Detection of cytomegalovirus in the gastric ulcer of a patient with drug-induced hypersensitivity syndrome

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Key words: cytomegalovirus; drug-induced hypersensitivity syndrome; gastric ulcer.

INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse systemic reaction.[1] DIHS is characterized by its limited number of causative drugs, late onset, clinical similarity to infectious mononucleosislike syndrome, and prolonged clinical course owing to relapse.[2] Subjects with DIHS are known to show reactivation of human herpesvirus (HHV)-6, cytomegalovirus (CMV), Epstein-Barr virus, and HHV-7.[3] This report describes the case of DIHS with a dramatic reactivation of CMV and a development of gastric ulcers, in which CMV was immunohistochemically detected.

Abbreviations used:

CMV:	cytomegalovirus
DIHS:	drug-induced hypersensitivity syndrome
DRESS:	drug reaction with eosinophilia and systemic symptoms
HHV:	human herpesvirus
WBC:	white blood cell

CASE REPORT

A 78-year-old Japanese man presented with a fever of 39°C; pruritic erythematous rash over the entire body; and marked swelling, erosions, and crusts on the lips (Fig 1, *A*). In addition, purpura was observed on the legs (Fig 1, *B*); no ocular involvement was noted. Lymphadenopathy was observed in the bilateral cervical and axillary lymph nodes. The patient recently started carbamazepine for epilepsy. He developed a high fever 2 weeks after starting and a skin rash on his trunk and extremities 1 month after starting. Blood test findings showed a leukocyte count of 20,570 (normal range, 4,320-9,420) with 21.0% atypical lymphocytes and 3.5% eosinophils. Furthermore, marked elevated levels of aspartate aminotransferase (151 IU/L; normal range, 13-33 IU/L), alanine aminotransferase (322 IU/L; 6-27 IU/L), γ-glutamyltransferase (1369 IU/L; 10-47 IU/L), lactate dehydrogenase (571 U/L; 115-359 U/L), total bilirubin (4.8 mg/dL; 0.2-1.3 mg/dL), and C-reactive protein (7.89 mg/dL; <0.29 mg/dL) were detected. A drug lymphocyte stimulation test was performed on the 20th hospital day, with a positive result for carbamazepine (202%; normal index, <179%). In addition, a histologic examination of a skin lesion on the abdomen found liquefaction degeneration in the epidermis in addition to lymphocyte infiltration in the epidermis and papillary dermis (Fig 1, *C*). Based on these findings, we tentatively diagnosed the skin lesion as DIHS and administered prednisolone (PSL) at a dose of 60 mg/d. Treatment with sulfamethoxazole/trimethoprim was also initiated to prevent *Pneumocystis carinii* infection. The patient's temperature immediately decreased, and the skin lesions and liver dysfunction gradually improved. The serum HHV-6 IgG titer was 1:20 on the first hospital day and subsequently increased to 1:640 on the 30th hospital day. The proportion of CMV-specific antigenemia (C7-HRP)−positive cells was 11/50,000 of white blood cells (WBCs) on the 15th hospital days and then increased to 1,354/50,000 WBCs on the 30th hospital day. Therefore, ganciclovir treatment was started on the 30th hospital day. However, the patient suddenly had hematemesis on the 38th hospital day. At that time, the dose of PSL was tapered to 30 mg/d, and no skin lesions developed. An emergency endoscopic examination found

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Funding sources: None.
Conflicts of interest: None declared.
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JAAD Case Reports 2015;1:215-8.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.04.017

