Reticular rash in drug reaction with eosinophilia and systemic symptoms syndrome: A clue to parvovirus B19 reactivation?

María Julia Cura, MD,[a] Ana Clara Torre, MD,[a] Karen Yoselin Cueto Sarmiento, MD,[a] María Luz Bollea Garlatti, MD,[a] Julia Riganti, MD,[a] Laura Barcan, MD,[b] Juan Bautista Blanco, MD,[c] and Luis Daniel Mazzuoccolo, MD[a]
Buenos Aires, Argentina

INTRODUCTION

The term drug reaction with eosinophilia and systemic symptoms (DRESS) refers to a complex syndrome characterized by cutaneous lesions, eosinophilia, and systemic symptoms that may be triggered by different medications. The reaction takes place 2 to 6 weeks after the initial exposure to the culprit drug.[1] Even after appropriate diagnosis and treatment have been conducted, patients may experience isolated or sequential relapses and slow clinical resolution that may be associated with viral reactivations of herpesvirus.[2]

Parvovirus B19 is a small, nonenveloped single-stranded DNA virus of the Parvoviridae family.[3] It is well known for its ability to persist in blood and bone marrow in immunocompromised patients due to different conditions, such as chemotherapy, HIV, congenital immunodeficiencies, and transplants.[4] It can also be found in many tissues of immunocompetent patients, like the skin.[5,6]

We describe 5 adult patients with DRESS syndrome who developed a rash in a lace-like pattern during the disease. Polymerase chain reaction (PCR) studies found parvovirus B19 DNA in skin biopsy specimens obtained from the rash sites in all patients. Therefore, we hypothesize that an association between DRESS syndrome and Parvovirus B19 reactivation may exist.

CASE REPORTS

We report 5 patients who developed DRESS syndrome. All patients were >40 years of age, and 4 were female. The culprit drugs were carbamazepine in 2 patients and clotiapine and vancomycin in 1 patient each. In our other case, we could not distinguish whether the trigger was vancomycin or aztreonam. In all cases there was a long interval (2-12 weeks) from the initial drug exposure to symptom onset. Four patients had fever and 4 patients presented with a pruritic morbilliform skin rash. Two patients developed targetoid lesions in the lower limbs, and 2 others presented with facial edema. All patients presented with eosinophilia in the blood laboratory tests, 1 patient had renal failure, another had liver failure, and a third developed both injuries. Blood cultures as well as serologies for HIV, syphilis, autoimmune and viral hepatitis, and antinuclear antibodies were performed. All tests were negative and alternative diagnoses were excluded. A liver biopsy specimen was obtained in 1 patient, which revealed intense inflammatory activity with eosinophil infiltration.

The diagnosis of DRESS syndrome was made in all cases, and all patients received treatment with oral prednisone with slow resolution. In 4 cases the symptoms persisted for >2 weeks. During the course of the disease, all patients developed an erythematous macular rash with a distinctive reticular pattern, associated with eosinophilia in the blood laboratory tests. PCR studies revealed parvovirus B19 DNA in all skin rash biopsy specimens. In addition, a positive blood PCR study for parvovirus B19 DNA was also found in 1 patient. The absence of the DNA virus in

From the Departments of Dermatology,[a] Internal Medicine,[b] Infectious Diseases Section, and Internal Medicine,[c] Hospital Italiano de Buenos Aires.
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Correspondence to: María Julia Cura, MD, Hospital Italiano de Buenos Aires, Departamento de Dermatología, Juan D. Perón 4230, Capital Federal, Ciudad Autónoma de Buenos Aires, Argentina. E-mail: maria.cura@hospitalitaliano.org.ar.

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Table I. Cases: Medical history, clinical findings, laboratory, histopathology, diagnosis, treatment, and viral isolation

