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KNEE ARTHROPLASTY

Revision total knee arthroplasty due to bone cement and metal hypersensitivity

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Abstract
Introduction Hypersensitivity to implants is a rare complication of total knee arthroplasty (TKA). Metal and, less frequently, bone cement can produce allergic symptomatology that if unresponsive to conservative treatment could lead to revision.
Materials and methods We present the case of a patient with generalized pruritus and metal taste starting during the first postoperative month after TKA. Dermal allergy exams revealed that the patient had hypersensitivity to nickel sulphate and cobalt chloride and bone cement. Conservative treatment with antihistamine medication and corticosteroids failed to control the symptoms. The patient underwent revision TKA with a hypoallergic prosthesis 8 months after the primary procedure.
Results Full disappearance of the symptoms occurred 3 months after revision. The latest follow-up evaluation (3 years post-revision) was unremarkable.
Conclusions In our opinion, an exhaustive medical history should be obtained from every candidate for total joint replacement and in cases of prior severe allergic reactions to metals, plastics or glues, patch testing of the components of the future prosthesis should be done. When an already implanted prosthesis causes symptoms like pain, edema, pruritus, erythema, limited range of motion and increase in joint's temperature, the possibility of allergy to metals and/or bone cement (in case of cemented prosthesis) should be checked after the exclusion of other reasons like infection. If symptoms cannot be controlled by conservative measures, revision should be decided and carried out with hypoallergic prosthesis.

Keywords Total knee arthroplasty · Nickel · Cobalt · Bone cement · Hypersensitivity

Introduction

Common causes leading to revision total knee arthroplasty (TKA) include aseptic loosening, periprosthetic infection, instability and patellar maltracking [1]. However, in a small number of patients the aetiology involves rare mechanisms such as ligament and tendon dysfunction, patellar clunk syndrome and hypersensitivity to TKA components [1]. Metal and, less frequently, bone cement allergies are reported in patients undergoing early revision TKA [2–6], while some support that these allergies could lead to aseptic loosening, especially after revisions [7]. We report the case of a patient who underwent revision TKA a few months after the primary procedure due to allergic reaction to nickel, cobalt and bone cement.

Case report

A 78-year-old woman presented to our clinic complaining about diffuse itching and metal taste 3 months after a TKA of the left knee (Trekking Knee Integrated System, Samo, Bologna, Italy) operated elsewhere. Her symptoms began during the first postoperative month. Initially, itching about the joint appeared, but after a few days the pruritus became diffuse. There was no erythema or other skin lesions at any time after surgery. The treating doctor prescribed antihistaminic medication (p. o. cetirizine 10 mg/day for 10 days)

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that led initially to mild alleviation of the pruritus. However, at the first follow-up visit (40 days after the operation) she continued complaining about itching and also reported metal taste. At that time she had just completed a 40-day course of anticoagulant postoperative treatment and was not under any other medication. A new course of antihistaminic medication (p. o. cetirizine 10 mg twice/day for 10 days) was prescribed, but symptoms deteriorated further.

Upon clinical examination no skin lesions were detected. The site of incision had healed well, but the operated knee was slightly warmer than the contralateral (manual subjective assessment). There was no joint pain and the range of motion (ROM) was 0°–115°. The patient was otherwise healthy with no other medical history. Plain radiographs of the operated knee showed good alignment of the prosthesis (Fig. 1a, b). In order to exclude the possibility of deep infection, a full laboratory workup was conducted [blood tests: WBC 8.7 $\times$ 10^9/L (reference value 4.0–10.8 $\times$ 10^9/L) with 61.5% neutrophils (reference value 40–75%), 32% lymphocytes (reference value 20–45%), 2% monocytes (reference value 2–10%), 4.5% eosinophils (reference value 1–6%), ESR 12 mm/h (reference value <20 mm/h), CRP 0.6 mg/dL (reference value 0.08–0.8 mg/dL) and synovial fluid cultures] which proved negative. Since the symptoms appeared after TKA there was a high suspicion of allergy.

