

CASE REPORT

A rare case of pseudotumor formation associated with methyl methacrylate hypersensitivity in a patient following cemented total knee arthroplasty

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Received: 27 November 2015 / Revised: 4 March 2016 / Accepted: 10 March 2016 / Published online: 29 March 2016
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Abstract Hypersensitivity to orthopedic implant materials has been well documented with potential catastrophic consequences if not addressed pre-operatively. The spectrum of reactions is wide, from mild non-specific pain with localized erythema to severe periprosthetic inflammatory destruction and pseudotumor formation. It is therefore essential to identify patients who have or are at risk for implant-associated hypersensitivity. Although metal sensitivity is commonly cited as the cause of these reactions, methyl methacrylate (MMA) has rarely been implicated. To the best of our knowledge, methyl methacrylate-associated pseudotumor formation has not yet been described. The following is a case report of a 68-year-old female who, after undergoing a routine cemented right total knee arthroplasty, developed a painless, enlarging mass during a 13-year period. This mass was found to be a pseudotumor in association with methyl methacrylate hypersensitivity. A review of pseudotumor pathogenesis, methyl methacrylate hypersensitivity, and preoperative preventative care is discussed.

Keywords Methyl methacrylate · Pseudotumor · Hypersensitivity · Total knee arthroplasty · Allergy

Introduction

Hypersensitivity to various orthopedic implant materials has been well documented as a potential cause of complications in total joint replacement surgery. Sequelae of these reactions can be mild to severe, ranging from minor cutaneous symptoms such as localized and generalized dermatitis, to extensive fibrosis, fistula formation, aseptic loosening, and periprosthetic fractures [1].

When these inflammatory responses are not well controlled and continue unabated, pseudotumors may form. A pseudotumor refers to a sterile, inflammatory cystic or solid lesion which resembles a tumor but is neither infectious nor neoplastic in nature [2]. Formation of these pseudotumors has been widely discussed in the orthopedic literature [1, 3–15]. Thakur, Ast, and Rodriguez et al. described similar manifestations in a case series of implant-associated allergic hypersensitivity. Their patients developed florid chronic synovitis in response to metal allergies, with histologic reports of “marked synovial hypertrophy and hyperplasia with perivascular lymphoplasmacytic aggregates and myxomatous degeneration” [16].

The exact etiology of pseudotumor formation is unclear, however hypersensitivity-mediated reactions and excessive mechanical wear are the commonly cited causes. Common allergens implicated include beryllium, nickel, cobalt, manganese, and chromium, as well as case reports of tantalum, titanium, and vanadium [17]. Methyl methacrylate (MMA) and various other acrylate compounds have rarely been implicated as sources of hypersensitivity, and to date, have never been

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documented as causing a pseudotumor [17–25]. This case report describes one such case.

Case presentation

A 68-year-old female with a history of hyperlipidemia and gastroesophageal reflux (GERD) underwent primary cemented total knee arthroplasty (TKA) of the right knee for degenerative knee osteoarthritis in July of 2001. An Optetrak Non-Modular Constrained Condylar Knee system composed of a cobalt-chromium alloy femoral component and a titanium alloy tibial component was utilized (Exactech, Gainesville, FL, USA). The patient developed progressive swelling during the course of the following months, which initially raised suspicions of septic arthritis. Arthroscopic incision and drainage of the knee 4 months postoperatively revealed a large fluid collection, however no signs of gross infection, component loosening, or solid mass formation were noted, with all intraoperative cultures negative for bacterial growth. The patient's swelling returned in the ensuing months and never resolved. The patient otherwise had no complaints of pain or weakness, thus no intervention was taken.

