



Case report

Drug reaction with eosinophilia and systemic symptoms syndrome after total knee arthroplasty infection and placement of antibiotic spacer

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ABSTRACT

Though 2-stage revision is considered the gold standard in North America for treatment of periprosthetic joint infection, complications can be associated with use of antibiotic-impregnated spacers. We present a unique case of drug reaction with eosinophilia and systemic symptoms syndrome in a patient with retained antibiotic-impregnated spacer placed for the treatment of a periprosthetic joint infection. Although drug reactions in general are common, severe drug reactions like the one described in this article are exceedingly rare. After discontinuation of intravenous antibiotics and the initiation of corticosteroids, the patient's symptoms resolved, despite retention of the spacer. Steroid administration and supportive care may result in resolution of symptoms without the need for surgical intervention for spacer removal.

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Introduction

Periprosthetic joint infection (PJI) is one of most devastating complications after a primary total knee arthroplasty (TKA), with an incidence of 0.5%–1% [1]. Two-stage revision is widely considered the gold standard in North America for treatment of PJI, with a reported success rate of 80%–90% [1,2]. Antibiotic spacers placed during the first stage have been associated with a number of potential complications, including breakage, dislocation, and allergic reactions [3]. We present a rare case of a drug reaction complication after placement of an antibiotic-impregnated cement spacer.

Case history

Informed consent was acquired from the patient for publication of his case report. A 60-year-old male initially presented to our

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practice with left knee pain after undergoing TKA 15 months prior. Following the primary TKA procedure, the patient had persistent drainage. At 1 year postop, he underwent a polyethylene liner exchange due to ongoing pain and instability, following which he sustained an atraumatic quad rupture for which surgical repair was performed on 2 occasions. Etiology of the quadriceps rupture was unknown, and both times a primary repair was attempted. He presented to our office with recurrent left knee pain, recurrent effusions, and an inability to extend his left knee. In addition, he had an elevated D-dimer (1.32 $\mu\text{g}/\text{mL}$) and abnormal synovial aspiration (1900 WBC/mm, 76% neutrophils) with negative cultures. Erythrocyte sedimentation rate was 5 mm/h and C-reactive protein was 0.30 mg/dL. His clinical presentation was felt to be consistent with culture-negative PJI. The patient was scheduled to undergo left TKA explantation, placement of static antibiotic spacer, and extensor mechanism repair. At the time of surgery, a very large defect of the extensor mechanism and previous capsular repair was found, with exposure of the implants to superficial tissue. The implants were removed without complication and an antibiotic spacer containing 3 batches of cement, 9 g of vancomycin, and 9 vials of tobramycin was placed, as per the standard practice of the operating surgeon (based on highest recommended dose that has been reported as safe to use in the literature) [4]. The capsular defect was mobile, and so the tissue was oversewn and imbricated, which allowed for

reconstitution of the extensor mechanism without the need for additional reconstruction. The patient had an incisional wound vacuum assisted closure device applied and was placed in a knee immobilizer. Intraoperative cultures were negative. Despite this, infectious disease consultation felt this was highly suspicious for a culture-negative infection, and recommended peripherally inserted central catheter line placement with treatment with vancomycin and cefepime (felt to be ideal for empiric coverage) for 4–6 weeks due to the preoperative clinical and laboratory findings. In regards to our empiric antibiotic choices, cefepime was chosen for its extended spectrum of activity that included many Gram-positive and Gram-negative organisms, and vancomycin was included for coverage of methicillin-resistant staphylococcus aureus.

The patient followed up to the office 2 weeks following surgery and was doing well. He was experiencing no issues with home antibiotic infusions and was gradually able to place more weight through the left lower extremity. His vancomycin trough value was within normal limits (11.5 µg/mL). At 3 weeks postop, the patient contacted the infectious disease doctor stating that he had begun to develop a red-appearing rash all over his body. Discontinuation of the peripherally inserted central catheter line and intravenous (IV) antibiotics was recommended. Two days following discontinuation of the antibiotics, the patient presented to the emergency room with progressive worsening of the rash, severe facial swelling, and contralateral groin lymph node enlargement. Laboratory findings at the time of presentation showed an elevated D-dimer (12.26 µg/mL), lactic acid level (5.2 mmol/L), eosinophil value (7.6%) on complete blood count, and creatinine value (1.20 mg/dL, increased from 0.9 mg/dL preoperatively). Liver function test values were normal and vancomycin trough was subclinical (<4.0 µg/mL). At the time of presentation, he was also diagnosed with multiple small pulmonary emboli, for which he was started on a heparin drip. IV steroids were started (methylprednisolone 125 mg bolus, maintenance of 60 mg every 8 hours), but the rash continued to progress.

