CASE REPORT

Delayed-type hypersensitivity reaction to piperacillin/tazobactam in a patient with an infected total knee replacement

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We describe a patient who developed a delayed-type hypersensitivity reaction to piperacillin/tazobactam in the cement beads and a spacer inserted at revision of total replacement of the left knee. We believe that this is the first report of such a problem. Our experience suggests that a delayed-type hypersensitivity reaction should be considered when a mixture of antibiotics such as piperacillin/tazobactam has been used in the bone cement, beads or spacer and the patient develops delayed symptoms of pain or painful paraesthesiae, fever, rash and abnormal laboratory findings in the absence of infection. The diagnosis was made when identical symptoms were induced by a provoked challenge test.

Allergic reactions to antibiotics may occur in the form of immediate or delayed hypersensitivity. Immediate reactions are usually immunoglobulin (Ig)-E-mediated whereas non-immediate or delayed-type hypersensitivity reactions are usually non-IgE or T-cell-mediated in which drug-specific memory T cells act as effector cells. The activation of Th1-type cells leads to the production of interleukin (IL)-2 and interferon (IFN)-γ and to the subsequent activation of cytotoxic T cells. The clinical manifestations of a late drug allergic reaction can present in a variety of ways, such as fixed drug eruptions, morbilliform rashes, other non-specific rashes, unexplained pyrexia, nausea, vomiting, diarrhoea, arthralgia, myalgia, eosinophilia, derangement of liver function, haematological abnormalities and lethargy. These delayed reactions are unlikely to be IgE-mediated. They are not classically associated with anaphylactic reactions and cannot be diagnosed by skin prick or intradermal testing. As a result drug provocation tests or challenge tests should be used when testing for delayed-type drug allergy. One of the indications for such testing is the need to establish a firm diagnosis when there is a history suggestive of drug hypersensitivity and tests for allergy are not available, negative or inconclusive. Treatment consists of withdrawal of the incriminated drugs and, if necessary, the administration of glucocorticoids although late drug allergy reactions may not be prevented by treatment with corticosteroids.

Late infection after total joint replacement is still a problem. Usually, a two-stage procedure is necessary for the treatment of chronic late infection involving the use of antibiotic-loaded beads and the insertion of an articulated spacer when required. However, antibiotic-loaded cements have the potential disadvantages of loss of mechanical strength, toxicity, allergic reactions, antimicrobial resistance and cost. To our knowledge no case of an allergic reaction associated with the use of antibiotics in bone cement has been reported.

When piperacillin/tazobactam is used intravenously, the most frequent side-effects are gastrointestinal symptoms, mainly diarrhoea, and skin reactions.

We describe a case in which pain, fever, a generalised skin rash and abnormal laboratory findings, were attributed to a delayed type hypersensitivity to piperacillin/tazobactam in a bone cement spacer and beads used during revision of an infected knee replacement.

Case report

One year after a left total knee replacement (TKR) performed using Simplex Antibiotic bone cement containing 0.5 g of erythromycin per 40 g of bone cement (Howmedica, Limerick, Ireland) a 69-year-old woman with a history of diabetes mellitus presented with the acute onset of pain, swelling and erythema in the left knee. The diabetes was poorly controlled with tablets. After admission, the diabetes was controlled by insulin. The results of
blood tests and knee aspiration were consistent with infection. The haematological findings showed a white blood cell count (WBC) of $10.1 \times 10^3$/mm$^3$, an ESR of 86 mm/hour, and a level of CRP of 21.07 mg/dl (normal range 0.0 to 0.3). The joint aspirate findings showed a WBC of $12.1 \times 10^3$/mm$^3$ (normal range for synovial fluid in a normal joint 0 to 200/mm$^3$ and the normal range for synovial fluid in a TKR joint; 1 to 700/mm$^3$) and neutrophils of 95%, but no specific organisms were seen on staining or culture. Loosening of the tibial component was seen on the plain radiographs (Fig. 1). The patient had no history of allergy and skin tests performed at the time for each antibiotic were negative. At revision the implant was removed and beads and an articulated spacer with antibiotic-loaded bone cement (CMW 3, DePuy Orthopaedics, Warsaw, Indiana) containing 1.0 g of gentamicin, 3.0 g of vancomycin and 4.5 g of Tazocin per 40 g package of cement were inserted (Fig. 2). Intra-operative and frozen biopsy findings showed suppurative synovitis with > 30 polymorphonuclear leucocytes per high-powered field in the ten cellular areas. On the fifth post-operative day, methicillin-resistant *Staphylococcus epidermidis* was isolated from the intra-operative cultures, and she was given vancomycin 1.0 g bid IV and oral rifampicin 300 mg bid, based on the sensitivities, instead of the first-generation cephalosporin (Cetrazole, 1.0 g bid IV) with which she had previously been treated. This new regimen was administered for one week. On the 12th post-operative day, the CRP, ESR and WBC had returned to normal and the symptoms of infection had disappeared. However, on the 15th post-operative day she developed moderate pain in the left knee without swelling and generalised erythematous changes accompanied by rigors. The following laboratory changes were noted: WBC $3.8 \times 10^3$/mm$^3$, ESR 81 mm/hour, eosinophils 11.2% and CRP level 6.1 mg/dl and an elevated level of IgE.

