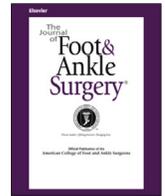


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Case Reports and Series

Type IV Cell-Mediated Hypersensitivity Reaction Caused by Titanium Implant Following Double Calcaneal Osteotomy and First Metatarsal-Cuneiform Arthrodesis: A Case Report and Review of the Literature



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ABSTRACT

Because of their inert character and desired biocompatibility, titanium implants have been universally accepted as safer alternatives to the conventional stainless steel orthopedic implants; however, recent emergence of type IV hypersensitivity reactions to titanium have included eczema, contact dermatitis, a prolonged febrile state, sterile osteonecrosis, and impaired fracture and wound healing. This report presents a patient with postoperative incision dehiscence and devascularization of surfaces in contact with titanium hardware after undergoing a double calcaneal osteotomy and a first metatarsal-cuneiform arthrodesis using titanium alloy implants. Titanium hypersensitivity was confirmed in this case through standard allergy patch testing by a board-certified immunologist. Complete healing occurred after diagnosis of the titanium allergy and hardware explant. To our knowledge, this is one of a few known allergies to titanium implants after foot and ankle surgery.

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Titanium alloys are more recently established biomaterials used in medical-grade implants (1). Because of a general lack of reported allergic reactions, titanium implants have been universally accepted as less reactive alternatives to the conventional alloys consisting of metals such as cobalt, chromium, and nickel (2). The inert character, strong resistance to corrosion, and desired biocompatibility to produce a protective oxide layer make it a superior commodity (3–6). Because of these attributes, titanium implants are commonly used in patients with known metal allergies. Although these features suggest that titanium would be less likely to incite hypersensitivity, we report a patient with postoperative incision dehiscence and devascularization of bony surfaces in contact with titanium hardware after metatarsal-

cuneiform arthrodesis and double calcaneal osteotomy for a flexible flatfoot deformity.

Case Report

A 25-year-old female presented to the clinic of the senior author (D.J. E.) for a surgical consult regarding a painful flexible flatfoot deformity of both lower extremities. The patient had been treated with over-the-counter and custom orthotics. Her medical and history included Pott's disease, remote history of swine flu, and pseudoseizures. The patient's surgical history was relevant for an excision of a benign nevus to her flank. The patient did report wound healing complications of that procedure, which she attributed to "braided absorbable suture." The patient's family history was significant for irritable bowel syndrome, pneumonia, delayed umbilical cord separation, pernicious anemia, hyperthyroidism, recurrent otitis media, alopecia universalis, and congenital adrenal hyperplasia. The patient also admitted to postsurgical healing complications in both her mother and sister, who had similar

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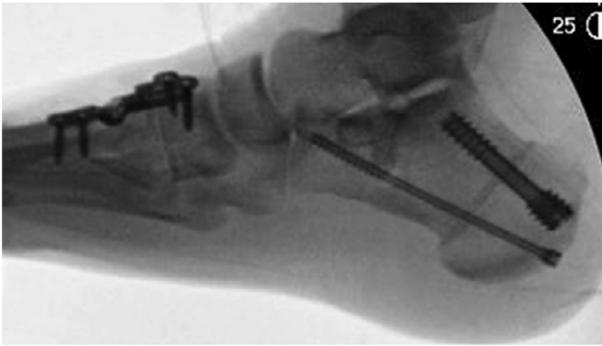


Fig. 1. Final intraoperative lateral fluoroscopic image from reconstructive procedures.

cases of delayed wound healing of elective surgical sites. Documented allergies included adhesives and braided absorbable suture. All other parts of the patient's medical history were negative, and the patient was not on any prescribed or over-the-counter medications before her initial surgery. Physical examination revealed a painful, but flexible, flatfoot deformity with gastrocnemius-driven equinus, hindfoot valgus, and residual forefoot varus positioning after hindfoot correction. Both left and right lower extremities were affected; however, symptoms were worse on the left side. Consent and medical clearance were obtained for surgical reconstruction including gastrocnemius recession, double calcaneal osteotomy, and first metatarsal-cuneiform arthrodesis of the left lower extremity.

