

## Allopurinol Hypersensitivity Syndrome and Acute Myocardial Infarction—Two Case Reports

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### Abstract

**Introduction:** Allopurinol hypersensitivity syndrome is an idiosyncratic drug reaction characterised by an acute and severe multiorgan disease. It usually begins 2 to 6 weeks after starting allopurinol. The most important and critical characteristics are the presence of visceral involvement and haematological abnormalities; hepatitis, interstitial nephritis and eosinophilia are most frequently seen. However, cardiac involvement has not been previously reported. **Clinical Picture:** Two previously well young Chinese men presented with fever, rash and hepatitis 3 weeks after taking allopurinol. The clinicopathological presentation was typical of allopurinol hypersensitivity syndrome. **Treatment and Outcome:** Both men received systemic corticosteroid therapy and had full recovery. A few months later, they each had an acute myocardial infarction with a fatal outcome, despite minimal cardiac risk factors and no family history of coronary artery disease. **Conclusion:** The immunologic process in allopurinol hypersensitivity syndrome may have caused coronary vasculitis and subsequent myocardial infarct. Alternatively, the idiosyncratic reaction may have damaged myocardium, with the resultant myocarditis masquerading as coronary artery disease. Patients with allopurinol hypersensitivity syndrome should be followed up for cardiac involvement.

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**Key words:** Chinese, Corticosteroid, Coronary vasculitis, Drug hypersensitivity syndrome, Myocarditis, Young man

### Introduction

Allopurinol hypersensitivity syndrome is an idiosyncratic drug reaction characterised by an acute and severe multiorgan disease.<sup>1</sup> It usually begins 2 to 6 weeks (up to 3 months) after starting allopurinol. The patient often presents with fever and a rash. The most important and critical characteristics are the presence of visceral involvement and haematological abnormalities; hepatitis, interstitial nephritis and eosinophilia are most frequently seen. However, cardiac involvement has not been previously reported. Systemic corticosteroids are usually recommended for life-threatening systemic involvement; however, controlled studies to evaluate this treatment are lacking. We report 2 previously well young Chinese men who presented with allopurinol hypersensitivity syndrome, received systemic corticosteroid therapy and had full recovery. A few months later, they each had an acute myocardial infarction (AMI) with a fatal outcome, despite minimal cardiac risk factors and no family history of coronary artery disease.

### Case Reports

#### Patient 1

A 35-year-old Chinese man presented in July 1999 with a week's duration of fever, jaundice and an extensive

erythematous maculopapular rash after taking allopurinol for 3 weeks. Allopurinol had been prescribed for right heel pain and hyperuricaemia (uric acid, 516  $\mu\text{mol/L}$ ). He was admitted to the ward and investigations revealed eosinophilia (eosinophil count,  $828 \times 10^6/\text{L}$ ; white cells,  $13.8 \times 10^9/\text{L}$ ; haemoglobin, 15.6 g/dL; platelets,  $196 \times 10^9/\text{L}$ ) and hepatitis (bilirubin, 88  $\mu\text{mol/L}$ ; alanine aminotransferase, 1180 U/L; alkaline phosphatase, 229 U/L; prothrombin time, 14.6 seconds). Viral hepatitis markers (HBsAg, anti-HAV IgM and anti-HCV) were negative. He had mild hypertriglyceridaemia (triglyceride, 2.27 mmol/L; total cholesterol, 3.39 mmol/L). Renal function (creatinine, 97  $\mu\text{mol/L}$ ), urine microscopy (no red blood cells) and electrocardiography (ECG) were normal. Ultrasound of the hepatobiliary system was normal. Skin biopsy revealed superficial and deep perivascular dermatitis with eosinophils, consistent with a drug eruption. He was treated for allopurinol hypersensitivity syndrome with oral prednisolone 60 mg daily, tapering over 2 months. His rash and hepatitis improved. He was discharged after 8 days. Blood pressure and blood glucose levels were normal on follow-up. He was reviewed on 29 July 1999; the rash had almost resolved and the liver function test had improved (bilirubin, 8  $\mu\text{mol/L}$ ; alanine aminotransferase, 181 U/L). Oral prednisolone was stopped on 31 August 1999.

