

Viscosupplementation of the knee: Three cases of acute Pseudoseptic Arthritis with painful and irritating complications and a literature review

Murat Aydın¹, Murat Arıkan², Güray Toğral², Onur Varış³, Güle Aydın⁴

Abstract

Acute pseudoseptic arthritis is a very rare complication that is associated with intra-articular hyaluronic acid injections, which normally involve minimal risk. The most common adverse events that are caused by hyaluronic acid injections are inflammatory reactions or flares at the injection site. In this study, we described three cases of acute pseudoseptic arthritis that was caused by hyaluronic acid; the symptoms in these cases were reminiscent of acute septic arthritis. Moreover, we performed a literature review on pseudoseptic arthritis following hyaluronic acid injections to determine the manner in which this condition can be described, diagnosed, and treated.

Keywords: Intra-articular injections, hyaluronic acid, experimental arthritis, infectious arthritis, osteoarthritis

Introduction

Osteoarthritis (OA) is a clinical condition that affects the joints whose most common symptoms are articular cartilage loss accompanied with pain, osteophyte formation, subchondral bone remodeling, and inflammation of joints. Non-pharmacological treatments of OA include exercise, weight loss, bracing, shoe and insole modification, local cooling/heating, acupuncture, and electromagnetic therapy. In addition, various substances, such as corticosteroids, viscosupplements, and blood-derived products, may be administered through intra-articular injection to increase joint viscoelasticity and to improve pain management.

Acute pseudoseptic arthritis is a rare complication affecting knee viscosupplementation. The most common treatment for osteoarthritis involves hyaluronic acid (HA) injections to the knee, particularly in elderly patients. Patients with level II–IV gonarthrosis are generally excluded from surgical procedures such as arthroscopy, chondrocyte scaffold techniques, and unicompartmental or total knee replacements. Such patients are instead administered platelet rich plasma that is prepared from blood or HA injections containing different forms of HA.

In this study, we evaluated patients with acute pseudoseptic arthritis who were being treated with viscosupplementation injections to the knee for the past 3 years to determine the manner in which this condition can be diagnosed, treated, and followed.

Case 1

The patient was a 62-year-old female with long-standing stage III OA who had been suffering from knee pain for 4 years, particularly at the medial site. Prior to her visit to Oncology Training and Research Hospital, she had been treated with non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy and rehabilitation and had refused to undergo surgical treatment. Approximately 5 h after the first injection of Genvisc® (sodium hyaluronate+N-acetyl glucosamine, Phibio GmbH; Frankfurt, Germany), the patient presented with acute monoarthritis. In her first examination, the patient was determined to have a fever (38.3°C) and severe pain and was hospitalized. Twelve hours after hospitalization, the patient developed major loss of function, and her fever symptoms continued to persist. A joint fluid analysis revealed 11,000 cells/mm³, with 81% neutrophils and 19% lymphocytes. A knee aspiration was conducted to evaluate the possibility of an infection in the joint; however, no crystallization was observed, and the culture on standard media was negative. The patient's erythrocyte sedimentation rate was 80 mm/h, while her C-reactive



1 Department of Orthopedics and Traumatology, Afyonkarahisar Suhut Public Hospital Medicine, Afyonkarahisar, Turkey

2 Department of Orthopaedics and Traumatology, Oncology Training and Research Hospital, Ankara, Turkey

3 Department of Orthopedics and Traumatology, Trabzon of Public Hospital Medicine, Trabzon, Turkey

4 Department of Clinical Microbiology and Infectious Diseases, Zübeyde Hanım Obstetrics and Gynecology Public Hospital, Afyonkarahisar, Turkey

Address for Correspondence:
Murat Aydın, Department of Orthopedics and Traumatology, Afyonkarahisar Suhut Public Hospital Medicine, Afyonkarahisar, Turkey

E-mail: opr.murataydin@gmail.com

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protein level was 54 mg/L and white blood cell count was 9200 cells/mm³. In addition to these findings, the possibility of an acute inflammation and septic arthritis was considered, and intravenous antibiotic therapy was initiated with 200 mg ciprofloxacin every 12 h and 1500 mg ampicillin sulbactam every 6 h, together with NSAIDs and the application of ice. The symptoms at the joint subsided at 2 days after the injection, and antibiotic therapy was discontinued after 10 days. All clinical and laboratory test abnormalities normalized within 5 days. Within 48 h, the patient's left knee had significantly improved with minimal effusion, and she could ambulate without pain. The patient was subsequently diagnosed with pseudoseptic arthritis.

