LETTER TO THE EDITOR

Custom-made cementless revision total knee arthroplasty in a patient with metal and bone cement hypersensitivity

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To the Editor,

Total knee arthroplasty (TKA) is the gold standard to treat end-stage knee osteoarthritis, with excellent long-term functional outcomes, but along with the increasing demand for this procedure, the number of revision total knee arthroplasties (RTKA) is rising (1). The most common causes of TKA failure are infection, aseptic loosening, periprosthetic fractures, implant instability, patellar maltracking and residual pain (2). Hypersensitivity to metals and polymethylmethacrylate (PMMA) bone cement has been reported in patients undergoing RTKA without other evident reasons, such as possible uncommon cause of pain, but its role as causative factor or consequence of a TKA loosening is still debated (3-6). Nevertheless, RTKA with hypoallergenic components is required in these cases (4). We herein report the first case of a 74-year old patient who had an aseptic loosening of TKA with bone cement and metal hypersensitivity, treated with RTKA using a custom-made hypoallergenic cementless condylar-constrained implant. This report has been written according with the CARE guidelines for case reports. The patient gave his informed consent to use his anonymized clinical data for scientific purposes.

Clinical case

A 74-year old male who had undergone a TKA on the left knee in 2012 for end-stage knee osteoarthritis, came to our department in July 2018 presenting left knee pain, major instability, and impossibility to weight-bearing. The symptoms had started six months after the left TKA procedure. During consultation, clinical examination revealed an antalgic gait with limping, 10° varus alignment and 10° fixed flexion contracture of the left knee. Diffuse skin rashes had appeared after TKA surgery, and edema were also seen around the knee. Range of motion was 10° to 90°. In addition, there were clinical signs of moderate laxity of the medial collateral ligament. The patient's

Key words: revision total knee arthroplasty; revision total knee replacement; metal allergy; metal hypersensitivity; PMMA allergy; bone cement hypersensitivity; custom-made cementless hypoallergenic TKA; TKA failure; metaphyseal sleeves; antibacterial coatings

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Table I. *Panel of the haptens tested through skin patch test.*

Hapten	Patch test positivity at 72 h	Hapten	Patch test positivity at 72 h
Benzoyl peroxide	-	Mercaptobenzothiazole Mix	-
Bisphenol A-glycidyl methacrylate	-	2-mercaptobenzothiazole	-
1,4 Butandiol diacrylate	-	Molybdenum	-
Butylacrylate	+ - -	Methyl methacrylate	-
Butyl methacrylate	+ - -	Pyrogallol	-
Carba mix	-	Paraphenylenediamine Mix	-
Dibutyl phthalate	-	Resorcin	-
Diethyl phthalate	-	Tetraethylene glycol dimethacrylate	-
N,N-dimethyl P-toluidine	-	Thiuram mix	-
Di-N-Octyl phthalate	-	Tricresyl phosphate	-
1,6-Hexanediol diacrylate	-	Triethylene glycol dimethacrylate	-
Ethyl acrylate	-	Triphenyl phosphate	-
Ethyl methacrylate	-	Trimethylolpropane triacrylate	-
Ethylene glycol dimethacrylate	-	Diurethane dimethacrylate	-
2-ethylhexyl acrylate	-	Titanium dioxide	-
Hydrazine hydrate	-	Potassium dichromate	-
Hydroquinone monobenzyl ether	-	**Cobalt(II) chloride hexahydrate**	+ - -
2-hydroxyethylmethacrylate	-	Nickel(II) sulfate hexahydrate	-
Hydroxypropyl methacrylate	-	Aluminium chloride	-
Isobutyl acrylate	+ - -	Chromium(III) chloride	-

