

Breaking out: The wild world of diagnosing and managing drug eruptions

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CASE

A man, aged 52 years, presented to the emergency department with a first-time presentation of sudden onset pruritic skin eruption after starting allopurinol 10 days prior for nephrolithiasis. He reported mild shortness of breath but no other significant systemic symptoms. The pruritic eruption was symmetrical, widespread with erythematous macules and papules involving his face, torso and limbs (Figure 1). He had slight facial swelling, was febrile to 38.3°C and had mild tachycardia (112 beats/min), but was otherwise haemodynamically stable. He was treated with a three-day course of 25 mg prednisone.

QUESTION 1

What are the differential diagnoses?

QUESTION 2

What history, examination and investigations are required?

ANSWER 1

The main differential diagnosis is morbilliform drug reaction. An important differential is an early evolving drug hypersensitivity syndrome known as drug reaction with eosinophilia and systemic

symptoms (DRESS) given pruritic skin eruptions and organ involvement commonly associated with allopurinol.¹ Other differentials include infection-associated exanthematous drug eruption, drug-induced exanthematous eruptions or acute viral illness (eg measles, acute HIV).

Less common differentials include early Stevens–Johnson syndrome or toxic epidermal necrolysis (SJS/TEN), acute generalised exanthematous pustulosis (AGEP) and acute cutaneous lupus. The timing of drug exposure supports morbilliform drug eruption, with high fever suggesting systemic involvement or impending SJS/TEN.

ANSWER 2

Table 1 outlines important factors for history, examination and investigations.

CASE CONTINUED

After admission, the eruption became more confluent and erythematous with dusky targetoid areas (Figure 2). There was no skin tenderness, detachment or mucosal involvement. Eosinophils, lymphocytes, liver function, renal function and troponin were normal. No new systemic features such as worsening fever, hypotension or lymphadenopathy were noted. The presently accepted diagnostic tool RegiSCAR (diagnostic scoring criteria used to assist in diagnosing DRESS) score assisted in confirming diagnosis (Box 1).¹

QUESTION 3

Why is morbilliform drug eruption diagnosed over DRESS?

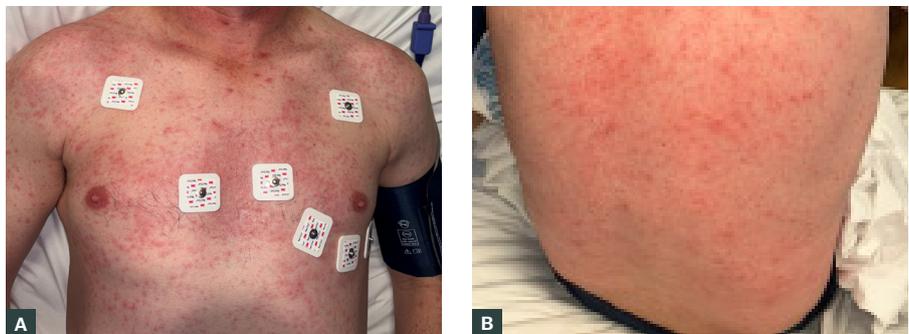


Figure 1. Initial presentation of the eruption on the patient's trunk. (A) Eruption on the chest wall and abdomen anteriorly. (B) Eruption on the back.

QUESTION 4

How common are allopurinol-induced skin eruptions?

QUESTION 5

Which common drugs cause adverse cutaneous reactions?

QUESTION 6

What is the definitive management?

ANSWER 3

DRESS must be excluded as it has high morbidity and a 10% mortality.² Typically, DRESS presents with high fever and lymphadenopathy with neutrophilia in early presentation, followed by lymphopenia and eosinophilia as the condition resolves (Table 2).^{3,4} Lack of lymphadenopathy, other organ involvement and normal blood tests support morbilliform drug eruption.

