



Letter

Aseptic loosening of a total knee prosthesis caused by delayed hypersensitivity to bone cement

Delayed hypersensitivity to metals remains the most common cause of allergic reactions to orthopedic prostheses.¹ Thus, when an allergic study of an implant failure is performed, metals are usually the only antigens tested, although sensitization to other materials included in prostheses is also possible. In this context, delayed hypersensitivity to bone cement has been previously described.² This product is used in dentistry and orthopedic surgery as a grouting agent to stabilize different prosthetic components and to fill spaces between prosthesis and the insertion cavity. It is also present in joint spacers and cemented prostheses themselves.³ We describe 2 patients with aseptic loosening of knee prosthesis caused by delayed hypersensitivity to different components of bone cement.

Patient 1 was a 73-year-old woman with a right gonarthrosis who underwent a knee replacement using a cemented prosthesis (NEX-GEN LPS; Zimmer Inc, Norcross, Georgia), which was poorly tolerated. Therefore, a subsequent surgery was performed, and a new cemented prosthesis (LCCK; Zimmer Inc) was implanted, which also had to be removed because of local pain. Cement spacer was placed before arthrodesis was performed, but inflammatory symptoms were maintained. In a detailed medical history, the patient had intolerance to dental implants and dermatitis after exposure to adhesive plasters and surgical tapes, but these conditions had not been previously assessed.

Patient 2 was an 80-year-old woman diagnosed as having right gonarthrosis. A knee prosthesis of unknown type was implanted, but it had to be removed because of a local infection. Cement spacer was placed after systemic antibiotherapy, but severe local inflammation appeared in her knee. Noteworthy, histopathologic findings of periprosthetic materials were consistent with the diagnosis of foreign-body reaction to biomaterials in both patients (Fig 1).

Written informed consent was obtained from both patients. Patch tests were conducted with the T.R.U.E. TEST (SmartPractice Denmark ApS, Hillerød, Denmark). Likewise, a specific panel of metals¹ and different substances included in bone cement (Bial-Aristegui, Bilbao, Spain), including 1% benzoyl peroxide, 11% hydroquinone, 5% dimethyl-paratoluidine, 10% methylmethacrylate monomer, 2% hydro-hexyl-methacrylate, 10% ethyl methacrylate, and 1% ethyl acrylate, were tested with Curatest (Lohmann & Rauscher International GmbH & Co, Rengsdorf, Germany). The vehicle used for testing all these substances was petrolatum, except for aluminum and copper, which were diluted in water. The test specificity (lack of irritant effect) of these commercial antigens belonging to Bial-Aristegui was supported by the laboratory and by our previous clinical experience.

Patch tests were applied to the upper back using Oper tape (IberHospitex, Barcelona, Spain) and removed after 2 days. Readings were performed at 48, 96, and 144 hours and categorized according to recommendations of the International Contact Dermatitis Research Group. Patch tests had strong positive results (2+) with all methacrylates in our first patient and negative results with other antigens. It was remarkable that an erythematous reaction appeared in the Curatest and Oper tape areas, probably because they carry acrylic adhesive.

Meanwhile, patient 2 had a weak positive result to benzoyl peroxide (1+), formaldehyde (1+), Kathon CG (1+), and quaternium 15 (1+), given that these 3 substances, included in the T.R.U.E. TEST, are not present in bone cement. Consequently, patient 1 was diagnosed as having aseptic loosening of cemented knee prosthesis because of delayed sensitization to methacrylate, together with allergic contact dermatitis to acrylate. A noncemented metallic prosthesis composed of cobalt-chromium-molybdenum alloy and ultrahigh-molecular-weight polyethylene was placed, banning bone cement during surgery. Good tolerance to the new prosthesis was found at a long-term follow-up.

In our second patient, the diagnosis was aseptic loosening of prosthesis probably because of delayed sensitization to benzoyl-peroxide. Placement of a new prosthesis was declined because of severe joint disorder, and a knee arthrodesis was performed.

Joint replacements are increasing worldwide, and implant failures are likely to increase accordingly, with an estimated fail rate of 2.1% in knee prosthetic surgery during 5 or more years.⁴ These failures can be caused by prosthetic infections but sometimes an aseptic loosening of prostheses is observed.¹ It can be caused by mechanical or structural factors and also by allergic reactions to any of the prosthetic components: metals (including cobalt, chromium, copper, molybdenum, nickel, manganese, aluminium, and titanium), polyethylene disks, niobium-zirconium ceramic alloys, antibiotics (aminoglycosides, mupirocin), and, interestingly, bone cements.²

Bone cement curing involves polymerization of a mixture of methylmethacrylate monomer and polymethyl methacrylate powder, using benzoyl peroxide as an initiator, hydroquinone as a stabilizer, and N,N-dimethyl-p-toluidine as an accelerator. Polymethyl methacrylate is obtained after polymerization of acrylic acid because its nonpolymerized particles are the main cause of allergic reactions among the component of bone cement. Its prevalence has been estimated at 1% to 1.4% among patients with contact dermatitis.⁵ Similarly, delayed hypersensitivity to N,N-dimethyl-p-toluidine,⁶ benzoyl peroxide,⁷ and hydroquinone⁸ has also been described.

