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Case report

Late hemorrhagic pseudoseptic arthritis encountered during total knee arthroplasty due to hyaluronic acid viscosupplementation

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis and affects approximately one-third of people in the United Sates aged 65 years and older. Since 2013, the American Academy of Orthopaedic Surgeons has not been able to recommended using hyaluronic acid for patients with symptomatic OA of the knee. Subsequent publications have also cautioned against the use of viscosupplementation based on lack of efficacy and the potential for harm. We present a case of late hemorrhagic pseudoseptic arthritis encountered during TKA due to hyaluronic acid viscosupplementation. Our triad of findings includes (1) acute and chronic inflammatory cells on frozen section, (2) synovitis with hemosiderin deposition, and (3) blackened cartilage with iron deposition on permanent histopathology. Our case is unique in that it shows a previously undescribed late complication of viscosupplementation.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and affects approximately one-third of people in the United Sates aged 65 years and older [1]. OA involves the progressive loss of hyaline cartilage with underlying bony changes. Patients with OA suffer from pain, joint effusions, and stiffness. Disease in weight bearing joints (eg, hips and knees) has greater impact. The majority of those affected report movement limitations, and approximately 25% have difficulty with activities of daily living [2]. OA is independently associated with excess mortality, morbidity, as well as high socio-economic costs [3-5]. Treatment of knee OA is based on many factors including age, severity, and functional status with total knee arthroplasty (TKA) being the most invasive but definitive option.

In 2013, the American Academy of Orthopaedic Surgeons published recommendations for the nonarthroplasty treatment of knee OA [6]. Nonarthroplasty treatment options included conservative measures such as weight loss, pharmacologic treatment with nonsteroidal anti-inflammatory drugs, and procedural treatments including intraarticular injections and arthroscopy. Intraarticular hyaluronic acid (HA) injections, a relatively new modality, aimed to restore the viscoelastic properties of joint fluid in patients with OA. At that time, the authors could not recommend using HA, with a strong strength of evidence, for patients with symptomatic OA of the knee. Where previous guidelines found inconclusive evidence, the 2013 guidelines reviewed 14 studies and found no clinically significant treatment effects for pain, function, or stiffness. Their meta-analysis showed a low likelihood that an appreciable number of patients achieved clinically important benefits.

Subsequent publications have also cautioned against the use of viscosupplementation. A industry-sponsored, multicenter, randomized, double-blind trial of nearly 200 patients with mild to moderate OA found no statistical difference on outcomes measures at 1, 3, and 6 months between intraarticular injection of HA vs placebo [7]. In addition, a systematic review of 19 trials found double-blind, placebo-controlled trials had much smaller treatment effects than open-label trials. Based on assessment of the best evidence, these authors concluded that HA injections offer no

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clinically important improvements in pain, function, or stiffness compared to placebo [8]. However, despite this clear lack of efficacy, viscosupplementation remains common especially in areas where there is a higher density of physicians [9].

Recent studies and case reports have revealed a potential harm from viscosupplementation. Both minor and severe inflammatory reactions have been documented and raise safety concerns. The most commonly reported adverse reaction is mild pain or swelling at the site of the injection, which occurs in 1%-20% of patients. This inflammatory response typically begins within 1-72 hours [10-12]. The likelihood of these reactions increases up to 8-fold in those who pursue multiple treatment sessions [12]. Studies have found a varying antibody response to different sources of hyaluronan with Synvisc (Sanofi-Aventis, Bridgewater, NJ) eliciting the greatest immunogenic response in limited animal models [13,14]. However, other products have also been described to cause similar reactions of varying severity [10]. Recently, more long-term risks have also been described. At the 2015 Annual Meeting of the American Association of Hip and Knee Surgeons, one paper showed a significantly higher incidence of postoperative infection and infection requiring reoperation in patients who had received therapeutic injection within 7 months before TKA [15].

Our case is unique in that it shows a previously undescribed complication of viscosupplementation. We present a case of late hemorrhagic pseudoseptic arthritis encountered during TKA. Our triad of findings includes (1) acute and chronic inflammatory cells on frozen section, (2) synovitis with hemosiderin deposition, and (3) blackened cartilage with iron deposition on permanent histopathology.

