Clin Rheumatol (2008) 27:395–397
DOI 10.1007/s10067-007-0753-4

CASE REPORT

Sulfasalazine-induced hypersensitivity syndrome and hemophagocytic syndrome associated with reactivation of Epstein–Barr virus

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Received: 24 August 2007 / Accepted: 17 September 2007 / Published online: 19 October 2007

Abstract A 58-year-old woman with rheumatoid arthritis (RA) developed fever, skin eruptions, leukocytopenia, and thrombocytopenia, 3 weeks after treatment with sulfasalazine. A skin biopsy showed hydropic degeneration of keratinocytes and lymphocytic infiltrate. A bone marrow aspiration demonstrated an increased number of macrophages with hemophagocytosis. Although serologic tests for Epstein–Barr virus (EBV) indicated a previous infection, EBV deoxyribonucleic acid was detected in her serum by polymerase chain reaction. Cessation of sulfasalazine and administration of steroids led to dramatic improvement. This case illustrates that the hemophagocytic syndrome associated with reactivation of EBV can occur as part of drug hypersensitivity reactions in RA patients taking sulfasalazine.

Keywords Drug-induced hypersensitivity syndrome · Epstein–Barr virus · Hemophagocytic syndrome · Sulfasalazine

Introduction

Drug-induced hypersensitivity syndrome (DIHS) is characterized by a severe multiorgan hypersensitivity reaction that usually appears 2–4 weeks after the exposure of certain drugs such as anticonvulsants [1, 2]. A possible etiologic role of herpesviruses including human herpes virus 6 (HHV-6) in the development of this syndrome has recently been suggested [3]. Sulfasalazine (salazosulfapyridine), a common therapeutic drug used to treat rheumatoid arthritis (RA) and inflammatory bowel disease, has been identified as a type of DIHS associated with reactivation of HHV-6 [4, 5].

We describe a previously unreported association of sulfasalazine-induced hypersensitivity syndrome, hemophagocytic syndrome (HPS), and reactivation of Epstein–Barr virus (EBV) in a patient with RA.

Case report

A 58-year-old Japanese woman with a 3-year history of Sjögren syndrome and a 1-month history of early RA had been treated with sulfasalazine (1 g/day) and prednisolone (10 mg/day) from May 12, 2006. On the 11th day after treatment was initiated, she developed fever and skin eruptions. These symptoms were improved by treatment with intravenous hydrocortisone sodium phosphate. However, she redeveloped high fever and progressive skin eruptions and was admitted to our hospital on June 5.

A physical examination showed a maculopapular rash over the face, trunk, and extremities and mild cervical lymphadenopathy. The liver and spleen was not palpable.

Leukocyte count was 1,100/μl (6% eosinophils and 7% atypical lymphocytes), hemoglobin 12.7 g/dl, platelet count 86,000/μl, lactate dehydrogenase 476 U/l (normal 119–229), triglyceride 152 mg/dl, ferritin 365.5 μg/l, C-reactive protein 1.65 mg/dl, and IgE 1,590 IU/ml (normal<250). Serologic tests for antibody titers to HHV-6 and EBV showed previous infections. However, EBV deoxyribonu-

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cleic acid was detected in her serum by polymerase chain reaction (Fig. 1).

A skin biopsy revealed hydropic degeneration and necrosis of keratinocytes at the basal cell layer and lymphocyte infiltrate in the dermis (Fig. 2). A bone marrow aspiration showed an increased number of macrophages with prominent hemophagocytosis (Fig. 3).

From these findings, we considered that she had sulfasalazine-induced hypersensitivity syndrome and HPS associated with reactivation of EBV. Treatment with sulfasalazine was discontinued, and methylprednisolone pulse therapy (0.5 g×3 days) was begun on the second hospital day. Thereafter, oral prednisolone was tapered with dramatic improvement of the clinical symptoms and laboratory findings.

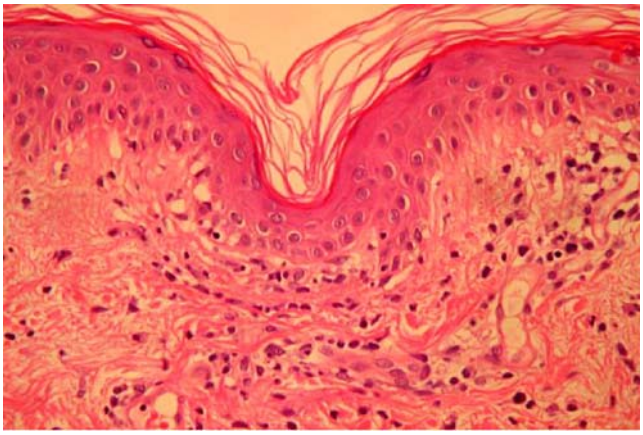

Fig. 2 A skin biopsy specimen showing hydropic degeneration and necrosis of keratinocytes at the basal cell layer and lymphocyte infiltrate in the dermis (hematoxylin–eosin, original magnification ×400)

