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Case Report

Attack of Gouty Arthritis After Intraarticular Injection of Naturally Derived Hyaluronic Acid

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Viscosupplementation by intraarticular administration of exogenous hyaluronic acid has been a favorable treatment option to alleviate the symptoms of knee osteoarthritis. The potential but uncommon adverse reactions associated with intraarticular hyaluronic acid injection are local pain, swelling, and allergic response. These reactions are typically mild, transient, and self-limiting. The focus of this report is an 80-year-old man who presented with acute painful swelling of his knee joint after an injection of naturally derived hyaluronic acid. Aspiration of knee joint effusion yielded 40 mL of turbid straw-colored fluid. Synovial fluid cell counts revealed numerous leukocytes with a marked predominance of neutrophils. Intraleukocytic needle-shaped crystals with intensely negative birefringence were identified with polarized light microscopy, indicating monosodium urate crystals that are typically seen in acute gouty arthritis. The synovial fluid was sterile in culture. His knee pain reduced significantly after arthrocentesis and non-steroidal anti-inflammatory drug treatment. To the best of our knowledge, this is the first description of an attack of acute gout following intraarticular injection of naturally derived hyaluronic acid. The possible mechanisms were discussed with a review of the relevant literature. (Tw J Phys Med Rehabil 2007; 35(2): 105 - 110)

Key words: hyaluronic acid, osteoarthritis, gout

INTRODUCTION

Hyaluronic acid (HA), synthesized and secreted mainly by the fibroblast-like synovial lining cells, is an essential component in human synovial fluid. Its unique viscoelastic property assists in the physiological protective functions of the synovial fluid.^[1] In patients with osteoarthritis (OA), these protective functions are reduced due

to both quantitative and qualitative changes in the HA and lead to joint stiffness and pain.^[1-2] Since the 1970s, intraarticular injections of exogenous HA have been used in the treatment of OA.^[3] Although some researchers doubted the effectiveness of intraarticular HA injection in the treatment of OA,^[4,5] its symptomatic benefit for knee OA has been proven in a significant number of studies.^[6-10]

There are three commercial HA preparations available for clinical use. Artz[®] (Seikagaku Corp., Japan) and

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Hyalgan® (Fidia Corp., Italy) are sodium hyaluronates naturally derived from rooster combs whereas Synvisc® (Hylan G-F 20, Genzyme Corp., USA) is a mixture of chemically cross-linked HA to increase its molecular weight. All these products have been shown to be well tolerated and considered safe under aseptic conditions. The most common adverse events are minor pain and swelling at the injection site which generally resolve spontaneously within days.^[10,11] Only one case report of gouty attack after injection of Synvisc® has been published in the literature.^[12] Herein we described a patient who developed acute gout following Artz® injection to a knee joint. This report presented the first description of acute gouty attack after intraarticular injection of a naturally derived HA and discussed the possible mechanisms that produced the attack.

CASE REPORT

The patient was an 80-year-old man who had been complaining of bilateral knee pain for years. He presented with a limping gait and difficulty in performing functional activities such as climbing stairs and squatting. Physical examination showed crepitation with minimal effusion, without warmth or redness, in both knees. Knee radiographs disclosed osteoarthritic changes with medial compartment narrowing (stage II in Ahlback staging),^[13] but no chondrocalcinosis. Although the serum uric acid level had been measured at 10.4 mg/dL, he denied any prior episode of gouty arthritis in his knees. The patient did not respond adequately to a variety of treatments, including analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy, exercise, and acupuncture. His age and co-morbidities with hypertension and diabetes made him unsuitable for knee surgery. He had been treated with intraarticular HA injections with Artz® three years earlier and obtained some benefits. After our thorough evaluation, further treatment course with five weekly injections of Artz® by an anterior approach was conducted again.

The injection procedure was performed under strict aseptic condition. With the exception of transient post-injection soreness, no major systemic or local adverse reaction was noted. However, after receiving the last dose of Artz® in his left knee, the patient began to feel

progressive knee pain at the injection site. The pain was initially considered to be a common post-injection reaction similar to that previously experienced, but it increased shortly afterwards and made the patient almost unable to walk in the following few days. Subsequent examination revealed marked swelling with local heat on his left knee. Bulge sign and Balloon sign were positive.^[14] He did not have a fever or chilliness. He denied any injury or performing strenuous activities after HA injection. Soft tissue echo further confirmed the presence of massive effusion within the joint (Figure 1). A total of 40 mL of turbid straw-colored synovial fluid was removed by arthrocentesis under sonography-guidance (Figure 2).