Case history

A 70-year-old female presented to us with a chief complaint of right knee pain. She had previously been treated by an outside orthopaedist for knee OA with a series of 3 weekly Orthovisc (DePuy Synthes, Warsaw, IN) injections 2 months prior. There was no effusion or acute inflammatory reaction after these initial HA injections. She reports having tried acetaminophen, various nonsteroidal anti-inflammatory drugs, narcotics, and topical medications over the past 8 months. All failed to provide any relief. She relates constant, debilitating pain when walking, kneeling, and going up or down the stairs that has acutely worsened.

Her past medical history includes asthma and hyperlipidemia. Her only medication is simvastatin. She has no known medical allergies. Her social history includes infrequent alcohol use, and she is a nonsmoker.

Physical examination revealed an overweight female with a body mass index of 29 kg/m^2. She had an antalgic gait. The dermis overlying her right knee was intact without erythema or warmth. Her knee examination revealed a moderate effusion, diffuse tenderness to palpation, and palpable crepitation during passive range of motion. Goniometer assessment exhibited a 20° flexion contracture, and maximal flexion was limited to 90°. Strength testing limited by pain but discernibly intact for age. Mechanical alignment showed a valgus deformity. Weight bearing radiographs were obtained, which showed severe tricompartmental arthritis (Fig. 1).

Taking into consideration her history of knee injections and the severity of her symptoms, inflammatory markers were obtained to rule out infectious or other inflammatory etiology. Her white blood cell (WBC) count and C-reactive protein (CRP) were within normal limits at 5.9 × 10^9 per liter and <0.5 mg/dL, respectively. Her erythrocyte sedimentation rate (ESR) was found to be slightly elevated at 38 mm/h. The decision was made to proceed with TKA.

In the operating room, the knee was prepped and draped in the usual sterile fashion. Preoperative antibiotics consisting of 2 grams cefazolin were administered before skin incision. A 12-cm longitudinal incision was made through the skin centered over

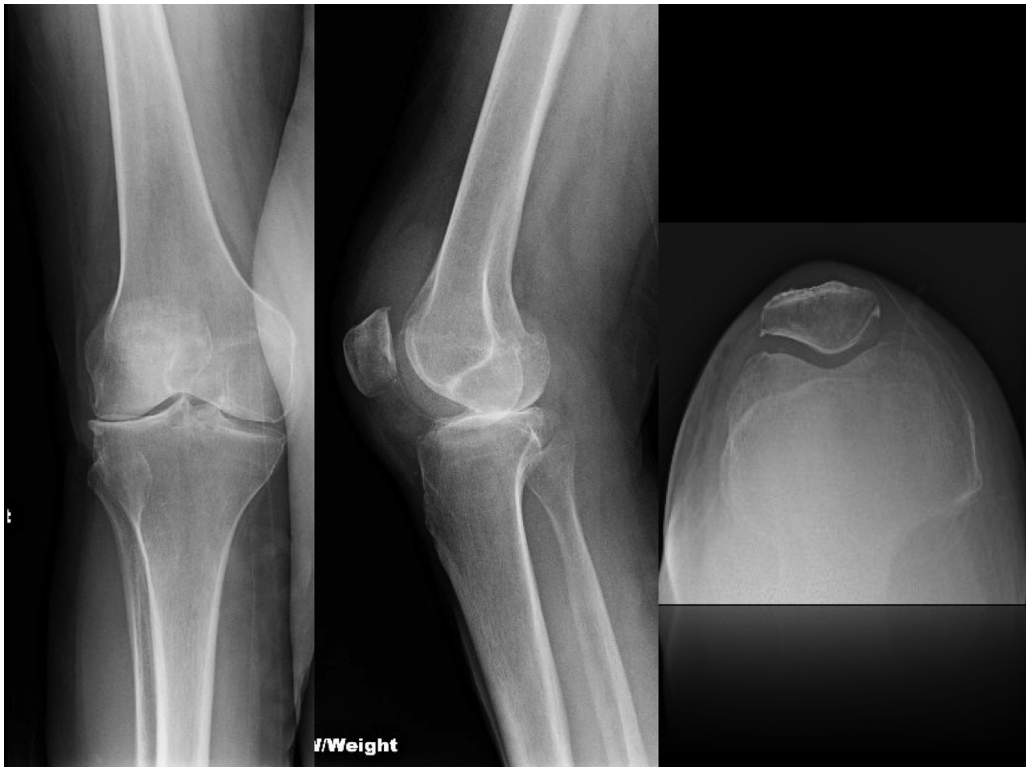

Figure 1. Preoperative radiographs. Preoperative anteroposterior (AP), lateral, and merchant weight bearing views of the right knee showing severe tricompartmental arthritis.

