DOI: http://dx.doi.org/10.3315/jdcr.2013.1150

Journal of Dermatological Case Reports

Pentoxifylline-induced drug rash with eosinophilia and systemic symptoms (DRESS) in a patient with caffeine intolerance

Rebecca B. Saunderson[1,5], *Roger Garsia*[2,5], *Alexander P. Headley*[2], *Geoffrey W. McCaughan*[1,5,6], *Sandra O'Toole*[3,4,5], *Simone I. Strasser*[1,5]

1. AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown, Australia;
2. Immunology Department, Royal Prince Alfred Hospital, Camperdown, Australia;
3. Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, Australia;
4. Kinghorn Cancer Centre, Garvan Institute of Medical Research, Australia;
5. Sydney Medical School, University of Sydney, Australia;
6. Centenary Institute, Camperdown, Australia.

Corresponding author:

Associate Professor Simone Strasser

AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital

Missenden Road, Camperdown, NSW 2050, Australia

E-mail: *simone.strasser@sswahs.nsw.gov.au*

Key words:

alcoholic hepatitis, caffeine, DRESS, adverse drug reaction, eosinophilia, methylxanthines, pentoxifylline

Abstract

Background: Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug reaction characterised by rash, eosinophilia and systemic involvement.

Main observations: We report a case of DRESS induced by pentoxifylline used for the treatment of severe alcoholic hepatitis, in a patient with longstanding caffeine intolerance. A history of intolerance to caffeine and other methylxanthines is listed as a contraindication to the use of pentoxifylline, yet this precaution is not mentioned in alcoholic hepatitis treatment guidelines.

Conclusions: Prescribers should always seek a history of intolerance to caffeine and related compounds prior to use of pentoxifylline, as severe life threatening reactions can occur. (*J Dermatol Case Rep*. 2013; 7(3): 77-81)

Introduction

Recent guidelines for the management of alcoholic liver disease from the European Association for the Study of the Liver recommend either pentoxifylline or corticosteroids for the treatment of severe alcoholic hepatitis.[1] In particular, pentoxifylline is recommended as first line therapy for patients with ongoing sepsis. However contraindications to the use of pentoxifylline are not mentioned in the guidelines, and it is likely that most clinicians are unaware that the product information for pentoxifylline includes a contraindication for patients with a history of intolerance to methylxanthines, including caffeine, theophylline, and theobromine.

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug reaction characterised by skin rash, eosinophilia and systemic involvement. Clinical manifestations include fever, lymphadenopathy and haematological abnormalities, including eosinophilia, which may be in conjunction with other blood abnormalities such as neutrophilia and atypical lymphocytosis. Systemic involvement may include interstitial nephritis, hepatitis, carditis and/or interstitial pneumonia. Onset is typically 2 to 6 weeks following the initiation of a specific medication, and commonly implicated medications include aromatic anticonvulsants (phenytoin, carbamazepine and phenobarbital), and sulphonamides, but many other medications, including allopurinol

have been frequently implicated. Early recognition and cessation of the associated medication is key to the management of this condition.[2-6]

We report a case of life-threatening DRESS induced by pentoxifylline used to treat severe alcoholic hepatitis in a patient with unrecognised caffeine intolerance.

Case Report

A 39-year-old male was referred from a peripheral hospital for further investigation and management of jaundice and liver function test derangement thought to be secondary to alcoholic hepatitis.

He initially presented with a 1-week history of sudden onset jaundice, pale stools, dark urine and malaise. He denied fevers, vomiting, abdominal pain, diarrhoea, respiratory tract symptoms or rashes. He had no history of tattoos, body piercings, or intravenous drug use, denied ingestion of wild mushrooms, and had no history of industrial exposures, recent general anaesthetic or travel. He had never travelled to countries with high incidence of hepatitis. He denied new sexual contacts or contact with sex workers. The patient had self-reported poor medication compliance, but was intermittently taking nizatidine and atorvastatin prior to admission. Of note, he had only received one prescription for each medication in the past 4 months. He denied the use of herbal remedies or other over-the-counter preparations.

His past medical history included gastro-oesophageal reflux disease requiring fundoplication, oesophageal dilatation, hypercholesterolaemia, cellulitis and unexplained syncope. Previous cerebral CT and MRI, and Holter monitoring were normal.

