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Abstract
Growing evidence in the medical literature has linked the coronavirus disease 2019 (COVID-19) vaccine as a potential trigger for development or exacerbation of various autoimmune rheumatic diseases. To the best of our knowledge, we report one of the first cases of Sero-positive Rheumatoid Arthritis (RA) diagnosed after mRNA COVID-19 vaccine.

Keywords: anti-CCP antibodies; case report; COVID-19; mRNA; rheumatoid arthritis; vaccine.

Introduction
Following the devastating global impact of COVID-19 pandemic on health care services and economics, the vaccine companies have successfully developed a variety of effective COVID-19 vaccines to provide protection from 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 mRNA, 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. Pfizer-BioNTech Vaccine is an example (2). Viral vector vaccines include Oxford-AstraZeneca containing replication-deficient chimpanzee adenovirus (ChAdOx1) and the SARS-CoV-2 spike protein gene (3). Sputnik vaccine is based on heterologous prime-booster 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 7/8 agonist molecule (5).
On the flip side, 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 (6,7,8), and less commonly new-onset rheumatic diseases (after viral vector or inactivated vaccine as per the reference (9) and (10) respectively). To the best of our knowledge, we report one of the first cases of Sero-positive 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 2-days after the second dose of COVID-19 Pfizer 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) was uneventful. After a week of her 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 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, which 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 clinical signs of connective tissue disorders. The table below summarizes her 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.

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

Discussion

The development and application of COVID-19 vaccines followed an unprecedented emergency fast track. With time, concerns about safety will rise especially in certain small populations such as people with autoimmune rheumatic diseases or possibly 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. Baimukhamedov et al. and Singh et al. (9,10) were the only two reports of new onset RA noticeably after different types of COVID-19 vaccines, which are the adenovirus vector vaccine and the inactivated vaccine respectively. Watad et al. (8) on the other hand, in the 27 subjects of his case series reported only 4 cases of established RA flaring after the mRNA vaccine (Pfizer) with a range of 2 to 4 days either after the first or the second dose of the vaccine. There were no new cases of RA reported in this series. Our case is unique in a way 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).

Toll-like receptors’ (TLRs) activation might be considered a common feature between the COVID-19 mRNA vaccine mechanism and the pathogenesis of autoimmunity. The COVID-19 virus is a novel single stranded RNA beta-coronavirus 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 (PAMPs) 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 titer of neutralizing antibodies with minimum antigen exposure accomplished through vaccine adjuvants (13). Although Pfizer/BioNTech does not explicitly mention the use of an adjuvant, mRNA preparation itself has immunostimulatory properties through its capability of activating PAMPs (16). Hence, mRNA vaccines possess self-adjuvantation by upregulating TLR-3, TLR-7 and TLR8 through immunostimulation (17). Interestingly, since TLRs 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.

**References**

1. COVID-19 vaccine tracker and landscape (who.int)


