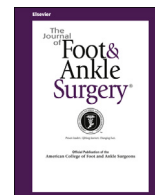




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Case Reports and Series

Long-Term Fever After Hallux Valgus Surgery Secondary to Titanium Allergy: A Case Report and Review of the Literature

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ABSTRACT

We present the case of a patient who had experienced a fever of unknown cause for >7 months after surgical treatment for hallux valgus. A patch test revealed a positive reaction to a titanium alloy. All symptoms subsequently disappeared after we removed the implanted titanium screws. Histopathologic examination of the tissue surrounding the screws showed macrophage infiltration in the tissue. For >1 year after removal of the titanium screws, the patient's body temperature remained <37°C. These results support a diagnosis of titanium allergy in our patient. To the best of our knowledge, a long-term fever caused by an allergic reaction to mini-titanium screws of such a small size has not been reported. A review of 16 cases of titanium allergy reported in the published data confirmed that titanium allergy is extremely rare and that the clinical symptoms can vary. Titanium allergy should be suspected when a patient presents with a fever of unknown cause, delayed wound healing, dermatitis, or impaired fracture healing after internal fixation with titanium materials. A patch test for titanium or the lymphocyte transformation test could offer guidance for the clinical diagnosis of titanium allergy. Finally, we recommend that all patients should be asked whether they have a history of an allergy to any metal before surgery.

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Titanium (Ti) alloys are widely used in orthopedic implants, and a few reports of hypersensitivity reactions to Ti-based materials have been published. Thus, few studies have investigated the mechanisms and outcomes of hypersensitivity to Ti (1). Ti is known to be highly corrosion resistant owing to the formation of thermodynamically stable and adherent oxide layers on the Ti surface (2,3); therefore, Ti is not expected to provoke allergic reactions (4). However, we report the case of a patient who presented with a long-term fever of unknown cause after surgical treatment for hallux valgus and was ultimately diagnosed with a Ti allergy. The purpose of the present clinical report was to demonstrate that even small Ti screws can induce an allergic reaction; thus, the patch test for Ti could be useful in the clinical diagnosis of this condition.

Case Report

An 18-year-old male patient presented with a prolonged low-grade fever that had lasted >7 months after surgical treatment for left hallux

valgus. For transfer metatarsalgia caused by left hallux valgus, the patient had undergone Scarf and Akin osteotomy with 24-mm Extremifix cannulated screws (YZB [medical device registration product standard], standard 0105-2013, as reported by the manufacturer, Double Co., Xiamen City, China) in our hospital 22 months previously. He reported the onset of fever 7 days after the first surgery without any signs of infection. The fever was intermittent, with his temperature remaining <38.5°C. By 2 weeks after surgery at suture removal, the patient had experienced good wound healing and satisfactory pain relief (Fig. 1). The radiographic examination showed that the fracture had healed by 3 months after surgery (Fig. 2A). The patient was satisfied with the deformity correction and pain relief and ignored the fever, because his body temperature never exceeded 38°C.

Because of the good curative effect of the surgical treatment of the left hallux valgus, the patient underwent surgical treatment for right hallux valgus in our hospital 5 months after the first surgery. The treating orthopedists were not aware of the patient's ongoing fever. The patient also experienced good wound healing and pain relief after the second surgery (Fig. 1). However, the fever began to occur more frequently, with the patient's temperature fluctuating from 37°C to 39°C. Anti-infection therapy with levofloxacin tablets (0.1 g given 3 times daily) had no effect on the fever, and symptomatic management had only short-term effects.

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Fig. 1. Good wound healing and deformity correction after surgical treatment for hallux valgus.

A series of related laboratory tests were conducted; however, the results of all examinations, including the erythrocyte sedimentation rate, C-reactive protein level, and levels of antibodies against cytomegalovirus IgM, were normal. Moreover, normal results were observed for the complete blood count, blood culture, urinalysis and culture, rheumatoid factor, lactate dehydrogenase, creatinine kinase, antinuclear antibodies, and appropriate region-specific serologic testing. Also, no sign of pneumonia or other infectious lung disease was seen on the chest computed tomography examination. We consulted our hematologic department and infectious disease department and conducted related examinations, including a bone marrow examination and anticytoplasmic autoantibody analysis. Because the results of these examinations were also normal, the cause of the fever remained unknown.

One day, the patient reported itching and erythema on contact with a watch or metal buttons. Thus, we questioned whether the implant material used in the surgical treatment of hallux valgus could



Fig. 3. The patch test outcome on the patient's right forearm showing a local eczematous contact allergic reaction to titanium alloy after 48 hours.

have caused an allergic reaction. We used a mini-Ti plate (obtained from Double Company, China) to perform a patch test. Patch testing was performed according to the guidelines of the German Contact Dermatitis Research Group (5), and the reaction was evaluated after 48 hours.

