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CASE BASED REVIEW

New-onset systemic lupus erythematosus following BNT162b2 mRNA COVID-19 vaccine: a case series and literature review

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Abstract

Emerging data evaluated the possible link between the Coronavirus 19 (COVID-19) vaccine and acute flares of rheumatic autoimmune diseases. However, the association between the COVID-19 vaccine and the development of de-novo rheumatic autoimmune diseases remained unclear. We report the first case series of three male patients who developed new-onset systemic lupus erythematosus following receiving Pfizer BNT162b2 mRNA vaccination. The clinical characteristics share some similarities with drug-induced lupus. More patients with SLE following COVID-19 may be diagnosed in the future. Additional studies will provide more significant insights into the possible immunogenic influence of the COVID-19 vaccine.

Keywords Systemic lupus erythematosus · COVID-19 · Vaccine

Introduction

The Coronavirus 2019 (COVID-19) pandemic has substantial influence globally. COVID-19 vaccine is highly effective in preventing COVID-19 complications, including hospitalization and death [1]. However, patients with autoimmune rheumatic diseases (ARD), including systemic lupus erythematosus (SLE), are of great concern regarding COVID-19-related adverse effects. SLE patients have a higher risk of COVID-19-related complications, including mortality than age, sex-adjusted controls, and other ARD conditions [2, 3]. In addition, disease-modifying anti-rheumatic drugs (DMARDs) interfere with the immunogenicity of the COVID-19 vaccines, which subsequently impairs their effectiveness among ARD and SLE patients [4, 5].

The risk of ARD flares following the COVID-19 vaccines has raised some concerns. The COVID-19 vaccine is safe among SLE patients, with a low rate of severe adverse effects [6]. The VACOLUP study reported that a flare following COVID-19 vaccination occurred in only 3% of SLE patients [7]. However, in further research, up to a third of SLE patients were reported to flare after receiving the COVID-19 vaccine, mostly with mild symptoms not requiring hospitalizations [8].

New-onset SLE among previously healthy patients vaccinated against COVID-19 has recently emerged sporadically. We report the new onset of SLE following COVID-19 vaccination among three patients and a relevant literature review on the topic.

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Case series

The clinical, laboratory, and therapeutic characteristics of our patients are shown in Table 1. We obtained written informed consent from all patients before conducting this analysis. ANA test was conducted via indirect immunofluorescence (IIF) assays using human epithelial type 2 cells (HEp-2 cells). Our institute's laboratory cutoff for positive ANA is ≥ 1:160, corresponding to the 95th percentile of local age-matched and gender-matched healthy individuals. Additional extractable nuclear antigen antibodies (ENAS) were tested using a multiplex flow immune assay. This assay test for the significant ENAS of autoimmune disease. Only in the case of a positive anti-double-strand-DNA result, a confirmation test using indirect immunofluorescence Crithidia is performed. In the current manuscript, we reported only the positive results of the ENAS tests.

The first patient is a 24-year-old male with no pre-morbidities or family history of autoimmune conditions. A rash appeared on the head, neck, and arms 3 days after he was vaccinated. In addition, he also reported a morning's stiffness of an hour of both wrists. On examination, there were psoriasiform–papulosquamous plaques over the face, neck, and arms, non-scarring hair loss over the head, and stress pain at the wrists without effusion. Initial laboratory results displayed a normal range of complete blood count and blood chemistry panels, a positive antinuclear antibody (ANA) (1:160) with a speckled pattern, and positive anti chromatin (nucleosomal) and ribosome P antibodies (1.6 IU/mL, > 8.0 IU/mL, respectively). The C3 and C4 levels were 70 mg/dL (normal range 90–180 mg/dL) and 21 mg/dL (normal range 10–40 mg/dL), respectively. The patient started hydroxychloroquine 200 mg BID, mometasone furoate cream 0.1% QD, and etoricoxib 90 mg QD as needed. In addition, the patient was instructed to avoid direct exposure to the sun and to use broad-spectrum sunscreens. The rash and arthritis resolved during the following months, and the alopecia substantially improved.

