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Case report

Adverse Reaction to Zirconia in a Modern Total Hip Arthroplasty with Ceramic Head

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A B S T R A C T

Hypersensitivity reactions to zirconia (ZrO2) or similar ceramics is highly unusual. Owing to the stable oxide formed between the base metal and oxygen, ceramics are considered relatively biologically inert. We report the case of an otherwise healthy 50-year-old woman with a 5-year history of progressively worsening right hip pain who underwent a ceramic-on-polyethylene total hip replacement and subsequently developed hypersensitivity reaction. After metal allergy testing showed her to be highly reactive to zirconium, the femoral head was revised to a custom titanium implant and her symptoms resolved.

Introduction

Total hip arthroplasty (THA) continues to enjoy the reputation as a highly successful operation for pain relief and restoration of function of the diseased hip [1-3]. To replace and restore the function of the hip joint without triggering an immunological response, many materials have been tried as the implant (Fig. 1) [4,5]. Although traditional metal-on-polyethylene hip prostheses enjoyed success, polyethylene wear continued to be a concern. [4,6,7] With an increasing volume of THA procedures performed in an ever growing population that is living longer and requiring operations at a younger age, surgeons sought orthopaedic implants with greater longevity and outcomes than traditional implants [8].

Hypersensitivity reactions in total joint arthroplasty were first recognized in 1966, and since then, more cases have been documented but remain unpredictable and poorly understood [9-14]. The literature does not definitively report the prevalence or resultant hypersensitivity to zirconia ceramics in THA, and to the best of our knowledge, this is the first reported case [15]. We present a case of delayed-type hypersensitivity reaction in a patient who underwent THA with a well-fixed ceramic-on-polyethylene implant, consisting of a modern ceramic femoral head made from alumina and zirconia. After metal allergy testing showed her to be highly reactive to zirconium, the femoral head was revised to a custom titanium implant and all her symptoms resolved.

Case history

Patient history and clinical and paraclinical examination

A 50-year-old woman presented with a 5-year history of progressively worsening right hip pain. The pain was sharp and stabbing, located in the groin, and worse after walking and significant

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activity. The pain had become constant, begun to wake the patient at night, and climbing stairs were becoming difficult to manage. She denied back pain, radicular pain, and knee pain. Her past medical history was significant for distal colitis and osteopenia diagnosed at 48 years of age. Medications included vitamin D and vitamin B supplementation and allergies consisted of nickel, ciprofloxacin, and penicillin. There was no history of steroid use, disease-modifying antirheumatics, biologic drugs, smoking, or alcohol. Previous surgeries included right knee arthroscopy and left wrist ligamentous repair. Family history was significant for colon cancer in the father and Alzheimer's and breast cancer in the mother.

On examination, she appeared to be in good health. She weighed 56.6 kg and was 5'1'' (BMI, 24). She walked with a coxalgic gait, and leg lengths appeared equal. There was no tenderness to palpation about the right hip, and the skin was clear and supple, without signs of erythema or rash. The range of motion was limited in the right hip with flexion to 100°, 30° abduction, 0° internal rotation which caused pain, and 30° external rotation. She had a flexion contracture of the right hip of 15°. Bilateral knees were without tenderness and exhibited a full range of motion. The right lower extremity was neurovascularly intact. Radiographic evaluation at the initial visit demonstrated bone-on-bone osteoarthritis of the right hip with osteophyte formation, subchondral sclerosis, and cyst formation (Kellgren-Lawrence grade 4). There was no femoral head collapse, dysplasia, or signs of a tumor (Fig. 2).

Initial treatment consisted of nonsteroidal anti-inflammatories, a fluoroscopic-guided steroid plus lidocaine injection into the hip, and physical therapy 3 times a week for 6 weeks in a formal setting. Initial treatment was effective but short lived. The decision was made at that time to proceed with a total hip replacement. The surgery was scheduled to ensure it would be outside of the 3-month window of having the injection to the hip. Preoperative laboratory test results were all within normal limits with the exception of the glomerular filtration rate, which was 58 (normal $\geq$ 60).

