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Case Report

A Case of Infectious Arthritis due to *Staphylococcus lugdunensis* in Seronegative Rheumatoid Arthritis, Diabetes Mellitus Patient, after Intraarticular Hyaluronic Acid Injection

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Intra-articular hyaluronic acid injections for symptomatic treatment of osteoarthritis are widely used but can result in complications, such as infectious arthritis. *Staphylococcus lugdunensis* is a common normal skin flora but can cause severe infectious disease, such as infective endocarditis. We present the first report of infectious arthritis caused by methicillin-sensitive *S. lugdunensis* after intra-articular hyaluronic acid injection in an immunocompromised patient in Korea. **(J Rheum Dis 2016;23:321-325)**

Key Words. Infectious arthritis, *Staphylococcus lugdunensis*

INTRODUCTION

Intra-articular hyaluronic acid injections are used for symptomatic relief and functional improvement in patients with osteoarthritis and can be more effective than systemic drug administration in elderly patients or in those with associated diseases. These injections are more advantageous than steroid injections in terms of duration of effectiveness and treating joint injuries. However, this type of injection can be accompanied by complications, such as severe acute reactions or infectious arthritis, and the main causative organism of a puncture-induced intra-articular infection is *Staphylococcus aureus*.

Likewise other coagulase-negative *Staphylococcus* (CoNS) strains, *Staphylococcus lugdunensis* is a CoNS as a skin normal flora and it may be the pathogen that causes a serious life-threatening infection such as infective endocarditis, showing the similarity to *S. aureus* in clinical features [1]. Infections caused by *S. lugdunensis* may be expressed in various forms, such as skin and soft tissue infections, infective endocarditis, sepsis, and artificial prosthesis-related infections. This species is sensitive to beta-lactam antibiotics but resistant strains have been reported.

Reports of domestic cases of infection by *S. lugdunensis* are relatively rare and, in particular, no domestic report of an intra-joint infection caused by *S. lugdunensis* is available. Here, we report our experience of an infectious arthritis case caused by *S. lugdunensis* after intra-articular injection therapy in an immunocompromised patient.

CASE REPORT

A 72-year-old man visited Anyang SAM Hospital with chief complaint of right knee pain.

Present illness

The patient had received three intra-articular hyaluronic acid (molecular weight, 3,000 kDa) injections to treat osteoarthritis symptoms 10 days before visiting the hospital due to discomfort and swelling in the right knee after a contusion 4 months previously. Severe pain developed in the right knee 4 days after the third injection, and the pa-

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tient visited the out-patient clinic.

Past medical history

The patient had been taking prednisolone and 100 mg hydroxychloroquine orally for 10 years due to seronegative rheumatoid arthritis, and was currently in remission while using 6 mg deflazacort for adrenal insufficiency. And he had been treated for atrial fibrillation, hypertension, diabetes mellitus and osteoporosis.

The family medical history and other specifics were unremarkable.

Social history

He did not smoke or drink alcohol.

Physical examination

At the time of Anyang SAM Hospital visit, showed blood pressure was 137/86 mmHg, pulse rate was 93 beats/min, respiratory rate was 20 times/min, and body temperature was 36.9°C. He had swelling of the right knee, but no redness, heat sensation, or tenderness accompanied the concerned joint. We aspirated a 70 mL of yellowish cloudy fluid from the right joint space.

Laboratory findings

A peripheral blood test showed hemoglobin 15.8 g/dL (normal, 12.4～16.9 g/dL); white blood cell (WBC) count, 13,450/mm^3 (normal, 3,700～10,600/mm^3); neutrophils, 86.3% (normal, 40%～75%); platelets, 274,000/mm^3 (normal, 139,000～406,000/mm^3); erythrocyte sedimentation rate (ESR), 33 mm/hr (normal, 0～12 mm/hr); and C-reactive protein (CRP), 151.0 mg/L (normal, 0～5.0 mg/L), which represented elevations in WBC, ESR, and CRP. A rheumatologist used a polarized light microscope on the joint fluid and found no monosodium urate crystals, but WBCs and neutrophils had increased to 10,880/mm^3 and 90% in the joint fluid, respectively (WBCs were 22.5/mm^3 in joint fluid from the right knee 2.5 months before symptomatic manifestation) (Figure 1).