ANSWER 4

Allopurinol is commonly used to treat gout and nephrolithiasis.⁵ The incidence of allopurinol causing severe cutaneous adverse reactions (SCARs) requiring hospitalisation is less than 1 in 1000, with in-hospital mortality as high

Box 1. RegiSCAR (diagnostic scoring tool) criteria for the diagnosis of DRESS

Criteria for diagnosis

- Acute rash
- Reaction suspected to be drug-related
- Hospitalisation
- Fever (>38°C)
- Laboratory abnormalities (at least one present)
 - Lymphocyte above or below normal level
 - Low platelet level
 - Eosinophilia
- Involvement of more than one internal organ
- Enlarged lymph nodes present at more than two sites

The first three criteria are necessary for diagnosis, along with the presence of three out of the other four features listed.¹

DRESS, drug reaction with eosinophilia and systemic symptoms.

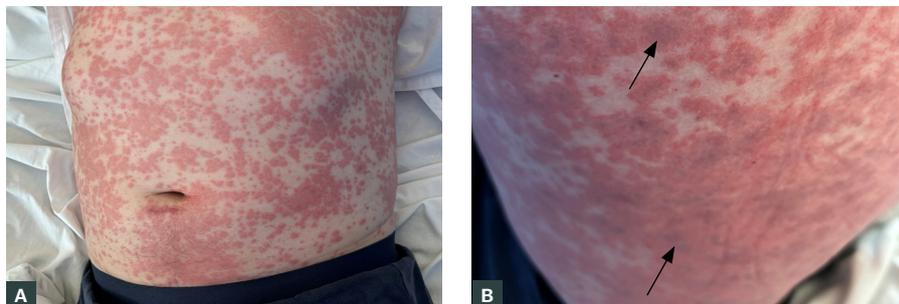


Figure 2. Progression of eruption on the patient's trunk. (A) Progression of the eruption on the chest wall and abdomen. (B) Progression of the eruption on the back with arrows indicating dusky targetoid areas.

Table 1. Important characteristics in history, examination and investigations for diagnosing and managing drug reactions

Characteristics	
History	<ul style="list-style-type: none"> • Drug exposure – Has the patient had the medication previously? • Timing – How long has the patient been taking the medication for? What is the timing of drug administration relative to the onset of rash and other symptoms? • Adherence – Has the patient been taking the medication as prescribed? • Complete medication and medical history with collateral information from the pharmacy including herbs, eye drops and vitamins • Medical history – Immunocompromised? Recent viral illnesses and viral symptoms? Vaccination history? • Social history – Infectious contacts and travel history • Skin pain • Systems review – Fevers, night sweats, weight loss, headache, vomiting, chest pain, shortness of breath, joint pain, nausea, abdominal pain, diarrhoea
Examination	<ul style="list-style-type: none"> • Vital signs • Lymph node examination – Are there palpable lymph nodes? Lymph nodes >2 cm are suggestive of DRESS • Mucous membrane examination – Are there any lesions or active bleeding in the gums or other mucosal areas? • Full skin examination looking for confluent erythema, facial oedema, blisters, erosions, necrosis and purpura • Cardiovascular and respiratory examinations – Are there any signs of infection, respiratory distress/pneumonia?
Investigations	<ul style="list-style-type: none"> • Assess for systemic involvement based on symptoms and presentation; some potential investigations include: <ul style="list-style-type: none"> – Full blood count – Leucocytosis (>11 × 10³/μL), atypical lymphocytosis (>5%) or eosinophilia (>1.5 × 10³/μL) suggestive of DRESS – Liver function tests – Elevated LFTs (liver transaminases values > twice the upper normal limit) suggestive of DRESS – Electrolyte, urea and creatine tests – Abnormal LFTs indicating interstitial nephritis suggestive of DRESS – Troponin – Elevated troponin indicating carditis suggestive of DRESS

DRESS, drug reaction with eosinophilia and systemic symptoms; LFTs, liver function tests.

