

Case Report

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Early Wiskott-Aldrich syndrome diagnosis and successful treatment in a 30-days-old male infant with congenital thrombocytopenia: Case report

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Abstract

Wiskott-Aldrich Syndrome (WAS) is a rare X-linked Inborn Error of Immunity (IEI), characterized by micro-thrombocytopenia, severe eczema, recurrent life-threatening infections, and tendency to malignancies and autoimmunity. Diagnosis during the neonatal period, in the absence of family history, is not only challenging, but also crucial for Hematopoietic Stem Cell Transplantation (HSCT) success and overall survival. We describe the case of a one-month-old male infant with congenital thrombocytopenia and bloody stools, initially misdiagnosed as alloimmune neonatal thrombocytopenia. Clinical picture and the implementation of flow cytometry led to prompt diagnosis of WAS. The patient was successfully treated with HSCT. Differential diagnosis of congenital thrombocytopenia is complex and multifactorial. Patients with severe WAS can display symptoms on the first day of life. Clinical picture, assessment of simple diagnostic tools such as blood cell count/peripheral blood smear and flow cytometry can lead to correct diagnosis and successful treatment. Finally, we highlight the importance of training pediatricians in IEI reference centers and continuous education on IEI, providing better treatment results and quality of life in WAS patients.

Keywords: Wiskott-Aldrich syndrome; Infants; Congenital thrombocytopenia; Transplantation.

Abbreviations: WAS: Wiskott-Aldrich Syndrome; HSCT: Hematopoietic Stem Cell Transplantation; IEI: Inborn Error of Immunity; CMV: Cytomegalovirus; IVIG: Intravenous Gamma Globulin; WAS-P: Wiskott-Aldrich Syndrome Protein.

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Introduction

Wiskott-Aldrich Syndrome (WAS) is a rare X-linked Inborn Error of Immunity (IEI), caused by mutations in the WAS gene located on the X chromosome (Xp11.22-p11.23). WAS is presented with a wide disease spectrum; in severe cases it is characterized by micro-thrombocytopenia, difficult to treat eczema, haematochezia, recurrent infections, increased malignancy risk, and autoimmunity phenomena later in life [1,2]. Median age of diagnosis occurs usually during late infancy, when the complete phenotype is unraveled, whilst diagnosis is more common in the three first months of life in patients with a positive family history [3]. Herein, the case of a one-month-old male infant with congenital thrombocytopenia and without family history for inherited disorders is presented; prompt diagnosis was achieved due to high clinical suspicion, careful assessment of blood cell counts and implementation of flow cytometry measurement of Wiskott Aldrich Protein (WAS-P). The patient was successfully treated with Hematopoietic Stem Cell Transplantation (HSCT) from a matched unrelated donor.

Case presentation

A one-month-old male infant was admitted via the emergency department for investigation of congenital thrombocytopenia. He was the first offspring of a non-consanguineous Caucasian couple, born in a neighboring country. Mother was referred to be infected with SARS-COV-2 and Cytomegalovirus (CMV) during the third trimester of pregnancy. On admission, the patient had thrombocytopenia, as revealed from blood cell count, mild facial eczema and occasionally bloody stools. Family history was negative for inherited or other disorders. The neonate presented with fever and thrombocytopenia on the first day of life. In the neonatal care unit, he had been treated with antibiotics and platelet transfusions. He had been discharged with normal platelet count, but three days later (at the age of 20-days-old) he was readmitted to the neonatal care unit due to bloody stools and thrombocytopenia ($33.000/\text{mm}^3$). He received further platelet transfusion and gamma globulin (IVIG) and was referred for further evaluation by hematologist and gastroenterologist. On admission, the patient had normal vital signs and satisfactory growth. Clinical examination revealed mild facial eczema, seborrheic dermatitis, and single palmar line. Initial blood cell count evaluation displayed eosinophilia and thrombocytopenia ($20.000/\text{mm}^3$) (Table 1). Infection investigation revealed positive IgG antibodies for CMV and positive urine CMV PCR. Fundoscopy, cardiologic evaluation, ultrasound of brain and abdomen were normal. X-ray of the right arm was not suggestive of Tar syndrome. On admission, the age of the patient, the absence of family history for genetic disorders, the possible asymptomatic infection with CMV, the good general state and growth of the infant, the mild eczema and the occasionally bloody stools could lead to misdiagnosis or the delay of correct diagnosis. Differential diagnosis of congenital thrombocytopenia included several etiological factors such as infectious agents (viral or bacterial, eg CMV), alloimmune thrombocytopenia, hematological diseases (congenital leukemia), genetic syndromes (trisomy 21,13,18), autoimmune and metabolic disorders and hereditary thrombocytopenia. Careful assessment of blood cell count revealed that platelets displayed low MPV (5fl), but a) it was not certain whether this finding was reliable

