CASE REPORT PEER REVIEWED | OPEN ACCESS

Inflammatory pseudoseptic reaction to Synvisc-One® injection requiring diagnostic arthroscopy

Richard Danilkowicz, Matthew Robinson, Matthew Steffes, Matthew Marcus

ABSTRACT

Introduction: Local and inflammatory reactions to hylan G-F 20 (Synvisc-One®) injections are a common occurrence generally controlled with non-steroidal anti-inflammatory medications and steroid injections. When reactions persist despite conservative measures, there is little literature on escalation of treatment. This case outlines the first instance of hylan G-F 20 induced pseudo-sepsis requiring diagnostic arthroscopy to our knowledge. Case Report: A 41-year-old female with a 10-year history of bilateral knee pain developed a unilateral local inflammatory reaction after receiving a second course of Synvisc-One® treatments. Arthrocentesis was performed twice after the reaction and was non-diagnostic each time. The patient continued to complain of pain after failing conservative therapy consisting of oral medications and physical therapy. A diagnostic arthroscopy was then performed that was significant for outerbridge grade 3 changes observed on the medial femoral condyle and lateral femoral condyle as well as fraying about the edges of the lateral meniscus with a small radial tear. The patient reported a subjective decrease in knee pain postoperatively, which returned shortly after. On four-month follow-up, the patient continued to experience pain despite negative physical exam findings and has been referred to a pain clinic for further treatment. Conclusion: This case outlines the first instance of hylan G-F 20 induced pseudo-sepsis requiring diagnostic arthroscopy to our knowledge. This instance highlights a unique treatment approach to a relatively common event in order to potentially guide treatment decisions in future cases.

Keywords: Arthroscopy, Inflammation, Pseudosepsis, Synvisc-One® injection

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INTRODUCTION

Hylan G-F 20 injections have been established as a safe and effective approach for the treatment of knee osteoarthritis (OA) [1–3]. Side effects of erythema, joint swelling, decreased range of motion, and pain at the site of injection are variable in incidence, with studies reporting between 1–21%, particularly in those receiving additional treatments [1, 3–10]. Although rare, more serious side effects have been documented and include severe acute inflammatory reaction (SAIR) also known as pseudo-sepsis, pseudo-gout, and injection induced calcium

pyrophosphate dihydrate arthritis [11–18]. Pseduo-sepsis is defined more specifically as an inflammatory reaction causing effusion in the knee that's not attributable to sepsis, gout/pseudo-gout or a traumatic event. Treatment for the side effects has typically involved non-steroidal anti-inflammatory medications and intra-articular corticosteroid injections, with patients experiencing complete or near complete symptomatic recovery [1, 11, 18]. It is unclear why some patients remain symptom free after hylan G-F 20 injections while others respond poorly, but it is important to identify the ideal treatment modality to counter these side effects when an adverse event occurs.

CASE REPORT

The patient is a 41-year-old female with a 10-year history of bilateral knee pain previously treated with oral pain relievers including acetaminophen/hydrocodone, tramadol, gabapentin, and ibuprofen, physical therapy, and corticosteroid injections. Initial X-ray imaging of the knees revealed only bilateral mild narrowing of the medial weight bearing compartments. Magnetic resonance imaging scan revealed no ligamentous damage but some evidence of lateral patellar tracking disorder. The patient underwent a successful first round of Synvisc-One® injections to her bilateral knees with no adverse reactions and adequate pain relief. Approximately, three months after the injections the patient experienced a traumatic injury to the left knee with follow-up MRI scan showing mild chondromalacia of the patella, with intact menisci, cruciate, and collateral ligaments. There was no large cartilaginous defect, lesion, or wear. After discussing treatment options the patient elected for a second course of Synvisc-One® injections, which was administered bilaterally approximately five months after the initial Synvisc-One® treatment.

Presentation

Two days after the injection, the patient presented to the emergency department complaining of left knee swelling, erythema, warmth, and pain, with no right sided symptoms. The patient also reported subjective fevers and chills. Physical examination was positive for significant effusion, overlying erythema anteriorly, with intact muscle strength and sensation. The patient was unable to ambulate, with range of motion limited to 15–25 degrees due to pain. Supine X-rays showed a mild suprapatellar joint effusion and re-demonstrated mild medial joint space compartment narrowing, similar to the prior exam. The osseous structures were intact without fracture, dislocation, or bony erosions. A bedside arthrocentesis was performed in the emergency department and sent for fluid analysis with complete results listed in Table 1. Patient was observed in the emergency department overnight and subsequently discharged the following day.

On clinic follow-up five days later, the patient reported continued pain and decreased range of motion in the left knee, but had improvement in swelling. On physical exam, there was a moderate effusion with diffuse tenderness, primarily over the medial and lateral joint lines. There was painful range of motion of the knee with only 15-60 degrees of flexion. The knee was slightly warm, but not erythematous. A second arthrocentesis was performed with results listed in Table 1. The patient was to return within one week for re-evaluation.

