CASE REPORT

Vancomycin-associated drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: masquerading under the guise of sepsis

Luke Maxfield,¹ Toni Schlick,² Angela Macri,³ James Thatcher⁴

¹Transitional Rotating Internship, Sampson Regional Medical Center, Clinton, NC, USA

²College of Medicine, Campbell University College of Osteopathic Medicine, Clinton, North Carolina, USA

³Dermatology, Sampson Regional Medical Center, Clinton, North Carolina, USA

⁴Family Medicine, Sampson Regional Medical Center, Clinton, NC, USA

Correspondence to

Dr Luke Maxfield,
luke.maxfield@Med.lecom.edu

Accepted 9 October 2017

SUMMARY

A patient presented with what appeared to be severe urosepsis. After admission and antibiotic administration, a newly developed rash and subsequent facial swelling appeared to be a reaction to penicillin class antibiotics. However, despite changing class of therapy with continued antimicrobial coverage, end organ damage continued, the rash worsened and facial oedema developed. Drug reaction with eosinophilia and systemic symptoms was ultimately diagnosed and was consistent with clinical and histopathological findings, as well as meeting all criteria for scoring systems. The patient was started on intravenous methylprednisolone 125 mg per 8 hours with rapid improvement of rash, swelling and end organ damage. Initial challenge to decrease dose failed, but the patient was ultimately able to be discharged on an extended taper.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an uncommon phenomenon, but prevalence is uncertain and diagnosis is missed as symptoms are characterised by delayed onset 2–6 weeks after the initial exposure to an offending drug. Similar yet distinct from a drug allergy, DRESS syndrome is considered a severe induced hypersensitivity reaction characterised by severe skin eruption, haematological abnormalities, lymphadenopathy and internal organ involvement.^{1,2} The time between insult and onset makes diagnosis difficult, and systemic involvement can be non-specific and attributed to other concomitant illness. Our patient typifies the classic example where criteria were met for severe urosepsis; however, it was not until accurately compiling the myriad of findings and clues that a correct diagnosis of DRESS syndrome was reached and subsequent rapid improvement occurred.

CASE PRESENTATION

A 52-year-old African-American man presented to the emergency department from a local nursing home with worsened altered mental status of 3 days' duration. Medical history was significant for recent hospital admission for a methicillin-resistant *Staphylococcus aureus* infection of the right hip for which he had completed therapy with intravenous vancomycin 3 weeks prior. The patient was neither alert nor oriented with a fever of 39.6°C

and tachycardia. The site of prior infection, the right hip, was without signs of infection. Initial labs included a urinalysis suggestive of a urinary tract infection, leucocytosis with bandaemia and eosinophilia, and elevated liver function tests. The patient was initially diagnosed with severe sepsis. Blood cultures were drawn and the patient was then prophylactically placed on broad-spectrum antibiotics consisting of piperacillin/tazobactam and intermittent infusion of vancomycin. On hospital day 2, a pruritic maculopapular rash developed on his trunk and proximal extremities (figure 1). This was thought to be secondary to a piperacillin/tazobactam allergy and the medication was discontinued. Blood cultures were negative but urine culture showed pansensitive *Pseudomonas aeruginosa*. Antibiotic regimen was switched to monotherapy with intravenous levofloxacin. Topical triamcinolone cream (0.1%) was begun to relieve pruritus. Over the next 3 days, the patient's rash worsened, and facial swelling developed diffusely,

Figure 1 Left antecubital fossa with overlying erythematous papules and plaques with overlying secondary excoriation.

CrossMark

To cite: Maxfield L, Schlick T, Macri A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221898

Figure 2 Histological examination at 10× magnification showing spongiosis in the deep layers of epithelium with minimal acanthosis and lymphocytic infiltrate in the dermal layers.

maximally involved the lower lip. Shotty anterior submandibular and cervical lymphadenopathy was noted as well. Serum creatinine tripled with a peak value of 3.8 mg/dL from 1.3 mg/dL on admission. Peripheral eosinophilia continued to rise, reaching a peak absolute eosinophil count of $6.1 \times 10^9/L$. Urinary eosinophils were negative and repeat urine culture showed resolution despite persistent leucocytosis. Very high-dose intravenous methylprednisolone 125 mg per 8 hours was started, and within 24 hours the patient had improved mental status, rash, facial swelling and white blood cell count. An attempt at tapering the patient's methylprednisolone the next day was met with a dramatic increase in the patient's eosinophilia, creatinine and worsening of his mental status.

On day 7 of hospitalisation, a diagnosis of DRESS syndrome was considered. Corticosteroid dose was decreased to 1 mg/kg/day and was tolerated well. Dermatology was subsequently consulted with a working diagnosis of DRESS syndrome triggered by his treatment with vancomycin started 5 weeks prior. Further testing included serology positive for elevated antibodies to Epstein-Barr virus (EBV), human herpes virus (HHV)-6 but not HHV-7, confirming reactivation. Punch biopsies were obtained from the left anterior thigh and findings were consistent with DRESS syndrome (figures 2 and 3). The rash on the trunk continued to improve and with superficial exfoliation as it resolved. Facial oedema resolved completely within a week of starting treatment. Liver function improved to near baseline and creatinine had decreased to 1.9 mg/dL from a peak of 3.8 mg/dL, and the patient was discharged with a 4-week taper of oral prednisone. The patient also received topical triamcinolone as needed and instructions to follow-up with his primary care provider, nephrology and dermatology.

