Systemic lupus erythematosus and antiphospholipid syndrome after COVID-19 vaccination. A case report.

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Abstract
Introduction: COVID-19 vaccines have some adverse effects, mostly mild. However, by presenting an immunological challenge to the individual, they could infrequently trigger immune-mediated diseases.

Case report: We report the case of a 42-year-old woman, with no previous medical history, who received the first dose of vaccine against COVID-19 and developed inflammatory arthralgias, associated with sudden onset dyspnea and hypoxemia. Pulmonary thromboembolism was documented and the diagnosis of systemic lupus erythematosus (SLE) and secondary antiphospholipid syndrome (APS) was suspected. Autoantibodies were measured confirming this suspicion. After a few days, she presented a massive pericardial effusion with cardiac tamponade that required surgical management. She received treatment with hydroxychloroquine, corticosteroids and anticoagulation with improvement of all symptoms.
Discussion: There is controversy regarding the potential of COVID-19 vaccines to induce autoimmunity. Studies addressing the safety of using these vaccines have reported the occurrence of mild local and systemic reactions, most frequently in young adults. So far there are few reports of patients who have developed autoimmune or autoinflammatory diseases after getting vaccinated with any of the COVID-19 vaccines. To the best of our knowledge, to date this is one of the first cases of new-onset SLE and secondary APS after COVID-19 vaccination.

**Keywords:** SARS-Cov-2, COVID-19, vaccines, systemic lupus erythematosus, cardiac tamponade.

**Introduction**

Coronavirus disease 2019 (COVID-19) is an emerging disease that was declared a pandemic in March 2020 and that has had a high social and economic impact worldwide. As of October 10, 2021, there were more than 238 million COVID-19 confirmed cases and more than 4 million deaths from it (1). The etiological agent of COVID-19 is the SARS CoV2 virus, and its high burden of disease worldwide is due to the high rate of spread and transmission of this virus. Therefore, the establishment of control and prevention measures such the use of face masks, frequent handwashing and social distancing, has been necessary in most countries to reduce its rapid spread. However, despite these measures, the pandemic has been difficult to control, and massive vaccination, using the vaccines that have been approved by the World Health Organization (WHO) so far, is of utmost importance to slow down the SARS-CoV-2 transmission rate (2). Somehow, after COVID-19 vaccines were developed and made available to the public, controversy has been raised about whether they induce autoimmune diseases (3). We present the case of a patient who was vaccinated (first dose only) against COVID-19 and subsequently developed multiple symptoms and clinical signs that led to diagnose her with systemic lupus erythematosus (SLE).

**Case description**

This is the case of a 42-year-old woman with an obstetric history of three pregnancies, with two of them resulting in spontaneous abortions of unknown etiology (the first at 8 weeks gestation and the second at 12 weeks gestation); the patient did not have any other relevant history of disease. Two weeks after receiving the first dose of the Pfizer/BioNTech® vaccine, she presented with inflammatory polyarthritis affecting her hands and feet, with
bilateral synovitis in metacarpophalangeal and proximal interphalangeal joints, wrists and elbows. Also, both of her fifth fingers were swollen, which was associated with signs of bilateral Achilles tendon enthesopathy.

Because of these signs and symptoms, the patient visited the emergency room of our hospital, where an elevated erythrocyte sedimentation rate and a high C-reactive protein level were documented, and, therefore, possible reactive arthritis secondary to immunization was initially considered. She was then hospitalized and treatment with oral sulfasalazine 500 mg twice a day was started; also, autoantibody tests were requested to rule out other differential diagnoses. Laboratory tests at hospital admission are shown in table 1. One day after hospital admission, she experienced left pleuritic chest pain associated with sudden onset dyspnea and hypoxemia, for which she required oxygen therapy. Additionally, elevated D-dimer levels (>10,000 ng/ml) and a negative troponin result were reported. Thus, pulmonary embolism was suspected and a CT pulmonary angiogram was performed the same day, showing a filling defect in the right pulmonary artery in the medial segment of the right middle lobe without signs of right ventricular dysfunction or pulmonary infarction. Anticoagulation treatment was started once the CT pulmonary angiogram finding was known. Treatment consisting of subcutaneous enoxaparin 1 mg/kg every twelve hours was started, and, due to the patient’s history of miscarriage, the CT findings and polyarthralgia, a possible diagnosis of SLE and secondary antiphospholipid syndrome (APS) to SLE was considered, so all studies necessary to confirm the presence of this disease were requested.