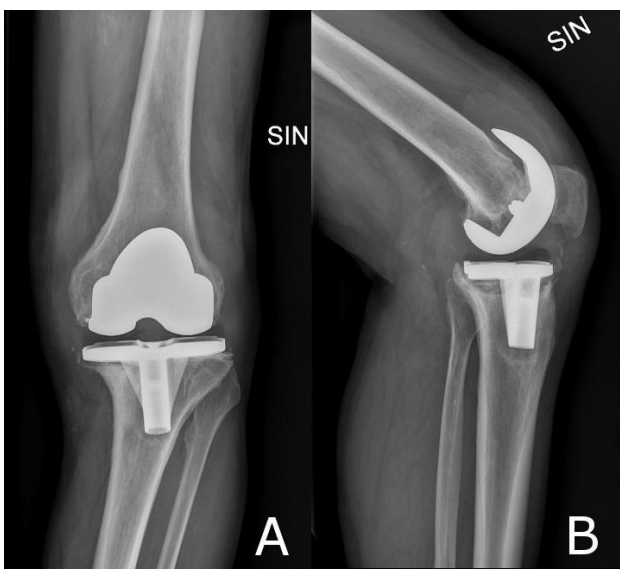

Fig. 1. *Preoperative X-rays showing TKA loosening.*

medical history was positive for asthma and restless leg syndrome. Patient-reported outcomes (PROs) on knee function revealed very low scores (WOMAC 76%, Oxford Knee Score 9/48). Knee Injury and Osteoarthritis Outcome Score (KOOS) resulted: symptoms 35.71%, pain 27.78%, daily function 23.53%, sport-related function 0%, quality of life 6.25%. SF-36 questionnaire showed very low results in the physical, emotional and social areas.

Plain radiographs revealed a severe loosening of the tibial tray with massive bone resorption involving the tibial metaphysis. The distal femur showed also diffuse radiolucency at the bone-implant interface (Fig. 1). The periprosthetic bone loss was classified as type 2a according to the Anderson Orthopaedic Research Institute (AORI) (Fig. 2). Computed

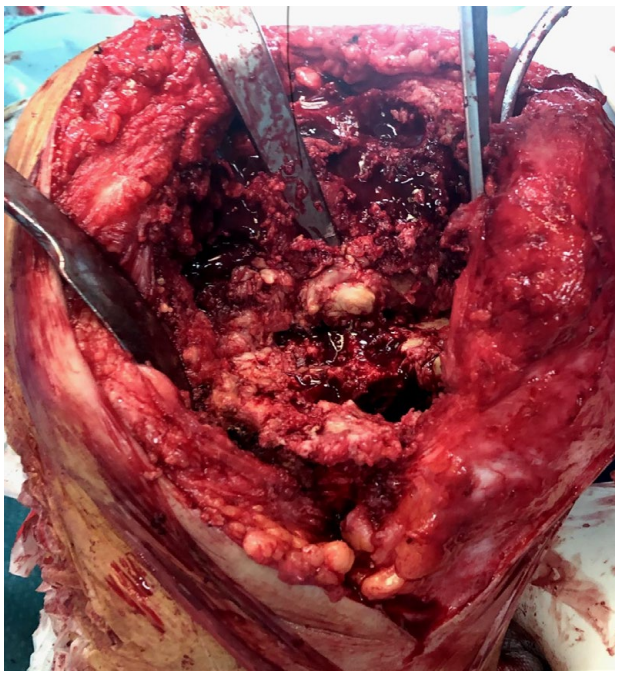

Fig. 2. *The periprosthetic bone loss.*

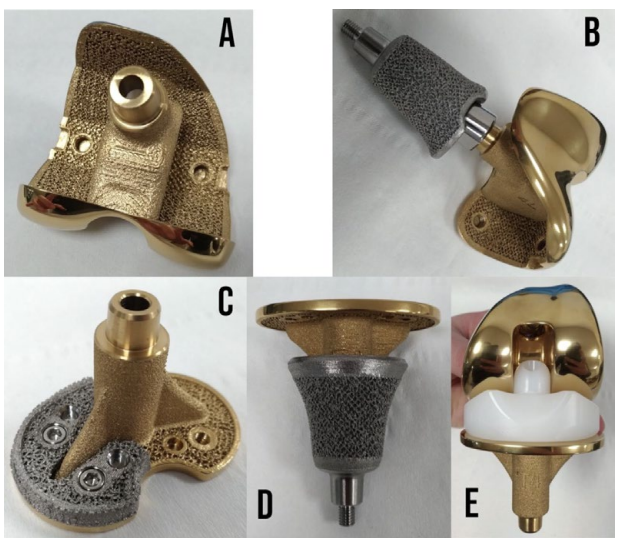

Fig. 3. *3D custom-made cementless condylar-constrained implant with meta-diaphyseal fixation (Adlerortho S.p.A, Cormano, Milano, Italy) (**E**). The femoral component was made of a zirconium alloy (97.5% zirconium- 2.5% niobium) (**A**) with a titanium metaphyseal sleeve (**B**) and a femoral stem that allowed for meta-diaphyseal fixation. Titanium tibial tray with a 5 mm medial wedge (**C**) was used to address the bone loss, and a metaphyseal sleeve (**D**) with a short stem was chosen to guarantee bone fixation and ingrowth.*

Tomography (CT) scans indicated a diffuse area of osteolysis around the implant, which was completely loosened, and a fluid collection of 5 x 3 cm in the subquadricipital recess.

