Clinical Communications

DRESS syndrome induced by antibiotic-loaded bone cements and a diagnostic algorithm for related delayed-type hypersensitivity reactions

Valerie Chiang, MBBS[a], Jane C.Y. Wong, MRCP[b], Heather H.F. Yeung, MSc[a], Elaine Y.L. Au, FRCPA[a], and Philip H. Li, FHKCP[b]

Clinical Implications

- Drug rash with eosinophilia and systemic symptoms syndrome is a potentially lethal severe cutaneous adverse reaction that can be caused by antibiotic-loaded bone cement. We present the first of such case with confirmed antibiotic culprit by our suggested diagnostic algorithm.

Drug rash with eosinophilia and systemic symptoms, known as DRESS syndrome, is a delayed type IVb hypersensitivity reaction hypothesized to be mediated by antiviral T cells.[1] DRESS syndrome is one of the drug-induced severe cutaneous adverse reactions (SCAR) with a mortality rate of up to 10%.[2] Antibiotics are among the most common culprits of DRESS syndrome, and 2 reports of suspected cases due to antibiotic-loaded bone cements (ALBC) have been previously published.[3,4] However, previous reports only suspected ALBC-induced DRESS syndrome based on clinical history alone, and no allergy investigations were performed to confirm the exact drug culprits. We present the first case of DRESS syndrome secondary to vancomycin in ALBC, which was identified by both *in vitro* and *in vivo* allergy testing.

A 46-year-old man with a chronic pelvic osteomyelitis infection underwent sequestrectomy with cementation of bone cavity using a combination of gentamicin and vancomycin-loaded bone cement. He also received intravenous cloxacillin for 4 weeks before and 1 week after the procedure. His postoperative complete blood count, liver, and renal function tests were all normal. Four weeks postoperatively, he developed a fever (39°C), generalized morbilliform rash including the operative site (>50% body surface area), and facial edema (Figure 1). Blood tests were significant for eosinophilia, presence of atypical lymphocytes, deranged liver function, and acute kidney injury (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Skin biopsy was compatible with a drug eruption. All septic, autoimmune, and hepatitis workup were negative. He was diagnosed with "definite DRESS syndrome" based on RegiSCAR criteria. In addition, quantitative real-time polymerase chain reaction (PCR) for human herpesvirus 6 (HHV6) DNA was positive at 2.0×10^9 copies/mL, further supporting the diagnosis according to the Japanese consensus group criteria on Drug-induced hypersensitivity syndrome. He was started on oral prednisolone 30 mg daily.[5] Lymphocyte transformation test (LTT) was performed within 1 week of symptom onset with vancomycin, gentamicin, and cloxacillin. LTT with vancomycin was positive but negative with gentamicin and cloxacillin (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). In view of likely DRESS secondary to ALBC, his bone implants were surgically removed. His morbilliform rash evolved into confluent erythema with subsequent desquamation. Serial blood tests showed gradual normalization of eosinophil counts as well as his liver and renal function. Repeat HHV6 DNA PCR became negative and his symptoms completely resolved after 2 months of prednisolone 30 mg daily, which was then gradually tapered off.

FIGURE 1. Morbilliform eruption compatible with drug rash with eosinophilia and systemic symptoms syndrome.

Two months after completion of steroid therapy, patch test (PT) was performed, which was negative with vancomycin, cloxacillin, and gentamicin (all 10% aqueous) up to day 14. In view of negative PT, delayed intradermal tests (IDT) were performed to the same drugs. Delayed reading of IDT was positive for vancomycin (5 mg/mL) but negative for gentamicin (4 mg/mL) and cloxacillin (5 mg/mL) (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). He was diagnosed with DRESS syndrome to vancomycin in his ALBC. The patient consented to sequential graded drug provocation tests (DPT) with gentamicin and cloxacillin, which were both negative.