The second patient is a 23-year-old male with no premorbidities or family history of autoimmune conditions. He was admitted to the hematology ward due to pancytopenia and fever, which started a month following the BNT162b2 mRNA COVID-19 vaccine administration. In addition, he reported a new non-resolving headache, oral ulcers, and malar rash over the face. The complete blood count at admission showed leukopenia 1800/μL (normal range 4800–10,000 μL), neutropenia 210 μL (normal range 1900–8000 μL), hemoglobin 9.1 g/dL (normal range 14.0–18.0 g/dL), and thrombocytopenia 12 μL (normal range 130–400 μL). The patient had positive ANA (1:160) with a fine-speckled pattern, positive anti-Ro/SSA (1.2 IU/

Table 1 Patient's clinical, immunological and therapeutic characteristics in the current series

Patient number	Age/sex	Time after COVID-19 vaccination	Type of vaccination	Clinical features	Immunological features	EULAR/ACR SLE classification criteria	Treatment	SLEDAI 2K (first visit)	SLEDAI 2K (last visit)
1	24/m	Seven days after the first dose	Pfizer BNT162b2 mRNA	Psoriasiform papulosquamous rash, a non-scarring alopecia, arthritis	Positive ANA 1/160, Ribosomal P, chromatin, and low C3	13	HCQ 200 mg BID, topical steroids, and etoricoxib	10	4
2	23/m	One month after the second dose	Pfizer BNT162b2 mRNA	Pancytopenia, fever, malar rash, oral ulcers, non-resolving headache, lymphadenopathy	Positive ANA 1/160, Ro/SSA, beta 2 glycoprotein IgG, direct Coombs	14	HCQ 200 mg BID, Prednisone 1 mg/kg, azathioprine 2 mg/kg, Granulocyte colony-stimulating factor and revolade	15	1
3	56/m	One month after second dose	Pfizer BNT162b2 mRNA	Arthritis, lymphadenopathy	Positive ANA 1/160, double-stranded DNA, smith, low c3	15	HCQ 200 mg BID and etoricoxib	8	4

COVID-19 coronavirus 19, *ANA* antinuclear antibodies, *EULAR/ACR* European League Against Rheumatism and the American College of Rheumatology, *BID* twice daily, *DNA* deoxyribonucleic acid, *mRNA* messenger ribonucleic acid, *SLEDA 2K* systemic lupus erythematosus disease activity index 2000, *HCQ* hydroxychloroquine

mL), and a positive anti-beta 2 glycoprotein IgG (18.7 U/mL). In addition, there were positive direct Coombs tests but normal levels of haptoglobin. Serological tests were negative for active Epstein–Barr virus, cytomegalovirus, Human immunodeficiency virus, Parvo-B19 virus, hepatitis B, and C. The patient underwent positron emission tomography–computed tomography (PET/CT) during hospitalization. The test showed an enlargement of right sub-clavicular and axillary lymph nodes at the same side the COVID-19 vaccine was administrated. Axillary lymph node biopsy revealed follicular hyperplasia without signs of malignancy, infection, or Kikuchi–Fujimoto disease. Bone marrow biopsy showed general hyperplasia without sign of malignancy or infection. The patient started 1 mg/kg prednisone, hydroxychloroquine 200 mg BID, Filgrastim [a granulocyte colony-stimulating factor (G-CSF)], and Eltrombopag 50 mg QD. In addition, we added azathioprine 2 mg/kg a month later, parallel to tapping the prednisone dosage to complete cessation in 6 months.

The third patient is a 56-year-old male without past medical conditions or a family history of ARD. He was admitted to the internal ward due to joint pain and swollen left axillary lymph nodes. The symptoms occurred a month following receiving the BNT162b2 mRNA COVID-19 vaccine on the left hand. On physical examination, there was bilateral knee and left wrist arthritis. In addition, there was a left-sided palpable, soft, and tender axillary lymph node. Complete blood count and chemistry were normal. The patient had positive ANA (1:160) with a homogenous pattern, maximal levels of anti-double-stranded DNA (> 200 IU/mL confirmed by Crithidia luciliae), and maximal levels of positive anti-smith > 8.0 IU/mL. C3 level was 65 mg/dL and C4 level was 11 mg/dL. Additional urinalysis and immunological tests were normal. A total body computed tomography showed enlargement of the left axillary lymph node. A biopsy of this region showed follicular hyperplasia without signs of malignancy, infection, or Kikuchi–Fujimoto disease. We started hydroxychloroquine 200 mg BID and etoricoxib 90 mg QD as needed. A resolution of arthritis was noted but not of axillary lymphadenopathy.

Literature review

We conducted a literature search in Pubmed/Medline, Google Scholar, and Cochrane databases of English peer-reviewed new cases of SLE following any COVID-19 vaccine. Our search included the keywords "systemic lupus erythematosus," "SLE" with "COVID-19 ", "vaccine," "vaccination," or "SARS CoV-2" between December 2020 and March 2022 (search strategy flowchart is presented in Supplementary Fig. 1). We expanded the search by reviewing the references for each case. We excluded cases of patients diagnosed with a highly suggestive background of SLE or antiphospholipid syndrome before receiving the COVID-19 vaccination or those who did not fulfill the 2019 EULAR/ACR SLE classification criteria [9]. We also excluded cases of subacute cutaneous lupus erythematosus without systemic manifestations. Although we did not limit the time between receiving a vaccination and the onset of symptoms, all cases occurred within a month following the COVID-19 vaccination. Our search identified six cases summarized in Table 2.

