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2-Minuten-Info

Titan-Unverträglichkeit

Allergische und immunologische Ursachen beachten !

Titan zeichnet sich durch ein hervorragendes Korrosionsverhalten aus und hat dadurch eine im Vergleich zu anderen Metallen gute immunologische Verträglichkeit. Allerdings wissen sowohl Orthopäden (Gelenkersatz) als auch Zahnmediziner (Implantation), dass bei einigen Patienten die Implantate unerwünschte Entzündungserscheinungen induzieren, die nicht selten zur fehlenden knöchernen Integration führen.

Bis heute sind die verantwortlichen Mechanismen der „Titan-Sensibilisierung" nur teilweise bekannt. Wir wissen, dass echte zelluläre Typ IV-Sensibilisierungen, wie wir sie im LTT finden, nur die „Spitze des Eisberges" darstellen. Selbst die seltenen positiven Reaktionen im LTT unterscheiden sich immunologisch eindeutig von denen klassischer Kontaktallergene wie Nickel, Palladium und Gold. Eine Ursache ist, dass ionisches Titan im mittleren pH-Bereich unmittelbar nach Freisetzung oxidiert wird.
Unsere Erfahrung, dass die LTT-Testung auf natives Implantatmaterial (Titan-Werkstoffprobe) deutlich reproduzierbarere Ergebnisse liefert, ist wahrscheinlich auf den Gehalt anderer Metalle wie Nickel, Aluminium oder Vanadium zurückzuführen. Im LTT müssen diese Metalle deshalb immer mitgetestet werden (siehe Inhalte des Profils LTT-Titan).

Die häufigere Ursache der „Titan-Sensibilisierung" ist die überschießende proinflammatorische Reaktivität der Immunzellen, die bei einigen Patienten nach Kontakt mit Titanpartikeln auftritt. Diese beruht nicht auf der Anwesenheit Titan-spezifischer Lymphozyten (daher LTT negative Ergebnisse) sondern auf einer erhöhten Entzündungsbereitschaft unspezifischer Immunzellen (Gewebemakrophagen, Monozyten) nach Kontakt mit partikulärem Debris (Titanpartikel). Es ist bekannt, dass derartige Partikel (Durchmesser 1-10 µm) immer in die Umgebung von Implantaten abgegeben werden und bei entsprechender hyperinflammatorischer Disposition eine Entzündung verursachen können.
Der Titan-Stimulationstest (siehe auch beiliegende Publikation aus der Zeitschrift Nature) wurde für diese Fragestellung entwickelt und validiert (siehe unten).

Bei der Diagnostik einer Titan-Überempfindlichkeit sollten immer beide möglichen ursächlichen Mechanismen analysiert werden:

1. Nachweis einer Sensibilisierung auf Implantatmetalle
LTT-Titan (Profil enthält neben Titan auch Nickel, Vanadium und Aluminium)
oder
LTT-Nativmaterial (falls Materialprobe vorhanden).

2. Nachweis einer hyperinflammatorischen Zytokinantwort auf Titanoxid.
Messung von TNF-α und IFN-γ nach Stimulation von Blutzellen (Monozyten) des Patienten mit Titan(oxid)partikeln.

Literaturservice- und Antwortfax – siehe Rückseite

Kurz und knapp

LTT-Titan (Profil)
(Titan, Nickel, Vanadium, Aluminium)

Untersuchungsmaterial:
20 ml Heparinblut + 5 ml Serum oder Vollblut
(bitte Abnahmeset bei uns kostenfrei anfordern)

Abrechnung:
Privat: 103,21 €
Selbstzahler: 89,75 €

oder
als Alternative zum LTT-Titan
(wenn Materialprobe vorhanden)

LTT-Nativmaterial (Titanprobe)

Untersuchungsmaterial:
20 ml Heparinblut + 5 ml Serum oder Vollblut

Abrechnung:
Privat: 65,01 €
Selbstzahler: 56,53 €

+

Titan-Stimulationstest (Zytokintest)

Untersuchungsmaterial:
10 ml Heparinblut

Abrechnung:
Privat: 46,92 €
Selbstzahler: 40, 80 €

Eine EBM-Abrechenbarkeit (Gesetzliche Krankenkasse) ist für die genannten Analysen leider nicht gegeben.

