Clinical Case Report

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Metal allergy in total-joint arthroplasty

Case report and literature review

Wei Bao, MD, Yao He, MD, Yuanjun Fan, MD, Yueming Liao, MD*

Abstract

Rationale: Due to the low incidence and lack of effective diagnostic measures for the diagnosis of metal allergy in patients undergoing total joint arthroplasty (TJA), diagnosis relies mainly on the exclusion of other causes, in particular infection. It remains a relatively unpredictable and poorly understood cause of implant failure. At present, skin patch testing, leukocyte migration inhibition test (LMIT) and lymphocyte transformation tests (LTT) are being commonly used to assess metal hypersensitivity.

This report presents both a case and literature review.

Patient concerns: A 61-year-old female patient experienced continuous swelling and pain in the right knee joint for 9 months after a right-side total knee arthroplasty (TKA).

Diagnoses: We believe this is the case report of metal allergy in TKA. The following were the reasons for this. First, no definite symptoms of infection during revision arthroplasty were observed, but with obvious hyperplasia of synovium. Furthermore, a frozen biopsy revealed an extremely low neutrophil count, which was considered to be caused by chronic inflammation. Second, the results of repeated post-operation reexaminations indicate a clear increase in the number of eosinophils, while no bacteria were found in the tissue bacterial smear performed during the operation. Third, improvements were clearly observed in the patient following synovectomy, revision of the polyethylene insert and anti-anaphylactic treatment.

Interventions: The patient underwent synovectomy, revision of the polyethylene insert and anti-anaphylactic treatment.

Outcomes: The patient's right knee remained mildly swollen; however, the pain has been relieved significantly. The range of motion could achieve 0 degrees of extension and 90 degrees of flexion.

Lessons: No consensus has been reached about the best diagnostic criteria for this disease, and most physicians would consider it to be a possibility when other diseases including periprosthetic joint infection (PJI) have been excluded. Although this case followed the same course, the outcome following synovectomy and anti-anaphylactic treatment further confirmed our hypothesis.

Abbreviations: APCs = antigen-presenting cells, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LIF = leukocyte migration inhibition factor, LMIT = leukocyte migration inhibition test, LTT = lymphocyte transformation test, PCT = procalcitonin, PJI = periprosthetic joint infection, ROM = range of motion, TJA = total-joint arthroplasty, TKA = total-knee arthroplasty, WBC = white blood count.

Keywords: infection, metal allergy, revision, total-joint arthroplasty

1. Introduction

Total-joint arthroplasty (TJA) is one of the most successful and effective orthopedic operations performed during the last century. As a treatment for disabilities of the hip and knee, it can relieve pain, correct deformity, and improve the patient's quality of life. However, not all TJA patients benefit from significant pain relief and functional improvement. Some patients experience persistent pain following this procedure. The most common cause of unsatisfactory outcomes, aside from intraoperative technical error, is periprosthetic joint infection. However, one should not forget that metal hypersensitivity, though quite rare (<1% of TJA recipients), is also a potential cause of unresolved pain and should be regarded as a differential diagnosis in this situation.[1,2]

The authors present here a case suffering from persistent debilitating pain and swelling of the operated knee following total-knee arthroplasty (TKA). Initially, a diagnosis of periprosthetic joint infection (PJI) was made. However, following investigation, the evidence pointed to a diagnosis of metal hypersensitivity and anti-anaphylactic treatment produced satisfactory results.

2. Case report

A 61-year-old female patient was diagnosed with degenerative osteoarthritis of the right knee and underwent TKA (NexGen high-flex TKA; Zimmer, Warsaw, IN) in our institution in September 2012. During hospitalization, her recovery and rehabilitation were uneventful, and 7 days after operation, the patient was discharged. However, she complained of continuous

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Ethical approval was not necessary for this manuscript, because it was a case report. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors report no conflicts of interest.

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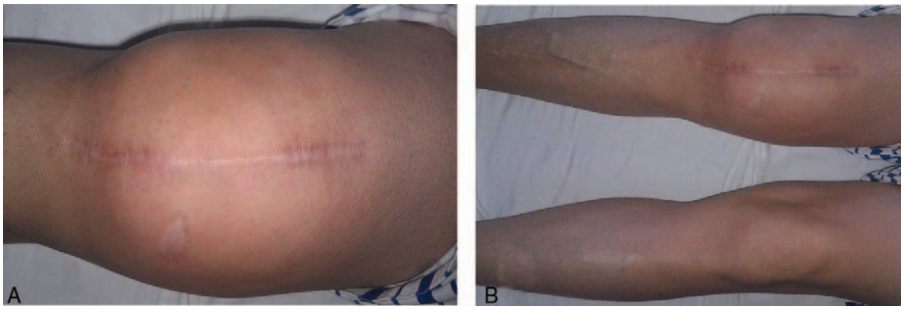

Figure 1. The patient's right knee is obviously swollen.

low-grade fever, swelling, stiffness, as well as pain of the operated knee at each follow-up, over a period of 9 months, which had an adverse effect on her daily activities. Her only significant medical history was an allergy to jewelry.