Discussion

We identified six case reports in the literature of new-onset SLE following the COVID-19 vaccine. Most cases of SLE were observed among women younger than 30 years (five out of six). The clinical picture described in these cases has shown considerable variation, and three reports described the presentation of lupus nephritis. Kim et al. described a 60-year-old female who developed class III lupus nephritis and pancytopenia (the exact time interval and vaccine type are not specified). The patients required treatment with high-dose glucocorticoids and intravenous cyclophosphamide [10]. Zavala-Miranda et al. described a 23-year-old female who developed class V lupus nephritis 2 weeks following the first dose of the Astra-Zeneca vaccine. The patient was treated with high-dose glucocorticoids and mycophenolate [11]. The third report by Baez-Negro'n et al. described a 27-year-old female who developed tiredness and symmetrical polyarthritis 2 weeks following the second dose of the Moderna mRNA-1273 vaccine [12]. Over several months she developed mild proteinuria (urine protein creatinine ratio 640 mg) and was treated with prednisone and mycophenolate. Although kidney biopsy was not performed, the patients had elevated anti-dsDNA antibodies, low C4 levels, and proteinuria, supporting the possible diagnosis of lupus nephritis in this case. A fourth patient was a 22-year-old female who presented 1 week following the Pfizer BNT162b2 mRNA vaccine. The patient had pancytopenia, cutaneous vasculitis, and pancreatitis [13]. She was treated with high-dose glucocorticoids, hydroxychloroquine, and azathioprine. The last two patients did not have significant organ involvement besides fever, arthritis, and cytopenias [14, 15].

The current research is the first reported case series of three patients who developed SLE following the COVID-19 vaccine. Although our series is composed of a relatively small number of patients, it has several advantages (Fig. 1). First, all patients in this series were evaluated in the same rheumatological clinic; they were diagnosed based on the EULAR/ACR SLE classification criteria and treated according to the 2019 EULAR recommendations for the management update of systemic lupus erythematosus [16, 17].

Table 2 Summary of previous case reports of new-onset of systemic lupus erythematosus following COVID-19 vaccine

References	Age/sex	Time after COVID-19 vaccination	Type of vaccination	Clinical features	Immunological features	EULAR/ACR SLE classification criteria	Treatment
Kim et al. [10]	60/f	Not specified	Not specified	Class III lupus nephritis, pancytopenia, fever, pneumonitis	Positive ANA 1/1280, double-stranded DNA, smith, low c3 and c4	20	Pulse methylprednisolone, I.V Cyclophosphamide, oral prednisolone (1 mg/kg) and hydroxychloroquine (100 mg BID)
Zavala-Miranda et al. [11]	23/f	Two weeks after the first dose	Astra-Zeneca (ChAdOx1-S)	Class V lupus nephritis, lymphopenia	Positive ANA 1/1280, double-stranded DNA, low c3 and c4	20	Mycophenolate mofetil, high-dose glucocorticoids, hydroxychloroquine, and diuretics (the exact dosages not specified)
Baez-Negron et al. [12]	27/f	Two weeks after the second dose	Moderna mRNA-1273	Tiredness, weight loss, arthritis, and later proteinuria	Positive ANA 1/160, Ro/SSA, La/SSB, double-stranded DNA, low C4	15	Hydroxychloroquine (300 mg Q.D.), prednisone 20 mg, and subsequently mycophenolate mofetil 1 g BID
Mousa et al. [13]	22/f	One week after the first dose	Pfizer BNT162b2 mRNA	Pancytopenia, cutaneous vasculitis, pancreatitis	Positive ANA 1/2000, double-stranded DNA, low c3 and c4	19	Pulse methylprednisolone, oral prednisolone (40 mg), hydroxychloroquine (200 mg Q.D.), and azathioprine 50 mg
Nune et al. [15]	24/m	Two weeks after the second dose	Pfizer BNT162b2 mRNA	Fever, arthritis, oral ulcers, leukopenia, lymphopenia, lymphadenopathy	Positive ANA 1/2560, double-stranded DNA, low c3 and c4	20	Prednisone (1 mg/kg) and Methotrexate 15 mg/week
Patil et al. [14]	22/f	Ten days after the first dose	Astra-Zeneca (ChAdOx1-S)	Fever, arthritis, rash, lymphadenopathy, anemia, pedal edema	Positive ANA 1/320, double-stranded DNA, histone	20	Hydroxychloroquine (400 mg Q.D.), prednisone 50 mg, and mycophenolate mofetil 2 g BID

COVID-19 coronavirus 19, *ANA* antinuclear antibodies, *BID* twice daily, *Q.D.* once daily, *mRNA* messenger ribonucleic acid, *DNA* deoxyribonucleic acid, *EULAR/ACR* European League Against Rheumatism and the American College of Rheumatology

