Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction?

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ABSTRACT

Introduction: Allopurinol is a widely-prescribed urate-lowering agent. Allopurinol hypersensitivity syndrome, a severe form of cutaneous adverse reaction, is associated with significant mortality and morbidity. The aim of this study was to document the clinical presentation of allopurinol hypersensitivity in a local population, examine the indications for urate-lowering therapy and to identify potential associations with such a syndrome.

Methods: Retrospective review was done for all patients who were referred to the dermatology unit of a tertiary hospital for allopurinol hypersensitivity syndrome over a four-year period.

Results: Over four years, there were 28 patients with allopurinol hypersensitivity syndrome, of which there were 27 (96 percent) Chinese and one (four percent) Malay. The average age was 69 years. At baseline, 24 patients (86 percent) had renal impairment, and 21 patients (75 percent) had higher dosages of allopurinol. The cutaneous manifestation included generalised maculopapular exanthem (22 patients, 79 percent), Stevens Johnson/toxic epidermal necrolysis overlap (two patients, seven percent) and Stevens-Johnson syndrome (two patients, seven percent) and generalised exfoliative dermatitis (one patient, four percent). Mortality rate was 18 percent. Indications for allopurinol therapy were clear in ten patients (36 percent).

Conclusion: Allopurinol hypersensitivity syndrome is a life-threatening cutaneous adverse reaction. Allopurinol should be initiated under clear indications with appropriate dosages. Potential associations with this syndrome include the Chinese race, the elderly, and patients with underlying renal impairment.

Keywords: allopurinol, cutaneous adverse reaction, drug hypersensitivity, drug-induced hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis

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INTRODUCTION

Gout is a common problem, affecting at least 1% of men in Western countries.[1] Allopurinol, a xanthine oxidase inhibitor, is an effective and widely-prescribed urate-lowering agent. Cutaneous adverse reactions to allopurinol are common, affecting 2% of patients prescribed.[2] Although allopurinol hypersensitivity syndrome, a severe cutaneous adverse reaction, is less common, affecting 0.4% of patients receiving therapy,[3] it is nonetheless associated with significant mortality and morbidity. The aim of this study is to document the clinical presentation of allopurinol hypersensitivity syndrome in a local population, examine the indications for urate-lowering therapy and to identify potential associations with such a syndrome.

METHODS

This is a retrospective review of all patients who were referred to the dermatology unit, Singapore General Hospital, for severe cutaneous adverse drug reaction secondary to allopurinol over a period of four years from September 2002 to September 2006. Patients who were included fulfilled Singer and Wallace's criteria for allopurinol hypersensitivity syndrome; viz:[4] (1) A clear history of exposure to allopurinol; (2) Lack of exposure

Table I. Allopurinol dosage adjusted according to creatinine clearance.[5]

Creatinine clearance (ml/min)	Allopurinol dose
0	100 mg 3 times per week
10	100 mg alternate days
20	100 mg daily
40	150 mg daily
60	200 mg daily
≥ 100	300 mg daily

Calculation of creatinine clearance (based on Cockcroft and Gault).
Males: creatinine clearance (ml/min) = (140 - age) × ideal body weight (kg) / 0.81 × serum creatinine (μmol/L)
Females: creatinine clearance for males × 0.85

Table II. List of comorbidities.

Comorbidities	No. patients (%) (n = 28)
Chronic kidney disease (defined as GFR < 60 ml/min)[6]	24 (86)
Hypertension	21 (75)
Diabetes mellitus	9 (32)
Hyperlipidaemia	9 (32)
Ischaemic heart disease	6 (21)
Total malignancy	4 (14)
• Haematological	3 (11)
• Renal cell carcinoma	1 (4)
Cerebrovascular accident	2 (7)

Table III. List of associated clinical features.

Clinical features	No. patients (%) (n = 28)
Fever (temperature > 38.0°C)	24 (86)
Transaminitis *	22 (79)
Eosinophilia (800/uL)	21 (75)
Acute renal impairment +	16 (57)
Oral erosions	16 (57)
Leucocytosis > 11.0 × 10^9/L	12 (43)
Conjunctivitis	5 (18)
Genital erosions	5 (18)
Anaemia (haemoglobin < 10 g/dL)	5 (18)
Thrombocytopaenia (platelets < 150 × 10^9/L)	5 (18)

* Defined as a rise in serum AST/ALT of > 2× normal.
+ Defined as an acute rise in serum creatinine from the baseline.

Table IV. Indications for allopurinol therapy.

