A 61 Year-old Man With Delayed Hypersensitivity Reaction to Joint Prosthesis

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Case Presentation

61 year-old male with a past medical history of coronary artery disease complicated by myocardial infarction in 1984, type 2 diabetes mellitus, hyperlipidemia, hypertension, and right total knee replacement in 2006 presents to the outpatient allergist's office for evaluation. The patient reports that he never fully recovered after the knee surgery and never regained function. The right knee remained swollen and painful with limited range of motion and weight bearing as a result. He denies any rash, redness, or itching in the area. He also denies any history of reactions to metals in the past. The orthopedic surgeon referred the patient to an allergist to assess for an allergic reaction to various components of the orthopedic hardware prior to the right knee revision surgery.

The patient has no known drug allergies. His medications include insulin 70/30 at breakfast and dinner, diltiazem CD 360 mg daily, simvastatin 20 mg daily, lisinopril 10 mg daily, metoprolol 12.5 mg twice daily, nitroglycerine patch for 12 hours daily, alprazolam 5mg three times a day for anxiety, and naproxen and percocet as needed for pain. The patient is a lifetime non-smoker and stopped drinking alcohol over 20 years ago. Family history is significant for coronary artery disease and prostate cancer. There is no family history of asthma or allergy.

At the initial visit, the patient was afebrile with stable vital signs. The physical exam was unremarkable except for right knee swelling, decreased range of motion, a well-healed midline scar, and 1+ edema of the right lower extremity up to the knee. The knee was non-tender and no warmth or erythema was noted.

To evaluate for delayed hypersensitivity reaction, a panel of allergens using the Thin-layer Rapid Use Epicutaneous (TRUE) patch test were placed on the patient's skin. A vitallium metal disk, a known component of the prosthesis, was also placed on the patient's skin. At 48 hours, the patch test was clearly positive for black rubber and possibly positive for potassium dichromate and Balsam of Peru. Since the patch did not stay entirely adherent to the skin, the adhesive was reinforced and the patient was instructed to return the next day for a 72-hour reading. At the second reading, the test remained strongly positive to black rubber. In addition, potassium dichromate showed strongly positive reaction, and cobalt dichloride showed weakly positive reaction. Upon re-examination, the reaction to Balsam of Peru appeared more likely to be irritation and not a true reaction. Given that the patient's knee prosthesis was composed of 30% chromium, suspicion for metal allergy to the prosthesis was high. The finding was communicated to the orthopedic surgeon for consideration in further management of the patient's condition.

Discussion

Metal hypersensitivity is common in the general population and often manifests as contact dermatitis to various everyday items including jewelry, watches, and belt buckles. The exposure may also occur in the form of metal ions dissolved in food and water. If ingested, metal ions can cause similar dermatological reactions or more systemic reactions such as asthma-like symptoms.[1] The most common metal hypersensitivity is to nickel, followed by cobalt and chromium.[2] Nickel and cobalt show significant cross-reactivity.

Metal allergy involves the type IV hypersensitivity response, also known as the cell-mediated delayed-type hypersensitivity (DTH). In DTH reaction, antigens are taken up and expressed on antigen presenting cells (APCs) which activate sensitized Th1 lymphocytes, a subpopulation of T-cells. The T-cells then release various cytokines, which in turn recruit and activate macrophages, monocytes, neutrophils, and other inflammatory cells.[3] Activated macrophages can trigger the activation of more T-cells, perpetuating the inflammatory response and leading to extensive tissue damage.[3] Metals or metal ions on their own are not known to activate the immune system. Rather, it is the metal-protein complexes, formed by the degraded metal products binding to the native proteins, that can function as antigens and elicit an immune response.[3] Specific APCs and T-cell receptors implicated in the DTH responses to metal are yet unidentified, and the current management for metal hypersensitivity is mainly based on exposure avoidance.

Metal prostheses, as with all metal exposed to biological environment, are known to corrode over time and release wear debris into the joint space. Nickel and cobalt ions seem to clear rapidly from the synovial space and are eliminated in the urine, but chromium appears to be stored in the tissue and eliminated more slowly.[5] Concern for metal hypersensitivity to joint prosthesis was first raised in several case reports from the early 1970s, which noted that some patients with metal-on-metal joint replacement developed reactions that may be allergic in nature.[1] Since then, implant-related metal hypersensitivity has been documented in numerous case reports and cohort studies. Still, as a clinical entity, it is only loosely characterized and poorly understood.

