Case report

Vancomycin induced DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) in a patient with tricuspid endocarditis

Lynsey Jane Hewitson¹

Medicine, Bristol Royal Infirmary,
Bristol, UK

Correspondence to
Dr Lynsey Jane Hewitson,
lynsey.hewitson@nhs.net

Accepted 30 August 2019

SUMMARY

A 57-year-old man presented for an elective pacemaker upgrade, complicated by the discovery of device infection. He had a background of complex congenital heart disease, including replacement of heart valves, and was treated for presumed infective endocarditis that was later confirmed by echocardiography. Antibiotic treatment, with intravenous vancomycin, was given as per the tissue sample sensitivities. On day 24 of treatment he deteriorated clinically, with the evolution of recurrent fever, epigastric pain, diarrhoea, widespread pruritic rash, lymphadenopathy and severe hypoxia over the subsequent 7–10 days. Blood tests revealed development of a marked eosinophilia, transaminitis and rising inflammatory markers. Further radiological imaging was non-diagnostic. On the basis of these clinical and biochemical features a diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome was made. This led to the cessation of vancomycin, the offending agent and the referral for specialist immunology advice. He was subsequently treated with oral prednisolone and made a full recovery.

BACKGROUND

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but severe and potentially life-threatening hypersensitivity drug reaction. It is a multisystem disorder with a broad spectrum of clinical manifestations and a heterogeneous presentation that can lead to a delay in diagnosis. This is crucial as early recognition of the syndrome with prompt cessation of the offending agent is critical to prognosis and outcomes.¹ This episode was associated with the use of vancomycin for treating infective endocarditis, an antibiotic frequently used in both methicillin-resistant *Staphylococcus aureus* (MRSA) and prosthetic valve infections.

CASE PRESENTATION

This case involved a 57-year-old man with a background of complex congenital heart disease, including replacement of aortic and pulmonary valves (metallic and percutaneous respectively), patent foramen ovale with right to left shunt, moderate to severe left ventricular impairment and a single chamber pacemaker with right ventricular lead. He presented electively for a device upgrade to a dual chamber pacemaker (cardiac

resynchronisation therapy with defibrillator) due to deteriorating left ventricular systolic function and pain at the original pacemaker site. When the original pacemaker was removed it was found to be infected and surrounded by pus.

Empirical antibiotic therapy (intravenous flucloxacillin) for pacemaker infection with presumed endocarditis was therefore started. On day 3, the wound tissue subsequently grew *Staphylococcus epidermidis* which was resistant to penicillin: treatment with flucloxacillin was therefore stopped and he was switched to vancomycin as per microbiology advice. Transthoracic echocardiography at this time confirmed a vegetation on his native tricuspid valve with associated valve dysfunction (severe regurgitation).

For the first 21 days of treatment he remained stable however, on day 24 he began to deteriorate clinically. Over the subsequent 7–10 days he developed a constellation of signs and symptoms including recurrent fever, epigastric pain, diarrhoea, a widespread maculopapular and intensely pruritic rash, axillary lymphadenopathy and severe hypoxia which ultimately led to transfer him to the coronary care unit for a higher level of care.

INVESTIGATIONS

Following the clinical deterioration on day 24, several investigations were performed. Blood tests revealed rising inflammatory markers with new transaminitis and eosinophilia, which evolved to a peak count of $6.7 \times 10^9/L$ on day 35. The chronology of these abnormalities is further illustrated in the treatment section below. The vancomycin level at the time of deterioration was 11.2 mg/L: within the target therapeutic range of 10–15 mg/L.

The chest X-ray revealed widespread interstitial infiltrates and was felt to represent pulmonary oedema and infection. A repeat transthoracic echocardiogram did not demonstrate any change from the previous imaging: there was no evidence of worsening endocarditis or abscess formation. A liver ultrasound and subsequent contrast enhanced CT of the chest, abdomen and pelvis were also performed to investigate the transaminitis and to look for any other occult source of infection. These demonstrated acalculous cholecystitis and a small volume of abdominal free fluid but were otherwise

© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hewitson LJ. *BMJ Case Rep* 2019;**12**:e229590. doi:10.1136/bcr-2019-229590

Figure 1 White cell count differentials at varying stages of treatment.

non-diagnostic. Importantly, there was no evidence of septic embolic phenomenon.

