Allergic Reaction to Vanadium Causes a Diffuse Eczematous Eruption and Titanium Alloy Orthopedic Implant Failure

Sally Engelhart, BA; Robert J. Segal, MD

PRACTICE **POINTS**

- Vanadium may be an underrecognized allergen in patients with metal implants.
- Consider vanadium allergy in those with surgical implants and signs of hypersensitivity reaction.
- Test for allergy with vanadium trichloride.
- Niobium is an alternative for implants in vanadium-allergic patients.

Allergy as a cause of adverse outcomes in patients with implanted orthopedic hardware is controversial. Allergy to titanium-based implants has not been well researched, as titanium is traditionally thought to be inert. We highlight the case of a patient who developed systemic dermatitis and implant failure after surgical placement of a titanium alloy (Ti6Al4V) plate in the left foot. The hardware was removed and the eruption cleared in the following weeks. The plate and screws were submitted for metal analysis. The elemental composition of both the plate and screws included 3 major elements—titanium, aluminum, and vanadium—as well as trace elements. Metal analysis revealed that the plate and screws had different microstructures, and electrochemical studies demonstrated that galvanic corrosion could have occurred between the plate and screws due to their different microstructures, contributing to the release of vanadium in vivo. The patient was patch tested with several metals including components of the implant and had a positive patch test reaction only to vanadium trichloride. These findings support a diagnosis of vanadium allergy and suggests that clinicians should consider including vanadium when patch testing patients with a suspected allergic reaction to vanadium-containing implants.

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Metal allergy in patients with orthopedic implants can cause serious problems including dermatitis and implant failure.[1] As life expectancy increases, the general population ages, and more metallic orthopedic implants are placed,[2] allergy to these implants is expected to be a problem of greater significance. Uncertainty remains regarding best practice for patients with suspected metal implant allergy.[1] The major questions are: Who should be tested? When should they be tested? What are the optimal tests to diagnose metal allergy?[3-8]

We report the case of a patient with vanadium allergy who developed a diffuse eczematous

Ms. Engelhart is from Harvard Medical School, Boston, Massachusetts. Dr. Segal is from the Division of Dermatology, University of Arizona, Tucson.
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Correspondence: Robert J. Segal, MD, Division of Dermatology, University of Arizona, 3838 N Campbell Ave, Tucson, AZ 85719 (rsegal@deptofmed.arizona.edu).

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dermatitis and implant failure after receiving a vanadium-containing titanium alloy orthopedic implant in the left foot. This case is remarkable because hypersensitivity reactions to titanium-based hardware are rare, as they traditionally have not been thought to provoke allergic reactions.[9]

Case Report

A 62-year-old woman who was otherwise healthy presented with an eruption of more than 80 pruritic, nummular, eczematous plaques on the arms, legs, back, and buttocks of 3 weeks' duration (Figure 1). She had a history of allergy to metal used in costume jewelry. Six weeks prior, the patient underwent implantation of a titanium alloy plate in the left foot for surgical repair of painful deforming osteoarthritis. A radiograph of the foot showed appropriate placement. According to the manufacturer, the plate was composed of the compound Ti6Al4V, which contained 90% titanium, 6% aluminum, and 4% vanadium. The lesions developed on the skin close to but not directly over the surgical site.

A punch biopsy of one of the lesions on the shoulder showed lymphoeosinophilic spongiosis consistent with a delayed hypersensitivity reaction (Figure 2). There was mild clinical improvement of the eruption with topical steroids. A course of prednisone for systemic effect resulted in clearing of the eruption, but it promptly recurred on cessation of the steroids. The patient was then patch tested using the North American 80 Comprehensive Series, with an additional 59 common textile, shampoo, fragrance, and several metal allergens, all of which were negative.

Figure 1. Vanadium allergy with eczematous plaques on the left leg (A) and right thigh (B).

The patient had persistent pain and swelling at the surgical site, and radiographs taken postoperatively at 6 months showed implant failure (Figure 3). The hardware was surgically removed 8 months after implantation (Figure 4) and the plate and screws were submitted to the Institute for Mineral Resources Geosciences LA-ICP-MS Facility and the Lunar and Planetary Laboratory at the University of Arizona (Tucson, Arizona) for analysis. The skin lesions began to improve days after the hardware was removed and the eruption cleared over the following 3 weeks with no additional treatment.