Because of the current COVID-19 pandemic and the presence of respiratory symptoms, a thrombotic episode and multilobar alveolar infiltrates, predominantly in the lung bases and random ground-glass opacities, two RT-PCR tests for SARS-CoV-2 were performed, both with negative results. Interstitial pulmonary edema was considered as a possible diagnosis due to the clinical findings and radiological changes observed in the pulmonary parenchyma. Laboratory and autoantibody tests results taken at hospital admission (table 1), together with the patient’s symptoms led us to diagnose her with APS secondary to SLE. Kidney failure was ruled out as normal creatinine levels, 24-hour urine protein levels, and urinalysis results were obtained. Treatment consisting of oral hydroxychloroquine 200 mg/day and intravenous methylprednisolone 250 mg/day for three days was started, followed by prednisolone 0.5 mg/kg/day. Sulfasalazine administration was continued until discharge due to a persistent enthesitis episode.

Ten days after hospital admission, the patient experienced a syncopal episode, together with diaphoresis, oxygen desaturation and hypotension, and the subsequent appearance of intense headache and severe retrosternal chest pain.
Grade III jugular engorgement, muffled heart sounds and decreased breath sounds in both lungs bases were reported on physical examination. Intravenous fluid resuscitation was performed and normal mean arterial pressure was achieved, however she required receiving an increased inspired fraction of oxygen using high-flow devices. The patient was immediately transferred to the intensive care unit (ICU) due to the risk of respiratory failure. Because of the suspicion of a new thrombotic event or a cardiac tamponade, a CT angiography of the chest was performed; during the procedure a large pericardial effusion with risk of obstructive shock secondary to cardiac tamponade (Figure 1) was documented, a finding confirmed by means of a transthoracic echocardiogram. So a pericardial window was carried out one day after ICU admission, in which approximately 300 cc of yellowish fluid were drained, and a thickened pericardium was also found. Lymphocytic infiltrates and fibrinoid deposits were informed in the histopathology report.

After undergoing the procedure, the patient’s clinical condition started to improve progressively. Anticoagulation treatment with warfarin 5 mg/day was indicated, in addition to colchicine 0.5 mg every 12 hours, and azathioprine 50 mg every twelve hours. Once an international normalized index between 2-3 was reached, enoxaparin was discontinued. She was discharged one week after the pericardial window was performed. A control was carried out fourteen weeks after hospital discharge with: Beta-2-glycoprotein IgG antibodies 90 U/mL (standard value 0-20 U/mL), Beta-2-glycoprotein IgM antibodies 46 U/mL (standard value 0-20 U/mL), negative Anti-cardiolipin IgG and IgM antibodies and improvement of her symptoms. No new lupus anticoagulant test was performed because she was receiving anticoagulation. Clinical follow-up was continued with a final diagnosis of SLE (18 points according to the ACR/EULAR classification criteria), and APS secondary to SLE (presence of venous thromboembolism, recurrent early miscarriages, and persistently positive antiphospholipid antibodies).

Discussion

It has been described that genetic, hormonal and environmental factors are involved in the origin of autoimmunity and autoimmune diseases. In addition, the role of infectious agents as triggers of this type of disorders in genetically predisposed subjects has been reported (4) and clearly identified in some autoimmune diseases such as reactive arthritis, rheumatic fever, or vasculitis secondary to hepatitis B. On the other hand, there is controversy regarding the potential of COVID-19 vaccines to induce autoimmunity, especially due to the reports that have been published since
their introduction describing the association between getting vaccinated against COVID-19 and the onset of autoimmune diseases, (5), recognizing not only the potential of the antigen, but also of the adjuvants used (6).

