Bone Cement Hypersensitivity in Patients With a Painful Total Knee Arthroplasty: A Case Series of Revision Using Custom Cementless Implants

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Abstract

Little is known about patients with bone cement hypersensitivity after total knee arthroplasty (TKA). We present 7 patients implanted with 8 TKAs with clinical failure and a cement hypersensitivity diagnosis. All demonstrated hypersensitivity to bone cement via skin patch and/or lymphocyte transformation testing. All 7 patients also showed hypersensitivity to metal, most commonly nickel. Patients underwent custom cementless TKA revision. Prerevision and postrevision outcome measures, radiographs, intraoperative findings, and postrevision complications are reported. Functional scores improved after revision except Veterans RAND-12 mental component scores, which declined. Four patients continue to exhibit symptoms postoperatively, while one patient has had 3 additional surgical procedures. Patients presenting with bone cement hypersensitivity after TKA are particularly challenging. Evidence-based guidelines are lacking, and revision surgery may not relieve the presenting symptoms.

Introduction

The clinical significance of hypersensitivity reactions to orthopedic implant materials continues to be a controversial topic. When present, these reactions are thought to result in an array of symptoms, including generalized or localized dermatitis, aseptic inflammation, persistent pain and swelling, and on rare occasions, aseptic loosening of the implant [1]. The management of a patient who presents with a painful total knee arthroplasty (TKA) and positive hypersensitivity testing is a challenge, as robust clinical validation of the significance of existing cutaneous and in vitro tests is lacking [2]. Yet most published reports, which focus specifically on an allergic reaction to metal components, do indicate improved outcomes in patients undergoing revision [3–5]. In addition, although not advocating widespread testing, published algorithms continue to recommend taking positive test results into consideration when planning revision TKA [2,6].

Severe hypersensitivity reactions to acrylic bone cement and its polymerization additives (benzoyl peroxide and N, N-dimethyl-p-toluidine) are now being posited as a cause for concern in TKA, similar to metal hypersensitivity [7–11]. Many centers now include the components of bone cement along with metal alloys in allergy testing panels [12,13]. In spite of this growing interest, there is currently a paucity of data reporting on patients undergoing revision for a poorly functioning TKA in the context of a bone cement allergy.

We report a case series of 7 patients with 8 painful TKAs who underwent revision using custom cementless components after being diagnosed with an allergy to a component of bone cement.

Case series

This case series analysis was approved by our institutional review board before initiation of this study. Our institution's
prospective, longitudinally maintained total joint arthroplasty database was used to identify all patients who had a documented preoperative cementless implant and underwent revision TKA with a custom cementless implant. The cementless implants were custom made for the patient by the vendor (Biomet or Depuy) but did not require institutional review board or Food and Drug Administration clearance (Table 1). Patients were excluded if they did not have a minimum of 1-year follow-up postoperatively. Informed consent was obtained before their participation in the database. Patient details were recorded, including demographic data, index TKA components, preoperative workup, and allergy testing method and results. Intraoperative findings at revision surgery were noted based on operative report documentation. Prerevision and postrevision radiographs and outcome measures including range of motion, Knee Society Scores (KSS), and Veterans RAND (VR)-12 mental (MCS) and physical component scores (PCS) were reviewed. Postrevision complications and subsequent revision surgeries were also reported.

Between 2011 and 2019, 7 patients (3 female and 4 male) presented to our institution with 8 TKAs that underwent revision by 3 different surgeons due to a reported cement allergy (Fig. 1). Details are summarized in Table 1. No patient had a history of arthroscopy before their primary TKA. The revisions were performed using conventional techniques, and all 3 surgeons are full-time joint replacement specialists. Patients underwent revision at an average of 66.3 months after their index TKA. Three out of 8 TKAs had a previous revision of their index TKA at an average of 50 months before their cementless revision. Five of 8 TKAs did not have a period of time after their index TKA when they were functioning well. The most common complaints before revision were pain (8/8) and chronic effusions (5/8). Physical examination findings included both arthrofibrosis and instability. No patients had any cutaneous findings.

Before revision surgery, patients underwent extensive blood, synovial fluid, radiographic, and allergy testing to rule out other causes of implant failure. All 7 patients had already undergone testing for a hypersensitivity reaction before presenting to our institution. No surgeon at our institution routinely screens for these allergies. Details are summarized in Table 2. The most common method of hypersensitivity testing used was patch testing (7 out of

