DRESS syndrome triple whammy: sulfasalazine, amoxicillin and HHV-7

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug hypersensitivity reaction with multisystemic involvement. This case discusses a 28-year-old Caucasian woman with anti-CCP positive rheumatoid arthritis treated with 2 weeks of sulfasalazine who developed earache after 1 week of treatment, which was treated with amoxicillin. She then presented with a temperature (40°C) and maculopapular rash. She later developed facial oedema, purpuric lesions, lymphadenopathy, splenomegaly and worsening liver function. Liver biopsy results were consistent with sulfasalazine toxicity. After the diagnosis of DRESS was made the patient was put on high-dose corticosteroid with significant improvement.

Discussion

DRESS syndrome is a recognized rare, multisystemic, delayed type IVb hypersensitivity reaction (Lerch and Pichler, 2004).

The mean onset of symptoms after introduction of sulfasalazine is around 2 weeks (Jasmeen et al, 2016). Skin eruptions are a very common manifestation (Aquino et al, 2008). There is an erythematous, macular rash, which often spreads and worsens even after withdrawal of the drug. Fevers are high grade, and the most common organ affected is the liver (Shiohara et al, 2012). Cases of massive hepatic necrosis and granulomatous hepatitis caused by sulfasalazine have been described (Namias et al, 1981; Rubin, 1994).

The role of amoxicillin in the development of DRESS syndrome remains unclear. However, it seems that it has some role in triggering the syndrome in patients already showing signs of intolerance to sulfasalazine. Girelli et al's (2013) case report of amoxicillin-triggered DRESS syndrome shows similarities to the current case in terms of clinical course.

Sulfasalazine has been reported several times to be involved in cases of human herpesvirus (HHV) reactivation, predominantly HHV-6, to the extent that Shiohara et al (2012) have suggested it as part of the diagnostic criteria for DRESS.

Ms Michelle Lang, Medical Student, University College London Medical School, London

Mr James Fish, Medical Student, University College London Medical School, London

Dr Claudia Covelli, Honorary Clinical Fellow, Department of Cellular Pathology, Royal Free London NHS Foundation Trust, London

Dr Benjamin E Schreiber, Consultant Rheumatologist, Departments of Rheumatology and Pulmonary Hypertension, Royal Free London NHS Foundation Trust, London NW3 2QG

Correspondence to: Dr BE Schreiber (Benjamin.schreiber@nhs.net)

CASE REPORT

A 28-year-old Caucasian woman with a previous diagnosis of seronegative post-viral arthritis, successfully treated many years ago with hydroxychloroquine and courses of intramuscular depomedrone, presented with increasing pain and discomfort over several joints in her body. She had no other past medical history and there was no family history of autoimmune disease.

On examination there was tenderness of some metacarpophalangeal and proximal interphalangeal joints without swelling, erythema or warmth. Blood tests showed anti-cyclic citrullinated peptide (CCP) levels of 86 U/ml (normal range 0–7 U/ml), rheumatoid factor levels of 54 IU/ml (normal range 0–30 IU/ml), and anti-nuclear antibodies 1:160 speckled pattern. A diagnosis of early seropositive rheumatoid arthritis was made and medication commenced. Methotrexate was avoided as the patient was hoping to conceive. Sulfasalazine 1 g twice daily and hydroxychloroquine 400 mg once daily were prescribed.

Two weeks later she presented to the emergency department with a fever of 38.9°C, pharyngitis, nausea and vomiting, diffuse pains, fatigue and chest pains. Her medications were stopped and she was discharged after paracetamol and intravascular fluids.

She was restarted on lower doses of both her medications (sulfasalazine 500 mg twice daily and hydroxychloroquine 200 mg). She again developed similar symptoms, with the addition of earache. The latter was treated with amoxicillin. Two days later she developed an erythematous rash over her face and chest, progressing over the course of a week into a spreading erythematous macular rash involving more than 50% of her body (*Figure 1*) with an associated temperature of 40°C. All other observations were normal. The antibiotic and anti-rheumatic drugs were stopped.

