

CASE REPORT

Two cases with HSS/DRESS syndrome developing after prosthetic joint surgery: does vancomycin-laden bone cement play a role in this syndrome?

Müberra Devrim Güner,¹ Semra Tuncbilek,² Burak Akan,³ Aysun Caliskan-Kartal⁴¹Department of Pharmacology, Ufuk University Medical School, Ankara, Turkey²Department of Infectious Diseases and Clinical Microbiology, Ufuk University Medical School, Ankara, Turkey³Department of Orthopaedics, Ufuk University Medical School, Ankara, Turkey⁴Department of Internal Medicine, Ufuk University Medical School, Ankara, Turkey**Correspondence to** Professor Semra Tuncbilek, semrakuli@yahoo.com

Accepted 8 May 2015

SUMMARY

We report two cases of hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) syndrome following systemic and local (via antibiotic laden bone cement (ALBC)) exposures to vancomycin. Both cases developed symptoms 2–4 weeks after the initiation of treatment. They responded to systemic corticosteroid treatment and were cured completely. Various drug groups may cause HSS/DRESS syndrome, and vancomycin-related cases do not exceed 2–5% of the reported cases. Almost all of these cases developed the syndrome following systemic exposure to vancomycin. ALBC seems to be the safer antibiotic administration method, as systemic antibiotic levels did not reach a toxic threshold level. However, local administration may not always be sufficient for bone-related/joint-related infections; these infections may require systemic antibiotics as well. As HSS/DRESS syndrome can mimic infectious diseases, it must be considered during differential diagnosis before suspecting failure of treatment and initiation of a different antibiotic course.

BACKGROUND

Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) syndrome is a severe and serious adverse drug reaction that has distinct characteristics but can be misdiagnosed.

HSS/DRESS syndrome often begins with fever (90–100%), followed by widespread skin eruption often progressing to exfoliative dermatitis (87%), involvement of at least one internal organ (hepatitis (50–60%) and other organs: pneumonitis, nephritis, myocarditis, pericarditis, myositis, pancreatitis, thyroiditis; 11%) and eosinophilia (50%) and other haematological abnormalities (atypical lymphocytosis, neutrophilia, neutropenia, thrombocytopenia, anaemia; 30% of cases). Lymphadenopathy (70–75% of cases) and periorbital or facial oedema (25% of cases) are other findings accompanying this syndrome (table 1).^{1 2}

It is a known fact that a wide range of drugs can cause HSS/DRESS syndrome. It has been reported that 44 different drugs are associated with HSS/DRESS.³ While aromatic anticonvulsants and sulfonamides are the most common cause of the syndrome, there are cases that developed after exposure to anti-inflammatory drugs, allopurinol, captopril, calcium channel blockers, mexiletine,

fluoxetine, β blockers, ACE inhibitors and antibiotics including vancomycin.^{1 3 4}

The pathogenesis of HSS/DRESS is not fully comprehended; however, it is known that it is multifactorial, involving immunological mechanisms and failure of detoxification pathways.^{1 3} The drugs act as an antigen and initiate an allergic hypersensitivity reaction.^{5 6} In addition, eosinophil activation and induction of an inflammatory cascade by interleukin 5 release from drug-specific CD4+ and CD8+ T cells may also contribute to the pathogenesis.⁷ It has also been suggested that reactivation of the human herpes virus family increases the risk of developing DRESS syndrome.^{1 3} Moreover, genetic predisposition to adverse drug reactions may also be responsible. In particular, human leucocyte antigen-related genes have been identified as predictors for certain severe cutaneous adverse drug reaction syndromes.⁶

Variable presentation may mimic many other diseases, and delay and make the diagnosis more difficult, as this type of drug reaction has a longer latency period than other drug reactions (ie, 2–6 weeks instead of 1–3 weeks after the start of a certain medication). While this type of drug reaction causes a disadvantage in making the diagnosis, delayed onset of symptoms is the most constant and consistent feature, present in almost all these patients.^{3 8} Fever, rash, lymphadenopathy, eosinophilia and liver dysfunction are the findings experienced by most of the patients, but they are not absolute symptoms. Cutaneous findings are observed in most of the patients, but they exist within a wide range of clinical variability.^{1 9}

Another challenge of HSS/DRESS syndrome is that it can be easily misdiagnosed as an infection due to its typical findings such as fever, lymphadenopathy, leucocytosis and abnormal liver function tests.⁶ Moreover, if misdiagnosed, antibiotics, a drug group having elements that can aggravate and/or cause this syndrome, might be empirically initiated. If the patient is already using a susceptible drug and the aforementioned findings are accompanied by cutaneous signs and haematological abnormalities, HSS/DRESS syndrome must be considered since this syndrome has a high mortality rate (up to 10–20%).^{2 3}