the patella. A medial parapatellar arthrotomy was performed, which revealed a significant effusion of purulent fluid. Marked synovitis was noted. Eversion of the patella reveled large areas of blackened articular cartilage on both the femoral condyles and underside of the patella (Fig. 2). An intraoperative pathology consult was obtained. Frozen section histopathology showed greater than 5 neutrophils per high-powered field. Specimens were obtained, and the decision was made to abort the knee replacement and instead perform an irrigation, synovectomy, and closure.

Postoperatively, the patient was placed on cefazolin for 3 days pending tissue and fluid cultures. All final cultures were negative, and antibiotics were discontinued before discharge. Postoperative inflammatory markers were obtained: WBC count 8.1 × 109 per liter, ESR 53 mm/h, CRP 14.1 mg/dL. Permanent histopathology showed synovial tissue with marked chronic inflammation, focal acute inflammation, and old hemorrhage. There were also abundant histiocytes containing foreign material.

Following the initial procedure, 2 months later, the patient's inflammatory markers had normalized: WBC 6.3×10^9 per liter, ESR 25 mm/h, and CRP <0.5 mg/dL. An arthrocentesis was done, and the Synovasure (Zimmer) panel for native septic arthritis was negative. The patient was taken for an uncomplicated TKA 3 months postoperative (Fig. 3). Synovium, cartilage, and bone were sent to pathology for special consideration. The specimens showed proliferative synovium with brown pigment (hemosiderin) in the stroma and inflammation around foreign material (Fig. 4.) Prussian blue stain showed hemosiderin (iron deposition) in the synovium and cartilage (Figs. 5 and 6). Foreign body material was seen in synovial giant cells at the various foci of inflammation (Fig. 7). This foreign body material was shown to be hyaluronate on alcian blue staining [13].

The patient was seen 2 weeks after TKA for staple removal. The incision was clean, dry, and nonerythematous. Her pain was well controlled. She was fully weight bearing and advancing well with outpatient physical therapy with improved range of motion. At the time of manuscript submission, the patient was doing well 6 months after TKA.

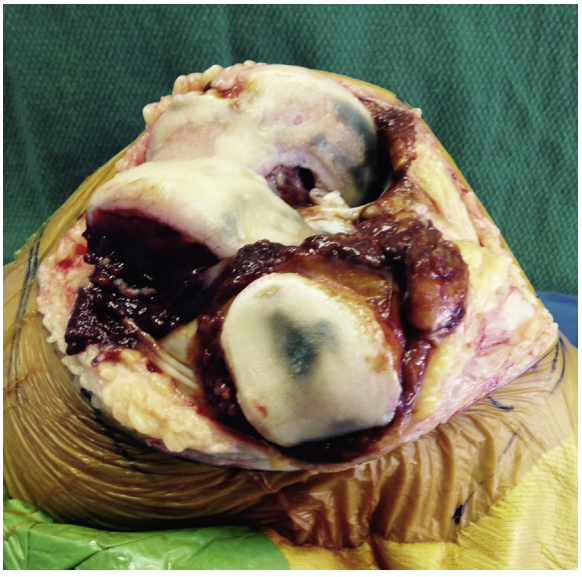

Figure 2. Intraoperative findings. Intraoperative photo showing marked synovitis and areas of blackened articular cartilage.

