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Case Report

A Case of Titanium Pseudotumor and Systemic Toxicity After Total Hip Arthroplasty Polyethylene Failure

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ABSTRACT

We describe the case of a 57-year-old female who underwent bilateral ceramic-on-polyethylene total hip arthroplasties performed in 2015. She presented to us in 2018 with headaches, fatigue, and right hip pain 5 months after an atraumatic right polyethylene liner failure for which she did not seek treatment. She was found to have imaging consistent with an adverse local tissue reaction and massive pseudotumor formation. During revision surgery, fracture of the acetabular liner was noted, with ceramic head wear through the titanium cup. In the months after her debridement and prosthesis revision, the patient continued to complain of systemic symptoms including weakness, fatigue, headaches, and vision problems. Serum titanium levels were found to be 100 times higher than normal. This case serves as a rarely reported example of titanium toxicity and titanium pseudotumor formation in the setting of polyethylene failure.

Introduction

Metallosis is a well-described phenomenon in the total hip arthroplasty (THA) literature, with an incidence of 1%-3% per year [1-3]. Briefly, the term encompasses the gross observation of inflammation, deposition of metallic debris, and soft-tissue necrosis resulting from metal wear at the taper junction of a prosthesis [4]. Pseudotumors are aseptic soft-tissue masses, seen traditionally in metallosis of metal-on-metal prostheses but may also be seen in a variety of implant types [3,4]. Systemic metal toxicity is a less common, but serious, sequela of metallosis. Indeed, the metal alloys used in arthroplasty, including cobalt, chromium, titanium, and aluminum, can release degradation products into the surrounding tissue. These, when circulated systemically, may cause dose-dependent symptoms of metal intoxication [5,6].

Although cobalt pseudotumor formation and toxicity have been rigorously reported in the literature, a paucity of studies explores these entities with respect to titanium [7-10]. A single report, to date, reported by Fabi et al. in 2011, describes a case of reversible renal failure secondary to elevated titanium levels in a patient with titanium acetabular component failure [11]. Titanium toxicity can elicit a number of symptoms, including fatigue, headaches, blurring of vision, respiratory inflammation, lymphedema, and hyperpigmentation of the nails and skin [12-14]. Here, we report a rare case of polyethylene liner failure, leading to titanium pseudotumor formation and systemic toxicity, associated with plasma titanium levels 100 times greater than normal.

Case history

In 2015, a 57-year-old woman underwent bilateral uncemented ceramic-on-polyethylene THA at an outside institution. The femoral implant design (Trabecular Metal Primary Hip Prosthesis; Zimmer Biomet, Warsaw, IN) consisted of a fit-and-fill titanium alloy substrate stem (Ti-6Al-4V; Tivanium, Zimmer Biomet, Warsaw, IN) with tantalum porous coating, with a ceramic femoral head. The acetabular implant design (Continuum Acetabular System; Zimmer Biomet, Warsaw, IN) consisted of a press-fit, tantalum-coated, titanium alloy substrate acetabular shell, with a highly cross-linked polyethylene acetabular liner. Both surgeries, performed using a posterior approach 6 months apart, were each complicated by early postoperative hematoma formation requiring hematoma evacuation and revision of modular components, including polyethylene liner exchange and femoral head exchange to ceramic heads with titanium trunnion adapter sleeves.

