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Case Report

Bilateral Pseudoseptic Arthritis in A 65-Year-Old Female Following Hyaluronic Acid Injection: Case Report and Literature Review

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Abstract

Intra-articular injections of steroids and hyaluronic acid are common treatments for osteoarthritis, yet pseudoseptic arthritis following hyaluronic acid injections is a rare occurrence. This report details a case of bilateral pseudoseptic arthritis in a 65-year-old woman post-hyaluronic acid injection, followed by a review of relevant literature. A 65-year-old woman developed bilateral knee pain, decreased range of motion, and fever three days after intra-articular hyaluronic acid injection. Despite being initially managed as septic arthritis, all investigations showed a sterile synovial fluid environment, confirming pseudoseptic arthritis. Although rare, pseudoseptic arthritis after hyaluronic acid injection has been documented in several reports. The differential diagnosis from septic arthritis is critical to avoid unnecessary prolonged antibiotic treatment and/or surgical surgical intervention.

Keywords: Hyaluronic Acid; Knee; Pseudoarthritis

Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease-causing pain, loss of function, and significant morbidity. Intra-Articular Hyaluronic Acid (IAHA) injections, alongside corticosteroids, are common in managing OA, especially when combined with physiotherapy and lifestyle changes [1,2]. The 2019 guidelines from both the European Society For Clinical And Economic Aspects Of Osteoporosis (ESCEO) and the Osteoarthritis Research Society International (OARSI) recommend IA injections as second- and third-line therapies for knee OA management, respectively [3,4]. These injections offer temporary relief and improved range of motion, though their safety and efficacy are still debated [1]. Pseudoseptic arthritis, or an acute local reaction, is a rare but recognized complication, especially after IAHA injections [5]. It mimics septic arthritis in its clinical presentation but is distinguished by the absence of infection in synovial fluid [6]. In this report, we present a case of bilateral pseudoseptic arthritis following a hyaluronic acid injection (Synvisc, Hylan g-f 20) in a 65-year-old woman.

Case Report

Patient is a 65-year-old female with multiple comorbidities, including well controlled type 2 diabetes, hypertension, and surgical history of total abdominal hysterectomy and bilateral salpingo-oophorectomy, chemo and radiotherapy for breast cancer. She first presented to the orthopaedic outpatient clinic for follow up of long-standing bilateral knee osteoarthritis. She initially presented with bilateral knee medial compartment osteoarthritis, for which she had analgesia and physiotherapy. She had the initial injection of Synvisc in June of 2018, in both knees. On her 6 monthly follow up, she was doing well, and the pain was well managed. She received the second IAHA injection synvisc around 1 year after the initial dose, as her symptoms recurred at that time. The third dose of synvisc was administered seven months later, and administered bilaterally, and was discharged in a stable condition. Three days later, she developed bilateral knee

swelling, heat over the joint, and decreased range of motion. She had pain mainly over the right knee, with a documented fever of 39 degrees Celsius. She presented to multiple health centres and reports being managed with oral analgesia, no antibiotics were administered, and she received no further treatment. Eventually, she presented to the hospital 3 weeks post injection, cited no improvement to the above-mentioned symptoms. Clinical examination showed bilateral swelling, tenderness, with painful and reduced range of motion to 90 degrees. Lab investigations showed elevated white cell count, and she underwent right knee arthrocentesis. Synovial sample showed turbid looking fluid, and samples were sent for culture and cytology. She refused left sided joint aspiration. She was admitted for further management and joint washout. On admission, she had a raised C-Reactive Protein (CRP) of 131 mg/L, Estimated Sedimentation Rate (ESR) pf 104, peripheral blood test showed a white cell count and neutrophil of 12400/uL and 8900/uL respectively. Right sided joint aspiration was performed, Synovial fluid was yellowish in colour, analysis showed 99% polymorphs, further raising the suspicion of septic arthritis. However, no organism was seen in gram stain. She was managed as a case of acute septic arthritis, bilateral joint washout was subsequently performed, and more samples were sent for bacteriology and analysis. Five days after bilateral joint washout and empiric antibiotics, she showed remarkable clinical improvement, and she remained afebrile for the duration of her stay. Later, blood and synovial cultures results were released, all blood and synovial cultures were negative. 16srRNA sequencing was performed on a synovial sample obtained pre joint washout, however, no bacteria were identified. She received a 2-weeks course of Cefazolin, among analgesia and supportive care. She had no further spikes of fever while in hospital, her ROM improved and returned to her baseline. She was discharged on a stable and improved condition, on oral cefuroxime.