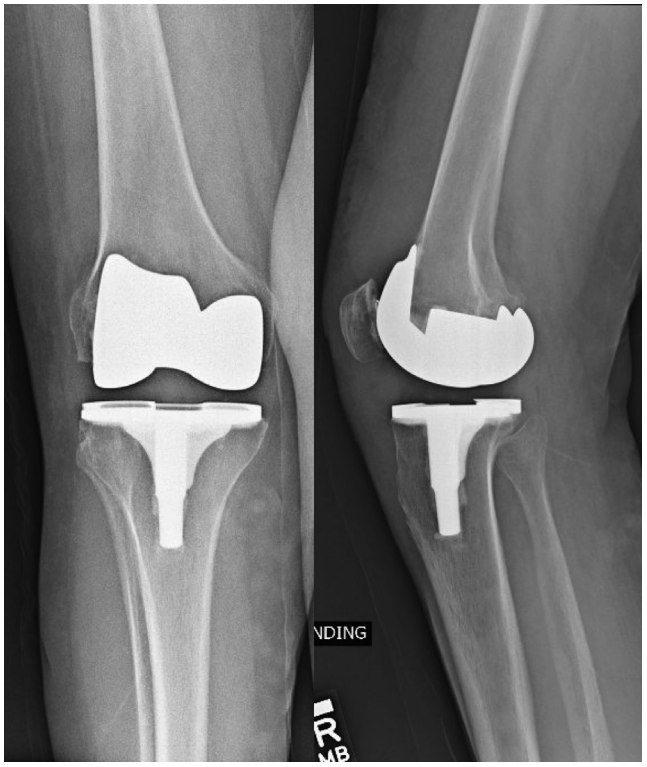

Figure 3. Postoperative radiographs. AP and lateral views of the right knee after TKA.

Discussion

There are no reports in the literature of delayed hemorrhagic pseudoseptic arthritis as a consequence of viscosupplementation. Acute inflammatory reactions to HA injection have been well described and usually begin within 48 hours of injection [10,11,16]. Our case is especially interesting because it was a late finding encountered during primary TKA, yielding the unique opportunity for laboratory testing and numerous pathology specimens.

One case series examined pathology specimens of 6 knees (5 patients) with a history of acute reactions to HA injection with complete resolution after 1-2 weeks that later underwent either arthroscopy or TKA for symptomatic OA. Surgical procedures

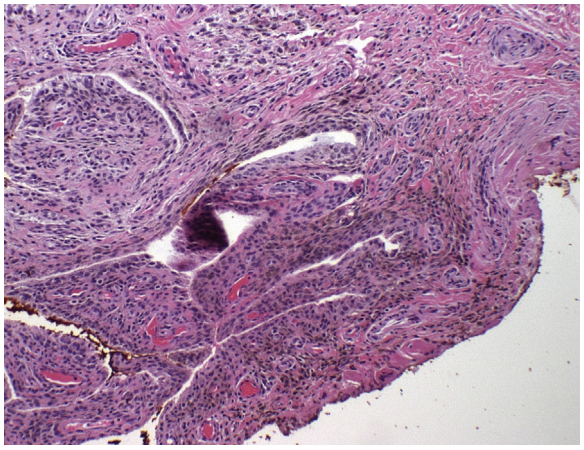

Figure 4. Inflamed synovium. Hematoxylin and eosin (H&E) stain, ×20 magnification: Proliferative synovium with brown pigment demonstrating hemosiderin in stroma. (Brown pigment on lower left of image is marking ink; pathology is on the lower right.)

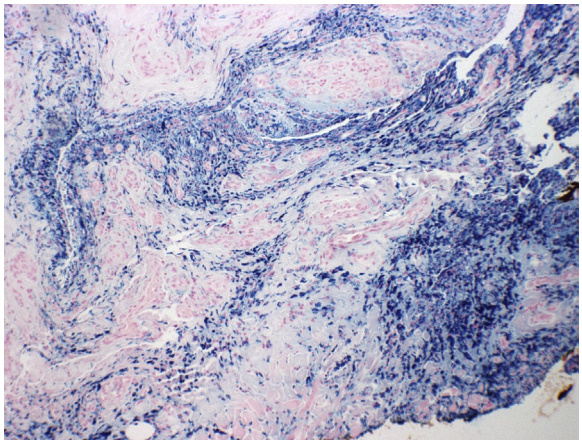

Figure 5. Iron in synovium. Prussian blue stain, ×20 magnification: blue pigment showing iron in synovium.

occurred between 2-9 months after last series of viscosupplmentation. Routine histolopathologic examination revealed inflamed synovium with giant cells surrounding foreign body material. This material also stained positive with alcian blue and disappeared after hyaluronidase digestion, which is consistent with hyaluronate [11]. During the course of this study, 2 patients underwent athroscopic debridement of the contralateral knee, which had not previously been treated with viscosupplementation. Granulomatous inflammation was not observed in either of these knees, therefore, eliminating the possibility of other systemic etiology. The study concluded that a component of viscosupplementation was likely responsible for the observed granulomatous inflammation. It was also hypothesized that this inflammation was a possible pathologic cause of intractable knee symptoms after supplementation [10].