In the diagnosis of delayed hypersensitivity to implants, patch tests are routinely used, but metals are often the only antigens

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.04.013>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

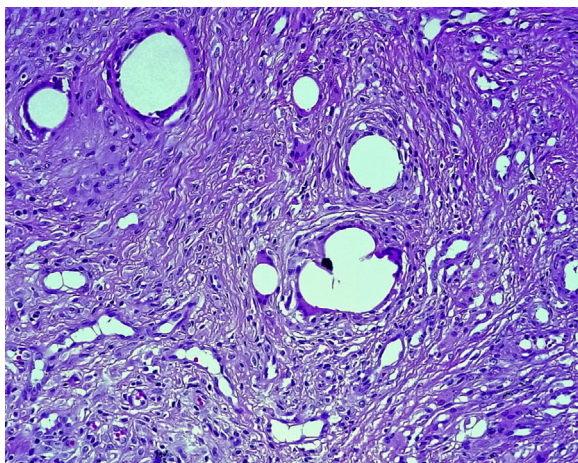


Figure 1. Histopathologic findings of periprosthetic tissues: multinucleated giant cells with lymphoplasmacytic infiltration around the cement particles (original magnification $\times 400$).

included in diagnostic panels. If we had tested just metals in our patients, we would not have reached a proper diagnosis. Therefore, a wider selection of antigens, according to prosthesis components, such as those from bone cement, would improve patch testing efficiency.

Weak patch test results to 1% benzoyl peroxide could be irritant, especially in cases of previous atopic dermatitis or irritable skin,⁹ but these conditions were not observed in our second patient. Moreover, a commercial antigen, whose specificity was tested by the manufacturer, has been used. These findings suggest that delayed hypersensitivity was involved in the above reaction, in agreement with the clinical history.

We recommend performing a histologic study of the material obtained when any prosthesis is removed. In our opinion, a type IV allergy is highly suggested when both a foreign-body reaction around the cement particles and a positive patch test result to implicated products are found. In the same way, a comprehensive assessment of the patient medical history could enable a better approach for the allergy study. Thus, incidents in previous orthopedic operations or any skin reaction after exposure to acrylic cements, dental implants, paints, inks, or surgical tapes suggest that a bone cement allergy should be ruled out.¹⁰ In fact, our first patient had a previous history of contact dermatitis to surgical tapes that, if it had not gone unnoticed, could have prevented the use of acrylates in her orthopedic surgery.

In conclusion, when a prosthesis loosening is present and once infection or mechanical issues are ruled out, a delayed allergy should be considered. Diagnostic panels for path testing to properly assess sensitization to implant components should include not only metals but also bone cement components, as previously suggested.^{1,2,10} Thus, a correct diagnosis would improve the preoperative planning of orthopedic surgery, allowing the surgeon to choose the most suitable prosthesis components.

Francisco Vega, MD*
 Raphaelle Bazire, MD*
 M. Teresa Belver, PhD*
 M. Victoria Mugica, PhD*
 Andres Urquia, MD†
 Carlos Blanco, PhD*

*Department of Allergy
 Hospital Universitario de la Princesa
 Instituto de Investigación Sanitaria Princesa
 Madrid, Spain

†Department of Anatomical Pathology
 Hospital Universitario de la Princesa
 Madrid, Spain

fvega13@hotmail.com

References

- [1] Pinson ML, Coop CA, Webb CN. Metal hypersensitivity in total joint arthroplasty. *Ann Allergy Asthma Immunol*. 2014;113:131–136.
- [2] Pacheco K. Allergy to surgical implants. *J Allergy Clin Immunol Pract*. 2015;3:683–695.
- [3] Leggat PA, Smith DR, Kedjarune U. Surgical applications of methyl methacrylate: a review of toxicity. *Arch Environ Occup Health*. 2009;64:207–212.
- [4] Kane RL, Saleh KJ, Wilt TJ, et al. Total knee replacement. *Evid Rep Technol Assess*. 2003;86:1–8.
- [5] Goon AT, Bruze M, Zimerson E, Goh CL, Soo-QueeKoh D, Isaksson M. Screening for acrylate/methacrylate allergy in the baseline series: our experience in Sweden and Singapore. *Contact Dermatitis*. 2008;59:307–313.
- [6] Haddad FS, Cobb AG, Bentley G, Levell NJ, Dowd PM. Hypersensitivity in aseptic loosening of total hip replacements: the role of constituents of bone cement. *J Bone Joint Surg Br*. 1996;78:546–549.
- [7] Bircher A, Friederich NF, Seelig W, Scherer K. Allergic complications from orthopaedic joint implants: the role of delayed hypersensitivity to benzoyl peroxide in bone cement. *Contact Dermatitis*. 2012;66:20–26.
- [8] Eben R, Dietrich KA, Nerz C, et al. Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty. *Dtsch Med Wochenschr*. 2010;135:1418–1422.
- [9] Ockenfels HM, Uter W, Lessmann H, Schnuch A, Geier J. Patch testing with benzoyl peroxide: reaction profile and interpretation of positive patch test reactions. *Contact Dermatitis*. 2009;61:209–216.
- [10] Granchi D, Cenni E, Trisolino G, Giunti A, Baldini N. Sensitivity to implant materials in patients undergoing total hip replacement. *J Biomed Mater Res B Appl Biomater*. 2006;77:257–264.