Successful management with ganciclovir of drug reaction with eosinophilia and systemic symptoms secondary to antituberculous drugs associated to human herpesvirus-6 reactivation

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Key words: antituberculous drugs; DRESS; drug reaction; ganciclovir; human herpesvirus 6.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity reaction is a systemic drug-related disease characterized by a skin eruption, fever, lymphadenopathy, abnormal hematological findings, and visceral involvement. Clinical manifestations usually begin between 2 and 8 weeks after the ingestion of the offending drug. Its pathogenesis is still poorly understood; however, different hypotheses regarding the sequential reactivation of certain herpesviruses, particularly the human herpesvirus type 6 (HHV-6), have been proposed. The incidence is still unclear, although it has been estimated to occur in 1 in every 1000 to 10,000 drug exposures with a mortality of approximately 10%.[1]

Aromatic amine antiepileptic agents are the most frequent associated drugs. Nevertheless, diverse causal drugs have been linked to the development of DRESS, including antituberculous (anti-tb) drugs. According to literature, rifampicin is the most common anti-tb drug associated with DRESS.[2] Herein, we present the case of a young female with proven HHV-6 viremia with a dramatic improvement after the administration of ganciclovir.

Abbbreviations used:

DRESS:	drug reaction with eosinophilia and systemic symptoms
HHV-6:	human herpes virus type 6
anti-tb:	antituberculous
CMV:	cytomegalovirus

CASE REPORT

A 24-year-old female with presumptive extrapulmonary tuberculosis arrived at the emergency department with sudden onset of fever, diarrhea, jaundice, and facial edema. She had a 6-month history of cervical lymphadenopathy followed by lymph node dissection that revealed granulomatous lymphadenitis without caseation necrosis or acid-fast bacilli. Culture for mycobacteria was negative. She was initiated on standard anti-tb therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol 2 months prior to her presentation.

On admission, physical examination revealed diffuse and confluent violaceous morbilliform exanthem with follicular accentuation and hepatomegaly (Fig 1). Laboratory tests revealed no abnormalities in hematological or renal function. Hepatic function panel showed total bilirubin of 4 (0.3-1.0 mg/dL), direct bilirubin of 3.1 (0.03-0.18 mg/dL), ALT of 403 (7-52 U/L), AST of 255 (13-39 U/L), and alkaline phosphatase of 333 (34-104 U/L). C-reactive protein level was 5 (0-1 mg/dL). DRESS was suspected. According to the RegiSCAR scoring system, the

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Funding sources: None.

IRB approval status: Not applicable.

Patient consent: The patient provided written consent for the publication of this article.

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JAAD Case Reports 2023;34:90-3.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.12.021

Fig 1. A, Morbilliform exanthema with a slightly purplish tone with fine scales in some areas, the presence of edema was striking on the face, which was more prominent on the eyelids. **B,** Grouped erythematous papules on the dorsal hands.

patient scored 4 points (possible) at the time of admission, and prednisone was started at a 1.0 mg/kg/d dose. All 4 anti-tb drugs were discontinued because tuberculosis was not confirmed after a comprehensive diagnostic approach. Skin biopsy revealed a vacuolar interface dermatitis with a superficial and mid-perivascular inflammatory cell infiltrate, focal areas of orthokeratotic hyperkeratosis, spongiosis, and acanthosis with a psoriasiform pattern. The inflammatory cell infiltrate was primarily composed of lymphocytes and scattered eosinophils. (Fig 2).

After 5 days, her condition worsened with persistent fever, hypotension, and accentuation of the previously described skin findings (Fig 3). Blood tests showed leukocytosis with 18.0×10^9 and 5.4×10^9 eosinophils (30%). HHV-6 polymerase chain reaction quantification was positive with 1296 copies/ml. DRESS with reactivation of HHV-6 was diagnosed and further treatment included ganciclovir (5 mg/kg), with a remarkable improvement after 48 hours of antiviral treatment. Following discharge, corticosteroids were tapered during the following month and eventually suspended as the patient's condition continued to improve (Fig 4).