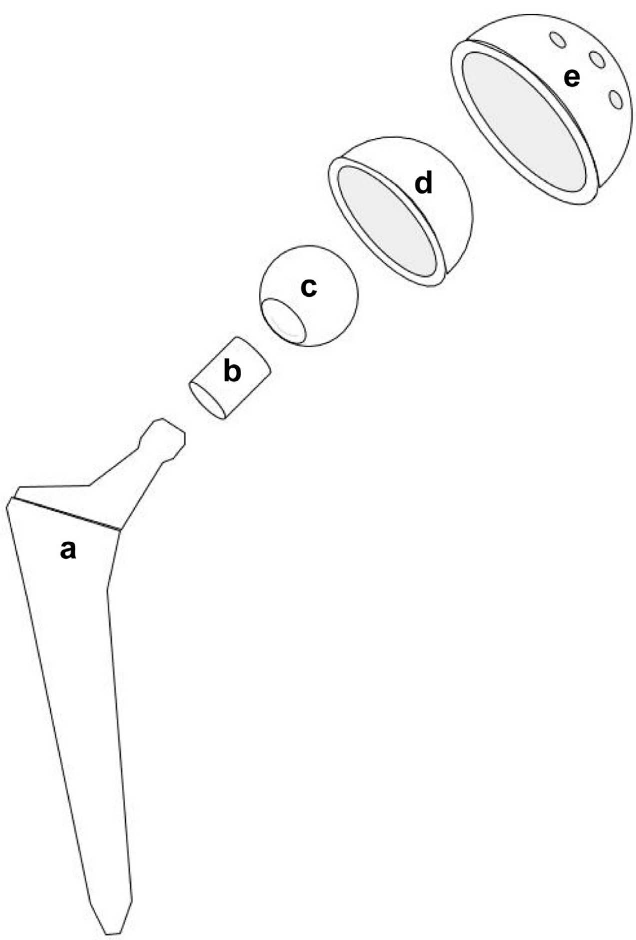

Figure 1. Orthopedic hip components. (a) Femoral stem: most used materials include CoCrMo-wrought, Ti-alloys, and stainless steel (SS). (b) Femoral head adapter sleeve: Ti-alloys. (c) Femoral head: CoCrMo-cast, SS, alumina (pure or zirconia-toughened), and zirconia, (d) Acetabular cup liner: UHMWPE, XLPE, CoCrMo-cast, alumina (pure or zirconia-toughened), and zirconia. (e) Acetabular cup shell: titanium, SS. SS, stainless steel; UHMWPE, ultra-high molecular weight polyethylene; XLPE, cross-linked polyethylene.

Primary THA and postoperative course

The patient underwent routine right THA through a direct anterior approach. Primary THA prostheses included an uncemented 50-mm titanium alloy acetabular cup (TiAl6V, Biomet G7; Zimmer Biomet, Inc., Warsaw, IN), combined with a 32 +0 mm alumina-zirconia ceramic head and titanium alloy head adapter sleeve (Biolox delta Option, Biomet G7, Zimmer Biomet, Inc., Warsaw, IN), which articulated with a neutral, highly cross-linked polyethylene liner (Biomet G7, Zimmer Biomet, Inc., Warsaw, IN). The stem consisted of an uncemented titanium alloy standard offset stem (Taperloc Complete, Biomet, Inc., Warsaw, IN) (Fig. 3). The surgery was completed without complications, blood loss was 250 cc, and the wound was closed in layers with Vicryl sutures and skin closed with 3-0 Monocryl and Dermabond.

On postoperative day (POD) 0, she was out of bed and progressed to walking with a walker with ease and, on POD1, was discharged home. In the first postoperative week, the patient developed hypersensitivity, along with paresthesia throughout the entire right lower extremity, swelling, and ecchymosis. Her wound was clean, dry, and intact, and there were no fevers or chills present. She had no other skin color changes or abnormal localized skin sweating characteristic of complex regional pain syndrome(CRPS). A diagnosis of atypical CRPS was initially suspected, and she was treated with gabapentin (Neurontin), physical therapy, and piroxicam. At 10 weeks after operation, the paresthesia continued along the entire length of the leg and progressed to involve the ipsilateral arm. Over the next 12 to 18 months, she began to develop bilateral polyarthralgias, new pain in the right hip and continued diffuse swelling and sensitivity in the right lower extremity that eventually involved most of her body. Further, the patient began to exhibit dermatologic and ophthalmologic pathology as her hair began to thin with progression to alopecia areata, and she reported a reduction in vision quality. Physical examination throughout the postoperative course demonstrated a well-functioning hip with

Figure 2. Preoperative anteroposterior right and left hips – osteoarthritis of the right hip with osteophyte formation, subchondral sclerosis, and cyst formation.