INVESTIGATIONS

Initial investigations

Haematological investigation with leucocyte count was 16.6×10^9 with 38% band neutrophils and peak eosinophils of $6.1 \times 10^9/L$. Alanine aminotransferase was 136 units/L, aspartate aminotransferase 102 units/L, alkaline phosphatase 240 units/L, prothrombin time 13.5 s, international normalised ratio 1.29, creatinine 1.3 mg/dL and peak 3.8 mg/dL. Urinalysis showed positive nitrite, small leucocyte esterase and 2+ bacteria.

Culture results

The urine culture grew >100 000 colony forming units of pansensitive *P. aeruginosa*.

Serology

Serology showed EBV capsid antigen IgG antibody >600, HHV-6 IgG antibodies elevated at 7.24, and HHV-7 IgG and IgM within normal limits <1:320 and <1:20, respectively.

Histology

Histology showed prominent spongiosis with variable acanthosis and lymphocytic perivascular infiltrate in the superficial and deep dermis.

DIFFERENTIAL DIAGNOSIS

- Severe sepsis
- Acute hypersensitivity to penicillin
- Acute interstitial nephritis.

TREATMENT

- Empiric broad-spectrum antibiotics piperacillin/tazobactam and intermittent infusion of vancomycin
- Targeted antibiotics: levofloxacin
- Corticosteroids: intravenous methylprednisolone 125 mg every 8 hours; discharged with prednisone orally 40 mg per day with decreasing 10 mg intervals weekly.

OUTCOME AND FOLLOW-UP

Follow-up through the patient's siblings occurred months after discharge from the hospital. Although rash, facial swelling and renal function improved, the patient was readmitted at a separate institution for sepsis and bacteraemia, missing follow-up with nephrology and dermatology.

DISCUSSION

DRESS syndrome is a name coined only as recent as the 1990s, unifying previous descriptions of insidious hypersensitivity reactions to an offending drug.¹ It is an uncommon adverse drug reaction with systemic involvement and an estimated prevalence of 1 in 1000–10 000.^{2,3} However, it is hard to estimate due to difficulty in diagnosis. Dermatological findings associated with this syndrome are described as a maculopapular rash or generalised erythematous rash progressing to an exfoliative dermatitis as it resolves. This primarily involves the trunk and proximal extremities, greater than 50% of the body surface area, and facial oedema in approximately half of cases.² Non-specific systemic symptoms and visceral involvement may manifest as fever, lymphadenopathy, elevated liver enzymes, renal involvement and pulmonary involvement. The most common organ

Figure 3 Histological examination at 10× magnification showing perivascular lymphocytic infiltrate around a collapsed vessel.

involved is the liver.² Death can occur and mortality rates have been reported to be up to 10%.⁴

Pathogenesis is not clearly understood, although the connection with an offending drug is well established. Most frequently antiepileptic drugs have been implicated with other drugs including but not limited to penicillins, aspirin, non-steroidal anti-inflammatory drugs and sulfa moieties.² As intravenous vancomycin use within hospitals increases, this agent has become recognised as an emerging inciting agent.^{2,5,6} Similar to other agents, time from exposure to symptom onset is often up to 4 weeks.⁵ While this time frame with vancomycin exemplifies the classic delay, re-exposure to other inciting agents has been shown to reduce the latency to a matter of days.⁷ As our patient developed the cutaneous manifestations on day 2 after repeat vancomycin administration, this may be another example of re-exposure causing a more rapid presentation. However, as our patient had eosinophilia and elevated liver enzymes the day of admission, it is possible the cutaneous manifestations were preceded by systemic involvement of DRESS.

Diagnosis is difficult as clinical findings are non-specific. While a rash is universally present, other most common findings, in descending order of prevalence, include eosinophilia, visceral involvement, high fever, atypical lymphocytes, mucosal involvement and lymphadenopathy.⁸⁻¹⁰ To coordinate the findings and likelihood of DRESS syndrome, scoring systems have been developed. The Registry of Severe Cutaneous Adverse Reactions uses a grading scale to determine the possibility of DRESS syndrome as no case, possible, probable or definite.⁸ There are a total of seven criteria: acute rash, suspicion of a drug-related reaction and hospitalisation; all must be met in addition to three of the following: fever $>38^{\circ}\text{C}$, lymphadenopathy involving at least two sites, involvement of at least one internal organ, and leucocytosis/leucopenia, eosinophilia or thrombocytopenia.^{8,11} Using the above mentioned grading scale certainty of diagnosis requires 2–3 criteria to be met for possible DRESS syndrome, 4–5 for probable, and ≥ 6 for definite.⁸ A similar scoring system was produced that identifies DRESS syndrome as drug-induced hypersensitivity syndrome. A notable addition in this second scoring system is the role of HHV-6 reactivation. If all criteria are met, then it is a typical drug-induced hypersensitivity syndrome.⁹ Our patient met all the criteria.