Radiological findings

Marginal spurs and mild subchondral sclerosis were observed on the medial side of the right knee on bilateral X-rays, whereas marginal erosion and juxta-articular osteoporosis were observed on the lateral tibial plateau. In addition, a large amount of intra-articular effusion was observed with soft tissue swelling on the right side supra patella pouch from a lateral view (Figure 2).

Treatment and prognosis

Considering that the symptoms started on day 4 after the last intra-articular hyaluronic acid injection, we ruled

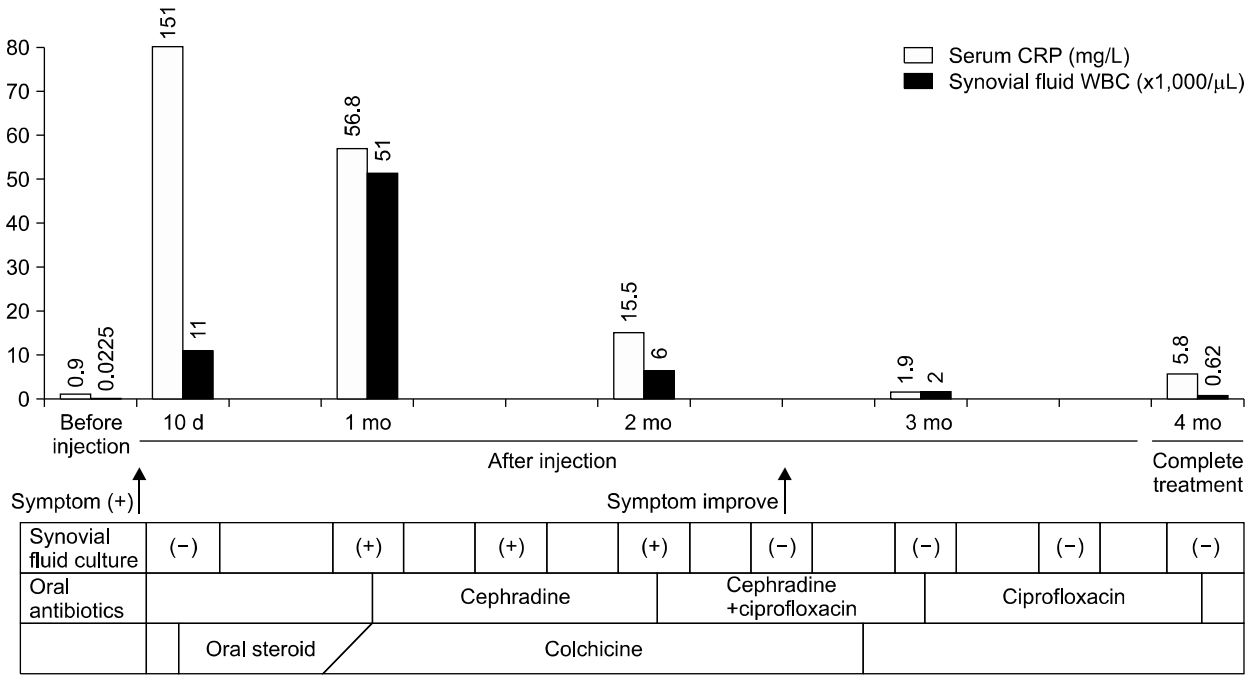

Figure 1. The patient's clinical course was improved after antibiotics treatment. WBC: white blood cell, CRP: C-reactive protein, d: day, mo: month.

