

# Acute arthritis after intra-articular hyaluronate injection: onset of effusions without crystal

C Bernardeau, B Bucki, F Lioté

## Abstract

**Side effects of intra-articular hyaluronate injection include aseptic acute arthritis, which develops within hours after injection. Based on standard crystal analysis, calcium crystal shedding has been postulated to explain this complication. However, it is not known whether apatite crystals or low amounts of calcium pyrophosphate dihydrate (CPPD) crystals are also involved as to determine this requires a complete synovial fluid (SF) analysis. Two cases of such an acute arthritis are reported in patients after receiving a second Hylan GF-20 intra-articular injection. The SF did not contain CPPD, monosodium urate, or calcium apatite microcrystals as examined by microscopic analysis (using a compensated polarised light microscope) after alizarin red staining. Further studies are required to investigate possible direct proinflammatory effects of hyaluronic acid degradation products.**

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Hyaluronic acid (HA), which can act as a lubricant, has recently been used in symptomatic treatment for knee pain due to osteoarthritis.<sup>1</sup> It is marketed as Hylan GF-20 (Synvisc, Biomatrix Inc) and given as weekly intra-articular injections for three weeks. A few cases of arthritis after HA injection,<sup>2-5</sup> possibly related to crystal formation, have been reported. Furthermore, it has been postulated that HA injection might cause calcium pyrophosphate dihydrate (CPPD) crystals to shed from the synovium and the cartilage. However, in some cases, such crystals could not be detected under a conventional light microscope. As the mechanism of this arthritis has not been fully understood, a more thorough examination of the possible presence of crystals in the synovial fluid (SF) should be performed. Here we report two cases of acute arthritis after intra-articular HA injection with no detection of CPPD, monosodium urate, or calcium apatite crystals, and discuss their mechanism.

## Methods for SF analysis<sup>6</sup>

Joint fluid samples without anticoagulant were analysed within two hours after arthrocentesis.

Microscopic analysis was systematically performed with a compensated polarised light microscope (Olympus) under 10×, 40×, and 100× objectives, by a trained rheumatologist (BB). Alizarin red S staining for calcium microcrystals (2% aqueous solution) was performed, as described.<sup>6</sup>

## Case reports

### PATIENT 1

A 73 year old woman had a long history of left knee pain. She was previously treated with non-steroidal anti-inflammatory drugs (NSAIDs), steroid intra-articular injections, and physical therapy. Surgery of a right Baker's cyst was performed six years ago. Physical examination showed crepitus with reduced flexion in both knees, a left popliteal cyst, and a slight left knee effusion. Knee radiographs showed osteoarthritic changes (stage III of Kellgren-Lawrence staging), bilateral genu valgum, and medial meniscocalcinosis at the right knee.

She underwent intra-articular injection of Hylan GF-20 in the left knee, under aseptic conditions and at the lateral injection site. Before the first injection, the knee was aspirated, yielding 5 ml of clear SF. White and red blood cell counts were  $90 \times 10^6/l$  and  $50 \times 10^6/l$ , respectively. No crystal was identified and routine cultures were negative. One week later, at the second injection, the knee aspiration yielded 10 ml of SF, with a low white cell count (table 1), sterile, and again with no crystals. Four hours after the second injection, she developed a severe left knee pain with local inflammation signs and fever (38°C). The SF contained  $80\,000 \times 10^6/l$  white cells with 82% polymorphonuclear cells and remained sterile after five days of culture. No crystal was detected. Treatment with piroxicam, paracetamol, and an ice pack resulted in partial recovery within seven days. At the third injection, a small effusion persisted and 20 ml of fluid was drained again. The SF white cell count had reduced to  $15\,750 \times 10^6/l$  with 72% granulocytes, and remained sterile without detectable crystals. A complete recovery was achieved within two weeks. The left knee pain has remained improved for 12 months.

### PATIENT 2

A 59 year old woman had right knee osteoarthritis for seven years. Her right knee had no effusion and no erythema. Knee flexion was limited. Radiographs of the knees showed osteoarthritic changes (stage II) without meniscocalcinosis. The pain did not improve after NSAIDs and steroid intra-articular injection. Before the first Hylan GF-20 injection, less

Fédération de  
Rhumatologie, Centre  
Viggo Petersen,  
Hôpital Lariboisière  
(AP-HP), 2 rue A  
Paré, 75475 Paris  
Cedex 10, France  
C Bernardeau  
F Lioté

Laboratoire de  
Radiologie  
expérimentale et de  
Physiopathologie  
articulaire, Université  
Paris VII (JE 2149)  
C Bernardeau  
B Bucki  
F Lioté