One of the most serious complications associated with orthopedic surgeries is the development of infections. Over the past 2 decades, ALBC has proven to be a valuable tool in the prophylaxis and treatment of orthopedic infections with reported success rates of >90%.[6] Its popularity has been accompanied by growing reports of hypersensitivity reactions, as exemplified in the above case vignette. Sufficient antibiotic release can persist over several months, which in some cases have led to serious side effects requiring removal of the ALBC up to 6 weeks after implantation.[7] Our case highlights many important aspects of

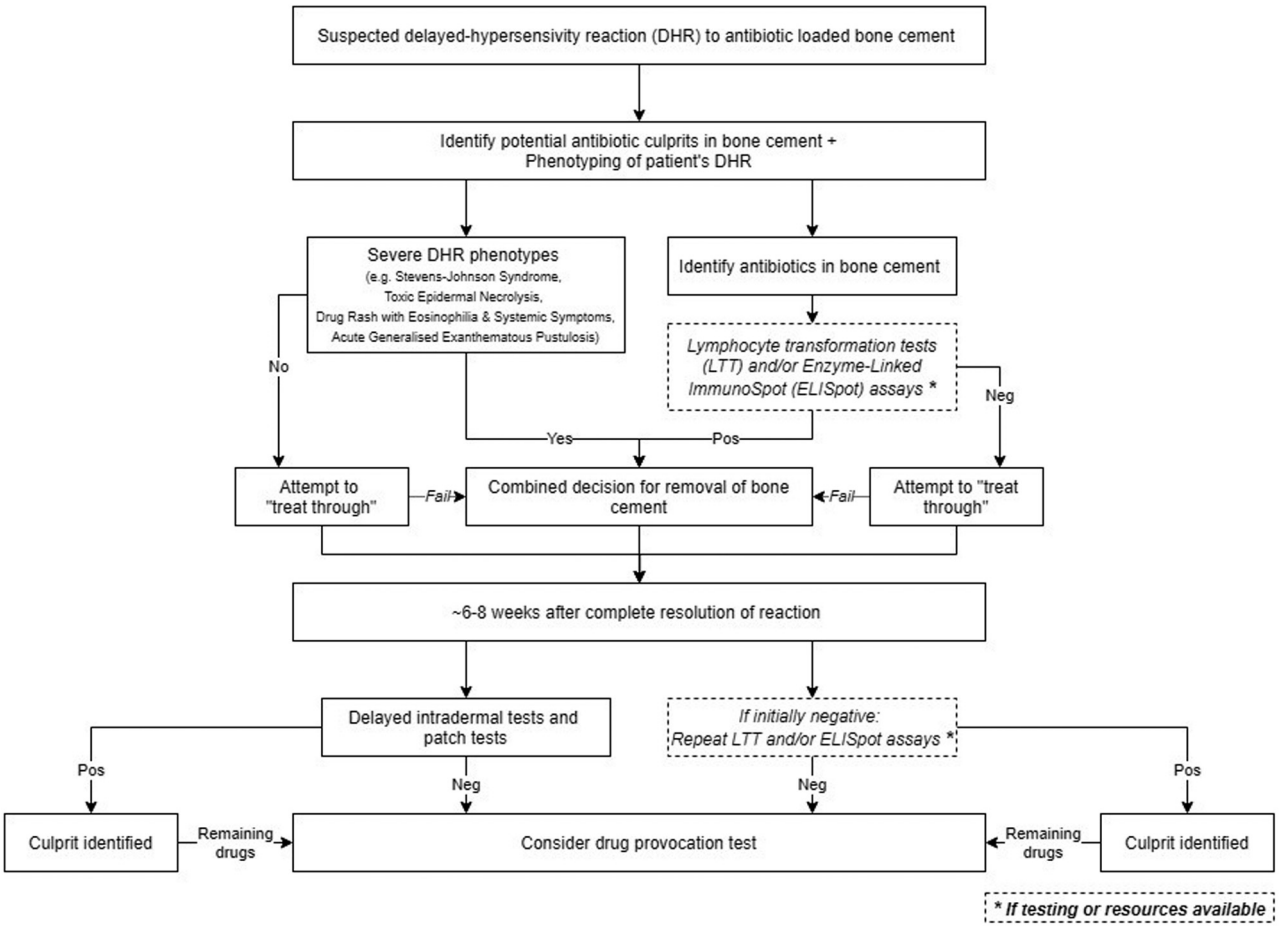

FIGURE 2. Diagnostic algorithm for suspected delayed-hypersensitivity reaction to antibiotic-loaded bone cement.

workup of suspected delayed-type hypersensitivity reactions to ALBC, which we have summarized in a suggested diagnostic algorithm (Figure 2).

First, allergies due to ALBC can be easily overlooked without a careful consideration of the patient's medical and surgical history. Furthermore, it is often difficult to pinpoint the exact culprit of suspected delayed-type hypersensitivity reactions while patients have been exposed to multiple drugs. This is especially true in the context of ALBC as cements are often loaded with the combination of different antibiotics, of which aminoglycosides (gentamicin, tobramycin) and glycopeptides (vancomycin) seem to be most popular.[7] Despite the invasiveness of a repeat operation to remove the bone implants, this was deemed necessary in view of the high morbidity and mortality associated with SCAR. Astute clinical judgment and a thorough review of the medication history (up to 8 weeks before onset of symptoms) are necessary. Adjunctive investigation results, such as human leukocyte antigen (HLA) typing (such as HLA-A-32:01 for vancomycin-associated reactions) and positive HHV6 DNA, can also be extremely helpful to aid diagnosis and decision for bone cement removal.