He had a long history of alcohol abuse, with reported alcohol consumption of 8 to 10 standard drinks daily since the second decade of life. Alcoholic steatosis was confirmed on liver biopsy in 2007. He was drinking heavily to the time of onset of jaundice. He was a non-smoker. He had previously developed a rash following treatment with amoxicillin-clavulanic acid, but had subsequently tolerated other penicillins, including ticarcillin-clavulanic acid. He had a history of anaphylaxis with shellfish ingestion.

On presentation to the referring hospital, the patient was awake, alert and orientated without haemodynamic compromise. There was marked scleral icterus, and jaundice. His abdomen was soft with tender hepatomegaly with a liver span of 18cm, and there was no ascites. Neurological examination revealed normal attention and there was no asterixis. Remaining examination was unremarkable.

Results of a full blood count were normal but for an elevated mean corpuscular volume. Liver function tests showed an elevated bilirubin at 340 mmol/L (reference range 2-20), alanine aminotransferase 64 U/L (< 55), aspartate aminotransferase 328 U/L (5-50), alkaline phosphatase 231 U/L (20-110) and gamma glutamyltransferase 1621 U/L (15-73). His prothrombin time was 18 sec (9-15). His electrolytes and renal function were unremarkable. The Maddrey score was 34. An abdominal ultrasound was performed and demonstrated fatty infiltration of the liver without focal lesions, a thickened gallbladder wall without cholelithiasis or intrahepatic biliary dilatation, and hepatosplenomegaly without evidence of ascites. The hepatic vessels were patent. Testing for EBV and CMV demonstrated past exposure, and the patient tested negative for hepatitis A, B, C and HIV. Anti-liver kidney microsomal antibodies, anti-smooth muscle cell antibodies, anti-nuclear antibodies, anti-mitochondrial antibodies and ANCA were not detected and caeruloplasmin and copper studies were normal. Alpha-fetoprotein was normal. Iron studies demonstrated an elevated ferritin at 485, with normal transferrin saturation, and genetic testing for haemochromatosis excluded the presence of HFE gene mutations.

A clinical diagnosis of alcoholic hepatitis was made (the referring hospital did not have the facilities to biopsy), and he was initially treated conservatively with thiamine, multivitamins and vitamin K. The bilirubin level progressively rose to 770 mmol/L and he developed a mild neutrophilia. At that time he was commenced on active treatment for alcoholic hepatitis with pentoxifylline 400 mg three times daily and oral prednisolone 40 mg daily. After 4 days of treatment the renal function deteriorated with creatinine rising to 150 mmol/L (60-110). A renal tract ultrasound was normal.

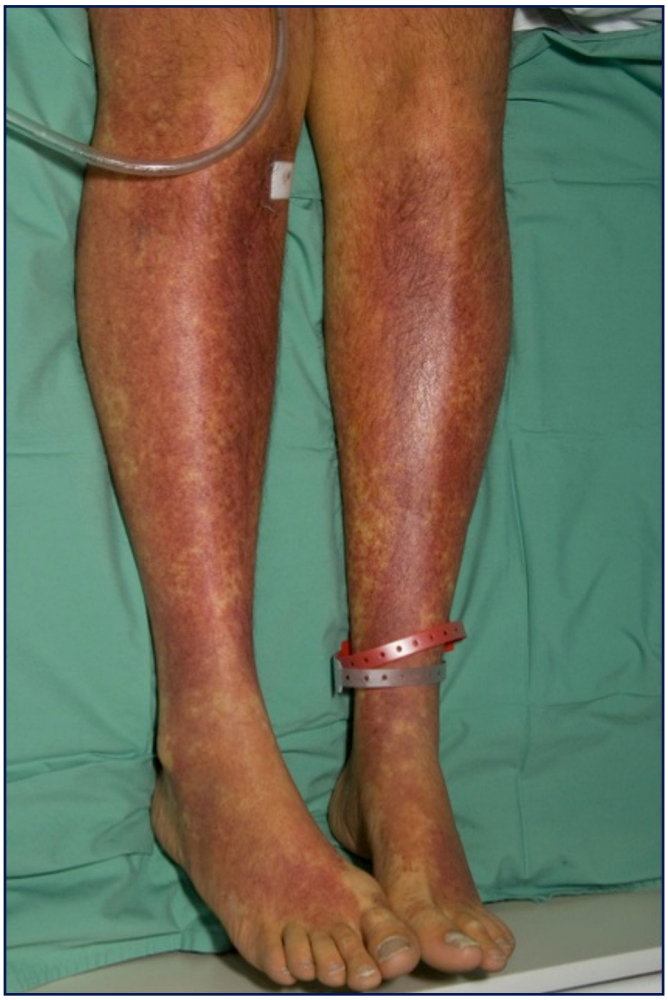


Figure 1

Diffuse morbilliform rash located over the legs. Similar rash was also present over his trunk and arms.