Over the course of the next few years, the patient developed degenerative knee osteoarthritis of the contralateral knee as well, undergoing left total knee arthroplasty in January of 2010. As part of her preoperative planning, skin patch allergy testing was performed, which was strongly positive for reactions to methyl methacrylate, ethyleneglycol dimethacrylate, and (2-hydroxyethyl) methacrylate (2-HEMA). The test was negative for other substances including cobalt, nickel, and various dyes. A focused allergic history was taken, which was remarkable for mild-to-moderate allergic reactions to Aleve, Penicillin, leather sandals, and components in hair removal wax. For her second arthroplasty, press-fit, non-cemented components were utilized, which led to an unremarkable postoperative course, without significant swelling or mass formation. Two years after her second knee arthroplasty, the patient, having forgotten to notify her dentist of her previous allergic history, sustained a moderate allergic reaction including lip swelling a day after a temporary crown was placed using methyl methacrylate. She immediately returned to her dentist who revised the crown using a MMA-free compound for which she was asymptomatic.

At 13 years postoperatively from her right total knee arthroplasty, the patient began experiencing severe right knee pain, which significantly limited her daily activities and ambulation. The patient's right knee swelling had progressed with well-defined borders as is seen in Fig. 1. She reported no history of trauma, fever, chills, malaise, weight loss, or changes in overall health. On physical examination, a mildly fluctuant, tender soft tissue mass measuring approximately 10 cm wide and 5 cm long was noted overlying her anterior

knee. No warmth, erythema, or cutaneous lesions were noted. The patient had limited knee range of motion of 0 to 100°. Plain radiographs and magnetic resonance imaging, shown in Figs. 2 and 3, were significant for a large T2-sensitive synovial-based mass in the suprapatellar recess with a large joint effusion causing mass effect on the subjacent structures, as well as a large erosion of the anterior distal femur with no evidence of component loosening or fracture.

The patient was afebrile, with all vital signs stable. White blood cell count (8.8 K/ μ l), erythrocyte sedimentation rate (7 mm/h) and basic metabolic panel were all within normal limits. ANA, lyme titers, and HLA-B27 results were negative. Bone scan revealed mild right knee tracer uptake compatible with osteoarthritis with no evidence of infection. The differential diagnosis included wear debris, metallosis, aseptic loosening, abscess, primary soft tissue or bone sarcoma and metastatic carcinoma. It was decided to proceed with an excisional biopsy to further characterize the lesion.

An incision was made through the original mid-patellar anterior scar. Deep dissection was carried out into the joint where an extensive, turbid joint effusion of about 400 ml was drained. Using careful dissection, a total synovectomy of the proliferative synovitis around the metal components and around the knee, extending into the suprapatellar pouch, was performed. A large mass was identified, which extended from the knee joint to the distal thigh. The mass had a well-defined pseudocapsule and was removed completely in one large segment measuring 15 cm in width and 10 cm in length. It was noted that the synovial proliferation and reactive tissue extended primarily from the femoral component cement–bone interface producing superficial osteolysis of the contact surfaces, without significant component loosening. This was not seen over the patella and tibial bone cement interfaces, possibly due to a better seal of the cement lining. The wound was irrigated and closed. Intraoperative cultures were negative for bacteria, fungi, and acid-fast bacilli.

The specimen consisted of a tan-white to brown cystic mass with slightly rough surfaces (Fig. 4). The cyst wall measured 0.5 cm in thickness. The inner wall of the cyst had areas of yellow to brown friable tissue. Histologically, the cyst contents consisted of abundant acellular fibrinous material (Fig. 5). Sections through the cyst wall demonstrated fibrinous tissue with prominent focal aggregates of histiocytic cells. Scattered perivascular aggregates of lymphocytes and fewer plasma cells were also present. No other inflammatory cells were observed. The findings were those of an inflammatory pseudotumor.