The double calcaneal osteotomy and first metatarsal-cuneiform arthrodesis were fixated using hardware consisting of 4.0- and 7.0-mm Stryker Fixos headless compression screws and the Stryker Anchorage™ plating system comprising anodized type II titanium (Stryker Corp., Kalamazoo, MI), respectively (Fig. 1). Suture used for closure included a monofilament absorbable (poliglecaprone 25) and monofilament nonabsorbable suture (polypropylene). Initially, the patient experienced normal postoperative pain and edema without wound compromise; however, she presented at approximately 3 weeks postoperatively with complaints of increasing pain. She was noted to have rapidly progressing

edema, erythema, and early signs of wound breakdown to the dorsal foot (Fig. 2). A diagnosis of postoperative infection was made, and the patient was placed on 1 week of oral cephalexin and ordered for daily dressing changes. At 4 weeks postoperatively, the patient's erythema and edema had somewhat subsided; however, wound necrosis near the orthopedic hardware continued to progress (Fig. 3A). She was admitted to the hospital for aggressive wound management including debridement, deep tissue cultures, and bone biopsy (Fig. 3B). During this hospital stay, an infectious disease specialist placed the patient on empiric antibiotic coverage. After cultures demonstrated no bacterial growth, a delayed primary closure with platelet-rich plasma augmentation was performed (Fig. 4). She was discharged home only on oral antibiotics as instructed by the infectious disease team.

Approximately 2 weeks after the patient's discharge, she had continued pain and burning, primarily around the surgical sites overlying the hardware. Examination revealed coaptation but no signs of formal healing of the closure site directly overlying the hardware (Fig. 5A). Examination of the posterior heel also revealed erythema and necrosis of the percutaneous incisions for the calcaneal screws (Fig. 5B). The gastrocnemius recession incision was pristine, raising suspicion for compromised hardware; however, review of the materials management documentation revealed all adequate steps were in place for standard instrumentation sterilization for the initial procedure. Consideration for titanium allergy was made and a referral to an allergist was completed. Standard allergy patch testing was completed by a board-certified immunologist, who confirmed type IV hypersensitivity to titanium salts and vanadium.

At approximately 8 weeks after the initial procedure, the patient underwent a fourth procedure for removal of all hardware. A computed tomographic scan immediately before that procedure revealed adequate trabeculation of the calcaneal osteotomies; however, the first metatarsal-cuneiform arthrodesis site showed little to no trabeculation. Intraoperative findings showed complete devascularization and graying of the bony surfaces in contact with the hardware. A bone biopsy was performed (Fig. 6), and formal histopathological examination revealed osteonecrosis and possible osteomyelitis. Bone cultures and deep tissue cultures were aseptic. The arthrodesis site was revised and augmented with Stryker's Bio4® (Stryker Corp., Kalamazoo, MI) graft as well as a



Fig. 2. Incision site appearance 3 weeks following the initial procedure.



Fig. 3. Appearance of dorsal incision site at 3 (A) and 4 (B) weeks following the index procedure.

MiniRail (Stryker Corp., Kalamazoo, MI) external fixator for stability of the arthrodesis site (Fig. 7). A bone-matrix graft containing cells (mesenchymal stem cells, osteoprogenitor, and osteoblasts) and growth factors was used. The pins for the MiniRail were made of surgical grade stainless steel and were approved to be safe by the immunologist before the procedure. Bone marrow aspirate concentration from the patient's proximal tibia and platelet-rich plasma were also used to support the devascularized soft-tissue complement and assist in angiogenesis because the pathology report findings included tissue necrosis. Postoperatively, the patient used a bone stimulator and remained non-weight-bearing for 12 weeks. Because of the significant necrosis and subsequent debridement, negative-pressure wound therapy was necessary on the dorsal foot wound. Under the guidance of the infectious disease team, the patient was placed on oral doxycycline and cephalexin



Fig. 4. Dorsal incision site immediately following delayed primary closure.

for 8 weeks because of the prolonged surgical wound as prophylaxis against joint sepsis and secondary osteomyelitis. A second computed tomographic scan 12 weeks after the revisional surgery demonstrated trabeculation across the arthrodesis site. The external fixator was removed and clinical stressing noted a solid arthrodesis.

Following the diagnosis of a complete union, the patient was referred to a second surgeon for delayed wound healing treatment at the initial first metatarsal-cuneiform incision site. The calcaneus healed well after hardware removal. To aid wound healing, negative-pressure wound therapy was used and an amniotic membrane graft was applied. The patient was entirely healed 30 weeks after the initial surgery (Fig. 8). She was seen 1 final time more than 2 years from the initial surgery without any complications (Fig. 9).

Throughout her postoperative course, the patient had multiple cultures obtained with no indication of bacterial contamination. A histologic analysis was performed, revealing skin and subcutaneous tissue with dystrophic calcification, fibrin and acute inflammation from the incision sample, and only bone and fibroconnective tissue with no osteomyelitis from the bone sample.

