ALLOPURINOL-INDUCED SEVERE HYPERSENSITIVITY WITH ACUTE RENAL FAILURE

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A 62-year-old male was sent to the emergency room due to a high fever and generalized skin rash after taking allopurinol for 9 days. Physical examination was normal except for the generalized skin rash presenting with erythematous macules. Complete blood count showed leukocytosis with eosinophilia. Blood biochemistry showed impaired renal and hepatic function. Pathologic examination concluded that the skin rash was erythema multiforme. These findings met the diagnostic criteria for allopurinol-induced hypersensitivity syndrome (AHS). Our patient not only had the most common skin lesion but soon developed acute renal failure that required intermittent hemodialysis, despite rapid discontinuation of allopurinol and adequate hydration and steroid therapy. No other causes of acute renal failure were found. Renal impairment was the worst part of the patient's condition and he never completely recovered. AHS should be considered in the differential diagnosis of acute renal and hepatic failure in patients with evidence of allergy and recent use of allopurinol.

Key Words: allopurinol hypersensitivity syndrome, erythema multiforme, acute renal failure
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Allopurinol, a purine inhibitor of the enzyme xanthine oxidase, inhibits the synthesis of uric acid and has become the most popular drug for hyperuricemia. It provides permanent symptom resolution in most patients with gout; 53% of patients receiving allopurinol 300 mg daily achieve optimal plasma urate concentrations [1]. In some patients, however, it is poorly tolerated and leads to a severe hypersensitivity reaction. We report a case of allopurinol-induced hypersensitivity syndrome (AHS) with acute renal failure that required intermittent hemodialysis, despite rapid discontinuation of allopurinol, adequate hydration, and steroid prescription. Impaired renal function was irreversible.

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CASE PRESENTATION

A 62-year-old man presented to our emergency room (ER) with a 4-day history of fever and widespread skin rash. He had taken allopurinol, 600 mg/day, for asymptomatic hyperuricemia for 9 days. Serum biochemistry revealed a blood urea nitrogen (BUN) of 7.14 mmol/L, serum creatinine of 132.6 μmol/L, aspartate aminotransferase (AST) of 86 U/L, alanine aminotransferase (ALT) of 180 U/L, and white blood cell count of 8.66×10^9/L. Physical examination was normal except for a generalized skin rash. He was given antihistamine and steroid under the impression of urticaria due to allopurinol-induced hypersensitivity. He left the ER with the advice to discontinue allopurinol and attend follow-up at the gastroenterology outpatient department (OPD) due to impaired liver function. No evidence of hepatitis B or C virus infection was found in the OPD, only fatty liver on sonographic examination. Due to the worsening rash and intermittent fever, he returned to the ER the next day. On physical examination, he was

moderately ill. His temperature was 39.3°C, blood pressure was 123/81 mmHg, and pulse rate was 87 bpm. The skin lesions had spread over the whole body surface as erythematous macules and his face was swollen and erythematous. Physical examination of the neck, heart, and lungs was normal. The liver was palpable 1 cm below the costal margin and the spleen was impalpable. Examination of the genitalia and rectum was normal. No edema was found on the extremities. Serum biochemistry showed leukocytosis (14.9×10^9/L) with eosinophilia (8.9%). Serum creatinine was elevated (159.1 μmol/L) and liver enzymes were also abnormal (AST, 41 U/L; ALT, 112 U/L). There was mild proteinuria (100 mg/dL), pyuria (white blood cell count, 5–10/high-powered field), and leukocyte cast (0–2/low-powered field). Chest radiography showed no abnormality. The patient was admitted to the infectious division under the initial impression of urinary tract infection. A first-generation cephalosporin and hydration therapy were prescribed soon after admission. Urine culture grew *Enterococcus*. Renal sonography revealed normal renal parenchyma without hydronephrosis. Since the skin lesions progressed from being wheals to erythematous macules, skin biopsy was performed and showed moderate superficial perivascular and periadnexal lymphocytic and eosinophilic infiltration. All of these findings were compatible with erythema multiforme. Combining this skin diagnosis with the clinical findings of fever, leukocytosis with eosinophilia, impaired liver and renal function, and the recent use of allopurinol, the diagnosis of AHS was made. He was then given steroid intravenously to relieve the hypersensitivity. Liver enzyme levels declined gradually. However, despite hydration and steroid treatment soon after admission, renal function impairment progressed with severe azotemia and even anuria. The patient then started intermittent hemodialysis therapy and was transferred to nephrology care. His urine output increased to 1,520 mL/day after the fifth hemodialysis but azotemia persisted. A second renal sonography revealed normal renal size with evidence of parenchymal injury. Renal function improved partially after eight intermittent hemodialysis treatments. He was discharged 25 days after admission and was followed regularly at our OPD but had remaining impaired renal function. His BUN level was 25.71 mmol/L and his creatinine level was 415.5 μmol/L 2 months after discharge.