There are no formal guidelines in place for the management of DRESS; however, certain treatment modalities are frequently employed. Immediate removal of the offending drug is necessary. Additionally, prolonged therapy with both topical and systemic corticosteroids is recommended. High-dose intravenous steroids are the most common treatment and intravenous immunoglobulin has been used with success.² It has been suggested that topical corticosteroids can be used as monotherapy in patients with mild DRESS syndrome whose complaint is mainly of rash and mild hepatitis¹⁰; however, systemic corticosteroids are generally administered, especially when end organ damage is noted.^{9,10} Relapse has been noted during both acute treatment and after prolonged taper.¹¹ Initial reduction, to what would have been a therapeutic dose, was tolerated poorly in our case. To prevent relapse, management should include a prolonged taper over weeks to months.⁹ In adults, treatment has been demonstrated effectively at 1 mg/kg with a taper of 4 weeks.¹² Treatment with high-dose steroids may increase infectious complications including candidiasis.^{10,13} The patient should be educated on the importance of avoiding the causative drug in the future to prevent any additional reactions.

In summary, our case demonstrated the complicated presentation and diagnosis whereby our patient met the criteria for sepsis

from a urinary tract infection with recent septic arthritis. Clues however, including eosinophilia on presentation, could have led to earlier investigation and therapy for hypersensitivity-mediated pathology. Diagnosis could have been reached earlier if dermatology had been consulted soon after the onset of the rash, and clinical course improved swiftly and dramatically after the diagnosis and treatment of DRESS syndrome. While the dose would have been expected to be supratherapeutic initially, the patient's notable clinical decline with initial dose reduction demonstrates the role for high-dose corticosteroids in early management.

Learning points

- ▶ Drug reaction with eosinophilia and systemic symptoms is a disease remote from time of injury. Our patient met the criteria for severe sepsis. Early clues including eosinophilia on presentation could have led to earlier investigation of allergy-related pathology.
- ▶ Confidence in diagnosis is made by clinical scoring systems and supported by histopathology. A comprehensive evaluation emphasises utilising scoring systems as well as all diagnostic tools available.
- ▶ Consulting dermatology much sooner after the onset of cutaneous manifestations and facial oedema likely have led to an earlier diagnosis and appropriate treatment. This emphasises the utility of dermatologists in evaluating patients with cutaneous pathology in the hospital setting.
- ▶ While dramatic improvement was noted after initiation of methylprednisolone, the dose would have been expected to be supratherapeutic. The patient's clinical decline to initial decrease in corticosteroid dose during early treatment is notable. The patient was weaned within 1 week to standard dosing; however, it demonstrates the role for high-dose steroids in early management.

Contributors LM: involved in the patient's care and acquisition of data, compilation of patient information, editing and formalising discussion, editing for journal format, is the corresponding author, and approved the final draft upon submission and agree to the integrity of the article. TS: involved in the patient's care and acquisition of data, initial compilation of discussion section, review and editing of manuscript, and approved the final draft upon submission and agree to the integrity of the article. AM: involved in the patient's care and acquisition of data, dermatology review and contributor of discussion of diagnosis, treatment and biopsy results, and approved the final draft upon submission and agree to the integrity of the article. JT: involved in the patient's care and acquisition of data, review and editing of the manuscript, approved the final draft upon submission and agree to the integrity of the article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 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;15:250–7.
- 2 Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med* 2011;124:588–97.
- 3 Fiszenson-Albala F, Auzeir V, Mahe E, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003;149:1018–22.
- 4 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.
- 5 Blumenthal KG, Patil SU, Long AA. The importance of vancomycin in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. *Allergy Asthma Proc* 2012;33:165–71.

- 6 Young S, Ojaimi S, Dunckley H, *et al.* Vancomycin-associated drug reaction with eosinophilia and systemic symptoms syndrome. *Intern Med J* 2014;44:694–6.
- 7 Avancini J, Maragno L, Santi CG, *et al.* Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome: clinical features of 27 patients. *Clin Exp Dermatol* 2015;40:851–9.
- 8 Kardaun SH, Sekula P, Valeyrie-Allanore L, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169:1071–80.
- 9 Husain Z, Reddy BY, Schwartz RA. DRESS syndrome. *J Am Acad Dermatol* 2013;68:693.e1–693.e14.
- 10 Funck-Brentano E, Duong TA, Bouvresse S, *et al.* Therapeutic management of DRESS: a retrospective study of 38 cases. *J Am Acad Dermatol* 2015;72:246–52.
- 11 Cardoso CS, Vieira AM, Oliveira AP. DRESS syndrome: a case report and literature review. *BMJ Case Rep* 2011;2011.
- 12 Gupta A, Srivastava VK, Rizvi I, *et al.* DRESS syndrome. *BMJ Case Rep* 2012.
- 13 Vaish AK, Tripathi AK, Gupta LK, *et al.* An unusual case of DRESS syndrome due to leflunomide. *BMJ Case Rep* 2011;4.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-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

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

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