A Case of Allopurinol Hypersensitivity Syndrome

Hyun Jin Jeon, M.D., Hyeong Don Bang, M.D., Kwang Ho Kim, M.D., Kwang Joong Kim, M.D.

Department of Dermatology, College of Medicine, Hallym University, Anyang, Korea

Allopurinol is a xanthine oxidase inhibitor widely used to control plasma uric acid levels. Serious and life threatening adverse effects such as the allopurinol hypersensitivity syndrome(AHS) are rare. We describe a 32-year-old female patient who was treated with allopurinol and developed fever, rash, and renal and liver dysfunction.
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Key Words : Allopurinol Hypersensitivity Syndrome

Allopurinol is a potent inhibitor of uric acid synthesis commonly prescribed for the treatment of hyperuricemic and hyperuricosuric states. Allopurinol may, however, cause a severe, and sometimes fatal hypersensitivity reaction in patients with pre-existing renal disease. In Korean dermatologic literature, 3 cases of AHS have been reported[1]. We describe a patient with a severe hypersensitivity reaction to allopurinol.

CASE REPORT

A 32-year-old female patient was admitted to hospital because of fever, rash, and malaise. Fourteen days before admission, a rash developed on the patient's trunk and extremities, and she was noted to be taking allopurinol. The patient had been taking furosemide irregularly for five years and she developed gout in her right great toe three years previously. Approximately two months after starting allopurinol(300mg/day) she first noticed the eruption. She had a history of psoriasis.

On examination, the patient appeared ill, had a temperature of 38.2℃ , a pulse rate of 78b.p.m, and a blood pressure 90/60mmHg. Generalized erythematous maculopapular rash was seen covering the whole body(Fig. 1). Initial laboratory tests showed leukocytosis(32.2×10^9/l). No left shift was seen. Her blood urea nitrogen level was elevated at 77.0mg/dl; serum creatinine, 3.9mg/dl; AST, 68IU/l; and ALT, 50IU/l. There was a proteinuria. A radiograph of the chest showed no abnormalities. Histopathologically, a biopsy revealed spongiosis, hydropic degeneration of basal layer, and extravasated erythrocytes. An inflammatry cell infiltrate composed of lymphocytes, neutrophils, and eosinophils was present in the dermis(Fig. 2). The combination of fever, rash, leukocytosis, and liver and renal insufficiency with recent use of allopurinol made the diagnosis of AHS likely. Allopurinol was discontinued and prednisolone(40mg/day) was instituted. Her cutaneous symptoms improved and liver and renal abnormalities subsided over 3 weeks. Two weeks after the subsidence of the skin lesions, patch and prick tests were performed with allopurinol. Results were negative.

DISCUSSION

Allopurinol is effective for the treatment of both

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Reprint request to : Hyun Jin Jeon, M.D., Department of Dermatology, College of Medicine, Hallym University, 896, Pyungchon-dong, Dongan-ku, Anyang, Kyunggi-do, 431-070, Korea
Tel. (031)380-3760, Fax: (031)386-3761
E-mail. hjinjeon@hanmail.net

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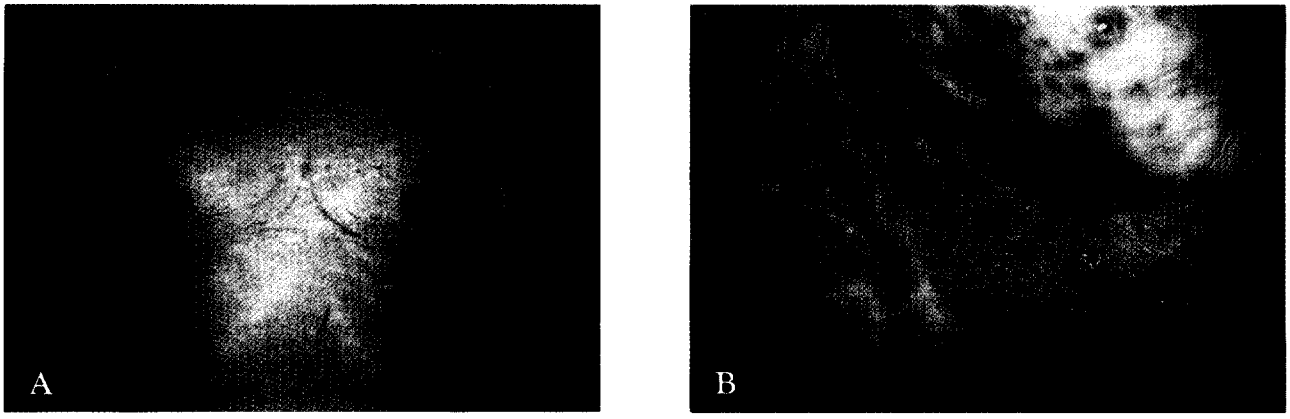

Fig. 1. A) Generalized erythematous maculopapules and papulopustules on the whole body. B) Close up view.

