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SHORT COMMUNICATION

Involvement of Human Herpesvirus 6 Infection in Renal Dysfunction Associated with DIHS/DRESS

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Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a life-threatening multi-organ hypersensitivity reaction that appears after prolonged exposure to a limited number of drugs. DIHS/DRESS is often related to reactivation of human herpesvirus 6 (HHV-6) (1–3). Renal dysfunction sometimes affects the prognosis (4). However, the pathomechanism of DIHS/DRESS-related renal dysfunction remains unknown. We report here a patient with DIHS/DRESS in whom HHV-6 infection may have been involved in the pathogenesis of renal failure.

CASE REPORT

A 62-year-old Japanese man developed a high fever, oedematous erythema with scale on the face and pallor around the eyes (Fig. 1a), diffuse pruritic maculopapular erythema on the trunk (Fig. 1b), and bilateral cervical lymphadenopathy on day 28 of continuous administration of trimethoprim/sulphamethoxazole (TMP/SMX) 320 mg/day and 1,600 mg/day, respectively, given to treat refractory iliopsoas abscess caused by *methicillin-resistant Staphylococcus aureus* (MRSA), which was resistant to many antibiotics except for TMP/SMX. Laboratory tests on day 9 after onset revealed a white blood cell count of 17.9×10^3/μl with 29% atypical lymphocytes and 1% eosinophils, high concentrations of thymus and activation-regulated chemokine (105,300 pg/ml) (5) and slightly high concentrations of creatinine (1.37 mg/dl). Liver function tests were normal at the initial visit to the dermatologist on day 8 after onset (AST 21 U/l, ALT 18 U/l), but AST and ALT levels were elevated on day 17 after onset (AST 106 U/l, ALT 102 U/l). No HHV-6 DNA was detected by quantitative PCR in the peripheral blood mononuclear cells (PBMC) on day 9 after onset. HHV-6 DNA became positive on day 15 (2×10^3 copies/ml) and continued to be detected thereafter. The patient was diagnosed with DIHS/DRESS due to TMP/SMX. His symptoms disappeared on day 9 after initiation of 30 mg/day oral corticosteroid (prednisolone). However, he suddenly developed renal failure with a creatinine level of 9.13 mg/dl on day 79 after onset. Since renal function did not improve despite intensive therapy, haemodialysis therapy was initiated. The patient subsequently died from an opportunistic infection and multiple organ failure. An autopsy revealed interstitial nephritis with lymphocytic infiltration and necrotized tubular epithelial cells (Fig. 2a). HHV-6 DNA (8×10^2 copies/mg) was detected in an autopsy specimen of the kidney, while HHV-6 DNA was almost undetectable in other organs (8 copies/mg). Immunofluorescence and immunohistochemistry with an anti-HHV-6 monoclonal antibody (OHV-3) (6) revealed that tubular epithelial cells were positive for the HHV-6 antigen (Fig. 2b, 2c). Staining for HHV-6 in the patient's skin did not reveal any viral antigen.

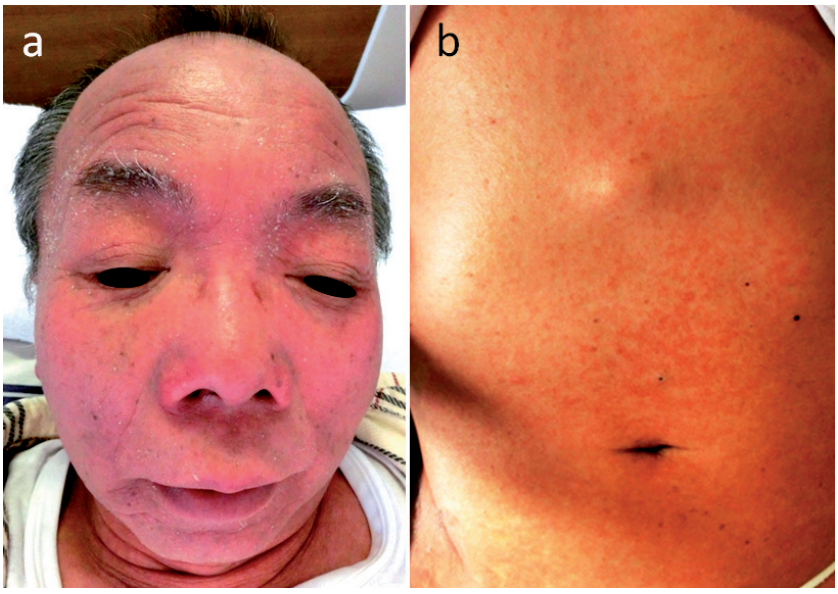

Fig. 1. Clinical appearance at onset. (a) Oedematous erythema with scale on the face and pallor around the eyes. (b) Diffuse pruritic maculopapular erythema on the trunk. The patient provided written permission to publish this photograph.

