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Titanium cutaneous metallosis after reverse total shoulder arthroplasty

Robert Garnier, MD[a,*], Joël Poupon, PharmD[b], Nouzha Djebrani-Oussedik, PharmD[b], Jérôme Langrand, MD[a]

[a]Centre antipoison de Paris, Fédération de toxicologie (FeTox), Hôpital Fernand-Widal, APHP, Paris, France
[b]Laboratoire de Toxicologie biologique, Fédération de toxicologie (FeTox), Hôpital Lariboisière, APHP, Paris, France

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Metallosis is the accumulation of metallic particulates and ions in the soft tissues surrounding a metallic implant. Mechanical abrasion of metallic joint prostheses generates particulate debris, which may be responsible for local inflammatory reaction with tissue discoloration, followed by aseptic soft tissue necrosis or masses (pseudotumors), as well as aseptic osteolysis and implant loosening.[14,16] In most cases, metallosis is confined to the joint capsule and periprosthetic tissues. However, rare cases of metal migration to the skin and skin discoloration have been reported.[1,3,5,7,9,20,28,31-33,37] Systemic metal toxicity is also a possible complication of extensive metallosis.[6]

Although uncommon, metallosis is not rare. It has been mostly reported after total hip arthroplasty, with an estimated risk of 1%-10%, accounting for three-quarters of all revision surgery.[14,16,17,24] The majority of reported cases concern metal-on-metal prostheses, but all types of implants can be involved. In the majority of published cases, cobalt is the main metal responsible for metallosis and occasionally for metal intoxication.

We report a case of metallosis with titanium skin discoloration after reverse total shoulder arthroplasty.

Case history

After a road accident causing a comminuted right proximal humerus fracture, a 64-year-old woman was treated with a humeral prosthesis. However, 10 months later, in the context of persistent pain and severe disability due to implant failure, the humeral component was explanted and replaced by a reverse total shoulder arthroplasty (RTSA). At revision, there was no evidence of deep tissue metallosis around the joint and/or the humeral prosthesis. Shoulder pain and disability persisted after this second operation and became increasingly severe over the following months. After 6 to 9 months, bluish-grey discoloration was observed on and around the operative scar and on the anterior aspect of the right shoulder, and subsequently, on the anterior surface of the right arm and the elbow.

The patient was referred to a dermatologist, who suspected allergic contact dermatitis, and performed patch-tests with chromium, cobalt, nickel, and methyl methacrylate, all of which gave negative results.

Serial radiographs and computed tomography showed progressive loosening of the humeral component with humeral osteolysis. Three years after the accident, a third surgical procedure was performed for humeral reconstruction with tibial allograft and RTSA replacement. At revision, extensive blue-greyish pigmentation was observed, not only involving the skin but also the deep tissues around the joint and the humeral prosthesis. All pigmented deep tissues were resected, but no histologic or toxicologic examinations were performed, and examination of the explanted components was also not reported.

Shoulder pain and disability were markedly improved after this last operation but did not resolve completely. Skin pigmentation, which was maximal before the third operation, neither progressed nor regressed.

Two years later, the patient was referred to our toxicology unit to investigate possible metal poisoning from the previous prosthesis components. She presented with blue-greyish discoloration of the right elbow and anterior aspect of the right shoulder and arm (Fig. 1). She still complained of moderate right shoulder pain with

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*Corresponding author: Robert Garnier, MD, Centre antipoison de Paris, Hôpital Fernand Widal, 200 rue du Faubourg Saint-Denis, 75010 Paris, France.
E-mail address: robert.garnier@aphp.fr (R. Garnier).