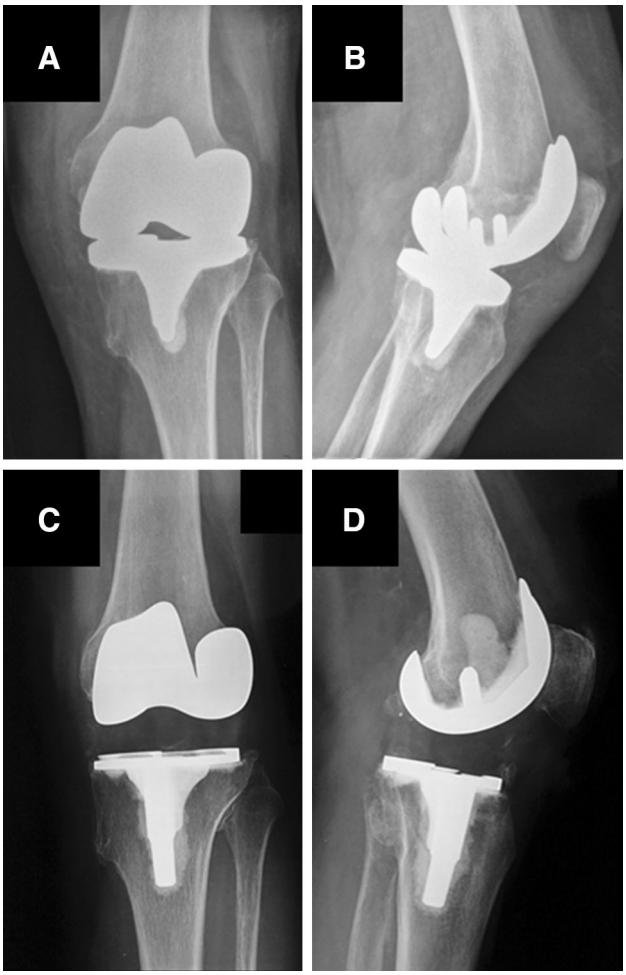

Fig. 1 Plain radiographs of the right knee. **a** Pre-revision anteroposterior view, **b** pre-revision lateral view, **c** anteroposterior view 3 years after revision TKA, **d** lateral view 3 years after revision TKA

We referred the patient to our allergologist who ordered dermal allergy exams to test the components of the prosthesis and other metals. Scratches of the bone cement used (Palacos, Zimmer) were also used in this examination. The tests revealed that the patient had hypersensitivity to nickel sulphate and cobalt chloride and bone cement. However, further patch testing for bone cement components, glues and plastics could not reveal the exact allergen. A more aggressive treatment with corticosteroids (p.o. methylprednisolone 16 mg twice/day for 2 days with gradual reduction of 4 mg every 2 days) and antihistamine drugs (p.o. levocetirizine 5 mg twice/-day for 20 days) followed, but did not result in resolution of the symptoms.

A revision TKA was decided 8 months after the primary procedure. The femoral part of the new prosthesis (Genesis II, Smith and Nephew, Memphis, TN—cruciate-retaining TKA) consisted of zirconium alloy (97.5% zirconium–2.5% niobium) and the tibial one of titanium alloy (Ti-6Al-4V). Unfortunately, at that time, the availability of the prosthesis was limited in our country and we could only use the cemented type without the all-polyethylene tibial component. We conducted a new patch testing for all available types of bone cement and chose the one that did not produce any allergy reaction (Gentafix-3, Teknimed). The postoperative period was uneventful with gradual resolution of the allergic symptomatology. Full disappearance of metal taste and pruritus occurred 3 months after revision. The latest follow-up evaluation (3 years post-revision) was unremarkable (Fig. 1c, d).

Discussion

Ten to 15% of the general population presents dermal symptomatology due to metal hypersensitivity, with nickel being responsible in most cases [7]. Cobalt, chromium, beryllium and less frequently tantalum, titanium and vanadium produce such reaction in a smaller number of patients [7]. The three most common alloys used in orthopaedics (stainless steel, cobalt alloy, titanium alloy) have a considerable content of the aforementioned metals [7]. In our case, the primary TKA prosthesis was made of a cobalt alloy and led to symptoms due to hypersensitivity to cobalt and nickel.

Our patient was also allergic to bone cement, even though we could not identify the exact component that caused this reaction. To our knowledge, such a combination is extremely rare and has not been reported before in the English orthopaedic literature. Bone cement allergies are more infrequent than metal allergies in orthopaedic patients. Previous reports described hypersensitivity to benzoyl peroxide [2, 8] and *N,N*-dimethylparatoluidine [9], while there is a report in which the authors, like us, could not identify the exact component of the polymerized methacrylate bone cement that caused the allergic reaction [10].