Indications	No. patients (%) (n = 28)
Chronic tophaceous gout	2 (7)
Urate nephropathy	0 (0)
Frequent recurrent gouty attacks (≥ 3 per year)	5 (18)
Infrequent attacks (≤ 2 per year)	9 (32)
Tumour lysis prophylaxis	3 (11)
Asymptomatic hyperuricaemia	7 (25)
Non-specific joint pain	2 (7)

to another drug which may have caused a similar clinical picture; and (3) A clinical picture including at least two of the following major criteria: (a) worsening renal function, (b) acute hepatocellular injury, (c) a rash including either toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), erythema multiforme, generalised maculopapular exanthem or generalised exfoliative dermatitis (GED); or one of the above major clinical criteria and at least one of the following minor criteria: (a) fever, (b) eosinophilia, (c) leukocytosis. Data collected included demographical, clinical and laboratory data, associated diseases, allopurinol prescription details and other medication history. Calculation of creatinine clearance was based on the Cockroft-Gault equation, and derivation of corrected allopurinol dosage was based on published guidelines (Table I).[5]

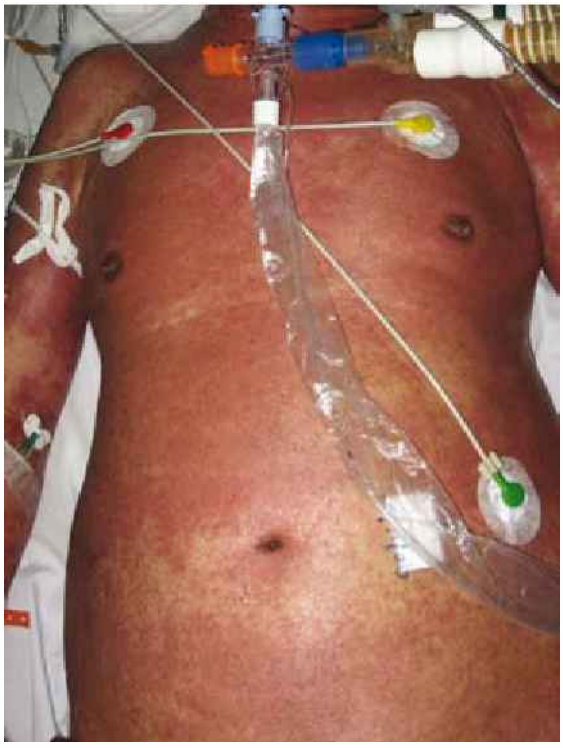

Fig. 1 Photograph of a patient with allopurinol hypersensitivity presenting with a maculopapular exanthem, requiring ICU care for multiorgan failure.

RESULTS

Over the four-year period, there were a total of 3,783 inpatient dermatology consultations. Among these, there were a total of 28 patients with allopurinol drug-induced hypersensitivity syndrome (DHS). Of the 28 patients, there were nine males (32%) and 19 females (68%), and their mean age on presentation was 69 (range 36–91) years. 27 (96%) of the patients were Chinese and one (4%) was Malay. Their baseline comorbidities are shown in Table II. All of the patients were referred to the dermatology department for a rash. Among the various cutaneous presentations, there were 22 (78%) patients with generalised maculopapular drug exanthem (Fig. 1), three (11%) patients with SJS/TEN overlap, two (7%) patients with SJS and one (4%) patient with GED. The cutaneous adverse reactions were also associated with various systemic manifestations (Table III). The onset of the various cutaneous manifestations occurred at a mean and median of 30 (range 13–42) days after initiation of allopurinol.

The reasons for initiating allopurinol therapy are shown in Table IV. The average uric acid level prior to initiation of allopurinol was 561 (range 364–821) µmol/L. Out of the 28 patients, 21 patients (75%) had higher doses than the suggested creatinine clearance-adjusted doses (Table I). The reason for admission for 27 (96%)

Table V. Characteristics of the five patients who died.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	83	85	70	65	76
Gender	Female	Female	Male	Male	Male
Race	Chinese	Chinese	Chinese	Chinese	Chinese
Dosage prescribed	300 mg daily	300 mg daily	100 g daily	300 mg daily	100 mg daily
Appropriate dosage*	150 mg daily	100 mg daily	100 mg EOD	150 mg daily	100 g EOD
Duration of therapy (days)	35	31	36	13	18
Comorbidites	Hypertension IHD	DM Hypertension	DM Hypertension	Mantle cell lymphoma	DM Hypertension
Clinical characteristics					
Fever	Yes	Yes	Yes	Yes	Yes
Transaminitis	Yes	Yes	Yes	No	Yes
Acute renal impairment	No	Yes	Yes	Yes	Yes
Conjunctivitis	Yes	Yes	No	No	No
Oral ulcerations	Yes	No	Yes	No	Yes
Cause of death	AMI	AMI	Sepsis	Sepsis	Sepsis

AMI: acute myocardial infarction; DM: diabetes mellitus; IHD: ischaemic heart disease; EOD: every other day
*Appropriate dosages based on creatinine clearance as suggested by guidelines[5]

of the 28 patients was for the DHS. The remaining patient developed the syndrome following tumour lysis prophylaxis while she was receiving chemotherapy for hairy cell leukaemia. Five patients died (18%) and their clinical characteristics are shown in Table V, and four (14%) required ICU care and emergent haemodialysis for multiorgan failure. Among the 23 patients who survived, the average length of stay was 16 (range 5–48) days.