Vancomycin has been used extensively since the late 1950s. Besides idiosyncratic side effects and the infusion rate-related ‘red man (or woman) syndrome’, vancomycin demonstrates not only a dose–response relationship, but also a clear dose–toxicity



CrossMark

To cite: Güner MD, Tuncbilek S, Akan B, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207028

Table 1 Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms syndrome diagnosis criteria

▶ Medication use that can be related to reaction	▶ Fever >38°C*
▶ Hospitalisation	▶ Lymphadenopathy at least at two sites (>2 cm in diameter)*
▶ Acute cutaneous rash	▶ At least one internal organ involvement*
▶ Abnormal lymphocyte count	▶ Blood count abnormalities*
▶ Eosinophilia	
▶ Thrombocytopenia	

*At least three of these four criteria must be present for diagnosis.

relationship, with a narrow therapeutic window. The adverse effects mainly involve the kidney and inner ear.¹⁰ In the literature, there are several case reports of HSS/DRESS syndrome that developed following systemic exposure to vancomycin.^{11–22}

In this article, we present two orthopaedic prosthetic surgery cases with HSS/DRESS syndrome that developed following parenteral+bone cement-laden vancomycin treatment.

CASE PRESENTATION

Case 1

A 73-year-old man was diagnosed with infection of the left hip prosthesis. After the removal of the implant, bone cement laden with gentamycin (0.5 g/40 g) and vancomycin (4 g/40 g) was applied. In addition, parenteral vancomycin (2 g/day) was administered postoperatively.

Investigations

The cultures of the tissue samples obtained during surgery were positive for *Enterococcus* spp that were resistant to ampicillin but susceptible to vancomycin.

On the 27th day of vancomycin treatment, the patient’s body temperature increased to 38.9°C, and remained high for 4 days. A diffuse maculopapular rash developed. His white cell count (WCC) count was 5810/mm³ and 25% was eosinophil. Blood urea nitrogen (BUN) was 21 mg/dL, creatinine 1.59 mg/dL, erythrocyte sedimentation rate 84 mm/h and C reactive protein was 126 mg/L (table 2 and figure 1).

Treatment

Vancomycin treatment was aborted and antihistaminic (pheniramine or cetirizine) and topical corticosteroids (clobetasol propionate or hydrocortisone acetate) were initiated. As the symptoms and signs did not diminish, systemic corticosteroid treatment (80 mg/day) was initiated and gradually decreased



Figure 1 Cutaneous lesions of case 1 at the initiation of symptoms (A) and after treatment (B).

after 8 days, and ceased on the 40th day of treatment. Concomitant medications included paracetamol 500 mg two times per day, diclofenac 75 mg/day, ranitidine 300 mg/day, metoclopramide hydrochloride 40 mg/day, gliclazide MR 60 mg/day, metformin 500 mg/day, enoxaparin 150 IU/kg/day, losartan/hydrochlorothiazide 100/25 mg and theophylline ethylenediamine 600 mg/day.

Outcome and follow-up

The patient’s findings and symptoms began to regress on the eighth day of systemic steroid treatment and continued to abate during follow-up visits.

Case 2

A 72-year-old woman who had left knee prosthesis surgery 2 years prior underwent revision surgery with a prediagnosis of infection of the prosthesis. During the surgery, the prosthesis was removed and samples were taken for microbiological analysis. Vancomycin (4 g/40 g) and gentamycin (0.5 g/40 g) laden bone cement was applied during the surgery. After the surgery, parenteral vancomycin treatment was also empirically initiated.

Investigations

None of the samples taken during surgery were culture positive. However, 15 days after the surgery, the patient’s creatinine (3.46 mg/dL) and BUN (48 mg/dL) levels increased. On the 18th day, her laboratory values were measured as: γ-glutamyl transferase 97 U/L (7–36), alkaline phosphatase 173 IU/L (30–150),

Table 2 Characteristics of patients

Number of patients	Dose of parenteral vancomycin	Vancomycin dose in bone cement	Positive diagnostic criteria
Case 1	2×1 g (23 days)	4 g/40 g	Fever Rash Eosinophilia Creatinine↑
Case 2	2×1 g (20 days)	4 g/40 g	Fever Rash Eosinophilia Creatinine↑ AST, ALT↑

ALT, alanine transaminase; AST, aspartate transaminase.