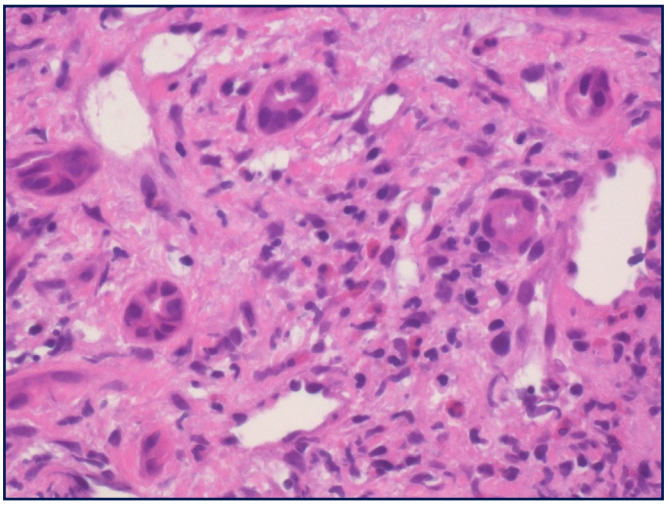


Figure 2

Bile ductular proliferation within fibrous septa associated with lymphocytes and scattered eosinophils (Haematoxylin & Eosin 400x).

A diagnosis of hepatorenal syndrome was made and he was started on terlipressin and albumin. The bilirubin level did not improve and therefore prednisone was ceased at day 5 of treatment and pentoxifylline was continued. Because of a cough and progressive neutrophilia, an intravenous broad-spectrum antibiotic (ticarcillin-clavulanic acid) was commenced.

The patient was transferred to the Liver Transplant Unit at Royal Prince Alfred Hospital for further investigation and treatment. At the time of transfer, he had received 11 days total treatment of pentoxifylline, and continued on ticarcillin-clavulanic acid, terlipressin and albumin. The pentoxifylline was ceased following transfer as his condition was clearly deteriorating.

3 days after transfer to our centre, the patient developed high fevers > 38°C and a diffuse morbilliform rash located over his trunk, arms and legs (Fig. 1). He developed marked elevation in his total white cell count to 27 x 10^9/L, with eosinophilia (7.1 x 10^9/L), neutrophilia (11.7 x 10^9/L) and an atypical lymphocytosis (6.5x 10^9/L).

A complete septic work up was undertaken, including 3 sets of blood cultures, testing for parvovirus and mycoplasma, all of which were negative, and a transthoracic echocardiogram was normal. Due to concern for a drug reaction, the ticarcillin-clavulanic acid was ceased. Despite these measures, the patients high fevers continued, the rash worsened and his renal function significantly deteriorated, with his creatinine rising to greater than 600 mmol/L. Urinary sodium was 26 mmol/L. The terlipressin was ceased. Due to clinical fluid overload and marked oliguria, intermittent haemodialysis was required.

The patient underwent skin and transjugular liver biopsies. The skin biopsy showed infiltration with eosinophils without evidence of vasculitis, most consistent with a drug reaction. The liver biopsy showed distorted architecture with prominent bands of fibrosis and thickened liver plates suggestive of cirrhosis. Marked intracellular cholestasis with scattered bile plugs and feathery degeneration was observed. Diagnostic Mallory bodies were not seen, although occasional eosinophilic globules were noted in some hepatocytes. There was also macrovesicular steatosis affecting around 30% of hepatocytes associated with pericellular fibrosis supporting a diagnosis of alcoholic steatohepatitis. In addition bile ducts displayed irregular nuclear spacing and cytoplasmic eosinophilia suggestive of damage. There was a bile ductular reaction at the periphery of portal tracts and inflammation was also noted within the fibrous bands consisting predominantly of lymphocytes as well as scattered eosinophils (Fig. 2). No vasculitis was seen and no granulomas were observed.