One case report in the literature describes abnormal adipose and synovium found during TKA. The described patient had a history of 3 HA injections with the last one being 3 months before the procedure. The authors described the synovium as brown and the adipose as firm and indurated. Histologic examination of the adipose revealed granulomatous inflammation with giant cells surrounding pools of intensely basophilic material, which was

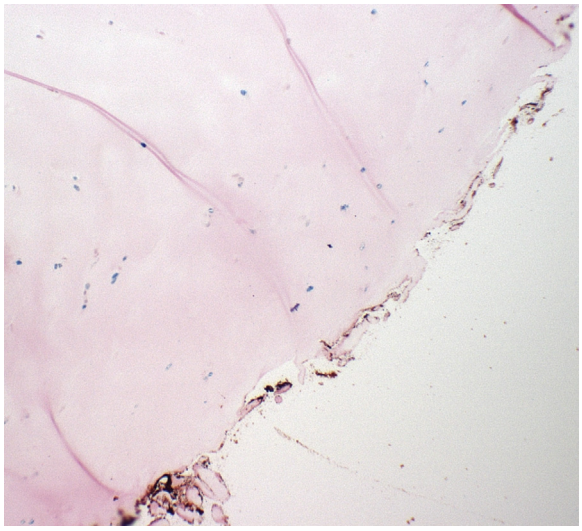

Figure 6. Iron in cartilage. Prussian blue stain, ×20 magnification: blue pigment showing iron in cartilage. Also, there is thinning of the cartilage with clefts and fibrillation representing osteoarthritis.

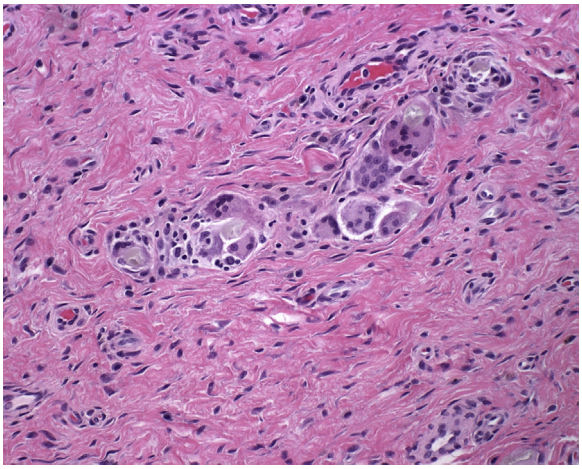

Figure 7. Foreign body material. Hematoxylin and eosin stain, ×20 magnification: foreign body material seen within synovial giant cells.

presumably hyaluronate. These authors termed this reaction "Synvisc perisynovitis" and attributed it to inadvertent injection into the fat pad. Speculation as to the cause of this reaction included hyaluronan breakdown products causing an increased production of proinflammatory cytokines [17].

Our histologic findings are similar to the above descriptions of granulomatous reactions to HA. However, our patient did not report any acute inflammatory reaction after injection. Instead, the abnormal synovium, bone, and cartilage were encountered months later during primary TKA, which caused the initial procedure to be aborted. This represents a previously unreported complication of HA.

Summary

We describe a case of late hemorrhagic pseudoseptic arthritis encountered during TKA due to HA viscosupplementation. Our triad of findings includes (1) acute and chronic inflammatory cells on frozen section, (2) synovitis with hemosiderin deposition, and (3) blackened cartilage with iron deposition on permanent histopathology. Histopathology revealed foreign body granulomatous inflammation consistent with previous reports of acute, adverse inflammatory reactions to HA. Our case is unique in that it shows a previously undescribed late complication of viscosupplementation.

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