Case report

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A new form of severe acute localized reactions following intra-articular hyaluronic acid injections in knee osteoarthritis. A case report

Daniela Fodor[1], Oana Șerban[1], Sergiu Gabriel Macavei[2], Lucian Barbu Tudoran[3], Paula Bora[4] Maria Bădărînză[1]

[1]2nd Internal Medicine Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, [2]National Institute for Research and Development of Isotopic and Molecular Technologies, Cluj-Napoca, [3]Electron Microscopy Center, Faculty of Biology and Geology, Babeș-Bolyai University, Cluj-Napoca, [4]Rheumatology Department, Dej City Hospital, Romania

Abstract

Intra-articular hyaluronic acid (HA) injections are widely used for the treatment of symptomatic knee osteoarthritis. Adverse reactions were described in a limited number of patients and consist in local inflammatory reactions and severe acute inflammatory reactions (pseudosepsis). We present the case of a 71-year-old woman who experienced a severe acute adverse effect immediately (within minutes) following intraarticular HA administration, attributed to HA precipitation. The severe very early local manifestations were accompanied by important systemic reactions, necessitating treatment with systemic corticosteroids besides joint lavage.

Keywords: knee; hyaluronic acid; severe acute inflammatory reactions; ultrasound; CEUS

Introduction

Intra-articular hyaluronic acid (HA) injections are used for over 20 years in the management of symptomatic knee osteoarthritis (OA). Despite ongoing debate regarding the efficacy of viscosupplementation, as can be seen from the currently published guidelines, HA injections remain a prevalent therapeutic option among clinicians. In 2021, a systematic review by Phillips et al identified 27 published guidelines on intra-articular therapies for knee OA, with only 20 guidelines providing strong or conditional recommendations in favour of intra-articular HA utilization. Analysing the guidelines from six important professional societies for knee OA treatment, Overton et al [2] found weak recommendations for its use, or conditional recommendation against the use of HA. Despite limited high-quality meta-analysis data supporting its efficacy, HA is widely utilized by clinicians in knee OA [3]. Various HA products for intraarticular administration exist on the market, differing in molecular size, source, and structure [4]. Ferkel et al [4] showed in their review that high molecular weight (HMW) HA products have higher efficacity compared to low molecular weight (LMW) ones, and avian-derived and cross-linked HA products are more likely to induce inflammatory events compared to non-avian-derived, non-cross-linked products.

The safety profile of intra-articular HA was well documented but, in a limited number of patients, adverse effects were described [1,3-6].

We present the case of a woman in who a severe acute adverse effect appeared immediately (within minutes) after intraarticular HA administration attributed to HA precipitation.

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Corresponding author: Maria Bădărînză, MD, PhD
2nd Internal Medicine Department,
"Iuliu Hatieganu" University of
Medicine and Pharmacy
2-4 Clinicilor street,
400006 Cluj Napoca, Romania
E-mail: deac_maria7@yahoo.com

Case report

A 71-year-old woman patient had a 5-year history of bilateral knee OA and had been receiving annual HMW HA injection in the left knee for the past 4 years, besides the other pharmacological and non-pharmacological treatment modalities [2]. She presented to rheumatologist with painful and swollen left knee. At presentation the laboratory data were normal (no biologic inflammatory syndrome) and radiographs indicated grade 3 Kellgren and Lawrence OA, with slight progression compared to prior radiograph. Ultrasound (US) revealed a large joint effusion and a medium-sized Baker's cyst. The rheumatologist aspirated 100 ml of clear, yellow synovial fluid from the joint and 40 ml from the Baker's cyst, followed by intraarticular administration of a mixture of 3.5 mg betamethasone and HMW HA (unexpired and sealed, the same product used in the previous 4 administrations). A few minutes postprocedure, the patient experienced pain in the knee and popliteal fossa, initially attributed to the procedure (paracetamol was prescribed). However, the pain intensified (8-9 on the visual analogue scale) within an hour, and the knee and popliteal fossa became swollen. By evening, she exhibited chills and fever (38.3°C). The rheumatologist interpreted the symptomatology to be acute pseudoseptic arthritis related to HA administration and prescribed non-steroidal anti-inflammatory drugs (NSAIDs), but no improvement was observed over the following weeks. The patient experienced a 4 kg weight loss and became asthenic. She was referred to our department for a second opinion 3 weeks later.

Upon presentation, the patient was afebrile, with a swollen, painful left knee. In the popliteal fossa a palpable and painful Baker's cyst was found. Laboratory data showed high degree of inflammation (erythrocytes sedimentation rate 100 mm/h, C-reactive protein 9.2 mg/dl, fibrinogen 785 mg%), but no leucocytosis or neutrophilia and a normal level of procalcitonin.

