CD22	19.1 %		Blasts	1.8%	<5%
Urine Analysis					
Urine Volume 24 hrs	2300 cc	500-1,500 cc			
Urinary Creatinine/24 h	460 mg	800-2000 mg			
Urine Protein/24h	4140 mg	0-150 mg			

WBC, White Blood Cell Count; RBC, Red Blood Cell Count; Hb, Hemoglobin; Plt, Platelets; PT, Prothrombin Time; PTT, Activated Partial Thromboplastin Time; TG, Triglycerides; LDH, Lactate Dehydrogenase; Chol, Cholesterol; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Na, Sodium; K, Potassium; Ca, Calcium; Mg, Magnesium; ALP, Alkaline Phosphatase; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; INR, International Normalized Ratio; IgG, Immunoglobulin; C3, Complement Component 3; C4, Complement Component 4; Alb, Albumin; Gamma GT, Gamma-Glutamyl Transferase

CT scan demonstrated evidence of bronchiectasis in the left lower lobe (LLL), along with a nodular lesion measuring 13 × 10 mm, as shown in **Figure 2**. Moreover, neck sonography confirmed that there were several hilum-exhibiting lymph nodes in the jugular chain. On the left side, between zones 2 and 3, there was one heterogenic lymph node measuring 20 × 10 mm (short axis diameter, SAD = 10 mm), which is probably supportive of inflammation and infection. Zone 2 on the right side showed a comparable heterogenic lymph node with a SAD of 10 mm that also had a hilum. The results of the testicular ultrasonography were consistent with bilateral epididymitis, indicating increased size and vascularity in both epididymides. In addition, there was a mild hy-

drocele on the right side and evidence of edema and inflammation in the left spermatic cord. The admission abdominal ultrasound revealed 20x8mm lymph nodes in the para-aortic region, along with several infiltrative lymph nodes lacking a clear hilum in both para-iliac zones, with the largest measuring 31 × 18 mm on the right side. Also, a subsequent abdominal ultrasound was performed to evaluate the bile ducts, intra-abdominal fluid, and lymph nodes.

As shown in **Figure 3**, an abdominal spiral CT scan showed that the spleen was the right size, there were lymph nodes in the para-aortic, mesenteric, and peripancreatic areas with a maximum SAD of 12 mm, and there were mild ascites in the abdomen and pelvis. Bilateral iliac and inguinal chains showed multiple lymphadenopathies (LAPs). A small amount of sludge and a rounded echogenic focus of roughly 23 × 10 mm were also observed in the gallbladder's neck. It is advised to confirm these results with additional ultrasonography testing as this discovery implies the existence of a stone or sludge ball. No evidence of invasion into adjacent structures was observed.

In subsequent abdominal sonography, a para-aortic lymph node measuring 9 mm in length was observed. Additionally, a heterogenic lymph node measuring 17 × 21 mm without a hilum was identified at the entrance of the inguinal canal. Consequently, the patient had been referred for a lymph node biopsy based on lymphadenopathy and suspected malignancy, but the Surgeon rejected the request because of the low platelet level. During his hospitalization, He was treated with Sirolimus, platelet transfusions, and a 25-gram vial of Intravenous immunoglobulin (IVIG). In addition, he was given antibiotics such as cefuroxime, clindamycin, imipenem, and cyclosporine for aphthous stomatitis, and a positive urine culture for Escherichia coli (E. coli). After the patient's urine examination showed that he had approximately 4 grams of proteinuria each day, nephrotic syndrome was diagnosed. His albumin level was also 1.8 g/dL, requiring two albumin injections. Prednisolone was additionally prescribed to him for his nephrotic syndrome. At the time of discharge, there were no major lymph nodes seen that required a biopsy. The patient improved abdominal pain and was discharged with a platelet count of 7.5 × 10^9/L.

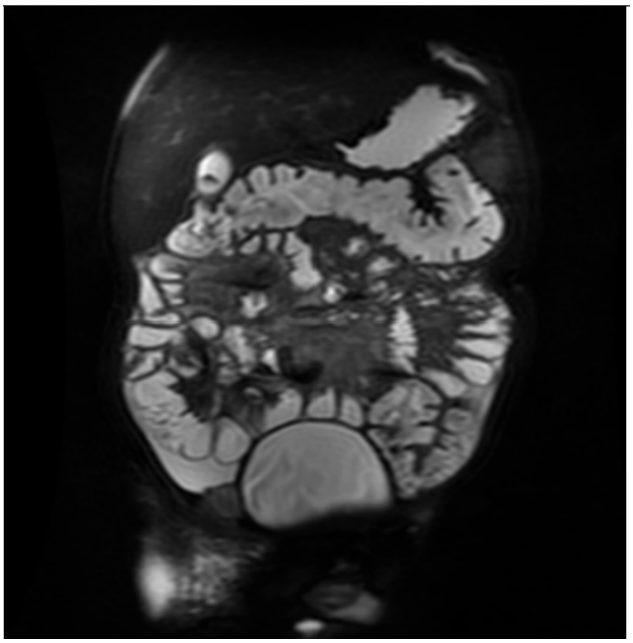

Figure 3. CT scan reveals numerous lymph nodes in the para-aortic, mesenteric, and peripancreatic regions along with minor ascites in the abdomen and pelvis. The spleen is normal at 120 mm, and the biggest node on the right side is 31 × 18 mm.

