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# Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness *in vitro*: case report and review of the literature

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There are very few reports on hypersensitivity reactions in association with titanium-based materials so that the existence of allergy to titanium is still put in question. We report on a patient in whom impaired fracture healing and eczema localized to the perioperative area developed upon titanium-based osteosynthesis. Patch testing gave no reactions to titanium nor to nickel, chromium, or cobalt. However, in the lymphocyte transformation test, the patient's lymphocytes showed markedly enhanced proliferation *in vitro* to titanium. After removal of the titanium material, fracture healing was achieved and the eczema cleared. Parallel to this, *in vitro* hyperreactivity to titanium disappeared. Although contact allergic reactions to titanium have been very rarely reported, these findings support a diagnosis of titanium allergy in our patient.

*Key words:* allergy; eczema; fracture; lymphocyte transformation test; osteosynthesis; titanium; T lymphocytes. © Blackwell Munksgaard, 2006.

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Metallic alloys are used in large number for osteosynthesis and long-term implants. In association with stainless-steel-based and cobalt-based materials, contact hypersensitivity reactions have been described and were mostly attributed to chromium, cobalt, nickel, and occasionally to molybdenum. In contrast, due to its excellent biocompatibility (1), titanium is not considered to provoke allergic reactions. However, in view of the few reports on contact dermatitis or granulomatous reactions to titanium upon its use in pace-makers or implants (2–4), the discussion about 'titanium allergy' is still ongoing.

## Patients and Methods

A 35-year-old male was referred for evaluation of suspected hypersensitivity to implant materials. He presented with a several months history of hand eczema and failure of healing of a hand fracture. Eczema had started within few weeks after an osteosynthesis of right metacarpal fracture by use of a pure titanium miniplate and screws. The patient had gradually developed itching, ery-

thema, and scaling of the right hand together with a vesiculopapular eruption on several fingers, mainly on their ventral parts. Over the next weeks, lesions extended also to the left hand (Fig. 1) and proximal part of the forearms. There was a history of seasonal rhinoconjunctivitis and asthma but not of previous contact or atopic eczema or hypersensitivity reactions to metals. The patient was otherwise healthy. Under the diagnosis of contact dermatitis, a corticosteroid-containing cream was prescribed and patch testing was planned.

*Patch testing* was performed according to the guidelines of the German Contact Dermatitis Research Group on the patient's upper back with the following series: standard, vehicles, disinfectants, and preservatives. In addition, TiO<sub>2</sub> was tested. Evaluation of the reactions was done after 2, 3, and 7 days. Removed implant materials were not available for subsequent, additional testing.

For the *lymphocyte transformation test*, peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood samples of the patient and a healthy control, as well as of 49 additional controls over the next months. Within



Fig. 1. Hand eczema upon titanium-based osteosynthesis.

these 50 control persons (28 females, 22 males, aged 19–82 years), 10 were nickel allergic. Because the patient volunteered over the next months several times as blood donor, blood samples could also be evaluated at the time of removal of osteosynthesis material and after disappearance of symptoms. PBMC were obtained by standard Ficoll–Hypaque<sup>®</sup> (Pharmacia, Uppsala, Sweden) density gradient centrifugation and were resuspended at  $10^6$  cells/ml in an enriched RPMI1640 culture medium (Sigma, Deisenhofen, Germany) supplemented with 10% human AB serum (CC Pro, Neustadt, Germany). Stimulation assays were done in triplicate in 96-well microtiter plates (Greiner, Frickenhausen, Germany;  $2 \times 10^5$  cells/well). Culture was done in the presence of medium alone or in the presence of phytohaemagglutinin (Biochrom, Berlin, Germany; 2  $\mu\text{g}/\text{ml}$ ), tetanus toxoid (TT; kindly provided by Chiron Behring, Marburg, Germany; 5  $\mu\text{g}/\text{ml}$ ),  $\text{TiO}_2$  (Sigma T-8141, Germany; 8 and 0.8  $\mu\text{g}/\text{ml}$ ), and  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  (Sigma N-4882, Germany; 26 and 2.6  $\mu\text{g}/\text{ml}$ ). After 5 days of culture, tritiated thymidine was added, and incorporated radioactivity was determined 16 hr later by scintillation counting. Results were expressed in relation to medium control cultures as stimulation index (SI).