US examination (LOGIQ™ E10 Ultrasound/GE Healthcare, United States, 6-15 linear transducer) found moderate joint effusion and proliferated synovia (fig 1a). The popliteal cyst, apart from the large effusion, contained a huge mass with an inhomogeneous appearance (moderate echoic with linear hyperechoic spots producing reverberation artifacts) and septa (fig 1b, video 1, on the journal site). No vascularization was detected during power Doppler examination. Contrast-enhanced US demonstrated no enhancement in the mass, but hyperenhancement in the periphery and septa was observed (video 2, on the journal site), confirming the inflammatory status of the joint pathology.

The fluid aspirated from joint and Baker cyst (40 ml and 150 ml, respectively) had intense turbid orange aspect, with many floaters (fig 1c). Cytologic examination found moderate number of neutrophils and lymphocytes, rare foamy cells and synovial cells. No crystals were identified in polarized light microscopy. Cultures were sterile (including for bacillus Koch).

Despite clinical, biological, and US evidence of inflammation superposed on OA, the cause of this intense, persistent reaction at distance from HA administration was unclear. For this reason, we requested electron microscopy analysis of the floaters. The samples were prepared by dropping a few µL of diluted ethanol suspension of the sample on the copper grid and examined by Scanning Transmission Electron Microscopy (STEM) at 200 kV and 10 µA. Energy dispersive X-ray spectra were obtained using Oxford Instrument windowless detector and AZtec Software and concluded that the composition of the samples is similar to HA (fig 2).

Given the lack of response to NSAIDs and the severity of the inflammatory process (including systemic reaction), we administrated 125 mg methylprednisolone i.v. followed by oral Prednisone 30 mg/day (in tapering doses) combined with articular lavage. The local and biological evolution was rapidly favourable. The patient

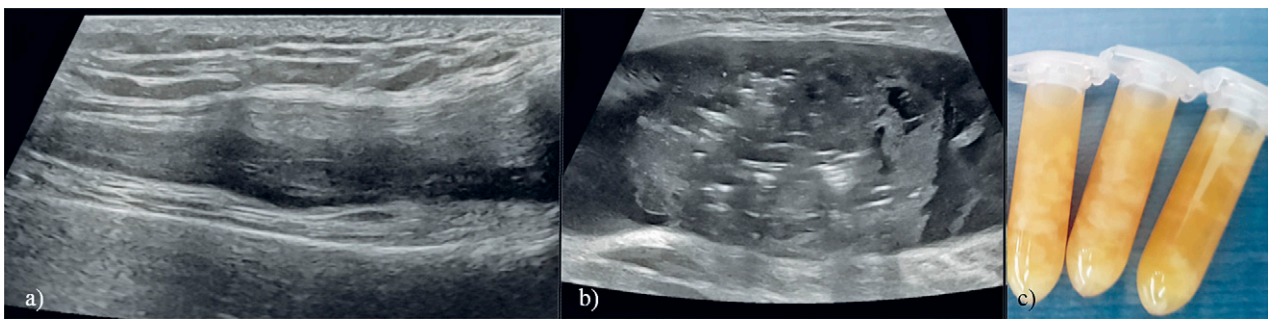

Fig 1. a) Longitudinal suprapatellar scan of the left knee. The joint has moderate proliferate synovia and fluid; b) transversal scan of the Bake's cyst – large effusion and a huge echoic mass with linear hyperechoic spots producing reverberation artifacts; c) the macroscopic aspect of the aspirated effusion (intensely turbid, orange, with many floaters).

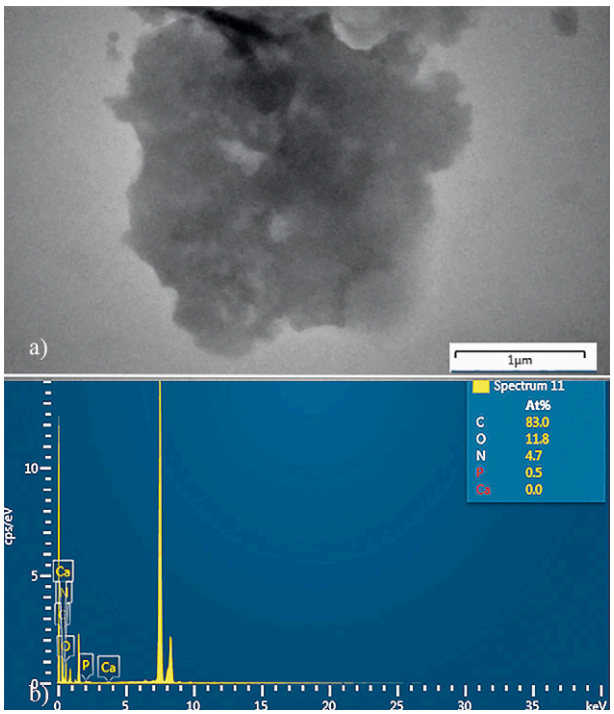

Fig 2. Transmission electron microscopy: a) the observed particles have various shapes and sizes; b) Energy dispersive X-ray spectra confirm the presence of carbon, oxygen, sodium chloride.

was discharged with recommendation for knee replacement.