Periprosthetic joint infections were excluded according to the Musculoskeletal Infection Society criteria (7). A complete laboratory workup was made, including: complete blood count with white blood cells 7.4 x 10^9/L (reference value 5-10 x 10^9/L), normal eosinophil count, C-reactive protein 1.2 mg/L (reference range, 0-10 mg/L), erythrocyte sedimentation rate 30 mm/h, and negative cultures and biochemical analysis of the synovial fluid. Blood exams were repeated preoperatively with similar results. Bone scans (three-phase scintigraphy) revealed an abnormally high uptake of the radiotracer around the medial tibial tray and medial femoral condyle, and ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy excluded a possible infectious etiology.

Due to the local presence of skin rashes, hypersensitivity to implant components was suspected. The patient underwent Patch testing, focused on the most common allergens contained in orthopaedic implants and cement (Table I). Patch testing was moderately positive to butylacrylate, butyl methacrylate, isobutyl acrylate, and cobalt (II) chloride hexahydrate. Subsequently, a diagnosis of TKA aseptic loosening with acrylates and cobalt hypersensitivity was made.

After meticulous preoperative planning, an RTKA was performed. Both the components of the prosthesis were loose. Five samples of periprosthetic tissue were sent for both cultural and histological examination (less than five neutrophils per high-power field; presence of chronic inflammation and foreign body giant cell reaction). Given the bone loss and the double hypersensitivity issue, a hypoallergenic 3D custom-made cementless condylar-constrained implant with meta-diaphyseal fixation (Adlerortho S.p.A, Cormano, Milano, Italy) was chosen. The femoral component was made of a zirconium alloy (97.5% zirconium, 2.5% niobium) with a titanium metaphyseal sleeve and a femoral stem that allowed for meta-diaphyseal fixation (Fig. 3). On the tibial side, a titanium tibial tray with a 5 mm medial wedge was used to address the

bone loss, and a metaphyseal sleeve with a short stem was chosen to guarantee bone fixation and ingrowth. Implant surfaces facing the bone were coated with an antibacterial hydrogel loaded with Vancomycin 500 mg and Meropenem 500 mg at 5% dilution (Defensive Antibacterial Coating – DAC®, Novagenit S.R.L, Mezzolombardo, Trento, Italy) just before implantation. At the end of the surgery, the implant was stable.

Postoperatively, plain radiographs were performed and confirmed the correct alignment. For the first six weeks after surgery, the patient was instructed to walk with partial weight-bearing. He completed the rehabilitation process without problems. At 1-year follow-up he could walk with full bearing and no pain, range of motion was 0°-110° and there were no radiological signs of osteolysis around the implant (Fig. 4). The skin rashes around the knee had fully disappeared. We observed an improvement in all the SF-36 items, especially in the physical and social areas, as well as in all the knee PROs (WOMAC 42.7%, Oxford Knee Score 33/48, KOOS: symptoms 67.86%, pain 69.44%, daily function 70.59%, sport-related function 30%, quality of life 31.25%). The patient himself said to be very satisfied with the surgery.

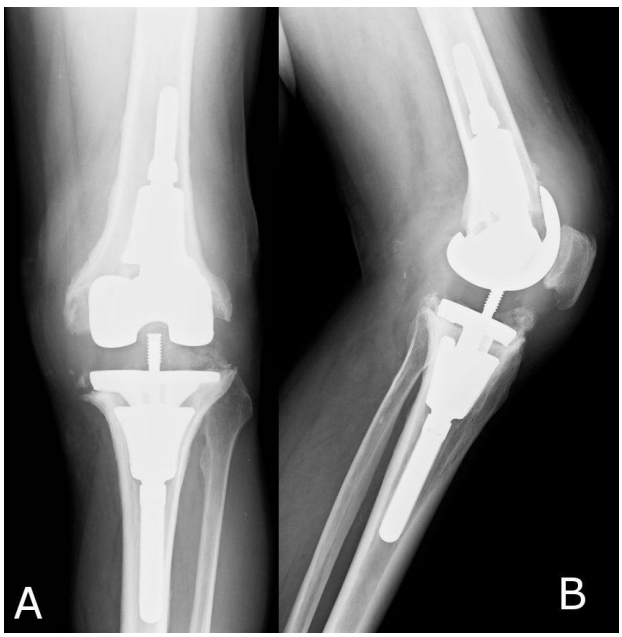

Fig. 4. *1-year follow-up X-rays showing no signs of implant loosening.*

DISCUSSION

To our knowledge, this is the second case in the English literature of aseptic TKA loosening associated with hypersensitivity to both acrylates and cobalt, and the first treated with a custom-made cementless hypoallergenic RTKA to face this uncommon double issue. Stathopoulos et al. reported a case of a patient who had an aseptic loosening with hypersensitivity to metals and bone cement components treated successfully with a hypoallergenic implant fixated with a cement to which the patient was not sensitized (5).

