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Case Report

Allopurinol-induced drug reaction with eosinophilia and systemic symptoms syndrome presenting with facial swelling: a case report

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Introduction

Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is recognised as one of the most severe cutaneous adverse reactions (SCAR) which can be life-threatening [1]. It is frequently linked with antiepileptics and sulphonamides. DRESS typically has a latent period of two to six weeks. It manifests mostly with a morbilliform cutaneous eruption with fever and lymphadenopathy. Severe disease can cause systemic involvement, resulting in multi-organ failure [1]. Since there is no established criterion for diagnosing DRESS syndrome and due to the wide range of presentations, diagnosing DRESS syndrome can be quite challenging in clinical settings [2]. The mainstay of DRESS syndrome treatment is discontinuing the offending medication [2].

Here we report a case of DRESS syndrome secondary to allopurinol presenting with fever and facial swelling.

Case presentation

A 42-year-old Sinhalese male was admitted to a tertiary care hospital in Kandy with fever for 4 days and facial swelling for 2 days. He reported having high grade fever with chills and rigors associated with arthralgia, myalgia and headache. In addition, he had loose stools for 4 days with nausea and vomiting. He had a background history of poorly

controlled type 2 diabetes mellitus, chronic kidney disease and epilepsy. On examination, temperature was 38.1C. He was hemodynamically stable. System examination was normal. Initial blood investigation results are shown in Table 1.

Table 1: Results of Initial Investigations

Investigation	Result	Normal ranges
White Cell Count	15.4 x 10^9/L	(4.0 – 11.0) x 10^9/L
Neutrophils	40.2% (6.1 x 10^3/µL)	(1.5 – 7.5) x 10^3/µL
Lymphocytes	23.4% (4 x 10^3/µL)	(1.0 – 4.0) x 10^3/µL
Eosinophils	24.6% (3.5 x 10^3/µL)	(0.02 – 0.5) x 10^3/µL
Haemoglobin	9.1 g/dL	13.5 – 17.5 g/dL
Platelet Count	381 x 10^9/L	(150 – 450) x 10^9/L
C-reactive Protein (CRP)	11.5 mg/L	< 5 mg/L
Erythrocyte Sedimentation Rate (ESR)	41 mm/hr	< 20 mm/hr
Serum Creatinine	244.9 µmol/L	62 – 115 µmol/L
Aspartate Transferase (AST)	101 U/L	10 – 40 U/L
Alanine Transferase (ALT)	128.2 U/L	7 – 56 U/L
Total Protein	7 g/dL	6.0 – 8.3 g/dL
Albumin	3.8 g/dL	3.4 – 5.4 g/dL
Globulin	3.2 g/dL	2.0 – 3.5 g/dL
Alkaline Phosphatase (ALP)	672.2 U/L	44 – 147 U/L
Total Bilirubin	8.22 µmol/L	3 – 21 µmol/L
Direct Bilirubin	4.46 µmol/L	0 – 5 µmol/L
Gamma-Glutamyl Transferase (GGT)	229.8 U/L	9 – 48 U/L

Blood film revealed leukocytosis with atypical lymphocytes, neutrophil toxic changes, moderate eosinophilia and moderate anemia due to anemia of chronic disease. Renal ultrasound was suggestive of chronic renal parenchymal changes. Blood, urine and stool cultures did not reveal any growth. Chest x-ray was normal. Urine full report revealed 4-6 pus cells and 2+ albumin. Urine protein to creatinine ratio was 200mg/mmol.

He was initially managed as for possible viral gastroenteritis with intravenous (IV) fluids and paracetamol, as needed, for fever.

On day 2 following admission he developed a generalized maculo-papular rash (Figure 1). This was initially noted to be in upper limbs, lower limbs and back but gradually became generalized over 2 days.

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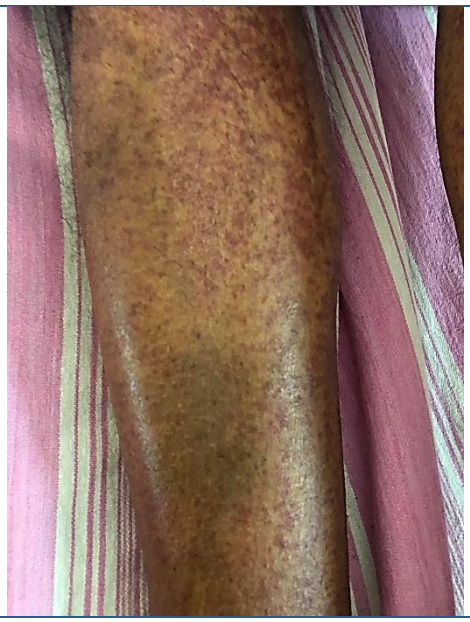

