A Case of Undifferentiated Connective Tissue Disease Triggered by the Coronavirus Disease Vaccine

Sir,

From its onset, the coronavirus disease (COVID-19) pandemic has proved to be a global health emergency, creating havoc in all spheres of human life. To prevent further propagation of the pandemic, safe and effective vaccines are the need of the hour. However, due to the expedited process of the development of COVID-19 vaccines and the rapid process of administration, sufficient data on adverse events after COVID-19 vaccination remains lacking. Among many vaccines for COVID-19, ChAdOx1 nCoV-19 Corona Virus Vaccine (COVISHIELD, Serum Institute of India) is one of the recombinant, replication-deficient chimpanzee adenovirus vector-based vaccines, which encodes the severe acute respiratory syndrome (SARS)-Coronavirus (CoV)-2 spike (S) glycoprotein. Following administration, the genetic material of a part of the coronavirus is expressed, which stimulates an immune response in the host.

Vaccines and viruses have long been associated with the activation of immune responses, sometimes culminating in autoimmune illnesses. A case of undifferentiated connective tissue disease (UCTD) has been discussed which was potentially triggered by the COVID-19 vaccine. Informed and written consent was obtained from the patient. UCTD is a clinical entity defined as serological and clinical manifestations of systemic autoimmune disease, not fulfilling any criteria of a definitive connective tissue disease (CTD) such as systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren’s syndrome, systemic sclerosis, polymyositis, dermatomyositis, or rheumatoid arthritis (RA). LeRoy et al. described UCTD as the early phase of major rheumatic disease in patients whose clinical features did not meet other classification criteria.[1] Studies suggest that up to 60% of UCTD cases remain undifferentiated and others progress to defined CTDs over time.

The patient, a 60-year-old Asian-Indian female, presented with fever of unknown origin and constitutional symptoms namely, fatigue, arthralgias, and myalgias for two months following the first dose of the COVID-19 vaccine, COVISHIELD. No signs and symptoms of specific organ involvement were reported. Past medical history was insignificant except for hypertension, and there was no history of similar complaints in the family. Over-the-counter medicines offered minimal relief. On receiving a short course of steroids in the outpatient setting, and broad-spectrum antibiotics and antipyretics in the inpatient setting, the patient reported only a temporary resolution of her symptoms. With time, the patient’s symptoms continued to worsen, affecting her activities of daily living.

Physical examination was within normal limits. Complete blood count was unremarkable apart from normocytic normochromic anemia and raised erythrocyte sedimentation rate. Inflammatory markers like c-reactive protein, lactate dehydrogenase, and ferritin were elevated. Kidney function and liver function tests were within normal limits apart from a raised level of globulin, a reversed albumin/globulin ratio, and borderline elevation of liver enzymes. Blood and urine cultures were negative. Serology for human immunodeficiency virus and hepatitis B/hepatitis C were negative. Tuberculin skin test was negative. Chest X-ray, high-resolution computed tomography (CT) scan of the chest, and contrast-enhanced CT scan of the abdomen revealed normal findings.

The diagnosis remained elusive despite extensive workup. With a high degree of suspicion, screening for autoimmune disease was performed which tested positive for anti-nuclear antibody (ANA). Further serological examination revealed anti-U1 RNP (ribonucleoprotein) and anti-Ro/SSA positivity while other antibodies, namely, rheumatoid factor (RF), anti-cyclic citrullinated peptide, anti-Smith (Sm), anti-dsDNA, anti-La/SSB, anti-Jo1, anti-Scl 70, and anti-centromere were negative. Creatine kinase and angiotensin-converting enzyme levels were unremarkable. Based on the clinical presentation and laboratory findings, a diagnosis of UCTD was made. The patient was started on hydroxychloroquine and prednisolone therapy for six months, and she reported marked improvement in her symptoms. Thereafter, the patient was continued on hydroxychloroquine monotherapy and was advised for regular follow-up visits. She refrained from receiving second dose of the COVISHIELD vaccine.

Due to wide range of variations in the inclusion criteria, up to 50% of patients diagnosed with a CTD may have underlying UCTD. Unlike other CTDs, there are no well-defined diagnostic criteria for UCTD. However, recently proposed a preliminary set of classification criteria which consists of the following features: (1) signs and symptoms suggestive of a CTD, but not fulfilling the criteria for any of the defined CTDs, for at least three years, and (2) presence of ANAs identified on two different occasions.[2] In the diagnostic criteria for UCTD, positive serological markers are considered essential and beneficial, especially anti-U1 RNP and anti-Ro/SSA. Like most CTDs, the etiology of UCTD is not well-understood. It is thought that some individuals have a genetic predisposition.
that is subsequently triggered by environmental factors such as infections, chemicals, and ultraviolet light.