The patient has been followed at our OPD for 3 years since his AHS episode and renal sonography has recently shown chronic renal parenchymal disease. The clinical course is summarized in the Figure; it included skin rash, fever, signs of oliguria, and initial deterioration and then partial recovery of renal function accompanying steroid therapy and intermittent hemodialysis during admission. It is noteworthy that he received steroids from our OPD. The serial changes in kidney and liver function and white blood cell and eosinophil counts are summarized in Table 1.

Discussion

Allopurinol is generally considered to be a safe and well-tolerated drug in treating hyperuricemia [2]; 53% of patients receiving allopurinol 300 mg daily achieve optimal plasma urate concentrations [1]. Nevertheless, there are variable adverse reactions, from itching, skin rash, low-grade fever, leukocytosis with eosinophilia, and bowel upset to severe life-threatening adverse effects of acute renal damage and

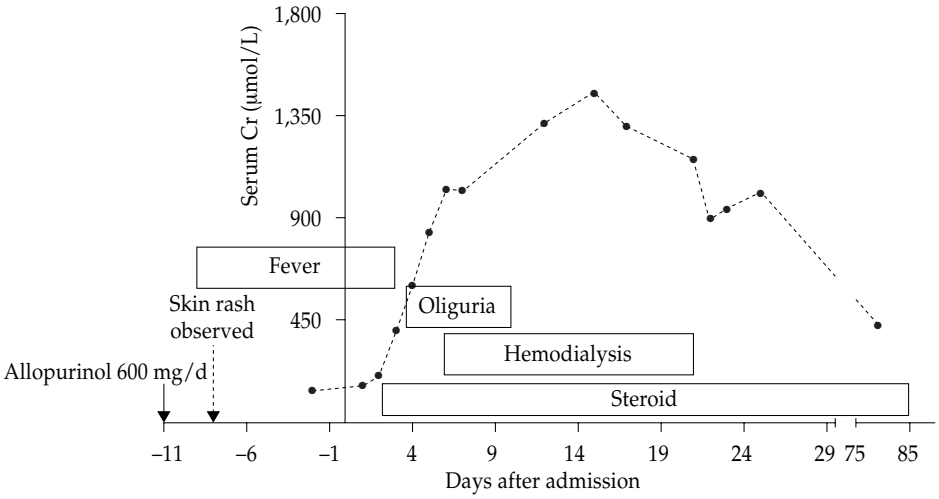

Figure. *Clinical course and changes in serum creatinine (Cr) levels.*

Table 1. Serial changes in kidney and liver function and white blood cell (WBC) and eosinophil counts

Component (normal range)	D–1 (O)	D1 (ER)	D2	D3	D4	D7	D12	D25
BUN, mmol/L (2.5–6.4)	7.1	7.9	10.0	20.7	29.6	41.4	58.0	42.5
Cr, μmol/L (53–115)	133	159	201	398	593	1,000	1,291	991
AST, U/L (10–42)	86	41	28				23	
ALT, U/L (10–40)	180	112	74				55	
WBC count, × 10^9/L (4.0–10.0)	8.66	14.99			10.98	9.24	8.39	6.97
Eosinophil count, % (0–4)		8.9					2.4	2.4

D–1 = 1 day before admission; DX = X days after admission; O = 1st visit to outpatient department; ER = 2nd visit to emergency room; BUN = blood urea nitrogen; Cr = serum creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

acute hepatocellular injury, termed AHS [3]. The frequency of AHS is about one in 260 (0.38%) patients receiving allopurinol therapy, and it begins within days or weeks of administration [3]. The acute renal failure in patients with AHS is usually reversible [1]. However, we report a patient with irreversible changes in renal function.

The development of AHS is related to the serum level of oxypurinol, the therapeutic metabolite of allopurinol. Oxypurinol inhibits xanthine oxidase by binding to it and preventing the conversion of hypoxanthine and xanthine to uric acid. Since the clearance of oxypurinol is dependent on renal excretion, AHS occurs mainly in patients with impaired renal function. The exact mechanism by which AHS develops is not clear. It is assumed that accumulation of oxypurinol triggers a type III hypersensitivity reaction, with development of diffuse vasculitis and even Guillain-Barre syndrome, due to damage of peripheral nerve myelin [4]. Previous studies also found the deposition of immunoglobulin (Ig) M at the dermal–epidermal junction and linear deposits of both γ-globulin and complement along the glomerular basement membrane [3,5]. Microscopic findings in the kidney are variable: acute interstitial nephritis [6], focal segmental glomerulosclerosis [7], and diffuse vasculitis [8] have all been described.