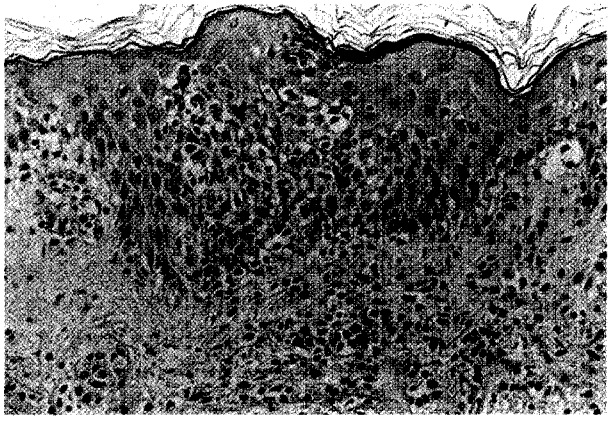

Fig. 2. Photomicrograph showing spongiosis, hydropic degeneration of basal layer, and extravasated erythrocytes. An inflammatory cell infiltrate composed of lymphocytes, neutrophils, and eosinophils is present in the dermis(H&E stain, ×200).

the primary hyperuricemia of gout and that secondary to hematological disorders or antineoplastic therapy. The drug is generally well tolerated, but it induces a severe reaction in 1 of 260 patients[2]. The cutaneous reaction caused by allopurinol is predominantly a pruritic, erythematous or maculopapular eruption, but occasionally the lesion is exfoliative, urticarial, or purpuric. Transient leukopenia, leukocytosis and eosinophilia, hepatomegaly and elevated levels of aminotransferase activities in plasma, and progressive renal insufficiency also may occur[3].

The incidence of AHS is unknown, although it is thought to be very low. AHS is defined by a clear history of allopurinol use; a clinical picture consisting of two of the following major criteria or one major and one minor criteria: major: rash(diffuse maculopapular or exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis), worsening renal function, or acute hepatic toxicity; minor: fever, eosinophilia, or leukocytosis; and a lack of exposure to another drug that may have caused a similar clinical picture[4]. In our patient, the diagnosis of AHS was made by combination of fever, rash, leukocytosis, and liver and renal insufficiency with recent use of allopurinol. Onset is typically two to six weeks after beginning treatment, but this time period was extremely variable, ranging from 1 to 728 days[5].

The risk of development of AHS is related to the level of oxypurinol, the therapeutic metabolite of allopurinol. The half-clearance time of oxypurinol is far more prolonged than that of allopurinol and it markedly increases in conditions associated with diminished uric acid clearance, such as fasting, thiazide therapy or renal failure. Although the exact mechanism leading to the development of AHS is unknown, it is assumed that accumulation of oxypurinol leads to tissue damage evoking an immunological response with development of antibodies against tissue component, the formation of immune complexes, and subsequent tissue damage[6]. Data regarding the development of AHS in conjunction with interstitial nephritis and generalized vasculitis and arteritis suggest type III reaction. Deposition of IgG and complement component C3 in glomerular basement membrane and deposition of IgG and complement in the skin also have been reported. More recently, it was suggested that a T cell mediated immune reaction is involved in the pathogenesis of AHS[7]. The negative

patch test to allopurinol shown in the case may suggest that humoral immune mechanism caused the development of AHS.

Overall mortality in the reported cases is about 25%. The mortality rate was increased among patients who had AST concentrations greater than 500IU/l[6].

There is no established therapy for AHS. Clearly early recognition of the syndrome, withdrawal of the drug, and supportive care remain the mainstay of therapy. The use of corticosteroids is controversial. Because of the suspected immunological reaction as the cause of AHS, the use of corticosteroids seems justified. Hemodialysis can be used to lower the level of oxypurinol[8], but the therapeutic effect on the course of AHS has never been examined. In a patient for whom allopurinol therapy is clearly indicated, the dosage must be adjusted for renal function. If treatment with allopurinol cannot be avoided and the patient has experienced a hypersensitivity, one could consider desensitization[9].

We report a patient with a severe hypersensitivity reaction to allopurinol which was used for the treatment of gout.

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