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Implant-related inflammatory arthritis

Thomas Dörner*, Judith Haas, Christoph Loddenkemper, Volker von Baehr and Abdulgabar Salama

SUMMARY

Background A 54-year-old woman presented with myalgia and arthralgia predominantly in the knees and small joints of the hands and feet with morning stiffness lasting for at least 2 h. The patient had received a wrought titanium 6-aluminium 4-vanadium alloy C cage implant 1.5 years previously, following a severe disc prolapse. No signs of rheumatic disease were evident before the C cage was implanted.

Investigations Physical examination, radiography, skin and muscle biopsies, serology tests, white blood cell count, HLA genotyping, tumor necrosis factor release assay, skin patch test, lymphocyte transformation test.

Diagnosis Implant-related inflammatory arthritis.

Management Combination therapy with corticosteroids, disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory drugs, and replacement of the titanium cage with a polyetherketone cage.

KEYWORDS arthritis, hypersensitivity, implant, titanium

CME

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THE CASE

A 54-year-old woman was admitted with myalgia and arthralgia predominantly in the knees and small joints of the hands and feet, with morning stiffness lasting at least 2 h. The patient had received a wrought titanium 6-aluminium 4-vanadium alloy C cage implant (ISO standard 5832-3:1996) 1.5 years previously in the course of ventral C5/C6 discectomy and bisegmental spondylosyndesis, because of narrowing of the spinal canal following a severe disc prolapse. The patient was taking the antihypertensive drug amlodipine 5 mg/day and L-thyroxine 125 µg/day for pre-existing conditions. Prior to the operation, the patient had felt well and had no signs of rheumatic disease or allergic diathesis. After the C cage was implanted, she increasingly developed nonspecific arthralgias, moderately swollen metacarpal and proximal interphalangeal finger joints, periarthritis humeroscapularis, painful knee and hip joints, and muscle stiffness, leading to an overall reduction of her daily living activities.

Physical examination revealed swollen and painful interphalangeal joints, and a reduced range of movement in her arms and legs. Radiography of the joints and WHOLE-BODY SKELETAL SCINTIGRAMS did not reveal any inflammatory joint changes, and the C cage implant appeared to be intact. A biopsy of skin and muscle revealed nonspecific perivascular accumulation of lymphocytes and nonspecific signs of inflammation (Figure 1). Serologic tests showed that the level of C-reactive protein was slightly elevated at 5.2 mg/dl (normal level <5.0 mg/dl), rheumatoid factor was present at a concentration of 24.8 U/ml (normal value <20 U/ml) and antinuclear antibodies were present at a titer of 1:100 (normal ratio 1:50). There was a granular nuclear staining pattern on conventional HEp-2 cells, but no identifiable antiextractable nuclear antigen specificity. The

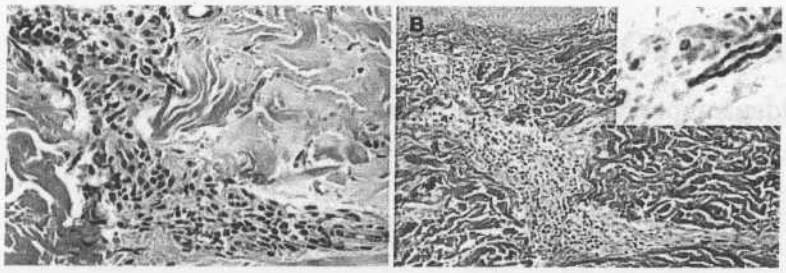

Figure 1 Skin and muscle biopsy. **(A)** Lymphocytic vasculitis with a predominantly lymphocytic infiltrate, involving and surrounding the wall of a small vessel in the dermis (hematoxylin-eosin staining). **(B)** Immunohistochemistry showing the lymphocytic infiltration of the vessel wall and the swelling of the CD31+ endothelial cells (elastica van Gieson staining; streptavidin-biotin peroxidase method).