Allergy-related implant failure is an exclusion diagnosis. Skin patch testing is useful, inexpensive, and represents the first line diagnostic test, but the response may vary from subject to subject and the overall sensitivity reported for acrylates is only 46.2-61.5% (4, 8). Other promising tests, such as the Lymphocyte Transformation Test (LTT), the Leukocyte Migration Inhibition test and the Memory Lymphocyte Immunostimulation Assay (MELISA), are not yet routinely available in several hospitals (4). Recently, Saccomanno et al. proposed an algorithm to guide diagnosis and implant choice in case of hypersensitivity (9). In our case, MELISA and LTT were not performed, as they are not available at our institution.

Nowadays, two options mainly exist for RTKA in case of metal hypersensitivity: cobalt-chrome implants, coated with inert substances, and revision systems with an oxidized zirconium femoral component and titanium tibial tray and stem (4, 10). Regarding hypersensitivity to bone cement, cementless replacements should be considered (10). Modern knee revision systems include osseo-integrative metal sleeves with a specially structured surface supporting bone ingrowth and enhancing durable stable fixation by a cementless technique. The femoral and tibial implants can be placed independently of where the sleeve is placed, so that the sleeve itself could be rotated to the best bone stock, and the components to the appropriate orientation (11). These implants showed up to 98% survival rate after 5 years (12). We opted for a 3D-customized condylar-constrained implant with meta-diaphyseal cementless fixation through

sleeves. Results were very satisfying after 1 year, although a longer follow-up is needed to test the long-term implant stability.

REFERENCES

1. Khan M, Osman K, Green G, et al. The epidemiology of failure in total knee arthroplasty: avoiding your next revision. Bone Joint J 2016; 98-B:105-112. doi: 10.1302/0301-620X.98B1.36293
2. Postler A, Lutzner C, Beyer F, et al. Analysis of Total Knee Arthroplasty revision causes. BMC Musculoskelet Disord 2018; 19:55. doi: 10.1186/s12891-018-1977-y
3. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 2001; 83:428-436. doi: 10.2106/00004623-200103000-00017
4. Innocenti M, Vieri B, Melani T, et al. Metal hypersensitivity after knee arthroplasty: fact or fiction? Acta Biomed 2017; 88:78-83. doi: 10.23750/abm.v88i2 -S.6517
5. Stathopoulos IP, Andrianopoulos N, Paschaloglou D, et al. Revision total knee arthroplasty due to bone cement and metal hypersensitivity. Arch Orthop Trauma Surg 2017; 137:267-71. doi: 10.1007/s00402-016-2614-6
6. Carulli C, Villano M, Bucciarelli G, et al. Painful knee arthroplasty: definition and overview. Clin Cases Miner Bone Metab 2011; 8:23-5.
7. Parvizi J, Gehrke T, International Consensus Group on Periprosthetic Joint I. Definition of periprosthetic joint infection. J Arthroplasty 2014; 29:1331. doi: 10.1016/j.arth.2014.03.009
8. Spencer A, Gazzani P, Thompson DA. Acrylate and methacrylate contact allergy and allergic contact disease: a 13-year review. Contact Dermatitis 2016; 75:157-64. doi: 10.1111/cod.12647
9. Saccomanno MF, Sircana G, Masci G, et al. Allergy in total knee replacement surgery: Is it a real problem? World J Orthop 2019; 10:63-70. doi: 10.5312/wjo.v10.i2.63
10. Faschingbauer M, Renner L, Boettner F. Allergy in total knee replacement. does it exist?: Review Article. HSS J 2017; 13:12-19. doi: 10.1007/s11420-016-9514-8
11. Burastero G, Cavagnaro L, Chiarlone F, et al. A Case report: custom made porous titanium implants in revision: a new option for complex issues. Open Orthop J.2018; 12:525-35. doi: 10.2174/1874325001812010525
12. Wirries N, Winnecken HJ, Lewinski GV, et al. Osteointegrative Sleeves for Metaphyseal Defect Augmentation in Revision Total Knee Arthroplasty: Clinical and Radiological 5-Year Follow-Up. J Arthroplasty 2019; 34:2022-9. doi: 10.1016/j.arth.2019.04.024