On physical examination, the right knee was obviously swollen (Fig. 1), and the range of motion (ROM) was −5° of extension to 15° of flexion. Her white blood cell (WBC) count and neutrophil differentiation were normal, but eosinophil differentiation was significantly increased (0.87×10^9/L, reference $0.02–0.52 \times 10^9$/L). Furthermore, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were mildly elevated (CRP 23.1 mg/L, reference 0–8 mg/L; ESR 34 mm/L, reference 0–20 mm/L) and procalcitonin (PCT) was normal (0.10 pg/mL, 0–0.25 pg/mL). Knee aspiration revealed no evidence of bacterial infection. Radiographs demonstrated appropriate position and fixation of the cemented implants (Fig. 2), and a technetium-99m bone scan showed mild increased uptake around the prosthesis.

As there was a possibility of PJI, she was scheduled for a debridement and revision TKA. However, no significant signs of infection were found during the operation. The only finding was obvious hyperplasia and hyperemia of synovial tissues surrounding the implant, particularly in the suprapatellar pouch (Fig. 3). A frozen biopsy revealed an extremely low volume of neutrophils, but a large amount of lymphocytes, which was verified by a postoperative pathology report (Fig. 4). The implant was well fixed and there is no evidence of PJI. Therefore, after examining all the available evidence, a diagnosis of metal hypersensitivity was made intraoperatively. Only the polyethylene tibial insert was changed as the implant was well fixed (Fig. 5). To suppress the allergic reaction, anti-anaphylactic treatment (promethazine hydrochloride, 25 mg im qd) was initiated immediately after the revision surgery.

At day 3 postoperatively, intraoperative multiple site bacteria culture results returned negative. The differentiation of WBC and neutrophils was normal. ESR, CRP, and PCT were mildly increased, but eosinophil differentiation was still significantly increased (1.30×10^9/L, reference $0.02–0.52 \times 10^9$/L). The patient experienced significant symptom relief and was discharged home on postoperative day 14.

At 4 years of follow-up, the patient's right knee remained mildly swollen; however, the pain has been relieved significantly.

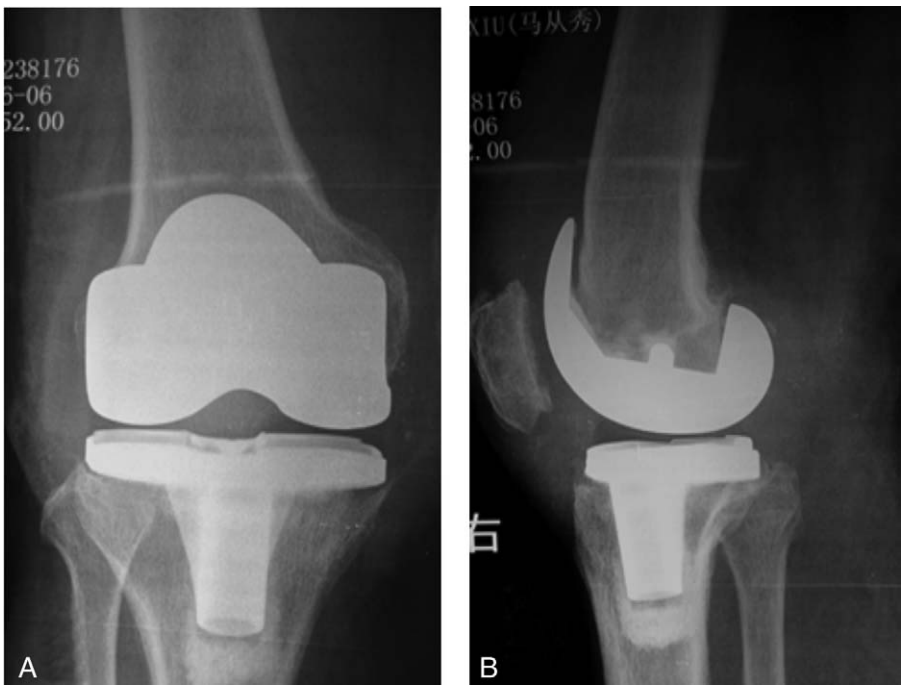

Figure 2. The implant is fixed well and the position is appropriate. (A) Anteroposterior radiograph. (B) Lateral radiograph.