Figure 2 Second patient's skin appearance at the initiation of symptoms (A) and after treatment (B).

creatinine 5.83 mg/dL and BUN 74 mg/dL. Meanwhile, her body temperature increased to 38.6°C and remained at this level for 3 days; a maculopapular rash developed followed by eosinophilia; WCC was 14 000/mm³ and total eosinophil was 851×10⁹/L. Vancomycin treatment was discontinued following these laboratory and clinical findings (table 2 and figure 2).

Treatment

As the patient did not respond to antihistaminic (pheniramine maleate) and topical steroid (clobetasol 17 propionate cream 0.05%) treatment, systemic corticosteroid (prednisolone) treatment was initiated on the 28th day of surgery at a dose of 60 mg/day, and the dose was gradually decreased after 7 days and discontinued 32 days later.

Concomitant medications included levothyroxine 50 µg/day, irbesartan/hydrochlorothiazide 150 mg/12.5 mg/day, enoxaparin 150 IU/kg/day and ranitidine 300 mg/day.

Outcome and follow-up

The patient's cutaneous symptoms showed regression after the fifth day of treatment while her renal and hepatic functions returned to normal after 11 and 12 days, respectively.

DISCUSSION

HSS/DRESS syndrome is defined as an adverse drug reaction with high fever (>38°C), disseminated cutaneous rash, lymphadenopathy, internal organ involvement (hepatitis, pneumonitis, myocarditis or interstitial nephritis), along with abnormal blood count (lymphocytosis or lymphopenia, eosinophilia, thrombocytopenia). HSS/DRESS syndrome generally occurs 1–8 weeks after initial use of the suspected drug. Persistence of clinical findings existent after 2 weeks following cessation of the suspected drug is also considered a diagnostic criterion. Consistent with this theory, the symptoms of our patients occurred within 2 and 4 weeks, respectively, following the use of the suspected drug, and the clinical findings ceased after more than 2 weeks. There are several cases reported to develop HSS/DRESS syndrome after parenteral vancomycin administration.^{11–22} In addition to systemic administration, our patients were exposed to local vancomycin (4 g/40 g) and gentamycin (0.5 g/40 g) released from the bone cement.

While most of the case reports support the safety of antibiotic-laden bone cements,^{23–27} there are several case reports of skin and systemic adverse events that developed after antibiotic exposure to bone cement.^{28–31} Our current findings do not support HSS/DRESS syndrome development after exposure to antibiotics from bone cement.

In these two cases, symptoms were diminished gradually after discontinuation of parenteral administration, and this finding suggested that vancomycin in bone cement does not have a significant role in the development of HSS/DRESS syndrome. Pharmacokinetic characteristics of antibiotics in bone cement also support this suggestion. Based on a study of 10 patients, blood vancomycin levels did not exceed 2.9 mg/L, but instead peaked around 6–24 h after implantation and decreased to below detection limit in 3–10 days. However, local vancomycin levels reached very high values, nearly five times higher than blood concentration in these patients.³² After 2-year follow-up, none of these patients showed any complication related to bone cement.³² The authors of this study suggested that the risk of vancomycin toxicity associated with use of the cement is very low since the peak blood level was only 3 mg/L.³² However, plasma peaks in the order of 60 mg/L are commonly achieved during intravenous vancomycin therapy, which has a higher possibility of adverse reaction.

Another case report of seven patients who had hip arthroplasty also showed that this drug delivery system offers the advantage of local release of high antibiotic concentrations, and this advantage considerably outweighs the benefits of those obtained after systemic administration, without even reaching the systemic detection limit of the drug.³³ In another retrospective review, 36 knees in 34 patients treated with 4 g of vancomycin and 4.8 g of gentamicin per 40 g of cement were evaluated.²³ The mean total dose of antibiotic reported per patient was 10.5 g of vancomycin and 12.5 g of gentamicin. The authors reported only a single case of transient elevation in serum creatinine and concluded that high-dose antibiotic cement spacers used for treatment of deep periprosthetic sepsis were relatively safe.²³ The number of serious adverse events reported following the use of vancomycin laden bone cement in prosthetic orthopaedic surgeries is not significant and most of the patients recover without an infection.^{23 32 33}

The first step in treatment of HSS/DRESS syndrome is prompt withdrawal of the suspected drug. Supportive therapeutic approaches must also be initiated with antipyretics, skin care and correction of electrolyte disturbances. Support of detoxification pathways using chelating agents and antioxidants may also be carried out.¹ A moderate-to-high dose of systemic corticosteroids is generally essential for treatment. However, it may not be sufficient and may result in prolonged glucocorticoid exposure. Immune suppressant agents may be required for the treatment in some cases, especially if corticosteroids are contraindicated or themselves result in complications/adverse events.^{1 5 6}

HSS/DRESS syndrome has clinical features that can easily be misdiagnosed as infection. It is essential to consider HSS/DRESS syndrome in differential diagnosis of such cases, especially if medication history includes the usage of suspected drugs.