Figure 3. Primary total hip arthroplasty anteroposterior radiograph demonstrating right-sided hip arthroplasty.

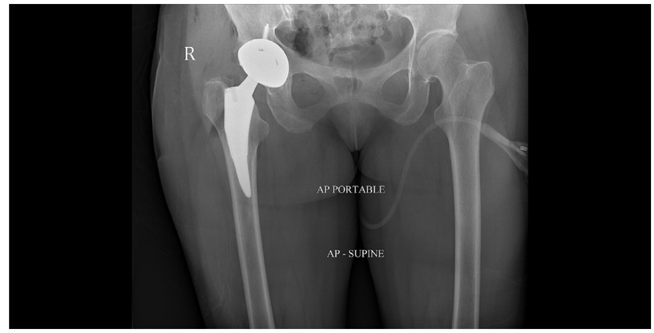

Figure 4. Revision total hip arthroplasty anteroposterior (AP) radiograph demonstrating right-sided hip revision components.

painless range of motion. She had a negative Stinchfield test and no tenderness over her greater trochanter.

All postoperative radiographs demonstrated well-aligned prostheses (inclination, anteversion, and the stem in an acceptable position) with no signs of loosening or other complications (Fig. 3). Computerized tomography of the hip showed slight anterolateral protrusion of the acetabular cup, possibly irritating the iliopsoas, although her symptoms did not correspond with this. Follow-up magnetic resonance imaging demonstrated a small amount of fluid in the iliopsoas sheath. Infection was initially ruled out with a normal erythrocyte sedimentation rate and C-reactive protein. A fluoroscopic lidocaine-steroid injection was administered as a diagnostic test for pain from the joint but provided only minimal relief of the pain and did not help with the swelling, ecchymosis, sensitivity, or polyarthralgia. Laboratory work was ordered, and referral to a rheumatologist brought a diagnosis of exclusion of seronegative inflammatory arthritis. Normal values were found with erythrocyte sedimentation rate, C-reactive protein, comprehensive metabolic panel, WBC, anti–citrullinated protein antibodies, anti–double stranded DNA, anti–extractable nuclear antigen, antinuclear antibodies, creatine kinase, parathyroid hormone, thyroid function tests, liver function tests, anti–Saccharomyces cerevisiae antibodies, Lyme, and urinalysis (Table 1) [16-27]. Blood testing for metal sensitivity showed high reactivity to zirconium and moderate sensitivity to nickel. The zirconium rated an 8.6 on the lymphocyte stimulation index and the nickel rated 7.2 (nonreactive ≤ 2, mildly reactive 2-4, reactive 4-8, highly reactive >8) (Hospital for Special Surgery Lab, New York, NY). Blood levels of metal ions were not drawn.

Revision THA

The decision was made to perform a revision THA at postoperative month 18, through her previous incision using a standard direct anterior approach. After dissection was carried out, the tissue on gross inspection during the revision appeared moderately inflamed. Owing to her nickel sensitivity testing, a custom titanium head was used to replace the zirconia ceramic femoral head (Biolox delta Option, Biomet G7, Zimmer Biomet, Inc., Warsaw, IN). Both the femoral stem and acetabular cup were well-fixed with no signs of loosening. Given the slight anterior overhang of the acetabular cup, with the potential to irritate the iliopsoas sheath, the acetabular shell was revised to a position with less overhang during the revision surgery. Revision prostheses included a 50-mm Zimmer Biomet trabecular metal acetabular cup (Zimmer Biomet, Inc., Warsaw, IN), a 32-mm Zimmer Biomet Trilogy acetabular liner (Zimmer Biomet, Inc., Warsaw, IN), and a custom 32-mm titanium femoral head component (Fig. 4). Pathology specimens were obtained during revision surgery.