Commonly reported findings include eczematous rash, either generalized or on the skin overlying the orthopedic implants, along with discomfort, pain, erythema, and swelling over the affected joint.[2] Some patients also report malaise, fatigue, and general weakness.[2] Most concerning of all, DTH to metal prostheses has been cited as at least partially responsible for "aseptic loosening" of the prosthetic joint, in which chronic imflammatory-mediated osteolysis around the implant leads to loss of fixation and eventual implant removal.[4] In suspected cases of implant-associated DTH reactions, the synovial fluid tends to be culture negative and have only few leukocytes. Histologically, inflammation and oligoclonal T-cell infiltrates are present in the peri-implant tissue, indicating an immune-mediated process, and cytokines typical of DTH, such as IL-6 and INF-γ, are expressed in high concentrations.[5]

The conventional method of diagnosing metal hypersensitivity is by patch testing, in which a panel of antigens is exposed directly onto the skin for 48 to 96 hours, and the resulting dermatological

reactions are graded.[3] It is a less-than-ideal method since the skin is a natural barrier that protects the immune system from antigen exposure. In the case of implant-associated metal hypersensitivity, patch testing is even more unreliable since the synovial cavity has a different cellular and biochemical composition than the skin.[2] Furthermore, there is at least the theoretical concern that patch testing could induce a hypersensitivity reaction in previously insensitive patient.[3] Several *in vitro* studies for testing DTH are available, although their value specifically in implant-associated metal hypersensitivity has not been studied extensively.

Lymphocyte transformation testing (LTT) measures the proliferative response of lymphocytes to a designated challenge antigen.[3] Leukocyte migration inhibition testing (LIF or MIF) measures the migration of lymphocytes on a culture medium in the presence of a sensitizing antigen which tends to inhibit migration.[3] Unfortunately, both LTT and LIF are labor-intensive and lack the sensitivity and specificity to be reliable in the clinical setting. At this time, diagnosis of implant-associated metal hypersensitivity is largely based on clinical presentation and exclusion of other etiologies.

Can patients be screened for metal allergy prior to undergoing joint replacement surgery? Some studies have suggested that patients with documented metal allergy have more symptoms of implant-associated DTH and that positive patch test to metal is more common in patients with failed joint prostheses than in those with well-functioning prostheses.[1] However, studies that looked at pre- and postoperative sensitization to metal showed that a significant number of patients develop metal sensitivity postoperatively.[1,3,4] Furthermore, only a fraction of those with positive patch test, both pre- and postoperatively, developed clinical manifestations of DTH to metal implants.[1,3,4] In fact, many of those with positive patch tests had no history of reaction to metal. Studies that used *in vitro* tests independently or in combination with the patch test also failed to produce any consistent findings. At this point, there is no reliable method to assess for implant-associated metal allergy preoperatively.

Since DTH does not involve the histamine-release pathway, the common allergy medications are ineffective in treating metal prosthesis allergy. Low-dose corticosteroids have been used as a temporary solution, but their numerous adverse side effects deem them inappropriate for long term treatment.[2] As with the cutaneous form of metal hypersensitivity, the definitive treatment for implant-associated metal hypersensitivity is elimination and avoidance, or, in other words, surgical removal of the metal prosthesis. Although removal of the offending prosthesis generally leads to complete and prompt healing, the revision surgery is obviously a serious undertaking. Biologically more inert materials are under investigation as alternatives to the currently available metal prostheses. Also, research is underway to determine genetic polymorphisms for factors involved in DTH and to develop targeted immunosuppressive agents.[4]

Implant-associated metal hypersensitivity is an extremely rare condition. However, in those few who are affected the consequences are grave. The condition is probably under-recognized and under-reported due to the difficulty of diagnosis. More research, including longitudinal prospective studies, are needed to better understand this immunological, rheumatological, and surgical enigma.

References

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