### Table 1
Preoperative and intraoperative patient data.

| Patient | Age | Sex | BMI | Date of primary surgery | Side implants | Prior revisions | Symptoms | Preoperative labs/ aspiration | Date of cementless revision surgery | Intraoperative findings | Revision implants |
|---------|-----|-----|-----|--------------------------|---------------|----------------|----------|-------------------------------|-----------------------------------|------------------------|-----------------|
| 1       | 72  | Male| 26.7| 6/2006                   | Right         | Stryker Triathlon | 8/2006: Revision to Depuy PFC Sigma PS 3/2009: Liner exchange | Pain, chronic effusions, instability | ESR: 1 CRP: 2.9 Cell count: 420 PMN: 24% | 7/2014 | None | Biomet Vanguard custom titanium alloy, hydroxyapatite coated, plasma sprayed Biomet Vanguard custom titanium alloy, porous coated, ion bombarded Depuy PFC Sigma TC3 custom porous coated |
| 2       | 69  | Female| 39.5| 12/2017                  | Right         | Aesculap Vega PS | None | Pain, chronic effusions, arthrofibrosis | ESR: 13 CRP: 8.39* Cell count: 422 PMN: 57% | 5/2019 | Femoral component loosening | Biomet Vanguard custom titanium alloy, porous coated, ion bombarded Depuy PFC Sigma TC3 custom porous coated |
| 3       | 71  | Male| 32  | 4/2009                   | Left          | Biomet Vanguard PS | 5/2010: Liner exchange | Pain, chronic effusions, arthrofibrosis | ESR: 5 CRP: 2.9 Cell count: 33 PMN: 20% ESR: 4 CRP: 2.9 Cell count: 1031 PMN: 65% | 7/2011 | None | Biomet Vanguard custom titanium alloy, porous coated, plasma sprayed Biomet Vanguard custom titanium alloy, porous coated, ion bombarded |
| 4       | 59  | Female| 26.3| 11/2009                  | Left          | Stryker Triathlon PS | None | Pain, chronic effusions | ESR: 4 CRP: 2.9 Cell count: 436 PMN: 47% | 4/2012 | Instability | Biomet Vanguard custom titanium alloy, porous coated, plasma sprayed |
| 5       | 68  | Male| 26.2| 10/2001                  | Right         | Depuy PFC Sigma PS | 2/2012: Liner exchange 11/2013: Revision to Depuy PFC Sigma | Pain, chronic effusions, instability | ESR: 4 CRP: 2.9 Cell count: 436 PMN: 47% | 11/2019 | Femoral component loosening | Biomet Vanguard custom titanium alloy, porous coated, plasma sprayed |
| 6       | 71  | Female| 32  | 7/2012                   | Left          | Smith & Nephew Legion CR (Oxinium) | None | Pain, instability | ESR: 5 CRP: 2.9 Cell count: 240 PMN: 8% | 2/2015 | None | Biomet Vanguard custom titanium alloy, hydroxyapatite coated, ion bombarded |
| 7A      | 65  | Male| 24  | 6/2014                   | Right         | Depuy Attune PS | None | Pain, arthrofibrosis | ESR: 2 CRP: 2.9 Cell count: 477 PMN: 19% | 9/2018 | None | Biomet Vanguard custom titanium alloy, porous coated, ion bombarded |
| 7B      | 65  | Male| 24  | 9/2014                   | Left          | Depuy Attune PS | None | Pain, arthrofibrosis | ESR: 2 CRP: 2.9 Cell count: 268 PMN: 13% | 10/2019 | Patellar component loosening, instability | Biomet Vanguard custom titanium alloy, porous coated, ion bombarded |

BMI, body mass index; CRP, C-reactive protein; PMN, polymorphonuclear; ESR, erythrocyte sedimentation rate; ROM, range of motion.

* Elevated value.
and lymphocyte transformation testing (LTT) (Orthopedic Analysis, Chicago, IL) (5 out of 8). All 7 patients also tested positive for a metal allergen, most commonly nickel. Four out of 7 patients (patients 1, 3, 5, and 7) underwent more than one type of allergy testing. All 4 patients had differing results from each method of hypersensitivity testing as seen in Table 2.

At the time of revision, it was determined that 3 of the 8 TKAs had loose components, and 2 had significant instability. Four of the 8 did not have any other documented mode of failure aside from cement hypersensitivity. All patients were revised to custom cementless implants. Intramedullary guides were used to cut the distal femur and tibia. Metaphyseal fixation with either cones or sleeves were used in both the femur and tibia in all cases. Femoral and tibial augmentation was used when indicated based on bone loss. No bone grafting or bone slurry was used.