The patient returned to clinic with unchanged left knee pain. Physical examination was positive for slight effusion, joint line tenderness medially and laterally, and pain with motion of her left knee. Exam was negative for significant instability to varus, valgus stress, or anterior, posterior testing. The patient was grossly neurovascularly intact. At this time, the treatment options were discussed including the possibility of a diagnostic arthroscopy. The patient opted to pursue surgery, as nonoperative treatment had been unsuccessful to that point. Surgery was scheduled for three weeks later.

Procedure

A left knee diagnostic arthroscopy was performed. Intra-operative findings included outerbridge grade 0 changes of the majority of the knee. There was a small area on the medial aspect of the medial femoral condyle with grade three changes to the cartilage measuring approximately a centimeter in diameter. The same was seen on the lateral femoral condyle. There was a small area of fraying on the trochlea as well in the mid-portion, but no loose fragment to debride. She had a hypertrophic fat pad. The anterior cruciate ligament (ACL) and

Table 1: Joint aspirate fluid characteristics

	ED Visit	Clinic Follow Up (5 days later)
Aspirate amount (ml)	55	25
Aspirate color	Orange	Bloody
Aspirate clarity	Turbid	Cloudy
Aspirate WBC/ul	20,804	800
Aspirate RBC/ul	18,150	195,000
Aspirate neutrophils (%)	89	52
Aspirate lymphocytes (%)	8	42
Aspirate eosinophils (%)	1	--
Aspirate mesothelial (%)	0	0
Aspirate macrophages (%)	2	6
Aspirate CPPD	Negative	Negative
Aspirate uric acid	Negative	Negative
Aspirate culture	Negative	Negative
Aspirate gram stain	Negative	Negative
CRP (mg/dl)	19.6	--
ESR (mm/hr)	31	--

posterior cruciate ligament (PCL) were intact as well as the ligamentum submucosa. The medial meniscus was intact. The lateral meniscus had some fraying about the edges with a small radial tear as well. The findings on the scope were consistent with normal degeneration for a 41-year-old female, nothing pathologic was observed within the knee that would cause this reaction. After the procedure the patient was made weight bearing as tolerated, given crutches for balance, and instructed to use a continuous passive motion (CPM) machine. Intra-operative photographs of the changes seen can be found in Figure 1.

Follow-Up

On follow-up one week postoperative, the patient reported improved subjective left knee symptoms with 45–50 degrees range of motion on the CPM. The patient also reported calf pain, but left lower extremity duplex scan ruled out DVT. Further treatment plans included physical therapy with scheduled follow-up in five weeks.

The patient returned to clinic as scheduled complaining that the original pain had returned to the pre-surgery level. She described the pain as 5/10, constant, located anteriorly, and aggravated by walking and stairs. She also complained of the occasional buckling sensation in the left knee. Only three physical therapy sessions had been completed due to scheduling issues. On exam, she had full range of motion of both knees from 0–120 degrees, with no clinical instability. No calf tenderness to palpation, no effusion, edema, erythema, or ecchymosis bilaterally. Portal sites were well healed. Our treatment plan involved increased physical therapy and pain control with over the counter medication. The patient was to continue to follow-up in our clinic for evaluation of pain, range of motion, and strength.

On four-month postoperative follow-up, the patient continued to experience knee pain despite a lack of further effusion or evidence of reaction. Physical examination revealed intact intra-articular structures with full active and passive range of motion and no point tenderness. Due to the unclear nature of the persistent pain, the patient has been referred to a pain clinic for further evaluation and treatment.

DISCUSSION

Pseudo-sepsis, also referred to as severe acute inflammatory reaction, is defined in literature as an instance of predominantly non-self-limiting severe inflammation causing pain within 72 hours, generally after a second exposure to an injection, with other causes such as sepsis, gout and pseudo-gout ruled out, and productive of a mononuclear rich effusion [15–17,19–21]. Studies have also suggested that the presence of macrophages in the aspirate fluid may be a sign of immunologic sensitization, as was seen in the subject of our report [18]. This case study presents another example of possible immune related reaction to hylan G-F 20 as it parallels outcomes observed in multiple case reports in patients receiving the same treatment, although the underlying cause remains unclear [16,17, 20].

Studies have suggested that injection technique may be to blame for a large number of the adverse reactions, up to 72%, but further data on the subject is limited and likely is not the cause of the more serious inflammatory effusions [19]. A second potential hypothesis involves a host-mediated response to foreign proteins. These antibodies would be targeted against the hyaluronan which is taken from chicken combs to produce the injection, or possibly the chemicals used to crosslink the hylan [8, 22–24]. Studies have shown increased titers in animals previously treated with Synvisc® suggesting that the involved cross-linked proteins may be antigenic if contaminated, however a small study with human subjects did not determine the reactions to be antibody mediated [25, 26]. In our case, the occurrence of a significant reaction in only one of the two injected joints is further evidence against a systemic cause. Without a clear cause, treatment for our patient required additional measures than traditionally used in the treatment of a pseudoseptic reaction.

