

Cutaneous manifestations in patients with Wiskott–Aldrich syndrome submitted to haematopoietic stem cell transplantation

Juliana Gomes Loyola Presa,¹ Vania Oliveira de Carvalho,² Laura Rogers Morrissey,³ Carmem Maria Bonfim,⁴ Kerstin Taniguchi Abagge,² Angélica Vasselai,⁵ Leide Parolin Marinoni²

¹Division of Pediatric Dermatology, Federal University of Paraná, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil

²Division of Pediatric Dermatology, Department of Pediatrics, Federal University of Paraná, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil

³Department of Dermatology, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

⁴Division of Bone Marrow Transplantation, Federal University of Paraná, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil

⁵Department of Pediatrics, Federal University of Paraná, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil

Correspondence to

Vania Oliveira de Carvalho, Division of Pediatric Dermatology, Department of Pediatrics, Federal University of Paraná, Hospital de Clínicas da UFPR, Rua General Carneiro 181, 14 Andar, Rua Richard Strauss 62, Vista Alegre, Curitiba, Paraná CEP 80.820-110, Brazil; rcarvalho50@hotmail.com, jgloyola@hotmail.com

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ABSTRACT

Introduction Wiskott–Aldrich syndrome (WAS) is an X-linked primary immunodeficiency caused by a mutation of the WAS protein gene. This protein actively participates in important cellular processes, and its presence is related to diverse clinical manifestations, including cutaneous alterations. The classical triad of WAS consists of recurrent infections, thrombocytopenia with small platelets and atopic dermatitis (AD)-like lesions.

Objective To evaluate the frequencies of cutaneous manifestations in patients with WAS prior to haematopoietic stem cell transplantation (HSCT).

Results Twenty-four boys diagnosed with WAS and treated with HSCT between 1992 and 2007 were included. The characteristic triad of WAS occurred in 46% of patients. Before HSCT, the most frequent cutaneous manifestations included eczema similar to AD (71%), followed by petechiae and/or ecchymosis (58%) and cutaneous infections (17%).

Conclusions Cutaneous manifestations in patients with WAS are frequent, especially those similar to the eczema found in AD.

INTRODUCTION

Wiskott–Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency caused by the defective expression of the WAS protein (WASp).¹ WASp is present in all haematopoietic lineage cells and plays an important role in the reorganisation of the cytoskeleton and the signalling of these cells. It is also an important element in the activation of immunologic synapses, which, in turn, makes it difficult for the immune system to carry out its functions adequately, resulting in cellular and humoral deficiencies, mainly related to T-cells. Therefore, recurrent bacterial and viral infections are frequently present in WAS.²

The presence of defective protein results in alterations in cellular structure and function. Thrombocytopenia with small platelets is the most common laboratorial finding in WAS patients and is due to defects in reorganising the cellular cytoskeleton as well as peripheral platelet destruction. These alterations account for the clinical symptoms of disordered bleeding, resulting in the presence of petechiae and ecchymosis.^{3 4}

Another important cutaneous manifestation in WAS is eczema. It is clinically similar to atopic

What is already known on this topic

- ▶ Wiskott–Aldrich syndrome (WAS) is a rare primary immunodeficiency resulting from genetic mutation of a protein present in all the haematopoietic lineage cells.
- ▶ The WAS triad comprises thrombocytopenia with small platelets, recurrent infections and atopic dermatitis-like eczema.
- ▶ Cutaneous manifestations on patients with WAS are frequent and characterised by petechiae, ecchymosis, infectious disease and eczema.

What this study adds

- ▶ Atopic dermatitis-like eczema and thrombocytopenia are important signallers for the diagnosis of Wiskott–Aldrich syndrome (WAS), but the diagnosis is not made in almost 50% of the patients.
- ▶ Early eczema with haemorrhagic features in boys should be readily recognised by health professional as a sign of WAS.
- ▶ Skin manifestations in WAS rapidly resolve after haematopoietic stem cell transplantation.

dermatitis (AD), with erythematous and pruritic lesions located at the same sites of classical AD. However, the eczema present in WAS usually appears to be haemorrhagic or ‘bleeding’ due to platelet dysfunction.

These features of WAS, including AD-like eczema, thrombocytopenia with small platelets and recurrent infections, comprise the characteristic clinical triad seen in this condition. Literature has shown that not all patients will present with all of these symptoms at once. Furthermore, few studies have evaluated the frequency of skin manifestations present in WAS in detail, nor their evolution before and after transplantation. Moreover, there are few descriptions of the eczema characteristically present in WAS.^{5 6} Nonetheless, cutaneous alterations are primary and important signallers for the diagnosis of this rare syndrome. In the present study, we retrospectively described the frequencies and

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clinical characteristics of the cutaneous manifestations in 24 WAS patients before haematopoietic stem cell transplantation (HSCT) to add knowledge in this dermatological field.