She then developed facial oedema, purpuric lesions around the site of sphygmomanometry and right sided post-auricular lymphadenopathy. Blood results showed worsening liver function, lymphocytosis, no eosinophilia and high ferritin (*Table 1*).

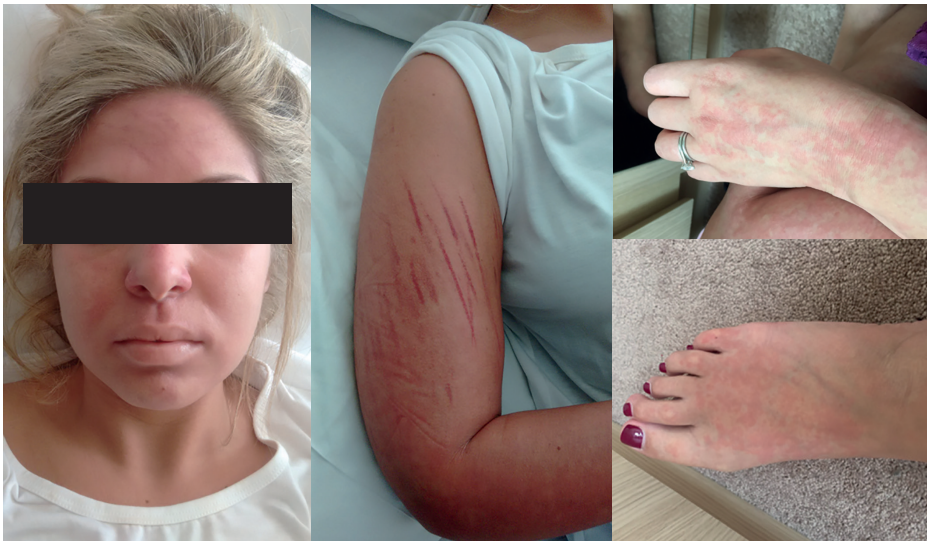
Urine dipstick showed 3+ blood. Blood cultures were negative. Blood films showed a reactive CD8-rich lymphocytosis. The patient was either immune to, or tested negative for broad viral screen in which human herpesvirus-6 DNA was not detected, but she was weakly positive for human herpesvirus-7. Ultrasound of the abdomen showed a normal liver size but splenomegaly, measuring 14.7 cm in size.

A liver biopsy report showed moderate, mixed portal and parenchymal inflammation. The inflammatory infiltrate was evenly composed of plasma cells, eosinophils and lymphocytes (*Figure 2*). Non-necrotizing portal tract granulomas were present. No lymphoid aggregate is seen. The overall appearance was in keeping with sulfasalazine toxicity.

A diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome was suspected and prednisolone 60 mg was started. She developed insomnia, euphoria and hallucinations until the dose was reduced to 40 mg. The patient showed significant improvement.

One month later the patient presented again with worsening joint pain. She was treated with intramuscular depomedrone and commenced on hydroxychloroquine. A low dose of prednisolone was continued.

Figure 1. Development of maculopapular rash.



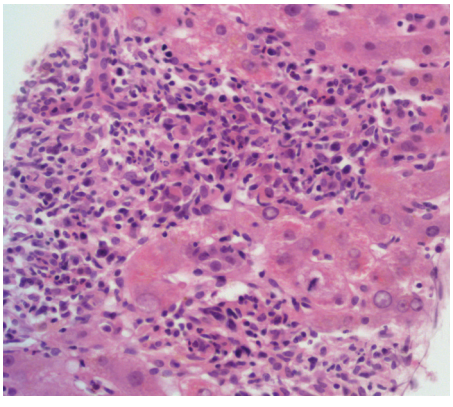
LEARNING POINTS

- This case presents further evidence for the role of amoxicillin in triggering sulfasalazine-related DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome within a few days of initiation of the antibiotic.
- The pathophysiology of the reaction remains unclear, and human herpesvirus-6 as well as human herpesvirus-7 reactivation has been proposed as a factor for the development of the syndrome, mediated by amoxicillin.
- In light of the evidence and the potential severity of DRESS syndrome reaction, the authors suggest withholding sulfasalazine when a course of amoxicillin is indicated.

