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

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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. 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.

Parvovirus B19 is a small, nonenveloped single-stranded DNA virus of the Parvoviridae family. 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. It can also be found in many tissues of immunocompetent patients, like the skin.

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 reticulate 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...
| 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/mm³ | 179/mm³ | 486/mm³ | 434/mm³ | 1980/mm³ |
| Highest eosinophil count | 8233/mm³ | 1569/mm³ | 2984/mm³ | 931/mm³ | 2878/mm³ |
| Thrombocytopenia | — | — | 147,000/mm³ | 141,700/mm³ | — |
| Atypical lymphocytes | No | No | No | No | No |
| Organ involvement | — | 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
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. 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. 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. 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.

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 Paroviridae family. Two hypotheses have been
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. 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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