Case 2

The patient was a 72-year-old female with stage IV OA who had been suffering from nocturnal knee pain for 7 years. Prior to visiting our clinic, the patient had been treated in another hospital with two knee injections of Ostenil® (Sodium hyaluronate, TRB Chemedica; Vouvry, Switzerland) 5 days earlier. At the time of our consultation, the patient had pain and swelling reminiscent of acute septic arthritis in the left knee. She was then hospitalized because of septic-like symptoms. A joint fluid analysis revealed 10,000 cells/mm³, with 80% neutrophils and 20% lymphocytes. Knee aspiration revealed no crystals, and a culture on standard

media was negative. The patient's erythrocyte sedimentation rate was 89 mm/h, while her C-reactive protein level was 66 mg/L and white blood cell count was 10,200 cells/mm³. In addition to these findings, acute inflammation and septic arthritis were considered, and intravenous antibiotic therapy was initiated with 200 mg ciprofloxacin every 12 h and 1500 mg ampicillin sulbactam every 6 h, together with NSAIDs and the application of ice. The symptoms at the joint subsided at 3 days after the symptoms had first presented, and antibiotic therapy was discontinued after 10 days. All clinical and laboratory test abnormalities normalized within 6 days. Within 72 h, the patient's left knee had significantly improved with minimal effusion, and she could ambulate without pain. The patient was subsequently diagnosed with pseudoseptic arthritis.

Case 3

The patient was a 55-year-old female with long standing stage III OA who had been suffering from knee pain for 4 years, particularly at the medial and lateral sites, and also from nocturnal knee pain for 9 months. Prior to our visit, the patient had been treated with NSAIDs and a corticosteroid knee injection (with triamcinolone hexacetonide) 7 months previously. Approximately 8 h after the third injection of Synvisc® (Sodium hyaluronate, Genzyme Biosurgery; Ridgefield, USA), the patient presented with acute monoarthritis. In her first examina-

tion, the patient was determined to have fever (38.1°C) and swelling and pain in the knee and was hospitalized because of septic symptoms. A joint fluid analysis revealed 9,000 cells/mm³, with 82% neutrophils and 12% lymphocytes. Knee aspiration was performed to evaluate the possibility of joint infection, although no crystals were observed and the culture on standard media was negative. The patient's erythrocyte sedimentation rate was 102 mm/h, C-reactive protein level was 74 mg/L, and white blood cell count was 9300 cells/mm³. In addition to these findings, acute inflammation and septic arthritis were considered, and intravenous antibiotic therapy with 200 mg ciprofloxacin every 12 h and 1500 mg ampicillin sulbactam every 6 h was initiated, along with NSAIDs and application of ice. The symptoms at the joint subsided at 3 days after the injection, and antibiotic therapy was discontinued after 10 days. All clinical and laboratory test abnormalities normalized within 4 days. Within 48 h, the patient's left knee had significantly improved with minimal effusion, and she could ambulate without pain. The patient was subsequently diagnosed with pseudoseptic arthritis. All study participants provided informed consent.

Discussion

Because of the developments in molecular and cell biology over the past 20 years, scientists have been able to synthesize HA *in vitro* and have succeeded in producing injectable HA forms.

Table 1. Main features observed in reported cases and our cases

Author	N	Sex	Mean Age	Agent	Systemic Symptoms	Starting Time	Injection Sequence	Additional Information	Treatment
Puttick et al.(4)	6	F=5, M=1	66.8	Synvisc®	None	24 hours	2-5	None	A / IA GC
Pullman-Moore et al.(8)	7	F=4, M=3	52.5	Synvisc®	None	1-48 hours	2-3	None	IA GC
Bernardeau et al.(1)	2	F=2	66	Synvisc®	Fever in one (38°C)	2-4 hours	2	None	NSAID + acetaminophen
Martens (Case report) (2)	1	F=1	70	Synvisc®	None	12 hours	4	Bilateral	Ketorolac / IA GC / A
Rees and Wojtulewski (Case report) (3)	1	F=1	79	Synvisc®	Fever (38°C)	12 hours	3	None	A / IA GC
Leopold et al. (9)	5	F=3, M=2	56.2	Synvisc®	None	6-36 hours	1-3	First time injection ¹	GC / A
Roos J et al. (Case report) (5)	1	F=1	70	Ostenil®	Fever (38.5°C)	9 days	2	None	Underwent surgical lavage
Idrissi Z (Case report) (6)	1	F=1	70	Ostenil®	None	6 days	2	None	A / NSAID
Tahiri L et al. (Case report)(7)	1	F=4, M=3	70	Curavisc®	None	48 hours	1	None	A / NSAID
Our study	1	F=1	62	Genvisc®	Fever (38.3°C)	5 hours	1	None	A / NSAID
Our study	1	F=1	72	Ostenil®	None	5 days	2	None	A / NSAID
Our study	1	F=1	55	Synvisc®	Fever (38.1°C)	8 hours	3	None	A / NSAID

¹Three patients experienced pseudoseptic arthritis following the first injection; two of them were treated with Synvisc® as part of their second treatment cycle
A: analgesics; IA GC: intraarticular glucocorticoids

The drugs commonly used in clinical practice are Ostenil®, Synvisc®, Genvisc®, Fermathron®, and Orthovisc®. Genvisc® contains sodium hyaluronate, n-acetylglucosamine, and chondroitin sulfate. We currently do not know the specific substance in this composition that might cause acute reactions. Our first case experienced acute pseudoseptic arthritis following Genvisc® administration.

Hyaluronic acid provides viscoelastic protection to the articular cartilages and synovial membranes. Intra-articular injections are a common type of treatment used by many clinicians, such as orthopedicians, rheumatologists, and physical therapists.