The diagnosis of hypersensitivity to orthopaedic implants is made by exclusion of other causes of painful prosthesis or dermatitis after arthroplasty. Topical dermal manifestations include hives, eczema, itching and edema [7, 11]. Other clinical findings such as pain, limited range of motion and elevated temperature at the operated joint have been described [3, 4, 11]. In our patient skin temperature over the prosthesis was slightly elevated in comparison to the contralateral joint upon manual assessment 3 months after TKA. However, increased skin temperature is often present for up to 18 weeks post-TKA [12], so such finding could not be definitely attributed to allergy in our case. Rarely, systemic reactions may occur leading to generalized pruritus and respiratory problems [11, 13]. Surprisingly, our patient's main complaints were metal taste, that presented about a month after primary TKA and continued regardless of treatment, and generalized pruritus, that initially responded fairly to antihistaminic medication. According to Gao et al. there are some criteria for the diagnosis of dermatitis caused by orthopaedic implants, namely the appearance of dermatosis in its definitive form after the insertion of the orthopaedic implants, the exclusion of other causes of dermal manifestations (such as deep periprosthetic infection), the chronic nature of the dermatosis and the subsidence of symptoms after the removal of the implants [5]. All aforementioned criteria were fulfilled in our case.

Currently, there is no consensus about the optimal testing for the detection of metal hypersensitivity. The simplest method is skin patch testing, which allows for simultaneous in vivo testing of many allergens, is relatively cheap and available in many laboratories. However, its ability to detect deep-tissue hypersensitivities is thought to be inferior to contact hypersensitivities [7, 14]. Other modalities detect allergy reactivity in vitro. The best studied is the lymphocyte transformation testing (LTT), which evaluates the proliferation of lymphocytes obtained from peripheral blood after contact with metals [15]. Its main disadvantage is high cost, but it is thought to be superior than patch testing for detection of implant-related hypersensitivity [7]. Unfortunately, we could not perform the more sophisticated method of LTT in our laboratory. Yet, we were able to test many (over 75) metal, plastic and cement components and also all available mixtures of cement by epidermal testing.

Peri-implant tissue biopsy is another modality that could be used to detect allergic reactions. According to a classification system widely accepted in German-speaking countries a type I (particle type) or IV (fibrous type) neosynovium/periprosthetic membrane would be expected [16]. Histopathologic findings include lymphocytic infiltration along with infiltrates of macrophages and multinuclear giant cells with phagocytized prosthesis' wear particles (type I) or connective tissue with high collagen content and a surface cell layer similar to the synovial lining with absent wear particles (type IV) [16]. Biopsy could differentiate allergy from low-grade infection by standard histologic criteria, namely the number of neutrophil granulocytes and presence of bacteria (type II—infectious type or type III—combined I and II type) [16]. However, as lymphocyte infiltrates are not always the result of allergic reactions, the diagnosis of implant allergy should be made with caution and only after consideration of dermatological, allergological, immunological and orthopaedic data [17]. A recent study pointed towards this concept by combining the results of dermal patch tests, LTT, biopsy and periprosthetic cytokine assessment in patients with suspected allergy to TKA [18]. In our opinion, biopsy is of great importance in cases that diagnosis is controversial, e.g. when allergological tests are weekly positive or negative in view of high clinical suspicion of allergy or low-grade infection. Our patient had strongly positive patch tests and negative blood and synovial fluid workup, so we considered that biopsy would not be beneficial.

Many patients with history of metal allergy do not present reactions to their metal prostheses and that fact makes preoperative screening for hypersensitivity in the prostheses components a matter of controversy. Niki et al. support pre-implantation screening for all patients, even though only two of the 92 patients in their study underwent revision TKA (not caused by loosening of the prostheses) [6]. On the other hand, the systematic review of Granchi et al. showed that there is no statistically significant predictive value in such screening, although the authors suggest its use in selected cases of known metal hypersensitivity [19].

There is evidence that orthopaedic implants result in metal sensitization. The majority of data comes from studies on metal on metal total hip arthroplasties and show a possible association between metal allergy and prosthesis failure [20]. There is also data showing that the prevalence of such allergies is higher in patients with TKA (either stable or loosened) in comparison to controls [14].