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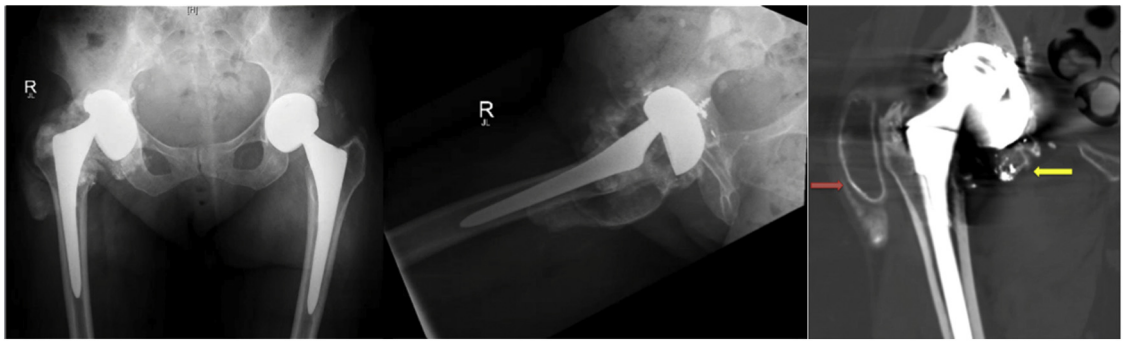

Figure 1. Anteroposterior pelvis and lateral right hip radiographs and coronal right hip computed tomography slice showing right total hip arthroplasty dislocation with extensive metallic debris deposition (yellow arrow) and soft-tissue reaction (red arrow).

In the summer of 2018, the patient reported sudden-onset right hip pain while she was traveling abroad. Her pain began while ambulating, without reported antecedent falls or other trauma. She presented to us in December 2018, complaining of 4 months of severe right hip pain and limited ambulation. She noted no fevers but did report weakness, fatigue, headaches, and trouble with her vision. During initial evaluation, the right hip demonstrated no gross swelling or erythema. Passive motion of the right hip was notable for an audible screeching sound with an internal rotation at 90° of hip flexion. Laboratory studies revealed a C-reactive protein < 0.5 mg/dL, erythrocyte sedimentation rate of 16 mm/h, and white blood cell count of 6.2 k/uL. Radiographs and computed tomography scan showed right hip dislocation with extensive periprosthetic metallic debris (Fig. 1). Aspiration of the hip yielded cloudy brown fluid with a white blood cell count of 2150 cells/uL and negative cultures. Serum cobalt and chromium levels were mildly elevated at 2.2 mcg/L (reference <2.0 mcg/L) and 3.7 mcg/L (reference <3.6 mcg/L), respectively. Magnetic resonance imaging subsequently revealed a pseudotumor within the trochanteric bursa measuring 153 cm^3 and scattered metallic debris (Fig. 2).

Intraoperative findings revealed massive metallosis and a large pseudotumor contiguous with the hip joint (Fig. 3a). After an extensive debridement, the acetabular liner was extracted and found to be fractured into several pieces (Fig. 3b). The ceramic femoral head eroded through the superior aspect of the acetabular cup, with extensive metal wear present at the point of contact (Fig. 3c). The femoral head was extracted; however, the titanium trunnion adapter sleeve remained attached to the trunnion (Fig. 3d). After several unsuccessful attempts at dissociating the trunnion adapter sleeve from the femoral component, a small fracture of the greater trochanter was noted. An extended trochanteric osteotomy was subsequently performed, and the femoral stem removed. After removal of the acetabular component, we noted the medial and anterosuperior aspects of the cup to be completely worn through. We proceeded with revision using a 58-mm acetabular shell (Continuum system, Zimmer Biomet, Warsaw, IN), a 36-mm highly cross-linked polyethylene neutral liner, and three posterosuperior bone screws. A 60-mm (vertical body height) modular tapered femoral stem with a standard neck was implanted (Arcos System, Zimmer Biomet, Warsaw, IN) along with a 36-mm ceramic femoral head. Finally, a trochanteric grip plate and 2 stainless steel cables were used for extended trochanteric osteotomy repair (Dall-Miles system, Stryker, Kalamazoo, MI). Postoperative radiographs were taken to confirm implant positioning and fracture reduction (Fig. 4). The patient was stable for discharge on post-operative day 7.