Pathology

A complete synovectomy was performed during the revision, and the tissue was sent for pathologic evaluation. Synovium and neosynovium demonstrated focal hyperplasia and macrophagic infiltrate containing particulate ceramic debris from the alumina-zirconia ceramic head (Biolox delta Option, Biomet G7, Zimmer Biomet, Inc., Warsaw, IN) (Fig. 5a). This was consistent with an inflammatory reaction secondary to the ceramic debris (Fig. 5b). Microscopic evaluation with high power demonstrated less than 5 polymorphonucleocytes per field, consistent with the absence of an infectious process. The removed prosthesis showed no abnormal signs of wear (Hospital for Special Surgery Lab, New York, NY).

Postoperative revision THA course and follow-up

The patient was made weight bearing as tolerated after the procedure and was discharged on POD2. She felt immediate resolution of the right lower extremity hypersensitivity and the pain in the hip was immediately gone. Over the following week, the swelling and polyarthralgias completely resolved. At 1-month follow-up, the patient continued to improve significantly with no complaints of hypersensitivity or systemic symptoms. At 24 months from revision surgery, patient remains pain free in the right hip and has no systemic symptoms.

Discussion

Ceramic biomaterials offered an alternative to traditional metal bearing implants [8]. Ceramic materials are made when a metal (ie, zirconium [Zr]) is bonded to an oxygen molecule (zirconia [ZrO_2]). In a 10-year study between 1970 and 1980, a French surgeon, Pierre Boutin, highlighted the advantage of alumina oxide (Al_2O_3) ceramic bearings owing to advantages of the material's low coefficient of friction, high biocompatibility, and wear resistance [8,28]. Unlike metal-on-metal or metal-on-polyethylene components, ceramics are composed of a base metal and oxygen, producing a stable oxide that becomes biologically inert in the body secondary to their ions being completely used in the bonds to the oxygen [8]. Thus, they generate less taper corrosion and therefore lower adverse local tissue reactions (ALTRs) leading to lower failure rates [29,30]. Initially, however, alumina ceramic prosthetics suffered from a high fracture rate, which drew researchers to further improve the performance of ceramic materials [8].

In the 1980s, zirconia (ZrO_2), a ceramic made from oxygen bound to zirconium, was introduced to solve the problem of alumina's brittleness [31]. Although zirconia also experienced early setbacks in commercial development (recalled in 2001), current