Repeated blood, stool and urine cultures were negative. Peripheral blood film showed an eosinophilia with atypical lymphocytosis (cell percentages unknown). Hepatitis A–E, Bartonella and Q-serology were all negative. On day 41, the PCR for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) DNA was negative, but human herpes virus 6 (HHV6) was positive to a high level: 42284 copies/ml, 6 days after the peak eosinophil count. The autoimmune profile was unremarkable.

DIFFERENTIAL DIAGNOSIS

Uncontrolled infective endocarditis and congestive cardiac failure were initially felt to be the most likely causes of his deterioration given the features of fever, worsening hypoxia and rising inflammatory markers. However, as mentioned previously, transthoracic echocardiography appearances were stable and repeat blood cultures were negative, and did not support this hypothesis. The widespread maculopapular rash was felt most likely to represent a drug reaction but was initially thought to be an isolated finding. There was no angioedema to raise concern about anaphylaxis, and there was no mucosal involvement to suggest toxic epidermal necrolysis (the extent of the rash being too large for Stevens-Johnson syndrome).

As there was no evidence of worsening endocarditis, investigations were performed to look for an alternative source of bacterial sepsis. Cross-sectional imaging revealed acalculous cholecystitis however, the general surgeons felt this was more likely a response to acute illness, rather than a source of sepsis itself. An infectious cause of diarrhoea, such as clostridium difficile infection, was also considered but disproved when repeated stool cultures were negative.

During the course of these investigations, the clinical deterioration was discussed with the microbiology specialists and antibiotic cover was broadened with the addition of piperacillin-tazobactam and metronidazole, while continuing vancomycin. However, he continued to deteriorate despite these treatment alterations. In combination with non-diagnostic imaging and negative microbiological investigations, this made a diagnosis of bacterial sepsis less likely.

A subsequent clinical microbiology consultant-review on the ward on day 31 led to the diagnosis of the DRESS syndrome. The symptomatology and clinical findings were consistent, as was the latent period from the onset of initiation of vancomycin (21 days). As this was the only new medication which fell within a consistent time period, it was deemed to be the most likely culprit. The patient was not known to have ever been treated with vancomycin previously.

TREATMENT

As described earlier, the initial management was by broadening the antibiotic therapy, supportive treatment and antihistamines for rash. On day 31, after the diagnosis of DRESS syndrome was suspected, vancomycin was stopped and supportive treatment was continued in the coronary care unit for the subsequent 7 days. However, there was no significant improvement in his condition over this time. He remained febrile with persistent abdominal pain and the eosinophil count continued to rise. A specialist immunological opinion was therefore obtained and as a result treatment with systemic corticosteroid therapy was commenced on day 38. Prednisolone was initiated at a dose of 0.5 mg/kg/day, a total of 40 mg once daily (for an 80 kg male). The eosinophil count had marginally improved by this time.

After 7 days of systemic corticosteroid therapy a significant clinical improvement was seen. There was no recurrence of fever or rash and there was improvement in all other clinical parameters, including hypoxia. There was also a significant biochemical response with improvement of eosinophilia, C-reactive protein (CRP) and transaminitis (alanine aminotransferase (ALT)). These findings are further illustrated in [figure 1](#) and [table 1](#).

Following completion of 7 days of oral treatment prednisolone 40 mg, the dose was subsequently weaned at a rate of 5 mg every 5 days, the total systemic steroid course, therefore, was for 42 days (6 weeks). There was no clinical deterioration or recurrence of symptoms as the steroids were weaned and ultimately stopped. A new pacing system (cardiac resynchronisation therapy defibrillator (CRT-D)) was implanted on day 58 and he was discharged from hospital on day 64.