However, the impact of such sensitization on the survivorship of the implant is not clear, even if the medical history for metal pre-implantation allergy is found to be a risk factor for TKA failure [14]. On the contrary, in a recent study based on the Danish Knee Arthroplasty Register, metal allergy prior to implantation was not associated with higher rates of complications or revision surgery and argued against pre-implantation screening for all patients [21]. This study also demonstrated that patients with two or more revisions had a higher prevalence of metal allergy supporting the concept of secondary sensitization and subsequent failure by the increased release of ions from wear [7, 21], as metal ions are thought to be contributors of osteolysis by increasing the concentration of osteoclast-stimulating cytokines such as interleukin 1β, interleukin 6 and TNF-α [22].

Currently, there is no study proving that hypersensitivity to metal or bone cement causes TKA failure by aseptic loosening [23]. Yet, there is indirect evidence that this might be the case in some patients. Histological findings from periprosthetic tissue of loosened TKAs and THAs are similar with findings from tissues which present delayed type IV hypersensitivity reactions, namely perivascular lymphocyte infiltration and diffuse lymphocytic infiltration [18, 20, 24, 25].

Revision of an allergenic TKA should be carried out when the symptoms do not respond to conservative treatment. The new prosthesis should consist of non-allergenic components. In our case the available hypoallergic prosthesis required cement fixation and was implanted after assuring that the bone cement would not cause allergy. In most of the reported cases the femoral components of the revision prosthesis contained zirconium and that was our choice also [3–5, 13, 26]. We used a titanium–aluminum–vanadium tibial base plate which might contain some remnants of nickel due to the unavailability of the all-polyethylene tibial component. Nevertheless, titanium–aluminum–vanadium and titanium–niobium nitride prostheses had good mid-term results in patients with known allergies to nickel, chromium or cobalt [27, 28].

In our patient full resolution of the symptoms occurred after only 3 months post-revision. A probable explanation is that metal taste and diffuse itching were caused by ions released in blood circulation from the primary prosthesis and at the 3-month period that followed the revision the level of these ions dropped dramatically in such concentration that could not produce any allergic reaction. This hypothesis correlates with findings after removal of metal on metal hip implants that showed a rapid 80% decline in metal ion blood levels 6 weeks post-revision followed by further reduction up to 90% after another 6 weeks [29].

Conclusions

In our opinion, an exhaustive medical history should be obtained from every candidate for total joint replacement and, in cases of prior severe allergic reactions to metals, plastics or glues, patch testing of the components of the future prosthesis should be done. When an already implanted prosthesis causes symptoms like pain, edema, pruritus, erythema, limited range of motion and increase in joint's temperature, the possibility of allergy to metals and/or bone cement (in case of cemented prosthesis) should be checked after the exclusion of other reasons like infection. If symptoms cannot be controlled by conservative measures, revision should be decided and carried out with hypoallergic prosthesis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient.

References

1. Villano M, Carulli C, Puccini S, Soderi S, Innocenti M (2011) Painful knee prosthesis: surgical approach. Clin Cases Miner Bone Metab 8:26–28
2. Edwards SA, Gardiner J (2007) Hypersensitivity to benzoyl peroxide in a cemented total knee arthroplasty: cement allergy. J Arthroplasty 22:1226–1228
3. Thomsen M, Rozak M, Thomas P (2011) Pain in a chromium-allergic patient with total knee arthroplasty: disappearance of symptoms after revision with a special surface-coated TKA—a case report. Acta Orthop 82:386–388
4. Bergschmidt P, Bader R, Mittelmeier W (2012) Metal hypersensitivity in total knee arthroplasty: revision surgery using a ceramic femoral component—a case report. Knee 19:144–147
5. Gao X, He RX, Yan SG, Wu LD (2011) Dermatitis associated with chromium following total knee arthroplasty. J Arthroplasty 26(665):e613–e666
6. Niki Y, Matsumoto H, Otani T, Yatabe T, Kondo M, Yoshimine F, Toyama Y (2005) Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 26:1019–1026
7. Hallab N, Merritt K, Jacobs JJ (2001) Metal sensitivity in patients with orthopaedic implants. J Bone Jt Surg Am 83-A:428–436
8. Jager M, Balda BR (1979) Loosening of a total hip prosthesis at contact allergy due to benzoyl peroxide. Arch Orthop Trauma Surg 94:175–178
9. Haddad FS, Cobb AG, Bentley G, Levell NJ, Dowd PM (1996) Hypersensitivity in aseptic loosening of total hip replacements. The role of constituents of bone cement. J Bone Jt Surg Br 78:546–549