The patient subsequently developed symptomatic nonunion of the greater trochanter diagnosed at 5 months postoperatively. She underwent revision of trochanteric hardware, nonunion takedown, and allograft augmentation (Fig. 5). Postoperatively, the patient was made toe-touch weight-bearing, and an abduction pillow was used to maintain posterior hip precautions for 6 weeks. Her intraoperative cultures were negative for infection. Her postoperative course included a brief intensive care unit admission for

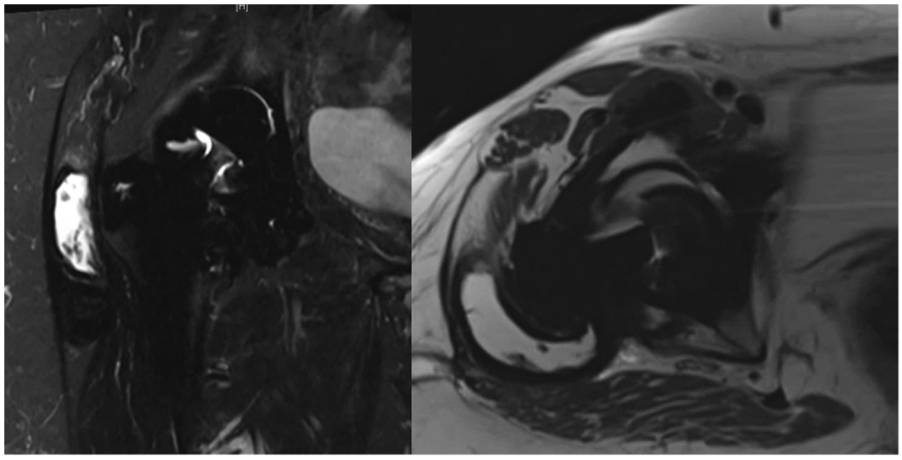

Figure 2. Right hip magnetic resonance imaging with metal artifact reduction sequence (MARS) coronal and axial slices showing pseudotumor formation within the trochanteric bursa.

