CASE REPORT

# Enigma: infection or allergy? Vancomycin-induced DRESS syndrome with dialysis-dependent renal failure and cardiac arrest

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## SUMMARY

A man aged 73 years with infective endocarditis presented with septic shock and was started on immediate antimicrobial therapy. His blood culture yielded no organism. Subsequently, he developed a severe allergic reaction to prolonged empirical vancomycin therapy. This manifested as fever, widespread maculopapular rash and severe progressive acute kidney injury ultimately requiring dialysis. In the context of eosinophilia, this was determined to be drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Deciphering this complication as allergy in the context of severe infection required extreme caution due to the polarity of treatment with immunosuppression. Ultimately, this was used, with improvement of renal function, resolution of symptoms and absence of recurrence of infection. In summary, we present a case of vancomycin-related DRESS syndrome leading to dialysis—which is unique in the literature—complicating the treatment of culture-negative infective endocarditis.

## BACKGROUND

Infective endocarditis is a not too uncommon presentation to tertiary cardiology centres and often requires prolonged treatment courses. The pathogens and their targets are myriad with differing optimal treatments. Empirical treatment courses with broad-spectrum antibiotics and prolonged hospital stay are associated with increased morbidity and mortality, making identification of the causative organism imperative.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening hypersensitivity reaction to a medication. The condition is characterised by heterogenous multisystem dysfunction, with mortality approaching 10% in extremis.[1] Minimising exposure of patients to precipitant medications beyond that which is absolutely required is therefore of utmost importance. Our patient's other life-threatening condition of infective endocarditis, proven on echocardiography, had forced us to fail to minimise that exposure, and this is presented herein.

## CASE PRESENTATION

A man aged 73 years presented to the Northern General Hospital in Sheffield on 17 August 2015 with a 1 week history of lethargy, anorexia and dark urine. He was previously fit and well and had a medical history of hypertension, myocardial infarction and prostate cancer in remission.

On examination, he was found to be approaching septic shock and, with bibasal crepitations on lung auscultation, intravenous Tazocin was instituted for a lower respiratory tract infection before blood cultures were obtained.

On subsequent cardiology review, bedside echocardiography revealed mobile masses on the aortic valve and a thickened mitral valve. The patient developed septic shock and was admitted to the high dependency unit until day 15, where antibiotics were escalated to meropenem and vancomycin for likely infective endocarditis.

Following confirmation of endocarditis through a trans-oesophageal echo (TOE), antibiotic therapy was paused and serial blood cultures taken over a 48-hour period in an unsuccessful attempt to identify the organism. Meropenem was restarted alone in the absence of methicillin-resistant *Staphylococcus aureus* positivity.

On day 23, the patient spiked a temperature for the first time since admission. As a result of possible failure of sepsis suppression and in conjunction with neutropenia likely related to the antibiotic, meropenem was stopped and vancomycin reintroduced in addition to gentamicin.

The following day, the patient developed a rash, in conjunction with a dose of paracetamol, which spread over a matter of days to become confluent, non-pruritic whole-body maculopapular erythema, with a tiger-print yellowish hue on the shoulders and purpura at the extremities (figure 1). The fever persisted and the patient felt unwell. A reaction to vancomycin was suspected and on day 29, both antibiotics were stopped.

On day 32, the patient suffered a cardiac arrest and underwent two cycles of cardiopulmonary resuscitation with a non-shockable rhythm before return of spontaneous circulation. His preceding cardiac trace demonstrated trigeminy (figure 2). He had collapsed in the bathroom, with preceding presyncopal symptoms and had significant postural hypotension on examination. Repeat echo revealed persistent yet smaller lesions on the aortic valve.

On day 33, the rash flared following a further dose of paracetamol, spreading to involve his palms with eventual desquamation. The patient developed fluid overload in the context of rapidly deteriorating renal function and haemodialysis was started. The decision was made to treat with steroids with a working diagnosis of DRESS syndrome, which led to a quick recovery of clinical state.

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**Figure 1** Medical photograph of rash on the left lower limb.