Advancing local drug application methods and developing appropriate pharmaceutical formulations may increase the success rate of treatment as it will locally provide high concentration without increasing the blood levels to toxic thresholds, especially in orthopaedic prosthesis surgeries. However, rational antibiotic therapy rules should always be applied, treatment duration must be shortened and medications with high risk of adverse events must be avoided as much as possible. This will significantly decrease the development of serious adverse events, and the mortality and morbidity related to these events.

In conclusion, as the symptoms of our two patients gradually diminished after discontinuation of parenteral administration, we believe that vancomycin in bone cement does not have a significant role in the development of HSS/DRESS syndrome. The previous reports support this assumption, as plasma levels of vancomycin are far below those achieved by parenteral administration of this antibiotic. Based on our cases and the literature, we suggest that application of antibiotic locally via cement compared with systemic administration of the same antibiotic, in selected patient groups, will increase the safety profile. However, prospective randomised clinical studies are needed to support this assumption.

Learning points

- ▶ Although it is rare, hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) syndrome is a serious condition that may have a clinical presentation mimicking infectious diseases. Considering the possibility of this syndrome in such cases is essential for treatment and prognosis.
- ▶ Late onset of the symptoms is a typical characteristics of HSS/DRESS syndrome.
- ▶ Bone cements laden with antibiotics may be safer than systemic antibiotic application, and may be considered as a treatment choice for appropriate cases.
- ▶ Rational antibiotic treatment principles must always be adhered to regardless of the administration route.

Contributors BA and AC-K contributed to analyses and interpretation of the data. MDG contributed to analysis and interpretation of the data and conception, design and drafting of the article. ST contributed to analysis and interpretation of the data and conception, design and revising of the manuscript critically for important intellectual content.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (HSS/DRESS syndrome): an update. *Dermatology* 2003;206:353–6.
- 2 Criado PR, Avancini J, Santi CG, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): a complex interaction of drugs, viruses and the immune system. *Isr Med Assoc J* 2012;14:577–82.
- 3 Cacoub P, Musette P, Descamps V, *et al.* The DRESS syndrome: a literature review. *Am J Med* 2011;124:588–97.
- 4 Sultan SJ, Sameem F, Ashraf M. Drug reaction with eosinophilia and systemic symptoms: manifestations, treatment, and outcome in 17 patients. *Int J Dermatol* 2015;54:537–42.
- 5 Eshki M, Allanore L, Musette P, *et al.* Twelve year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2009;145:67–72.
- 6 Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (HSS/DRESS): a clinical update and review of current thinking. *Clin Exp Dermatol* 2011;36:6–11.
- 7 Choquet-Kastylevsky G, Intrator L, Chenal C, *et al.* Increased levels of IL5 are associated with generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol* 1998;139:1026–32.
- 8 Peyriere H, Dereure O, Breton H, *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a HSS/DRESS syndrome really exist? *Br J Dermatol* 2006;155:422–8.
- 9 Kardaun SH, Sidoroff A, Valeyrie-Allanore L, *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609–11.
- 10 Vandecasteele SJ, De Vriese AS, Tacconelli E. The pharmacokinetics and pharmacodynamics of vancomycin in clinical practice: evidence and uncertainties. *J Antimicrob Chemother* 2013;68:743–8.
- 11 Wai AO, Lo AMS, Abdo A, *et al.* Vancomycin-induced acute interstitial nephritis. *Ann Pharmacother* 1998;32:1160–4.
- 12 Hsu SH. Biopsy-proved acute tubulointerstitial nephritis and toxic epidermal necrolysis associated with vancomycin. *Pharmacotherapy* 2001;21:1233–9.
- 13 Yazganoglu KD, Ozkaya E, Ergin-Ozcan P, *et al.* Vancomycin-induced drug hypersensitivity syndrome. *J Eur Acad Dermatol Venereol* 2005;19:648–50.
- 14 Zuliani E, Zwahlen H, Gilliet F, *et al.* Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. *Clin Nephrol* 2005;64:155–8.
- 15 Vauthey L, Uckay I, Abrassart S, *et al.* Vancomycin-induced DRESS syndrome in a female patient. *Pharmacology* 2008;82:138–41.
- 16 Boet S, Noblet C, Haas-Hubscher C, *et al.* Severe vancomycin-induced drug rash with eosinophilia and systemic symptoms syndrome imitating septic shock. *Eur J Anaesthesiol* 2009;26:791–3.
- 17 Vinson AE, Dufort EM, Willis MD, *et al.* Drug rash, eosinophilia, and systemic symptoms syndrome: two pediatric cases demonstrating the range of severity in presentation—a case of vancomycin-induced drug hypersensitivity mimicking toxic shock syndrome and a milder case induced by minocycline. *Pediatr Crit Care Med* 2010;11:e38–43.
- 18 O'Meara P, Borici-Mazi R, Morton AR, *et al.* DRESS with delayed onset acute interstitial nephritis and profound refractory eosinophilia secondary to vancomycin. *Allergy Asthma Clin Immunol* 2011;7:16.
- 19 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.
- 20 Diaz-Mancebo R, Costero-Fernández O, Vega-Cabrera C, *et al.* Dress syndrome and acute tubulointerstitial nephritis after treatment with vancomycin and beta-lactams. Case report and literature review. *Nefrologia* 2012;32:685–7.
- 21 Della-Torre E, Yacoub MR, Pignatti P, *et al.* Optimal management of DRESS syndrome in course of infectious endocarditis. *Ann Allergy Asthma Immunol* 2013;110:303–5.
- 22 Song SM, Cho MS, Oh SH, *et al.* Liver transplantation in a child with acute liver failure resulting from drug rash with eosinophilia and systemic symptoms syndrome. *Korean J Pediatr* 2013;56:224–6.
- 23 Springer BD, Lee GC, Osmon D, *et al.* Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. *Clin Orthop Relat Res* 2004;(427):47–51.
- 24 Hsieh PH, Chang YH, Chen SH, *et al.* High concentration and bioactivity of vancomycin and aztreonam eluted from simplex cement spacers in two-stage revision of infected hip implants: a study of 46 patients at an average follow-up of 107 days. *J Orthop Res* 2006;24:1615–21.
- 25 Chiu FY, Lin CF. Antibiotic-impregnated cement in revision total knee arthroplasty. A prospective cohort study of one hundred and eighty-three knees. *J Bone Joint Surg Am* 2009;91:628–33.