DISCUSSION

DHS is a serious adverse systemic reaction that usually appears after a 3–6 week exposure to certain drugs. Drugs implicated include anticonvulsants, allopurinol and sulphonamides. It is characterised by the presence of fever, skin rash and systemic involvement (liver, kidney, pulmonary, cardiac, eosinophilia, atypical monocytosis). Although the presentation is similar, renal dysfunction is a prominent feature of allopurinol hypersensitivity syndrome, affecting up to 84% of cases as compared to other forms of drug hypersensitivity (which affects less than 30%)[7] and the mortality may be higher (25% as compared to 10% of other forms of drug hypersensitivity).[8]

Allopurinol is an effective and widely-prescribed urate-lowering drug. Though it is generally safe, allopurinol hypersensitivity syndrome has been reported to occur in about 0.4% patients receiving therapy. In the 1980s, more than 240 million doses of allopurinol were prescribed, or 70 tonnes ingested annually.[9] Being such a widely-prescribed medication, the at-risk population for severe adverse reactions is considerable. Accepted indications for urate-lowering therapy include the following:[10,11] (1) Frequent, recurrent attacks (defined as three or more attacks per year); (2) Chronic tophaceous gout; (3) Uric acid nephrolithiasis; and (4) Prophylaxis for tumour lysis during chemotherapy. Adherence to such indications is often suboptimal.[4] Similar findings are shown in our study. Only ten (36%) of the patients had clear indications for initiation of therapy. The indications for therapy for the remaining 18 (64%) patients were more tenuous, and included asymptomatic hyperuricaemia, infrequent gouty arthritis and nonspecific joint pains.

Among the patients who developed allopurinol hypersensitivity, 27 (96%) of them were Chinese, 24 (86%) of them had baseline renal impairment, 21 (75%) had higher dosages than recommended according to their glomerular filtration rate (GFR), and their mean age on presentation was 69 years. These results suggest that the age, Chinese ethnicity, baseline renal impairment and inappropriately high allopurinol dosages are potential associations with this syndrome. Other studies have also reported similar findings with age, high allopurinol dosages and renal impairment as possible risk factors.[4,5]

The exact pathogenesis of DHS still remains unclear, but it is likely to involve a complex interaction of many factors including immunology, genetics, drug metabolism/accumulation and reactivation of latent viruses of the human herpes virus family.[12,13] The accumulation of oxypurinol, the active metabolite of allopurinol, is believed to play an integral role in the pathogenesis. Oxypurinol is slowly cleared via the kidneys and has a serum half-life of 14–26 hours in patients with normal renal function. In the event of renal impairment, the half-life is prolonged to more than 125 hours. Raised levels of this metabolite have been found to correlate with the risk of developing allopurinol hypersensitivity syndrome in previous studies.[14] Similarly, the clearance of oxypurinol is reduced in the elderly, leading to higher allopurinol

toxicity in old age.[15]

It is recommended that the allopurinol dosage should be adjusted according to the renal function of the patient. However, plasma creatinine levels in itself is notoriously insensitive in detecting a decline in renal function, and using it as a marker may predispose patients to higher dosages and the risk of severe toxicity. Instead, adjusted dosing should be based on creatinine clearance.[16] Recommended dosages according to creatinine clearance have been proposed (Table I). Poor compliance to such standards of care is common in other published studies, suggesting that this is a universal albeit remediable problem.[17,18] The role of genetic and racial influences remains unclear. Familial clustering has been previously reported.[19] Although the high incidence of allopurinol hypersensitivity in Chinese may be indicative of our underlying population demographics, recent reports in Taiwan showed that there was a 100% association between allopurinol severe cutaneous adverse reaction and HLA-B5801 in the Han Chinese, as compared to 15% in tolerant controls.[20]

Allopurinol hypersensitivity syndrome is associated with high morbidity and mortality. Studies have quoted a mortality of about 25%.[9] We report a similar mortality rate of 18%. Although a previous local paper did not report any mortality in that case series,[21] possible explanations could be due to the variations in patient populations. Being a tertiary referral and burns centre, it is possible that patients who were admitted to our hospital were sicker and had more comorbidities, hence the higher mortality. Interestingly, two patients in our series died from acute myocardial infarction. A previous local study also reported two patients with minimal cardiac risk factors and who developed acute myocardial infarction several months after experiencing the allopurinol hypersensitivity.[22] It remains to be seen if there is a true association between allopurinol hypersensitivity and myocardial infarction. It is possible that myocarditis, as part of the systemic involvement of the syndrome, may mimic the clinical presentation of acute myocardial infarction.

Allopurinol therapy is not without its risk, and consideration of the risk and benefit involved is imperative. In view of our findings, we recommend that: (1) Allopurinol should be initiated with clear indications; (2) In view of the possible association, the decision to initiate allopurinol in the following patient populations: elderly, Chinese race, patients with underlying renal disease, should not be taken lightly; (3) Allopurinol dosage should be corrected according to the creatinine clearance; (4) Upon initiation of allopurinol, the patient should be monitored during the first two months for possible drug hypersensitivity; and (5) Patients and doctors should be educated on early recognition of drug hypersensitivity and the importance of prompt withdrawal of the drug in such an event. With these recommendations, it is hoped that the severe morbidity and mortality associated with allopurinol hypersensitivity syndrome may be prevented.

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