Discussion

The most frequently reported adverse effects of intra-articular HA are local inflammatory reactions or "flare" – especially injection site pain or reaction, but also arthralgia, joint swelling, joint effusion, and stiffness (which are usually mild and resolve spontaneously or with local therapy). Pseudosepsis or severe acute inflammatory reactions are less frequent [1,3-8]. Goldberg et al [7] defined pseudosepsis as being a "*severe inflammation of the joint often with significant cellular effusion and significant pain, normally occurring within 24 and 72 hours after intraarticular injection*" after exclusion of sepsis and pseudogout. This condition is not self-limited and often requires clinical intervention (NSAIDs, arthrocentesis, intraarticular corticosteroids injections).

Our case does not fit any of the previously mentioned scenarios: the adverse reaction occurred immediately post-injection, general symptoms were present (fever, weight loss, asthenia), biologic inflammatory test were consistently increased and no response to NSAIDs was obtained. Moreover, the addition of the glucocorticoid in the initial intraarticular administration did not protect the joint from inflammatory reaction. The US aspect of a non-vascularized mass with hyperechoic spots and the macroscopic fluid appearance are the ones that caught our attention and suggested the possibility of HA precipitation/aggregation/coagulation in the joint. Although we cannot confirm the correctness of this interpretation, electron microscopy proved the presence of HA in the floaters. We cannot attribute this reaction to a specific type of HA product, as the product was previously injected 4 times without issues, was within the warranty period, and properly sealed. No similar published case reports were found. The main pathological findings in our case were found in the Baker's cyst - probably a large communication between the joint and cyst existed, allowing HA migration there.

The adverse reaction observed in this case, characterized by immediate severe local and systemic symptoms, expands the spectrum of potential complications associated with intraarticular HA injections. The patient's rapid clinical deterioration and the unusual findings on US and electron microscopy suggest a complex interplay between the HA product and the host's immune system. Future studies should explore the mechanisms underlying such severe reactions.

In **conclusion**, we reported a new severe adverse effect of intra-articular HA injection, characterized by very early local manifestations accompanied by significant systemic reactions.

References

1. Phillips M, Bhandari M, Grant J, et al. A systematic review of current clinical practice guidelines on intra-articular hyaluronic acid corticosteroid and platelet-rich plasma injection for knee osteoarthritis. An international perspective. Orthop J Sports Med 2021;9:23259671211030270.
2. Overton C, Nelson AE, Neogi T. Osteoarthritis Treatment Guidelines from Six Professional Societies: Similarities and Differences. Rheum Dis Clin North Am 2022;48:637-657.
3. Bowden DJ, Eustace SJ, Kavanagh EC. The value of injectable viscoelastic supplements for joints. Skeletal Radiol 2023;52:933-940.
4. Ferkel E, Manjoo A, Martins D, Bhandari M, Sethi P, Nicholls M. Cartilage. Intra-articular Hyaluronic Acid Treatments for Knee Osteoarthritis: A Systematic Review of Product Properties 2023;14:424-432.
5. Kim JG, Kim KI, Park KB, et al. Safety and effectiveness of intra-articular injection of a highly cross-linked hyaluronic acid, LBSA0103 (Synovian): Results from a post-marketing surveillance study in South Korea. PLoS One 2023;18:e0287222.
6. Ong KL, Farr J, Gudeman AS, et al. Risk of Severe Acute Localized Reactions for Different Intraarticular Hyaluronic

Acid Knee Injections in a Real-World Setting. Cartilage 2021;13(1_suppl):376S-386S.
7. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. Clin Orthop Relat Res 2004;419:130-137.
8. Sedrak P, Hache P, Horner NS, Ayeni OR, Adili OA, Khan. Differential characteristics and management of pseudoseptic arthritis following hyaluronic acid injection is a rare complication: a systematic review. J ISAKOS 2021;6:94-101.

Video 1. Gray scale ultrasound of the Baker's cyst.
Video 2. Contrast-enhanced ultrasound of the Baker's cyst.