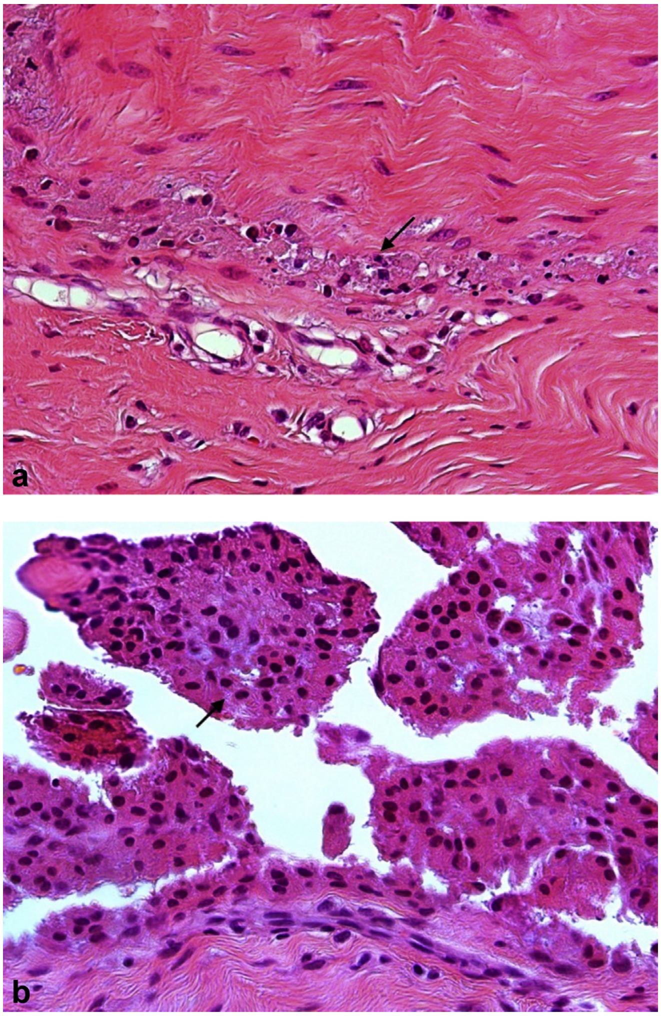

Figure 5. (a) Histology of right hip joint tissue – dense connective tissue and hyperplasia of neosynovium. Black arrow points to a macrophage containing ceramic particles, suggestive of ceramic wear debris. (b) Histology of right hip joint tissue – dense connective tissue and hyperplasia of neosynovium. Black arrow points to a small particle with morphological features suggestive of ceramic debris.

ceramics have minimized the risk of fracture by adding zirconia through more streamlined manufacturing processes [32,33]. Although ceramics, such as zirconia composites, are biologically inert, they may still incite adverse biological reactions [34-39].

While extremely rare, and yet reported, delayed–type IV hypersensitivity reactions to zirconia ceramics should be considered in the differential of complications after THA [37]. The current thought behind delayed–type IV hypersensitivity reactions in arthroplasty involves a susceptible patient encountering inorganic or organic debris small enough to be phagocytized [40]. Wear debris is formed at prosthetic joint articulations, modular interfaces, and areas of impingement [15]. The particle debris then interacts with predominately Th1-type lymphocytes of immune system inciting an inflammatory cascade and creating ALTRs [34,38,41]. Although ceramics have been described as biologically inert, sufficiently small enough particulates of zirconia, if released, may produce an immune reaction similar to those seen with polymers and metal debris [34,35]. Zirconia hypersensitivity and ALTR due to wear debris are multifactorial; however, we will describe what we believe to be the likely etiology in our case in the following paragraph [3,8,32,33,40,42-47].

Implant-related causes may include the biocompatibility of zirconia and phase changes [32,34,43,48,49]. Biocompatibility of an implant is the ability to be nontoxic and to resist mechanical wear [34,43]. With mechanical wear, particles can be generated through cyclical loading and in joint replacement can be immediately released owing to friction of the joint [8,40,47]. If debris particles are sufficiently small, having a size less than 10 μm, phagocytes may take up ceramic debris and initiate an inflammatory cascade [5,34,40]. Ceramic wear debris is small in size, with an average size of 0.71 μm, thus able to be phagocytosed to initiate an inflammatory cascade leading to hypersensitivity [34,50]. Finding ceramic debris in the synovium at revision surgery was evidence of these processes occurring in our patient (Fig. 5a and b). Phase changes at the surface play an important role in the life expectancy of zirconia ceramics. Phase transformation of zirconia is unique to zirconia ceramics because of the ability of zirconia to exist between 3 phases (ie, monoclinic, cubic, and metastable tetragonal). Each phase contributes to the overall strength of the final composition by the unique way they respond to temperature, liquid media, and stress during manufacturing and use. Retrieval and simulated aging studies have demonstrated these findings both in vivo and in vitro [32,43,49,51-53]. Current literature suggests zirconia ceramics in vivo undergo greater wear compared with in vitro studies owing to the presence of salts, proteins, and pH of physiologic serum compared with steam autoclaving in artificial aging simulations [32,34,48,49,51-53].

Summary

In patients with suspected allergy, we recommend the following steps. Step 1, a thorough history and physical. Step 2, based on guidelines surrounding postoperative THA complications, a diagnostic workup (Table 1) to rule out common causes of failed hip replacements [9,36]. As periprosthetic joint infections, neuroendocrine, and autoimmune pathology may present similarly to hypersensitivity reactions, it is critical to keep a broad differential [34,38,41]. Step 3, comprehensive testing for metal allergy includes skin patch testing or blood testing (ie, lymphocyte transformation test, leukocyte migration inhibition test). Although no clinically validated preimplant or postimplant testing currently exists, the most commonly used test by clinicians is the skin patch test. It remains that the definitive diagnosis for suspected implant hypersensitivity is a resolution of symptoms upon removal of the offending implant [9,36].