Discussion

There have been few documented cases of allergy to titanium implants. Common adverse effects include eczema, contact dermatitis, a prolonged febrile state, sterile osteomyelitis, and impaired fracture and wound healing (1,7,8). The mechanism as to what specifically causes titanium to evoke such an allergic reaction is still unknown. It has been speculated that titanium follows a similar sequence found in other metal implant allergic reactions such as cobalt and nickel; ions and microparticles released from the metal induce a type IV hypersensitivity response (5,8–10). Type IV cell-mediated hypersensitivity response to metals has been identified as a vascular infiltration of lymphocytes to postcapillary venules leading to vasculitis, swelling of the vessel endothelium, localized bleeding, bone resorption, and necrosis (11–14). Histologic examination of the periprosthetic tissue will show high endothelial venules, diffuse infiltration of plasma cells and B lymphocytes, extensive fibrin emission, and multinuclear and mononuclear macrophages next to vessels (13,15).

A study in 2010 conducted by Harloff et al (16) observed that titanium-based hardware may contain impurities. Beryllium, cadmium, cobalt, and nickel are among the many metals incorporated into titanium implants, and cobalt and nickel specifically have a high incidence of inducing an inflammatory reaction (17,18). Unlike other metals, the



Fig. 5. Incision site appearance of the dorsal foot incision (A) and calcaneus incision (B), two weeks after delayed primary closure of the dorsal foot incision.

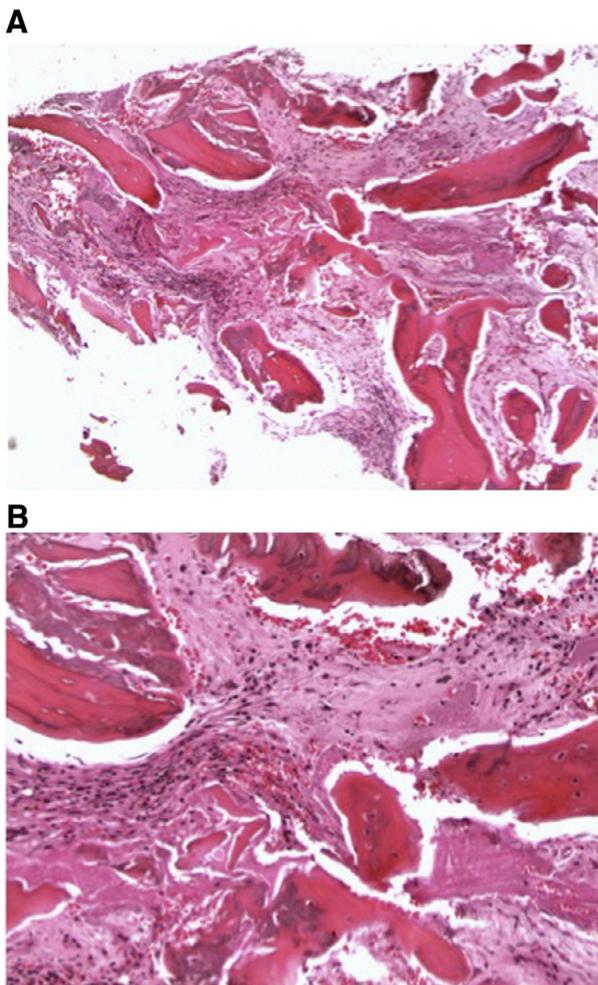


Fig. 6. Histopathology image of bone biopsy showing chronic inflammatory cells (A and B).



Fig. 7. Final intraoperative dorsoplantar fluoroscopic image following hardware removal, revision of the first metatarsal-medial cuneiform arthrodesis site, and placement of the MiniRail external fixator.

biocompatibility of titanium is derived from the passive oxide layer that forms, preventing corrosion and the release of ions (19–21). The release of ions may occur in ways other than corrosion, however, such as improper placement, stress, and wear of an orthopedic implant (3,6,22). This was demonstrated in a 2002 case report by Frisken et al (23), in which elevated titanium levels in lymph nodes were discovered in a



Fig. 8. Dorsal incision site at 8 months following the reconstructive procedure.