Average length of follow-up after revision was 44.2 months. Details are summarized in Table 3. Average range of motion improved from 103.1 degrees preoperatively to 118.9 degrees postoperatively. The KSS improved above the minimal clinically important difference (MCID) of 6 in 6 knees, with the average KSS improving from 51.3 preoperatively to 71.9 postoperatively [14]. There was also an improvement in VR-12 PCS above the MCID of 5 in 2 knees, with the average declining from 52.3 preoperatively to 50.0 postoperatively. One patient required 3 subsequent revisions, one for tibial component loosening requiring tibial component revision 1 year after index cementless revision, a second for recurrent hemarthroses requiring a complete synovectomy and liner exchange 2 and a half years after index cementless revision, and the third for lateral patellar facet pain requiring a lateral facetectomy 6 years after index cementless revision (Table 4). Four patients continue to have postoperative symptoms: Two continue to experience chronic effusions, another suffers from end-of-stem pain from the tibial component, and the fourth continues to have significant chronic knee pain. Of the 4 patients with an isolated cement allergy, 2 have had a resolution of symptoms while 2 continue to experience symptoms: Patient 3 continues to have chronic effusions, while patient 7 has pain at the end of his tibial stem.

**Table 2: Hypersensitivity testing results.**

| Patient | Patch testing | LTT |
|---------|---------------|-----|
| 1       | Nickel        | Bone cement particles, nickel, titanium |
| 2       | NT            | Bone cement monomer, nickel, cobalt |
| 3       | Benzoyl peroxide | Nickel |
| 4       | Bone cement monomer part A and bone cement powder part B, nickel | NT |
| 5       | Negative      | #1: Bone cement monomer |
|         |               | #2: Bone cement particles, aluminum, nickel, titanium | NT |
| 6       | Cobalt, nickel, bone cement, bone cement monomer A, benzoyl peroxide | NT |
| 7A      | Bone cement monomer part A and bone cement powder part B | Cobalt, vanadium, zirconum |
| 7B      | Bone cement monomer part A and bone cement powder part B | Cobalt, vanadium, zirconum |

NT, not tested.

**Discussion**

This case series reports on 7 patients who presented to our institution with 8 painful TKAs and documented cement allergy. All patients underwent revision TKA with custom cementless revision implants. Chronic effusions, arthrofibrosis, pain, and instability were among the presenting symptoms and physical examination findings. Preoperative and intraoperative investigation revealed that 4 of the 8 knees did not have any other modes of “failure.” Prerevision and postrevision functional outcome measures showed trends of improvement, except for VR-12 MCS. Four patients continue to experience symptoms, including chronic effusions, end-of-tibial stem pain, and chronic knee pain, and one patient has had 3 additional revision surgeries.

While there is extensive literature on allergic reactions to metal components in TKA, less attention has been paid to elements of bone cement [2,4–6,16,17]. There is a lack of clinical evidence to support a causal relationship between hypersensitivity to acrylics such as polymethyl methacrylate, polymerization additives (N, N-dimethyl-p-toluidine), initiators (benzoyl peroxide), stabilizers (hydroquinone), and radiodensification media (zirconium dioxide and barium sulfate) and knee replacement failure [10]. Patients can have previous exposure to acrylics in dental procedures, paint, hearing aids, cosmetics, inks, surgical tape, and rubber stamp making among various other materials [18]. A patient history can be vital in discovering any exposure resulting in an allergic reaction to these materials in the past. Similar to prior reports, chronic effusions were the main presenting symptom in 5 out of 8 TKAs, and...
component loosening was observed in 3 of 8 TKAs in this series [7,8]. Unlike previous reports, cutaneous manifestations and pseudotumors were not observed [7,10,11].

The allergic reaction to bone cement or its components is considered a type-IV hypersensitivity reaction that develops in a genetically predisposed patient [19]. A component of bone cement combines with a large carrier to create a neoantigen. This neoantigen then stimulates an immune response that can have both local and systemic effects. Allergic reactions to orthopedic implants can introduce an array of symptoms including generalized or local and systemic effects. Allergic reactions to bone cement components, and skin patch hypersensitivity testing (which identifies dermatitis when contact allergens are exposed to the skin). All patients displayed reactions to bone cement components either through LTT or patch testing. It is interesting to note that none of the 4 patients who underwent both patch testing and LTT had consistent hypersensitivity reactions between the 2 tests. This may be partially explained by the difficulty in evaluating benzoyl peroxide allergy using patch testing. More highly concentrated benzoyl peroxide solutions (eg, 1.0% in Sweden and Singapore, respectively [27]. The prevalence of positive acrylate/methacrylate patch testing to be 1.4% and 1.0% in Sweden and Singapore, respectively [27]. Although patients in this series generally showed a trend toward improvement, half of the knees in this series continued to have symptoms postoperatively. While there may be a role for the implantation of custom cementless implants in these patients, the high rate of continued complaints makes it difficult to attribute their preoperative symptoms solely to a diagnosis of cement hypersensitivity. Surgeons involved in the design of custom cementless revision implants for patients with a bone cement hypersensitivity should be aware of concomitant metal hypersensitivities, as all patients in this series also tested positive for a metal allergy.