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He presented on 6 September 1999 with 3 days of epigastric pain and breathlessness. Full blood count was normal (eosinophil count,  $248 \times 10^6/L$ ; white cells,  $12.4 \times 10^9/L$ ; haemoglobin, 14.9 g/dL; platelets,  $404 \times 10^9/L$ ). Electrocardiogram revealed ST segment elevation in the anterior and inferior leads. The creatine kinase was raised (654 U/L). Chest X-ray (CXR) showed a small left pleural effusion. Echocardiography showed akinesis in the anterior segment of the heart with a poor left ventricular ejection fraction of 25%. The liver function test and urine microscopy were not done. He was treated for AMI with tissue-type plasminogen activator, heparin and aspirin. Unfortunately, he developed ventricular fibrillation and died 7 hours after admission.

#### *Patient 2*

A 36-year-old Chinese man presented in December 1999 with 3 days of fever and a generalised erythematous maculopapular rash after taking allopurinol for 18 days for left heel pain. Initial investigations revealed that he had a mildly deranged liver function test (bilirubin, 17  $\mu\text{mol/L}$ ; alanine aminotransferase, 123 U/L; alkaline phosphatase, 104 U/L; prothrombin time, 13.2 seconds). Full blood count revealed no eosinophils; white blood cells,  $13.4 \times 10^9/L$ ; haemoglobin, 10.1 g/dL; platelet,  $234 \times 10^9/L$ ; haemoglobin electrophoresis was consistent with beta-thalassaemia minor and serum iron was normal. Viral hepatitis markers (HBsAg, anti-HAV IgM and anti-HCV) were negative. Ultrasound of the hepatobiliary system, renal panel (creatinine, 68  $\mu\text{mol/L}$ ), urine microscopy (red blood cells, 1-2/high power field), ECG and CXR were normal. He was diagnosed to have allopurinol hypersensitivity syndrome.

Treatment with corticosteroids was started: intravenous hydrocortisone 100 mg 6-hourly for 2 days and subsequently oral prednisolone 45 mg om. However, the liver function test progressively worsened, being most deranged on the 12<sup>th</sup> hospital day (bilirubin, 42  $\mu\text{mol/L}$ ; alanine aminotransferase, 2032 U/L; alkaline phosphatase, 131 U/L; prothrombin time, 15.6 seconds). He was restarted on intravenous hydrocortisone 100 mg 6-hourly on the 10<sup>th</sup> hospital day. His skin condition and the liver function tests gradually improved (bilirubin, 10  $\mu\text{mol/L}$ ; alanine aminotransferase, 102 U/L; alkaline phosphatase, 100 U/L on the 28<sup>th</sup> hospital day). Hence, intravenous hydrocortisone was gradually tailed off over 2 weeks and he was converted to oral prednisolone. The rash and hepatitis gradually improved. He was discharged on the 43<sup>rd</sup> hospital day with a normal liver function test and oral prednisolone 50 mg daily. Blood pressure and blood glucose levels were normal on follow-up. The dose of prednisolone was tailed over 3 months.

He presented on 13 April 2000 with a week's duration of

retrosternal chest pain and breathlessness. He was then on oral prednisolone 10 mg daily. He had a 10-year history of smoking 10 cigarettes daily which he stopped 5 months ago. The blood pressure was 99/72 mm Hg and auscultation of the lungs revealed bilateral basal crepitations. Electrocardiogram revealed widespread ST segment depression. Blood investigations revealed: haemoglobin, 9.5 g/dL; white blood cells,  $11.75 \times 10^9/L$ ; eosinophil count,  $258 \times 10^6/L$ ; normal liver function test (bilirubin, 12  $\mu\text{mol/L}$ ; alanine aminotransferase, 74 U/L; alkaline phosphatase, 54 U/L); and normal urine microscopy (no red blood cells). The creatine kinase-MB fraction was raised (30  $\mu\text{g/L}$ ). CXR showed pulmonary congestion. Echocardiography revealed multiple regional wall motion abnormalities and severe left ventricular dysfunction, with an ejection fraction of only 20%. Lipid profile was normal. He was treated for acute non-Q myocardial infarct with cardiac failure, receiving anti-anginal and anti-failure drugs. However, he continued to have exertional chest pain and was found dead in bed on the 14<sup>th</sup> hospital day.