Synovial fluid analysis identified low viscosity with a negative string effect. A high white blood cell count with a predominance of neutrophils verified inflammatory joint disease (lymphocytes: neutrophils = 11:89). Moderate amounts of needle-shaped crystals were found in the synovial fluid, many of which were phagocytosed by neutrophils (Figure 3). These crystals displayed a strong negative birefringence under a polarized light microscope, which is the distinguishing characteristic of monosodium urate (MSU) crystals. These intracellular MSU crystals, detected in synovial fluid with a high leukocyte count, were diagnostic criteria of acute gouty arthritis.^[14] A synovial fluid culture for bacteria was negative. The patient was treated with oral NSAID under the diagnosis of acute gout attack. His knee pain diminished significantly after joint tapping and treatment with NSAID.



Figure 1. Soft tissue sonography revealed massive effusion within the patient's left knee

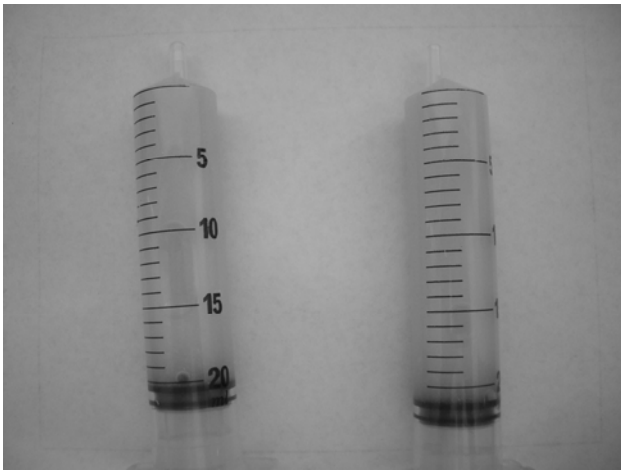


Figure 2. A total of 40 mL of turbid straw-colored synovial fluid was aspirated from the patient's left knee

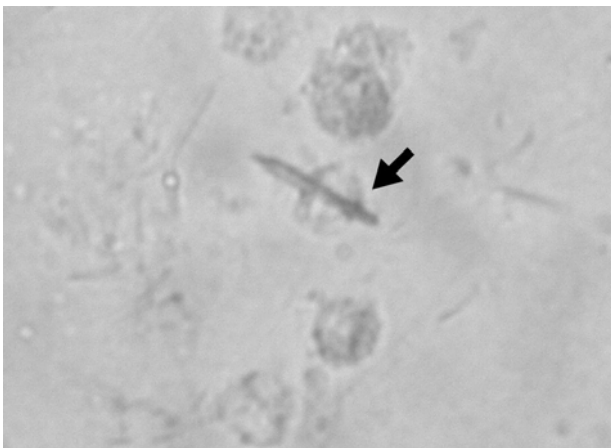


Figure 3. Intracellular monosodium urate crystal pierces the outer membrane of the inflammatory cell (arrow) in synovial fluid (polarized light, 400X)

DISCUSSION

Viscosupplementation preparations are viscous solutions containing a high molecular weight fraction of purified HA. These preparations are believed to decrease pain and stiffness in osteoarthritic knees by providing joint lubrication and shock absorption. Known hypersensitivities to HA or avian-based products are contraindicated for HA administration since the preparations are typically extracted from rooster combs. Another contraindication is infection or skin disease in the area of the

injection site. The intraarticular procedure should follow a strict sterile administration strategy to prevent complications from infection.

Intraarticular HA injection, an invasive procedure, may lead to adverse events despite its reported good patient tolerance. Most reported adverse events were minor pain or swelling localized in the injected joint.^[10,11] They usually resolved quickly without sequelae and did not require further treatment. Subsequent injections could often be administered, and generally these adverse reactions would no longer be observed. Indeed, the majority of patients experiencing localized reactions still benefit from subsequent injections.^[15] This scenario indicated that adverse reactions might be less likely immune-mediated. Conversely, localized adverse effects might happen unexpectedly after several successful injections without reactions. Thus, the occurrence of adverse events after intraarticular HA injection might be hard to be predicted.