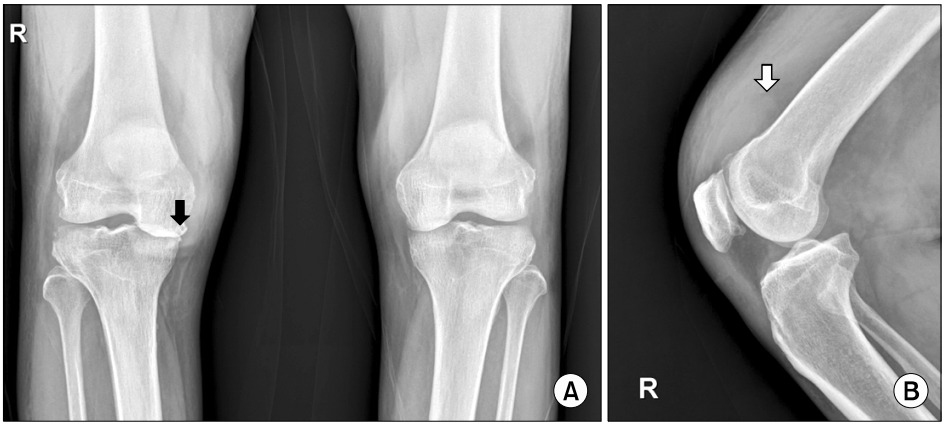

Figure 2. (A) The anteroposterior view of both knee. (B) The lateral view of right knee. Marginal spurs and mild subchondral sclerosis in medial femorotibial (black arrow) & patellofemoral compartments at right knee joint. Marginal erosion and juxtaarticular osteoporosis at lateral tibial plateau are noted in the right knee joint with large amount effusion (white arrow).

out a severe acute reaction from the injection. We considered a possible crystal-associated arthropathy rather than aggravation of osteoarthritis even though we found no monosodium urate crystals and rhomboid shape calcium pyrophosphate dehydrate in polarized light microscopy but the patient had abruptly aggravated swelling and pain in the joint and WBCs had increased in the joint fluid. Therefore, we performed a joint fluid culture and started oral administration of 10 mg prednisolone after the morning and evening meals. No further evaluation was made for personal reasons given by the patient, so the follow up was conducted on an out-patient basis.

The bacterium was not identified after the first joint fluid culture, the patient complained of discomforts after 2 weeks of oral prednisolone, so we performed a joint fluid culture and added 0.6 mg colchicine twice daily (total 8 weeks). The methicillin-sensitive *S. lugdunensis* was finally identified about 3.5 weeks after the last intra-articular hyaluronate injection.

The patient was started on 500 mg cephradine twice daily as an oral antibiotic agent, which was about 1 month after the last intra-articular hyaluronate injection, and as the same bacteria was detected with no change in antibiotics sensitivity repeatedly from the later joint fluid culture assay conducted over 2 times and as there was no notable improvement in the clinical profile, at week 3 of dosing cephradine (about 2 months after the last intra-articular hyaluronate injection), oral dose of ciprofloxacin 500 mg twice daily was added to the medication.

S. lugdunensis was absent from the joint fluid culture assay after 5 weeks of cephradine (with 2 weeks of ciprofloxacin) treatment (about 2.5 months after the last intra-articular hyaluronate injection). ESR had normalized (33 → 3 mm/hr), and serum CRP decreased. Therefore, the each oral antibiotic agents were terminated after 2 months administration (about 4 months after the last intra-articular hyaluronate injection). The patient is under observation at the outpatient clinic without any symptomatic aggravation for 8 months (Figure 1).

DISCUSSION

Intra-articular hyaluronic acid injections of the knee are widely used for symptomatic relief of osteoarthritis. However, complications, such as severe acute reactions with local pain and swelling, can occur mainly within 24 hours after the injection and can be accompanied by crystal-associated arthropathy or infectious arthritis. A local response occurs 47% of patients, and about 11% of these patient discontinue treatment due to such problems [2]. The mechanism of the severe acute reaction is not fully known, but it could be associated with a hypersensitivity reaction to the injection solvent or protein contained in the drug. In addition, adhesion molecules may be involved due to interactions between the CD44 receptor and hyaluronate and the likelihood of a pro-inflammatory agent generated as hyaluronate is degraded has been discussed [2].