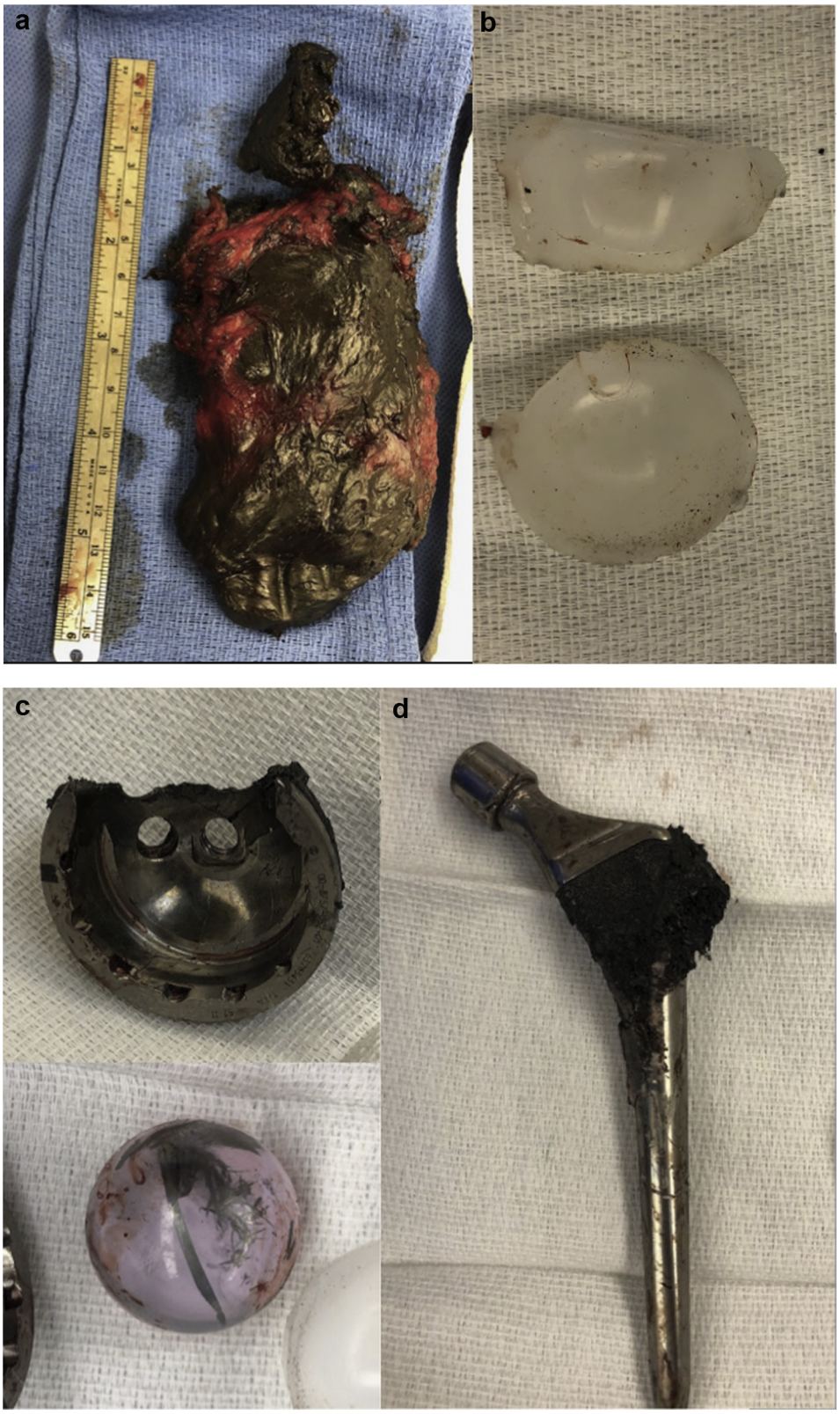

Figure 3. Clinical photographs of the resected hip pseudotumor (a), fractured polyethylene liner (b), femoral head and acetabular shell with extensive erosion at the point of contact (c), and femoral stem with retained trunnion and extensive metallosis (d).

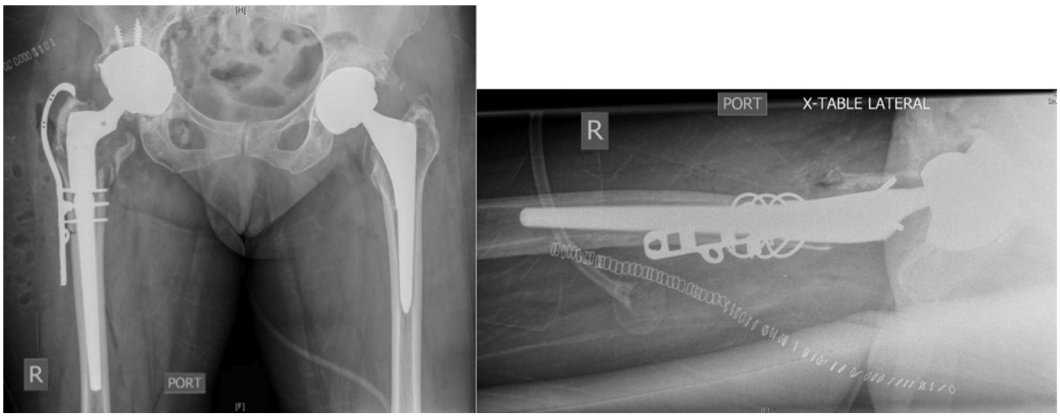

Figure 4. Postoperative AP pelvis and lateral right hip radiograph status after right THA revision, ETO repair with plate and cable construct.

postoperative hemodynamic monitoring, and she was subsequently discharged on POD 13.