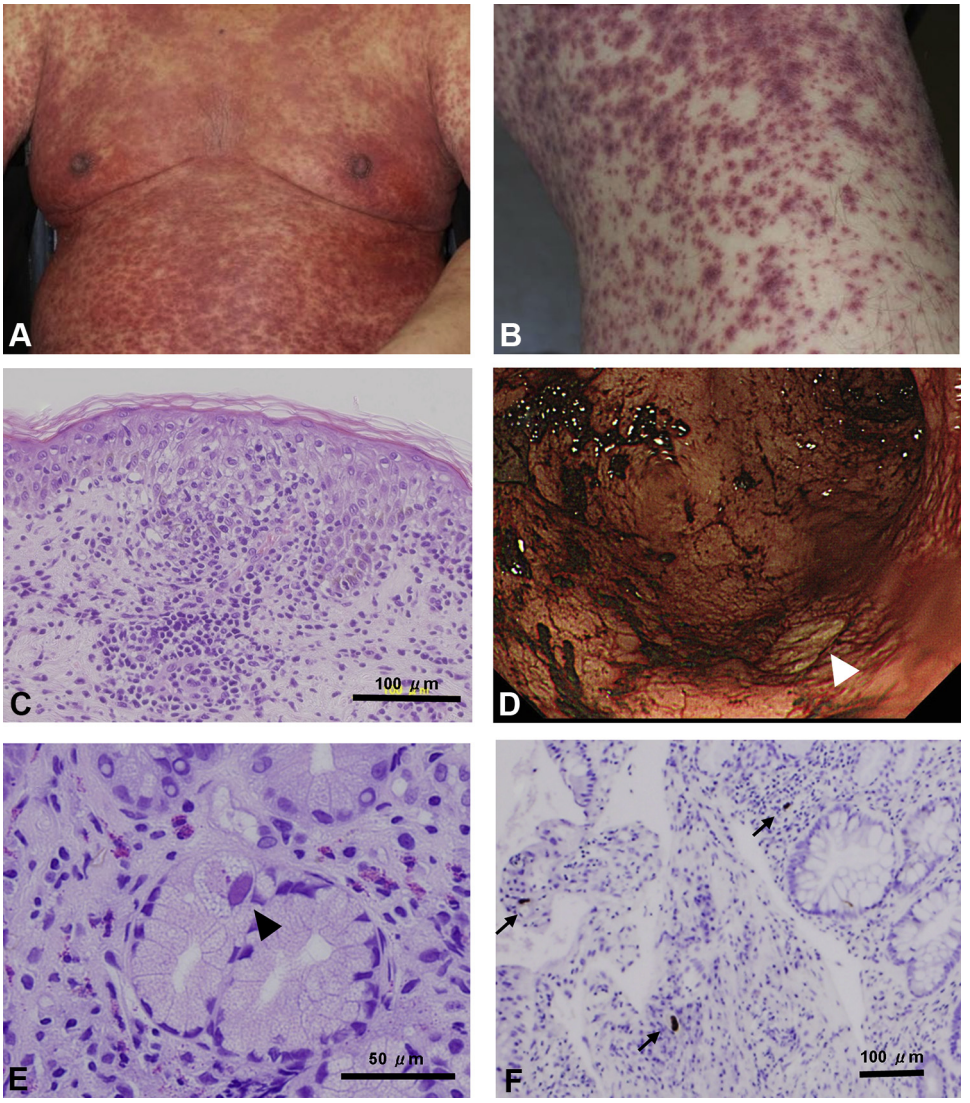

Fig 1. Clinical and histopathologic findings. **A**, Erythematous rash on the entire body. **B**, Purpura on the bilateral legs. **C**, Liquefaction degeneration in the epidermis and lymphocyte infiltration in the epidermis and papillary dermis. **D**, A punched-out ulcer (*arrowhead*) in the gastric wall. **E**, An intracellular inclusion body (*arrowhead*) in the pyloric gland. **F**, The detection of CMV antigens (*arrows*) around the fundic glands. (**C** and **E**, Hematoxylin-eosin stain.)

punched-out ulcers in the gastric wall (Fig 1, *D*), although the patient exhibited no clinical symptoms of gastric ulcers upon admission. Furthermore, intracellular inclusion bodies were histologically observed in the pyloric glands (Fig 1, *E*), and an immunohistochemical examination found CMV antigens around the fundic glands (Fig 1, *F*). These findings suggested a CMV-associated gastric ulcer. The gastric ulcer improved after treatment with a proton pump inhibitor and ganciclovir, and the number of C7-HRP–positive cells decreased to 1/50,000 WBCs on the 40th hospital day. However, the patient died thereafter of respiratory failure caused by pneumocystis carinii pneumonia on the 64th hospital day despite being on prophylaxis with sulfamethoxazole/trimethoprim. His clinical course is shown in Fig 2.

