



Systemic lupus erythematosus after Pfizer COVID-19 vaccine: a case report

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Received: 5 November 2021 / Revised: 1 March 2022 / Accepted: 2 March 2022 / Published online: 16 March 2022
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Abstract

The Pfizer-BioNTech COVID-19 vaccine has been authorized by the U.S. Food and Drug Administration as it demonstrated 95% effectiveness against the SARS-CoV-2 virus. Although the initial vaccine trials showed a favorable side effect profile, there have been concerns regarding activation of aberrant immune responses, triggering autoimmunity. This is a case report of a 68-year-old woman without history of autoimmune conditions, who presented to our emergency department 7 days after receiving the Pfizer-BioNTech COVID-19 vaccine. Her initial symptoms were suggestive of polymyalgia rheumatica, and she had nearly complete response to steroids. Interestingly, she later met criteria for classified systemic lupus erythematosus given the development of inflammatory arthritis, positive ANA, and positive dsDNA. The temporal relationship of her symptoms that started 2 days after vaccine administration could suggest a possible association between the Pfizer-BioNTech COVID-19 and the development of systemic lupus erythematosus.

Keywords Systemic lupus erythematosus · Covid-19 vaccine · Autoimmunity · Polymyalgia rheumatica

Introduction

Pfizer-BioNTech COVID-19 vaccine is part of a novel class of mRNA vaccines that instructs human cells to create viral spike protein, invoking the immune system to create antibodies against SARS-CoV-2. Although highly effective against the SARS-CoV-2 infection [1], shared peptides between the spike protein and human proteins propose a mechanism for development of autoimmunity through molecular mimicry [2] that could be similar to the mechanism behind autoimmunity following COVID-19 infection [3]. Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease with diverse clinical presentation. Multiple factors, including genetic, environmental, and immunologic, have been linked to its pathogenesis [4]. We present the first reported case of SLE following Pfizer-BioNTech COVID-19 vaccination.

Case

This is a 68-year-old Caucasian woman without history of autoimmune conditions that presented to our emergency department with bilateral proximal upper and lower extremity muscle weakness, stiffness, and pain. She received the first dose of the Pfizer-BioNTech COVID-19 vaccine 2 days prior to symptom onset and 7 days prior to hospital presentation. Initially, she developed a mild headache and experienced soreness at the injection site that resolved the day after vaccination. Two days after receiving the vaccine, she developed acute onset of bilateral shoulder pain, morning stiffness that lasted at least 30 min, and weakness that started in her right shoulder and then progressed to her left shoulder. She also developed bilateral antero-lateral hip pain radiating into her thighs, stiffness and weakness. Over the course of a week, the muscle weakness and pain became so profound, that she was unable to ambulate. During her hospitalization, she did not experience fever, headache, jaw claudication, scalp tenderness, chest pain, rash, other muscle involvement, or respiratory symptoms. Patient reported intentional 47-pound weight loss over the last couple of months. On examination, she had tenderness and 3/5 proximal muscle

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Table 1 Laboratory results

	Admission laboratories	3 weeks after discharge	3 months after discharge	4 months after discharge	6 months after discharge
ESR	> 130 mm/h (RR < 40)	55 mm/h (RR < 30)	68 mm/h RR (< 30)		29 mm/h (< 30)
CRP	15.9 mg/dl (RR < 0.8)	52.6 mg/dl (RR < 7.7)	149.3 mg/dl (RR < 8)	64.7 mg/dl (RR: 0.0–7.5)	6.1 (RR: 0.0–7.5)
ANA*	1:640 cytoplasmic pattern				
p-ANCA	Positive on ethanol	1:320			
c-ANCA	Positive on formalin				
Anti-MPO	3.1 (RR < 1)	2.2 (RR < 1)			
RF	Negative		Negative		
Anti-CCP	Negative		Negative		
SSA/SSB	Negative		Negative		
Sm-RNP	Negative		Negative		
C3/C4	Normal		Normal		Normal
CPK	21 IU/L (RR < 200)			43 IU/L (RR 30–175)	
Urinalysis	Unremarkable		100 protein, calcium oxalate crystals		
ds-DNA**			Positive, 221 IU/mL		125 IU/mL (RR < 4 negative)
Cardiolipin antibody			IgG neg IgM 14 (RR < 12)		
B2 glycoprotein anti- body			Negative		
LAC			Negative	Detected 41H (RR < 40)	
IgG4			Unremarkable		
Blood cultures			Negative		
Lyme screen			Negative		
Anti-jol				Negative	
Aldolase				Negative	
Urine drug screen				Negative	