Based on synovial lining integrity, cellular features of the inflammatory cell infiltrate and tissue architectural organization, a histologic ALVAL score of seven out of ten was obtained. Breakdown of the score is as follows, A) marked loss of synovial surface with abundant fibrin attachment resulting in a score of 2/3, B) predominantly macrophage cellular

Fig. 1 Anterior and lateral photographs of the right knee of a 68-year-old female with chronic swelling 13 years status post right cemented total knee arthroplasty



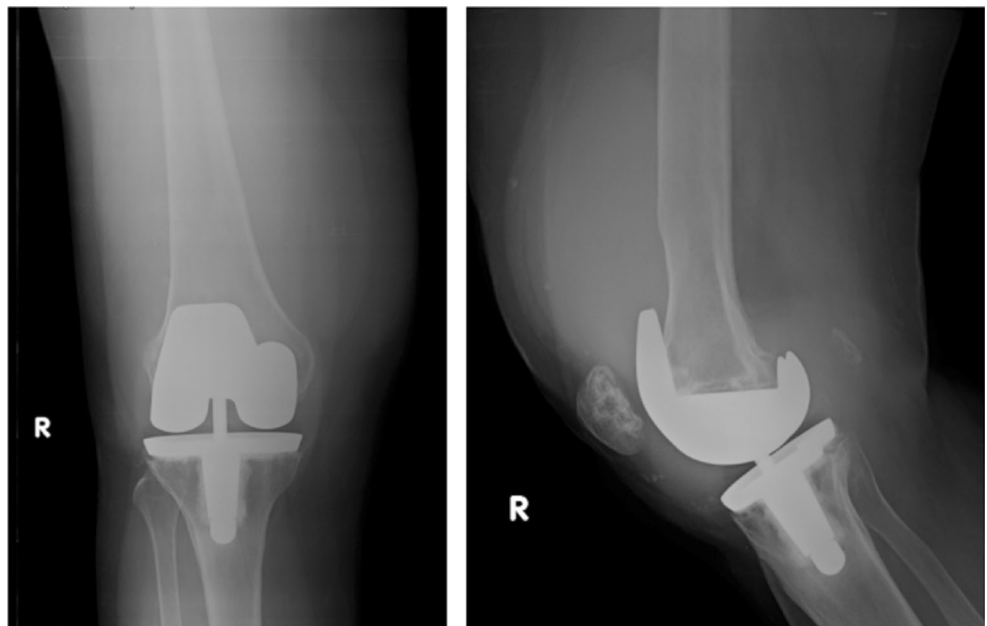
infiltrate with focal perivascular lymphocytic aggregates resulting in a score of 3/4 and C) marked loss of tissue organization resulting in a score of 2/3.

The patient gradually returned to a full level of activity, initially weight bearing as tolerated with crutches, transitioned to full unrestricted ambulation. The need for future revision arthroplasty was emphasized to the patient, however the patient declined any further operative intervention. At her 2-year postoperative visit, the patient was doing well and her pain was controlled. Her range of motion was 0 to 100° with an associated mild joint effusion, without any palpable masses assessed on physical exam.

Discussion

This case highlights a unique example of progressive pseudotumor formation after cemented total knee arthroplasty in a patient with confirmed allergy to methyl methacrylate. The pseudotumor had an indolent growth pattern, enlarging over a period of 13 years. A predilection of pseudotumor growth towards areas where methyl methacrylate had excessive intra-articular exposure, such as the anterior femoral component, was noted. This was unlike the tibial and patellar surfaces, which had a better seal at the cement-implant interface. With no anterior mechanical boundary inhibiting its

Fig. 2 AP and lateral radiographs with obvious soft tissue mass seen overlying the right distal femur with associated anterior femoral cortical erosion