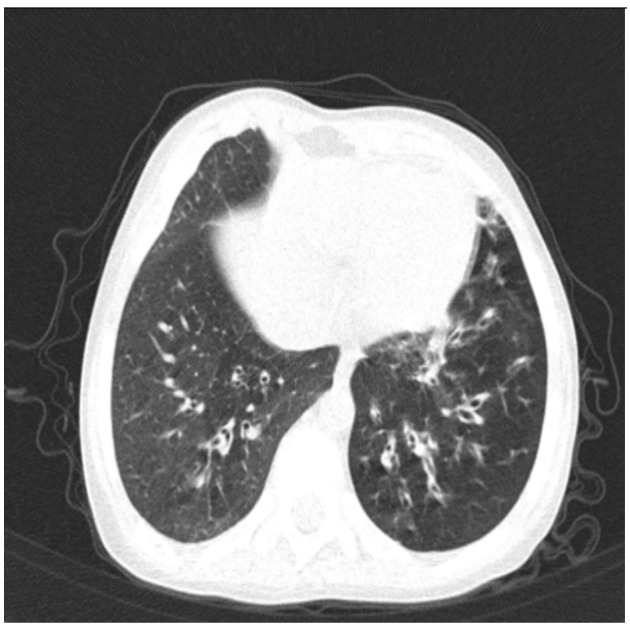

Figure 2. CT scan showing a 13 × 10 mm nodular lesion and signs of bronchiectasis in the left lower lobe (LLL).

After six months, it was reported that this WAS patient displayed repeated fever, cough, and chills, and he was hospitalized due to arthritis affecting his left ankle, the sole joint, and the third and fourth metacarpophalangeal joints of his right hand, and mild swelling in his hands, extending from the wrist to the fingers. During his several-month hospital stay, the patient received 30 grams of IVIG monthly, antiviral medication, and

antibiotics. Upon discharge, his complete blood count (CBC) results were as follows: white blood cells (WBC) 7.8 × 10^9/L, hemoglobin (Hb) 11.8 g/dL, and platelets (Plt) 32 × 10^9/L. Following his discharge, he had stable vital signs and was prescribed ciprofloxacin and cotrimoxazole. He was advised to return for further IVIG administration. Subsequently, the patient developed lymphoma, responded successfully to chemotherapy, and did not require hematopoietic stem cell transplantation. The patient's parents were actively involved in his care, and his condition was regularly monitored by platelet counts, immunoglobulin levels, and general health examinations. His condition remains stable, and he is currently in good health.

Discussion

This case report presents a 12-year-old Iranian boy with Wiskott-Aldrich Syndrome (WAS), which was confirmed by the c.777+1 G> A mutation in the WAS gene. This mutation likely disrupts the splicing of exon 8, impairing the function of the Wiskott-Aldrich Syndrome Protein (WASp), which is crucial for immune system regulation and actin cytoskeleton reorganization in hematopoietic cells. The characteristic symptoms of WAS were observed in this case, including thrombocytopenia and eczema. The mechanisms underlying the occurrence of autoimmune complications in WAS patients are confirmed, and this WAS case has shown Crohn's disease and autoimmune disorders related evidence such as rheumatoid arthritis (17, 18).

This WAS case developed nephrotic syndrome characterized by significant proteinuria and hypoalbuminemia. However, the primary kidney diseases are not typically associated with the syndrome. Furthermore, he indicated the wide-ranging systemic consequences of WAS, like bronchiectasis, epididymitis, and recurring arthritis, were among the several systemic infections that affected this patient's clinical outcome. So, the immunosuppressive medication, persistent infections, and immunological dysfunction in WAS are probably secondary causes of renal involvement. The lack of renal histopathology in WAS cases hinders understanding, but similar cases and animal studies suggest immune complex deposition may contribute to pathogenesis (19).

Distinguishing between primary kidney disorders and secondary renal complications is crucial for the management of WAS patients, and this case highlights the value of a multidisciplinary approach including nephrologists and immunologists in the care of WAS patients with renal involvement. Furthermore, stabilizing the patient's condition required careful handling of these problems, especially the use of intravenous immunoglobulin (IVIG) and long-term antibiotics. So, further research is needed to elucidate the mechanisms underlying renal involvement in WAS, particularly the role of aberrant immune responses and autoantibody production, as observed in WASp-deficient mice (19). Studies provide a possible therapy strategy by indicating that in WAS patients with nephropathy, splenectomy, and reduction of immunosuppressive medication may be able to enhance renal function and cause remission of proteinuria (20).

Conclusion

This research enhances clinical understanding of WAS gene mutations, highlighting comorbidities, renal issues, and the need for personalized therapy to address immunodeficiency disorders and their systemic implications.

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