ESR, erythrocyte sedimentation rate; CRP, C reactive protein; ANA, antinuclear antibodies; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; c-ANCA, antineutrophil cytoplasmic antibodies; anti-MPO, anti myeloperoxidase antibodies; RF, rheumatoid factor; anti CCP, anti cyclic citrullinated peptide antibodies; Sm-RNP, Smith-ribonucleoprotein antibodies; CK, creatine kinase; ds-DNA, double stranded DNA; LAC, lupus anticoagulant. *ANA was obtained by indirect immunofluorescence. **dsDNA was obtained by multiplexed assay on BioPlex 2200 (Bio-Rad)

strength at the hip and shoulder girdles. She had tenderness with active and passive range of motion. She could not get out of bed without assistance. Laboratory studies showed reactive ANA with positive titer 1:640 and presence of cytoplasmic pattern, ESR greater than 130 mm/h, CRP 15.9 mg/dl, and total CPK 23 IU/L (Table 1). The patient tested negative for Covid-19 but Covid-19 antibodies were positive. Further serological work up was negative for RF, anti-CCP, anti-SSA, and anti-SSB antibodies. Complement levels, vitamin D, TSH, and morning cortisol were normal. She had a positive p-ANCA with anti-MPO specificity; however, CT of the chest/sinuses, and urinalysis

were unremarkable. She had no features suggestive of vasculitis. CT of the chest, abdomen and pelvis were performed to rule out malignancy, which were all negative. She underwent MRI of the cervical, thoracic, and lumbar spine that showed disc disease with mild impingement at C3-C4 with moderate central canal stenosis, these findings did not explain patient's symptoms. By the time she was admitted to our hospital, lumbar puncture was performed at outside facility due to concern of possible Guillain-Barré. Our neurology team did not consider Guillain-Barré as a possible working diagnosis given her physical examination was not consistent with it. Her lumbar puncture was normal:

WBC 1, RBC 4, protein 39, and glucose 58, with negative gram stain. Serum electrophoresis showed no evidence of monoclonal proteins. Initial clinical manifestations pointed towards a possible presentation of polymyalgia rheumatica (PMR). For this reason, she received prednisone 20 mg daily and described a “90% improvement” in her muscle weakness and pain on the following day. Muscle strength and tenderness on range of motion in shoulders and hips girdles almost normalized after 2 days of prednisone. Her repeat inflammatory markers after a short interval of 3 days on prednisone were ESR 112 mm/h and CRP 7.7 mg/dl. She was discharged home on a prednisone taper of 20 mg daily for 2 weeks, with instructions to taper by 5 mg every 2 weeks.

Three weeks after discharge, patient’s muscle weakness, pain and stiffness had continued to improve. Follow-up blood work was noted for decreased inflammatory markers with ESR 55 mm/h, CRP 52.6 mg/dl (Table 1). However, 2 months later, she experienced recurrent symptoms, developing significant joint pain in shoulders, wrists, hips, knees, and ankles along with morning stiffness lasting all day. She endorsed swelling in her ankles and metacarpophalangeal joints as well as a rash on her forearm and palm of hands. More extensive work-up showed positive ds-DNA (titer 221) and rising inflammatory markers with ESR 68 mm/h and CRP 149.3 mg/dl (Table 1). According to the EULAR/ACR-2019 classification criteria, positive ANA with scores more or equal to 10 are indicative of classified SLE. Our patient met this criteria with a total score of 12 points, based on positive ANA, plus joint involvement (+6 points) for the clinical domains, as well as the presence of positive ds-DNA (+6 points) in the immunological domains [5]. The presence of immune mediated rash did not provide any points as it was not clear if it was consistent with acute cutaneous lupus erythematosus given rash was reported but not evidenced on physical exam. Further, the patient had active disease given SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score more than 4 points. Her SLEDAI was 10 points. Points were given for: arthritis (+4 points), pyuria (+4 points), dsDNA (+2 points). There were no other organs affected besides the joints and skin, she did not have lupus nephropathy given no evidence of proteinuria, hematuria, and normal creatinine. She was started on a steroid-sparing agent with azathioprine 50 mg daily for 2 weeks with instructions to increase to 100 mg daily thereafter. Unfortunately, she developed generalized hives when increasing the azathioprine dose for which the medication was stopped. Therefore, the patient was started on methotrexate 20 mg weekly and maintained on prednisone 5 mg daily with improvement of symptoms. Our patient elected to forgo the second dose of COVID-19 vaccine.