On day 3 of hospital admission, after 3 days of continued IV steroids (methylprednisolone 60 mg every 8 hours), the rash now covered his entire body (Figs. 1–3). Skin biopsy samples taken from the abdomen and right thigh showed “necrotic keratinocytes, spongiosis, perivascular lymphocytes, and eosinophils with extravasated erythrocytes, consistent with erythema multiforme or drug eruption.” A diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was made in collaboration

with dermatology, medicine, and infectious disease. The patient was started on topical steroids and converted from IV to oral steroids (prednisone 120 mg daily) in preparation for home therapy. He was discharged home on hospital day 6. He continued to take oral steroids on a tapered course (prednisone 120 mg starting, tapering down over 45 days at 5-day intervals), and his rash resolved 23 days after initial presentation (Figs. 4 and 5).

At the time of submission of this manuscript, the patient had completed the full course of spacer treatment while retaining the spacer without the rash returning. At the time of evaluation for spacer removal and reimplantation, the patient was found to have persistent infection (now culture positive with methicillin-sensitive staphylococcus aureus and Enterobacter), and underwent repeat antibiotic spacer implantation (with tobramycin, chosen based on bacteria sensitivities) per standard of care treatment recommendations. He is being treated with IV daptomycin (for coverage of methicillin-sensitive staphylococcus aureus) and ciprofloxacin (for coverage of Enterobacter) based on sensitivities. He is not currently experiencing any drug reaction issues and is awaiting reimplantation.

Discussion

To our knowledge, this is only the third case of DRESS syndrome described to occur in patients with retained antibiotic-impregnated cement spacers, with one additional study identifying a case of Stevens-Johnson syndrome in a patient with antibiotic cement spacer [5]. Although drug reactions in general are common, occurring in up to 15% of hospitalized patients [6], severe drug reactions like the one described in this article are exceedingly rare. DRESS syndrome falls under a classification known as severe cutaneous adverse reactions, which also include more commonly known entities like Stevens-Johnson syndrome and toxic epidermal necrolysis [7,8]. It has up to a 10% mortality rate [9] and an incidence of 1 in 10,000 exposures [10]. DRESS syndrome was first identified in 1996 [11], with symptoms typically involving the skin and multiple organs, and patients present with fever, eosinophilia,



Figure 1. Picture of the patient's right arm 4 days after the onset of the rash.



Figure 2. Picture of the patient's right (nonoperative) leg 4 days after the onset of the rash.



Figure 3. Picture of the patient's left (operative) leg 4 days after the onset of the rash.

lymphadenopathy, and organ failure (kidney, liver, pulmonary) [12]. Patients typically present after a latency period of between 2 and 6 weeks during which they may experience no symptoms [13], similar to our patient who presented 3 weeks after the initiation of antibiotic therapy.

Treatment options for DRESS depend on the severity and degree of organ involvement. Although reports do exist of organ failure requiring transplantation [14], the majority of patients can be treated through a combination of oral and IV medications. Recommendations regarding treatment include the immediate withdrawal of the offending medication and initiation of IV corticosteroid treatments [15,16]. Transition to oral corticosteroids can occur once symptoms have stopped progressing. In rare circumstances, immunosuppressant medications may need to be added to treat refractory cases [17].

When a patient is taking multiple antibiotics at once, it can be difficult to identify the causative medication. The multidisciplinary



Figure 4. Picture of the patient's right arm after resolution of the rash 23 days after presentation.



Figure 5. Picture of the patient's right (nonoperative) leg after resolution of the rash 23 days after presentation.

team within our institution believed that the IV antibiotics administration was the inciting source. They felt that the most likely source of the reaction was the cefepime but could not entirely rule out vancomycin as the source due to the fact that both drugs were started simultaneously. Vancomycin was considered a less likely source of the reaction due to the low incidence of vancomycin induced DRESS (~2%-5% of all cases) [15]. This presented the orthopedic team with a dilemma in regards to the retained antibiotic spacer, which contained vancomycin. Since the treatment for DRESS syndrome is removal of all sources of the inciting medication, retaining the spacer if vancomycin was the cause could cause the immune process to continue, thus putting the patient at risk. Referring to the previous cases described in the literature involving antibiotic-impregnated cement, these cases were felt to be the result of vancomycin, and spacers contained vancomycin [18]. The onset of symptoms in these patients began 2-4 weeks after beginning IV antibiotic treatment, matching our patient's presentation. Due to the delayed presentation of DRESS, it was felt that the amount of antibiotic elution remaining (reported anywhere from 0.05% to 0.4% for gentamicin and 0.8% to 3.3% for vancomycin at 10 days postimplantation [19]) in the in situ spacer was negligible at the time of diagnosis [20-22], and removal would offer no benefit to the patient [18]. Both previous patients went on to resolve their symptoms (at 8 and 12 days, respectively) with corticosteroid treatment without further complication while also retaining the spacer [18]. This in large part helped dictate our reasoning for leaving the spacer in situ.

Summary

We present a unique case of DRESS syndrome in a patient with retained antibiotic-impregnated spacer for the treatment of a PJI. After discontinuation of IV antibiotics and the initiation of corticosteroids, the patient's symptoms resolved, despite retention of the spacer. This case report demonstrates that further surgical intervention for removal of the spacer may be unnecessary, and

symptom resolution may be possible despite retention of the spacer.

If the reaction had occurred earlier in the postoperative course, we would have been more inclined to remove the spacer.

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