### Results

Patch testing gave no reactions. At the first examination, the patient's lymphocytes showed enhanced proliferative response to  $\text{TiO}_2$  (SI = 3.35 at 8  $\mu\text{g}/\text{ml}$ , SI = 3.16 at 0.8  $\mu\text{g}/\text{ml}$ ). In accordance with recent immunization, the patient's TT-specific proliferation was also enhanced (SI = 83.44). In the blood sample taken shortly after removal of osteosynthesis material, the reactivity of the patient's PBMC to  $\text{TiO}_2$  was again markedly elevated (SI = 16.16 at 8  $\mu\text{g}/\text{ml}$ , SI = 5.74 at 0.8  $\mu\text{g}/\text{ml}$ ) compared to controls (SI =  $0.95 \pm$

0.39 at 8  $\mu\text{g}/\text{ml}$ , SI =  $1.06 \pm 0.43$  at 0.8  $\mu\text{g}/\text{ml}$ ) (Fig. 2a). Due to the high reactivity of the patient's PBMC to  $\text{TiO}_2$ , we had performed control experiments in 10 nickel allergic and 40 non-allergic blood donors. However, no such titanium hyperreactivity was observed. T-cellular reactivity to nickel was seen (SI =  $6.42 \pm 4.67$  at 26  $\mu\text{g}/\text{ml}$ ) in the 10 nickel allergic blood donors but not in the patient. The time-course of the reactivity of the patient's PBMC to  $\text{TiO}_2$  reflected a probable booster in the perioperative period (osteosynthesis material was removed because of absence of fracture healing) and furthermore also showed subsequent decline (Fig. 2b). In parallel, the eczema gradually resolved under concomitant external therapy, and prompt fracture healing was achieved.

### Discussion

Titanium and its alloys are used for medical purpose like osteosynthesis, arthroplasty, pacemaker encasing, orthodontical wires, or in daily-use articles like spectacle frames. At a composition of 50% nickel and 50% titanium, the material

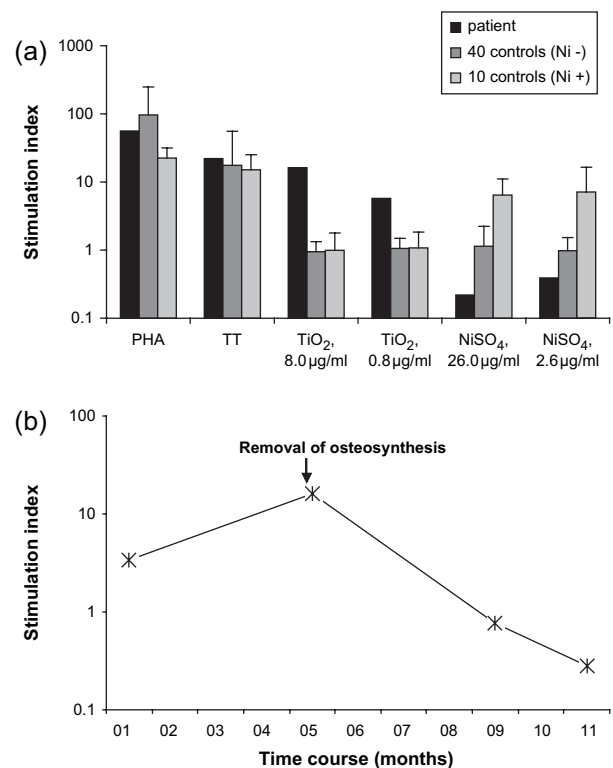


Fig. 2. (a) Proliferative response indicated as stimulation index (SI) of peripheral blood leucocytes from the patient, 10 nickel allergic and 40 non-allergic individuals to titanium dioxide ( $\text{TiO}_2$ ,  $10^{-4}\text{M}$  = 8  $\mu\text{g}/\text{ml}$  and  $10^{-5}\text{M}$  = 0.8  $\mu\text{g}/\text{ml}$ ), nickel sulfate ( $\text{NiSO}_4$ ,  $10^{-4}\text{M}$  = 26  $\mu\text{g}/\text{ml}$ ,  $10^{-5}\text{M}$  = 2.6  $\mu\text{g}/\text{ml}$ ), or TT (5  $\mu\text{g}/\text{ml}$ ). (b) Time-course of reactivity of the patient's peripheral blood mononuclear cells to  $\text{TiO}_2$ . PHA, phytohaemagglutinin; TT, tetanus toxoid.