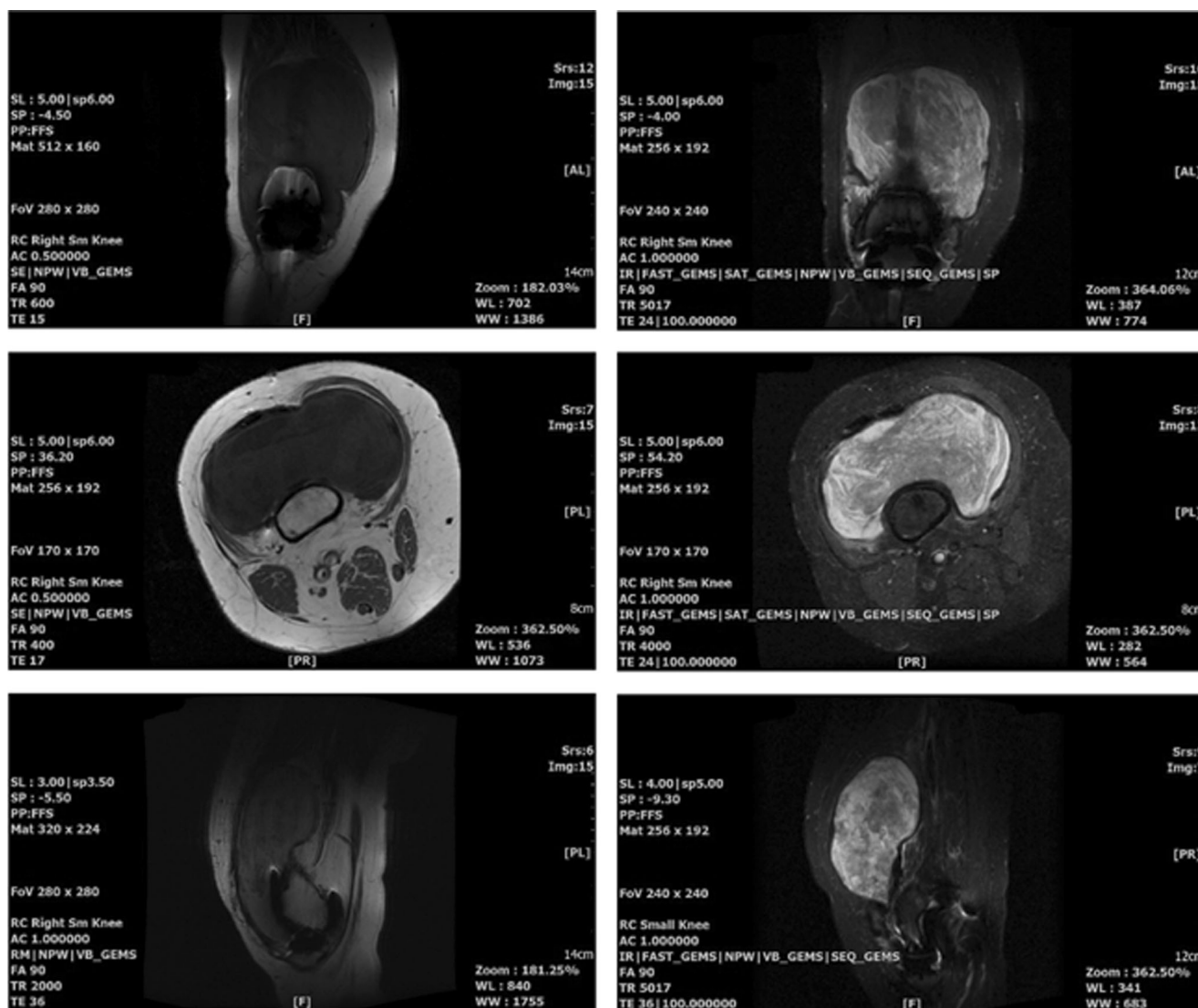


Fig. 3 Coronal, axial, sagittal T1- (*left*) and T2 (*right*)-weighted magnetic resonance images

growth, the mass spread freely through the synovial cavity and up the suprapatellar pouch, causing a mass effect. No pseudotumor formation was seen intraosseously, presumably due to the mechanical blockage by the underlying bone. These findings, along with a history of an allergic reaction to a methyl methacrylate dental crown, positive allergy testing to methyl methacrylate and negative testing to cobalt and nickel further supports pseudotumor formation in response to methyl methacrylate hypersensitivity.