Nine months after her index procedure, the patient demonstrated progressive bony healing of her right hip (Fig. 6). By 12 months, she ambulated without an assistive device, although with a slight Trendelenburg gait. Despite this, she continued to have symptoms of weakness, fatigue, headaches, and vision problems progressive in nature to those present on initial presentation. A

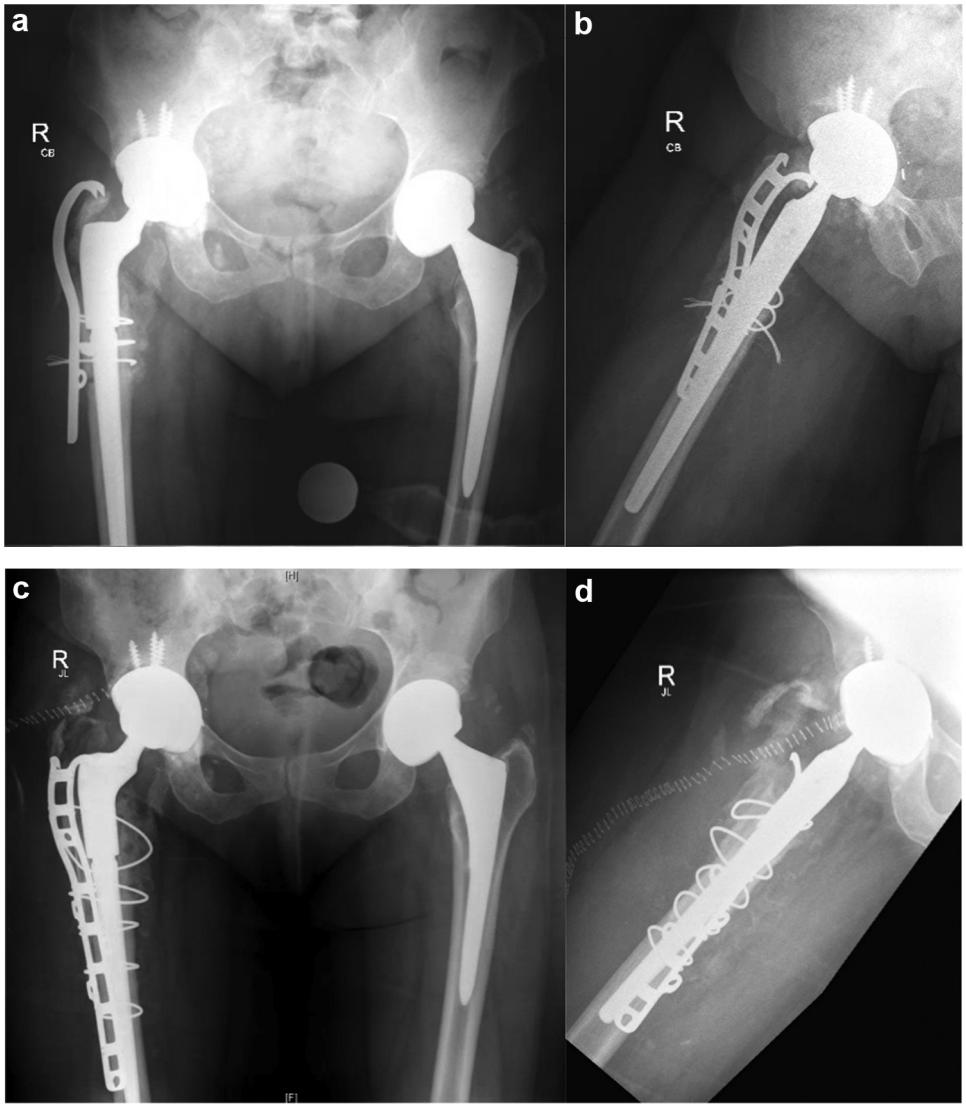

Figure 5. (a-d): AP pelvis and lateral right hip radiographs at 5 months postoperatively (a and b) showing ETO nonunion; AP and lateral hip radiograph status after revision fixation of ETO nonunion (c and d).