Fig. 9. More than 2 years since initial procedure and >1 year from reconstructive procedure with a healed incision.

sheep model following aseptic implant loosening. In 1999, an in vitro study by Pioletti et al (24) researched the effects of pure titanium particles on osteoblasts, discovering a direct correlation between titanium and the depression of viability, proliferation, and bone-matrix protein production of osteoblasts. An apparent release of cytotoxic products was also noted when osteoblasts were subjected to titanium particles (14,22,24). This accounts for the pathophysiology of titanium on fracture healing, wound healing, and inflammation. Titanium-coated hardware has even been associated with systemic contact dermatitis (25).

Because an allergy to titanium is a rare occurrence, the initial findings can often be wrongly interpreted and appropriate treatment may be delayed. The diagnosis of a titanium allergy can be difficult because the symptoms regularly mirror more common complications including wound infection, osteomyelitis, nonunion, malalignment, other inflammatory diseases, and mechanical failure of the implant (26,27). Foremost, a bacterial infection should be ruled out with laboratory values such as a complete blood count, erythrocyte sedimentation rate, or C-reactive protein, as well as tissue and bone cultures. Cultures should undergo a Gram stain and be cultivated in both aerobic and anaerobic conditions. In the case of this patient, these tests were negative for acute osteomyelitis. Eliminating other potential pathologies is frequently how a titanium allergy diagnosis is made. Diagnostic tools for metal allergies are available and include a patch test, lymphocyte transformation test, memory lymphocyte immunostimulation assay, leukocyte migration inhibition test, and lymphocyte activation test (8,14,28,29). If a patch test is positive, then no further testing may be necessary; however, false negatives have been reported. In 2006, Thomas et al (1) described a case in which a patient had a nonhealing fracture because of a titanium implant. Patch test findings for a titanium allergy came back negative, most likely because of the lack of penetration of titanium salts through the epidermis, but a positive lymphocyte transformation test revealed increased T lymphocytes in response to titanium dioxide (30). Following removal of the titanium hardware, which is the definitive treatment for suspected titanium hypersensitivity, the patient's reaction resolved and the fracture healed appropriately (30); thus, a lymphocyte transformation test can be used to further investigate the possibility of titanium hypersensitivity (28). In the case of our patient, the patch test produced a positive result for a titanium allergy; therefore, no lymphocyte transformation test was necessary.

Following the diagnosis of an allergic response to titanium, case management is dependent on the patient profile. Treatment options include administration of immunosuppressants, removal of titanium hardware, and stabilizing the affected site. In 2012, Loyo et al (31) reported a case in which a patient presented as febrile with extreme malaise and arthralgia 1 year after a cosmetic nickel-titanium chin implant. Intravenous methylprednisolone was administered and the symptoms subsided; however, the patient returned to the clinic 2 years later with similar symptoms and opted for extraction of the chin implant. At a 3-month follow-up visit, the patient was completely asymptomatic. Sakamoto et al (32) chronicled a case in which a full titanium hardware implant from a pectus excavatum repair incited a hypersensitivity response in 2 brothers. Following removal of the hardware, the febrile symptoms diminished and no further treatment was required. Wang et al (33) reported on a recent case in which a titanium implant was used to surgically correct hallux valgus deformity. Following surgery, the patient had an intermittent febrile state of unknown etiology, but no other signs of infection. A positive patch test confirmed that the patient had an allergic reaction to titanium. After implant removal, the febrile state resolved and the wound healed.

Oftentimes, to maintain necessary anatomic structure after an internal titanium implant is removed, external fixation is implemented (34,35). In cases in which external fixation cannot be achieved, hardware can be coated or replaced with materials that minimize the risk of an immunologic reaction (18,36). Syburra et al (18) describes the use of

a gold-coated pacemaker following a hypersensitivity reaction to a titanium pacemaker in an 86-year-old man. The titanium pacemaker was replaced with one that was gold plated and the symptoms subsided. Oliva et al (37) removed titanium dental implants from a young patient and replaced them with zirconium oxide bridges, alleviating hypersensitivity symptoms. An immunology consult can confirm the safety of replacement hardware. In the case of our patient, the arthrodesis was externally fixated with a MiniRail made of surgical grade stainless steel, which was approved by the immunologist.

In conclusion, a hypersensitivity reaction to titanium may not be as prevalent as it is with other metals; however, it should remain a possible diagnosis for a patient presenting with symptoms such as prolonged febrility and impaired wound healing. Diagnostic tools, such as the patch test and lymphocyte transformation test, can be used to help detect such allergic reactions in the future. Treatments for titanium hypersensitivity should be customized to fit the patient's needs and potentially include complete removal or substitution of the titanium hardware, external fixation, and immunosuppressants to manage symptoms.

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