The patch test revealed a local eczematous contact allergic reaction to the Ti alloy after 48 hours (Fig. 3). We later repeated the patch test 2 days after the disappearance of the allergy symptoms, and the results were the same. Because the radiographic examination confirmed fracture healing (Fig. 2), the titanium screws were removed completely with consent from the patient (Fig. 4). No signs of chronic inflammation or hypotoxic infection were observed in the deep tissue during surgery (Fig. 5). A sample of the tissue surrounding the screws was collected for histopathologic examination, which showed macrophage infiltration into the tissue (Fig. 6). After the surgery, we did not administer anti-infection or corticosteroid therapy, because we wished to observe the effect of screw removal on the patient's



Fig. 2. Radiologic evaluation at 3 months after osteotomy showing bone healing in the (A) left and (B) right feet.



Fig. 4. Extremifix cannulated screws removed from the patient.

body temperature. After several days, the patient's temperature had returned to normal. The patient was followed up for >1 year, and his body temperature remained <37°C during this time.

Discussion

Metal allergy, which can be histologically described as a type of aseptic lymphocyte-dominated vascular-associated lesion, is characterized by diffuse perivascularly located lymphocyte infiltration with necrosis and a limited numbers of macrophages (6). It is a type IV allergic reaction caused by metal corrosion and a lesion resulting from the constant release of ions into the tissue environment (7,8). The severity of the reaction depends on the material and the sensitivity of the patient (9). Owing to the formation of thermodynamically stable and adherent oxide layers on its surface (2), Ti is highly corrosion resistant (3). Ti has even been recommended as a substitute material for patients who are allergic to other metallic materials (3,11,12). To the best of our knowledge, a long-term fever caused by an allergic reaction to mini-Ti screws has never been reported.

It is known that the Ti alloys used to fabricate implants might not be completely pure, containing trace amounts of elements such as beryllium, cobalt, chromium, copper, iron, and nickel, which might induce allergic reactions in patients who receive Ti implants (9). However, in our patient, the Extremifix cannulated screws were made of pure Ti according to YZB (medical device registration product standards) standard 0105-2013, as reported by the manufacturer.

To analyze the clinical presentation of Ti allergy, the corresponding patch test results, and outcomes of histopathologic examination, we searched the MEDLINE/PubMed database (National Library of Medicine, Bethesda, MD) for appropriate studies using the following keywords: "titanium allergy," "titanium hypersensitivity," and "titanium release" and selecting the case report format. We screened the titles and abstracts of reports that satisfied our selection criteria by reporting the data regarding the allergy history, specific symptoms, patch test results, and treatment outcomes. A total of 14 studies (4,10–22) were finally chosen (Table); the full texts of these reports were read and independently assessed by 3 of us (L.-F.W., J.W., C.Z.).

We reviewed the cases of 16 patients with Ti allergy reported in published studies, including our patient (Table). The patients included 7 females and 9 males who ranged in age from 8 to 86 years (mean $\pm$ standard deviation 45 ± 23 years). Of the 16 patients, 11 had a history of a metal allergy. All the patients were symptomatic, with 10 patients experiencing dermatitis or local eczema, 6 experiencing delayed or poor wound healing, and 4 experiencing fever. One patient even presented with an impaired fracture (10). Patch tests were performed in all 16 patients, and 13 (81.2%) had a positive reaction. The lymphocyte transformation test was performed for 7 patients, and all 7 (100%) showed markedly enhanced proliferation of lymphocytes exposed to Ti in vitro. In 5 patients, the tissue surrounding the Ti implant was taken for histopathologic examination, and all specimens showed lymphocyte or macrophage infiltration. Finally, in all patients, the symptoms disappeared after removal of the Ti material. All 16 reviewed cases demonstrated that the phenomenon of Ti allergy can occur in clinical practice, and a patch test using a Ti plate and lymphocyte transformation test can be beneficial in diagnosing a Ti allergy.