Currently, COVID-19 vaccines approved by the World Health Organization (WHO) are BNT162b2 (produced by Pfizer/BioNTech), mRNA-1273 (developed by Moderna), AZD1222 (produced by AstraZeneca - Oxford University), Ad26.COV2 (produced by Janssen), BIBP (produced by Sinopharm), and Sinovac-CoronaVac (developed by Sinovac). In this regard, studies addressing the safety of using these vaccines have reported the occurrence of mild local and systemic reactions, most frequently in young adults (7).

So far there are few reports of patients who have developed autoimmune or autoinflammatory diseases after getting vaccinated with any of the aforementioned COVID-19 vaccines. For example, An et al. (8) reported the case of a 23-year-old woman who presented with reactive arthritis after being administered the CoronaVac vaccine, but the course of the disease was benign and symptoms resolved quickly (8), and Terracina et al. (9) described the case of a 55-year-old man who experienced a rheumatoid arthritis flare after receiving the BNT162b2 vaccine that quickly resolved after being treated with intra-articular steroids (9). Similarly, Obeid et al. (10) reported the case of a 78-year-old woman with IgA vasculitis in remission, who after receiving the mRNA-1273 vaccine experienced an exacerbation of gastrointestinal symptoms, renal function deterioration and palpable purpura, for which she was treated with methylprednisolone, resulting in the resolution of all symptoms (10).

So far the largest report of patients with autoimmune or autoinflammatory manifestations after getting vaccinated against COVID-19 vaccination was carried out by Watad et al. (11), who evaluated immune-mediated diseases (IMD) flares or new autoimmune disease onset after COVID-19 vaccination in five tertiary centers located in countries with early vaccination adoption: three in Israel, one in the United Kingdom, and one in USA. Out of the 27 cases included, all of them showed any type of IMD-related symptoms, and a new onset of IMD was reported in only 10 cases (11). Of these 10 patients, one presented with leukocytoclastic vasculitis, another developed severe Myasthenia Gravis, for which mechanical ventilation and management in the intensive care unit were required, another suffered from transitory urticarial lesions, and the last one presented with polymyalgia rheumatica. None of these 10 patients experienced a new-onset SLE.

Until now, there are few reports of patients with new-onset SLE after getting vaccinated with any of the COVID-19 vaccines. Zavala-Miranda et al. (12) reported the case of a 23-year-old woman without previous medical history of disease, who presented with class V lupus nephritis 1 week after vaccination with the first dose of the
AstraZeneca/Oxford vaccine. Unlike our patient, antiphospholipid antibody panel was negative. She received treatment with prednisolone, hydroxychloroquine and mycophenolate mofetil. Patil et al. described the case of a 22-year-old female who presented with pain in right knee while climbing up and down the stairs after 2 weeks of receiving first dose of COVID-19 vaccination with AstraZeneca/Oxford vaccine. She received the second dose of vaccine, about 2 months after the first dose, and developed fever, polyarthritis, bipedal edema, cutaneous rash over fingertips, and petechiae over lower limb. She was diagnosed with new-onset SLE and received treatment with prednisolone, hydroxychloroquine and mycophenolate mofetil with a good clinical response. Moreover, Hidaka et al. (14) reported a case of a 53-year-old Japanese woman, who had medical histories of bronchial asthma, Vogt-Koyanagi-Harada disease, and Hashimoto disease. She received two doses of Pfizer/BioNTech® vaccine. After the second dose she developed thrombocytopenia and hemolytic anemia. ANA was positive and positivity of lupus coagulant were observed. However, unlike our patient, thrombotic events were not documented. Diagnosis of Evans syndrome associated with SLE was made, and she received treatment with prednisone. Nune et al (15) described the case of a 24-year-old Caucasian gentleman with a 4-week history of polyarthralgia, joint stiffness, fever and fatigue; 2 weeks after receiving the second dose of Pfizer-BioNTech® SARS-CoV-2 vaccine. The laboraroty workup confirmed leukopenia, positive ANA of 1:2560 with a raised anti-dsDNA levels, and low serum complements C3 and C4 level. Diagnosis of new-onset SLE was made, and he required treatment with prednisolone and methotrexate with improvement of his symptoms.