There have been few cases of methyl methacrylate hypersensitivity reactions documented in the orthopedic literature and none to date that have progressed to pseudotumor formation. Thus far, most cases of MMA reactions have been detailed in various journals of dentistry and dermatology, with rare cases seen in the orthopedic literature [25–32]. Hart et al. defined pseudotumors as “sterile, inflammatory lesions within the periprosthetic tissues and have been variously termed

masses, cysts, bursae, collections, or aseptic lymphocytic vasculitis-associated lesions (ALVAL)” [3]. According to Hart, the prevalence of periprosthetic pseudotumors is unclear, largely due to the use of the term “pseudotumor” for a wide spectrum of lesions ranging from small benign cysts to large, complex destructive lesions. A literature review showed prevalence rates ranging from as low as 0.09 % to as high as 61 % [3, 4].

Most pseudotumors have been documented in association with metal-on-metal (MoM) implants, however, there have been many reports of metal-on-polyethylene pseudotumor formation as well [1, 5, 11–15, 33, 34]. The etiology of these pseudotumors is unclear, however, it is most likely a result of a delayed hypersensitivity reaction or of poor mechanics with extensive wear of implants [35]. Etiologic factors include immunologic responses to implant components, increased component wear due to wear-prone bearings, suboptimal



Fig. 4 Removed specimen measuring 15 cm in width and 10 cm in length

component positioning, or damaged components [5, 6]. A recent retrospective study of patients who developed pseudotumors after metal on metal hip implants versus control subjects determined the pathogenesis as being due to a type IV cell-mediated hypersensitivity reaction. They noted a decreased predominance of memory T cells (T_h and T_c) as well as type 1 T_h cells in the peripheral blood of patients who developed pseudotumors as opposed to those that did not, attributing this decrease to either a toxic effect of the wear products or a sequestration of these cells at the implant site from the periphery [7].

Campbell et al. attempted to distinguish between the two main etiologies by analyzing histologic characteristics. Their “ALVAL” score (aseptic lymphocyte-dominated vasculitis-associated lesions), is a 10-point based ranking method to help identify wear versus allergen hypersensitivity origins of pseudotumors. This score is based on synovial lining, inflammatory infiltrate and tissue organization, with higher ALVAL scores seen with hypersensitivity reactions [8]. It is important to note that Campbell et al.’s conclusions were drawn based on metal on metal implants, therefore, the ALVAL score may not be entirely applicable to our patient. Nevertheless, the ALVAL scoring system, when applied for our patient, was found to be

7/10, consistent with a hypersensitivity pseudotumor formation. This score lies between an average score of 3.6 for suspected wear related pseudotumor formation and 8.5 for suspected metal hypersensitivity documented in a study of 32 patients with revised metal on metal hip replacements with pseudotumor-like reactions [8]. The authors of this study emphasize that the histologic scoring is a quantitative methodology with some intra and inter-observer variability and needs to be interpreted in conjunction with clinical and radiologic findings. Additional studies using the ALVAL scoring system related to pseudotumors unassociated with metal on metal implants are necessary to determine its validity. In our patient, clinical, radiologic, and pathologic findings correlate best with pseudotumor formation due to hypersensitivity as opposed to a component wear response.

Initial radiographic evidence of pseudotumor formation is variable, ranging from 6 months to 15 years postoperatively. A study by Griffiths et al. described a median time between joint replacements to pseudotumor appearance of 6 years, with features of discrete, ovoid, or rounded lucencies being the early radiographic signs of pseudotumor formation [9]. Osteolysis around the pseudotumor may be due to PGE2, collagenase, interleukin 1 and tumor necrosis factor produced by the synovial-like membrane of the pseudotumor [10]. Pseudotumors may be associated with thick pus-like effusions and extensive collateral damage including muscle necrosis, bone necrosis, periprosthetic fractures, nerve palsies and dislocations [2].