While the biopsy showed evidence of alcoholic hepatitis, it was felt the additional features were consistent with a superimposed drug reaction. A diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was made on the basis of the clinical features, marked eosinophilia, skin rash and liver histology in the setting of multiple drug exposure.

The patient's allergy history was revisited. He relayed a lifelong intolerance to caffeine-containing beverages. This was first noted around the age of 11, when he found that he developed marked nausea and vomiting when consuming caffeine-containing beverages, and had subsequently learnt to always avoid drinks or food containing caffeine. It was then recognised that methylxanthines such as theophylline and pentoxifylline are contraindicated in patients with a history of caffeine-intolerance. Subsequently all medications were ceased and he was commenced on prednisolone 50 mg daily.

The patient clinically responded well to this regime, with improvement in his rash, renal function and haematological abnormality, with eosinophils and other subsets returning to baseline. His liver function also improved and he was discharged from hospital 24 days after admission.

Discussion

This case highlights DRESS in a patient with caffeine-intolerance treated with pentoxifylline, with systemic manifestations including rash, fever, interstitial nephritis and hepatitis.

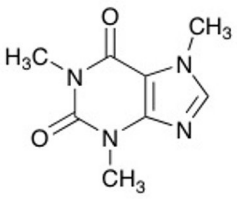
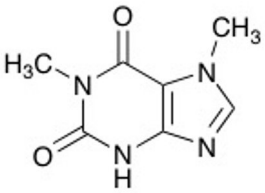
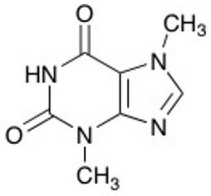
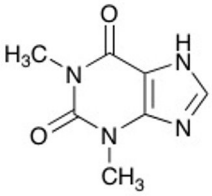
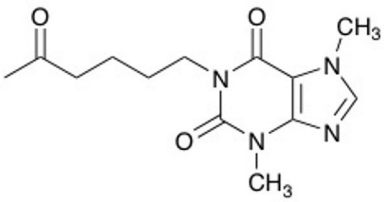
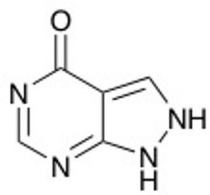
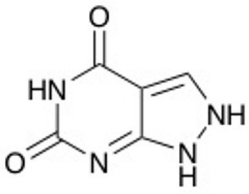
Pentoxifylline is a methylxanthine used for the treatment of intermittent claudication,[7] and more recently in the treatment of alcoholic hepatitis.[1,8] A randomized placebo-controlled trial demonstrated a reduction in short-term mortality, and death related to hepatorenal syndrome, in patients with severe alcoholic hepatitis treated with pentoxifylline[9] and pentoxifylline has been recommended as an alternative first-line therapy to corticosteroids in patients with sepsis in treatment guidelines.[1] In the case described, the treating clinicians decided to combine the use of pentoxifylline with oral prednisone, however it should be noted that a recent, large randomized controlled trial failed to show any benefit of the combination of pentoxifylline and corticosteroids over corticosteroids alone in patients with severe alcoholic hepatitis.[10]

Pentoxifylline (1-(5-oxohexyl)-3,7-dimethylxanthine), has structural similarities to xanthine derivatives such as caffeine, theobromine and theophylline, displaying a 1, 3, 7-trimethyl

substitution pattern like caffeine, a 3, 7-dimethyl substitution pattern similar to theobromine, and 1, 2-dimethyl substitution to theobromine.[7] Caffeine is metabolised to paraxanthine, theobromine and theophylline via demethylation by Cytochrome P450 1A2. Therefore, in addition to sharing a similar chemical structure to caffeine, pentoxifylline has structural homology to the metabolites of caffeine, namely theobromine and theophylline. Allopurinol is a structural analogue of hypoxanthine and its major metabolite, oxypurinol, is also a xanthine analogue. Table 1 highlights the structures and similarities of pentoxifylline, caffeine and allopurinol and their metabolites.