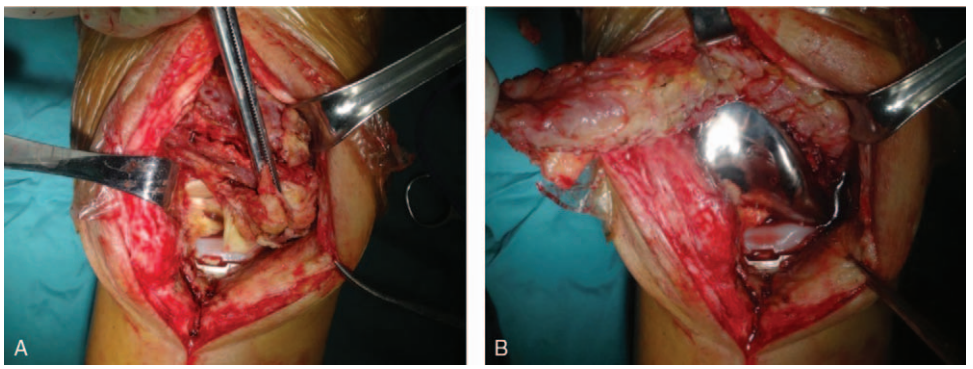

Figure 3. The image shows both hyperplasia and congestion of the synovial tissues. The implant was fixed well and prosthetic joint infection was not observed.

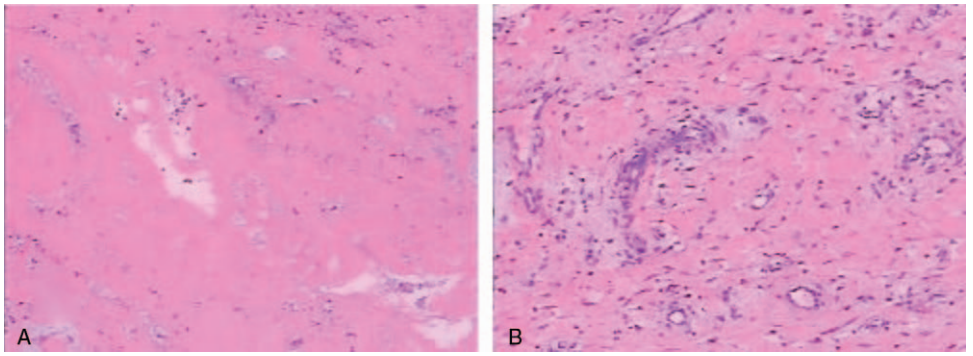

Figure 4. Photomicrograph of the tissues showing hyperplasia, glassy degeneration, and mucoid degeneration of fibrous tissue and blood vessel. Acute or chronic inflammatory cell infiltrates are present in the necrotic tissue.

The ROM could achieve 0° of extension and 90° of flexion. The levels of all inflammatory markers were within the normal range and eosinophil differentiation was also normal.

3. Literature review

3.1. Prevalence of metal hypersensitivity

Strictly speaking, the prevalence of metal hypersensitivity discussed in this report was determined by the positive rate by 1 specific testing method, but did not cover the real incidence of this issue. In the general population, the prevalence is 10% to 15%[2,5,11] and the most common allergy-inducing metals are nickel (19.7–24.4%), cobalt (2–8.8%), and chromium (2.4–5.9%).[12] In some cases, cross-hypersensitivity reactions have been observed for all three metals.[3] However, the prevalence of metal allergy can be influenced by multiple factors. For example, female patients are more sensitive to nickel[25] and male patients to chromate.[13] The prevalence of metal hypersensitivity varies according to the status of the implant: it is found in 20% to 25% of patients with well-functioning implants and in approximately 60% of patients with poorly functioning implants or loosening prosthesis.[2,11] This phenomenon may be caused by the fact that the hypersensitivity reaction is elicited by continuous contact with metal ions; therefore, a loosening prosthesis could release more ions than an intact implant, thus inducing an allergic reaction.[14] Modern implants are all coated with plasma spray to limit metal ion exposure[2,15]; however, such coating could also provide a rough surface, which may increase the available area for ion release.