To the best of our knowledge, to date this is one of the first cases of new-onset SLE and secondary APS after COVID-19 vaccination. She presented high ESR and CRP levels at hospital admission as findings suggestive of acute inflammatory response. Like the cases of Patil et al. and Nune et al, our patient started with joint symptoms without renal disease. However, strikingly she presented a large pericardial effusion with risk of obstructive shock secondary to cardiac tamponade, which are not frequent in these patients. Taking into account the history of spontaneous abortions of unknown etiology and the disease course, we consider that she had genetic susceptibility to present SLE and APS and the COVID-19 vaccine behaved as a triggering factor to develop these diseases (16). Unlike the previously described cases, our patient presented a life-threatening SLE that needed to be managed in ICU. Similarly to the cases described above, after hospital discharge her evolution has been favorable and the symptoms have improved significantly.
Finally, it should be noted that despite the occurrence of these rare adverse effects after getting vaccinated against COVID-19 is a possibility, massive use of these vaccines in the general population must be encouraged due to their high efficacy in preventing COVID-19 and the development of severe illness from COVID-19 and the multiple benefits derived from it.

**Patient Consent**

The patient has given written consent to the inclusion of material pertaining to himself, he acknowledged that he cannot be identified via the paper; and we have fully anonymized the case report.

**Conflict of interest:** None

**Ethical Approval:** Not Applicable

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**References**

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hospkins University (JHU). https://coronavirus.jhu.edu/map.html.
2. García-Montero C, Fraile-Martínez O, Bravo C, Torres-Carranza D, Sanchez-Trujillo L, Gómez-Lahoz AM, et al. An updated review of sars-cov-2 vaccines and the importance of effective vaccination programs in pandemic times. Vaccines. 2021;9(5):1–22.
3. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol. 2010 Jun;29(3):247-69.
4. Albert LJ, Inman RD. Molecular mimicry and autoimmunity. N Engl J Med 1999;341:2068–74 -----Fourneau JM, Bach JM, van Endert PM, Bach JF. The elusive case for a role of mimicry in autoimmune diseases. Mol Immunol 2004; 40:1095–102.
5. Vadala M, Poddighe D, Laurino C, Palmieri B. Vaccination and autoimmune diseases: is the prevention of adverse health effects on the horizon? EPMA J. 2017 Jul 20;8(3):295-311.

6. Guimarães LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacol Res. 2015 Oct; 100:190-209.

7. Chen M, Yuan Y, Zhou Y, Deng Z, Zhao J, Feng F, Zou H, Sun C. Safety of SARS-CoV-2 vaccines: a systematic review and meta-analysis of randomized controlled trials. Infect Dis Poverty. 2021 Jul 5;10(1):91.

8. An QJ, Qin DA, Pei JX. Reactive arthritis after COVID-19 vaccination. Hum Vaccin Immunother. 2021 Sep 2;17(9):2954-2956.

9. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. Lancet Rheumatol. 2021 Jul;3(7): e469-e470.

10. Obeid M, Fenwick C, Pantaleo G. Reactivation of IgA vasculitis after COVID-19 vaccination. Lancet Rheumatol. 2021 Sep;3(9):e617.

11. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N, et al. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. Vaccines (Basel). 2021 Apr 29;9(5):435.

12. Zavala-Miranda MF, González-Ibarra SG, Pérez-Arias AA, Uribe-Uribe NO, Mejia-Vilet JM. New-onset systemic lupus erythematosus beginning as class V lupus nephritis after COVID-19 vaccination. Kidney Int. 2021 Dec;100(6):1340-1341.