	Patient no.				
	1	2	3	4	5
Sex	Female	Male	Female	Female	Female
Age, y	70	47	89	50	85
Medical history	Dermatomyositis and tonic seizures	HIV, diabetes, and osteomyelitis	Trigeminal neuralgia	Major depression	Infectious cellulitis
Associated drug	Carbamazepine	Vancomycin	Carbamazepine	Clotiapine	Vancomycin or aztreonam
Time interval from drug exposure to symptom onset, weeks	3	4	12	2	2
Fever	Yes	Yes	No	Yes	Yes
Enlarged lymph nodes	No	No	No	No	No
Facial edema	No	No	No	Yes	Yes
Morbilliform skin rash location	Trunk and abdomen	Face, trunk, and upper limbs	—	Trunk, abdomen, and lower limbs	Dorsal surface of the abdomen, upper limbs, and thighs
Skin rash extend >50%	Yes	No	Yes	No	Yes
At least 2: edema, infiltration, scaling, and purpura	Yes	Yes	Yes	Yes	Yes
Purpuric targetoid lesions	Lower limbs	Lower limbs	–	–	–
Initial eosinophil count	768/mm^3	179/mm^3	486/mm^3	434/mm^3	1980/mm^3
Highest eosinophil count	8233/mm^3	1569/mm^3	2984/mm^3	931/mm^3	2878/mm^3
Thrombocytopenia	–	–	147,000/mm^3	141,700/mm^3	–
Atypical lymphocytes	No	No	No	No	No
Organ involvement	–	Kidney Liver	Kidney	Liver	–
Skin biopsy specimen findings	Vacuolization of basal layer and lymphocytic perivascular and junctional infiltrates	Vacuolization of basal layer, necrosis of keratinocytes, and mononuclear and eosinophilic perivascular infiltrates	Focal keratinocyte necrosis, lymphocyte exocytosis, lymphocytic and eosinophilic perivascular and junctional infiltrates	Focal keratinocyte necrosis, lymphocyte exocytosis, and lymphocytic and eosinophilic perivascular and junctional infiltrates	Spongiosis and mononuclear and eosinophilic perivascular infiltrates
Points in the RegiSCAR score	5	6	5	4	4
Alternative diagnosis excluded	Yes	Yes	Yes	Yes	Yes
Skin relapses	3	1	0	1	1
Treatment	Meprednisone 1 mg/kg/day	Meprednisone 1 mg/kg/day	Meprednisone 0.5 mg/kg/day	Meprednisone 1 mg/kg/day	Meprednisone 1 mg/kg/day

Continued

Table I. Cont'd

	Patient no.									
	1		2		3		4		5	
Resolution delay ≥ 15 days	Yes		Yes		Yes		Yes		No	
Erythemato-purpuric rash in reticular pattern location	Lower limbs (Fig 1, *A*)		Upper limbs (Fig 1, *B*)		Neckline, upper limbs, and thighs (Fig 2, *A*)		Neckline, dorsum, upper and lower limbs (Fig 2, *B*)		Dorsum, abdomen, upper limbs, and thighs	
HHV-6 DNA in skin	+		−		−		−		−	
EBV DNA in skin	+		+		−		−		−	
CMV DNA in skin	−		−		−		−		−	
Parvovirus B19 DNA in skin	+		+		+		+		+	
HHV-6 DNA in serum	N/A		N/A		−		−		−	
EBV DNA in serum	N/A		N/A		−		+		−	
CMV DNA in serum	N/A		N/A		−		−		−	
Parvovirus B19 DNA in serum	N/A		N/A		−		+		−	

CMV, Cytomegalovirus; *EBV*, Epstein–Barr virus; *HHV-6*, human herpesvirus-6; *N/A*, not assessed; *RegiSCAR*, Registry of Severe Cutaneous Adverse Reactions.

the skin was confirmed after the resolution of skin lesions in 1 patient.

Regarding the Registry of Severe Cutaneous Adverse Reactions diagnosis score, two patients scored 4, another two scored 5, and the remaining one scored 6. In patients who had a score of 4 and 5 (probable DRESS), we made an early diagnosis and initiated prompt treatment. Otherwise, perhaps the score could have been higher than the one we found (Table I).

DISCUSSION

We observed that during the clinical progress of DRESS syndrome, some patients developed an erythematous-purpuric exanthema in a reticular pattern, and parvovirus B19 DNA was found in the skin rash biopsy specimens by PCR. We consider that in these cases, the typical rash in a lace-like pattern and the isolation of parvovirus B19 DNA in the skin make them unlikely to be merely a random occurrence. In fact, in our first patient who tested positive for parvovirus B19 DNA in the skin, PCRs became negative for the virus in studies performed after the resolution of the skin lesions. This fact may suggest that reactivation of parvovirus B19 may occur in DRESS syndrome.