Discussion

Pfizer-BioNTech COVID-19 vaccine has been approved by the U.S. Food and Drug Administration (FDA) in response to the SARS-CoV-2 pandemic. In the phase 3 trial, the vaccine demonstrated 95% efficacy in preventing the SARS-CoV-2 infection [1] with relatively common side effects that included fatigue, headache, chills, muscle pain, and injection site pain [6]. Systemic adverse effects began a median of 1–2 days after vaccination and resolved 1 day later [6]. The FDA briefing of the Moderna vaccine reported three serious adverse events, in which one was the development of rheumatoid arthritis but vaccine contribution could not be excluded [7]. Similarly, some cases of possible Pfizer-BioNTech vaccine association with the development de novo immune thrombocytopenia [8], acquired hemophilia A [9], anterior uveitis [10], and recurrent Bell’s palsy [11] have been published in the literature. Multiple cases of cutaneous lupus erythematosus (CLE) have been observed following Pfizer-BioNTech vaccine administration [12], as well as one case of pre-vaccination CLE developing into SLE following the AstraZeneca adenovirus vector vaccine [13]. Current evidence suggests cases of SLE following hepatitis B [14] and meningococcal [15] vaccines, but conclusive evidence of causation remains unestablished [16]. Likewise, apart from the above presumptive associations, to date, there is no definitive data indicating that SARS-CoV-2 mRNA vaccines cause autoimmunity.

Autoimmunogenicity incited by mRNA vaccines is currently an avenue of intense research. It has been proposed that the response to SARS-Cov-2 infection may trigger autoimmunity through molecular mimicry between the virus and human proteins [3]. Kanduc et al. analyzed peptide sharing between the SARS-CoV-2 spike protein and human proteins and noted significant sharing at the heptapeptide level [2], hence, it is plausible that the antibodies produced against SARS-CoV-2 spike protein, in response to the vaccine, can cross-react with the host and cause autoimmune diseases in predisposed individuals. Following mRNA vaccination, multiple pro-inflammatory pathways are activated as a result of the mRNA itself, liposomes or lipid-nanoparticles used to encapsulate mRNA, as well as the binding of receptors required for the spike protein translation; which could explain the reactogenicity associated with mRNA vaccines and the development of immune-mediated diseases [17]. Because mRNA is a single-stranded RNA, it is a ligand for toll-like-receptor (TLR-7) [18]. TLR-7 has increased expression in SLE humans and mice [19, 20]. In addition, the mRNA and adenovirus vaccines both stimulate the production of type 1 interferons, which are integral to the development of SARS-CoV-2 immunity

[21] but also have been implicated in the pathogenesis of SLE and other autoimmune conditions [22, 23]. We speculate that individuals who are pre-disposed to SLE may show an exacerbated innate inflammatory response and elevated inflammatory cytokine profile that may contribute to the onset of profound systemic inflammation post-vaccination.

SARS-CoV-2 is known to hyper-stimulate the immune system, which could cause formation of autoantibodies and trigger autoimmune disease. More severe disease correlates with higher level of pro-inflammatory cytokines such as IL-6, TNF, and interferon gamma (IFN-gamma), the latter had been described as an independent risk factor of mortality in moderate to severe COVID-19 infection [24]. These cytokines are also elevated in SLE and correlate with disease activity [25]. Interestingly, p-ANCA and c-ANCA positivity has been frequently reported in severely ill patients who have autoimmune vasculitis [3]. While our patient did not get infected with COVID-19, a similar pathway is likely elicited by the vaccine, and these cytokines also are elevated in the pathogenesis of SLE.