Other causes of pyrexia of unknown origin were investigated with patch tests for cement, gentamicin, vancomycin, Tazocin, first-generation cephalosporin and rifampicin. However, no definitive findings were obtained. Accordingly, a provocation challenge test using a low-dose intravenous injection of gentamicin, vancomycin, Tazocin and first-generation cephalosporin, respectively, was carried out on the 26th day. Seven hours after intravenous injection of a half dose of piperacillin/tazobactam, rigors with a fever > 38°C developed, lasting for two days accompanied by a reddish skin rash and an itching sensation over the entire body (Fig. 3). Laboratory findings showed an increase in the WBC ($12.7 \times 10^3$/mm$^3$ to > $16.1 \times 10^3$/mm$^3$), the CRP level (3.5 to > 12.7 mg/dl), and the ESR (90 to > 97 mm/hour). The patient reported no previous exposure to piperacillin/tazobactam. She developed no abnormal symptoms after a provocation challenge test for any of the other drugs tested. We therefore concluded that the reaction resulted from the piperacillin/tazobactam in the bone cement.

Accordingly, the cement spacer and all the beads were removed and a second-stage revision TKR with vancomycin-loaded bone cement was performed (Fig. 4) at 30 days after confirming that all infections had been controlled. All the
symptoms had resolved and laboratory findings returned to normal one month after the second revision. Six months later she had no pain on walking or exercise and a range of movement at the knee from 5° of extension to 100° of flexion.

**Discussion**

Piperacillin/tazobactam is a combination of a semisynthetic ureidopenicillin and a β-lactamase inhibitor and has broad-spectrum activity which makes it useful for treating polymicrobial and Gram-negative bacterial infections. Because our patient had diabetes mellitus and the initial bacterial culture result was negative, we used a combination of vancomycin and the heat-stable antibiotic, piperacillin/tazobactam, to cover the possibility of the presence of Gram-negative bacteria. Cerretani et al.\(^1\) observed that a combination of vancomycin and imipenem cilastatin provided about 50% more elution from beads or spacers. However, it is likely that the effects observed in their study were related to the increased porosity of the bone cement as progressively higher amounts of powdered antibiotics were added.\(^3\)

No previous reports have been published on the adverse effects of vancomycin-loaded bone cement or piperacillin/tazobactam-loaded bone cement, but delayed-type hypersensitivity has been reported after prolonged intravenous administration of piperacillin/tazobactam, usually for more than ten days.\(^11,12\)

In our patient we diagnosed piperacillin/tazobactam-related delayed-type hypersensitivity after identical symptoms of pain or painful paraesthesia, fever, generalised skin rash, rigors and abnormal laboratory findings had been induced by a provocation challenge test. We concluded that this had resulted from an allergic reaction to the antibiotics in the cement and the symptoms completely resolved after the antibiotic-loaded cement beads and spacer were removed.

As a result of our experience with this patient we suggest that delayed-type hypersensitivity should be considered when symptoms such as pain or painful paraesthesia, fever, generalised skin rash, rigors and abnormal laboratory findings developed when mixed antibiotics like piperacillin/tazobactam have been used in the bone-cement beads or spacer during revision TKR.

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**References**