After the hardware was removed, it was analyzed to determine the elemental composition of the plate and screws, and the patient was then patch tested with the major metal components of the implant: aluminum chloride hexahydrate 2.0% pet, elemental titanium 10.0% pet, titanium dioxide 10.0% pet, titanium (III) nitride 5.0% pet, titanium (III) oxalate

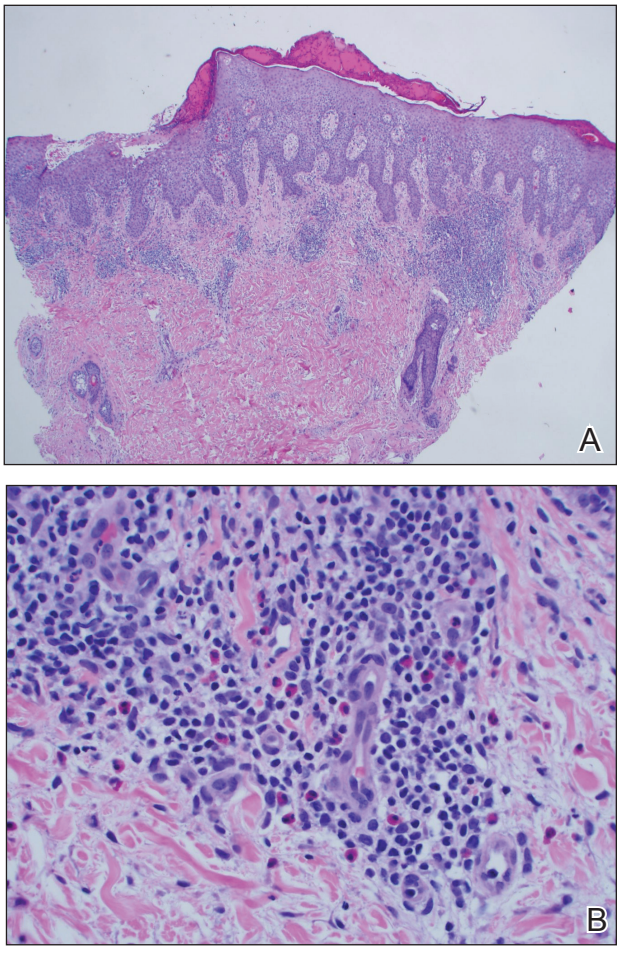

Figure 2. Vanadium allergy histopathology from a punch biopsy of a lesion showing lymphoeosinophilic spongiosis (A) and numerous eosinophils (B)(H&E, original magnifications ×10 and ×40). Photographs courtesy of Keliegh Culpepper, MD (Tucson, Arizona).

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decahydrate 5.0% pet, elemental vanadium 5.0% pet, and vanadium (III) chloride 1.0% pet. She demonstrated a 1+ reaction (erythema and induration) to vanadium trichloride at 72 and 96 hours.

The plate and screws removed from the patient were sterilized and submitted for analysis. Electron microprobe analysis confirmed that the major elemental composition of the plate and screws essentially matched the manufacturer's listing (Table 1). The trace elements were determined using laser ablative inductively coupled mass spectroscopy, which demonstrated that the screws were of different metal composition from the plate (Table 2). Electron microprobe analysis also was used to determine the microstructure of the plate and screws. The plate had 2 distinct phases consisting of a titanium-aluminum phase and a vanadium phase, whereas the screw was much more homogeneous. Basic electrochemical studies were performed in a salt solution replicating the tissue of the foot. These studies showed that galvanic corrosion could have occurred between the plate and screws due to the differences of composition.

Table 1.

Major Components Determined by Electron Microprobe Analysis

Metal	Plate, wt/wt	Screws, wt/wt
Titanium	90.005	90.260
Aluminum	6.243	6.348
Vanadium	4.025	3.829

Comment

Titanium is an attractive metal to use in orthopedic implants. It has a high strength-to-weight ratio, a low modulus of elasticity, and good resistance to corrosion. Titanium can be categorized as either commercially pure titanium (cp-Ti) or a titanium alloy. Colloquially, both cp-Ti and titanium alloys are often referred to simply as titanium, but the distinction is important when it comes to medical implants and devices. Commercially pure titanium is more than 99% pure titanium, but up to 1% of its volume can be comprised of impurities.[10] In titanium alloys, the alloy elements are intentionally added to create a material with optimal properties. The 2 most common types of titanium that are used for orthopedic implants are cp-Ti and Ti6Al4V, a titanium alloy containing approximately 90% titanium, 6% aluminum, and 4% vanadium. Similar to cp-Ti, titanium alloys also can contain impurities such as aluminum, beryllium, cobalt, chromium, iron, nickel, and palladium, among many others. Although these impurities often are considered negligible from a metallurgy perspective, as they do not change the

Figure 3. Radiograph of the left foot prior to removal of the implant showed implant failure due to vanadium allergy.

Figure 4. Surgical hardware containing vanadium after removal from a patient who demonstrated an allergic reaction.

