

CLINICAL VIGNETTE

A Case of Bilateral Pseudo-septic Knee Arthritis

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Case Summary

A 66-year-old female presented with bilateral knee pain, swelling, and warmth, one week after bilateral knee injections with hylan G-F 20 (Synvisc®). This was the first in a planned series of three bilateral knee injections for knee osteoarthritis. Symptoms began two to three days following injections. She has long-standing bilateral knee osteoarthritis, treated multiple times in the past with hyaluronic acid (HA) injections. She reported tolerating prior hylan injections and review of prior rheumatology notes indicated that she had received sodium hyaluronate (Euflexxa®) injections. In addition to these injections she also received hylan knee injections from an outside orthopedist, which she felt had helped the most.

Her past medical history included lupus, fibromyalgia, kidney stones, psoriasis, and psoriatic arthritis which was well controlled on chronic etanercept. She was not on current therapy for lupus, which had improved significantly after removal of breast implants. She had prior left knee arthroscopy. She reported allergy to an antibiotic, but could not remember which one and denied other medication allergies.

On exam she was in moderate discomfort. Her temperature was 97.5 F, had she had bilateral knee swelling, tenderness, and warmth. She was able to range her knees with moderate discomfort.

Due to concern for possible iatrogenic septic arthritis, both knees were aspirated with 30 mL of cloudy yellow fluid from the left knee, and 40 mL cloudy yellow fluid from the right knee. Gram stain was negative for both aspirates. Cell count for the left knee revealed 12,000 white blood cells (41% neutrophils, 26% lymphocytes, 32% monocytes, 1% eosinophils), and crystal analysis showed extracellular calcium pyrophosphate crystals. Cell count for the right knee revealed 9,000 white blood cells (36% neutrophils, 32% lymphocytes, 31% monocytes, 1% eosinophils). There were no crystals seen in the right knee aspirate. Synovial fluid culture was negative in both knee aspirates and she was felt to have bilateral pseudo-septic arthritis secondary to hylan injections.

Discussion

Approximately 14 million adults in the United States suffer from symptomatic knee osteoarthritis (OA).¹ Treatment options include physical therapy, nonsteroidal anti-inflammatories (NSAIDs), pain medications, intra-articular corticosteroid in-

jections, and surgery. There is also evidence to support the HA injections for symptomatic knee OA,² and this continues to be an effective treatment strategy for many patients.

HA is a naturally occurring glycosaminoglycan present throughout the body. It is intrinsic to the knee joint and is responsible for the viscoelastic properties of synovial fluid.³ As knee OA progresses, the average molecular weight (MW) of HA within the joint decreases, leading to decreased viscoelasticity of the synovial fluid and increased pain.⁴ Intra-articular HA injection aims to increase the average MW of HA within the arthritic joint.³ A systematic review of basic science literature identified several likely mechanisms of benefit of intra-articular HA injections. These include chondroprotective, mechanical, anti-inflammatory, and analgesic effects, in addition to increased synthesis of proteoglycans and glycosaminoglycans, and strengthening of subchondral bone.⁵

There is evidence suggesting high MW HA provides greater benefit in terms of viscoelastic, anti-inflammatory, and proteoglycan synthetic properties.^{3,6} The definition of high MW HA is not clearly defined in the literature; however, one study used a definition of $\geq 3,000$ kilodaltons (kDa). The same study defined low MW HA as $\leq 1,500$ kDa and sizes between 1,500 and 3,000 kDa were defined as moderate MW.⁷

Most formulations of HA are derived naturally using molecular sieving techniques (non-cross-linked), however hylan is chemically modified through covalent cross-linking of hyaluronan molecules to form larger polymers of increased MW (~6,000 kDa). It is felt that these larger polymers have a greater number of potential antigenic sites, and therefore increased immunogenic potential and risk of inflammatory or pseudo-septic reaction.⁸

Also, avian derived products such as hylan, which is manufactured from rooster combs are felt to have a higher risk of pseudo-septic reactions. There is an immunologic basis for this, as one study showed antibodies to chicken protein in a patient who had an acute local reaction to intra-articular hylan injection.⁹ There is also relatively strong evidence that high MW HA such as sodium hyaluronate, Euflexxa® made from biological bacterial fermentation has significantly lower incidence of pseudo-septic reaction than hylan with similar benefit for arthritic symptoms.¹⁰

Acute pseudoseptic reactions occur in up to 11% of knees injected with hylan.⁹ With rare exception they occur with follow-up injection, as opposed to first time injections. This implies that immune sensitization to hylan is a pre-requisite. Reactions typically occur within 48 hours of injection, and are associated with knee effusions between 30 and 70 mL in volume. Synovial fluid usually demonstrates 3,500 to 100,000 nucleated white blood cells, predominantly polymorphonuclear or mononuclear. Synovial fluid is culture negative.¹¹ Rarely, an acute pseudogout flare can be triggered by hylan injection, typically two to three days following injection.¹²

The most important aspect of addressing a pseudoseptic reaction is to first rule out a septic joint. This is achieved by aspirating the knee and sending synovial fluid for gram stain and culture analysis. Assuming no evidence of septic joint, treatment often involves icing, NSAIDs, and intra-articular steroid injection to arrest the inflammatory response. Interestingly, having a pseudoseptic reaction does not appear to affect the ultimate benefit patients can get from the HA injection.¹¹ There is some controversy regarding the safety of re-injecting patients with hylan if they have had a prior pseudoseptic reaction, however it is generally not recommended.^{8,11}

Our Patient

After her synovial fluid cultures returned negative, the patient returned for steroid injections to the bilateral knees. These helped significantly with her inflammatory symptoms. She then completed her injection series with sodium hyaluronate (Euflexxa®), which she tolerated well. Unfortunately, however, she only perceived modest benefit from the injection series.

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