Table 1. Results of investigations

Investigation	Value	Reference range
White cell count	22.87 x 10^9/litre	3.5–11 x 10^9/litre
Lymphocytes	19.7 x 10^9/litre	0.8–3.1 x 10^9/litre
Eosinophil	0.02 x 10^9/litre	0–0.5 x 10^9/litre
C-reactive protein	76 mg/litre	0–5 mg/litre
Ferritin	1850 ng/litre	20–230 ng/litre
International normalized ratio	1.3	0.9–1.3
Alanine aminotransferase	566 U/litre	0–33 U/litre
Aspartate transaminase	402 U/litre	0–31 U/litre
Bilirubin	42 µmol/litre	3–22 µmol/litre
Albumin	30 g/litre	35–50 g/litre

Figure 2. Portal inflammatory infiltrate with interface hepatitis: haematoxylin and eosin 20x. The inflammatory infiltrate was composed of lymphocytes, plasma cells and eosinophils.



Amoxicillin has been shown to upregulate HHV-6 replication (Mardivirin et al, 2010). Cacoub et al (2011) found that, for those tested for HHV-6, 80% of patients showed positive serology for reactivation. There has also been evidence of HHV-7 reactivation in patients with DRESS syndrome, and the virus could have played a role in the current case, although the link is not as well established as HHV-6.

Other viruses, including Epstein–Barr virus, have been implicated. Picard et al (2010) found that reactivation of one of these three viruses (HHV-6, HHV-7 or Epstein–Barr virus) was seen in 76% of patients studied with DRESS syndrome. BJHM

Aquino RT, Vergueiro CS, Magliari ME, de Freitas TH (2008) Sulfasalazine-induced DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). *Sao Paulo Med J* **126**(4): 225–226. https://doi.org/10.1590/S1516-31802008000400006

Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC (2011) The DRESS syndrome: a literature review. *Am J Med* **124**(7): 588–597. https://doi.org/10.1016/j.amjmed.2011.01.017

Girelli F, Bernardi S, Gardelli L et al (2013) A new case of DRESS syndrome induced by sulfasalazine and triggered by amoxicillin. *Case Rep Rheumatol* **2013**: 409152. https://doi.org/10.1155/2013/409152

Jasmeen, Krishnan P, Varma S, Kalra H, Vohra K (2016) Sulfasalazine Induced DRESS Syndrome: A Review of Case Reports. *British Journal of Medicine & Medical Research* **11**(7): 1–11. https://doi.org/10.9734/BJMMR/2016/20558

Lerch M, Pichler WJ (2004) The immunological and clinical spectrum of delayed drug-induced exanthems. *Curr Opin Allergy Clin Immunol* **4**(5): 411–419. https://doi.org/10.1097/00130832-200410000-00013

Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E et al (2010) Amoxicillin-induced flare in patients with DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on Human Herpesvirus 6 replication in vitro. *Eur J Dermatol* **20**(1): 68–73. https://doi.org/10.1684/ejd.2010.0821

Namias A, Bhalotra R, Donowitz M (1981) Reversible sulfasalazine-induced granulomatous hepatitis. *J Clin Gastroenterol* **3**(2): 193–198. https://doi.org/10.1097/00004836-198106000-00017

Picard D, Janela B, Descamps V et al (2010) Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl Med* **2**(46): 46ra62. https://doi.org/10.1126/scitranslmed.3001116

Rubin R (1994) Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. *Am J Gastroenterol* **89**(5): 789–791.

Shiohara T, Kano Y, Takahashi R, Ishida T, Mizukawa Y (2012) Drug-induced hypersensitivity syndrome: recent advances in the diagnosis, pathogenesis and management. In: French LE, ed. *Adverse Cutaneous Drug Eruptions.* Karger Publishers, Basel: 122–138