DISCUSSION

The pathogenesis of DRESS is not completely understood; it is believed to be secondary to a complex interplay between immunologic predisposition, drugs, aberrant metabolic pathways such as the deficiency of epoxide hydroxylase enzyme, and viral interactions with the common reactivation of HHV-6, HHV-7, Epstein-Barr virus, and cytomegalovirus.[3] The reactivation of HHV-6 has been reported in prospective studies in 45% to 62% of cases and is considered to be specific for DRESS.[4] DRESS is a type IV-b hypersensitivity reaction mediated by T cells, with the subsequent release of cytokines and chemokines such as interleukin 4, interleukin 5, and interleukin 13.[5] The immunological mechanism inherent to HHV-6 reactivation remains unknown. Interestingly, systemic reactivation of HHV-6 is frequent in hematopoietic cell and solid organ transplant recipients, in these cases, a skin rash may be present, whilst encephalitis is the most devastating complication.[6]

Clinical manifestations usually begin within 2 to 8 weeks of the initial drug administration. Patients with DRESS can have heterogeneous manifestations, many of which have a gradual onset. Fever, disseminated rash, lymphadenopathy, hematological abnormalities, and involvement of 1 or more internal organs are frequently observed. The liver is the most affected organ in DRESS and its severe dysfunction is the most common cause of DRESS-associated death. Different scoring systems are available to differentiate DRESS from other severe cutaneous adverse reactions such as the RegiSCAR scoring system and the Japanese SCAR diagnostic criteria.[7]

Supportive therapy and discontinuation of the causative drug are imperative for all patients with DRESS. An initial corticosteroid dose of 1.0 mg/kg per day of prednisone or an equivalent dose is recommended with gradual tapering after clinical improvement. There is no approved antiviral treatment by the U.S. Food and Drug Administration for HHV-6 infection; nevertheless, drugs initially developed to target human CMV have proved to be efficient against HHV-6 infection. The use of ganciclovir for the treatment of DRESS has been suggested.[8] In addition, in cases where corticosteroids are contraindicated, administration of cyclosporine, intravenous immunoglobulin, and plasmapheresis may be considered.[9]

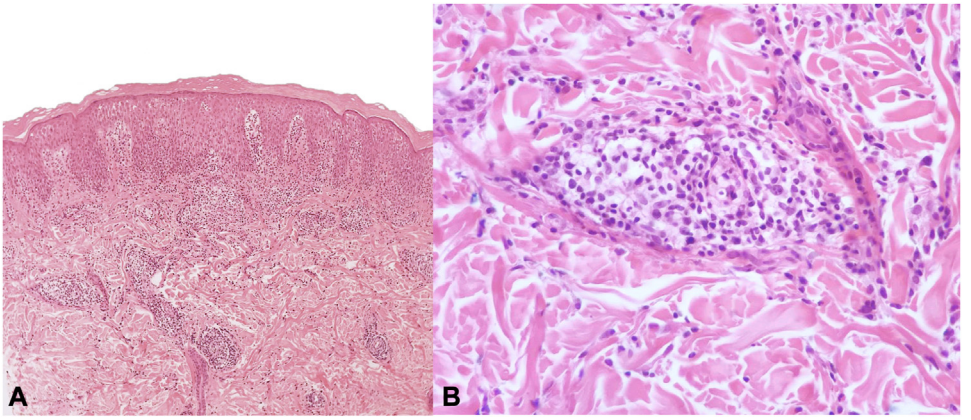

Fig 2. A, Vacuolar interface dermatitis with a superficial and middle perivascular inflammatory infiltrate, as well as focal areas of orthokeratotic hyperkeratosis, spongiosis, and acanthosis with a psoriasiform pattern. **B,** The inflammatory infiltrate was mainly composed of lymphocytes and histiocytes with scattered eosinophils.

Fig 3. A, Increase in previously documented facial edema. **B,** Bilateral tonsillar exudate. **C** and **D,** Well-defined *purple* plaques were seen on the abdomen and legs.

In this case, at the time of admission and possible diagnosis of DRESS, all anti-tb drugs were discontinued, and prednisone was administered at 1 mg/kg per day; however, after 5 days, her condition worsened and HHV-6 reactivation was demonstrated; thus, ganciclovir (5 mg/kg twice daily) was

Fig 4. Dramatic improvement in facial edema 48 hours after starting ganciclovir. Exfoliative dermatitis is observed.

started. Clinical and HHV-6 viral load improvement was identified at 48 hours of treatment. Ganciclovir was discontinued once the viral load was undetectable 8 days later and continued with oral valganciclovir for an additional month. The prevalence of DRESS sequelae is unknown, most patients recover completely within a few weeks. Patients should be closely followed up and screened for autoimmune diseases such as autoimmune thyroid disease, systemic lupus erythematosus, type 1 diabetes mellitus, and hemolytic anemia.[10]

DRESS is a life-threatening condition and early diagnosis, and removal of the causative drug are crucial. DRESS secondary to anti-tb drugs is rare, and a high index of suspicion is required. Patients need to be followed-up and monitored for long-term sequelae. All potential drug causes must be avoided in the future. Antivirals should be considered in patients with proven herpesvirus reactivation and clinical deterioration. Controlled studies, however, are needed to verify the role of antivirals in DRESS.

Conflicts of interest

None disclosed.

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