#### **Discussion**

Allopurinol should be prescribed only when it is truly indicated, for example in tophaceous gout, major uric acid overproduction, frequent gouty attacks unresponsive to prophylactic colchicine, recurrent uric acid renal calculi and in prophylaxis of acute urate nephropathy associated with chemotherapy.<sup>2</sup> These 2 young men were prescribed allopurinol for heel pain which was most likely plantar fasciitis; they had never had clinical symptoms or signs to suggest gout. A high proportion of patients with allopurinol hypersensitivity syndrome (76/101) in a review paper was treated for asymptomatic hyperuricaemia, a disturbing finding as this is not an established indication.<sup>3</sup> The pathogenesis of allopurinol hypersensitivity syndrome has not been fully established but existing data suggest that reactive metabolites of the drug are responsible for the idiosyncratic drug reaction.<sup>4</sup> The working hypothesis that has been used to explain the association between the formation of reactive metabolites and the induction of idiosyncratic drug reactions is the hapten hypothesis, that the reactive metabolite covalently binds to proteins and the altered proteins are then seen as foreign by the immune system; an immune response is thus induced.<sup>5</sup> However, not all drugs that form reactive metabolites are associated with a high incidence of idiosyncratic reaction. Hence, in order for the idiosyncratic reaction to occur, a reactive metabolite may, in addition to modifying protein, also have to injure or stress cells in order to induce an immune response.<sup>6</sup> The immune response thus induced can lead to substantial multiorgan damage.

The treatment of allopurinol hypersensitivity syndrome with systemic corticosteroids is controversial. Systemic

corticosteroids are usually recommended for life-threatening systemic involvement; however, controlled studies to evaluate this treatment are lacking. Dramatic improvements in symptoms and laboratory abnormalities have been observed in some patients treated with systemic corticosteroids (0.5 mg/kg daily).<sup>7</sup> In others, corticosteroids have been unsuccessful and these patients have succumbed to fulminant hepatitis and sepsis. Supportive therapy, including fluid and electrolyte replacement, nutritional support, and prevention of infection, may be the most valuable treatment in allopurinol hypersensitivity syndrome.

We explore the possible relationship between allopurinol, corticosteroids, allopurinol hypersensitivity syndrome and coronary artery disease. Allopurinol has not been shown in clinical or experimental studies to cause coronary artery disease. Chronic use of systemic steroids in patients with systemic lupus erythematosus has been shown to be associated with coronary artery disease. Petri<sup>8</sup> found that the cumulative dose of prednisolone (but not the highest dose used or the use of intravenous methylprednisolone) predicted coronary artery disease. Short-term use of systemic steroids, as in our 2 patients, has not been shown to be a significant risk factor for coronary artery disease.

Allopurinol hypersensitivity syndrome has not been reported to be associated with coronary artery disease. One patient in Lupton's case series,<sup>7</sup> a 64-year-old black woman with pre-existent organic heart disease, died of cardiac disease 6 months after the onset of allopurinol hypersensitivity syndrome; however, this was thought to be unrelated.

In the period 1980 to 1984, the mortality rate attributed to AMI in Singaporean Chinese males aged 30 to 39 was 5.4 per 100,000.<sup>9</sup> This figure is low. Hence, the association between allopurinol hypersensitivity syndrome and coronary artery disease may not be mere coincidence. Alternatively, could there be another explanation for the sudden death due to cardiovascular cause in our 2 patients?