The patient described developed DRESS following administration of a methylxanthine with structural similarities to caffeine and its metabolites. Whilst it is recognised that administration of methylxanthines to patients with caffeine allergy is contraindicated, and highlighted in the product information, a history of caffeine intolerance was not elicited at the time of prescription. This case was also complicated by the clinical manifestations of DRESS occurring following the cessation of pentoxifylline. Whilst it is known that the half-life of pentoxifylline is more than doubled in patients with cirrhosis,[11] allergic drug reactions are not predictably based on drug pharmacotherapy, and are more likely to relate

Table 1. Structural similarities between pentoxifylline, caffeine and allopurinol and their metabolites.

Chemical structure	Metabolites
 Caffeine	 Paraxanthine  Theobromine  Theophylline
 Pentoxifylline	
 Allopurinol	 Oxypurinol

to pharmacogenetic factors.[12] Failure to recognise this phenomenon in this patient with serious comorbidity resulted in a delay in diagnosis and treatment.

DRESS has not previously been reported with pentoxifylline administration in a caffeine-intolerant patient but it is notable that DRESS has recently been reported in a paediatric patient following ingestion of high doses of caffeine.[13] The structural similarity of allopurinol to pentoxifylline is noteworthy, as allopurinol has previously been implicated as a drug leading to DRESS. This has been thought to be due to the metabolite oxypurinol, which as previously mentioned, is structurally similar to the xanthines. The HLA-allele associated with allopurinol induced DRESS is B*5801.[14] It would have been interesting to have genotyped our patient, as the T-cell reaction in both cases may be driven by structurally similar metabolites of allopurinol and pentoxifylline, however, HLA status and caffeine allergy is not well established.

Pentoxifylline has previously been implicated in causing acute generalized exanthematous pustulosis,[15] but to our knowledge, this is the first report of DRESS due to treatment with pentoxifylline.

Conclusions

Prescribers of pentoxifylline and other methylxanthines, and related compounds such as allopurinol, should be aware that such agents are contraindicated in patients with caffeine intolerance or allergy. Failure to recognise this potential cross reaction can lead to serious adverse events, including life threatening systemic reactions.

Acknowledgements

Special thanks goes to Derrick Roberts for his review of the chemistry and submission of the chemical structures.

References

1. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol*. 2012; 57: 399-420. PMID: 22633836.
2. Hauben M. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1995; 332: 959-960. PMID: 7877661.
3. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg*. 1996; 15: 250-257. PMID: 9069593.
4. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol*. 2001; 137: 357-364. PMID: 11255340.
5. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology*. 2003; 206: 353-356. PMID: 12771485.
6. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am*. 2009; 29: 481-501. PMID: 19563993.
7. Dettelbach HR, Aviado DM. Clinical pharmacology of pentoxifylline with special reference to its hemorrheologic effect for the treatment of intermittent claudication. *J Clin Pharmacol*. 1985; 25: 8-26. PMID: 3882773.
8. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009; 360: 2758-2769. PMID: 19553649.
9. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double blind, placebo-controlled trial. *Gastroenterology*. 2000; 119: 1637-1648. PMID: 11113085.
10. Mathurin P, Louvet A, Dao T, Nahon P, Diaz E, Carbonell N, Boursier J, Anty R, Lebrec D, Moirand R, Thabut D, Moreno C, Talbodec N, Paupard T, Naveau S, Silvain C, Pageaux GP, Sobesky R, Salleron J, DuhamelA. (2011): Addition of Pentoxifylline to Prednisolone for Severe Alcoholic Hepatitis Does Not Improve 6-Month Survival: Results of the Corpentox Trial. *Hepatology*, 54 S1: 391A-391A.
11. Rames A, Poirier JM, LeCoz F, Midavaine M, Lecocq B, Grange JD, Poupon R, Cheymol G, Jaillon P. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther*. 1990; 47: 354-359. PMID: 2178853.
12. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. *Pharmacogenomics*. 2012; 13: 1285-1306. PMID: 22920398.
13. Mahapatra S, Belgrad JL, Adeoye MA. Psychotropic drug-related eosinophilia with systemic symptoms after acute caffeine ingestion. *Pediatrics*. 2011; 127: e235-e238. PMID: 21135003.
14. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, Chen YT. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA*. 2005; 102: 4134-4139. PMID: 15743917.
15. Patrizi A, Tabanelli M, Antonucci A, Neri I. Acute generalized exanthematous pustulosis induced by pentoxifylline. *Int J Dermatol*. 2007; 46: 1310-1312. PMID: 18173533.