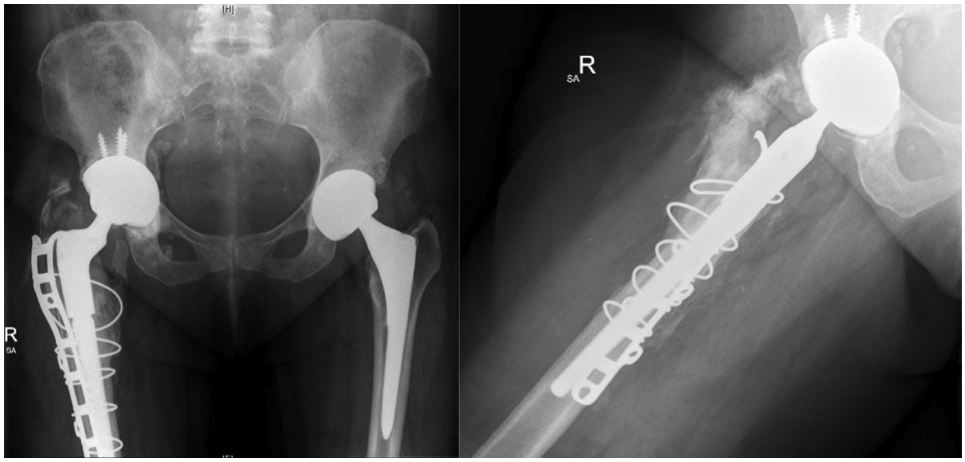

Figure 6. AP pelvis and lateral right hip radiographs 9 months after the initial revision procedure showing well-positioned hardware and ETO union.

blood titanium level obtained at this time was found to be markedly elevated at 460 mcg/L (ref <5 mcg/L), whereas cobalt, chromium, and aluminum levels were found to be normal.

Discussion

In the context of joint arthroplasty, baseline titanium levels in patients who underwent THA have only recently been explored. In one series of 95 patients undergoing THA, Swiatkowska et al. report a mean plasma titanium level of 2.5 micrograms/L to be indicative of a well-functioning implant at 8.5-year follow-up [15]. Savarino et al. similarly report an upper limit of normal for serum titanium in these patients to be 4.5 mcg/L at 10 years and 5.1 mcg/L at 2- to 7-year follow-up, respectively [16,17]. Despite this, routine measurement of serum titanium levels within patients who underwent THA with suspected metallosis remains uncommon.

Indeed, the sparsity of routine testing of titanium levels may be explained by the relative rarity of titanium toxicity documented within the THA literature. A number of animal studies explore the potential mechanism of titanium alloy–related toxicity. One such study on the function of rat macrophages performed by Haynes et al. analyzed the effect of Ti-Al-V alloy particles similar in composition to those found in failed THA. They found that when compared with Co-Cr, Ti-Al-V particles exhibited less cytotoxicity but more potently released the inflammatory mediators Tumor necrosis factor alpha, interlukin-1, interlukin-6, and prostaglandin-E2 [18]. The robust inflammatory response generated by titanium alloys has since been demonstrated by in vitro experiments within human lymphocytes, osteoblasts, fibroblasts, and macrophages [19-21]. Maloney et al. report a dose-dependent increase in cellular toxicity at titanium concentrations >0.0084% within human fibroblasts. At these concentrations, titanium particles decrease intracellular proteolysis, while increasing lysosomal destruction of cell membrane components [22].

Although no concrete mechanism of titanium pseudotumor formation has been described, the intense inflammatory response elicited by titanium microparticles is thought to play an integral role. Sakamoto et al discuss the case of a 77-year-old female who underwent a metal-on-polyethylene THA, complicated by intraoperative fracture of the greater trochanter requiring trochanteric grip plate and cable fixation. They describe the formation of a titanium pseudotumor secondary to wear of the titanium femoral stem against a cable. Similar to our findings, serum cobalt and chromium levels of their patient were within normal limits, whereas serum titanium was substantially elevated. Spectrometry was used to confirm the overwhelming presence of titanium within the pseudotumor. They concluded that a chronic host inflammatory response and a delayed foreign-body hypersensitivity response were both integral to titanium pseudotumor formation. Despite being unable to perform atomic spectrometry for our samples, intraoperative pathology obtained from our patient's pseudotumor was consistent with that of Sakamoto et al., who reported the presence of many inflammatory cells (CD3-, CD4-, and CD8-positive lymphocytes; plasma cells; and histiocytes) and metal debris [23].