Table 2. Clinical features of SJS/TEN, DRESS and exanthematous drug reactions

Clinical features	SJS/TEN	DRESS	Exanthematous drug reactions
Cutaneous features	Severe blistering, Nikolsky sign positive with significant epidermal necrosis (10–30% TBSA affected is SJS, >30% TBSA is TEN)	Widespread rash (>50% TBSA) with erythroderma, purpuric eruptions	Widespread, symmetrically distributed rash composed of pink-to-red macules and papules that might coalesce to form plaques
Mucosal involvement	Mucosal involvement highly frequent	Mucosal involvement infrequent	Mucosal involvement rare
Timing	4–21 days after first dose of medication	>14 days after first dose of medication	4–21 days after first dose of medication
Systemic features	High fever (>38.5°C) Malaise, sore throat, dysphagia, dysuria or photophobia initially	High fever (>38.5°C) Malaise, lymphadenopathy, involvement of at least one internal organ	Mild fever, malaise, sore throat and conjunctivitis
Laboratory findings	Epidermal necrosis on skin biopsy, with full thickness loss of epidermis	Eosinophilia, lymphocytosis or lymphopenia, atypical lymphocytes, thrombocytopenia	Blood investigations typically at patient baseline

DRESS, drug reaction with eosinophilia and systemic symptoms; SJS/TEN, Stevens–Johnson syndrome or toxic epidermal necrolysis; TBSA, total body surface area.

as 27%.⁵ Certain groups, including those with kidney disease or those taking thiazide diuretics, are more susceptible to reactions.^{4,6} Southeast Asian ethnicities, such as Han Chinese, Indians and Koreans, should undergo HLA-B5801 screening before starting allopurinol, as this allele is strongly linked to severe reactions.⁷ Given the high percentage of Chinese ancestry in Australian regions like Sydney (29%), this is especially relevant for drug-related skin eruptions in clinical practice.⁸ Although our Caucasian patient was not eligible for HLA testing, patients should be informed of the risks with allopurinol and seek medical care if skin reactions occur.

ANSWER 5

Common drugs causing adverse cutaneous reactions are:^{4,6}

- allopurinol (3.75%)
- anticonvulsants containing aromatic rings (eg lamotrigine, carbamazepine, phenytoin and phenobarbituates; 33%)
- antibiotics (eg penicillins, cephalosporins, trimethoprim-sulfamethoxazole, minocycline, dapsone, vancomycin; 34%)
- non-steroidal anti-inflammatories (22%).

ANSWER 6

The offending medication should be promptly ceased and not rechallenged. For pruritus

relief, antihistamines, cool creams and showers with gentle patting are recommended. Topical therapy includes emollients and steroid creams for severe cases.^{4,6} Wet dressings for very erythematous and inflamed skin assist with symptom relief. Systemic corticosteroids (0.5–1 mg/kg) are reserved for severe cases with suspected DRESS or significant systemic involvement as they cause side effects like mania, hypertension and hyperglycaemia, causing more harm than benefit if used for mild drug reactions.² Isolated exanthems improve in two weeks, whereas DRESS might take 6–12 weeks or longer for full recovery.^{9,10}

CASE CONTINUED

The patient developed no new systemic symptoms, and blood tests remained normal. He was managed conservatively with topical steroids (methylprednisolone 0.1% fatty ointment), loratadine 10 mg when needed, cooled emollients and cool showers. He was discharged, and the eruption resolved without issue on follow-up.

Key points

- DRESS is a potentially life-threatening drug reaction with high morbidity and

mortality; absence of systemic symptoms and normal blood tests suggests an exanthematous eruption.

- Discontinue the offending medication immediately, where symptom management involves topical treatments like emollients and steroid creams.
- Allopurinol can cause severe reactions, especially in patients from ethnic groups like Han Chinese, Indian or Korean who should be screened for HLA-B5801 and should be aware of SCARs, seeking medical care if needed.

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