There exists substantial evidence that infectious agents are involved in the induction of autoimmunity. For instance, the influenza virus was linked to multiple sclerosis, Campylobacter to Guillain-Barré syndrome, parvovirus B19 to RA, coxsackie virus to type 1 diabetes, etc. ANAs and autoimmune cell-mediated responses have been commonly observed during and after viral infections. Nevertheless, intractable infection-induced autoreactive mechanisms are capable of transforming into autoimmunity in genetically susceptible individuals. Several studies suggest that vaccine components such as inactive viral/bacterial agents, live-attenuated microorganisms, or wild superimposed infectious agents can induce autoimmune diseases in genetically predisposed individuals. For instance, the hepatitis B vaccine, tetanus vaccine, and diphtheria, pertussis, tetanus vaccine have been linked to autoimmune disorders like SLE, RA, polymyositis, etc. Guiserix et al.[3] identified the first case of SLE in a 26-year-old woman who presented with fever; cutaneous eruption of the face, arms, and legs; and chills after one week of the first dose of recombinant hepatitis B vaccine (GenHevac-B). The authors asserted that hepatitis B surface antigen protein could play a significant role in the pathogenesis and that the patient with SLE clinical picture should stop the immunization protocol and repeat the ANA test three months later.[4] Gatto and coworkers (2013) investigated cases of SLE in women following human papillomavirus (HPV) vaccination and found that the onset of SLE occurred during the later doses of HPV vaccination schedule and all the women had a family history of autoimmune diseases. The majority of patients who went into remission with immunosuppressive therapy had mild adverse reactions to the vaccine immediately following the first dose of HPV vaccine and later developed dramatic symptoms of SLE within two months after subsequent vaccine administration.[4]

Different immune mechanisms are involved in the pathogenesis of autoimmune diseases. Molecular mimicry is the main mechanism by which viruses or bacteria trigger immune responses against autoantigens. In a susceptible host, infectious agents carrying immunologically similar antigens to the host tissues trigger an unusual immune response when presented to T-cells. This leads to breakdown of self-tolerance to autoantigens and host tissue damage. In addition, microbes sequestered self-antigens from host tissues by the process of bystander activation. This activates antigen-presenting cells and dormant autoreactive T-helper cells and B-cells which, in turn, produce cytokines leading to the inflammatory response. [3] Similar mechanisms are involved in anti-infective immune responses. This explains why some individuals develop autoimmune disorders following vaccination although rarely. However, the timeline of these phenomena remains unclear.

Accordingly, antibodies against SARS-CoV-2 spike glycoproteins may potentially cross-react with structurally similar host protein amino acid sequences (host epitopes), playing an important role in the autoimmune response. Recent evidence indicates that COVID-19 vaccines may potentially be associated with adverse events like vaccine-induced thrombotic thrombocytopenia, immune thrombocytopenic purpura, IgA nephropathy, SLE, Graves’ disease, etc. Rocco et al. reported a case of autoimmune hepatitis in an 80-year-old woman presenting with jaundice, hyperchromic urine, elevated liver enzymes, and interface hepatitis one week after receiving BNT162b2 mRNA vaccination. Laboratory findings revealed ANA and total IgG positivity and the patient responded well to treatment with prednisone.[5] Another case of autoimmune hepatitis was reported by Clayton et al. in a 36-year-old male physician from Iraq, who had mild febrile reaction, markedly abnormal liver function tests and interfascial hepatitis 26 days after vaccination with ChAdOx1 nCoV-19.[4]

Nevertheless, a direct causal-effect relationship is difficult to establish between the COVID-19 vaccine and autoimmune disorders based on limited evidence. Regardless of these rare adverse events, the benefit of vaccination in controlling the spread of coronavirus cannot be undermined in these unprecedented times.

Moreover, whether the effectiveness of the COVID-19 vaccine will get accomplished or diminished in individuals who develop autoimmune responses is not well understood. Also, the administration of the second and the booster doses of COVID-19 vaccines in such individuals is debatable. Further research on immune mechanisms activated by the COVID vaccines will provide data to the policymakers to formulate the guidelines regarding COVID-19 vaccination for different subsets of the population. This case report adheres to the reporting guidelines (CARE).

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There are no conflicts of interest.

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