nitinol can be folded but returns at given temperatures to its original form without damage. This shape memory effect is used for spectacle frames, flexible tubes, intravascular stents, or orthodontic wires. When exposing the latter to an acidic environment, a substantial nickel and titanium release can be observed (5). However, even 'pure' titanium materials used for implant alloys may contain nickel as result of the production process. Standard titanium alloys (TiAl6Nb7, TiAl6V4) and pure titanium discs supplied by five different titanium manufactures were shown to contain up to 0.034 wt % nickel, with iodide-titanium having the lowest percentage (0.002 wt %) (6). Here, the nickel atoms are reported to be in solid solution in the titanium lattice. Suspected delayed-type hypersensitivity reactions to titanium were first reported as pacemaker dermatitis, but their existence is still put in question due to not always complete allergological work up and insufficient patch test preparations. In 1984, Peters et al. described a patient who had repeatedly cardiac pacemakers implanted and removed because pruritus, redness, and swelling of the skin overlying the pacemaker had developed within several weeks after insertion. These reactions were interpreted as contact sensitivity to the pure titanium encasing of the pacemaker, as there was a ++ patch test reaction to a thin square of metallic titanium applied with artificial sweat (7). In addition, a + reaction to nickel was found in this patient. One year later, Verbov (2) reported on a similar patient in whom disturbed wound healing and local sterile discharge had developed after each of 4 consecutive insertions of a titanium-encased pacemaker. Histology showed granulomatous reaction, but no patch testing to titanium materials had been performed. Granulomatous dermatitis in association with a titanium-containing pacemaker was also observed both by Brun and Hunziker (8) and by Viraben et al. (3). Viraben and colleagues interpreted their case of pacemaker dermatitis – with the restriction of unsuccessful testing to titanium dioxide and a square of the metallic pacemaker base – as granulomatous hyperreactivity to titanium. In view of unsatisfying patch test preparations, Yamauchi and colleagues chose a different approach to evaluate dermatitis provoked by a titanium pacemaker. Eluates from the titanium encasing were prepared by coincubating it with the patient's serum and tested intracutaneously on the patient's forearm. A reaction to it at D2 together with an *in vitro* lymphocyte hyperreactivity (SI = 2.35) to the eluate was interpreted as titanium sensitivity in this patient (9). With regard to orthopaedic implants, Lalor et al. (4) described a series of

patients with failed titanium-based total hip replacement, in whom periimplantar tissue showed lymphohistiocytic inflammation. The authors unsuccessfully tried to detect titanium sensitivity by testing with titanium salicylate, titanium tannate, titanium dioxide, and titanium peroxide at different concentrations. However, some patients reacted to an ointment containing a mixture of those components. Gingival hyperplasia adjacent to intraoral titanium implants (10) or persistent irritation around titanium osteosynthesis material (11) has been described, but no allergological testings were done in those patients. These different case reports all reflect the difficulty in evaluating suspected titanium hypersensitivity, as no standardized valid patch test preparation exists for this. Nickel impurities may further act as alternative elicitors of hypersensitivity. Occasionally, patients may present with hypersensitivity reactions to other than the suspected titanium component. Romaguera and Grimalt reported on a patient with a 3+ reaction to epoxy resins who had received a pacemaker and subsequently developed local eczema (12). In another patient, the onset of generalized eczema was linked to his pacemaker. Here, stainless steel screws were exposed to surrounding tissue and contact allergy to nickel, chromium, and cobalt was found (13). Furthermore, in materials claimed to be made of titanium, alternative allergy elicitors may be found, like palladium in titanium spectacle frames (14) or nickel in frames erroneously declared as being made of titanium (15). In our patient, the osteosynthesis miniplate and screws were made of pure titanium, as indicated by the manufacturer. No patch test reactivity was found to titanium dioxide. By evaluating the T-lymphocyte reactivity *in vitro*, as done to assess sensitization in the case of drug or nickel hypersensitivity (16–18), we, however, found a marked hyperreactivity of the patient's cells to titanium. Because this vanished after removal of the titanium material and was paralleled by disappearance of the eczema, we believe that the patient's impaired fracture healing and eczema have been caused by titanium hypersensitivity. With regard to the time-course of contact allergy, usually a long-lasting T-cell memory is postulated. In the case of nickel, a continuous external exposure and also systemic contact by daily alimentary uptake would maintain T-cellular responsiveness in Lymphocyte Transformation Test (LTT). In our patient, the source of titanium exposure, e.g. implant material, was removed and thus absence of further exposure could be an explanation for the unusually rapid decay of the patient's *in vitro* reactivity to titanium. With regard to influence of tetanus immunization

upon LTT reactivity to contact allergens, respective studies are not known to the authors. However, nickel reactivity remains unaffected in nickel allergic individuals with high concomitant tetanus reactivity in LTT (own observation). In conclusion, the case reports and studies published so far reflect the diagnostic uncertainties in evaluating suspected titanium hyperreactivity and show that this condition is very rare. Perhaps other titanium salts, as suggested by Basketter et al.(19) and Okamura et al.(20), may prove useful for testing in case of suspected titanium allergy.

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