10. Kaplan K, Della Valle CJ, Haines K, Zuckerman JD (2002) Preoperative identification of a bone-cement allergy in a patient undergoing total knee arthroplasty. J Arthroplasty 17:788–791
11. Basko-Plluska JL, Thyssen JP, Schalock PC (2011) Cutaneous and systemic hypersensitivity reactions to metallic implants. Dermatitis 22:65–79
12. Mehra A, Langkamer VG, Day A, Harris S, Spencer RF (2005) C reactive protein and skin temperature post total knee replacement. Knee 12:297–300
13. Innocenti M, Carulli C, Matassi F, Carossino AM, Brandi ML, Civinini R (2014) Total knee arthroplasty in patients with hypersensitivity to metals. Int Orthop 38:329–333
14. Granchi D, Cenni E, Tigani D, Trisolino G, Baldini N, Giunti A (2008) Sensitivity to implant materials in patients with total knee arthroplasties. Biomaterials 29:1494–1500
15. Hallab NJ, Mikecz K, Jacobs JJ (2000) A triple assay technique for the evaluation of metal-induced, delayed-type hypersensitivity responses in patients with or receiving total joint arthroplasty. J Biomed Mater Res 53:480–489
16. Krenn V, Morawietz L, Perino G, Kienapfel H, Ascherl R, Hassenpflug GJ, Thomsen M, Thomas P, Huber M, Kendoff D, Baumhoer D, Krukemeyer MG, Natu S, Boettner F, Zustin J, Kolbel B, Ruther W, Kretzer JP, Tiemann A, Trampuz A, Frommelt L, Tichilow R, Soder S, Muller S, Parvizi J, Illgner U, Gehrke T (2014) Revised histopathological consensus classification of joint implant related pathology. Pathol Res Pract 210:779–786
17. Thomas P, Summer B, Krenn V, Thomsen M (2013) Allergy diagnostics in suspected metal implant intolerance. Orthopade 42:602–606
18. Thomas P, von der Helm C, Schopf C, Mazoochian F, Frommelt L, Gollwitzer H, Schneider J, Flaig M, Krenn V, Thomas B, Summer B (2015) Patients with intolerance reactions to total knee replacement: combined assessment of allergy diagnostics, periprosthetic histology, and peri-implant cytokine expression pattern. Biomed Res Int 2015:910156
19. Granchi D, Cenni E, Giunti A, Baldini N (2012) Metal hypersensitivity testing in patients undergoing joint replacement: a systematic review. J Bone Jt Surg Br 94:1126–1134
20. Thomas P, Braathen LR, Dorig M, Aubock J, Nestle F, Werfel T, Willert HG (2009) Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. Allergy 64:1157–1165
21. Munch HJ, Jacobsen SS, Olesen JT, Menne T, Soballe K, Johansen JD, Thyssen JP (2015) The association between metal allergy, total knee arthroplasty, and revision. Acta Orthop 86:378–383
22. Magone K, Luckenbill D, Goswami T (2015) Metal ions as inflammatory initiators of osteolysis. Arch Orthop Trauma Surg 135:683–695
23. Middleton S, Toms A (2016) Allergy in total knee arthroplasty: a review of the facts. Bone Jt J 98-B:437–441
24. Verma SB, Mody B, Gawkrodger DJ (2006) Dermatitis on the knee following knee replacement: a minority of cases show contact allergy to chromate, cobalt or nickel but a causal association is unproven. Contact Dermatitis 54:228–229
25. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Jt Surg Am 87:28–36
26. Hofer JK, Ezzet KA (2014) A minimum 5-year follow-up of an oxidized zirconium femoral prosthesis used for total knee arthroplasty. Knee 21:168–171
27. Pellengahr C, Mayer W, Maier M, Muller PE, Schulz C, Durr HR, Trouillier H, Steinborn M, Jansson V, Refior HJ (2003) Resurfacing knee arthroplasty in patients with allergic sensitivity to metals. Arch Orthop Trauma Surg 123:139–143
28. Thienpont E (2015) Titanium niobium nitride knee implants are not inferior to chrome cobalt components for primary total knee arthroplasty. Arch Orthop Trauma Surg 135:1749–1754
29. Ball ST, Severns D, Linn M, Meyer RS, Swenson FC (2013) What happens to serum metal ion levels after a metal-on-metal bearing is removed? J Arthroplasty 28:53–55