- | | |
|---|---|
| <p>26 Randelli P, Evola FR, Cabitza P, <i>et al.</i> Prophylactic use of antibiotic-loaded bone cement in primary total knee replacement. <i>Knee Surg Sports Traumatol Arthrosc</i> 2010;18:181–6.</p> <p>27 Corona PS, Barro V, Mendez M, <i>et al.</i> Industrially prefabricated cement spacers: do vancomycin- and gentamicin-impregnated spacers offer any advantage? <i>Clin Orthop Relat Res</i> 2014;472:923–32.</p> <p>28 Patrick BN, Rivey MP, Allington DR. Acute renal failure associated with vancomycin- and tobramycin-laden cement in total hip arthroplasty. <i>Ann Pharmacother</i> 2006;40:2037–42.</p> <p>29 Dovas S, Liakopoulos V, Papatheodorou L, <i>et al.</i> Acute renal failure after antibiotic-impregnated bone cement treatment of an infected total knee arthroplasty. <i>Clin Nephrol</i> 2008;69:207–12.</p> | <p>30 McGlothlan KR, Gosmanova EO. A case report of acute interstitial nephritis associated with antibiotic-impregnated orthopaedic bone-cement spacer. <i>Tenn Med</i> 2012;105:37–40, 42.</p> <p>31 Williams B, Hanson A, Sha B. Diffuse desquamating rash following exposure to vancomycin-impregnated bone cement. <i>Ann Pharmacother</i> 2014;48:1061–5.</p> <p>32 Chohfi M, Langlais F, Fourastier J, <i>et al.</i> Pharmacokinetics, uses, and limitations of vancomycin-loaded bone cement. <i>Int Orthop</i> 1998;22:171–7.</p> <p>33 Regis D, Sandri A, Samaila E, <i>et al.</i> Release of gentamicin and vancomycin from preformed spacers in infected total hip arthroplasties: measurement of concentrations and inhibitory activity in patients' drainage fluids and serum. <i>ScientificWorldJournal</i> 2013;2013:752184.</p> |
|---|---|

Copyright 2015 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