The most common composition of metallic implants for orthopedic surgery includes stainless steel, titanium alloy, cobalt-chromium-molybdenum alloy, and zirconium alloy.[7,8] Since these alloys contain different types of metals (stainless steel: 19% chrome, 15% nickel, 4% molybdenum, and 1% nickel, cobalt-chromium-molybdenum: 67% chrome, 30% cobalt, 2% molybdenum, and 1% nickel, titanium alloy: 91% titanium, 5% aluminum, 3.9% vanadium, and 0.1% nickel), their allergenicity varies substantially.[2,6,16] Stainless steel is widely used in internal fixation for trauma patients; therefore, metal allergy is more common in trauma patients than in patients undergoing TJA.

3.2. Laboratory tests for metal hypersensitivity

Clinical symptoms of metal hypersensitivity include local or systemic allergic dermatitis, such as eczema, urticaria, bullous eruption, erythema multiforme, and vasculitis.[17,18] Surgical site pain, aseptic inflammation, and prosthetic loosening are also common manifestations.[5] Different metal ions may induce diverse allergic symptoms, for example: nickel ions may create implant loosening, and release of chrome can cause eczema and other skin problems.[19,20]

With respect to standard laboratory examinations, the skin patch test, leukocyte migration inhibition test (LMIT), and lymphocyte transformation test (LTT) are the most popular diagnostic tests for metal hypersensitivity. None of the tests have been universally accepted and applied. The skin patch test is easier and cheaper than in vitro tests; therefore, it is more widely used in clinical settings and is more suitable for larger-scale screening. However, the antigen-presenting cells (APCs) localized

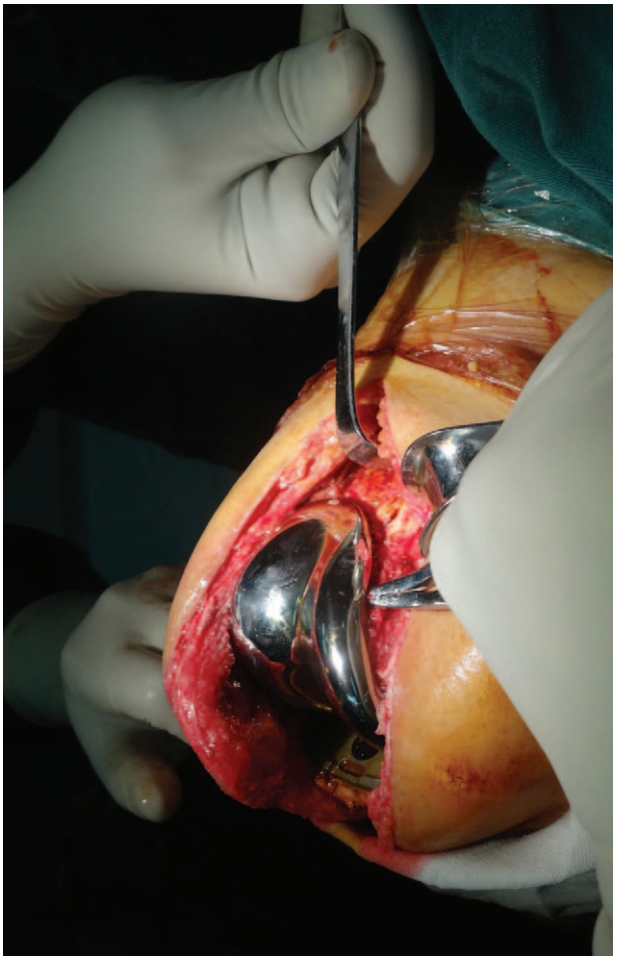

Figure 5. The metal implant is fixed well and prosthetic joint infection is absent in the intraoperative presentation.

to the skin are dendritic cells and epidermal Langerhans cells, while systemic APCs are macrophages and monocytes. This difference invalidates this test.[4,10,21] According to previous reports, the sensitivity of patch test is as high as 100%, but its specificity is quite low (64%). Although a diagnosis of metal hypersensitivity can be excluded with confidence following a negative patch test result, a positive test result may not provide much valuable information.[11] In fact, many patients with positive patch test results may never display any symptoms of metal hypersensitivity.[15,21] The reaction grading of the skin patch test is listed in (Table 1).[22]