OUTCOME AND FOLLOW-UP

After the initial improvement with oral corticosteroid therapy a sustained recovery was seen. He remained an inpatient for over 1 month after the diagnosis of the DRESS syndrome was made and there was no recurrence of symptoms or disease during this time period. Post discharge, he was followed up at 2 weeks, 4 weeks and at regular intervals thereafter. He has now been followed up for over 1 year by both the adult congenital heart disease and microbiology teams. While he has remained symptomatic from a heart failure perspective and has recently been started on sacubitril/valsartan, no complications or sequelae of the DRESS syndrome had been reported or identified in the 18 months after the initial diagnosis. He remains under follow-up from an adult congenital heart disease and heart failure perspective.

DISCUSSION

DRESS syndrome is a rare but potentially life-threatening drug hypersensitivity reaction. It is typically a multisystem disorder, first described in 1966, as a combination of skin rash, fever, pharyngitis lymphadenopathy and visceral organ involvement.² There is a latent period before onset of the symptoms, normally 2–6 weeks after initial exposure, or as little as 3 days if there is a second contact with the offending agent.³ While the syndrome is perhaps most recognised with anticonvulsants it has been described with a variety of therapeutic agents, including antibiotics and rarely, vancomycin. It is more common in adults than children, with an estimated incidence of 1 in 1000 to 1 in 10 000 drug exposures.^{1 4} The mortality rate of DRESS syndrome has been repeatedly estimated at 10%, with liver failure being the most common cause of death.^{5 6} The delay in withdrawal of the culprit drug is directly related to prognosis.⁵

The exact pathogenesis of the DRESS syndrome is not fully understood, however, the interaction of at least 2 of the

Table 1 Additional biochemical markers at varying stages of treatment

	On admission	Symptom onset	Diagnosis of DRESS	Peak eosinophilia	Onset of steroids	Discharge
Total WCC (10 ⁹ /L) <i>Ref range 4.0–10.0</i>	5.3	3.8	9.0	19.3	16.0	6.6
Neutrophils (10 ⁹ /L) <i>Ref range 1.5–7.5</i>	2.3	2.5	5.9	6.3	6.9	3.4
Lymphocytes (10 ⁹ /L) <i>Ref range 1.0–4.0</i>	2.4	0.7	1.6	4.0	3.0	1.8
Eosinophils (10 ⁹ /L) <i>Ref range <0.51</i>	0.2	0.7	1.8	6.7	4.7	0.6
Creatinine (mg/L) <i>Ref range 59–104</i>	69	104	89	95	81	72
ALT (IU/L) <i>Ref range 10–50</i>	44	750	1166	856	754	145
CRP (mg/L) <i>Ref range <5</i>	2	14	159	74	76	21
Globulin (g/L) <i>Ref range 22–36</i>	26	30	24	N/A	28	34
Vancomycin level	N/A	11.2	7.1	N/A	N/A	N/A

ALT, alanine aminotransferase; CRP, C-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; WCC, white cell count.

following is proposed to result in the syndrome.⁵ First, there is a genetic deficiency of cytochrome P450 detoxifying enzymes which leads to accumulation of drug metabolites, modifying the immunological response and resulting in cell death. Second, human leucocyte antigen serotypes have been associated with hypersensitivity drug reactions: for example, HLA B*1502 with carbamazepine-induced Stevens Johnson syndrome. The final factor is thought to be a viral trigger or drug reaction involving reactivation of latent viruses. In 2007 Shiohara *et al* reported that the sequential reactivation of several viruses (HHV6/7, EBV and CMV) could be detected contemporaneously with clinical manifestations as a result of the expansion of virus specific and non-specific T-cells.^{1 5 7} In this case HHV6 was found to be positive to a high level of copies (>40 000 copies/mL) at 17 days after symptom onset, 10 days after the diagnosis of DRESS syndrome was suspected and 6 days after the peak eosinophil count, respectively. This is consistent with the expected time frame for HHV6 reactivation demonstrated in other studies as 2–3 weeks post symptom and disease process onset.⁸ PCR for EBV and CMV DNA in this patient was negative at this point in time.