Some of the first documented cases of methyl methacrylate allergy in orthopedics were described in the 1970s, associated with adverse complications including intraoperative death [36, 37]. Monteny et al. described a 76-year-old female undergoing total hip arthroplasty who developed sudden hypotension during implantation of the acrylic cement. Postoperatively she was found to have a positive allergy to MMA on skin patch testing. They postulated that methyl methacrylate is displaced into the injured osseous blood vessels resulting in a sensitization reaction as the elimination of the monomer via the respiratory system is reduced [37]. Donaldson et al. described this phenomenon as “bone cement

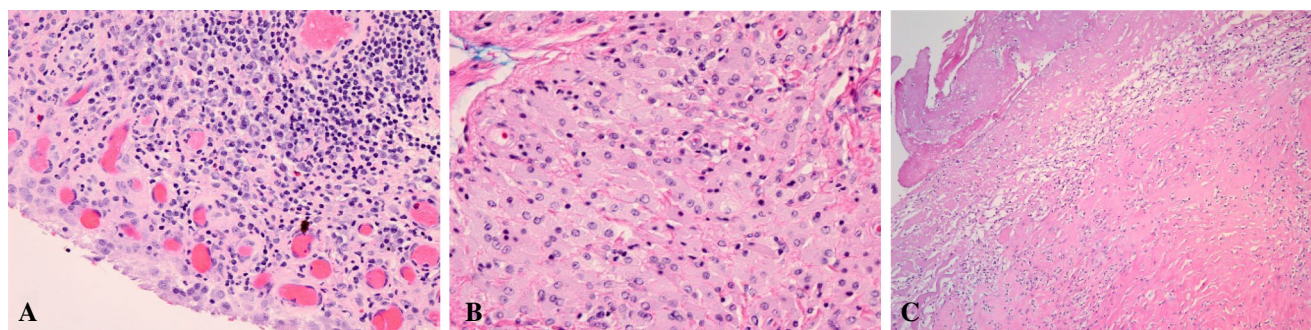


Fig. 5 **a** Focal preservation of synovial lining with subsynovial perivascular lympho-plasmocytic infiltrate. **b** Dense infiltration of histiocytes with ground glass cytoplasm. **c** Fibrinous exudate with loss of synovium and underlying dense collagenous tissue

implantation syndrome” (BCIS), which is characterized by hypoxia, hypotension, cardiac arrhythmias, increased pulmonary vascular resistance, and cardiac arrest. Pathogenesis of BMIS may involve histamine release, complement activation, endogenous cannabinoid mediated vasodilation, and embolic showers [37].

A case described by Romaguera et al. involved a 31-year-old male who was being treated for recurrent osteomyelitis of his femur after ORIF with antibiotic impregnated MMA cement beads. Fifteen days postoperatively, he developed a red, scaly, and itchy eczematous patch around his thigh, which later progressed to generalized urticaria. Subsequent allergy tests were positive for methyl methacrylate. The eczematous lesions later disappeared after removal of the beads [38].

Erpenbach et al. reported a case of MMA allergy in a 56-year-old female who underwent cemented right shoulder hemiarthroplasty following a proximal humerus fracture. During the 4–12 weeks after the procedure, the patient complained of nonspecific shoulder pain. By 4 months, the patient developed a 6 × 7-cm area of erythema over her shoulder. With the suspicion of a septic joint, arthroscopy was performed, which revealed extensive fibrosis with no signs of component loosening, with all intraoperative cultures negative for any organism growth. Subsequent patch testing showed delayed contact hypersensitivity to methyl methacrylate and no sensitivities to various metals that were tested. After 3 years of various failed attempts at pain control including physical therapy, analgesics, acupuncture and steroids, the patient underwent complete removal of her shoulder implants including the methyl methacrylate cement. Postoperatively, there was total resolution of the erythema and significant improvements in her pain [39].

One case by Kaplan and Zuckerman et al. involved preoperative identification of methyl methacrylate allergy after a focused history was obtained. They described a 60-year-old female with degenerative joint disease in need of total knee arthroplasty who on careful history taking was found to have a previous allergic reaction to artificial acrylic-based fingernails, as well as blister formation after a temporary dental filling using methyl methacrylate cement. The decision was made to use non-cemented implants for her TKA, which led to an uneventful postoperative course [18].