The HA preparations used in clinical practice vary in molecular weight (from 500 kDa for Hyalgan[®] to 6,000 kDa for Synvisc[®]) and differ in adverse events frequency as well. Peyron estimated the mean incidence of adverse reactions following Artz[®] injections to be 1% (28 events for 2,769 injections), which was roughly equal to that of Hyalgan[®] (18 events in 1,642 injections).^[10] Synvisc[®] is a chemically cross-linked HA preparation with higher molecular weight. Its adverse event frequency was calculated at 2.7% per injection according to Lussier et al.^[13] In reality, even with identical HA preparations, local reaction rates in different reports vary significantly.^[10,16]

Puttick et al. retrospectively reviewed their knee OA patients treated with HA injections and found no crystals in the effusions of patients with acute synovitis after injections.^[11] Based on their finding, an acute local reaction was typically not related to crystal deposition. In practice, crystalline arthritis is an extremely rare complication following intraarticular HA injection. The first description of an acute attack of pseudogout following HA injection was presented by Luzar and Altawil in 1998.^[17] They suggested that the injection procedure effected a shedding of calcium pyrophosphate dehydrate crystals from the synovium or cartilage and, thereby, precipitated pseudogout attack. Though similar reports have been described subsequently, the exact mechanism

was not well understood.^[18-20]

To date, there has been only one case of gout following intraarticular HA injection reported in the literature. Yacyshyn and Matteson presented a patient who developed acute gout after intraarticular injection of Synvisc® in 1999.^[12] Synvisc® is produced by covalently cross-linking HA molecules using formaldehyde and vinylsulfone to increase its average molecular weight. The chemical modification used in the manufacture of Synvisc® has been shown to be responsible for the increased incidence of adverse reactions.^[21]

This report presented the first description of acute gouty attack after intraarticular injection of a naturally derived HA. Whether this adverse reaction was caused by the injection procedure or the HA preparation was uncertain. Lussier et al noted that the incidence of adverse reactions was higher for the medial injection technique applied to a partially bent knee as compared with the straight medial and straight lateral approaches, and no adverse event was reported for the anterior approach.^[13] They suggested that inaccurately placed injections of HA to the extraarticular locations contribute to local tissue reactions. In this case, the injection was applied with an anterior approach, a technique with the least incidence of adverse reactions based on findings by Lussier et al. Moreover, injection into the extraarticular soft tissue rather than the joint space may cause a periarticular localized response but should not produce intraarticular inflammatory effusion. It implied that the injection technique was not directly related to this patient's acute arthritis.

In a randomized double-blind placebo-controlled trial to assess the safety and efficacy of intraarticular HA injection for knee OA, Henderson et al. found that adverse effects occurred more than twice as often with HA than with placebo injections of saline. They claimed that HA, or at least one of its metabolites, was responsible for the reactions by acting as a primary irritant or as an inflammatory mediator.^[5] It is known that the interaction between HA and its receptor CD44, an adhesion molecule involved in leukocyte migration during inflammation, can augment interleukin-6 production in synovial cells.^[22] Increased production of these pro-inflammatory cytokines in the joint can subsequently trigger an acute inflammatory process such as that identified in this case. However,

further study is required to determine the pathogenesis of acute crystalline arthritis following HA injection.

CONCLUSION

Viscosupplementation through injection of HA into the joint has an acceptable safety profile in clinical applications. However, its relative safety does not preclude complications. Physicians should be aware of this possible occurrence despite its rarity. In cases with unusual pain and swelling after intraarticular HA injection, crystalline arthritis such as gout should be considered and, if identified, treated promptly.

REFERENCES

1. Balazs EA, Watson D, Duff IF, et al. Hyaluronic acid in synovial fluid. Molecular parameters of hyaluronic acid in normal and arthritic fluids. *Arthritis Rheum* 1967; 10:357-76.
2. Dahl LB, Dahl IM, Engstrom-Laurent A, et al. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann Rheum Dis* 1985;44:817-22.
3. Peyron JG, Balazs EA. Preliminary clinical assessment of sodium hyaluronate injection into human arthritic joints. *Pathol Biol* 1976;22:731-6.
4. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. *Arthritis Rheum* 1994;37:521-8.
5. Henderson EB, Smith EC, Pegley F, et al. Intraarticular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomized single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis* 1994;53:529-34.
6. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis Cartilage* 1993;1:233-41.
7. Goorman SD, Watanabe TK, Miller EH, et al. Functional outcome in knee osteoarthritis after treatment with hylan G-F 20: a prospective study. *Arch Phys Med Rehabil* 2000;81:479-83.