Our elderly patient that debuted with clinical manifestations suggestive of PMR and had initial marked improvement with moderate dose steroids, was later confirmed to have classified SLE according to the EULAR/ACR-2019 classification criteria. Interestingly, she also was found to have positive p-ANCA/MPO without evidence of vasculitis further supporting her unusual presentation and autoantibody profile. Given that the constellation of symptoms presented within days after receiving the Pfizer-BioNTech COVID-19 vaccine, this could suggest but not prove a possible etiologic association between the vaccine administration and the development of SLE.

It is worth mentioning that SLE in the elderly is rare, with an incidence of 12–18% and a prevalence of 15–124/100,000 of population worldwide. Diagnosis is often delayed given the low prevalence in this age group as well as nonspecific and sometimes atypical presenting symptoms. These factors usually contribute to diagnosis uncertainty, delay in diagnosis, or misdiagnoses. The disease course is considered to be more benign; and the most common symptoms in this population include fever, weakness, fatigue, arthritis/arthralgias, weight loss, serositis, neuropsychiatric manifestations, lung disease, Raynaud's, and sicca. Other typical lupus symptoms such as rash, glomerulonephritis, photosensitivity, or discoid lupus are uncommon in the elderly population. ANA remains the usual test to screen for disease, although, positive anti-dsDNA and hypocomplementaemia is of lower prevalence. SLE management remains the same in this age group

except considering comorbidities and side effect profile of medications in the elderly [26, 27].

By the time our patient was vaccinated, a total of 26,413 patients were partially vaccinated with mRNA vaccines in Pennsylvania [28]. Notably, this was the only case of possible mRNA-induced SLE known in the University of Pittsburgh Medical Center system, suggesting a very low incidence of disease. Therefore, we hope this report does not discourage against vaccination but raise awareness about the possible association of SLE development after mRNA vaccination in the susceptible population (Table 1).

Conclusion

Autoantibody formation and autoimmune disease have been observed following SARS-CoV-2 infection as a result of a robust immune response and molecular mimicry. Likewise, the SARS-CoV-2 spike protein shares a significant portion of peptides with human proteins and could incite autoimmune disease or trigger pre-existing autoimmune conditions. Given the strong temporal association between COVID-19 vaccine administration and the development of SLE in our patient, we hypothesize that the mRNA vaccine could have caused hyperstimulation of the patient's immune system. Her aberrant immune response required that she be closely monitored for evolution of her autoimmune disease. We report this case to increase awareness for the possibility of autoimmunity, specifically SLE, following mRNA vaccination against SARS-CoV-2 virus.

Author contribution All authors contributed to the care of the patient and gathering of data. Dr Lemoine and Dr Padilla drafted the initial version. All authors offered corrections, read and approved the final version.

Declarations

Other disclosure This case report has not been submitted elsewhere and is not under consideration by another journal. The case report information will not be submitted or published elsewhere while it is under review by this journal unless rejected by journal or withdrawn by the authors.

Conflict of interest Dr. Aggarwal has received research grant and consulting fee from Pfizer. The other authors have disclosed no conflict of interest.