The etiology of pseudosepsis varies depending on whether it is associated with autoimmune inflammatory arthritis or microcrystalline inflammatory arthritis. In clinical practice, pseudoseptic arthritis has almost the same clinical presentation as infectious arthritis. It is consequently often confused with infectious arthritis, and surgical procedures may be needlessly performed to eliminate the supposed infection.

Pseudosepsis that is caused by viscosupplementation with hylan is associated with certain features (1-3), which include (1) intra-articular knee effusion with severe pain, most often within 24 and 72 h of administration; (2) requirement for two or three injections prior to the development of immune sensitization; (3) absence of infectious agents and calcium pyrophosphate crystals in the synovial fluid aspirate; (4) possibility of elevated mononuclear cell levels (majority of macrophages, infrequent neutrophils, and increased eosinophils) in the synovial fluid; and (5) disease prognosis that is not self-limiting and that requires treatment in nearly all cases (arthrocentesis, intra-articular steroid injection, and NSAIDs).

Although articular HA injections are associated with few and tolerable complications, Puttick et al. (4) reported that local acute reactions following HA injection can be observed in up to 11% of injected knees. An inflammatory reaction or a flare at the injection site is the most commonly encountered adverse event following HA injection (5). However, in most patients, these reactions can be treated with NSAIDs, ice compressions, and sometimes with cortisone. At a practical level, intra-articular HA injections appear to involve minimal risks. Among various case series evaluated in the literature, Synvisc®, a polymer of hyaluronic acid, appears to be the injectable HA form that most frequently results in pseudosepsis (Table 1). There have been only two cases to date wherein pseudosepsis

was observed with Ostenil® and only one with Curavisc® (5-7).

Pseudosepsis may be rarely observed with monosodium urate or calcium apatite microcrystals (3). The patients need to be first sensitized before injections to develop pseudosepsis with Synvisc® and Ostenil®. As such, patients generally develop pseudosepsis following the second or third injections of these agents. However, Leopold et al. (9) described a case wherein pseudosepsis developed after the first injection of Synvisc®. Pseudosepsis following the first injections of Curavisc® and Genvisc® have also been observed, with no sensitization period being involved, in a manner similar to our own cases (7).

The timing of pseudosepsis symptoms is variable, with symptoms generally appearing within 2–48 h after injection. However, Ostenil® injections have been reported to cause pseudosepsis symptoms at 6–9 days after injection (5-6). Tahiri et al. (7) report one case of a patient injected with Curavisc® whose symptoms began 48 h later and did not involve fever or chills. Pseudosepsis symptoms associated with Genvisc® are generally observed within 5 h and are similar to those of Curavisc®, with no fever or chills. On the basis of these findings, it can be observed that pseudosepsis associated with Synvisc® and Ostenil® usually occurs with the second or third injection, and fever or chills are involved in fewer cases.

In pseudoseptic arthritis, the blood test results of the patients considerably vary from one case to another; however, in most patients, C-reactive protein and sedimentation levels are generally high and close to their upper limits.

The treatment course for pseudoseptic arthritis is evident. First, it is necessary to exclude the possibility of acute septic arthritis by administering antibiotic therapy until negative bacteriological tests are obtained. NSAIDs, ice application, and elevation should also be applied to decrease edema, local warming, and tension at joints. If there is little or no regression of symptoms, intra-articular cortisones may be administered to immediately resolve the complications. Daily knee aspirations can be performed to eliminate joint distention and to ensure effective pain management.

The mechanism of acute pseudoseptic arthritis following HA injections has not yet been elucidated. A few hypotheses have proposed an immunological basis to explain the physiopathology of pseudoseptic arthritis. One of the hypotheses posits that proinflammatory cyto-

kines may play an important role in the occurrence of immunological reactions (1). The most important indication of this is hyaluronic acid immunosensitization that develops following several injections (8). This is observed in all cases that are administered with two or more Synvisc® and Ostenil® injections, except for a single case reported by Leopold et al. (9), where pseudosepsis occurred following a first injection. Hyaluronan and CD44 have a ligand-receptor association, and their association increases the migration and recruitment of inflammatory cells (10). Production of hylan antibodies and sensitization of the immune system at the knee joint has the subsequent effect of engendering pseudoseptic arthritis. Flares at the injection site with Synvisc® are probably not type-1 hypersensitivity reactions but instead type-4 hypersensitivity reactions (10).

We believe that differential diagnosis is essential for distinguishing pseudosepsis from true sepsis during clinical treatment. In the case of an incorrect or incomplete diagnosis, pseudosepsis may lead to further and severe complications. It must be noted that septic arthritis incidence with HA injections is lower than the incidence observed with cortisone administration. The literature also indicates that septic arthritis following hyaluronic injections usually occurs among patients who received cortisone a few months previously.

In our study, we examined three cases of acute pseudoseptic arthritis caused by HA injections. The patients' clinical history, clinical examination findings, and bacteriological tests were important for differential diagnosis. Acute pseudoseptic arthritis is possibly associated with immunological pathologies. Further studies should be conducted to obtain a better understanding of the disease mechanism.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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