Discussion

In some patients with sulfasalazine-induced hypersensitivity syndrome, reactivation of HHV-6 has been reported [4, 5]. Our case suggests that reactivation of EBV can also occur in patients with DIHS because of sulfasalazine, like in carbamazepine- and allopurinol-induced hypersensitivity syndrome [3, 6]. On the other hand, Halmos et al. [7] reported a case of a patient with marked peripheral blood lymphoplasmacytosis associated with a reaction to sulfasalazine and a concurrent acute EBV infection.

It is well known that adult HPS is caused by viral and bacterial infections, especially by EBV infection [8]. This syndrome is also caused by autoimmune disorders: There are several cases of HPS in patients with RA [9–11]. In these cases, HPS was caused by infections, and the onset of RA alone was never found to be responsible for HPS. In the case reported by Onishi and Namiuchi [10], reactivation of EBV was suggested. We therefore consider that HPS in our patient was due to reactivation of EBV.

To our knowledge, there is only one case report suggesting an association of DIHS, HPS, and reactivation of virus [12]. In this case of a patient with epilepsy, phenobarbital was the causative drug, and HSP was possibly associated with reactivation of HHV-6. Our case illustrates that HSP associated with reactivation of EBV can occur as part of drug hypersensitivity reactions in RA patients taking sulfasalazine. Virus-associated HSP should be taken in consideration in the event of unexplained progressive cytopenia during the course of DIHS.

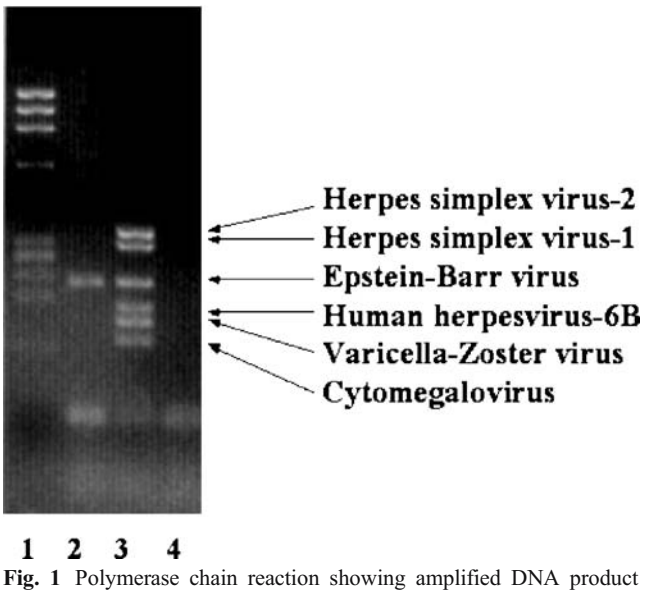

Fig. 1 Polymerase chain reaction showing amplified DNA product for EBV in the serum. *Lane 1*, size marker; *lane 2*, patient's serum; *lane 3*, positive control; *lane 4*, negative control

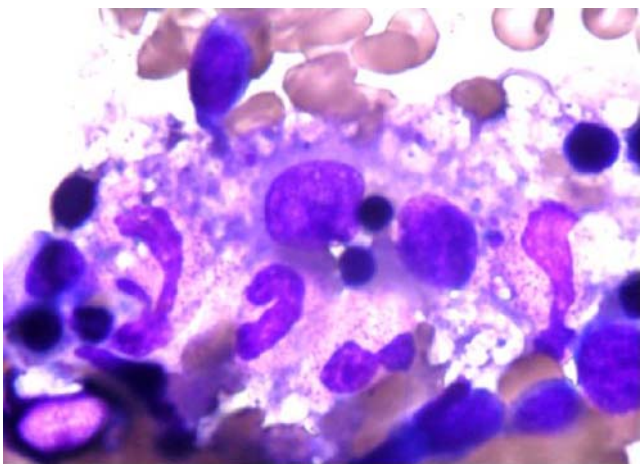

Fig. 3 A bone marrow aspirate showing macrophage with prominent hemophagocytosis (May–Giemsa, original magnification ×1,000)

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