Allopurinol Hypersensitivity Syndrome Associated with Systemic Cytomegalovirus Infection and Systemic Bacteremia

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Abstract

A 43-year-old man developed fever, skin rash, eosinophilia, and severe renal and liver dysfunction following treatment with allopurinol. The patient died after 3 months of hospitalization. Autopsy revealed systemic cytomegalovirus infection and bacteremia.

Key words: AHS, CMV, HHV-6

Introduction

Allopurinol, a xanthine oxidase inhibitor, has become established as the drug of choice for preventing and treating conditions where there is an overproduction of uric acid. Allopurinol may, however, cause a severe, and sometimes fatal, hypersensitivity reaction in patients with pre-existing renal disease. Since the first reported case of allopurinol hypersensitivity in 1970 (1), more than 100 cases have been reported, to the best of our knowledge. We report what appears to be the first case of allopurinol hypersensitivity syndrome (AHS) associated with systemic cytomegalovirus (CMV) infection.

Case Report

A 43-year-old man with a history of hypertension, hyperlipidemia and chronic renal insufficiency (serum creatinine, 5.4 mg/100 ml) was admitted to our hospital because of malaise and subfebrile temperature on May 21, 1999. One month before admission, allopurinol (100 mg/day) was prescribed for his asymptomatic hyperuricemia in our outpatient clinic. Two weeks later, the patient developed high fever with an itching rash covering the whole body. A consultant dermatologist suspecting drug eruption, prescribed pastaron soft cream and white petrolatum. The patient stopped taking his medication consisting of allopurinol, imidapril hydrochloride, and kremedin 3 days before admission, and he stopped taking nifedipine and prarestatin sodium 6 days after admission.