DISCUSSION

The following criteria for the diagnosis of DIHS/DRESS have been proposed by the Japanese consensus group: 1) morbilliform eruption developing greater than 3 weeks after starting therapy with a limited number of drugs, 2) lymphadenopathy, 3) a fever (>38°C), 4) leukocytosis (>10 × 10^9/L), atypical lymphocytosis (>5%) or

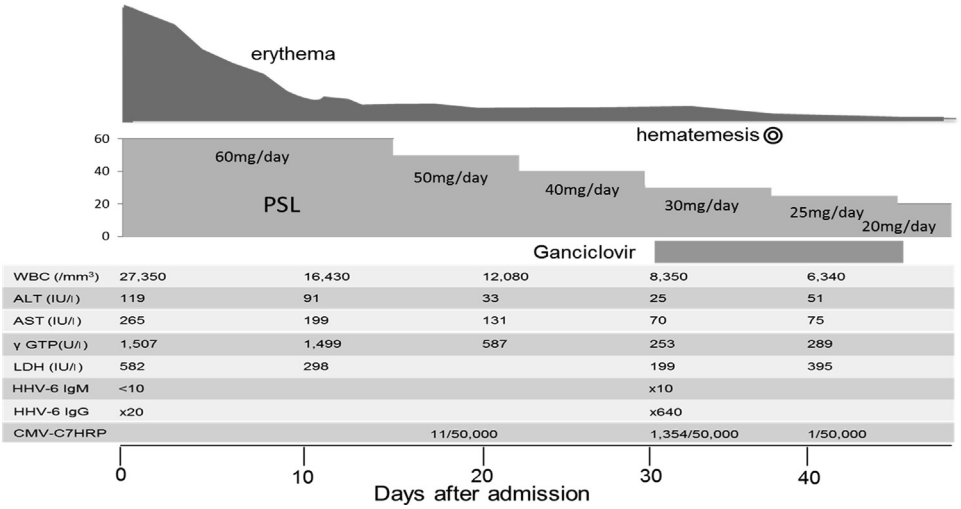

Fig 2. Clinical course of the patient. *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *GTP*, guanosine-5′-triphosphate; *LDH*, lactate dehydrogenase.

eosinophilia (>1.5 × 10^9/L), 5) hepatitis (alanine transaminase >100U/L), and 6) HHV-6 reactivation. The diagnosis requires the presence of 5 of the 6 criteria including HHV-6 reactivation.[4] CMV reactivation can cause serious symptoms in immunocompromised subjects, such as organ transplant recipients and those receiving immunosuppressive agents.[5] The reactivation of CMV is also experienced by severe DIHS patients, and it has been previously reported in approximately 30% of DIHS patients.[6] A patient with CMV reactivation clinically has recurring transient fever, cutaneous eruptions, or various severe complications. In particular, gastrointestinal bleeding, myocarditis, and pneumonia may occasionally be fatal in DIHS patients. Asano et al[7] previously reported the case of 2 DIHS patients with CMV reactivation who had gastrointestinal hemorrhage and red papules with erosions on the trunk and CMV antigens in tissue specimens obtained from the skin lesions.[7] In this case, the number of C7-HRP–positive cells drastically increased during the period between the 15th and 30th hospital days, and CMV antigens were detected in the tissue specimen of the gastric ulcer; therefore, we speculate that marked CMV reactivation may have occurred in this patient and that immunosuppression caused by treatment with high-dose PSL may have exacerbated this situation. CMV is rarely observed in cases of gastric ulcers in immunocompromised patients[8,9]; however, to our knowledge, there are no previous reports of the detection of CMV antigens in the gastric mucosa of patients with DIHS.

Elderly and male DIHS patients, similar to this patient, are reported to have increased risk of CMV disease.[7] In the event of no response to oral steroids, pulsed intravenous high-dose corticosteroid therapy during the acute stage is considered a therapeutic option for DIHS patients, although the degree and duration of HHV-6 and CMV reactivation may be enhanced.[10] In addition, a rapid reduction in the WBC count during the clinical course may be a useful predictor of the development of CMV disease. Gastrointestinal bleeding caused by CMV is unpredictable and often takes a rapidly fatal course; therefore, early recognition of CMV reactivation is required for proper management in DIHS patients, and the prompt administration of anti-CMV treatment may prevent DIHS patients from having serious symptoms from CMV infection.

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