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Case Report

Surgically treated reactive arthritis of the ankle after COVID-19 infection: A case report



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ABSTRACT

A 37-year-old man developed right ankle pain and swelling six days after being diagnosed with coronavirus disease (COVID-19). Despite conservative treatment, his ankle symptoms persisted. Magnetic resonance imaging and computed tomography showed synovial hypertrophy and bone erosion in the ankle. Following arthroscopic synovectomy, performed 69 days after the COVID-19 diagnosis, the pain improved significantly. The clinical course was consistent with that of reactive arthritis following severe acute respiratory syndrome coronavirus 2 infection. The pathological findings resembled rheumatoid nodules. The bone erosion may have originated from the inflammatory pathway, which resembles the mechanism of rheumatoid arthritis.

1. Introduction

Coronavirus disease 2019 (COVID-19) infection has been reported to secondarily cause non-pulmonary manifestations and there are many reports about arthritis after COVID-19. Most cases presented with arthralgia which was relieved by non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections [1,2]. We report a case of ankle arthritis after COVID-19 infection that was resistant to conservative treatment but improved through surgery.

2. Case report

The patient was a 37-year-old man with a history of right ankle fracture and hyperuricemia. He had several right ankle gout attacks yearly. There was no history of overseas travel within the last year. Medical history or findings suggestive of infectious diseases, including sexually transmitted diseases, were not found. In February 2021, he had a fever of 38 °C; his nasopharyngeal swab test was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since his respiratory symptoms were mild, neither antibiotics nor steroid therapy were administered. The fever lasted for five days; however, he developed right ankle pain and swelling six days after his diagnosis of COVID-19. Despite taking NSAIDs, his ankle symptoms persisted, which

prompted a consultation 31 days after his diagnosis.

Blood tests revealed a marked inflammatory state characterized by a white blood cell (WBC) count of 9,500/μL, and a C-reactive protein level of 17 mg/L (Table 1). Joint aspiration revealed highly inflammatory synovial fluid (SF), with 96,000/μL WBCs, of which 85% were polymorphonucleates. No crystals were detected under polarized light microscopy (Table 2). Intra-articular injection of betamethasone sodium phosphate provided temporary relief. At 45 days post-diagnosis, the ankle pain recurred. Magnetic resonance imaging showed synovial hypertrophy in the medial tibiotalar joint (Fig. 1 a, b). There was no obvious articular cartilage wear. Computed tomography also detected bone erosion consistent with the synovial area of the lesion (Fig. 2). The investigations for systemic rheumatic disease markers were negative, including antinuclear antibodies, rheumatoid factor, anti-citrullinated protein antibody, and human leukocyte antigen-B27 typing. Arthroscopic synovectomy was performed 69 days after the COVID-19 diagnosis to address the persistent ankle pain. Preoperative evaluation through arthrocentesis revealed a clear, yellow SF with no inflammatory findings (WBCs 352/μL, 37% polymorphonucleates, Table 2). A quantitative antibody test for SARS-CoV-2 and a SF culture for bacterial agents were negative. Arthroscopy showed a bone defect in the posterior part of the medial malleolus that was filled with synovium (Fig. 3). The SARS-CoV-2 real-time polymerase chain reaction of the excised

; COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ReA, reactive arthritis.

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Table 1
Laboratory data at first visit of our outpatient.

WBCs(/ μ L)	9800
Neutrophils (/ μ L)	6390
Lymphocytes (/ μ L)	2479
Monocytes (/ μ L)	578
Eosinophils (/ μ L)	343
Basophils (/ μ L)	10
Hgb(g/dL)	14.6
PLTs ($\times 10^3$ / μ L)	259
ESR (mm/h)	14
CRP (mg/L)	17
D-dimer (μ g/L)	800
Fibrinogen (g/L)	4.2
Ferritin (μ g/L)	562
UA (mg/dL)	7.8

WBC: white blood cell, Hgb: hemoglobin, PLT: Platelet, CRP: C-reactive protein, UA: uric acid.

Table 2
Synovial fluid analysis during clinical course.

Aspect	at first visit to our outpatient (31 days after)	at surgery (69 days after)
	COVID-19 diagnosis)	COVID-19 diagnosis)
Cell count (/ μ L)	Bloody and cloudy 112164	Yellow and clear 951
polymorphonucleate (/ μ L)	95564	352
monocyte (/ μ L)	1570	345
Lymphocytes (/ μ L)	157	345
Macrophages (/ μ L)	1480	253
Polarized light microscopy	Negative	Negative
SARS-Cov2 RT-PCR	—————	Negative
Culture	—————	Negative

SARS-Cov2 RT-PCR : severe acute respiratory syndrome coronavirus 2 real-time polymerase chain reaction



Fig. 2. Computed tomography image showing the bone erosion area (red circle) consistent with right ankle synovitis.