On physical examination at admission, the patient was moderately ill. His temperature was 37.5°C; blood pressure, 140/60 mmHg; and pulse rate, 100 b.p.m. Erythema multiforme was seen covering the whole body, and aphtha with erosion was seen in the oral cavity. Stevens-Johnson’s syndrome was diagnosed by a dermatologist. Edema was seen on the face and lower extremities. Results of examination of the heart, lung and abdomen were normal. Laboratory data on admission showed no leukocytosis (6,300/mm3) with 12% eosinophils and 7% atypical lymphocytes. Serum creatinine was markedly elevated (10.9 mg/100 ml) and liver enzymes were abnormal (L-asparate: 2-oxogulutarate aminotransferase, 411 ZUl/l; L-alanine: 2-oxoglutarate aminotransferase, 796 ZUl/l; LDH, 1,641 IU/l; alkaline phosphatase, 646 ZUl/l; and y-glutamyl transferase, 100 IU/l). Mild proteinuria (1.2 g/day) was recognized. The urine sediment showed red cells, 5/high-power field; white cells, 20/high-power field; epithelial cells, 5/high-power field; and granular and waxy casts. The results of a test for human immunodeficiency virus were negative. A radiograph of the chest and ultrasound examination of the abdomen showed no abnormalities except for atrophic kidneys. Because of the persistence of high fever, enlargement of the rash and progression of renal dysfunction, treatment with prednisolone (20 mg/day) and hemodialysis was started on May 27, 1999. The results of a lymphocyte-stimulating test for allopurinol, which was performed on June 1, were negative. The rash gradually improved and the patient became afebrile. However, on June 10, fresh diffuse rashes with erosion appeared over the whole body, and Nikolsky’s sign was recognized, and ulcerous lesions were seen in a glans of the penis. A dermatologist made a diagnosis of toxic epidermal necrosis. A high fever appeared again on June 12, 1999. Pulse therapy with methylprednisolone (250 mg/day×3 days followed by 1,000 mg/day×3 days) was started on June 18, and plasma exchange with fresh frozen plasma (40 units) was started in combination with hemodialysis on June 23. On June 17, the anti-CMV IgM antibody titer was 0.53 and the anti-CMV IgG antibody titer was 8.6. Serologic
Figure 1. Clinical course. Antibiotics used were: cefotiam hydrochloride, fosfomycin sodium, panipenem/betamipron and fluconazole. Aty Ly: atypical lymphocyte, ALT: L-alanine: 2-oxoglutarate aminotransferase, AST: L-aspartate: 2-oxoglutarate aminotransferase, BUN: blood urea nitrogen, BT: body temperature, Eo: eosinophil, GCV: ganciclovir, LDH: lactate dehydrogenase, HD: hemodialysis was performed 20 times, methylprednisolone: 250 mg/day from June 18 to June 20, 1,000 mg/day from June 21 to June 23 and 500 mg/day from July 12. PE: plasma exchange was performed 12 times. PL: platelet, prednisolone; 20 mg/day from May 27 to June 17, 40 mg/day from June 24 to June 28, 80 mg/day from June 29 to July 5 and 40 mg/day from July 6. S-cr: serum creatinine, WBC: white blood cell, VC: vancomycin hydrochloride.
titers against other viruses (EB, mumps, measles, rubeola, VZV, and HSV) were not significantly high. Examination of CD4/CD8 showed 0.34 on June 17. Blood cultures examined on May 27 and June 15 showed negative results, but a blood endotoxin titer examined on June 22 was positive (35.3). An examination for CMV-DNA (PCR) from serum and skin swab performed on June 22 showed positive results. The results of examination for CMV antigenemia on June 12 and July 2 were as follows: C7HRP, 353 cells/42,000 WBC counts and 230 cells/38,000 WBC counts; C10, 128 cells/150,000 WBC counts and 138 cells/150,000 WBC counts; and C11, 92 cells/150,000 WBC counts and 149 cells/150,000 WBC counts. The titer of HHV6 IgG (FA) on June 24 was ×5,120, and it’s titer changed to ×640 on July 12. The titer of HHV6 IgM was negative. A blood culture showed positive for MRSA on July 7. Treatment with ganciclovir (50 mg/day) was started on July 7, and treatment with vancomycin (0.5 g/day) was started on July 9. Due to gradual progression of anemia and thrombocytopenia, treatment of red blood cells and platelets were given as necessary after June 23. Tarry stool was seen on July 7. Because of a decrease in the level of the patient’s consciousness, a leftward shift in the patient’s pupils, and appearance of convulsions, artificial respiration was started on July 9, but the patient died on July 17. A blood coagulation test was performed 6 times during the clinical course (on May 21 and 24, June 17, 21 and 28, and July 8) and all data (prothrombin time, thrombo test, activated partial thromboplastin time, and fibrinogen) were within normal limits, except for the abnormal data of the serum fibrin degradation products (FDP) examined on July 8 (20 μg/ml). The clinical course of the present case is shown as Fig. 1. An autopsy was performed with the consent of the patient’s family. Autopsy results showed that the primary glomerular lesion was mesangioproliferative glomerulonephritis. Microscopic examination of the skin lesion revealed that adjacent...
capillaries were dilated with a sparse distribution of perivascular mononuclear cell infiltrates and occasional endothelial cells exhibiting amphophilic intranuclear inclusion characteristics of CMV (Fig. 2). Immunohistochemical study revealed disseminated CMV infection involving the lung, myocardium, kidney adrenal gland, liver, pancreas, spleen, and skin(Fig. 3A, B). Hemophagocytosis was recognized in the spleen (Fig. 4). Septicemia (MRSA), with numerous microabscesses developing in many organs and with bacterial embolism causing ischemic organ injuries, was seen (Fig. 5).

**Discussion**

It was thought that the present case met the criteria of AHS because the patient had a clear exposure to allopurinol, a clinical picture of hepatic injury and acute on chronic failure, and a rash of toxic epidermal necrosis. Before the appearance of a rash, the patient was medicated with allopurinol, imidapril hydrochloride, nifedipine, kremedin, and parestatin sodium. All drugs except for kremedin and parestatin sodium are known to cause exanthema as a side effect (drug information). Although we should have observed the clinical course, stopping the administration of drugs one by one, we started treatment with prednisolone because of the patient’s clinical condition, which became worse day by day. And so, we could not determine which drug or drugs contributed to the appearance of rash. However, the drugs other than allopurinol have not been reported to cause drug-induced hypersensitivity syndrome. It was therefore thought that the patient’s rash was due to the medication with allopurinol (2–5).

The results of a lymphocyte stimulating test for allopurinol performed on June 1 (5 days after the start of medication with prednisolone) were negative, and it was thought that the medication with prednisolone may have caused the negative results.