The reactivation of parvovirus B19 in DRESS syndrome, as well as the pathogenic potential of its DNA persistence, have not been fully studied or understood so far. Bonvicini et al[7] reported that the parvovirus B19 genome is usually harbored in human skin, and the association between infection and cutaneous diseases should be established using biologic markers other than viral DNA. Moreover, Santonja et al[8] have recently argued that it is possible to find parvovirus B19 DNA in skin samples of patients with other skin diseases, but they state that an etiopathogenic role should not be attributed to the virus in the absence of clinical findings of recent infection. On the other hand, Coughlin et al[9] linked parvovirus B19 infection with DRESS in 2 pediatric patients in whom the virus had been involved in the development of liver failure during this syndrome. Parvovirus B19 PCR was positive in both blood samples. Neither of the 2 patients showed skin lesions associated with the virus infection.[9]

Although parvovirus B19 reactivation remains controversial in several diseases, we consider that the mechanisms proposed to explain the reactivation of the herpesvirus family members (human herpesvirus-6 and -7, Epstein–Barr virus, and cytomegalovirus) that take place in the course of DRESS syndrome might also be true for this member of the Parvoviridae family.[2,7] Two hypotheses have been

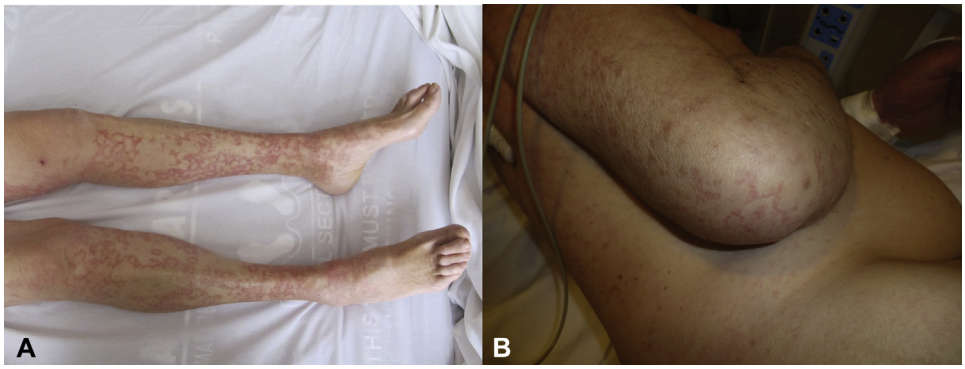

Fig 1. Macular erythematous-purpuric rash in a reticular pattern in the (**A**) lower and (**B**) upper limbs.

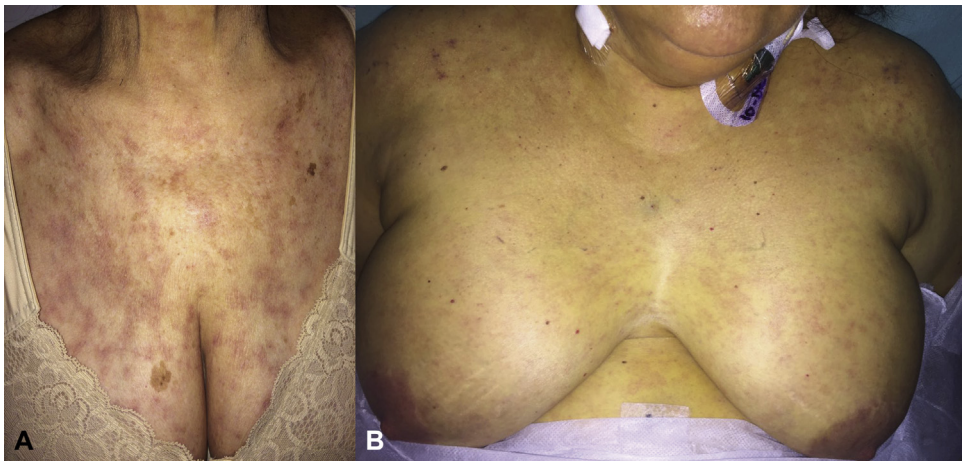

Fig 2. **A**, Macular erythematous-purpuric generalized rash in a reticular pattern in the neckline. **B**, Jaundice and maculopapular erythematous rash in a reticular pattern in the neckline and shoulders.

suggested, and both are related to genetic factors. The first proposal is that an immune response against the drug with secondary viral reactivation related to a cytokine storm may occur. The second theory suggests that certain drugs that may trigger DRESS syndrome have immunomodulating effects, such as hypogammaglobulinemia, a decrease in B lymphocyte count, and activation of monocytes and T lymphocytes, that may promote an early viral reactivation.[10-15] Both mechanisms may explain our clinical and PCR findings in these patients.

In summary, the reactivation of parvovirus B19 may takes place in the evolution of DRESS syndrome. We consider that further studies on the association between parvovirus B19 and DRESS syndrome are required to clarify the meaning of these findings.

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