Our review of Ti allergy cases reported to date revealed that Ti allergy is extremely rare and the clinical presentation varies. In 2006, Thomas et al (10) reported a case in which impaired fracture healing and local eczema occurred after treatment of a right metacarpal fracture using a pure Ti miniplate and screws. They performed the lymphocyte transformation test and observed markedly enhanced proliferation of lymphocytes exposed to Ti in vitro. Furthermore, after removal of the Ti material, fracture healing was achieved and the eczema had resolved. A repeated lymphocyte transformation test also showed that the in vitro hyperreactivity to Ti had disappeared. Five years later, Thomas et al (13) reported another case of a 59-year-old female with a trimalleolar ankle fracture who experienced delayed wound healing with moist dermatitis, but no signs of infection after open reduction and internal fixation with a titanium plate. In that patient, they applied a patch test for Ti and obtained a positive result. The wound had finally healed at 6 months after surgery; however, scaling dermatitis overlying the lateral malleolus persisted until the Ti plate and screws had been completely removed 9 months after

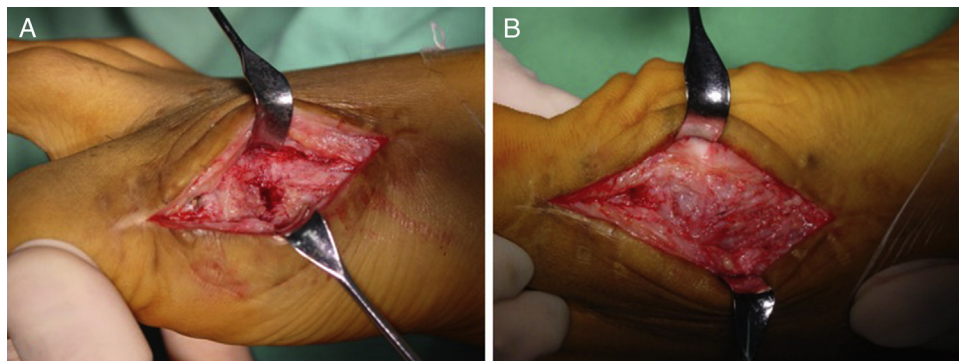


Fig. 5. No signs of chronic inflammation or hypotoxic infection were observed in the deep tissue on the (A) right or (B) left side.

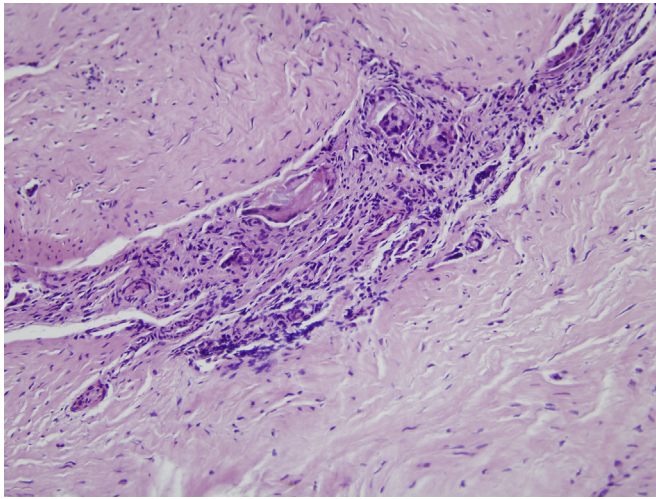


Fig. 6. Histologic staining of a biopsy sample of tissue that had adhered to a titanium screw showing infiltration of a number of macrophages into the tissue (original magnification $\times 40$).

surgery. Histologic examination of a biopsy specimen showed dense lymphocyte infiltration into the tissue adjacent to the Ti plate. Therefore, they concluded that the Ti plate had caused the skin hypersensitivity.

Owing to its low incidence and occult presentation, the diagnosis of Ti allergy is difficult, with the possibility of misdiagnosis such as wound infection, fat liquefaction, or persistent foreign body inflammation, resulting from delayed treatment (23). A patch test and the lymphocyte transformation test can be used to support a diagnosis when metal allergy is suspected, especially when a patient presents with a persistent fever or poor wound healing with no signs of infection (24,25).

However, a negative outcome on a Ti patch test does not exclude the possibility of Ti allergy. In 2009, Syburra and Schurr (14) described an 86-year-old male who had undergone pacemaker implantation. After the surgery, the wound showed poor healing without any evidence of infection, and a skin patch test to Ti was negative. However, the wound healing complications resolved after removal of the

pacemaker system and implantation of a gold-plated generator. In 2004, Sakamoto et al (11) reported the cases of 2 brothers, 17 and 23 years old, who experienced a high fever, chest pain, and pleural effusion after a standard operation for repair of pectus excavatum using Ti bars, with no signs of infection. Preoperatively, they both had a history of metal allergy, but the results of patch tests using a Ti plate were negative. Blood tests revealed elevated eosinophil counts and IgE levels, and steroid therapy was effective in managing the symptoms in these patients. Once the Ti bars were removed 2 years later, the symptoms disappeared, with no additional treatment required. These 3 cases demonstrate that a negative skin patch test to Ti does not exclude the possibility of an allergic reaction to a Ti alloy.

