Acute Promyelocytic Leukemia with Drug-induced Hypersensitivity Syndrome Associated with Epstein-Barr Virus Infection

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Abstract

We report a case of acute promyelocytic leukemia (APL) with drug-induced hypersensitivity syndrome associated with Epstein-Barr virus (EBV) infection. A 33-year-old woman was admitted because of APL. After complete remission was obtained with the use of all-trans retinoic acid (ATRA), intensive chemotherapy was administered. She developed high grade fever and severe systemic erythematous eruptions followed by cervical lymphadenopathy, hepatosplenomegaly, hepatitis and hypotension in a state of myelosuppression during consolidation chemotherapy. Systemic corticosteroids alleviated the symptoms. Since an anti-EB VCA IgM antibody titer was continuously positive, persistent infection of EBV was suspected. In this case, EBV infection may have contributed to the development of drug-induced hypersensitivity syndrome.

Introduction

Hypersensitivity syndrome is a type of severe cutaneous adverse reaction to drugs (1). These reactions are characterized by pleomorphic eruption, fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, hepatitis and multiple organ failure, and usually occur 2 to 5 weeks after initiating treatment with the drugs (2). Some recent reports suggest that the reactivation of viruses, such as human herpes virus 6 (HHV-6), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), may contribute to the development of drug-induced hypersensitivity syndrome (3–5). Here, we report a case of drug-induced hypersensitivity syndrome associated with EBV infection, which occurred in an acute promyelocytic leukemia (APL) patient receiving intensive chemotherapy.
based on a presumptive diagnosis of bacterial and fungal sepsis, but failed to improve, and developed severe systemic erythematous eruptions (Fig. 2) followed by cervical lymphoadenopathy, hepatosplenomegaly and hypotension (blood pressure 88/62 mmHg). She had no respiratory symptoms, and blood culture did not yield bacteria or fungus. As we suspected drug-induced eruptions, the antibiotics and antifungal agents were discontinued, and oral dexamethasone, 3 mg/day, was administered. The patient’s general condition and skin eruptions improved rapidly. EBV serological tests were performed on the 71st hospital day: early antigen IgG antibody, 0.5 (negative <1.0), virus capsid antigen (VCA) IgM antibody, 4.0 (negative <1.0), VCA IgG antibody, 11.5 (negative <1.0), Epstein-Barr virus nuclear antigen, 15.7 (negative <1.0). It was thought that the cause of fever, rash, cervical lymphadenopathy and hepatosplenomegaly was primary infection or persistent infection of EBV. Bone marrow examination after the first cycle of consolidation chemotherapy revealed that the complete remission was maintained.

High grade fever and severe systemic erythematous eruptions developed again during the second cycle of consolidation chemotherapy (cytarabine and idarubicin hydrochloride) starting on the 120th hospital day. Hepatitis occurred, with alanine aminotransferase 67 IU/l (normal <34), and aspartate aminotransferase 99 IU/l (normal <40). Drug-induced eruption due to cytarabine was considered; however the symptoms progressed even after cytarabine was discontinued. Oral dexamethasone, 3 mg/day, alleviated the symptoms again. The anti-EB VCA IgM antibody titer was positive after the second cycle of consolidation chemotherapy. Anti-CMV IgM and IgG antibody titers were negative. Anti-HHV-6 IgM antibody titer was negative, and anti-HHV-6 IgG antibody titer was 1:320 at the same time and 14 days later. We diagnosed that EBV infection activated persistently. A skin biopsy specimen obtained from the upper portion of the patient’s right arm showed infiltration of eosinophils and lymphoid cells in the epidermis and dermis (Fig. 3). Patch tests for 50% of imipenem/cilastatin sodium, panipenum/betamipron, cefozopran hydrochloride and fluconazole were examined. Cefozopran hydrochloride and fluconazole were positive. The patient was diagnosed as having hypersensitivity against antibiotics and antifungal agents.

We used dexamethasone, 3 mg/day orally for prevention of drug-induced hypersensitivity syndrome during and after the third cycle of consolidation chemotherapy (daunorubicin hydrochloride, etoposide and enocitabine), and no fever or systemic eruptions developed.