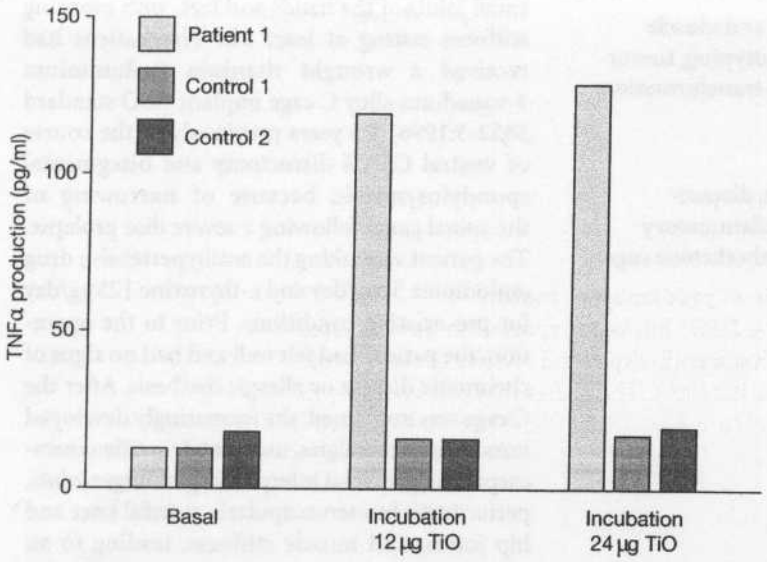

Figure 2 Tumor necrosis factor production after incubation of the patient's peripheral blood mononuclear cells with and without different concentrations of titanium dioxide, compared to controls.

GLOSSARY

WHOLE-BODY SKELETAL SCINTIGRAM
A scan of the complete skeleton that uses specific radionuclides to evaluate bone turnover

patient's white blood cell count was 10.31×10^9/l, with 76% neutrophils, 16.7% lymphocytes, and 3.2% monocytes. The patient's HLA genotype was determined to be *A*02, A*32, B*18, B*27, Bw4, Bw6, DRB1*03, DRB3*, DQB1*02.*

In order to characterize the underlying immune activation in this patient, tumor necrosis factor (TNF) production was measured after incubating peripheral blood mononuclear cells (PBMCs) from the patient with titanium dioxide (maximum particle diameter 0.5 µm) at concentrations of 12 µg/ml and 24 µg/ml, suspended in Roswell Park Memorial Institute (RPMI) control medium. The patient's PBMCs produced 118 pg/ml TNF in response to 12 µg/ml titanium dioxide and 127 pg/ml TNF in response to 24 µg/ml titanium dioxide; control samples incubated in RMPI control medium produced an average of 15.2 pg/ml and 25.4 pg/ml of TNF, respectively (Figure 2). A skin patch test using titanium dioxide was negative, which excluded the possibility of delayed-type hypersensitivity (DTH) against this compound. In a lymphocyte transformation test, purified lymphocytes from the patient were also exposed to different concentrations of titanium dioxide and did not show enhanced lymphocyte proliferation compared to healthy controls.

Initial treatment with methylprednisolone 1 g/day for 5 days led to some symptom relief, but further treatment with paracetamol, the nonsteroidal anti-inflammatory drugs ibuprofen, diclofenac and celecoxib, and the disease-modifying antirheumatic drug methotrexate, did not control the symptoms. Finally, prednisolone 30 mg/day in combination with leflunomide 20 mg/day controlled the symptoms of the arthritis, but none of the drugs prevented ongoing activity of the disease. After 8 months of uncontrolled disease, a diagnosis of inflammatory arthritis related to the C cage implant was suspected.

Subsequently, the patient underwent surgery to replace the initial C cage with a polyetherketone cage. The patient's joint and muscle complaints disappeared almost completely within 14 days of removal of the wrought titanium 6-aluminium 4-vanadium alloy implant, and the patient did not need any additional treatment apart from continued treatment with amlodipine and L-thyroxine. Furthermore, serology showed that the patient's levels of C-reactive protein, rheumatoid factor and antinuclear antibody titer had returned to normal levels. The patient is still doing very well clinically 7 months after explantation of the initial C cage, and is not suffering from arthralgias.

DISCUSSION OF DIAGNOSIS

After receiving a wrought titanium 6-aluminium 4-vanadium alloy implant, the patient, who had no previous history of rheumatic complaints, developed arthritis that was almost completely resistant to conventional treatment. The observation that the arthritic complaints occurred after implantation and disappeared following explantation supports the diagnosis of inflammatory arthritis related to the implant.

Metal sensitivity

As this case demonstrates, immune activation by an implant could have a key role in the development of arthritis. Implants have also been implicated in the development of allergic dermatitis, urticaria and vasculitis.[1] In studies of metal sensitivity, immune-system activation after implantation was seen either in response to the metallic implant itself or to particulate debris generated by the implant; metal particles are known to be released from miniplates into tissues.[1,2] The degradation products of metallic biomaterials include particulate wear debris, colloidal organometallic complexes, free metallic ions, inorganic metal salts or oxides, and precipitated organometallic storage forms.