DISCUSSION

Renal dysfunction is occasionally observed in patients with DIHS/DRESS (10%) and sometimes affects the prognosis of these patients (4). In the case

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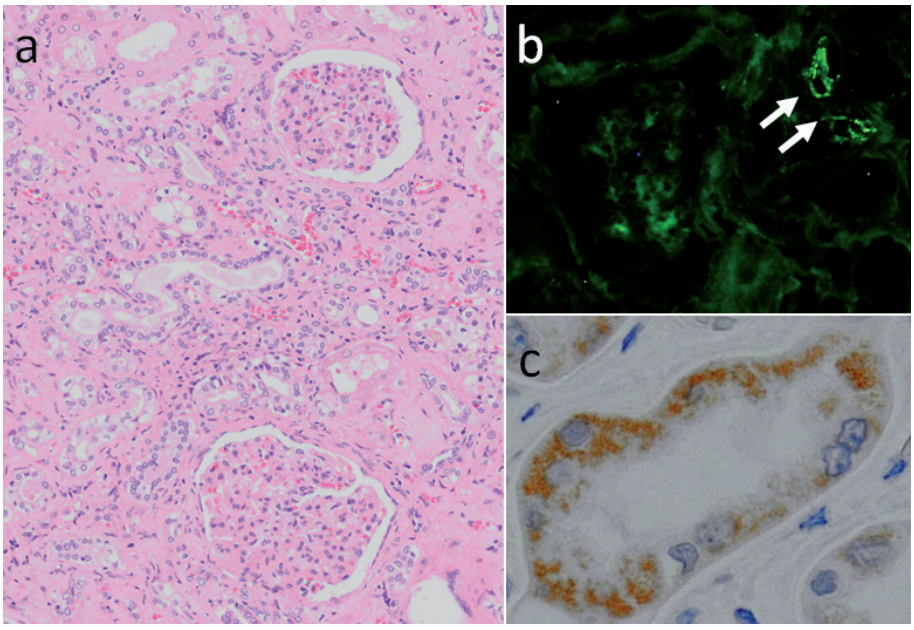

Fig. 2. Histopathological findings of the renal specimen. (a) Degenerated tubular epithelial cells, with lymphocytic infiltration in the renal interstitial region and minor abnormalities in the glomeruli. (H&E × 200) (b) Expression of human herpesvirus 6 (HHV-6) antigen in tubular epithelial cells by immunofluorescence with anti-HHV-6 monoclonal antibody (OHV-3, × 200) (*arrows*). (c) Expression of HHV-6 antigen in the cytoplasm of tubular epithelial cells by immunohistochemistry with OHV-3 (× 400).

described here, interstitial nephritis with lymphocytic infiltration was observed in a renal specimen from a patient with DIHS/DRESS, persistent HHV-6 infection was detected in the PBMC, significantly high HHV-6 viral load in renal specimens, and HHV-6 antigen expression in tubular epithelial cells. As no other cause of renal dysfunction was suspected in this case, these results suggest that HHV-6 may infect tubular epithelial cells and cause acute renal dysfunction in the course of DIHS/DRESS. The role of HHV-6 infection in allograft rejection has been examined in renal transplant recipients. Helanterä et al. (7) and Hoshino et al. (8) showed that HHV-6 antigen was expressed in tubular cells in renal transplant recipients, but they described no clear association of HHV-6 infection with renal dysfunction. On the other hand, some researchers have suggested that reactivation of HHV-6 may induce rejection of renal transplants (9). HHV-6 expression in affected organs of patients with DIHS/DRESS has not been reported previously. Although the involvement of HHV-6 infection in rejection of renal transplant is controversial, we conclude that HHV-6 may be associated with the pathogenesis of renal failure in this DIHS/DRESS case.

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