McPherson et al. describe a massive pseudotumor found in a 59-year-old female 13 years after revision ceramic-on-polyethylene THA with all titanium components [24]. Preoperatively, a lymphocyte T-cell proliferation test demonstrated that the patient was presensitized to titanium. The authors proposed that the mechanism of pseudotumor formation involved initial polyethylene wear, subsequent third-body wear of the titanium-alloy femoral stem, and finally a hypersensitivity reaction to the liberated ultrafine titanium particles. This proposed mechanism has its basis in previous work completed by Thomas et al. and Lalor et al., among others [25,26]. Although our patient did not undergo formal preoperative testing for metal hypersensitivity, she has a documented history of eczema, autoimmune thyroid disease, and allergies to numerous food and environmental antigens. Thus, it is likely that pseudotumor formation in our patient occurred at least in part via a hypersensitivity mechanism.

Systemically, titanium-ion deposition within the bone marrow, spleen, lungs, skin, nails, and various mucosal surfaces has been reported [11-13,20,27]. "Yellow nail syndrome" (YNS), first described by Samman and White, refers to systemic deposition of titanium throughout the body, resulting in mucositis of the respiratory and ocular systems, lymphedema, skin changes, and thickening of the nails [28]. Despite being well documented in the dental and toxicology literature, YNS has not been reported in the orthopaedic literature [20,27,28]. Although our patient did not appear to have the characteristic skin and nail changes of YNS, she was found to have blurring of her vision and ocular inflammation identified by her ophthalmologist. Furthermore, the pathogenesis of YNS appears to be accelerated in the setting of chronic hypoalbuminemia, for which our patient was notable. Our patient did not exhibit any other elevated serum metal ions, nor did she have chronic exposure to heavy elements such as lead, iron, copper, silver, or mercury. In the absence of elevated circulating levels of alternative metal ions,

we conclude that titanium toxicity reasonably explains the patient's presentation and symptomatology.

Summary

We report on a rare case of titanium pseudotumor formation and titanium toxicity in a 57-year-old female after failure of her right THA polyethylene liner. A comprehensive review of the literature in conjunction with the patient's intraoperative findings, laboratory results, and tissue biopsy all suggest titanium to be the culpable agent. The authors suggest that although THA polyethylene fracture remains rare, it may lead to the production of titanium microparticles that can lead to substantial local and systemic consequences.

Conflict of interests

The authors declare there are no conflicts of interest.