We present a case in which a patient developed a hypersensitivity reaction after ceramic-on-polyethylene total hip replacement. After a thorough workup, we diagnosed her with a reaction to the zirconia debris and revised her implant, resolving all her symptoms. Hypersensitivity reactions to debris generated from zirconia ceramic wear are likely multifactorial [3,34,54]. With an aging population that is living longer, THA is very common [8,15,34]. Zirconia exposure and sensitization may increase as indications for ceramic-on-polyethylene THA now includes a population that is more active and requiring THA at earlier ages [8,15,55]. Until clinically validated preimplant and postimplant tests are available to determine the risk of hypersensitivity, it remains important to conduct a complete workup and to consider the diagnosis of a zirconia-induced hypersensitivity reaction.

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Appendix

Table 1
Frequently used terminology in the context of laboratory tests and their clinical use.

Test	Clinical use
Erythrocyte sedimentation rate (ESR)	A test that measures the rate at which red blood cells (RBCs) in whole blood settle in a test tube. Inflammatory states cause RBCs to settle faster [16]
C-reactive protein (CRP)	A protein in blood whose levels rises in high inflammatory states [16]
Comprehensive metabolic panel (CMP)	A panel of 14 blood tests that provides a broad analysis of kidney, liver, endocrine, and electrolyte status [17]
Complete blood cell (CBC) count	A test that provides information on the patient's cell count for each blood type and hemoglobin [16]
Anti–citrullinated protein antibodies (ACPAs)	A test that detects the presence of autoantibodies against citrullinated proteins. High specificity and predictive value toward diagnosing rheumatoid arthritis [18]
Anti–double stranded (anti-dsDNA)	A test that detects the presence of antibodies against double-stranded DNA. High sensitivity and specificity toward diagnosis lupus (SLE) or connective tissue diseases [19]
Anti–extractable nuclear antigen (anti-ENA)	A panel of 6 tests that detects the presence of antibodies against cytoplasmic and nuclear antigens. Used in the detection of SLE, mixed connective tissue diseases and Sjögren's syndrome [20]
Antinuclear antibodies (ANA)	A test that detects the presence of antibodies against cells. Used in the detection of autoimmune disorders in conjunction with other laboratory and clinical findings [19]
Creatine kinase (CK)	A test that measures blood levels of an intracellular enzyme present in skeletal muscle, heart muscle, and brain. High levels may indicate damage to CK-rich tissues [17]
Parathyroid hormone (PTH)	A test that measures blood levels of a hormone secreted by the parathyroid glands. Used to assess neuroendocrine pathology and function [21]
Thyroid function tests (TFTs)	A test that measures blood levels of thyroid hormones such as thyroid-stimulating hormone, thyroxine, and triiodothyronine. Used to assess thyroid pathology and function [22]
Liver function tests (LFTs)	A test that measures blood levels of enzymes and end products of the metabolic pathway. Used to assess hepatic pathology and function [23]
Anti-saccharomyces cerevisiae antibodies (ASCA)	A test that detects the presence of antibodies against antigens to a yeast protein. High specificity in the diagnosis of Crohn's disease and ulcerative colitis [24]
Lyme antibodies	A test that detects the presence of antibodies, IgG and IgM, released during infection with *Borrelia*. Used in diagnosis of Lyme disease in conjunction with other laboratory tests [25]
Urinalysis (UA)	A test that detects and measures levels of ions, proteins, blood cells, drugs, and other molecules in urine [26]
Lymphocyte stimulation index (LSI)	A value obtained from a lymphocyte proliferation test (LTT or LST) that reflects lymphocyte proliferation in the presence of an allergen. Believed to be more useful for prognosis and diagnosis of metal sensitivity compared to skin patch testing; however, more research is needed to determine the validity and clinical use [27]