The exact prevalence of methyl methacrylate sensitivity is difficult to assess due to the variety of different compounds used in bone cement. Polymerization of bone cement involves the use of a mixture of methyl methacrylate monomer and polymethyl methacrylate powder using benzoyl peroxide as a catalyst and *N,N*-dimethylparatoluidine (DMT) as an accelerator [19]. Antibiotics such as gentamicin, tobramycin, clindamycin, erythromycin, and vancomycin are often added. One series of 113 patients in a Munich implant allergy clinic found a 24.8 % prevalence of contact allergies to bone cement components, including 16.8 % to gentamicin, 8.0 % to

benzoyl peroxidase, 1.8 % to (2-hydroxyethyl) methacrylate (2-HEMA), and 0.9 % to methyl methacrylate [20]. Another study found positive MMA patch test results in approximately 25 % of a 42-patient cohort who underwent total hip arthroplasty [40]. A larger, multicenter study from Sweden and Singapore consisting of a total of about 2800 patients found the prevalence of acrylate/methacrylate allergy using patch testing to be 1.4 and 1.0 % in Sweden and Singapore, respectively [41]. Based on these studies, allergy to bone cement in general may be quite prevalent, however allergies specific to methyl methacrylate are quite rare.

Conclusions

We have described the occurrence of a sizeable, rare inflammatory pseudotumor in a 68-year-old female who underwent right cemented total knee arthroplasty. We identified the cause as an inflammatory-mediated allergic response to methyl methacrylate. This was confirmed by the histologic and radiographic findings, in conjunction with a positive allergic reactivity to methyl methacrylate on skin patch testing and negative cultures. To our knowledge, pseudotumor formation of this caliber due to methyl methacrylate hypersensitivity has not yet been described.

As is evident in this case report, performing total joint replacement on patients without conducting a proper screening for sensitivities can have disastrous results. Materials such as cobalt, chrome and nickel, as well as various antibiotics have been commonly implicated as culprits to implant failure, with methyl methacrylate associated implant failure being a rarity. These adverse reactions are typically more common in patients with significant atopic histories. A thorough allergic history should be obtained from every patient prior to surgery. Questions concerning dental implants, jewelry, makeup, and occupational exposure should be addressed.

There are a variety of options available to the orthopedist who encounters a patient with a positive allergic history. It is advisable to use non-cemented components in patients with hypersensitivity to bone cement. For patients with various metal allergies, there are special surface coated implants, which may be utilized. Thakur, Ast, and Rodriguez et al. showed significant improved postoperative outcomes in patients with nickel-, cobalt-, or manganese-associated total knee implant failures who were revised to oxidized zirconium femoral and titanium tibial components [16].

As part of preoperative clearance, it is essential to identify patients who have or are at increased risk of implant-associated hypersensitivity. Complete history and physical examination may be supplemented with various screening modalities. With advances in skin patch testing methods and novel in vitro techniques such as lymphocyte transformation tests, screening for orthopedic implant sensitivity should become a

standard of patient care based on prior atopic history. Currently, research supports preoperative screening for individuals who report a history of “cutaneous reactions to metals or bone cement components prior to device implantation... and symptomatic individuals after implantation” [42]. Many of these tests, however, are not readily accessible for patients due to cost and/or availability. A validated questionnaire, which correlates with orthopedic implant material hypersensitivity, should be developed to help identify patients at risk who may benefit from more specific tests such as the lymphocyte transformation test. Physician awareness of hypersensitivity will reduce the incidence of allergy-mediated revision orthopedic surgery and result in better patient satisfaction and outcomes.

Compliance with ethical standards

Conflicts of interest Shachar Kenan, Leonard Kahn, and Samuel Kenan: No funding was provided for this manuscript

Noga Haramati: No funding was provided for this manuscript. Other conflicts of interest include:

- Bioprotect, LTD / Stock Shareholder (directly purchased) / Shareholder, Board Member
- Orthospace, LTD / Stock Shareholder (directly purchased) / Shareholder, Board Member
- Kryon Systems, LTD / Stock Shareholder (directly purchased) / Stockholder, Board Member
- General Electric Healthcare IT / Consultant / Executive Committee
- AFC Industries / Consultant / Consultant

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