Toxic Epidermal Necrolysis Due to Zonisamide Associated With Reactivation of Human Herpesvirus 6

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Background: Recently, human herpesvirus 6 (HHV-6) reactivation has been frequently observed in patients with drug-induced hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms but not in patients with other types of drug eruptions, eg, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). This finding suggests that there is a close relationship between HHV-6 reactivation and drug-induced hypersensitivity syndrome.

Observations: A 71-year-old man who was not immunocompromised developed TEN because of zonisamide therapy. After the onset of the rash, significant increases in HHV-6 IgG titers and HHV-6 DNA levels were observed in the patient’s whole blood samples, indicating that an HHV-6 reactivation had occurred. Furthermore, the patient’s clinical manifestations of TEN appeared to recur concurrently with HHV-6 reactivation.

Conclusion: Our case suggests that HHV-6 reactivation may also occur in several types of drug eruptions, including Stevens-Johnson syndrome and TEN.

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It is well recognized that viral infections may play some role in the development of drug eruptions.1 Human herpesvirus 6 (HHV-6) is a member of the β-herpesvirus subfamily, which is in the Roseolovirus genus along with HHV-7.2 Like other herpesviruses, after the primary infection it establishes latency in different cells and organs, including monocytes and macrophages, salivary glands, brain, and kidneys. Reactivation of HHV-6 can occur both in normal individuals and in immunocompromised patients such as organ transplant recipients, resulting in various clinical symptoms. Recently, a number of reports have described a close relationship between HHV-6 reactivation and a severe form of drug-induced reaction, referred to as drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms.3-6 Drug-induced hypersensitivity syndrome is characterized by systemic mononucleosislike symptoms, including fever, rash, lymphadenopathy, eosinophilia, leukocytosis with atypical lymphocytes, and hepatic dysfunction. It is closely associated with adverse reactions to a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, zonisamide, allopurinol, sulfasalazine, dapsone, and meclozine. Reactivation of HHV-6 has been observed in the vast majority of patients with DIHS.7-12 Also, recurrence or worsening of signs and symptoms of DIHS is often seen concurrently with HHV-6 reactivation. As HHV-6 reactivation has not been previously reported (to our knowledge) to be associated with other types of drug eruptions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN),9,10,13 it is thought to be the most important diagnostic marker for DIHS that is reliable and easy to determine on a routine basis.7,14

Zonisamide is a synthetic 1,2-benzenoxazole-3-methanesulfonamide with anticonvulsant properties. According to the manufacturer, rash occurs in 1% to 2% of Japanese patients who take zonisamide. In Japan, zonisamide therapy is known to be the main cause of both DIHS and TEN, followed by carbamazepine and phenobarbital. We report a case of TEN caused by zonisamide therapy that was associated with HHV-6 reactivation.

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CASE REPORT

A 71-year-old man was referred to our hospital with a fever and a rash that involved his entire body. He had been receiving long-term valproate sodium therapy for...
symptomatic epilepsy that developed after surgical treatment of a cerebral aneurysm. However, convulsions had recently recurred, and zonisamide therapy (300 mg/d) was initiated. Twenty-three days later, after a rash developed and the patient’s temperature increased (to 40.2°C), the zonisamide therapy was discontinued. Physical examination revealed numerous flat targetlike lesions on the trunk and extremities, some of which had flaccid blisters (Figure 1A). The erythematous macules rapidly increased in number and size and became confluent, resulting in diffuse areas of erythema with erosions and blisters located on the trunk and upper extremities (Figure 1B). Finally, approximately 40% of the total body surface area became detached, and the Nikolsky sign was present. There were extensive hemorrhagic erosions on the lips, oral mucosa, pharynx, and larynx; conjunctival injection was also noted (Figure 1C). Laboratory studies disclosed the following values: alanine aminotransferase, 48 U/L (reference range [RR], 4-43 U/L); lactate dehydrogenase, 379 U/L (RR, 115-280 U/L); γ-glutamyl transpeptidase, 111 U/L (RR, 10-47 U/L), and C-reactive protein, 11.3 mg/L (to convert to nanomoles per liter, multiply by 9.524) (reference value, <0.3 mg/L). The complete blood cell count was within normal limits. On analysis of the peripheral blood lymphocyte surface markers, 10.4% were CD4⁺ T cells and 62.5% were CD8⁺ T cells. The serum levels of IgG, IgA, and IgM were 1650 mg/dL (RR, 870-1700 mg/dL), 233 mg/dL (RR, 110-410 mg/dL), and 52.8 mg/dL (RR, 33-190 mg/dL), respectively (to convert to milligrams per liter, multiply by 10). A urine sample was positive for blood (3+). A skin biopsy specimen obtained from an erythematous macule on the dorsum of the foot showed prominent eosinophilic necrosis of the keratinocytes and a subepidermal blister. A moderate inflammatory infiltrate consisting of mononuclear cells was observed in the upper dermis (Figure 2). Therefore, the diagnosis of TEN was made clinically and histopathologically.¹⁵