13. Patil S, Patil A. Systemic lupus erythematosus after COVID-19 vaccination: A case report. J Cosmet Dermatol. 2021 Oct;20(10):3103-3104.

14. Hidaka D, Ogasawara K, Sugimura S, Fujii F, Kojima K, Nagai J, et al. New-onset Evans syndrome associated with systemic lupus erythematosus after BNT162b2 mRNA COVID-19 vaccination. Int J Hematol. 2021 Oct 23:1-4.

15. Nune A, Iyengar KP, Ish P, Varupula B, Musat CA, Sapkota HR. The Emergence of new-onset SLE following SARS-CoV-2 vaccination. QJM. 2021 Dec 20;114(10):739-740.

16. Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, et al. Systemic lupus erythematosus. Nat Rev Dis Primers. 2016 Jun 16;2:16039.
Figure legend

Figure 1. CT angiography of the chest

Large circumferential pericardial effusion (white arrow) in coronal (panel A) and axial (panel B) window, with an intrapericardial distance up to 3.2 cm. It exerts a compressive effect on the cardiac silhouette, a finding compatible with cardiac tamponade.

Table 1. Laboratory data on admission.

| Assay (Standard value)          | Result |
|---------------------------------|--------|
| WBC (μL)                        | 5310   |
| Neutrophils (%)                 | 84     |
| Lymphocytes (%)                 | 11     |
| Hemoglobin (g/dl)               | 13.1   |
| Platelet count (×10^9/UL)       | 307    |
| Serum creatinine(mg/dl)         | 0.53   |
| BUN (mg/dL)                     | 9.17   |
| CRP (mg/dL)                     | 91     |
| ESR (mm/h)                      | 55     |
| PT (sec)                        | 13.4   |
| Test                                      | Result          |
|-------------------------------------------|-----------------|
| PT-INR                                    | 1.17            |
| APTT (sec, day control 29)                | 44.4            |
| Direct coombs test                        | Negative        |
| Proteinuria (Urinalysis)                  | Negative        |
| Hematuria (Urinalysis)                    | Negative        |
| LDH (U/L)                                 | 249             |
| ANAs (dils)*                              | 1:1280 – smooth nuclear envelope – AC -11 |
| Anti-dsDNA (dils)*                        | 1/160           |
| Complement C4 (mg/dl, 15-57)a             | 10.6            |
| Complement C3 (mg/dl, 83-193)b            | 86.5            |
| Anti-cardiolipin IgG (U/mL, 0-12) *       | 4.97            |
| Anti-cardiolipin IgM (U/mL, 0-12) *       | 3.16            |
| Beta 2 Glycoprotein IgG (U/mL, 0-20) *    | 83              |
| Beta 2 Glycoprotein IgM (U/mL, 0-20) *    | 56.2            |
| Lupus anticoagulant, confirmatory test (Russell's Viper Venom Trial) Ratio: 2.29 |
| HLA B27c                                  | Negative        |
| Rheumatoid factora                        | Negative        |
| Anti-SSb (La) (U/mL, 0 - 20) *            | 2.00            |
| Anti-SSa (Ro) (U/mL, 0 - 20) *            | 3.05            |
| Anti-Sm (U/mL, 0-20) *                    | 4.49            |
| Anti-RNP (U/mL, 0-20) *                   | 2.85            |
| Anti-HCV                                  | Negative        |
| Hepatitis b surface antigen               | Negative        |

*Indirect immunofluorescence
+Enzyme immunoassay (SYNLAB laboratories)
a-Immunoturbidimetry
b-Immunochromatography
Flow cytometry
WBC: white cell blood count, BUN: urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, PT: prothrombin time, INR: International Normalized Ratio, APTT: Partial Thromboplastin Time, AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, ANA: Antinuclear antibodies, dsDNA: Double-stranded DNA, HCV: hepatitis C virus.