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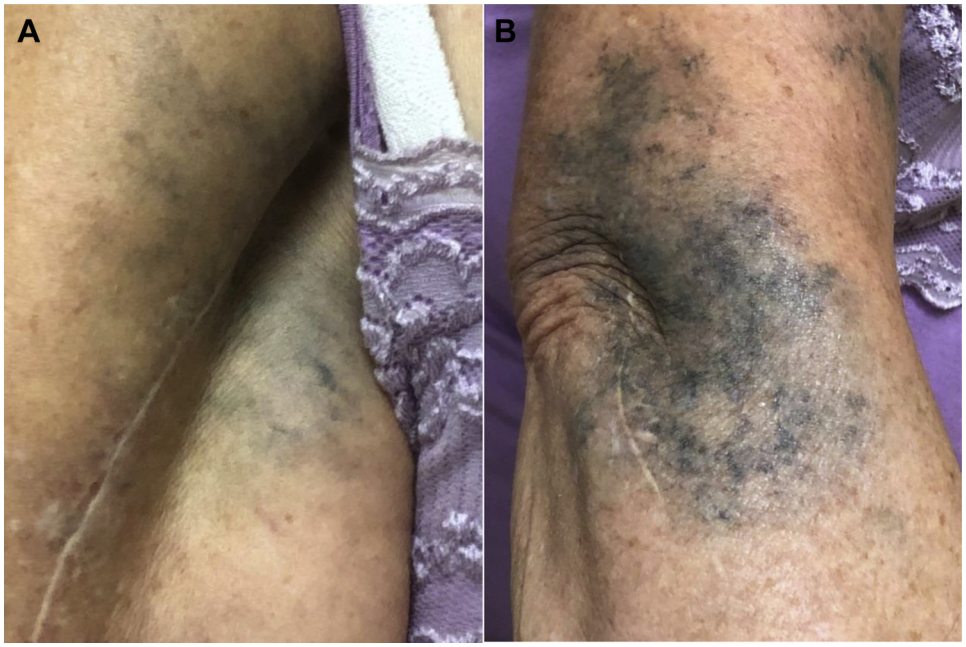

Figure 1 Skin discoloration of (**A**) scar and surrounding area, and (**B**) elbow, at 2-year follow-up after arthroplasty revision.

limited range of motion, and clinical examination showed limitation of active elevation and rotation.

Routine laboratory tests, including blood count, serum urea, and creatinine and liver function tests, yielded normal findings. As microalbuminuria, urine retinol-binding protein, and alpha-1-microglobulin were also in the normal ranges, there were no signs of glomerular or tubular renal impairment.

The composition of the metallic components of the previous (second) shoulder prosthesis was investigated. The humeral insert, stem, spacer, cup, baseplate, and screws were made of titanium-based alloys with low concentrations of vanadium (3.5%-4.5%) and aluminum (5.5%-6.5%). The glenosphere was made of a cobalt-chromium alloy with low concentrations of molybdenum and nickel.

Blood and urine samples were collected using collection systems suitable for trace metal ion analysis. Chromium and nickel were determined by Electrothermal Atomic Absorption Spectrometry (PinAAcle 900Z, Perkin Elmer), titanium and aluminum were determined by Inductively Coupled Optical Emission Spectrometry (iCAP 6300DV, Thermo Fisher Scientific), and cobalt, molybdenum, and vanadium were determined by Inductively Coupled Plasma-Mass Spectrometry (Elan DRCe, Perkin Elmer). The results of these determinations are presented in Table I. Serum titanium concentration was substantially elevated. Serum levels of all other metals were in the normal ranges, as were urine concentrations of all elements, including titanium.

The patient refused skin biopsy but agreed to follow-up urine and serum metal assays 1 year after the first assessment. At this second evaluation, serum titanium was still elevated (33.9 μg/L). Serum and urine levels of all other elements were in the normal ranges. Urine titanium was not assayed. Shoulder, arm, and elbow pigmentation remained unchanged.

Discussion

Skin discoloration is a rare manifestation of metallosis complicating joint arthroplasty. To our knowledge, only 12 publications have reported a total of 13 cases of this type of local cutaneous metallosis.[1,3-5,7,9,20,28,31-33,37,3-13,23]

In one case, light blue discoloration was observed following hip arthroplasty with metallic components composed of either tantalum or a titanium-aluminum vanadium alloy.[4] This skin pigmentation was associated with clinical and radiological signs of prosthesis failure. Revision surgery revealed extensive metallosis of the tissues surrounding the acetabular component, and X-ray fluorescence analysis showed that the main metallic component responsible for this metallosis was tantalum; serum tantalum level was also dramatically elevated.