8. Tang SF, Chen CP, Chen MJ, et al. Changes in sagittal ground reaction forces after intra-articular hyaluronate injections for knee osteoarthritis. *Arch Phys Med Rehabil* 2004;85:951-5.
9. Tang SF, Chen CP, Chen MJ, et al. Improvement of muscle strength in osteoarthritic knee patients after intraarticular knee injection of hyaluronan. *Am J Phys Med Rehabil* 2005;84:274-7.
10. Peyron JG. Intraarticular hyaluronan injections in the treatment of osteoarthritis: state-of-the-art review. *J Rheumatol* 1993;20(suppl 39):S10-5.
11. Puttick MP, Wade JP, Chalmers A, et al. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. *J Rheumatol* 1995;22:1311-4.
12. Yacyshyn EA, Matteson EL. Gout after intraarticular injection of Hylan GF-20 (Synvisc). *J Rheumatol* 1999;26:2717.
13. Ahlback S. Osteoarthrosis of the knee: a radiographic investigation. *Acta Radiol* 1968;suppl 277:7-72.
14. Johnson MW. Acute knee effusions: a systematic approach to diagnosis. *Am Fam Physician* 2000;61:2391-400.
15. Lussier A, Cividino AA, McFarlane CA, et al. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol* 1996;23:1579-85.
16. Hamburger MI, Lakhanpal S, Mooar PA, et al. Intra-articular hyaluronans: a review of product-specific safety profiles. *Semin Arthritis Rheum* 2003;32:296-309.
17. Luzar MJ, Altawil B. Pseudogout following intraarticular injection of sodium hyaluronate. *Arthritis Rheum* 1998;41:939-40.
18. Ali Y, Weinstein M, Jokl P. Acute pseudogout following intra-articular injection of high molecular weight hyaluronic acid. *Am J Med* 1999;107:641-2.
19. Disla E, Infante R, Fahmy A, et al. Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection. *Arthritis Rheum* 1999;42:1302-3.
20. Kroesen S, Schmid W, Theiler R. Induction of an acute attack of calcium pyrophosphate dihydrate arthritis by intra-articular injection of hylan G-F 20 (Synvisc). *Clin Rheumatol* 2000;19:147-9.
21. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. *Clin Orthop* 2004;419:130-7.
22. Fujii K, Tanaka Y, Hubscher S, et al. Crosslinking of CD44 on rheumatoid synovial cells augment interleukin 6 production. *Lab Invest* 1999;79:1439-46.

關節內注射天然成份玻尿酸後之痛風發作

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關節內注射玻尿酸已被認為是膝退化性關節炎的有效治療方法之一。注射後可能發生的副作用，包括局部疼痛、腫脹、與過敏反應，但並不常見；即使發生這些副作用，症狀多半相當輕微、短暫，且為自限性。本病例報告為一 80 歲男性病患，因膝退化性關節炎接受關節內注射天然成份之玻尿酸製劑後，出現急性關節腫痛。膝關節經由穿刺，抽吸出 40 毫升混濁之關節液。關節液之細胞計數顯示有大量以嗜中性球為主之白血球，置於偏光顯微鏡下檢查可見呈陰性雙極偏光之針狀結晶被吞噬於白血球細胞內，此為急性痛風性關節炎發作所特有之單鈉尿酸鹽結晶。關節液之細菌培養則為陰性。病患在經由關節液抽吸與口服非類固醇類消炎止痛藥後，關節疼痛的症狀大幅緩解。回顧文獻，此病例應為注射天然成份玻尿酸後引發痛風發作之首例報告，本文也針對此副作用發生的可能機轉做詳盡的探討。（台灣復健醫誌 2007；35(2)：105 - 110）

關鍵詞：玻尿酸(hyaluronic acid)，退化性關節炎(osteoarthritis)，痛風(gout)