More than 80% of reported cases of allopurinol hypersensitivity had evidence of renal functional impairment before treatment, and most patients took the standard dose of 300 mg daily without any modification. Normally, the dose of allopurinol given to patients should be based on creatinine clearance (Table 2) [5]. In this patient, the dose of 600 mg/day was apparently too high for his age and too high for such an asymptomatic patient. AHS could have been avoided with diet control and a lower dose of allopurinol based on creatinine clearance if hyperuricemia had persisted.

The presence of a generalized skin rash presenting with erythematous macules, determined by skin biopsy to be erythema multiforme, accompanied by other signs such as fever, leukocytosis with eosinophilia, impaired renal and liver function, and a history of exposure to allopurinol in this case met the criteria for AHS [3]. Management of AHS depends on early recognition of the problem and withdrawal of allopurinol as soon as possible. Without early intervention, progressive renal failure is often inevitable and dialysis therapy is needed. There was an apparent delay in the diagnosis of AHS in this patient, as he was initially admitted to the infectious division under the impression of a urinary tract infection and was then transferred to the nephrology department due to progressive renal function deterioration. Delay in referral is often due to the fact that patients usually present with symptoms and signs mimicking urinary tract infection, such as hematuria, pyuria, as well as leukocyte cast. These findings, however, reflect the interstitial nephritis induced by the drug [9]. Various drugs simulate AHS, which is then termed drug hypersensitivity syndrome (DHS) (Table 3) [10]. DHS should be differentiated from protracted viral infection, hyper-eosinophilic syndrome, auto-immune disease, and lymphoma [10]. This

Table 2. Maintenance dose of allopurinol based on individual creatinine clearance rates (Ccr)

Ccr (mL/min)	Allopurinol
0	100 mg/3 days
10	100 mg/2 days
20	100 mg/day
40	150 mg/day
60	200 mg/day
80	250 mg/day
100	300 mg/day

Table 3. Drugs inducing hypersensitivity syndrome

Aromatic antiepileptics	Phenytoin
	Phenobarbital
	Carbamazepine
Dapsone	
Allopurinol	
Minocycline	
Antiretroviral drugs	Nevirapine
	Abacavir

patient was initially diagnosed as having ordinary urinary tract infection because the life-threatening events of kidney and liver failure were ignored. The increases in serum creatinine concentration from 132.6 to 159.1 μmol/L in less than 2 days in this patient should have alerted doctors to the rapid progression of renal damage.

In addition to the cessation of allopurinol in suspected cases of AHS, supportive and steroid therapies are also important. The length of steroid treatment should be adequate, since the early tapering of steroid may induce relapse of AHS and permanently impaired renal function [3]. In our case, the steroid was given early, the second day after admission, until after the hospitalization period was over. In spite of this management, irreversible renal damage occurred and the patient's kidneys progressively shrank. In patients for whom allopurinol is absolutely necessary, desensitization could be considered in those who have experienced a mild hypersensitivity reaction [11]. Alternatively, benzbromarone has been suggested as an effective serum uric acid-lowering drug in patients with both hyperuricemia and renal insufficiency [1,12].

Some patients have no reaction after higher-dose allopurinol treatment of hyperuricemia. The low prevalence of AHS in these patients cannot be adequately explained. A recent study of Han Chinese showed a strong association of a genetic marker, the human leukocyte antigen HLA-B*1502, with Stevens-Johnson syndrome induced by carbamazepine, a drug commonly prescribed for managing seizures [13]. Whether there is also any association with a genetic marker in AHS requires further investigation.

In summary, we report the development of a severe hypersensitivity reaction with acute renal failure in a patient with impaired renal function who took a high dose of allopurinol to treat asymptomatic hyperuricemia. Since renal function was not completely restored in this patient, we would emphasize that the adverse reactions of allopurinol should be kept in mind and that dose modification is needed in patients with pre-existing impaired renal function.

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服用 Allopurinol 治療高尿酸血症造成嚴重過敏反應合併急性腎衰竭

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一位 62 歲男性在服用 allopurinol 9 天之後因為發高燒和全身出現紅疹而被送到急診室。身體物理檢查除了全身紅疹之外，其餘均正常。完整血球數目檢查結果呈現白血球數目增多且有嗜伊紅血球症的現象。血液生化檢查則顯示有不正常的肝腎功能。住院後此病患接受皮膚切片檢查，病理診斷為多形性紅斑。這些以上的發現均符合allopurinol hypersensitivity syndrome (AHS) 之診斷條件。不幸的是儘管迅速停止 allopurinol 的服用和接受輸液以及類固醇治療，他仍因為急性腎衰竭接受了 8 次間斷性的血液透析治療才存活下來。而且最差的情況是他的腎臟功能並沒能完全恢復！因此當病人在使用 allopurinol 後有過敏的現象而且合併急性腎衰竭及肝衰竭時，allopurinol 過敏症候群 (AHS) 應該被考慮。

關鍵詞：allopurinol 過敏症候群，多形性紅斑，急性腎衰竭

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