**Discussion**

Cutaneous eruptions frequently occur in leukopenic patients who receive multiple drugs, including antineoplastic agents, antibiotics and antifungal agents. The differential diagnosis of these eruptions includes sepsis, viral exanthema, leukemia or lymphoma cutis, and drug-related hypersensitivity or toxicity. Hypersensitivity syndrome is marked by severe cutaneous adverse reactions to drugs, and typically includes pleomorphic eruption, fever, lymphoadenopathy, eosinophilia, atypical lymphocytosis, hepatitis and multiple organ failure (2). The clinical features are similar to those of infectious mononucleosis, and usually appear two to six weeks after administration of the drugs (1). Severe cutaneous adverse drug reactions can become lethal with time. Drug-induced hypersensitivity syndrome is potentially life-threatening, and the mortality rate is estimated at about 10% (6). The syndrome has been reported with administration of sulfasalazine, anticonvulsants, dapsone, allopurinol, and several other medications (7–9). The present case was considered to be induced by multiple drugs, such as antibiotics and antifungal agents.

Skin eruptions occur in 3–15% of patients with primary EBV infection. However they are observed in 90% of these
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patients treated with ampicillin (10, 11). Patients infected with human immunodeficiency virus have a 1,000-fold higher risk of developing a severe drug eruption (12). These observations suggest that underlying viral infections contribute to the pathogenesis of severe cutaneous drug reactions. Recently evidence for a possible association between drug-induced hypersensitivity syndrome and HHV-6 infection has been reported (2, 3, 5). HHV-6 is a cause of exanthema subitum, which infects at least 90% of individuals by 2 years of age. This virus can persist in the host in a latent form after primary infection and is thought to be reactivated only during immunosuppression. In addition, HHV-6 is an important agent for fevers of unknown origin, interstitial pneumonia, diarrhea, and myelosuppression after bone marrow transplantation (13). Although the pathogenesis of drug-induced hypersensitivity syndrome is still unclear, Tohyama et al hypothesized that T cell activation develops as an immune response to reactive drug metabolites, and HHV-6 reactivated by activated T cells affects the general condition of patients and causes infectious mononucleosis-like symptoms (2). In the present case, the possibility of HHV-6 reactivation was low since the anti-HHV-6 IgG antibody titer was relatively low.

Primary EBV infection in infancy appears to be mostly asymptomatic, and approximately 50% of primary infections in adolescence or early adulthood present symptoms in the form of infectious mononucleosis (14). It has been demonstrated that EBV, like HHV-6, is associated with the drug-induced hypersensitivity syndrome (5). EBV encodes a protein homologous to cellular cytokine IL-10, which is a negative regulator of IL-12. Mizukawa and Shiohara suggested that drug-specific T cells could be activated through an increased level of proinflammatory cytokines resulting from EBV infection (5). The occurrence of EBV reactivation has rarely been reported in conventionally treated patients with acute leukemia (15, 16).

The diagnosis of hypersensitivity syndrome may be delayed because of its relatively late onset, slow evolution, and clinical similarity to many infectious illnesses (1). In the present case, we first suspected an acute infectious disease as the cause of fever, eruption, sore throat, cervical lymphadenopathy, hepatosplenomegaly, hepatitis and hypotension mimicking septic shock. Pediatr Dermatol 22: 2285–2290, 1995.

However, no data supporting acute bacterial and fungal infections became evident: blood cultures were negative, endotoxin and beta D glucan were negative in serological studies, and the patient failed to improve with systemic antibiotics and antifungal agents. The anti-EB VCA IgM antibody titer was continuously positive throughout the clinical course, indicating persistent infection of EBV. Further, since this patient did not have a rheumatoid factor, the possibility of false-positivity for anti-EB VCA IgM antibody was excluded. It is possible that EBV infection may have contributed to the development of drug-induced hypersensitivity syndrome in this case.

The symptoms of hypersensitivity syndrome often progress for several weeks after treatment with the drug is discontinued. Systemic corticosteroid therapy generally improves the condition and has been widely recommended (1, 8). Corticosteroids suppress an excessive immune response to drug metabolites and/or inhibit the production of cytokines triggered by massively replicated viruses (2). In the present case, the symptoms improved dramatically with corticosteroid therapy. Moreover, the appearance of symptoms was successfully suppressed by corticosteroid therapy during and after the third course of consolidation chemotherapy.

In conclusion, we have demonstrated that a case of drug-induced hypersensitivity syndrome due to antibiotics and antifungal agents, which was thought to be associated with EBV infection, occurred in an APL patient receiving intensive chemotherapy. Our findings suggest that a synergistic interaction between virus and drug-induced immune responses should be considered when fever and systemic eruptions present in leukopenic patients during chemotherapy, and it is necessary to measure antibody titers such as those to EBV, HHV-6 and CMV.

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References

13) Michel D, Muller S, Worz S, et al. Human herpesvirus 6 DNA in...