One year after discharge, she presented again for follow up. Clinically, she had no concerning signs of septic arthritis. Lab investigations showed raised WBC count of 11.7, ANCs of 7.8 and CRP of 91. She was due for the 4th dose of Synvisc, and a bilateral knee synovial sample was obtained prior to HA injection. Joint aspiration standard bacterial cultures were negative bilaterally, however, WBC count and CRP remained elevated. Three-phase bone scan: Tc99m, HDP and 789 MBq was performed: showed non-specific and infection could not be ruled out based on it, suggested Leukoscan. Leukoscan 650 mbq was performed, not suggestive of infective process. One and a half years later, she was admitted for bilateral total knee replacement, starting with the left side. Prior to this admission, she had no increase from baseline arthritis pain, no acute changes in her condition and no new complaints. Upon arthrotomy of the left knee, she was found to have turbid looking synovial fluid with fibrinous exudate (Figure 1). A synovial resection was done (Figure 2), synovium showed florid synovitis with areas of arthrofibrosis coupled with arthritic changes. Multiple tissue biopsies were obtained, in addition to a fresh frozen section, and sent for analysis and bacteriology. She underwent left knee debridement and washout and started on antibiotics cefazolin. Synovial analysis showed WBC count of 3042, gram stain showed no organisms. MRI scan was performed post operatively, showed thick, irregular and shaggy synovium with strong enhancement seen with IV contrast. These findings were suggestive of septic arthritis of the left knee. During this admission, all her blood cultures showed no growth after five days, synovial fluid analysis showed no microorganisms, and synovial culture showed no growth. She had further blood cultures all of which were negative. 16srRNA sequencing was performed on a synovial sample, however, no bacteria were identified. A sample was sent to test for mycobacteria, no Acid-Fast Bacilli (AFB) was sent, no mycobacteria was isolated on culture neither brucella antibody, nor no mycobacterium tuberculosis was detected by GeneXpert MTB/RIF. She was later discharged on oral antibiotics. She received a full course of antibiotics, in addition to analgesia and IV fluids. She received no corticosteroids or any other drug of relevance. Her Condition improved and was subsequently discharged.

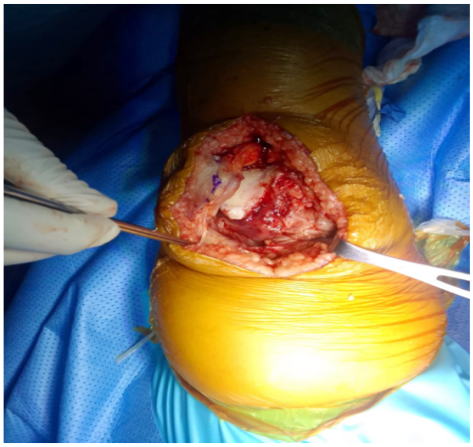

Figure 1: Knee exposure after arthrotomy and showing turbid looking synovial fluid with fibrinous exudate.

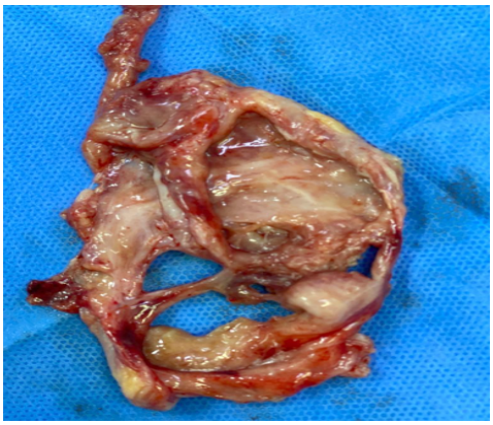

Figure 2: The gross specimen of synovium resection.

Consent: The patient's consent was obtained for publication purpose

Discussion

IAHA injections were first approved in Japan and Italy in 1987 [1]. U.S FDA approved Synvisc and hyalgan as the first two HA-IAIs in 1997. While the exact mechanism of action is yet to be confirmed, laboratory-based literature reported that IAHA injections have chondroid protective properties, by stimulating chondrocyte proliferation and inhibiting apoptosis. In addition, IAHA has been shown to stimulate proteoglycan and glycosaminoglycan production and optimises its location within the cellular matrix. It also provides subchondral protection, and anti-inflammatory effects [7]. Pseudoseptic arthritis mimics septic arthritis in the history, clinical presentation, and biochemical laboratory tests. It is diagnosed when septic arthritis is ruled out by having sterile synovial fluid and or biopsies, even if synovial fluid is turbid or purulent. They both typically present with a painful swollen joint, coupled with erythema and warmth. Occasionally they present with fever, inability to bear weight, and reduced range of motion [8]. Symptoms typically present within 48 hours of HA injection, compared to a longer time of onset in true septic arthritis. Tahiri et al [9]. reported a case of knee acute arthritis, that occurred 48 hours following the initial injection of HA Curavisc, in a 70-year-old woman with osteoarthritis. She presented with joint effusion, no fever or chills. Peripheral blood sample showed normal cell counts, c reactive protein of 6mg/l and ESR of 12mm/h. Joint aspiration showed purulent synovial fluid. Laboratory analysis revealed a cell count 24,000 cells/mm3, 87% of which were neutrophils, and 13% lymphocytes. Synovial samples were sent for cultures, in addition to blood and urine cultures. The patient was treated as a case of septic arthritis and started on empirical antimicrobial therapy. All cultures showed no growth of any micro-organism. She remained Afebrile and the joint effusion improved rapidly in 4 days. Septic arthritis was deemed unlikely, and antibiotics were stopped. She received NSAIDs and rehabilitation therapy and was discharged home three weeks after admission.

In 2012, Idrissi [10] reported a similar case of a 60-year-old woman, who developed acute arthritis six days following the second dose of Ostenill IAHA injection. Her clinical presentation was consistent with septic arthritis, and empiric antibiotics were started after obtaining synovial samples and blood cultures. All these cultures showed no microorganism growth, and the case was labelled as pseudoseptic arthritis. Antibiotics were subsequently stopped, and the patient was managed with NSAIDS and rehabilitation therapy. Sedraak et al [8]. conducted a systematic review of 28 cases of knee pseudoseptic arthritis, following HA injections. Five cases out of seven reported elevated CRP levels above 50, and six out of seven reported elevated ESR above normal physiological values. Out of the examined cases that reported synovial aspiration results, 12.5% reported white cell count above 50,000 and 66.7% reported cell counts between 5000 and 50000. Only five samples showed cell counts below 5000. Cases vary in regard to white cell differential count; thus, white cell subtype predominance cannot be accurately used as a diagnostic factor for pseudoseptic arthritis.

The mechanism of psudoseptic arthritis is not fully known, however, the cases of acute pseudoseptic arthritis following HA-IAI were first reported as early as 1995 [11]. Furthermore, these cases are extremely rare, with an incidence of 1 in 100000 for Synvisc based HA injections, and 2 in 100000 for non-synvisc HA [2,12]. Many theories exist for the pathological mechanisms behind pseudoseptic arthritis, however, establishing an exact mechanism has been challenging. One hypothesis put forward by andrew marino et al [2]. reported that pseudseptic arthritis is a T cell mediated hypersensitivity reaction (type 4 hypersensitivity reaction). However, many cases were reported of pseudoseptic arthritis following the very first dose of HA, where there should not be any sensitised T cells. An allergic mechanism behind these reactions is unlikely, due to reports that HA injections following an episode of pseudoseptic arthritis do not necessarily trigger a reaction. From the case reports, the reaction occurred with different preparations of HA, including curavisc, ostenil, and synvisc. 82.8% of cases reported in Sedrak's et all systematic review has used synvisc. The exact pathophysiology of these reactions remains unclear, with further investigation needed.

Conclusion

Pseudoseptic arthritis is an uncommon, but well recognised phenomenon following intra articular injections. Patients are usually managed as a case of septic arthritis and subjected to a prolonged course of antibiotics. It is important to consider pseudoseptic arthritis when there is a significant clinical

improvement in suspected septic arthritis cases following intra articular injections. It is essential to explore the usefulness of other inflammatory markers such procalcitonin in future publications, and to explore the role of steroids in those conditions.

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