Crystal-associated arthropathy that occurs after hyaluronic acid injection can appear by shedding of calcium pyrophosphate dehydrate (CPPD), monosodium urate, and calcium apatite crystals into the synovium and cartilage. The crystal can be observed in synovial fluid under a polarizing microscope or by alizarin red-S stain, but it is not always possible to identify the crystal [2]. Hyaluronic acid injections may affect intra-articular concentrations of calcium and magnesium, leading to crystal-associated arthropathy. However, more studies are needed on the pro-inflammatory effects of hyaluronic acid degradation products.

Although the frequency is rather rare, infectious arthritis is a complication that should not be overlooked because mortality ≥15% and joint impaired movement have been reported in ≥50% of survivors. This complication appears more frequent in patients >80 years, those with a history of diabetes mellitus or rheumatoid arthritis, patients with a recent artificial joint or joint surgery, a history of intra-articular steroid injection therapy, and in those taking immunosuppressive agents [3].

S. lugdunensis was reported for the first time by Freney et al. in 1988 [4]. It commonly exists as normal skin flora but can also act as a pathogen in soft tissue infections or infective endocarditis [4]. *S. lugdunensis*-induced infectious arthritis was reported by Maria et al. in 2009 [5], but no domestic case has been reported.

S. lugdunensis can be treated with antibiotics common used to treat *Staphylococcus* infections, such as cephalosporins, fluoroquinolones, glycopeptides, and aminoglycosides, but strains resistant to the beta-lactam series including penicillin and aminoglycosides have been reported [1]. In addition, 15% of *S. lugdunensis* culture-confirmed cases are considered contaminant flora or a colonized microbe so the probability of actual pathogenicity is high. In addition, careful treatment is required because many cases associated with severe infection have a clinical profile similar with that of *S. aureus* compared to other CoNS. One mortality case due to infective endocarditis caused by *S. lugdunensis* has been reported [6].

Intra-articular infections due to *S. lugdunensis* usually occur in immunocompromised patients (diabetes mellitus, rheumatoid arthritis, psoriatic arthritis, or psoriasis) in connection with treatments, such as arthrocentesis, intra-articular steroid injections, total knee arthroplasty, and bone-patellar-tendon-bone allograft achilles reconstruction. However, one case occurred in a native joint without a previous invasive procedure [7]. Biofilm formation plays an important role in *S. lugdunensis* infection and the presence/absence of a biofilm affects the antibiotic treatment outcome. Guidelines for these cases, such as duration of antibiotic treatment, have not been established due to the limited number of cases.

The present case was considered to have relatively higher probability of infectious arthritis because the pateint was older with a history of diabetes mellitus and was immunocompromised by taking deflazacort for adrenal insufficiency incurred as a complication of long-term steroid use due to rheumatoid arthritis, even though it is a rare scarce complication (0.002%~0.33%) after hyaluronic acid injections. In addition, a straight medial injection technique was used to puncture the knee joint in our case; some studies have described that this method (5.2%) results in a higher incidence of local adverts events compared to that of lateral injection (1.5%) [2].

We did not consider *S. lugdunensis* a contaminant bacterium when it was identified in the synovial fluid culture even though the patients had history of rheumatoid arthritis and trauma. And the negative results of the initial synovial fluid culture assay contributed to the confusion over the diagnosis of infectious arthritis [8].

The limitations of this case include that we did not detect on calcium apatite or CPPD crystals because alizarin red-S stain was not implemented in the initial diagnosis process and we failed to start empirical antibiotics at an earlier stage when WBC levels increased in the joint fluid while administrating the steroid and colchicine.

SUMMARY

Intra-articular hyaluronic acid injections are generally used to as treat knee joint osteoarthritis but they can be accompanied by complications, such as crystal-associated arthropathy and infectious arthritis, which are more common in immunocompromised or older patients.

S. lugdunensis is a CoNS strain that is normal resident on the skin but there are reports of its association with severe bacteremia and infective endocarditis. Therefore, *S. lugdunensis* may not be a contaminant if identified from a clinical test sample and could be pathogenic and should be treated with an appropriate antibiotic.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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