Figure 1: maculo-papular skin rash over the left leg noted on day 2 of admission

The differential diagnoses at this point were a viral infection, vasculitis and drug reaction. There was no history of high-risk sexual behavior or a history of blood transfusion. Viral screening, including tests for human immunodeficiency virus (HIV), herpesvirus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and hepatitis B and C, all came as negative. Additionally, the vasculitis screen was also negative. The patient's regular medications include gliclazide and carbamazepine. Upon further inquiry, the patient revealed that he had recently been prescribed a new medication, allopurinol, by his general practitioner approximately two weeks ago. At this point a drug reaction was suspected as the diagnosis. Considering the high eosinophil count, acute kidney injury, transaminitis, generalized skin rash with recent allopurinol use, DRESS syndrome was the main working diagnosis. Allopurinol was discontinued. Following dermatology input he was started on prednisolone 60mg once daily. Skin biopsy was suggestive of DRESS syndrome. Prednisolone was tapered slowly over 8 weeks. On review at the medical clinic, two months following discharge, the patient was asymptomatic, with the skin rash partially resolved. Renal and liver functions were back at baseline.

Discussion

DRESS syndrome is a severe hypersensitivity reaction to a drug or its reactive metabolites. Medications most commonly associated with DRESS include sulphonamides such as dapsone and sulfasalazine, as well as aromatic anticonvulsants like phenytoin, carbamazepine, and phenobarbital. Of these, carbamazepine is the most frequent culprit. Although the exact etiology of DRESS syndrome is still unknown, three complexly interacting factors are thought to be involved in instances linked to anticonvulsants: (i) a lack or malfunction of the enzyme epoxide hydroxylase, which detoxifies the byproducts

of aromatic amine anticonvulsants; (ii) a herpes virus family reactivation that occurs sequentially; and (iii) ethnic predisposition due to specific human leukocyte antigen (HLA) alleles. DRESS syndrome often appears two months after the offending medication is consumed, usually two to six weeks after the initial usage [1].

DRESS syndrome is characterized by a collection of symptoms affecting several organs, including the skin, liver, and hematologic system, with cutaneous alterations being the most noticeable. The reaction often begins with a low-grade or high-grade fever, followed by a cutaneous reaction, lymphadenopathy, and pharyngitis which may develop over the course of the next one to two days after. The involvement of other internal organs follows, most frequently the liver, though there may also be pulmonary, renal, or hematologic damage [1].

Currently there is no gold standard investigation for diagnosing DRESS syndrome. Clinicians use their judgement to determine the diagnosis by comparing test results with clinical signs. Histopathology of skin lesions in DRESS syndrome commonly reveals perivascular lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis of epidermis. The gold standard treatment for DRESS is systemic corticosteroids [1].

Darren Kong et al reported a case of DRESS associated with perimyocarditis following initiation of anti-tuberculosis therapy. They described peri-myocarditis as a rare complication of DRESS which occur due to degranulation and the release of harmful substances into cardiac cells [2]. The patient in this case was a young male who presented with fevers, rash, and generalized fatigue. Payal Shah reported a case of DRESS presenting with colitis secondary to sulfasalazine. This was a young female with rheumatoid arthritis who presented with fever, abdominal pain and diarrhoea for 2 weeks. She developed erythema and generalized skin pustules, facial erythema and cervical lymphadenopathy. Sulfasalazine was withheld and she was successfully treated with steroids [3]. A case of phenytoin induced DRESS was reported in 2012 is Australia. This patient presented with a skin rash, lymphadenopathy and altered liver enzymes 4 weeks following drainage abscess. This was successfully managed by discontinuation of phenytoin [4].

There were a few case reports on allopurinol induced DRESS in the available literature [5,6,7,8]. One case was complicated with interstitial nephritis. This patient presented with fever, skin rash, cervical lymphadenopathy and was successfully treated with steroids. Patients in most of the other cases presented with typical symptoms including fever, skin rash and cervical lymphadenopathy and were treated with steroids.

In contrast to the patients mentioned above, our patient presented with fever and facial swelling. According to statistics, 76% of patients exhibit facial oedema, which is a hallmark characteristic of the disease. [9]. However, interestingly cases of DRESS syndrome presenting with facial swelling are rare in the available literature. Although the exact mechanism underlying the development of facial oedema in DRESS syndrome is still

unknown, it's thought to be related to vascular endothelial growth factor pathway [9]. Our case emphasises the importance of considering DRESS syndrome as a differential diagnosis in patients presenting with fever, facial swelling and eosinophilia. Further it highlights the importance of obtaining a detailed medication history, since continuation of the causative agent could result in muti-organ failure and progression of the disease.

Conclusion

DRESS syndrome is a potentially life-threatening hypersensitivity reaction which can result in multi-organ involvement. Clinicians should have a high index of suspicion for DRESS syndrome in patients presenting with fever, facial swelling and eosinophilia in the setting of introduction of new medications. If not, since the typical skin rash takes few days to develop, the diagnosis could be missed or delayed. Early diagnosis and prompt treatment is mandatory to prevent morbidity and mortality.

Consent

Informed written consent was obtained from the patient for writing the case report and publishing clinical images.

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