In the other 12 published cases, the skin discoloration was similar to that observed in our case, bluish-grey to bluish-black[1,3,5,7,9,20,28,31-33,37] and occurred after hip,[1,7,9,33] knee,[7,20,28,32,37] elbow,[3] or, as in our case, shoulder[20,28] arthroplasty. In most cases, skin discoloration was associated with clinical and sometimes radiologic signs of prosthesis failure. When joint revision surgery was performed, it always showed, as in our case, extensive metallosis of deep tissues surrounding one or several of the metallic prosthetic components, with bluish-black discoloration.[5,9,20,28,31-33,37] When the compositions of the alloys constituting the prosthesis components were indicated in the case report, they always consisted of titanium-based alloys, sometimes together with cobalt-chromium alloys.[1,3,9,28,31,32] When performed, histologic examination of the skin and/or tissues surrounding the prostheses showed black granules both outside the cells and inside macrophages, histiocytes, and sometimes multinuclear giant cells, together with moderate inflammatory infiltrate.[1,3,5,7,9,28,31,32,37] Chemical characterization of the pigmented granules was performed in only 3 cases and showed that the main elemental component was titanium in 2 cases.[28,31] In the third case,[3] an analytical error is highly probable, as the main components of metallic granules were identified to be iron and copper, although the metallic prosthetic components were made of a titanium alloy or cobalt-chromium alloy.

The previously published case reports of skin discoloration associated with metallic joint prostheses did not include any blood or urine metal assays. In our case, all metals present in the composition of the prosthetic components were assayed in serum and/or urine. All concentrations were situated within the normal ranges, except for serum titanium, which was substantially

Table I
Results of serum and urine metal analysis.

	LOD	LOQ	Results	Reference value (RfV)	Definition of the RfV
Urine aluminum	0.5 μg/L	1.5 μg/L	2.4 μg/L	11.5 μg/L	P95 of the distribution in a sample representative of the general population (Northern France, 2008-2010)[26]
Serum chromium	0.05 μg/L	0.15 μg/L	0.17 μg/L	0.79 μg/L	P95 of the distribution in volunteers from the general population (France, 2012)[8]
Urine chromium	0.1 μg/L	0.3 μg/L	<LOQ	0.65 μg/L 0.54 μg/g creatinine	P95 of the distribution in a sample representative of the general population (France, 2006-2007)[11]
Serum cobalt	0.003 μg/L	0.009 μg/L	0.51 μg/L	0.59 μg/L	P95 of the distribution in volunteers from the general population (France, 2012)[8]
Urine cobalt	0.003 μg/L	0.009 μg/L	0.47 μg/L 0.85 μg/g creatinine	1.40 μg/L 1.13 μg/g creatinine	P95 of the distribution in a sample representative of the general population (France, 2006-2007)[11]
Serum molybdenum	0.05 μg/L	0,17 μg/L	0.75 μg/L	1.15 μg/L	P95 of the distribution in volunteers from the general population (France, 2012)[8]
Urine molybdenum	0.15 μg/L	0.30 μg/L	18.7 μg/L 34.0 μg/g creatinine	137 μg/L 123 μg/g creatinine	P95 of the distribution in a sample representative of the general population (USA 2015-2016)[25]
Serum nickel	0.3 μg/L	0.9 μg/L	<LOQ	1.26 μg/L	P95 of the distribution in volunteers from the general population (France, 2012)[8]
Urine nickel	0.3 μg/L	0.9 μg/L	2.7 μg/L 4.9 μg/g creatinine	4.54 μg/L 3.77 μg/g creatinine	P95 of the distribution in a sample representative of the general population (France, 2006-2007)[11]
Serum titanium	0.5 μg/L	1.5 μg/L	**40.8 μg/L**	2.56 μg/L	P95 of the distribution in patients with well-functioning hip implants.[35]
Urine titanium	0.5 μg/L	1.5 μg/L	< LOQ	<1 μg/L <1 μg/g creatinine	60 to 80-year-old individuals with no metallic prostheses[22]
Urine vanadium	0.02 μg/L	0.06 μg/L	0.6 μg/L 1.1 μg/g creatinine	1.21 μg/L 1.12 μg/g creatinine	P95 of the distribution in a sample representative of the general population (Northern France, 2008-2010)[26]