Secondly, after recovery, patients are often either left with a list of multiple suspected allergies (which severely limit future medication options), or remain at continued risk of inadvertent re-exposure. Therefore, it is imperative that confirmatory allergy tests are performed to accurately identify the causative agent(s). *In vivo* and *in vitro* tests offer complimentary roles. *In vitro* tests such as LTT and interferon-γ release enzyme-linked immunospot (ELISpot) assays have demonstrated their utility in diagnosis.[8] Unfortunately, the ELISpot assay is not available at our center. We performed LTT given its availability, safety, and proven utility in diagnosis of SCAR. If the initial LTT is uninformative, repeat testing should be considered around 6 to 8 weeks later. Although *in vitro* tests provide valuable information, their sensitivity and specificity remain ill-defined. Therefore, interpretation should be complemented by *in vivo tests* whenever possible, as demonstrated in our case with a positive IDT to vancomycin.[8,9] Given the agreement between *in vivo* and *in vitro* tests, the patient consented to sequential DPT to confidently exclude allergies to other implicated drugs.

Our report illustrates the only published case of DRESS syndrome secondary to ALBC, which was identified by allergy testing, and highlights the importance of a comprehensive diagnostic algorithm. Vancomycin in the bone cement was identified as the culprit, whereas cloxacillin and gentamicin allergies were excluded with LTT, PT, delayed IDT, and DPT. Offering a comprehensive workup in this case excluded nonculprit drugs and allowed reintroduction of beta-lactams and aminoglycosides back into the patient's medication repertoire.

[a]Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Pokfulam, Hong Kong
[b]Division of Rheumatology & Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong
No funding was received for this work.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication June 30, 2020; revised September 11, 2020; accepted for publication September 16, 2020.
Available online ■■
Corresponding author: Philip H. Li, FHKCP, Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Pokfulam, Hong Kong. E-mail: liphilip@hku.hk.
2213-2198
© 2020 American Academy of Allergy, Asthma & Immunology
https://doi.org/10.1016/j.jaip.2020.09.040