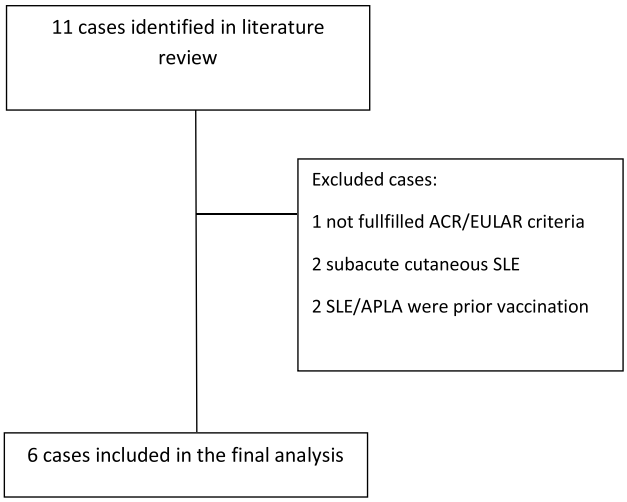

Fig. 1 Literature strategy flowchart

Second, all the patients in this series were men, as opposed to a significant predominance of SLE among women [18]. Third, SLE activity during the initial stage was high. One patient had severe disease activity (SLEDAI 2K of 15 points), and two had moderate activity (SLEDAI 2K of 10 and 8 points). Fortunately, no major organ was involved, and a few months after treatment initiation, all patients fulfilled the EULAR definition of low disease activity [17]. The lack of female predominance and the non-major organ involvement reported in drug-induced lupus may suggest that the mechanism of post-COVID-19 vaccine SLE has similar features [19]. Of note, anti-histone antibodies did not test in any of the patients in this series. Yet, these antibodies are not pathognomonic for drug-induced lupus and are also observed in 80% of primary SLE patients [20, 21]. We also acknowledge that cutaneous biopsy could support the diagnosis of SLE in two of our patients, yet this procedure was not conducted.

It has been postulated that some vaccines can trigger the new onset of SLE. Two mechanisms have been suggested to explain the association between the foreign antigen (of the vaccine) and autoimmunity: molecular mimicry and activation of antigen-presenting cells toll-like receptors (TLRs) [22]. In addition, there are anecdotal reports in the literature of de-novo lupus that emerge after certain vaccines (e.g., hepatitis B, tetanus, and human papillomavirus) [23–25]. For instance, Gatto et al. reported six cases of SLE following anti-human papillomavirus vaccine uptake [25]. Yet, unlike our cohort, all of these patients had a family susceptibility to autoimmunity. Moreover, vaccines (including those mentioned above) are safe for most patients, and their protective effect mounts these anecdotal reports [26].

Other than SLE, the diagnosis of new-onset autoimmune conditions following COVID-19 vaccination has been reported previously (rheumatoid arthritis, immune thrombotic thrombocytopenia, autoimmune liver diseases, Guillain–Barré syndrome, IgA nephropathy) [27]. Two mechanisms have been suggested to explain the association between vaccination and the development of autoimmune conditions. The former is molecular antigen mimicry induced by a vaccine (e.g., against hepatitis B, human papillomavirus, and influenza) that may generate a new-onset or flare of autoimmune response [23, 24]. The latter is related to vaccine adjuvant activation, which activates endosomal Toll-like receptors (TLRs) TLR-7 and TLR-8, triggers the NLR pyrin domain containing 3 (NLRP3) inflammasome, and produces type I interferon [25, 26]. Both mechanisms have been proposed to explain a possible relationship between certain vaccines and SLE diagnosis [28, 29]. In addition, molecular mimicry induced by the bindings of hapten to a drug or its metabolite was also suggested as a possible mechanism in the pathogenesis of drug-induced lupus [30].

Conclusion

We report the first case series of three male patients who developed new-onset SLE following the COVID-19 vaccine. Although causality between vaccination and SLE diagnosis is difficult to determine, the very low incidence of SLE among men supports the conjecture that the COVID-19 vaccine can trigger autoimmunity by molecular mimicry or vaccine adjuvant. Furthermore, male predominance and rapid clinical improvement after treatment initiation support the possibility that the COVID-19 vaccine may induce autoimmune reactions similar to other regimens that cause drug-induced lupus. Thus, it is likely that clinician's awareness of this phenomenon may improve the management of COVID-19 and its implications.

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Author contributions IS and MAS are responsible for study conception and design. IS and LZ extracted the data. IS and LZ drafted the manuscript. TP, YR, and MAS gave critical revisions.

Declarations

Conflict of interest All authors declare no conflicts of interest

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