3. Discussion

This case involved right ankle pain after COVID-19 infection with mild respiratory symptoms; furthermore, its progression was consistent with reactive arthritis (ReA) following COVID-19 infection. ReA characteristics that have been advocated include onset after pre-infection after a period of days to weeks, and asymmetric monoarthritis or oligoarthritis of the lower extremities [3]. ReA is also a diagnosis by exclusion [3].

Reports of post COVID-19 ReA have been gradually increasing during the COVID-19 pandemic. Recently, COVID-19 has been reported to affect angiotensin-converting enzyme 2 receptors in the gastrointestinal tract, which weakens the gut immune function [4]. ReA usually manifests as arthritis following genitourinary or gastrointestinal infections [5]. Therefore, this mechanism can link COVID-19 with ReA. In addition, a new review [6] showed that post-COVID-19 ReA tended to be seen in the 20, 30, and 50 year age groups. Men were affected more

synovium was negative. Pathological examination showed that the subintimal area was heavily infiltrated by inflammatory cells, including lymphocytes and plasma cells. Furthermore, epithelioid cells were arranged in a palisaded manner and surrounded by central necrosis (Fig. 4). Postoperatively, the pain improved significantly. To date, the patient has no signs of arthritis recurrence.

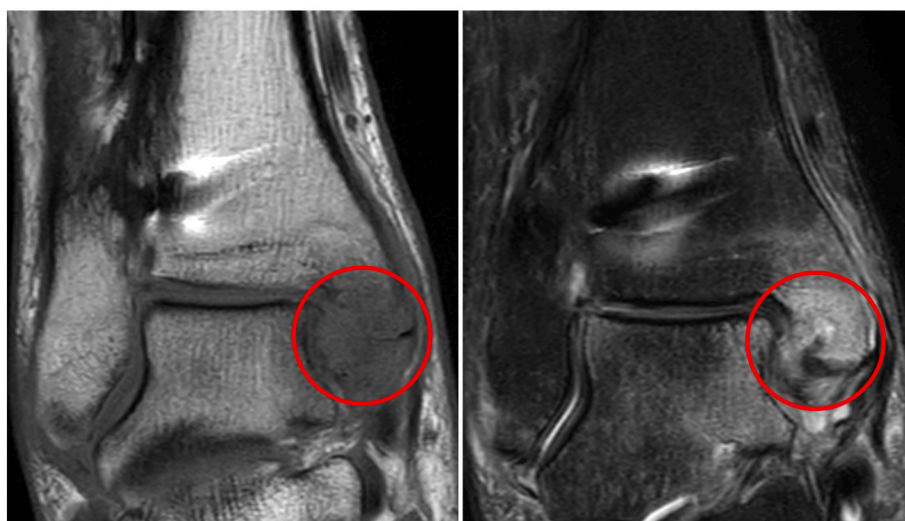


Fig. 1. (a and b): Magnetic resonance images (T1-weighted image (a) and short T1 inversion recovery sequence (b) are presented. Synovial hypertrophy observed in the medial tibiotalar joint (red circle).

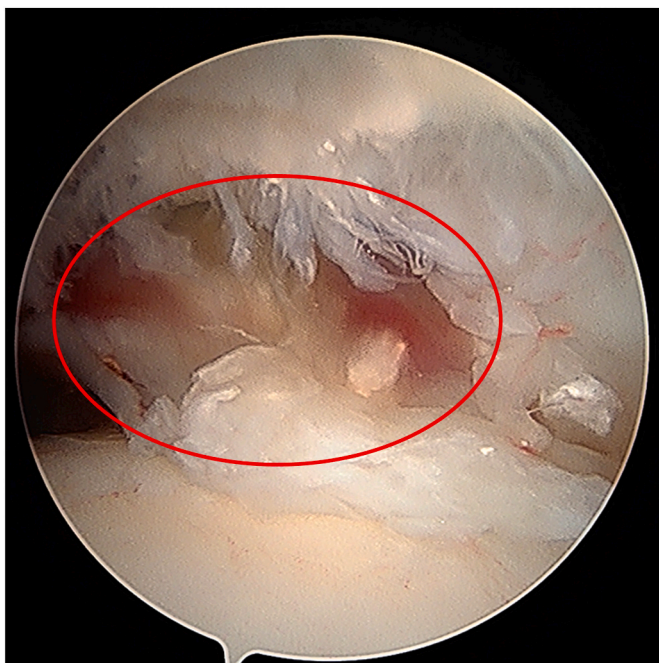


Fig. 3. The arthroscopic image of bone erosion (red circle) area at the posterior part of the medial malleolus.