While a drug challenge is the gold standard for diagnosing drug eruptions, this is not practical in DRESS syndrome due to the potential for life-threatening complications. Patch testing has been employed in cases secondary to anticonvulsant therapy but has not been shown to be valuable in cases due to other agents.⁵ Additionally, lymphocyte transformation testing can also be useful: a positive result of this test demonstrates sensitisation of T-cells and an enhanced proliferative response to the relevant drug. This test is safe and has been used successfully even years after the exposure to the offending agent. However, other authors suggest that its sensitivity is limited and may vary depending on the agent being investigated. It was not performed in this case but due to the longevity described previously, it could be considered in the future if there was symptom recurrence, concern regarding complications or need to evaluate the vancomycin reaction for future treatment purposes.^{9 10}

The diagnosis of DRESS, as in this case, is therefore often clinical. Typical features are fever and rash, eosinophilia in >50%, lymphadenopathy and visceral organ involvement, most frequently the liver. Microscopically there may be an atypical lymphocytosis (as was seen in this patient), perivascular

lymphocytic infiltration and extravasation of eosinophils.¹ During diagnosis, careful consideration should be given to the latency period and to the exclusion of other inevitably more common and non-drug induced conditions. While there are no validated diagnostic criteria for DRESS syndrome, scoring systems have been developed to aid diagnosis. Perhaps the most well-known of these is the RegiSCAR criteria, which is depicted below in table 2.⁵ In this case, the RegiSCAR score was 7, consistent with a definite diagnosis of DRESS syndrome. For reasons unknown, a skin biopsy was not performed on this patient, which is the only factor that potentially impacts negatively on the diagnosis.

The treatment of DRESS syndrome is primarily supportive: therefore, a timely diagnosis and early cessation of the culprit agent are critical. The disease often manifests as a severe or life-threatening illness. Additionally, the disease course may often result in clinical deterioration, frequent relapses or persistent fever, even many weeks after termination of the offending agent: indeed this is part of the diagnostic criteria mentioned above.¹

While there is no treatment proven in a randomised control trial setting to be effective, systemic corticosteroid therapy, in association with the cessation of the offending agent, is generally accepted as the gold standard of treatment, particularly in severe cases of the disorder. However, there is no global consensus on the optimal steroid type, dose combination or duration of therapy. Additionally, there are also case reports of good resolution with supportive treatment alone.¹¹ Steroids are thought to not only induce an acute response, but also to regulate autoimmune processes at the resolution stage of disease.¹² A recently published paper by Mizukawa *et al* proposes a severity scoring system to help determine which patients should receive the steroid treatment. In addition to features of fever, rash and organ involvement – as included in the RegiSCAR diagnostic criteria – the severity score also includes variables such as age, appetite/oral intake and CRP. The disease is then classified into either mild, moderate or severe. In this case, the severity score would be 5, equating to a severe case of DRESS syndrome.¹³ For severe disease, Mizukawa *et al* propose an oral prednisolone dose >50 mg/day. This is consistent with other studies that propose a dose of 1–1.5 mg/kg/day: a total dose of 60–90 mg for a 60 kg adult.¹¹

Table 2 RegiSCAR diagnostic score for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

Features	No	Yes	Unknown	This case
Fever ($\geq 38.5^{\circ}\text{C}$)	-1	0	-1	0
Enlarged lymph nodes (≥ 2 sites, ≥ 1 cm)	0	1	0	1
Atypical lymphocytes	0	1	0	1
Eosinophilia	0		0	
700–1499 or 10%–19.9%		1		
≥ 1500 or $\geq 20\%$		2		
Skin rash:	0		0	
Extent $>50\%$	0	1	0	1
At least 2: oedema, infiltration, purpura, scaling	-1	1	0	
Biopsy suggesting DRESS	-1	0	0	-1
Internal organ involvement	0		0	2
One		1		
Two or more		2		
Resolution more than 15 days	-1	0	-1	1
>3 biological investigations, negative for other diagnosis	0	1	0	
Final score <2 = no, $2-3$ =possible, $4-5$ =probable, >5 = definite				7

In this case, the patient received 0.5 mg/kg/day, a total of 40 mg daily. While this is lower than the dose generally proposed in literature for severe DRESS syndrome there was clear clinical improvement with prednisolone 40 mg once daily. The optimal duration of steroid therapy is also unknown, though ultimately will depend on an individuals' disease course and the risks of prolonged steroid therapy. Previous case report series have proposed a gradual tapering of systemic corticosteroids over a 2–3 month period.¹³ For this patient, the total duration of steroid therapy was shorter, at 42 days: he experienced no clinical deterioration or disease recurrence either within this time frame or after steroids were stopped. Both of these factors raise a potential question regarding the optimal steroid dose and duration for severe DRESS syndrome. Mizukawa *et al* propose that severe cases of DRESS are more likely to result in CMV reactivation, which in turn increases the risk of adverse outcomes and complications.¹⁴ One proposed mechanism for this patient's favourable

outcome on a lower dose, shorter duration regimen of systemic corticosteroids is that he was CMV-DNA negative.