REFERENCES

1. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. Int J Mol Sci 2017;18:1243.
2. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146:1373-9.
3. Guner MD, Tuncbilek S, Akan B, Caliskan-Kartal A. Two cases with HSS/DRESS syndrome developing after prosthetic joint surgery: does vancomycin-laden bone cement play a role in this syndrome? BMJ Case Rep 2015;2015:bcr2014207028.
4. Harper KD, Incavo SJ. Drug reaction with eosinophilia and systemic symptoms syndrome after total knee arthroplasty infection and placement of antibiotic spacer. Arthroplast Today 2019;5:148-51.
5. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, 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.
6. Anagnostakos K. Therapeutic use of antibiotic-loaded bone cement in the treatment of hip and knee joint infections. J Bone Jt Infect 2017;2:29-37.
7. Anagnostakos K, Kelm J. Enhancement of antibiotic elution from acrylic bone cement. J Biomed Mater Res B Appl Biomater 2009;90:467-75.
8. Trubiano JA, Strautins K, Redwood AJ, Pavlos R, Konvinse KC, Aung AK, et al. The combined utility of ex vivo IFN-gamma release enzyme-linked immunospot assay and in vivo skin testing in patients with antibiotic-associated severe cutaneous adverse reactions. J Allergy Clin Immunol Pract 2018;6:1287-12896.e1.
9. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016;71:1103-34.

ONLINE REPOSITORY

TABLE E1. Lymphocyte transformation tests

	Stimulation index* (net counts per minute/10^6 cells)	
Drug	**Patient (during reaction)**	**Healthy control**
Cloxacillin	1.4	1.4
Gentamycin	1.4	1.8
Vancomycin	2.5	1.0

*Stimulation index calculated by: [proliferation (cpm) with drug]/[proliferation (cpm) without drug]. A stimulation index >2 generally considered positive, based on negative values in exposed but not allergic individuals.

TABLE E2. Relevant blood, skin biopsy, and intradermal test results

Parameters	Value	Reference range
Hemoglobin	10.0 g/dL	13.3-17.1
White blood cell	19.41×10^9/L	3.89-9.83
Neutrophil	4.73×10^9/L	2.01-7.42
Lymphocyte	5.51×10^9/L	1.06-3.61
Atypical lymphocyte	2.30×10^9/L	–
Monocyte	0.62×10^9/L	0.18-0.65
Eosinophil	6.26×10^9/L	0.02-0.45
Basophil	0.38×10^9/L	0.01-0.07
Platelet	162×10^9/L	154-371
Erythrocyte sedimentation rate	108 mm/h	<12
Alkaline phosphatase	950 IU/L	42-110
Alanine aminotransferase	519 IU/L	8-58
Aspartate aminotransferase	326 IU/L	15-38
Gamma-glutamyl transferase	412 IU/L	11-62
Creatinine	183 μmol/L	67-109
Urea	16.6 mmol/L	3.6-7.8
Human herpesvirus 6 DNA	1.98×10^2 copies/mL	–
Human herpesvirus 7 DNA	Not detected	–

Skin biopsy: The epidermis shows focal parakeratosis. There is focal lymphocytic exocytosis in the basal layer. There are a large number of lymphocytes, plasma cells, eosinophils, and neutrophils around the dermal papillary capillaries and at the dermal-epidermal junction. Focal cytoid bodies, karyorrhexis, and melanin pigmentary incontinence are identified. The papillary dermis is focally edematous. Definitive vasculitis is not seen. The deep dermis is unremarkable. Alcian blue section does not show significant mucinosis. PAS section does not show any fungal elements. Frozen section shows similar morphology. Direct immunofluorescence study does not show any deposits of IgA, IgG, IgM, C3, C1q, or fibrinogen. Overall features consistent with drug eruption.

Intradermal tests

Drug	Immediate reading (20 min)	Delayed reading (48 h)
Vancomycin	Negative	Positive with 5 mm infiltrated erythema
Cloxacillin	Negative	Negative
Gentamicin	Negative	Negative