References

- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC, and C4591001 Clinical Trial Group (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 383(27):2603–2615
- Kanduc D, Shoenfeld Y (2020) Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol Res* 68(5):310–313
- A. Dotan, S. Muller, D. Kanduc, P. David, G. Halpert, and Y. Shoenfeld (2021) “The SARS-CoV-2 as an instrumental trigger of autoimmunity.” *Autoimmun. Rev.*, vol. 20, no. 4, p. 102792.
- Justiz Vaillant AA, Goyal A, Bansal P, Varacallo M (2021) Systemic Lupus Erythematosus. in StatPearls. StatPearls Publishing, Treasure Island
- Fanourakis A, Tziolos N, Bertias G, Boumpas DT (2021) Update on the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis* 80(1):14–25
- Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, McClung N, Campos-Outcalt D, Morgan RL, Mbaeyi S, Romero JR, Talbot HK, Lee GM, Bell BP, Dooling K (2020) The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. *MMWR Morb Mortal Wkly Rep* 69(50):1922–1924
- “Vaccines and Related Biological Products Advisory Committee Meeting.” <https://www.fda.gov/media/144434/download>. Accessed May 2021
- King ER, Towner E (2021) A case of immune thrombocytopenia after BNT162b2 mRNA COVID-19 vaccination. *Am. J. Case Rep* 22:e931478
- Radwi M, Farsi S (2021) A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost* 19(6):1515–1518
- Renisi G, Lombardi A, Stanzione M, Invernizzi A, Bandera A, Gori A (2021) Anterior uveitis onset after bnt162b2 vaccination: is this just a coincidence? *Int J Infect Dis* 110:95–97
- Repajic M, Lai XL, Xu P, Liu A (2021) Bell’s Palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell’s palsy. *Brain Behav Immun Health* 13:100217
- Kreuter A, Licciardi-Fernandez MJ, Burmann SN, Burkert B, Oellig F, Michalowicz AL (2021) Induction and exacerbation of subacute cutaneous lupus erythematosus following messenger-RNA or adenoviral-vector based SARS-CoV-2 vaccination. *Clin Exp Dermatol* 47(1):161–163
- Kreuter A, Burmann SN, Burkert B, Oellig F, Michalowicz AL (2021) Transition of cutaneous into systemic lupus erythematosus following adenoviral vector-based SARS-CoV-2 vaccination. *J Eur Acad Dermatol Venereol* 35(11):e733–e735
- Agmon-Levin N, Zafirir Y, Paz Z, Shilton T, Zandman-Goddard G, Shoenfeld Y (2009) Ten cases of systemic lupus erythematosus related to hepatitis B vaccine. *Lupus* 18(13):1192–1197
- Holmes AD, Abbasi OZ, Jacoby JL (2018) Systemic lupus erythematosus following meningococcal vaccination. *Am J Emerg Med* 36(1):170.e3-170.e4
- Mason A, Anver H, Lwin M, Holroyd C, Faust SN, Edwards CJ (2021) Lupus, vaccinations and COVID-19: what we know now. *Lupus* 9612033211024356
- Talotta R (2021) “Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to ‘potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol* 224:108665
- Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, Lipford G, Wagner H, Bauer S (2004) Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science* 303(5663):1526–1529
- Weindel CG, Richey LJ, Bolland S, Mehta AJ, Kearney JF, Huber BT (2015) B cell autophagy mediates TLR7-dependent autoimmunity and inflammation. *Autophagy* 11(7):1010–1024
- Yokogawa M, Takaishi M, Nakajima K, Kamijima R, Fujimoto C, Kataoka S, Terada Y, Sano S (2014) Epicutaneous application of toll-like receptor 7 agonists leads to systemic autoimmunity in wild-type mice: a new model of systemic Lupus erythematosus. *Arthritis Rheumatol* 66(3):694–706
- Teijaro JR, Farber DL (2021) COVID-19 vaccines: modes of immune activation and future challenges. *Nat Rev Immunol* 21(4):195–197
- Banchereau J, Pascual V (2006) Type I interferon in systemic lupus erythematosus and other autoimmune diseases. *Immunity* 25(3):383–392
- Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB (2020) Type I interferon in the pathogenesis of systemic lupus erythematosus. *Curr Opin Immunol* 67:87–94
- Gadotti AC, de Castro Deus M, Telles JP, Wind R, Goes M, Garcia Charello Ossoski R, de Padua AM, de Noronha L, Moreno-Amaral A, Baena CP, Tuon FF (2020) IFN- γ is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. *Virus Res* 289: 198171
- Tang Y, Tao H, Gong Y, Chen F, Li C, Yang X (2019) Changes of Serum IL-6, IL-17, and complements in systemic lupus erythematosus patients. *J Interferon Cytokine Res* 39(7):410–415
- Rovenský J, Tuchynová A (2008) Systemic lupus erythematosus in the elderly. *Autoimmun Rev* 7(3):235–239
- Lazaro D (2007) Elderly-onset systemic lupus erythematosus. *Drugs Aging* 24(9):701–715
- Department of health Pennsylvania. <https://www.health.pa.gov/topics/disease/coronavirus/Vaccine/Pages/Dashboard.aspx>. Accessed February, 2022

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