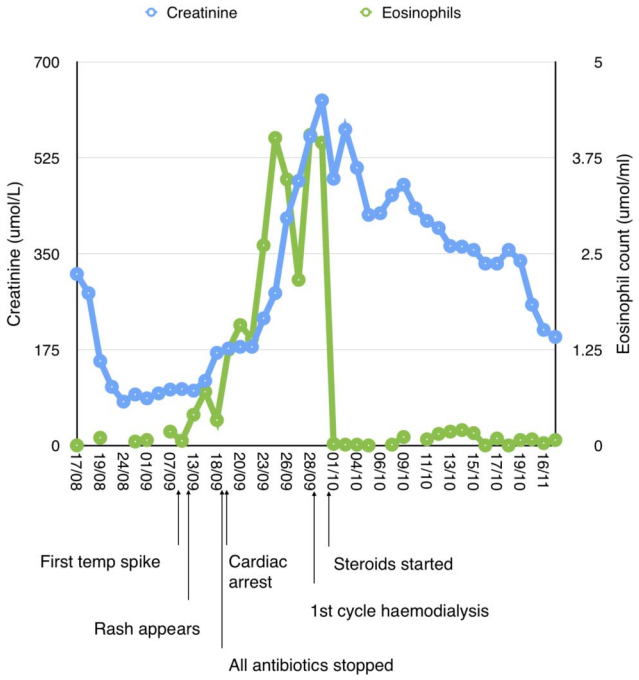



**Figure 3** Scatterplot of serum creatinine and eosinophil count over time, with critical event annotation.

## INVESTIGATIONS

*Bloods*: Creatinine, neutrophil count and eosinophil count were key serum markers throughout the course of the patient's admission (figure 3). He underwent two episodes of neutropenia, first while on meropenem alone and latterly immediately following re-institution of vancomycin, in conjunction with the onset of rash, acute kidney injury and eosinophilia.

*Cultures*: Twenty-four sets of blood cultures were taken, all of which were negative.

*TOE (day 15)*: this demonstrated multiple vegetations of the aortic and posterior mitral valve leaflet, in the absence of abscess formation or raised pulmonary pressure.

*Skin punch biopsy (day 43)*: this revealed epidermal and perivascular lymphocytic and eosinophilic infiltration in the absence of vasculitis, in keeping with DRESS syndrome.

## DIFFERENTIAL DIAGNOSIS

The temporality of the onset of allergic features in this case raised the possibility of paracetamol allergy. According to the patient, he had been lifelong paracetamol naive until this admission. He received two doses earlier in the admission without adverse effect, before a third dose that closely preceded the onset of the rash and a fourth dose that was immediately associated with a flare of it. We know from observation of hypersensitivity to other substances, for example, latex in the healthcare industry, that hypersensitivity can arise after tolerated exposure to the substance for a variable amount of time, from the second administration to years.[2] Paracetamol hypersensitivity is a relatively rare, yet increasingly recognised entity. Features of IgE-mediated hypersensitivity appear to predominate through cutaneous erythema (94%), urticaria, angioedema, cough, rhino conjunctivitis to full anaphylaxsis.[3] Paracetamol is also associated with toxic epidermal necrolysis and Stevens-Johnson syndrome.[4] Our patient experienced full desquamation of his palms and soles, although there was no mucosal involvement. Paracetamol-mediated DRESS syndrome is not a recognised entity and cannot be seen to fully explain the clinical picture, but the temporality of the rash in relation to paracetamol doses raises the possibility of a synergistic effect.

Mural and valvular thromboses are a definite stage in the pathogenesis of Loeffler's endocarditis. We presume our patient had an infective endocarditis, but we were unable to isolate any organism in a multitude of blood cultures. Could this whole clinical syndrome have been a primary allergic syndrome—that is, Loeffler's endocarditis? Against this diagnosis are the absence

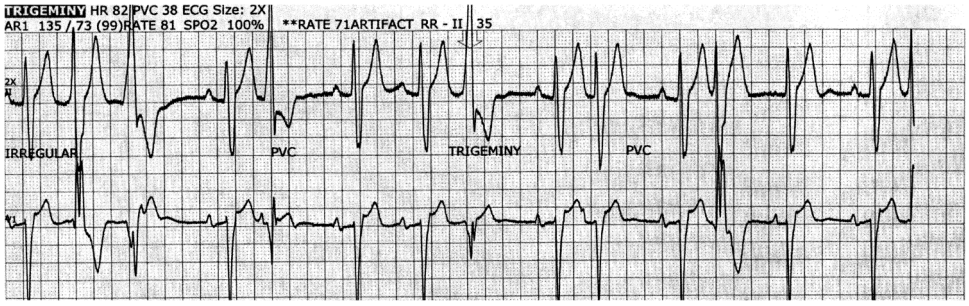



**Figure 2** Trace from cardiac monitor capturing trigeminy prior to cardiac arrest.

of eosinophilia at the outset of the presentation and good biventricular function on discharge.

The working diagnosis is DRESS syndrome. This is the diagnosis that unifies the patient's clinical presentation, course and biochemistry and is supported by relevant histology.

## TREATMENT

*Broad-spectrum antibiotics (day 2)*: culture-negative infective endocarditis was the index case of the presentation, necessitating empirical antibiotic therapy.

*Haemodialysis (day 33)*: severe acute kidney injury with fluid overload necessitated the institution of haemodialysis.

*Steroid therapy (day 34)*: with a diagnosis of DRESS complicating infective endocarditis, there was uncertainty over the potential for steroid therapy to worsen a potentially ongoing infective process. While repeat trans-thoracic echocardiography revealed the persistence of smaller vegetations, it is recognised that infective vegetations do not fully disappear despite treatment and that fibrin meshes remain behind in their place.[5] As such, prednisolone at a dose of 40 mg/day was started which led to resolution of the syndrome.