Goldberg and Coutts outline the basic approach for pseudo-sepsis from hylan GF-20 injection, starting with rest and cold compress in addition to analgesics or NSAIDs as needed [15]. More aggressive treatment includes intra-articular steroids as well as arthrocentesis, performed to both diagnose and provide relief [19]. Unfortunately, treatment modalities are seemingly

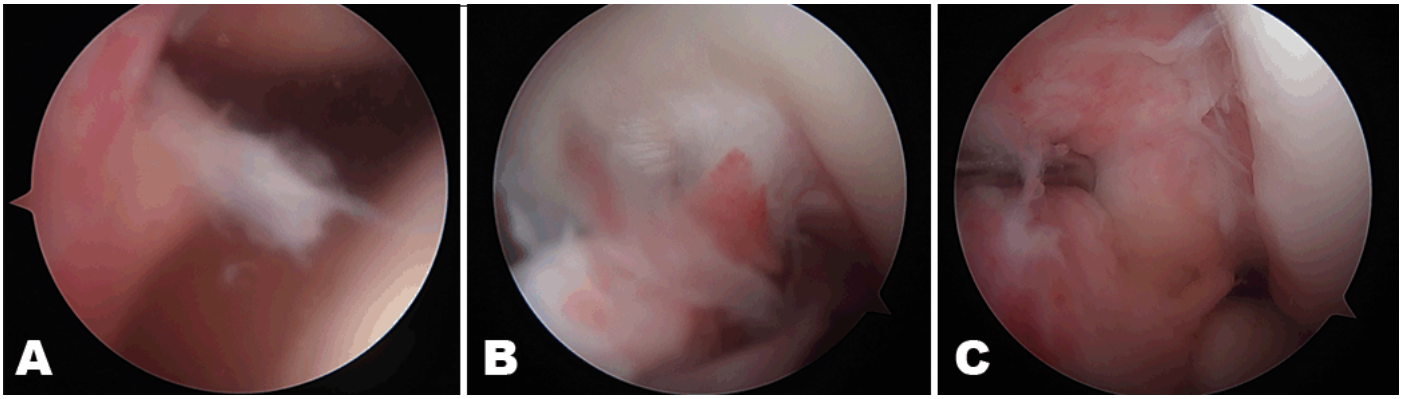

Figure 1: (A–C) Left knee intraoperative arthroscopic picture demonstrating joint synovitis and inflammation.

limited to these in literature. There was no evidence on how to proceed in cases that were not adequately resolved with the above mentioned interventions outside of surgical intervention to address a chronic granuloma, which did not apply in this specific case [15]. As the joint in our patient was determined to be non-septic there was no need to administer antibiotics. An intra-articular steroid injection was also deferred in this case based on shared decision making with the patient, who wished to proceed directly to surgical intervention at this point.

Diagnostic arthroscopy with before mentioned additional procedures appeared to resolve her pain and persistent effusion. The patient's physical examination at the end of six weeks improved overall, including a reduction in swelling and erythema with an associated increased range of motion, despite the continuation of pain symptoms. Based on these findings the surgical intervention to counteract the adverse reaction was justified on follow-up physical examination. Although the patient reports continued pain at a pre-surgery baseline the acute phase of the reaction appears to have passed and should allow for further physical therapy to improve strength and reduce pain.

Potential confounding aspects of this case to consider are the subjective nature of knee pain and the adherence to treatment. As the patient improved clinically on exam, one could argue that the interventions were successful despite the continuation of knee pain. One other intervention that could have been considered is an intra-articular corticosteroid injection postoperatively, which could have provided pain relief. The joint in question was no longer erythematous, swollen, or with decreased ROM and strength on testing although a limp and reported lack of functional capacity remained. The lack of adherence to a prescribed physical therapy regimen since the onset of the adverse reaction may also have contributed to the need for surgical intervention. Despite these drawbacks, this case still serves as an informative example of a treatment progression when dealing with a seemingly treatment refractory hylan GF-20 induced case of pseudo-sepsis.

CONCLUSION

Pseudoseptic reactions to hylan G-F 20 (Synvisc-One®) injections are a common occurrence, particularly after a second or third round of treatment. Although distressing to the patient, the reactions are predominately controlled with non-steroidal anti-inflammatory medications and steroid injections. When a reaction persists despite conservative treatments, it may be necessary to advance to diagnostic surgical intervention. This decision is one that must be made in direct collaboration with the patient based on treatment history and available options.

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Author Contributions

Richard Danilkowicz – Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Matthew Robinson – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Matthew Steffes – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Matthew Marcus – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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