and b) micro-thrombocytopenia on blood smear was not certain. The combination of a possible micro-thrombocytopenia with eczema and colitis, led to targeted immunologic evaluation which revealed marginal low IgM serum levels and CD8+ lymphopenia (Table 1). Assessment of WAS-protein expression was performed as soon as possible, on first week of hospitalization. WAS-P was undetectable by flow cytometry, indicating severe WAS phenotype (Figure 1). Subsequent HLA analysis was performed, in order to find HLA compatible donor for HSCT awaiting for genetic confirmation of diagnosis, targeting to one gene (WAS gene) and not to whole exome sequencing. Sequence analysis and deletion/duplication of the WAS gene revealed hemizygous mutation c.631C>T (pArg211) at exon 7, which could be accounted for the absence of WAS protein [3]. This is a rare mutation that has been described in few patients with severe WAS [3]. Severe WAS leads to progressive immunodeficiency, and patients are prone to severe infections, cancer and autoimmunity, conditions that shorten dramatically life expectancy. The patient received supportive treatment for almost six months, remaining mainly hospitalized in our clinic before his transfer to the HSCT care unit. Supportive treatment included periodic infusions of intravenous gamma-globulin, chemoprophylaxis, and rationalization of platelet transfusions. The infant presented with oral petechiae and gradually severe dysphagia due to deep painful oral ulcers. He also displayed severe diapers dermatitis that partially responded to a short course cortisone treatment. Eczema also spread to the rest of the body, mimicking the clinical picture of atopic dermatitis. Skin dermatitis, local bleeding, and infection at the Hickman catheter entry point, prevented catheter stabilization [4] (Figure 2). At the age of seven months old, the patient received peripheral blood stem cell transplant from fully matched unrelated adult donor, following a myeloablative conditioning regimen. Engraftment was achieved on day 18 post-transplantation, with subsequent platelet rise ($>20.000/\text{mm}^3$) and neutrophil rise $>500/\text{mm}^3$ on day 41+. The early post-transplant period was uneventful, apart from acute GVHD grade II reaction, which responded to steroids. The patient had full donor chimerism and received periodic gamma globulin infusions and cyclosporine. He also received treatment for mild CMV infection. At discharge from the transplantation department he received immunosuppressive agents, corticosteroids for two months and cyclosporine for twelve months. The infant currently two and a half-year old, is asymptomatic, with a normal blood cell count. Follow-up assessment of the patient is performed annually by the transplantation department as well as from our clinic. No adverse or unanticipated events occurred.

Discussion

In the case presented, thrombocytopenia was accidentally revealed on the first day of life due to a possible neonatal bacterial infection, but immunological evaluation was not considered even when the neonate presented with colitis and thrombocytopenia. Differential diagnosis of congenital thrombocytopenia is complex and includes numerous etiological factors, infectious, genetic, hematological, and hereditary. Diagnosis was established very early, at the age of one month old, mainly to careful assessment of a) clinical picture of the patient and b) the availability of quick WAS-P assessment by flow cytometry. Avoidance of unnecessary laboratory investigation and proper

Table 1: Blood cell count and immunologic evaluation of the patient at his admission.

Blood cell count		Reference values	IgS	Values	Age matched normal range	Lymphocyte subpopulations	%	Absolute numbers	Normal ranges
White Blood cells	18300/mm ³	6000-17500	IgA	31 mg dl	6-81 mg/dl	CD3+	48.4%	3630	2500-5600
Neutrophils	39,2%	40-75	IgM	31 mg/dl	31-135 mg/dl	CD4	36,7%		
Lymphocytes	35,9%	20-45	IgG	761 mg/dl	224-1072 mg/dl	CD8+	17%		
Monocytes	15,7%	2-10	IgE	8,42	<1,94	CD3+CD8+	8,3%	622/μl	590-1600
Eosinophiles	7,6%	0-4				CD3+CD4+	36.1%	2708/μl	1800-4000
Baseophiles	1,6%	0-1				CD19+	27,6%	2070/μl	430-3000
Band neutrophils	11%					CD4+CD45RO+	6,4%		
Hb g/dl	10,7 mg/dl	10-18				CD4CD45RA+	25,7%		
Hct%	32,2	31-55				CD16+/CD56+	18,5%	1388/μl	170-1400
MCV fl	95,3	85-123				HLA-DR+	30,8%		
MCH fl	31,7	28-38				NKT	2,3%		
PLTs	27000/mm ³	130.000-400.000				CD4+/CD8+	2,1%		
MPV	5 fl								

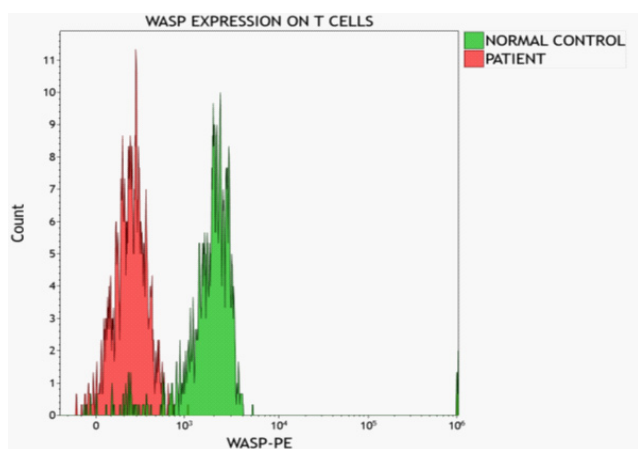


Figure 1: Absence of WASP expression in our patient by flow cytometry.



Figure 2: Eczema of the patient at 6-months-old and constant infection at the entry point of the Hickman catheter.

management of the patient were established [5-7]. Transplantation was performed, before immune deterioration led to opportunistic infections with subsequent worst outcome. It should be noted that the median age of diagnosis of WAS is reported to be 12 months old [1,2,3,5], while onset of symptoms is usually at 3 months of age in severe cases. Early diagnosis at the age of one month old is extremely rare and usually is referred in cases with family history. Furthermore, initial presentation may be not as specific as to warrant referral to an immunologist, unless there is increased awareness for IELs. Finally, since WAS cannot be readily detected by the neonatal IEL screening programs [8], which are currently performed in a limited number of countries worldwide, training general pediatricians in IEL reference centers and continuous education on immunodeficiencies is of utmost importance.

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