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Table 2.

Trace Elements Determined by Laser Ablative Inductively Coupled Mass Spectroscopy

Element	Plate, ppm	Screws, ppm
Silicon	1739.000	2497.000
Iron	1741.834	1857.000
Sulfur	309.533	686.489
Nickel	89.860	107.200
Chromium	152.800	80.373
Zinc	36.968	46.310
Copper	34.570	42.640
Molybdenum	5.680	32.090
Tin	3.727	25.890
Arsenic	5.201	24.980
Phosphorus	11.110	18.887
Zirconium	5.514	16.180
Niobium	4.654	11.690
Gallium	8.079	9.400
Tungsten	0.457	6.796
Cobalt	3.202	5.098
Manganese	32.640	3.936
Lead	0.278	0.764
Tantalum	0.224	0.424
Hafnium	0.126	0.156
Scandium	0.094	0.087
Uranium	0.048	0.064
Thorium	0.047	0.011

properties of the material, these trace elements may be present in large enough quantities to cause hypersensitivity reactions.[11]

Several weeks after implantation of a titanium alloy metal plate in the left foot, a widespread eczematous eruption developed in our patient who had no prior skin disease. The eruption was steroid responsive but did not clear until the plate was removed. Detailed metallurgy analysis confirmed that vanadium was present and was not homogeneously distributed in the plate. The plate also was different in composition from the screws. Additional studies showed that galvanic corrosion between the plate and the chemically different screws might have contributed to the release of vanadium in the tissue.

Vanadium is known to be allergenic, especially in the presence of implant failure.[12,13] In our patient, patch testing with more than 100 allergens was negative, except for vanadium trichloride 1%. Our patient's presentation strongly suggested that she developed a vanadium allergy manifesting as systemic allergic contact dermatitis. She demonstrated no history of skin disease, a widespread eczematous eruption after exposure, histology consistent with systemic contact allergy, a positive patch test to vanadium, and clearance of the eruption on removal of the antigen, which have been proposed as objective criteria that support a diagnosis of metal implant allergy.[14] She refused our suggestion to reimplant a portion of the remaining plate under the skin without screws and monitor for recurrence of the eruption. She did not have a lesion overlying the surgical site, but she did develop lesions near the surgical scar. The literature indicates that cutaneous manifestations of allergy to metallic implants can be both localized and generalized.[14]

Although reports are rare, other researchers have found vanadium allergy in patients with metal orthopedic implants.[5,12,13,15] The scarcity of literature on vanadium allergy seems to suggest that it is a rare entity, but we believe that it may be more common. Vanadium allergy may be underdiagnosed because it is not a standard patch test allergen. Furthermore, many of those who do choose to test for it use what we believe to be ineffective formulas of vanadium when patch testing patients. Our patient demonstrated a positive patch test reaction only to vanadium trichloride and not to pure vanadium, which is consistent with the small number of other studies that investigated vanadium allergy.[5,12,13,15] We believe that vanadium trichloride is more water soluble than elemental vanadium,[16] and thus more likely to identify true vanadium allergy than other test materials.

Although reports of vanadium allergy in patients with metal implants are rare in the medical literature, the material science literature clearly states that vanadium is toxic and that vanadium-containing implants are problematic.[17-20] It has been shown that although Ti6Al4V implants are considered highly resistant to corrosion, they will slowly and continuously corrode in a physiologic environment and release titanium, aluminum, and vanadium ions, both systemically and into the peri-implant space.[11] To address these problems with vanadium, vanadium-free titanium alloys such as Ti6Al7Nb have specifically been developed for medical use to address the problems caused by vanadium. Ti6Al7Nb contains 7% niobium rather than vanadium and appears to have some improved qualities in surgical implants.[17]

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There is still a great deal of uncertainty around metal implant allergy. Allergy to metal implants can be difficult to diagnose for several reasons. Some metals are not conducive to patch testing because of their low bioavailability. Additionally, we lack validated and standardized patch test formulas for metals that can be diagnosed by patch testing. Furthermore, there is uncertainty about what to do after allergy to a metal implant is diagnosed; in some cases (eg, with more extensive procedures such as total joint replacements), removal or replacement of the implant may be associated with increased risk of further complications.[6,21]

Conclusion

We suggest that manufacturers consider vanadium-free alloys such as Ti7Al6Nb, which contains niobium instead of vanadium, in their surgical implants,[22] and if surgeons have a choice, they should consider using titanium implants with niobium rather than vanadium.[10] We suggest that clinicians consider vanadium allergy in patients with Ti6Al4V surgical implants and signs of a hypersensitivity reaction, and include vanadium trichloride 1% when patch testing.

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