ineffectiveness of conventional acne treatments and, histopathologically, a voluminous sebaceous hyperplasia with a lack of inflammation. Since Dupre et al.'s report, eight cases of PSH have been reported in the English literature and the authors have emphasized these characteristics as being essential diagnostic elements (2–5). Of the eight previously reported cases, there was one case with a simultaneous acneiform eruption (6). Our case had a solitary PSH on his eyebrow for 10 years and simultaneous acneiform lesions. We propose that the absence of an acneiform eruption is not essential for a diagnosis of PSH. A solitary PSH is rare, but it can develop as an early presentation of multiple PSH or as a solitary PSH itself. There is no report presenting as a solitary PSH.

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Sequential Reactivation of Herpesvirus in Drug-induced Hypersensitivity Syndrome

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Sir,

Human herpesvirus 6 (HHV-6) reactivation has been implicated in the development of a drug-induced multiorgan system reaction that has been reported under a variety of names (1–3), such as anticonvulsant hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS). Recently we (2) and Hashimoto et al. (4) have demonstrated that HHV-6 reactivation is a reliable marker for an increased risk of developing this reaction and proposed to use the term 'drug-induced hypersensitivity syndrome (DIHS)'. We report here a patient with DIHS, in which not only anti-HHV-6 antibody titres but also other herpesvirus antibody titres were increased in sequential order during the course of the syndrome. Interestingly, similar sequential occurrence of herpesvirus reactivation has been well documented in immunocompromised patients after bone marrow transplantation (5, 6).

CASE REPORT

A 43-year-old man with a brain aneurysm had been treated with phenobarbital 300 mg daily. After 44 days, he noticed flu-like symptoms and erythematous rashes on his trunk. He was admitted to our hospital with suspicion of having acute hepatitis 3 days after the onset. Examination revealed a high-grade fever, bilateral cervical and inguinal lymphadenopathy, and hepatomegaly. No mucosal lesions were observed. Laboratory studies gave the following values: white blood cell count 11.8×10^9/l with eosinophil count 3.08×10^9/l; aspartate aminotransferase (AST) 273 IU/l (normal range 8–33); alanine aminotransferase (ALT) 770 IU/l (3–30); lactate dehydrogenase (LDH) 582 IU/l (200–470); C-reactive protein 12.7 mg/dl (<0.4). Serum IgG, IgA and IgM levels were 769 mg/dl, 47 mg/dl and 76 mg/dl (IgG 778–1794, IgA 80–413, IgM 37–254), respectively. A skin biopsy specimen obtained from the trunk revealed a dense infiltration consisting mainly of mononuclear cells and eosinophils in the upper dermis.

Generalized erythematous rashes coalesced to form erythroderma. The patient was treated with intravenous fluids for dehydration; neither systemic corticosteroids nor antibiotics were given during the admission period. Initially phenobarbital was not suspected as a causative drug, because the increased AST, ALT and LDH started to decrease after admission despite an increase in eosinophil number. These discrepant results are features of DIHS and often lead to a delay in diagnosis. Phenobarbital was finally discontinued, because his rash continued to deteriorate. Nevertheless, this was not followed by a prompt improvement of all symptoms, but 4 weeks later his manifestations finally subsided. Decreased serum immunoglobulin levels returned to normal 3 weeks after the onset.

Virological investigations were carried out on sequentially collected serum samples. The dramatic increase in anti-HHV-6 IgG titre was observed at first in the serum sample at 19 days after the onset. A similar increase was

detected in the anti-cytomegalovirus (CMV) IgM level. Anti-HHV-7 IgG titre was also markedly increased following the increase in HHV-6 IgG and CMV IgM levels. In contrast, no increases in either IgM or IgG antibodies against Epstein–Barr virus (EBV) or antibodies against EBV nuclear antigen were observed. Serological tests for hepatitis C virus, human immunodeficiency virus and human T-cell leukemia virus-1 were negative.

DISCUSSION

HHV-6 reactivation has frequently been observed in DIHS (1–3, 7, 8) but not in other severe drug-induced reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (9). Furthermore, recent articles have suggested that reactivation of other herpesviruses besides HHV-6 might also be involved in the development of DIHS (10, 11). We previously demonstrated that reactivation of HHV-7 together with HHV-6 occurred in a patient with DIHS (2). Aihara et al. (10) reported that reactivation of CMV, but not HHV-6, may occur in phenytoin-induced hypersensitivity syndrome. Descamps et al. (11) implicated EBV infection in the development of DIHS. HHV-7, CMV and EBV, along with HHV-6, are members of the herpesvirus family and share a propensity to cause illness characterized by fever and rash, and the capacity to reactivate under immunosuppressed conditions.

Considering the clinical similarity between DIHS and graft-versus-host disease (GVHD) (12) and the sequential occurrence of herpesvirus reactivation in these conditions, reactivation of HHV-6 and other herpesviruses may be responsible for the clinical manifestations of DIHS and result from immunosuppressive conditions. Indeed, we have provided evidence that DIHS could result when long-term use of anticonvulsants causes a decrease in immunoglobulin production and circulating B cells, probably via HHV-6 reactivation (9). If sequential reactivation is a possibility, then one may expect that higher incidence of HHV-6 reactivation detected around the third week after onset of DIHS may represent a secondary event that requires prior reactivation of other herpesviruses. Whether these herpesviruses reactivate from latency in obligate sequential order in DIHS, as demonstrated in GVHD (5, 6), is however unknown. A more frequent sampling of serum samples and peripheral blood in patients with DIHS is required to better determine the ordered sequential reactivation of these herpesviruses.

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