

COVID-19 VACCINATION AND RHEUMATOLOGICAL MANIFESTATIONS: RS3PE SYNDROME?

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Abstract. *Rheumatological manifestations of SARS-CoV-2 infection and of COVID-19 vaccination have been increasingly reported for the past few years. Herein, we describe a case of a 75-year-old woman who presented with pitting edema of the hands and feet, as well as arthritis of small joints, following the administration of the first dose of the BNT162b2 (BioNTech-Pfizer) mRNA vaccine. We also discuss potential mechanisms that might explain the occurrence of RS3PE as a rheumatological manifestation of COVID-19 vaccination.*

Key words: arthritis, hand, joint disorders

INTRODUCTION

Recently, a flare of rheumatoid arthritis (RA) has been reported after the second dose of BNT162b2 (BioNTech-Pfizer) mRNA vaccine in a patient in clinical remission [1]. Previously, SARS-CoV-2 infection had been associated with the onset of anticyclic citrullinated peptide antibodies (ACPA)-positive RA [2, 3]. Arthralgia, arthritis, and dactylitis have also been reported after SARS-CoV-2 infection, and their prevalence may be underestimated when hydroxychloroquine and steroids are used [2, 4-6]. Several cases of reactive arthritis (ReA) have also been described, whereas viral-associated arthritis (VAA) appears to predominantly affect males and involve the lower limb joints in a mono- or oligoarticular pattern during the convalescent period [4-6]. Finally, a case of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome has been described following COVID-19 vaccination [7].

CASE PRESENTATION

On 6 April 2021, a 75-year-old woman received the first dose of the BNT162b2 vaccine. She had no previous rheumatological or cardiovascular disorders. On April 13, she presented to the emergency department complaining of arthralgia, stiffness, and swelling of the peripheral joints. These symptoms were mostly prominent in the distal and proximal interphalangeal and metacarpophalangeal joints, limiting hand function. However, pain and edema were also noted in the wrists, ankles, and metatarsophalangeal joints to a lesser extent, resulting in an antalgic gait. Pitting edema of the hands and feet was the most remarkable finding, according to the medical report. A routine blood test revealed only elevated

inflammatory markers (C-reactive protein, 1.97 mg/dL), while testing for D-dimers was negative. She was discharged from the hospital and treated with furosemide, flavonoids, and a nonsteroidal anti-inflammatory drug. She reported partial improvement of the edema but no improvement in joint symptoms and therefore attended our outpatient clinic on May 7, 2021. She also complained of malaise, fatigue, and insomnia, and the pitting edema of the hands and feet was less pronounced but still evident during physical examination (see Figure 1), along with arthritis of small and medium joints, as assessed by the squeeze test of the hands and feet. Inflammatory markers remained elevated (erythrocyte sedimentation rate 67 mm/hour and C-reactive protein 1.48 mg/dL). Antinuclear antibodies were positive (1:320, nuclear speckled and cytoplasmic granular pattern), but the patient was negative for anti-double-stranded DNA antibodies, RF, ACPA, and extractable nuclear antigen antibodies, while complement levels were normal.

After discontinuation of the abovementioned drugs, the patient was started on prednisolone at a dose of 20 mg/day, with a dramatic improvement observed within a few hours of glucocorticoid initiation. Radiographic erosions were excluded. Normalization of inflammatory markers was documented after one week of treatment, and prednisolone was rapidly tapered without clinical relapse. A probable diagnosis of RS3PE syndrome was established, and secondary causes were excluded. A full-body CT scan, as well as breast ultrasound and mammography, revealed no suspicious lesions.

RS3PE syndrome was initially thought to constitute a subset of RA, being typically characterized by symmetrical arthritis and pitting edema of hands and



Fig. 1. Small joint arthritis and residual pitting edema of hands after treatment with non-steroidal anti-inflammatory drugs and diuretics

feet, negative autoantibodies, absence of radiographic erosions and subcutaneous nodules, lack of association with HLA-DRB1 alleles, an excellent prognosis, and a dramatic response to medium-dose glucocorticoids [8]. Unilateral involvement and radiographic erosions occur in approximately 5% of cases, and the syndrome predominantly affects older individuals, particularly men [8]. In our patient, no clear causative factor for RS3PE syndrome was identified. However, it is possible that the temporal association with vaccination was coincidental. The diagnoses of VAA, ReA, and RS3PE syndrome are all under the method of exclusion and inclusion. If RS3PE syndrome is confirmed as a rheumatological manifestation of COVID-19 vaccination, a similar association may also be observed following SARS-CoV-2 infection. In both settings, RS3PE syndrome may be underrecognized, as it is less prevalent and less well-known than VAA, ReA, and RA, and, unlike the last disorder, it is not associated with specific autoantibodies. Moreover, RS3PE syndrome shows an excellent response to steroids, which are frequently used in the treatment of patients with SARS-CoV-2 infection.

Molecular mimicry between the viral spike peptides and host peptides, or a non-specific adjuvant effect, may underlie this rheumatological manifestation, as previously proposed for rheumatoid arthritis flares and VAA [1, 4]. Vascular endothelial growth factor (VEGF) is probably involved in the pathogenesis of RS3PE syndrome, as serum levels decrease after glucocorticoid treatment, while interleukin-6 and matrix metalloproteinase-3 levels may also be elevated [8]. VEGF promotes vascular permeability in SARS-CoV-2-infected lung tissues and contributes to inflam-

mation; accordingly, the anti-VEGF drug bevacizumab has shown efficacy in improving oxygenation in patients with severe COVID-19 [9]. Therefore, VEGF hyperproduction may represent a shared pathogenic mechanism linking RS3PE syndrome, SARS-CoV-2 infection, and COVID-19 vaccination.

To our knowledge, this is the first vaccine for which RS3PE syndrome has been reported as an adverse effect [7]. Nevertheless, the benefits of vaccination clearly outweigh the potential risk of triggering or exacerbating rheumatic disease, even though clinicians should always remain aware of possible adverse effects. Indeed, other rheumatological manifestations have been described, including cases of polyarthralgia and myalgia syndrome following ChAdOx1 nCoV-19 (AstraZeneca) [10].

Moreover, comorbidities in patients with rheumatic diseases should also be carefully addressed to prevent severe complications of COVID-19, including obesity, hypertension, diabetes, cardiovascular disease, chronic kidney disease, stroke, heart failure, and lung disorders [11].

Author Contributions

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