The most common in vitro diagnostic tests for metal hypersensitivity are LMIT and LTT. The LMIT measures the limitation of leukocyte migration by detecting migration inhibitory factor or leukocyte migration inhibition factor (LIF). Those 2 factors can prevent lymphocytes from leaving a site where foreign antigens are present.[9] Thus, a positive result indicates an active immune response and metal sensitivity, and is closely associated with swelling, pain, and allergic dermatitis. After removing the allergen, the result of the test may turn negative,[2,19] therefore a serial test could be used to monitor response to therapy. The LTT measures the proliferation of lymphocytes activated by metal ions and indicates the cellular immune function. In that test, a radioactive marker is added to lymphocytes, and the proliferation factor is calculated by measuring radiation counts per minute of the incorporated marker.[23] LTT is more reliable than the skin patch test and is currently more widely performed than LMIT, but its clinical practicability is limited by the high cost and need for a specialized lab.[2,24]

Thyssen et al have proposed objective diagnostic criteria for allergic metal dermatitis overlying the implant (Table 2) and objective criteria for metal-allergy-related prosthesis loosening, pain, and chronic inflammation (Table 3).[19]

Table 1

The reaction grading of skin patch test.

A	−	No reaction
B	+−	Weak erythema only
C	+	Erythema with edema that covering at least 50% of the patch test site. A few vesicles may be present
d	2+	Erythema and papules covering at least 50% of the patch test site. A few vesicles may be present
e	3+	Erythema or bullae covering at least 50% of the patch

Table 2

The objective diagnostic criteria of allergic metal dermatitis overlying the implant.

1	Chronic dermatitis beginning weeks to months after metallic implantation
2	Eruption overlying the metal implant
3	Morphology consistent with dermatitis (erythema, induration, papules, vesicles)
4	In rare instances, systemic allergic dermatitis reaction (characterized by universal dermatitis reactions, typically localized in body flexures)
5	Histology consistent with allergic contact dermatitis
6	Positive patch test reaction to a metal used in the implant (often strong reactions)
7	Serial dilution patch testing give positive reactions to low concentrations of the metal under suspicion
8	Positivein vitro test to metals, e.g., the lymphocyte transformation test
9	Dermatitis reaction is therapy resistant
10	Complete recovery following removal of the offending implant

3.3. Treatment for implant hypersensitivity

Allergen removal is always the most effective treatment for all types of hypersensitivities. However, since revision surgery is associated with significant trauma, cost, and inferior survivorship of the prosthesis, nonsurgical treatment is considered to be the first choice in the setting of metal hypersensitivity following TJA. For mild eczema and other dermatitis, local dermatologic treatment is the treatment of choice. If the allergic symptoms are systemic, oral prednisolone may be a good choice. Radiosynoviorthesis has been reported to be effective in the treatment of recurrent joint effusions after total-knee replacement.[26] If all of the abovementioned options fail to produce satisfactory results, the prosthesis should be removed and revised with an

Table 3

Objective criteria that metal allergy related implant loosening, pain, and chronic inflammation.

1	Histology consistent with a delayed-type hypersensitivity reaction
2	Positive patch test reaction to a metal used in the implant (often strong reactions)
3	Positivein vitro test to metals, e.g., the lymphocyte transformation test
4	Complete recovery following removal of the offending implant material

oxidized zirconium Zr-2.5Nb alloy (Oxinium; Smith & Nephew, Memphis, TN).[6,27,28] Other implant options include Oxinium components for the femoral side and hardened titanium for the tibial side,[29] or revision with a titanium-niobium (Biomet or Stryker) prosthesis.[31,32]

4. Conclusion

Metal hypersensitivity following TJA is a poorly studied issue due to its extremely low incidence, vague clinical manifestations, and diagnostic difficulty. At present, no consensus has been reached to determine the best diagnostic criteria for this disease and most physicians would consider it only when other diseases like PJI have been excluded.[30] In our case, PJI also had to be excluded. Initially, the patient was diagnosed with an infection and debridement as well as revision surgery was planned. However, no signs of infection or positive culture results were demonstrated intra- and postoperatively. Instead, we observed an elevated eosinophil count, positive history of metal jewelry allergy, and significant hyperplasia of synovial tissues leading to the hypothesis of metal hypersensitivity.[33–35] A satisfactory outcome was achieved following synovectomy and anti-anaphylactic treatment, which further confirmed our hypothesis. Nevertheless, longer term follow-up is needed to better appreciate the progression of this condition.

Author contributions

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Formal analysis: Wei Bao.
Investigation: Wei Bao, Jun Yuan Fuan, Yao He.
Supervision: Ming Yue Liao.
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