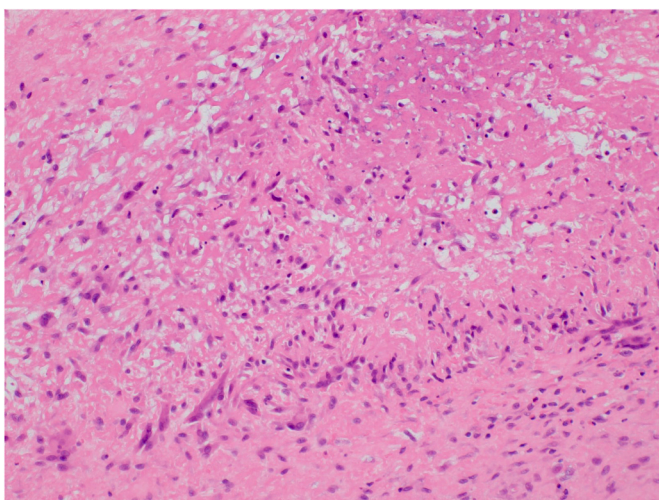


Fig. 4. Representative image of the synovial tissue (Hematoxylin & Eosin staining, $\times 200$). Epithelioid cells arranged in a palisade, with surrounding central necrosis.

frequently than women. Knee and ankle were the predominant joints. The characteristic features of this case were consistent with these reports.

In the present case, the WBC count in the SF at the first visit was much higher than that of the previous reports [2,4,6]. Few reports describing SF findings of post-COVID-19 arthritis showed WBC counts less than $20,000/\mu\text{L}$. In ReA, viral antigens might be transported from the primary site into the synovial membrane of the ankle joint, leading to the activation of T-lymphocytes and release of a large number of inflammatory cytokines [7]. Circulating serum concentrations of most pro-inflammatory effector cytokines including tumor necrosis factor (TNF), interleukin (IL)- 1β , IL-6, IL-8, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor are elevated in patients with COVID-19 [1]. Additionally, the level of IL-17, which is mainly produced by T helper 17 cells, is high in patients with

COVID-19 [8]. This cytokine induces the production of IL-1 and TNF which enhance osteoclastogenesis [9]. One case of chlamydia-induced ReA diagnosed during gout flares has been reported [10]. In the report, ReA was resistant to conventional synthetic disease-modifying anti-rheumatic drugs, and achieved remission with salazosulfapyridine and adalimumab. The author suggested that the cumulative effects of the pathologies of the two diseases may have contributed to exacerbation of the arthritis. Because gout and ReA share some pathological conditions, more inflammatory cytokines could have been released in this case. Consequently, NSAIDs and intraarticular corticosteroid injections could not control the intense inflammation, which might have progressed the bone erosion in a short period.

In this case, the pathological finding in synovium in the bone erosion area suggested rheumatoid nodules (RN). Central eosinophilic necrobiosis caused by fibrin deposition should prompt consideration of RN [11]. The formative mechanism of RN is not known; however, one hypothesis suggested that macrophage activation and IL-1 release might be involved. This inflammatory reaction then leads to fibrin deposition, subsequent necrosis due to slow cytolytic and enzymatic degradation, and finally containment by surrounding palisading macrophages. Pro-inflammatory effector cytokines in the alveolar membranes during severe COVID-19 are similar to those associated with rheumatoid arthritis (RA) [1]. Thus, ReA after COVID-19 was considered to have a high possibility of expressing RN. In contrast, the synovial pathology in this case was unlikely to be caused by gout because it lacked urate deposits and foreign body type giant cells [12].

In this case, surgical treatment was effective. It is widely known that synovectomy is useful for improving pain and preventing bone erosion in patients with RA [13]. Due to the hypertrophic synovium with infectious agents was removed, it is effective for ReA, as well [14]. Surgical treatment is a good option for ReA patients who are unresponsive to pharmacologic treatment.

This report has some limitations. Firstly, we could not be completely rule out other diseases, such as seronegative RA. Secondly, there was no data that showed a direct association with COVID-19.

This is the first report to present the pathological finding of bone erosion after COVID-19 by biopsy. Bone erosion could have originated through an inflammatory pathway that resembles RA. Arthroscopic synovectomy could be useful for arthritis after COVID-19 that is resistant to conservative treatment.

Authorship statement

All authors meet the ICMJE authorship criteria. KS drafted the manuscript. AT edited the manuscript. TY supervised and edited the report. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Declaration of competing interest

None.

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