Myocarditis can occur in drug hypersensitivity syndrome. Fenoglio et al<sup>10</sup> reviewed the clinical histories and histological findings in 24 patients with drug hypersensitivity and myocarditis. The myocarditis was characterised by uniform features of a patchy interstitial inflammatory infiltrate rich in eosinophils, focal myocytolysis, prominent perivascular infiltrates and an absence of myocardial fibrosis. Twenty of the 24 patients had died suddenly and unexpectedly. Non-specific cardiac findings suggestive of myocarditis (tachycardia, electrocardiographic changes, cardiac enzyme elevations) were found on retrospective review of these patients. Burke et al<sup>11</sup> studied autopsy tissue specimens of 69 cases of hypersensitivity myocarditis. The commonly implicated drugs were methyl dopa, hydrochlorothiazide, ampicillin, frusemide, digoxin, tetracycline, aminophylline, phenytoin,

benzodiazepines and tricyclic antidepressants. A non-necrotising vasculitis was present in 28 cases. Cardiac arrhythmias or unexplained death occurred in 29 patients. Galiuto et al<sup>12</sup> reported a case of eosinophilic myocarditis manifesting as myocardial infarct. A 67-year-old woman with a history of drug hypersensitivity presented to them with a diagnosis of AMI on the basis of chest pain, ST elevation on an electrocardiogram and slight increase in cardiac enzymes. Electrocardiography disclosed left ventricular dysfunction and apical asynergy. Coronary angiography revealed normal arteries and prompted the performance of endomyocardial biopsy, which revealed active eosinophilic myocarditis. After corticosteroid therapy, left ventricular function returned to normal.

We postulate that the immunologic process in allopurinol hypersensitivity syndrome may have caused coronary vasculitis and subsequent myocardial infarct. Alternatively, the idiosyncratic reaction may have damaged the myocardium, with the resultant myocarditis masquerading as coronary artery disease. However, we are unable to explain why these 2 patients developed coronary vasculitis or myocarditis despite having a good response of the other organs, e.g. skin and liver, to steroid therapy. Nonetheless, we feel that the association between allopurinol hypersensitivity syndrome and AMI (or myocarditis) is not a coincidental one. Therefore, we would like to suggest that patients with allopurinol hypersensitivity syndrome should be followed up for cardiac involvement.

#### REFERENCES

1. Vaillant L. Drug hypersensitivity syndrome: drug rash with eosinophilia and systemic symptoms (DRESS). *J Dermatol Treat* 1999; 10:267-72.
2. Singer J Z, Wallace S L. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986; 29:82-7.
3. Arellano F, Sacristan J A. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; 27:337-43.
4. Knowles S R, Uetrecht J, Shear N H. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 2000; 356:1587-91.
5. Park B, Pirmohamed M, Kitteringham N. Role of drug disposition in drug hypersensitivity: a chemical, molecular, and clinical perspective. *Chem Res Toxicol* 1998; 11:969-88.
6. Uetrecht J. New concepts in immunology relevant to idiosyncratic drug reactions: the "danger hypothesis" and innate immune system. *Chem Res Toxicol* 1999; 12:387-95.
7. Lupton G P, Odom R B. The allopurinol hypersensitivity syndrome. *J Am Acad Dermatol* 1979; 1:365-74.
8. Petri M. Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. *Lupus* 2000; 9:170-5.
9. Hughes K, Lun K C, Yeo P B. Cardiovascular disease in Chinese, Malays and Indians in Singapore. I. Differences in mortality. *J Epidemiol Community Health* 1990; 44:24-8.
10. Fenoglio J J, McAllister H A, Mullick F G. Drug related myocarditis. I. Hypersensitivity myocarditis. *Hum Pathol* 1981; 12:900-7.
11. Burke A P, Saenger J, Mullick F, Virmani R. Hypersensitivity myocarditis. *Arch Pathol Lab Med* 1991; 115:764-9.
12. Galiuto L, Enriquez-Sarano M, Reeder G S, Tazelaar H D, Li T C, Miller F A, et al. Eosinophilic myocarditis manifesting as myocardial infarction: early diagnosis and successful treatment. *Mayo Clin Proc* 1997; 72: 603-10.