The lymphocyte transformation test is a cell-mediated immunologic response to assess the ability of lymphocytes to proliferate, recognize, and respond to antigens (1,26). It is a noninvasive test to determine lymphocyte reactivity to metals such as Ti. As an *in vitro* test, it will not sensitize the patient. The positive reaction prevalence to metals using the lymphocyte transformation test was 94.4% (25). We hypothesized that the diagnosis will be more accurate when combined with the patch test. It is interesting that Thomas et al (10) found that the lymphocyte hypersensitivity disappeared after implant removal, but the mechanism is still unclear. We recommend performing the test before the implant metal material is removed.

For extensive application of internal fixation materials, it is necessary to take measures to avoid allergic reactions to Ti. First, we should ask patients whether they are allergic to metallic materials such as watches, rings, or coins. In a randomized control study, Pigatto et al (25) demonstrated a prevalence of metal allergy among patients with multiple chemical sensitivities. Therefore, a patch test is generally recommended before surgery for patients with a reported history of metal sensitivity. Second, substitute materials, such as a ceramic implant, could be used in patients for whom a hypersensitivity to metal is highly suspected (27). Third, patients should be informed of the possibility of an allergic reaction, because it is important that patients understand the necessity of reporting symptoms after surgery. Fourth, in cases of Ti hypersensitivity related to internal fixation failure, surgical revision ultimately could be required, with replacement using an implant that does not contain Ti or another metal material to which the patient is less sensitive.

In conclusion, Ti allergy should be suspected when a patient presents with fever, delayed wound healing, dermatitis, or impaired

Table

Clinical data from 16 patients with titanium allergy reported in published studies

Investigator	Patient Characteristics		Allergy History	Operation Site	Symptoms				Patch Test	LTT	Histologic Findings	Symptom Improvement After Implant Removal
	Gender	Age (y)			Fever	PWH	Pain	Dermatitis				
Bernard and Baeck (12), 2013	Female	8	Metal	Oral cavity	No	No	No	Yes	+	ND	ND	Yes
Oliva et al (15), 2010	Female	38	Metal	Oral cavity	No	No	No	Yes	+	+	L	Yes
Thomas et al (10), 2006	Male	35	Metal	Hand fracture	No	No	No	Yes	+	+	L and M	Yes
Thomas et al (13), 2011	Female	59	Metal	Ankle fracture	No	Yes	Yes	Yes	+	+	L and M	Yes
Sakamoto et al (11), 2014	Male	23	Metal	Pectus excavatum	Yes	Yes	No	No	—	+	ND	Steroid therapy
Sakamoto et al (11), 2014	Male	17	Metal	Pectus excavatum	Yes	Yes	No	No	—	+	ND	Steroid therapy
Oluwajana and Walmsley (4), 2012	Male	63	Metal	Oral cavity	No	Yes	No	No	+	ND	ND	Yes
Bircher and Stern (16), 2001	Female	66	Metal	None	No	No	No	Yes	+	ND	ND	Yes
Lim et al (17), 2012	Female	70	None	Oral cavity	No	No	Yes	Yes	+	ND	ND	Yes
Nawaz and Wall (18), 2006	Male	19	Metal	Spine	Yes	Yes	No	Yes	+	ND	ND	Yes
Syburra and Schurr (14), 2009	Male	86	None	Heart	No	Yes	No	No	—	ND	M	Yes
Hettige and Norris (19), 2012	Female	64	None	Skull	No	No	Yes	No	+	+	ND	Yes
Egusa et al (20), 2008	Female	50	None	Oral cavity	No	No	No	Yes	+	+	ND	Yes
Connolly et al (22), 2001	Male	39	None	Hand	No	No	No	Yes	+	ND	ND	Yes
High et al (21), 2006	Male	68	Metal	Ear	No	No	Yes	Yes	+	ND	M	Yes
Present patient	Male	18	Metal	Foot	Yes	No	No	No	+	ND	M	Yes
Total	9 Males, 7 females	45 ± 23	11/16	—	4/16	6/16	4/16	10/16	13/16	7/7	5/5	16/16

Abbreviations: L, lymphocyte; LTT, lymphocyte transformation test; M, macrophage; ND, not done; PWH, poor wound healing.

fracture healing after implantation of a Ti device in the absence of any other cause. A patch test for Ti or the lymphocyte transformation test might offer guidance for the clinical diagnosis of Ti allergy. In cases of Ti allergy, the Ti materials should be removed completely once the bone has healed or sooner if severe hypersensitivity has occurred. Finally, we also recommend that it should be a routine to ask patients about their history of metal allergies before surgery, with the aim of preventing an allergic reaction to Ti.

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