METHODS

This is a single-centre retrospective and descriptive study including all patients diagnosed with WAS and treated with HSCT between 1992 and 2007 at a university hospital in Brazil. The ethical committee of the institution approved this study.

The diagnosis of WAS was established based on clinical and laboratorial manifestations of eczema with small platelet thrombocytopenia, and recurrent infections; these criteria are used by most clinicians, as molecular determination for the protein is not available in all medical centres. To determine platelet counts, the limit value considered was 70 000 platelets/mm³, chosen due to the diagnostic criteria used for immunodeficiencies proposed by the Immunodeficiency Pan-American Group and the European Immunodeficiency Society in 1999.⁷ The mean platelet volume was considered normal between 7 and 10 fl.

A family history of WAS was considered positive when there was clinical and/or laboratorial confirmation of WAS in the family. The possibility of WAS in the family was determined by death of a male member due to bleeding and repeated infections. Eczema diagnosis was positive when a description of specific cutaneous inflammatory signs was present in the patient's clinical history.

The data in this study detail the clinical history and physical exams performed before and 30 days after HSCT. A paediatric dermatologist performed the skin examination and the term eczema was used when the skin showed inflammatory signs.



Figure 1 Eczema similar to atopic dermatitis with erythema and excoriation.

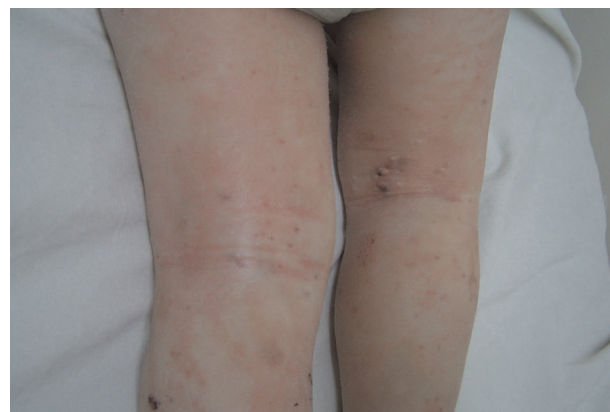


Figure 2 Cutaneous infections: numerous clustered *Molluscum contagiosum* lesions.

Absolute values, percentages, the median and the IQR summarise the clinical manifestations in this study.

RESULTS

Twenty-four boys were found and included from the hospital data bank. The characteristic clinical triad was observed in 11 patients. Dermatological manifestations were: eczema with a median age of 120 days (1–450 days) for the first signs, and/or cutaneous infections (five with impetigo, three with *Molluscum contagiosum* and one patient with both infections), petechiae and ecchymosis with a median age of 30 days (1–3000 days) for the first signs. Recurrent infections were observed in 20 patients. The physical exam prior to HSCT revealed eczema similar to AD in 17 patients, mainly at the extensor surface of the members in 11 (figure 1), and 14 patients with petechiae and ecchymosis (figures 2 and 3). Clinical history data and physical exam data are listed in table 1.

The analysis of the data demonstrated that only 10 patients had WAS as the initial suspected diagnosis. The characteristic triad of the syndrome occurred in 11 patients. Genetic laboratorial confirmation was obtained in 10. Patients' characteristics as well as transplant data are summarised in table 2.



Figure 3 Signs of skin bleeding: ecchymosis and petechiae.

Table 1 Clinical history data and physical exam data

		Number of patients
Clinical history data		
Symptoms at birth	Eczema	2
	Signs of thrombocytopaenia	9
First sign/symptom of WAS	Eczema	6
	Skin/gastrointestinal bleeding	18
Dermatological findings at clinical follow-up	Eczema	21
	Cutaneous infection	9
	Petechiae/ecchymosis	19
Classic WAS clinical triad	Eczema	11
	Small platelet	
	thrombocytopenia	
	Recurrent infections	
First platelet count	<70 000/mm ³	22
WAS family history	Positive	13
	Probable	6
	Negative	5
Physical exam data		
Pre-transplant period	Signs of atopia (xerosis/atopic pleats)	21
	Eczema	17
	Popliteal and antecubital	8
	Trunk	8
	Face	8
	Extensor surface of members	11
	Cutaneous infections	4
	Petechiae and ecchymosis	14
	Eczema	2
30 days post-transplant		

WAS, Wiskott–Aldrich syndrome.

DISCUSSION

Twenty-four boys diagnosed with WAS and treated with HSCT were retrospectively evaluated. This disease was initially suspected in less than half of the patients, and diagnosis was not easily performed even in cases with a positive family history, stressing the difficulty in diagnosing this rare syndrome, despite the fact the characteristic cutaneous manifestations in this group of patients consistently appeared prematurely and could have been used for earlier diagnosis.