The worsening of exanthema and the poor control of fever in spite of medication with prednisolone suggested secondary infection with bacteria and/or virus in the present case. Serological examinations revealed CMV reactivation and immunohistochemical study showed that multiple organs except for the brain, were infected with CMV. This is the first reported case of AHS associated with CMV infection.

A previous study showed that underlying viral infections may trigger and activate drug-induced hypersensitivity syndrome in susceptible individuals receiving certain drugs (5). On the other hand, in the case of chronic renal failure, it was reported that cellular immune responses were impaired and the level of both CD4 and CD8 lymphocytes were decreased but the CD4/CD8 ratios were within the normal range (6). Moreover, it has been reported that cell-mediated immunity directed toward allopurinol and more importantly to its oxipurinol metabolite is involved in the pathogenesis of AHS with chronic renal failure (7), and a significant increase in CD8 cells is found in the peripheral blood (8). On the other hand, coinfection with CMV and human herpes virus 6 (HHV6) (9) and the reactivation of CMV due to coinfection with HHV6 have been reported (10).

In the present case, as the patient had a long history of chronic renal failure, it was speculated that the patient had impaired cell immunity and that the medication with allopurinol accelerated the degree of impairment of cell immunity, as demonstrated by the low CD4/CD8 ratio. Moreover, treatment with prednisolone may reduce the T-cell response to the viral reactivation (11). These conditions may have induced the reactivation of HHV6 and CMV together, or the reactivation of CMV may have occurred due to coinfection with HHV6, though we should mind a possibility of the effect of treatment with prednisolone and/or plasma exchange on the titer of HHV6-IgG, which changed from ×5,120 (on June 24) to ×640 (on July 12). Retrospectively, we speculate that a discrepancy between LDH and AST/ALT, which examined on May 27 and 31, may have reflected the presence of the viral reactivation.

We thought that the possibility of underlying CMV infection before appearance of AHS could be excluded in the present case because the level of atypical lymphocytes in the peripheral blood was not remarkable and the patient had no lymphadenopathy or hepatosplenomegaly in the initial stage (12).

In the present case, although virus-associated hemophagocytic syndrome (VHPS) was speculated as a role of pathogenesis of cytopenia, a diagnosis of VHPS was not made because of the absence of splenomegaly (13).

It was previously reported that the presence of secondary sepsis must be suspected when the course of AHS is prolonged (1, 14, 15). Repeated blood cultures (May 27 and June 15) showed negative results, and a blood culture on July 7 showed positive results for MRSA for the first time in the present case. Autopsy examination revealed the presence of severe sepsis, and the presence of both sepsis and CMV infection must have been the life-threatening factors in the present case.

Septicemia (MRSA) and generalized CMV infection were recognized in the present case. Moreover, examination of autopsy specimens revealed spotty hemorrhages dispersed on the epicardium and gastric, pharyngolaryngeal and renal pelvic
mucosa. The results of a blood coagulation test showed the level of serum FDP to be weakly positive. The findings suggested an association with disseminated intravascular coagulation syndrome (DIC) in the present case (based on the diagnostic guideline for DIC by the 'DIC' Research Project from the Ministry of Health and Welfare, Japan).

It has been previously reported that the only means of minimizing the incidence of AHS is to limit the allopurinol therapy to accepted indications and to adjust the dosage for the patient's renal function (16). The dosage of allopurinol used in the present case (100 mg/day) was appropriate for a case of prolonged chronic renal failure (2), and the remission of rash should be expected with prednisolone therapy (1, 2, 9, 14, 15). Although the initial eruption decreased following the initiation of prednisolone therapy, a new rash appeared and developed into toxic epidermal necrosis. We speculated that the new rash might have been induced by CMV infection (17). If this was true, treatment with ganciclovir and tapering of the treatment with prednisolone should have been started as soon as possible. Although it was previously reported that skin biopsy is useful for the diagnosis of CMV-induced eruption (18-20), neither histological or immunohistochemical examination of two skin biopsies (June 24 and July 6) demonstrated CMV infection in the present case.

Examination of CMV-DNA antigens in the peripheral blood was the most useful diagnostic method until autopsy for CMV infection in the present case. Thus, if the clinical course of AHS is prolonged, CMV infection should be suspected, and an examination for CMV-DNA antigenemia in the peripheral blood should be performed.

References