Because the patient’s family declined therapy with systemic corticosteroids, intravenous immunoglobulin therapy (5 g/d) was administered for 3 days. The progression of the skin lesions appeared to slow, and the patient’s temperature decreased. However, 9 days after the onset, the skin eruption recurred, accompanied by a high fever. Targetlike lesions reappeared, and the residual targetlike lesions also flared. Leukocytosis with eosinophilia was transiently observed. At this time, pneumonia with pulmonary atelectasis developed but improved with antibiotic treatment. Three weeks after the initial onset, the patient’s clinical symptoms, including the skin lesions, resolved.

Serum and peripheral blood samples were obtained for virological examination 4 and 22 days after the onset of the rash. Titers of IgG antibodies to HHV-6 were determined using immunofluorescent antibody assay. The HHV-6 IgG antibody titers increased from 1:10 on day 4 to 1:1280 on day 22. However, there were no significant changes in specific IgG titers for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus between days 4

Figure 1. A, Numerous targetlike lesions on the abdomen; B, diffuse erythema with detachment of necrotic epidermis on the back; and C, extensive hemorrhagic erosions on the lips.

Figure 2. Biopsy specimen obtained from an erythematous macule on the dorsum of the foot shows prominent eosinophilic necrosis of the keratinocytes and a subepidermal blister (hematoxylin-eosin, original magnification ×100).
patients with DIHS. Therefore, in this case, the HHV-6 reactivation, as has been previously described in fever, which seemed to occur concurrently with the also had a recurrence of the skin eruption accompanied produced by an event specifically related to TEN. Our patient was not treated with systemic corticosteroids or other immunosuppressive therapy, and the intravenous immunoglobulin that was administered in this case and 22. Real-time quantitative polymerase chain reaction was used for the detection of HHV-6 DNA in a sample of peripheral blood. Results were expressed as HHV-6 DNA genome equivalents per 10^6 peripheral blood mononuclear cell equivalents on day 4 to 1.3 × 10^2 copies on day 22 (Figure 3).

Lymphocyte transformation tests (LTTs) for zonisamide were also performed on days 4 and 22. A stimulation index value of more than 1.8 was interpreted as a positive result. The results of LTTs were negative for zonisamide on day 4 (stimulation index, 1.5) but positive on day 22 (stimulation index, 46.1).