Table 2 Patients' characteristics and transplant data

Data	Median (range)
Median age of first symptoms of WAS	30 days (1–150 days)
Median age when WAS was diagnosed	480 days (30–3240 days)
Median age at first evaluation in the BMT division	532 days (64–4724 days)
Median age at the HSCT	961 days (303–6017 days)
Type of donor and stem cell source	Bone marrow
	7 (related donor)
	2 (unrelated donor)
	Cord blood
Preparatory regimen	15 (unrelated donor)
	Bussulfan, cyclophosphamide and thymoglobuline
Graft versus host disease prophylaxis	Cyclosporine/methotrexate or cyclosporine/steroids

BMT, bone marrow transplant; HSCT, haematopoietic stem cell transplant; WAS, Wiskott–Aldrich syndrome.

Cutaneous manifestations of thrombocytopaenia, petechiae and ecchymosis were observed in 19 of the 24 patients. These symptoms were observed during the physical exam in fewer patients than what was reported in the clinical history. Frequent blood transfusions—to which these patients are subject—as well as the use of corticosteroids may explain this difference.⁸

In the current research, eczema was the first symptom described in six patients and it was observed in 88% of patients during the evolution of the disease. The same manifestation was found in 10 out of 11 patients with WAS evaluated by Lee *et al*⁸ and in 81% of the patients studied by Sullivan *et al*.⁹ The age for the appearance of eczema's first symptoms was found to be quite early in our patients and this same finding was observed in one other study.⁸ The appearance of eczema in the first few months of life and the lack of response to treatment, coupled with the haemorrhagic aspects of these lesions, should be considered manifestations for a clinical suspicion of WAS. Despite the importance of eczema, there are few studies on this topic. It is possible that due to the severity of the immunodeficiency manifestations and the thrombocytopaenia, the cutaneous manifestation might be overlooked.

A differential diagnosis for the eczema found in WAS must be carried out with AD. Eczema lesions exhibit a rise in the number of T lymphocytes, as well as Langerhans cells and other dendritic cells, which actively participate in the inflammatory process.¹⁰ In WAS, the defects in cytoskeleton reorganisation and the cellular signalling, secondary to the genetic mutation, result in an inadequate immune response. Therefore, cells which directly participate in AD physiopathology have their immune functions compromised in WAS. It is possible that the similarity between these cell alterations that are involved in the development of the clinical manifestations might aid in clarifying the similarities between the eczema seen in these two diseases.

In this study, cutaneous infections present before HSCT were common. They were mainly related to *Molluscum contagiosum*. Orange *et al* stated that *Molluscum contagiosum* lesions can be present in up to 9% of patients with WAS.² Ochs and Thrasher state that patients with the syndrome show an increase in viral and bacterial skin infections in areas with eczema.¹¹ Disseminated disease may occur due to the incapacity of the immune system to respond adequately to some antigens.

The classic clinical WAS triad was observed in half of the patients described here. Sullivan *et al* found the classic clinical WAS triad in 30% of the patients studied.⁸ Orange *et al* reported that the triad is found in one out of every four patients.² Both authors observed a delay in the patient's diagnosis when they lacked classical symptoms related to the triad. Early diagnosis increases the possibility of effective treatment, such as HSCT, and offers a better prognosis when performed before 5 years of age.^{12 13}

Before HSCT, 71% of the patients in this sample had signs of eczema. Ozsahin *et al*, in a retrospective study, found the presence of eczema in 100% of patients with WAS prior to transplantation.¹⁴ Wietstruck *et al* also reported the appearance of eczema in all six patients studied.¹⁵ The fact that not all the patients in the present study had eczema in the dermatological evaluations might be related to the variation of the genetic mutation and, consequently, the clinical manifestations of WAS. Another possibility is that the eczema might have periods of remission and could therefore be absent when the physical exam was completed.

The patients' median age at the time of the HSCT in the current research was 5 years, relatively similar to that found by Litzman *et al* and Wietstruck *et al*, which differs quite a bit from

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Kobayashi *et al* at 1.6 years.^{15–17} As molecular analysis was not readily available, some patients came to the transplant unit only when they presented with the classical syndrome. Interestingly, the eczema showed clinical improvement 30 days after HSCT. This improvement may have been caused by several factors such as the chemotherapy used during preparatory regimens, the use of cyclosporine and steroids after transplant or possibly the immunological recovery expected from the treatment.

CONCLUSIONS

In this study, eczema similar to AD with haemorrhagic features was the most frequent skin finding, followed by petechiae and ecchymosis in patients with WAS. These cutaneous alterations serve as important cues to the diagnosis of this rare syndrome and should be recognised by health professionals who offer primary health services to paediatric patients. Early recognition is critical in order to initiate treatment promptly and to improve patient outcomes and prognosis for those with WAS.

Contributors JGLP was responsible for the overall content of the manuscript. VOC was responsible for the overall content of the manuscript. LRM was responsible for reporting the results. CMB carried out the research. KTA carried out the research and reported the results. AV carried out the research. LPM was responsible for planning and carrying out the research.

Competing interests None.

Patient consent Parental/guardian consent obtained.

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