## OUTCOME AND FOLLOW-UP

The patient began a slow symptomatic, clinical and biochemical improvement. He was discharged home after 63 days in hospital. He was subsequently admitted on two occasions, first for atrial fibrillation and subsequently for fluid overload, both of which were managed during short in stays. At his latest cardiology follow-up at the time of writing, the patient's creatinine had plateaued to a value between 160 and 170 μmol/L.

## DISCUSSION

### Culture-negative endocarditis

The definitive treatment of infective endocarditis requires a prolonged course of antibiotics, especially in the context of prosthetic valves, cerebral emboli and culture negativity. Of the latter, there are three main categories: those caused by fastidious, difficult to culture organisms of the HACEK group, those caused by antibiotic sterilisation and those caused by intracellular organisms that cannot be cultured using standard techniques.[6] Antibiotic sterilisation is the one controllable factor and this case demonstrates the importance of taking blood cultures before antibiotics in sepsis to avoid this, as mandated in sepsis guidelines.[7] Failure to achieve this inevitably leads to the need for prolonged empirical broad-spectrum antibiotic therapy and the myriad risks that this poses.

### Drug reaction with eosinophilia and systemic symptoms

DRESS syndrome was first recognised in the literature in the 1930s, with formal diagnostic criteria proposed in 1996 by Bocquet *et al*.[8] The pathogenesis is a T-cell-mediated type IV hypersensitivity reaction associated with a latency of 11–35 days post stimulus.[9]

Core features of the condition include fever (96%), maculopapular rash (85%), hepatitis (85–96%) and, to a lesser extent, renal dysfunction.[10 11]

Drugs associated with the development of the condition are diverse. The most common class is anticonvulsants (65–77%),[10] followed by allopurinol, vancomycin, leflunomide, nitrofurantoin and antituberculous agents.[9 12]

Unlike other precipitants, vancomycin is particularly associated with renal manifestation of DRESS. This may be explained in part by the much more frequent non-allergic nephrotoxicity associated with the drug, which is proposed to be related to free radical production in the renal medulla[13] and may work synergistically with the further nephrotoxins in this case of amino glycoside antibiotics and hypotension.[14] Biopsy demonstrates acute interstitial nephritis as the renal pathophysiology[15–17] and treatment necessitates high-dose steroid therapy[18] with or without prolonged courses of immunosuppressive agents.[19]

There are no previous cases of vancomycin-mediated DRESS leading to dialysis-dependent renal failure in the literature.

### Questions raised

Despite vancomycin being withdrawn soon after the onset of rash, the eosinophilia and creatinine rose exponentially and persistently after this. This may be explained by the persistence of vancomycin in the patient's bloodstream 1 week post cessation, or perhaps a setting in effect of the allergic injury, reflecting recoverable damage to the renal interstitium, as seen in other pathophysiology such as acute tubular necrosis.

The precipitant for cardiac arrest in this patient is unclear. Complex ventricular ectopy (figure 2), as demonstrated on cardiac monitoring preceding the event, is associated with increased risk of ventricular fibrillation arrest in the context of previous myocardial infarction, as in this case.[20] It is possible that the raised eosinophil count itself was the cause, as demonstrated by the multiorgan failure that is induced by primary hypereosinophilia syndrome.[21] Indeed, hypereosinophilia is associated with extensive tissue infiltration which leads to damage via the release of cytokines, toxic granules or signalling to inflammatory cells and has the potential for a similarly heterogeneous presentation to DRESS syndrome.[22] The primary eosinophilic syndrome has an estimated cardiac manifestation rate of up to 50% with a pathological process comprising acute necrosis, thrombosis and fibrosis: in other words, Loeffler's endomyocarditis.[23] Individual case reports demonstrate occurrence of primary cardiac arrest in this syndrome with or without evidence of ischaemia.[21 24 25] Moreover, a whole disease subset of coronary vasospasm, manifesting as angina or myocardial infarction, secondary to hypersensitivity reactions is recognised by the term Kounis syndrome.[26] A further explanation for the arrest, in keeping with the presyncopal symptoms and signs noted, is profound vasodilatation and underfilling of the right ventricle.

It is feasible that eosinophilia could have a primary pathophysiological role in DRESS syndrome as opposed to simply being a biochemical sign. Recognising this would permit greater understanding of the disease process and the possible outcomes of DRESS syndrome.

### Learning points

- Every attempt should be made to obtain blood cultures before the timely institution of antibiotics in sepsis, even in the presence of septic shock.
- Dialysis-dependent renal failure and cardiac arrest are extreme complications of vancomycin-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.
- The manifestations of DRESS can be refractory to the withdrawal of the trigger.
- Hypereosinophilia is a possible primary pathological process in DRESS syndrome and can be used to predict possible outcomes.

**Contributors** PSW designed the theme of the case report, performed the literature search, wrote the first and second draft of the manuscript, designed the figures and co-approved the final version. AA-M identified the case and co-designed the theme of the paper, edited and provided further content to the manuscript and approved the final version to be submitted. Both authors are accountable for the work. There are no further authors of this work who have not been included and there were no other contributors to the work.

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**Patient consent** Obtained.

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