References

[1] Hall DJ, Pourzal R, Jacobs JJ. What surgeons need to know about ALTR in THA. J Arthroplasty 2020;35(6S):S55.
[2] Jacobs JJ. Corrosion at the head-neck junction: why is this happening now? J Arthroplasty 2016;31(7):1378.
[3] Hussey DK, McGrory BJ. Ten-year cross-sectional study of mechanically assisted crevice corrosion in 1352 consecutive patients with metal-on-polyethylene total hip arthroplasty. J Arthroplasty 2017;32(8):2546.
[4] Marinescu R, Socoliuc C, Botezatu I, Laptoiu D, Voinescu D. Metallosis-literature review and particular cases presentation. In: Key Engineering Materials, Vol. 745. Budapest: Trans Tech Publications Ltd; 2017. p. 77.
[5] Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am 1998;80(10):1447.
[6] Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? Clin Orthop Relat Res 2005;438:177.
[7] Oldenburg M, Wegner R, Baur X. Severe cobalt intoxication due to prosthesis wear in repeated total hip arthroplasty. J Arthroplasty 2009;24(5):825.e15.
[8] Steens W, Loehr JF, Von Foerster G, Katzer A. Chronic cobalt poisoning in endoprosthetic replacement. Der Orthop 2006;35(8):860.
[9] Lison D. Cobalt. In: Handbook on the toxicology of metals. London: Academic Press; 2015. p. 743.
[10] Danzeisen R, Williams DL, Viegas V, Dourson M, Verberckmoes S, Burzlaff A. Bioelution, bioavailability, and toxicity of cobalt compounds correlate. Toxicol Sci 2020;174:311.
[11] Fabi D, Majoras N, Levine BR. Chronic renal failure associated with catastrophic failure of an acetabular component: a case report. J Bone Joint Surg Am 2011;93(12):e681.
[12] Ataya A, Kline KP, Cope J, Alnuaimat H. Titanium exposure and yellow nail syndrome. Respir Med case Rep 2015;16:146.
[13] Decker A, Daly D, Scher RK. Role of titanium in the development of yellow nail syndrome. Skin Appendage Disord 2015;1(1):28.
[14] Chen XX, Cheng B, Yang YX, et al. Characterization and preliminary toxicity assay of nano-titanium dioxide additive in sugar-coated chewing gum. Small 2013;9(9-10):1765.
[15] Swiatkowska I, Martin NG, Henckel J, Apthorp H, Hamshere J, Hart AJ. Blood and plasma titanium levels associated with well-functioning hip implants. J Trace Elem Med Biol 2020;57:9.
[16] Savarino L, Greco M, Cenni E, et al. Differences in ion release after ceramic-on-ceramic and metal-on-metal total hip replacement: medium-term follow-up. J Bone Joint Surg Br 2006;88(4):472.
[17] Savarino L, Padovani G, Ferretti M, et al. Serum ion levels after ceramic-on-ceramic and metal-on-metal total hip arthroplasty: 8-year minimum follow-up. J Orthop Res 2008;26(12):1569.
[18] Haynes DR, Rogers SD, Hay S, Pearcy MJ, Howie DW. The differences in toxicity and release of bone-resorbing mediators. J Bone Joint Surg Am 1993;75:825.
[19] Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Orthopaedic implant related metal toxicity in terms of human lymphocyte reactivity to metal-protein complexes produced from cobalt-base and titanium-base implant alloy degradation. In: Molecular Mechanisms of Metal Toxicity and Carcinogenesis. Boston, MA: Springer; 2001. p. 127.
[20] Kim KT, Eo MY, Nguyen TT, Kim SM. General review of titanium toxicity. Int J Implant Dent 2019;5(1):10.
[21] Dalal A, Pawar V, McAllister K, Weaver C, Hallab NJ. Orthopedic implant cobalt-alloy particles produce greater toxicity and inflammatory cytokines than titanium alloy and zirconium alloy-based particles in vitro, in human osteoblasts, fibroblasts, and macrophages. J Biomed Mater Res A 2012;100(8):2147.
[22] Maloney WJ, Smith RL, Castro F, Schurman DJ. Fibroblast response to metallic debris in vitro. Enzyme induction cell proliferation, and toxicity. J Bone Joint Surg Am 1993;75(6):835.
[23] Sakamoto M, Watanabe H, Higashi H, Kubosawa H. Pseudotumor caused by titanium particles from a total hip prosthesis. Orthopedics 2016;39(1):e162.
[24] McPherson E, Dipane M, Sherif S. Massive pseudotumor in a 28mm ceramic-polyethylene revision THA: a case report. Reconstr Rev 2014;4(1).
[25] Thomas P, Bandl WD, Maier S, Summer B, Przybilla B. Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: case report and review of the literature. Contact Dermatitis 2006 Oct;55(4):199.
[26] Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA. Sensitivity to titanium. A cause of implant failure? J Bone Joint Surg Br 1991;73(1):25.
[27] Lima MA, Santos VM, Demachki S, Lazo J. Titanium pigment in tissues of drug addicts: report of 5 necropsied cases. Rev Hosp Clin Fac Med Sao Paulo 2004;59(2):86.
[28] Samman PD, White WF. The "yellow nail" syndrome. Br J Dermatol 1964;76(4):153.