Metal sensitivity can occur in patients with implants made of metals thought to be biocompatible.[1] Titanium, in contrast to beryllium, nickel, chromium and cobalt, has only occasionally been implicated in causing sensitization; however, titanium alloys often contain very low levels of nickel which can lead to allergic reactions.[3] In the present case, the implant contained wrought titanium 6-aluminium 4-vanadium, and therefore nickel contamination missed by patch testing[4] is an unlikely cause of the arthritis.

Macrophage activation

Previous reports have suggested that orthopedic implants can trigger a chronic inflammatory response in surrounding tissues, similar to those found in a DTH reaction. Hunt *et al.*[5] and Katou *et al.*[6] identified $CD4^+$ and $CD8^+$ lymphocyte infiltration in the tissue surrounding the implants, consistent with a chronic and sustained immune response to titanium, and Ungersboeck *et al.*,[7] similar to Lalor *et al.*,[8] found that patients with titanium bone plates symptomatic of a sensitivity reaction had significantly more lymphocytes and macrophages in the soft tissues surrounding the plate than asymptomatic patients. Testing for DTH is conducted *in vivo* by skin testing (patch testing or intradermal testing), but the test risks boosting existing hypersensitivities or active sensitization.

In our patient, muscle biopsy revealed perivascular accumulation of lymphocytes, consistent with a DTH reaction. Allergy to titanium, however, was unlikely to be the cause of the reaction because of titanium's rapid oxidation to titanium dioxide. The results of the patch test for titanium dioxide were negative and therefore excluded the likelihood of a DTH reaction to this compound. The patch test result was consistent with previous studies, where five patients with titanium hip-replacement failure had negative skin patch tests for titanium salt.[8,9] An alternative explanation for the arthritis, other than a DTH reaction, is that macrophages of a predisposed host can be rapidly activated by phagocytosis of debris from the implant that might lead to sustained TNF release, known to foster arthritis.

In the TNF-release assay, our patient demonstrated enhanced TNF production by PBMCs incubated with different concentrations of titanium dioxide 2 months prior to explantation, whereas there was no proliferation identified in the lymphocyte proliferation test. This is consistent with the notion that the macrophages of the patient were preactivated or conditioned to respond to chemically stable titanium dioxide leading to an enhanced release of TNF. Therefore, macrophage activation might play a greater role than classic DTH in patients with inflammation secondary to an implant.

Role of predisposing factors

HLA-DRB1 has been reported to be associated with susceptibility to and severity of rheumatoid arthritis (RA). The alleles that confer susceptibility to RA (*DRB1*0401, *0408, *0405, *0101, *0102, *1001,* and **1402*) contain a conserved sequence of amino acids in the third hypervariable region of the DRβ molecule. This 'shared epitope'[10] consisting of amino acids Arg72, Ala73 and Ala74, and modulated by the amino acids at positions 70 and 71 (known as the QKRAA amino-acid motif), is important for the susceptibility of RA.

HLA genotyping of our patient detected the *DRB1*0103* haplotype. The *DRB1*0103* allele with its different amino-acid sequence in this same region (DERAA) belongs to the so-called S1 group. This group has an overall frequency of occurrence of 24%, and confers a lower risk of RA. Although it remains speculative in this patient, the low genetic susceptibility associated with *HLA-DRB1*0103* might have prevented the development of a more characteristic RA-like picture after the occurrence of implant-induced arthritis.

An additional genetic marker detected in this patient was the MHC class I molecule HLA-B27, an established marker of susceptibility to spondylarthopathy. Although no firm conclusion

Competing interests
The authors declared they have no competing interests.

can be drawn, we believe that the genetic HLA class II haplotype of this patient might have contributed to the development of arthritis, a condition where TNF is of key importance. Since we found no evidence of DTH in this patient, this might relate to the associated TNF polymorphisms in this haplotype.

DISCUSSION OF TREATMENT OPTIONS

In the case of implant-related arthritis presented here, combination therapy with corticosteroids, disease-modifying antirheumatic drugs and non-steroidal anti-inflammatory drugs failed to produce a sufficient therapeutic response. Only long-term, intermediate dosage of prednisolone (30 mg/day) in combination with leflunomide (20 mg/day) was able to control the symptoms. Whether TNF blocking therapy might have been of benefit was not tested. Notably, removal of the titanium device led to the prompt and significant alleviation of arthritic complaints.

CONCLUSIONS

Clinicians should be aware of the possibility of implant-related immune activation when patients develop symptoms of arthritis after receiving implants. Diagnostic testing by TNF-release assay could be a diagnostic tool in these patients, although comprehensive studies are needed to test the validity of this method of diagnosis in broader populations. The arthritic complaints were alleviated in the case patient following removal of the implant.

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