Correspondence to:  
Professor Lioté  
frederic.liote@  
lrh.ap-hop-paris.fr

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Table 1 White cell count in synovial fluids ( $\times 10^6/l$ )

	Before injection 1	Before injection 2	After injection 2	Before injection 3
Patient 1	90	310	80 000	15 750
Patient 2	90	90	32 600	ND

ND = not done.

than 1 ml of SF was aspirated and examined (table 1). After the first injection, the knee had a small effusion and swelling within four days and improved spontaneously. At the second injection, a SF examination again yielded a low cell count (table 1), with sterile cultures, without crystals. Two hours after the second injection, she presented with severe knee pain, swelling, and effusion. Knee aspiration yielded 50 ml of inflammatory SF. The white cell count was  $32\,600 \times 10^6/l$  with 87% granulocytes, and the red cell count was  $2600 \times 10^6/l$ . The SF was sterile in culture and no crystals were found. The arthritis resolved within seven days after treatment with paracetamol alone. The patient declined a third Hylan injection. Nevertheless, her knee has been significantly improved for one year.

### Discussion

Local acute reactions after HA injection are not rare and represent up to 11% of injected knees as reported by Puttick *et al.*<sup>4</sup> Henderson *et al* reported that 47% of patients developed local adverse events and discontinued the treatment in 11% of cases.<sup>7</sup> However, the presence of microcrystals in the SF was not examined in these studies. Gout and pseudogout after HA injection have been reported in several case reports.<sup>2-5</sup>

Moreover, a report of arthritis without crystal detection after an HA injection has been recently published. Puttick *et al* reported six cases of acute synovitis in a total of 88 Hylan injections.<sup>4</sup> The SF was analysed in four of the six cases and light microscopic crystal analysis was negative in all. However, alizarin red staining was not performed in this study and thus, calcium apatite or a small amount of CPPD microcrystals might have been misdiagnosed. More recently, Schumacher *et al* reported 10 cases of acute arthritis after Hylan injections, without crystal deposition under complete SF examination.<sup>8</sup> Combined with our study, 12 cases of arthritis without crystal detection have been collected so far. Electron microscopy is the best method of finding microcrystals in the SF, and was not used in our study. Nevertheless, false negative results with the polarised microscope and alizarin red S staining are rare.<sup>9</sup>

The mechanism of acute arthritis after HA injection is not clearly understood. There are different HA preparations used in the treatment of osteoarthritis, depending on the molecular weight of the product (from 750 kDa for sodium hyaluronate (Hyalgan) to 6000 kDa for Synvisc). Another difference between Hyalgan and Synvisc is that an anti-inflammatory effect has only been described with the former.<sup>10</sup> Both low and high molecular weight HA produced the same local side effect. Pain and knee swelling was reported in 21/45 patients after Hyalgan in Henderson's study.<sup>7</sup> Puttick *et al* reported six local reactions in 22 patients injected with Synvisc.<sup>4</sup>

The relation between CPPD crystals in SF and arthritis after HA injection is not clear. Osteoarthritis and chondrocalcinosis are common in middle aged people and they coexist

frequently. Nevertheless, arthritis after HA injection is not as common as chondrocalcinosis. In a recent study Daumen-Legré *et al* injected with Hylan GF-20 the osteoarthritic knees of two groups of 30 patients. CPPD crystal deposition was detected in one group, as judged by the knee radiographs.<sup>11</sup> After the Hylan GF-20 injection, no adverse event was seen in either group. Therefore, the presence of CPPD crystals in arthritis after HA injection may be just a coincidence, or might have been shed from the cartilage or the synovial membrane.

Lussier *et al* noticed significantly more adverse events with the straight medial injection technique as compared with the straight lateral one.<sup>12</sup> Therefore, they suggested that extra-articular injection might contribute to the onset of local reaction. Technical conditions for injection have not been seen in any other studies. In our two cases, all injections were done into a straight knee by the lateral approach and SF was obtained in each case.


Finally, it is interesting to consider the mechanism by which HA interacts with its receptor CD44, an adhesion molecule involved in leucocyte migration during inflammation.<sup>13</sup> Degradation of HA may have a pathogenic role by producing proinflammatory agents.<sup>14</sup> Therefore, HA alone might also trigger such an acute inflammatory process.

In conclusion, patients who developed arthritis after HA injection should be fully evaluated, including an SF analysis, to rule out infection and crystal induced inflammation. Red polarised light microscopy and even alizarin red staining for crystal analysis should be performed in these cases. Patients should be warned of the occurrence of such an event. Overall, as seen in our cases, acute arthritis after HA injection does not seem to influence a patient's recovery.

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