Although patients in this series showed no other mode of failure, 3 patients did have concomitant loosening of one of their TKA components. This raises the question as to whether component loosening is due to the hypersensitivity reaction to bone cement, or vice versa. A previous case series by Haddad et al. described 7 patients who demonstrated rapid aseptic loosening of their cemented total hip arthroplasties and were found to have a hypersensitivity reaction to bone cement [28]. It is theorized that the allergy to bone cement may cause a significant inflammatory reaction which may then accelerate the process of aseptic loosening. Conversely, it may be that the very act of cementation of an implant can predispose a patient to a positive bone cement allergy test. One study of 42 patients who received a cemented hip prosthesis found a 25% positive patch test result for methyl methacrylate at 6 months postoperatively. This is in contrast to a study that found the overall prevalence of positive acrylate/methacrylate patch testing to be 1.4% and 1.0% in Sweden and Singapore, respectively [27].

Although patients in this series generally showed a trend toward improvement, half of the knees in this series continued to have symptoms postoperatively. While there may be a role for the implantation of custom cementless implants in these patients, the high rate of continued complaints makes it difficult to attribute their preoperative symptoms solely to a diagnosis of cement hypersensitivity. Surgeons involved in the design of custom cementless revision implants for patients with a bone cement hypersensitivity should be aware of concomitant metal hypersensitivities, as all patients in this series also tested positive for a metal allergy.

| Patient | Subsequent revisions | Current symptoms |
|---------|----------------------|------------------|
| 1       | -                    | None             |
| 2       | -                    | None             |
| 3       | -                    | Chronic effusions |
| 4       | 2/2013: Tibia revision for aseptic loosening 12/2014: Synovectomy for recurrent hemarthrosis 6/2018: Lateral facetectomy for lateral patellar facet pain | Chronic pain |
| 5       | -                    | Chronic effusions |
| 6       | -                    | None             |
| 7A      | -                    | End of tibial stem pain |
| 7B      | -                    | None             |

Table 3
Functional scores.

| Patient | Postoperative follow-up (mo) | Preoperative functional scores | Postoperative functional scores |
|---------|-------------------------------|-------------------------------|--------------------------------|
|         | ROM extension | ROM flexion | ROM score | Total function | Total KSS | VR-12 MCSI | VR-12 PCS | ROM extension | ROM flexion | ROM score | Total function | Total KSS | VR-12 MCSI | VR-12 PCS |
| 1       | 60               | 0             | 127       | 25           | 60        | 40        | 22        | 3            | 125         | 24          | 55         | 59        | 42         | 28        |
| 2       | 12               | 0             | 66        | 13           | 75        | 58        | 52        | 37          | 0           | 114         | 23          | 70        | 98        | 61         | 48        |
| 3       | 96               | 0             | 120       | 24           | 50        | 49        | 63        | 21          | 0           | 115         | 23          | 50        | 58        | 59         | 35        |
| 4       | 90               | 0             | 110       | 22           | 60        | 39        | 20        | 33          | 0           | 115         | 23          | 45        | 39        | 18         | 24        |
| 5       | 12               | 0             | 124       | 25           | 50        | 40        | 74        | 19          | 0           | 120         | 24          | 45        | 59        | 65         | 21        |
| 6       | 48               | 0             | 123       | 25           | 30        | 65        | 52        | 27          | 0           | 130         | 25          | 70        | 95        | 21         | 26        |
| 7A      | 24               | 5             | 85        | 16           | 90        | 49        | 52        | 34          | 0           | 115         | 23          | 100       | 88        | 67         | 43        |
| 7B      | 12               | 0             | 75        | 15           | 80        | 50        | 65        | 24          | 0           | 120         | 24          | 100       | 79        | 67         | 43        |

ROM, range of motion.
Summary

Patients who present with hypersensitivity reactions to components of bone cement and a painful TKA present a considerable challenge. It remains unclear whether these hypersensitivity reactions are the sole cause of failure, or are a coincidental finding that is associated with a more traditional mechanical mode of TKA failure, or perhaps both. When evaluating a patient with a painful TKA, a bone cement hypersensitivity should be treated as a diagnosis of exclusion, with traditional modes of failure (infection, loosening, instability, malrotation) first investigated and appropriately addressed at the time of revision surgery. If the diagnosis remains unclear, hypersensitivity testing with LTT is recommended, due to the difficulty in evaluating benzyl peroxide allergy using patch testing. Revision implant selection should be carefully considered, as all the patients in this series also presented with a variety of metal allergies on testing. Cementless revision implants in this series provided a good result at the latest follow-up. Additional investigation into both the diagnosis and pathophysiology of bone cement hypersensitivity is necessary to further elucidate its role in TKA failure.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Informed Patient Consent

The author(s) confirm that informed consent has been obtained from the involved patient(s) or if appropriate from the parent, guardian, power of attorney of the involved patient(s); and, they have given approval for this information to be published in this case report (series).

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