New-onset Seropositive Rheumatoid Arthritis Post-mRNA COVID-19 Vaccine: A Case Report

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ABSTRACT
Growing evidence in the medical literature has linked the COVID-19 vaccine as a potential trigger for the development or exacerbation of various autoimmune rheumatic diseases. To the best of our knowledge, we report one of the first cases of seropositive rheumatoid arthritis diagnosed after the messenger RNA COVID-19 vaccine.

Following the devastating global impact of the COVID-19 pandemic on healthcare services and economics, pharmaceutical companies have successfully developed a variety of effective COVID-19 vaccines to provide protection against severe disease and reduce its spread. Currently, there are several types of vaccines used in different parts of the world. These are classified according to different technological platforms including messenger (m) RNA, viral vector, inactivated whole virus, and other methods.[1]

The main mechanism of the mRNA vaccines is to express the spike glycoprotein to trigger immunogenicity. The Pfizer-BioNTech vaccine is an example of this.[2] Viral vector vaccines, including the Oxford-AstraZeneca vaccine, containing replication-deficient chimpanzee adenovirus and the SARS-CoV-2 spike protein gene.[3] Sputnik vaccine is based on a heterologous prime-boost scheme using different adenoviruses in each dose to reduce the likelihood of developing antibodies against the vector.[4] BBV152 Covaxin is an inactivated whole virion SARS-CoV-2 formulated with a toll-like receptor (TLR) 7/8 agonist molecule.[5]

There is emerging evidence to suggest vaccine-associated side effects including thrombosis and autoimmunity. Most of the published articles report autoimmune rheumatic disease flare-ups,[6–8] and less commonly new-onset rheumatic diseases (after viral vector or inactivated vaccine).[9,10] We report one of the first cases of seropositive rheumatoid arthritis (RA) diagnosed after administration of the second dose of mRNA COVID-19 vaccine and in the absence of other associated risk factors.

CASE REPORT

A 32-year-old woman presented two days after the second dose of the Pfizer-BioNTech vaccine with severe multiple joint pain and swelling, myalgia, and fatigue. She also had a fever lasting for one day without other symptoms to suggest an underlying infection. Her first dose of COVID-19 vaccine (Pfizer-BioNTech) was uneventful. One week after presentation, the rheumatology team evaluated her due to persistent joint symptoms. The affected joints included both the large and small joints peripherally and symmetrically. Her symptoms started in the hands and then spread to her shoulders, knees, ankles, and feet, with significant prolonged morning stiffness, swelling, and local warmth. There were no associated systemic symptoms or other features of connective tissue disease. Her medical history included autoimmune hypothyroidism, she was on adequate levothyroxine hormone replacement. She had no family history of autoimmune rheumatic diseases. Her obstetric history was uneventful. Clinical examination revealed synovitis of both the corresponding large and small joints without other

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Table 1: Blood analysis.

Test	Result	Reference
Anti-CCP	> 200	0–5 U/mL
Rheumatoid factor	72	0–10 IU/mL
Antinuclear antibodies	Positive > 640 (homogeneous)	
Extractable nuclear antibodies	Positive anti-RNP	
Anti-double-stranded-DNA antibodies	Negative	
CRP	15	0–5 mg/L
Hemoglobin	12.1	11–14 g/dL
Platelets	389	150–450 × 10^9/L
White cell counts	5.9	2.4–9.5 × 10^9/L
Neutrophils	3.3	1–4.8 × 10^9/L
Eosinophils	0	0.1–0.5 × 10^9/L
Biochemistry	Unremarkable	

CCP: cyclic citrullinated peptide; CRP: C-reactive protein; RNP: ribonucleoprotein.

clinical signs of connective tissue disorders. Table 1 summarizes the patient's investigations, which show mildly raised inflammatory markers with strongly positive RA autoantibodies. Initiated treatment targeted inflammatory polyarthritis, where she received intramuscular methylprednisolone injection and continued on hydroxychloroquine along with a tapered dose of prednisolone. Follow-up showed a remarkable resolution of her arthritis and normalization of her inflammatory markers.

DISCUSSION

The development and application of COVID-19 vaccines followed an unprecedented emergency fast track. With time, safety concerns will rise especially in certain small populations such as people with autoimmune rheumatic diseases or at risk of developing other autoimmune diseases. Safety in these populations is difficult to assess because the randomized controlled trials' endpoint designs highlight vaccines' efficacy and safety in the general population. Very few articles are published reporting new cases of RA after vaccination. There were only two reports of new-onset RA noticeably after different types of COVID-19 vaccines, the adenovirus vector vaccine and the inactivated vaccine.[9,10] On the other hand, in a case series of 27 subjects, there were only four cases of established RA flaring after the mRNA vaccine (Pfizer) with a range of two to four days either after the first or the second dose of the vaccine.[8] There were no new cases of RA reported in this series. Our case is unique in that it illustrates the temporal relationship between acute-onset RA and the specific mRNA type of COVID-19 vaccine. There were no previous records of symptoms or investigations to suggest that the patient had a subclinical inflammatory joint disease prior to vaccination, however, she is a person with another autoimmune phenomenon, which could increase her susceptibility to autoimmunity.[11]

TLRs activation might be considered a common feature between the COVID-19 mRNA vaccine mechanism and the pathogenesis of autoimmunity. COVID-19 is a novel single-stranded RNA betacoronavirus and spike protein in the primary target for neutralizing antibodies.[12,13] TLRs, present in various innate immune cells, are activated by pathogen-associated molecular patterns found on different pathogens such as viruses, leading to the production of inflammatory mediators essential for fighting infection.[14] Expression of TLR3, TLR7, TLR8, and TLR9 has shown to increase in COVID-19-infected subjects, and TLR4 in specific plays a role in disease severity.[15] Looking at the basics of synthesizing an effective vaccine, one should induce high titers of neutralizing antibodies with minimum antigen exposure accomplished through vaccine adjuvants.[13] Although Pfizer-BioNTech vaccine does not explicitly mention the use of an adjuvant, mRNA preparation itself has immunostimulatory properties through its capability of activating pathogen-associated molecular patterns.[16] Hence, mRNA vaccines possess self-adjuvantation by upregulating TLR-3, TLR-7, and TLR8 through immunostimulation.[17] Interestingly, since TLR signaling showed a critical link between the innate and adaptive immune systems, the malfunctioning of this pathway may be a culprit in the pathogenesis of autoimmunity. For example, self-nucleic acid components in systemic lupus erythematosus subjects can form immune complexes inducing TLRs 7, 8, and 9. On the other hand, RNA material found in the synovial fluid and the sera of RA subjects may activate TLR3 and TLR4. This data on TLRs' role in autoimmune rheumatic diseases suggests a possible additional signal in the aberrant adaptive immune cascade.[18]

CONCLUSION

There is established evidence that COVID-19 infection can trigger various rheumatic diseases. Vaccination data, on the other hand, remains scarce. This case may be considered as possible evidence of acute-onset RA induced by mRNA COVID-19 vaccination. Further studies are needed to delineate this proposed link and its mechanism.

Disclosure

The authors declared no conflicts of interest. Written consent was obtained from the patient.

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