To date, there has been little evidence that SJS or TEN is associated with HHV-6 reactivation. However, in the present case of TEN, which was caused by zonisamide therapy, HHV-6 reactivation was confirmed by the increase in HHV-6 IgG titers and HHV-6 DNA levels in whole blood samples during the course of the disease. Because our patient was not treated with systemic corticosteroids or other immunosuppressive therapy, and the intravenous immunoglobulin that was administered in this case contained only low titers (1:40) of antibodies against HHV-6, the HHV-6 reactivation appeared to have been induced by an event specifically related to TEN. Our patient also had a recurrence of the skin eruption accompanied by fever, which seemed to occur concurrently with the HHV-6 reactivation, as has been previously described in patients with DIHS. Therefore, in this case, the HHV-6 reactivation may have played some role in the development of TEN. Because, to our knowledge, HHV-6 reactivation has not been previously reported in patients with SJS or TEN, it may be suggested that this case of TEN is exceptional. However, it should be noted that in the vast majority of patients with DIHS, HHV-6 reactivation can be detected at a particular time, namely 2 to 3 weeks after the onset of the eruption, which indicates that HHV-6 reactivation can easily be missed, even in patients with DIHS. In fact, to our knowledge, there are no detailed data on the collection times in patients with SJS or TEN. In the present case, the HHV-6 reactivation was indeed detected 3 weeks after the onset of the eruption. Therefore, we cannot exclude the possibility that HHV-6 reactivation has not been detected in previously reported cases of SJS or TEN owing to sampling being done at an inappropriate time.

The trigger of HHV-6 reactivation in DIHS remains to be clarified. Kano et al demonstrated that serum immunoglobulin levels decrease at the onset of DIHS, although it is known that anticonvulsant agents sometimes induce hypogammaglobulinemia, even without inducing DIHS. They suggested that hypogammaglobulinemia might induce HHV-6 reactivation through immunosuppressive effects. However, in the present case, no significant decreases in serum immunoglobulin levels occurred during the patient’s illness. Furthermore, given the fact that HHV-6 reactivation is not commonly observed in patients with hypogammaglobulinemia, hypogammaglobulinemia is not likely to be an important triggering factor of HHV-6 reactivation.

An allergic reaction to certain drugs or to their reactive metabolites might induce reactivation or propagation of HHV-6. In the vast majority of patients, only a very limited group of drugs have been found to be responsible for the development of DIHS. In Japan, zonisamide is known to be an important cause of both DIHS and TEN. A long lag time, commonly more than 3 weeks, between the initiation of medication treatment and the onset of clinical manifestations is characteristic of DIHS. In this context, it should be noted that it takes about 3 to 4 weeks before the eruption develops in most patients with TEN caused by zonisamide. Therefore, HHV-6 reactivation might be seen in patients with SJS or TEN owing to the limited number of drugs that cause DIHS.

Of interest, in our patient, the results of LTTs for zonisamide were negative during the development of the rash but became strongly positive after recovery. The value of LTTs as an in vitro assay for detecting drug-specific lymphocyte activation remains controversial. However, LTTs have proved to be rather useful both in cases of DIHS and in cases of TEN. In contrast to TEN cases, however, the results of LTTs for the responsible drug tend to be positive after recovery in DIHS cases. In this respect, the results of our LTTs for zonisamide are similar to those seen in cases of DIHS.

Although DIHS is characterized by fever, rash, lymphadenopathy, eosinophilia, leukocytosis with atypical lymphocytes, and hepatic dysfunction, most of these symptoms could be regarded as a consequence of HHV-6 reactivation. Therefore, in Japan, the determination of HHV-6 reactivation has been considered to be the most important diagnostic marker for DIHS. However, the present case of TEN associated with HHV-6 reactivation suggests that HHV-6 reactivation might not be the “gold standard” test for DIHS. Careful examination is needed to

Figure 3. Clinical course of the patient. HHV-6 indicates human herpesvirus 6; HHV-6 IgG is expressed as antibody titers, which were determined using immunofluorescent antibody assay; HHV-6 DNA is expressed as HHV-6 DNA genome equivalents per 10^6 peripheral blood mononuclear cell equivalents; IVIG, intravenous immunoglobulin; and LTT, lymphocyte transformation test (values are expressed as stimulation index [positive result, >1.8]).
determine whether HHV-6 reactivation can be detected in other types of drug eruptions, especially those caused by the drugs known to be responsible for the development of DIHS.

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REFERENCES