Case Report

DRESS Syndrome caused by allopurinol

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Key Learning Points
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a potentially fatal complication of allopurinol therapy.
- Dose adjustment of allopurinol is essential in patients with renal failure, and reduces the risk of developing DRESS syndrome.
- Prompt withdrawal of allopurinol is essential in the initial management of DRESS.

Abstract
DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome is a potentially fatal and probably under-recognized complication of allopurinol. We present the case of a 33 year old male with this condition who required intensive care support and subsequently improved following corticosteroid therapy. We review the literature considering optimal strategies for treatment and prevention of this condition. We believe that acute physicians clinicians should have greater awareness of this complication of allopurinol therapy.

Keywords
Allopurinol; DRESS syndrome; Hyperuricaemia.

Case report
A 33 year old male presented with fever, malaise, fatigue and a generalized morbilliform rash. The rash had been progressive over the previous week and was preceded by a 3 day history of a sore throat. He had not taken any antibiotics, non-steroidal anti-inflammatory drugs or over-the-counter preparations. He had a previous history of IgA nephropathy with a baseline urea of 9.0mmol/L and creatinine, 220umol/L. He was taking lisinopril 20mg OD and losartan 100mg OD. Allopurinol 300mg OD was commenced 6 weeks previously following the chance finding of asymptomatic hyperuricaemia. He was a non-smoker and consumed 5 units of alcohol each week.

Initial examination revealed him to be pyrexial (39.5°C), hypotensive (70/40mmHg), tachycardic (110bpm in Sinus Rhythm), tachypnoeic (20/min) and clinically hypovolaemic. He had a diffuse erythodermatous morbilliform rash with sparing of the plantar surfaces of his feet and his axilla. There was marked peri-orbital oedema and neck swelling with no obvious lymphadenopathy.

His initial blood tests demonstrated a leucocytosis with a marked eosinophilia (1.62 × 10^9/L), a deterioration of his renal function and raised alanine transaminase (ALT) (see Table 1).

	Patient's results	Reference values
Serum Haemoglobin	12.7	14.0-17.7 g/dL
Total White Cell Count	22.5	4-11×109/L
Neutrophil Count	12.22	2.0-7.5×109/L
Lymphocyte Count	4.63	1.5-4.0×109/L
Monocyte Count	3.35	0.2-0.8×109/L
Absolute Eosinophil Count	1.62	0.04-0.4×109/L
Basophil Count	0.65	<0.01-0.1×109/L
Serum Sodium	134	136-144mmol/L
Serum Potassium	5.1	3.5-5.0mmol/L
Blood Urea	10.7	2.5-6.7mmol/L
Serum Creatinine	330	60-110μmol/L
Serum Albumin	41	36-53g/L
Total Bilirubin	6	<17μmol/L
Serum Alanine Transaminase	237	5-40U/L
Serum Alkaline Phosphatase	106	25-115U/L
C Reactive Protein (CRP)	33	<10 mg/L
Serum Bicarbonate	22	22-26mmol/L

Table 1. Patient's initial blood results with reference values.

He was treated with fluid resuscitation via a central venous cannula and broad spectrum antibiotics for a presumed septicaemia of unknown origin. The allopurinol, lisinopril and losartan were stopped.

After 48 hours he remained unwell with continued fever, hypotension and further progression of the rash. Three sets of blood cultures (including those taken on admission), viral serology and an autoantibody screen were negative. His blood

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film demonstrated the presence of atypical lymphocytes, but was otherwise unremarkable.

Following further review and his limited response to antibiotics it was considered that his presentation was in keeping with a hypersensitivity reaction and a diagnosis of DRESS syndrome. Antimicrobial therapy was discontinued and he was commenced on high dose oral prednisolone. He was transferred to the intensive care unit and received 48 hours of vasopressor support with noradrenaline.

After 1 week of treatment with steroids and discontinuation of his allopurinol his rash had resolved. His ALT normalised and his renal function returned to baseline levels.

1. A documented intake of allopurinol
2. Lack of exposure to a different drug causing a similar clinical picture
3. Presence of at least 2 major criteria and 1 minor criterion

Major criteria

I - Worsening renal function

II - Acute hepatocellular injury

III - Rash - manifesting by toxic epidermal necrolysis, erythema multiforme, diffuse maculopapular rash or exfoliative dermatitis.

Minor criteria - Fever, eosinophilia, leukocytosis.

Table 2. Criteria for the diagnosis of allopurinol-induced DRESS syndrome.[2]

Discussion

Hyperuricaemia is a common metabolic disorder which can lead to nephrolithiasis, arthropathy and nephropathy. Allopurinol, a xanthine oxidase inhibitor, is widely used to lower urate levels. Rarely, allopurinol can precipitate a hypersensitivity syndrome, characterized by rash, fever, lymphadenopathy and single or multiple organ failure. This usually occurs within 8 weeks of commencing the medication.[1] Table 2 shows the diagnostic criteria for allopurinol hypersensitivity syndrome.[2] Recently this has been redefined as DRESS syndrome.

The pathophysiology of DRESS syndrome is not fully understood and is probably multifactorial; it is recognized that the accumulation of oxypurinol, a metabolite of allopurinol, plays a significant role.[3] Oxypurinol excess probably results in tissue damage triggering an immunological response. There may also be an association with Human Herpes Virus Six.[4]

Oxypurinol excretion is reduced in patients with renal failure, which makes this group of patients more at risk of developing DRESS syndrome. The concomitant use of thiazide diuretics appears to be a further risk factor for its development.[5] The use of combination therapy with ACE inhibitor and Angiotensin II receptor blockers, as in this patient, has not been previously described as increasing the risk of allopurinol related DRESS syndrome but captopril has been independently reported as causing the syndrome.[6]

It is essential that dose adjustment of allopurinol in patients with renal failure is undertaken which reduces the risk of developing DRESS syndrome. Furthermore, asymptomatic hyperuricaemia does not require treatment.

Mortality from DRESS syndrome is around 10%, primarily due to liver failure as a result of eosinophilic infiltration.[1] Arellano *et al* reported a 26.7% mortality from allopurinol hypersensitivity syndrome.[7] A Toxic Epidermal Necrolysis(TEN) type rash and a 10 fold increase in transaminases are indicators of a poor prognosis in DRESS syndrome.

Prompt withdrawal of allopurinol is the essential initial management. This can sometimes be delayed due to a lack of recognition or consideration of the diagnosis. Supportive treatment with anti-pyretics, fluid resuscitation and anti-histamines is required. Occasionally, in more severe cases such as our patient, organ support with vasopressor drugs is required.

The use of systemic corticosteroids is controversial. It has been suggested that they may decrease eosinophilic accumulation that contributes to organ dysfunction in DRESS syndrome. Case reports have shown dramatic improvements with the use of steroids[8] and our case supports this finding. Furthermore, relapses of DRESS syndrome have been reported after the tapering of steroids.[9] In those patients with TEN type rashes the use of Intravenous Immunoglobulin has been shown to decrease mortality significantly.[10]

High dose N-acetylcysteine has been used with promising results to treat DRESS syndrome related to anti-convulsants.[11] However, there is no evidence to support its use in cases induced by allopurinol.

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