On a wider treatment scale, promising results have also been reported with N-acetylcysteine, intravenous immunoglobulins, plasmapheresis and rituximab. However, further research is required before routine use could potentially be recommended.¹⁶

Contributors LJH is the sole author and contributor, responsible for writing the manuscript, obtaining consent and reviewing the literature surrounding the case.

Funding The author has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Waseem D, Latief M, Sofi N, *et al*. Dress syndrome: a review and update. *Skin Dis Skin Care* 2016;1.
- Roujeau J-C. UpToDate. Drug reaction with eosinophilia and systemic symptoms (DRESS). 2013 <https://www.uptodate.com/contents/drug-reaction-with-eosinophilia-and-systemic-symptoms-dress> (cited 1 Oct 2018).
- NICE. Clinical guideline [CG183]. Drug allergy: diagnosis and management. NICE guidelines. 2014 <https://www.nice.org.uk/guidance/cg183> (cited 1 Oct 2018).
- Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part 1. Clinical perspectives. *J Am Acad Dermatol* 2013;68:693.e1–14.
- Choudhary S, McLeod M, Torchia D, *et al*. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. *J Clin Aesthet Dermatol* 2013;6:31–7.
- Lee HY, Walsh S, Creamer D. Initial presentation of DRESS: often misdiagnosed as infections. *Arch Dermatol* 2012;148:1085–7.
- Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. *Clin Rev Allergy Immunol* 2007;33:124–33.
- Shiohara T, Kano Y, Hirahara K, *et al*. Prediction and management of drug reaction with eosinophilia and systemic symptoms (DRESS). *Expert Opin Drug Metab Toxicol* 2017;13:701–4.
- Karami Z, Mesdaghi M, Karimzadeh P, *et al*. Evaluation of lymphocyte transformation test results in patients with delayed hypersensitivity reactions following the use of anticonvulsant drugs. *Int Arch Allergy Immunol* 2016;170:158–62.
- Nyfelor B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1997;27:175–81.
- Bommersbach TJ, Lapid MI, Leung JG, *et al*. Management of Psychotropic Drug-Induced DRESS Syndrome: a systematic review. *Mayo Clin Proc* 2016;91:787–801.
- Shiohara T, Kano Y. Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. *Expert Opin Drug Saf* 2017;16:139–47.
- Cho Y-T, Yang C-W, Chu C-Y. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): an interplay among drugs, viruses, and immune system. *Int J Mol Sci* 2017;18:1243.

Learning points

- ▶ Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening drug hypersensitivity reaction which can be seen as a complication of frequently used therapeutic agents including anticonvulsants and antibiotics.
- ▶ Clinical presentation is diverse but classically includes fever, rash, eosinophilia and lymphadenopathy with or without visceral organ involvement.
- ▶ Early recognition of the syndrome, with cessation of the offending agent, is critical to prognosis and outcomes.
- ▶ Alongside cessation of the offending agent, steroids are considered part of the gold standard of treatment. Severity scores can be used to help determine which patients should be considered for systemic corticosteroid therapy.
- ▶ This case report presents a history of at least moderate to severe DRESS syndrome that responded to a lower dose and shorter duration of systemic corticosteroid therapy than has previously been reported as optimal. This favourable outcome may be related to the absence of CMV reactivation in this specific patient.

- 14 Mizukawa Y, Hirahara K, Kano Y, *et al.* Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: A useful tool for

assessing disease severity and predicting fatal cytomegalovirus disease. *J Am Acad Dermatol* 2019;80:670–8.

Copyright 2019 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow