Journal of Southeast Asian Orthopaedics
ISSN 2821-9848 (Print)
ISSN 2821-9864 (Online)
https://doi.org/10.56929/jseaortho-023-0179 https://jseaortho.org

Acute Pseudoseptic Arthritis after Intra-Articular Sodium Hyaluronate Injection: A Case Report and Literature Review

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Purpose: This report describes the case of 59-year-old woman with right medial compartment knee osteoarthritis (OA) who experienced an unusual adverse reaction to intra-articular sodium hyaluronate injection.

Methods: The patient received an intra-articular sodium hyaluronate injection for treatment of knee OA. Ten days after injection, she experienced severe pain in her right knee wherein laboratory test results showed inflammatory profiles that could not rule out septic arthritis. Joint lavage was performed, after which the patient was monitored for any changes in her symptoms or laboratory test results.

Results: The patient experienced severe pain in her right knee after intra-articular sodium hyaluronate injection. Additionally, laboratory test results showed inflammatory profiles that could not rule out septic arthritis. One month after joint lavage, the patient's symptoms resolved, and her laboratory test results returned to normal range.

Conclusions: An inflammatory flare could occur as an adverse effect of intra-articular sodium hyaluronate injection, mimicking septic arthritis. Importantly, both physicians and patients should be aware of this potential reaction, particularly, patients should report any unusual symptoms to their healthcare provider.

Keywords: Knee osteoarthritis, sodium hyaluronate injection, pseudoseptic arthritis

A 59-year-old female public officer presented with a history of right knee osteoarthritis (Kellgren-Lawrence grade II). While walking, she felt continuous pain, leading to limited mobility. She received only oral medication, without undergoing any injections. However, upon this presentation, she was injected with 3 ml of 1,4-butanediol diglycidyl ether (BDDE)-crosslinked sodium hyaluronate (Hyruan One®), which was carried out in a sterile setting. Following injection, the patient was able to move freely without knee swelling.

Ten days after the intra-articular injection of Hyruan One®, she presented to the emergency room with significant limping, low-grade fever, and acute monoarthritis of the knee. Due to her intense pain and limited knee range of motion, a knee aspiration was performed to test for any potential joint infections. Fluid analysis showed white blood cell (WBC) count of 197,000 cell/mm3 (neutrophil: 91%). Moreover, blood test results revealed erythrocyte sedimentation rate (ESR), 52

Article history:
Received: October 8, 2022, Revised: March 20, 2023
Accepted: April 27, 2023
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mm/h; C-reactive protein (CRP), 59 mg/dL; and uric acid, 2.5 mg/dL. Since the WBC count was quite elevated, septic arthritis could not be ruled out. Therefore, the surgeon decided to perform arthrotomy for debridement. The intraoperative findings showed 40 ml of clear yellow fluid without pus. The articular cartilage was intact without significant chondrolysis.

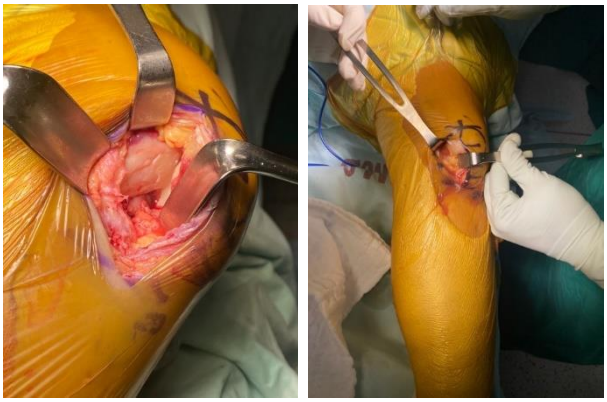

Fig. 1 Intraoperative findings of right knee arthrotomy show neither pus discharge nor significant chondrolysis.

After surgery, the patient received intravenous cefazolin. Thereafter, synovial fluid and tissue analyses indicated negative results of Gram staining and bacterial culture. Furthermore, polymerase chain reaction testing for tuberculosis showed negative results. After obtaining negative culture results and consulting with an infectious disease specialist, we immediately discontinued the antibiotic treatment. The duration of the intravenous antibiotic treatment was less than 10 days. After receiving supportive care, the knee pain and edema quickly subsided within 3 days postoperatively. Only five days after admission, although the ESR level was still elevated at 57 mm/h, the CRP level decreased to 13 mg/dL. The patient was discharged and treated with non-steroidal anti-inflammatory drugs (NSAIDs) and knee rehabilitation. We did not prescribe any oral antibiotics or steroids for home medication. Three weeks following the onset of inflammation, from the initial visit to the follow-up at the outpatient department, the inflammation gradually improved. Additionally, all laboratory test values returned to normal range.

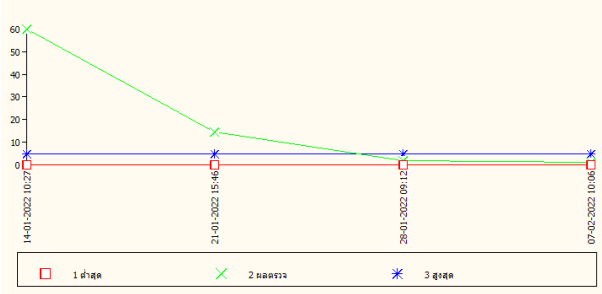

Fig. 2 CRP trend.

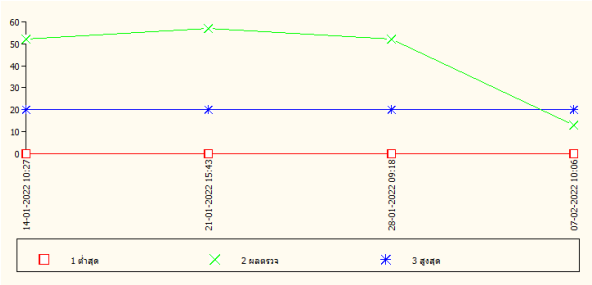

Fig. 2 ESR trend.

DISCUSSION

The use of intra-articular injections of hyaluronic acid (HA) for the treatment of osteoarthritic pain was recommended according to the American College of Rheumatology guidelines for the treatment of osteoarthritis of the knee, published in September 2000. It has been proven that HA injection as viscosupplementation was a remarkably successful non-surgical treatment of knee osteoarthritis. In general, HA injection has been shown to be very safe[1,2]. Compared with other knee joint injections, such as steroid injections, infection was incredibly rare. According to the Korean registry[3], there were approximately 3 in 100,000 cases of infection following HA injection of the knee. However, since HA injections into the knee joints have gained growing popularity nowadays, improving infectious conditions surveillance is mandatory.

Acute local skin reaction has been reported to be the most frequent HA injection side effect that could occur in 11% of knee injections according to Puttick et al. However, there have been reports of patients with acute pseudoseptic arthritis after

HA injection, causing acute inflammation of the knee with swelling, redness, and warmth. Inflammatory markers such as ESR, CRP could elevate in patients with acute pseudoseptic arthritis, which mimicking infection. However, in our case, the findings of the knee joint fluid analysis revealed no infection or crystals. In addition, the symptoms could spontaneously resolve after receiving conservative care with NSAIDs and other anti-inflammatory drugs. The drugs that have been reported to cause such reactions included: Hylan G-F 20 (Synvisc®), which is an elastoviscous high-molecular-weight fluid containing hylan A and hylan B polymers extracted from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate). Hylan G-F 20 is unique in that the hyaluronan is chemically crosslinked. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine, as indicated in another report of sodium hyaluronan (Ostenil®)[4,5].

Table 1 summarizes the clinical and demographic features of cases of acute septic and pseudoseptic arthritis after HA injection reported in the literature. Of note, although several incidences of aseptic arthritis after HA injection have been documented as in the article by Goldberg et al.,[6] none involved Hyruan One®.

Table 1 Review of studies regarding agents used and clinical data.

Study	Patients	Agent	Clinical data
Puttick et al. [1]	6 in 28 knees	hylan	24 h after injection: pain, warmth, and swelling
Leopold et al. [2]	6 in 19 knees	hylan GF-20 (Synvisc)	within 6 to 36 h after injection: acute mono-arthritis
Bernadeau et al. [8]	2 case reports	hylan GF-20 (Synvisc)	2, 4 h after injection: pain, fever with local inflammation signs
Pullman-Mooar et al.	8 cases report	hylan GF-20 (Synvisc)	within 12 to 48 h after injection: local swelling, high fluid WBC count
Idrissi et al. [4]	1 case report	sodium hyaluronan (Ostenil®)	6 days after injection: acute mono-arthritis, major functional impotence, and fever
Ross et al. [5]	1 case report	sodium hyaluronan (Ostenil®)	8 days after injection: acute mono-arthritis, purulent fluid without crystal

Abbreviation: WBC, white blood cell.

The patient's symptoms were strikingly comparable to those in individuals previously identified, including knee pain and edema after injection of synthetic knee joint fluid. The distinction was that the onset in this case was 10 days after injection, which was delayed compared with other cases: typically occurred 3–4 days after injection. The product is 1,4-butanediol diglycidyl ether (BDDE)-crosslinked sodium hyaluronate (Hyruan One®, LG Chem, South Korea), which has never been reported to cause such a reaction. The product is widely used in many areas such as dermal fillers, a vitreous humor substitute, and viscosupplementation for the knee. More than 50 studies including more than 9,000 patients have been conducted since the first BDDE crosslinked HA dermal filler for cosmetic application was introduced in 1996, reporting on the safety and tolerability of this product[7] Based on the information available so far and the patient's follow-up, there is currently no evidence of any infection found. Therefore, the current working diagnosis is acute pseudoseptic arthritis.

The mechanism underlying this condition remains unclear. A study by Bernadeau et al. suggested that this condition may have been caused by an immune sensitization phenomenon during HA degradation. Inflammation was caused by pro-inflammatory cytokines being activated by interaction with CD44 receptors[8]. Another study reported that the leukocyte count in arthroscopic fluid could range between 3,150 and 103,000/ mm3.[9] This could be confused with septic arthritis of the knee, leading to different treatments.

CONCLUSIONS

Based on the findings of this case, it is the first known example of acute pseudoseptic arthritis due to Hyruan One® viscosupplementation. It may be necessary to further study on how such substances could induce inflammatory reactions with their onset being slower compared with similar agents. In addition to encouraging the physicians and personnel involved know about this condition, our report emphasizes how crucial sterile injection is. Physical examination, blood tests, and synovial fluid results that are compatible with this condition should be carefully interpreted to distinguish this condition from acute septic arthritis and give proper treatment. However, patients should always be informed that there might be a risk of infection before receiving an intra-articular injection, despite the extremely low probability.

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