LOD, limit of detection; *LOQ*, limit of quantification; *P95*, 95th percentile.
Bold = It is the only metal level above the corresponding reference value, in the table.

elevated when measured for the first time, 5 years after the onset of skin discoloration, and 2 years after the last revision surgery that had improved shoulder function and stabilized skin discoloration (Table I). Serum titanium was in the same range when assayed 1 year later. Urine titanium level was normal (Table I), which is not surprising, as renal excretion of titanium is known to be very slow,[12,15] and several publications have shown that metal concentrations may be elevated in the blood (whole blood, plasma, or serum),[18,19,22,27,29,30] but not in urine[18,22] in patients with titanium alloy prostheses. Patients with loosened titanium components generally exhibit elevated blood titanium levels (up to 620 μg/L for serum or plasma).[2,10,34,36] Blood titanium level can be considered to be a biomarker of orthopedic implant wear. The current Mayo clinic laboratory guidelines indicate that a serum titanium concentration > 10 μg/L suggests prosthesis wear.[23] However, this recommended cutoff value is based on the studies by Liu et al,[22] and Jacobs et al,[19] both published in 1998, and using analytical methods and instruments with quantification limits that are now considered not to be sufficiently low. In a recent work, based on a series of 95 patients with well-functioning hip implants, with a mean follow-up of 8.5 years, the 95th percentile of the distribution of plasma titanium level was 2.56 μg/L and 2.20 μg/L for whole-blood titanium level. The authors proposed these 2 values as laboratory reference levels in patients with well-functioning titanium implants.[34]

In only 2 published cases, possible signs of systemic toxicity were associated with titanium metallosis following arthroplasty failure. In the first case, a 57-year-old woman with failure of her hip arthroplasty and massive titanium metallosis also complained of weakness, headaches, and unspecified visual disorders. Plasma titanium level was 460 μg/L, and plasma cobalt, chromium, and aluminum levels were in the normal ranges. The case report did not describe any further investigations, and the clinical course after surgical revision is unknown.[36] In the second case, a 64-year-old male patient with arterial hypertension was also found to have renal failure (serum creatinine: 2.26 μg/dL) at the time of discovery of the failure of his hip arthroplasty. At the time of the surgical revision, he presented massive titanium metallosis with high serum titanium (457 μg/L) and only moderately elevated serum cobalt (1.6 μg/L), chromium (0.9 μg/L), and nickel (0.5 μg/L) levels. Six months after revision, serum titanium and serum creatinine levels had both decreased to 150 μg/L and 1.6 mg/dL, respectively.[10] Experimentally, the ionic form of titanium mainly accumulates in the kidneys,[13] which are also the main target organs for toxic effects.[21] No sign of systemic effects was present in our case, but serum titanium levels were much lower.

In our case, skin pigmentation appeared 6 to 9 months after RTSA, then progressively extended for 3 years until arthroplasty revision with resection of pigmented deep tissues. Skin discoloration subsequently remained unchanged for the next 3 years. The clinical course of skin pigmentation after arthroplasty revision has been described in only 2 previously published cases: in the first case, discoloration of the left hip remained unchanged during the 14-year follow-up of a well-functioning revision total hip arthroplasty[9]; in the second case, metallic discoloration of the right shin progressively faded and disappeared within 4 years, after revision of a right knee arthroplasty.[28]

Conclusion

Greyish-blue skin discoloration of scars and/or para-articular areas is a rare manifestation of titanium alloy prosthesis failure. It is always associated with extensive deep tissue metallosis, whereas most cases of metallosis after arthroplasty do not include skin pigmentation. The presence of skin pigmentation always indicates the need for revision and warrants assessment of systemic diffusion of metals by assaying blood titanium, as well as blood cobalt and chromium levels, as titanium alloy components of articular prostheses are generally associated with cobalt/chromium alloy components.

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