Case Report

Rapid Progressive Systemic Sclerosis Following mRNA COVID-19 Vaccination

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Rapid Progressive Systemic Sclerosis following mRNA COVID-19 Vaccination

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Abstract: The coronavirus disease (COVID-19) is a respiratory tract infection caused by the new virus SARS-CoV-2. In March 2020, the World Health Organization (WHO) declared a worldwide COVID-19 pandemic. Since then, there has been a rush to find preventative or curative treatment. This arrived with the appearance of the COVID-19 vaccine, months after the declaration of the pandemic. In the setting of global COVID-19 immunization, there have been reports of rare skin immune-mediated diseases (IMD) after COVID-19 vaccination, particularly systemic sclerosis. Systemic sclerosis (SSc) is the most reported new onset IMD following messenger RNA (mRNA) COVID-19 vaccination. The pathogenesis of SSc is not fully understood, and the diagnosis is based on clinical symptoms. We report a 54-year-old male, with no prior history of autoimmune disorder, with rapid and progressive skin thickening (Modified Rodnan skin score 30/51), weeks after his mRNA COVID-19 vaccination. Antinuclear antibodies (ANA) showed a strongly positive nuclear fine-speckled pattern, but no SSc autoantibodies were found. The patient was diagnosed with SSc based on the persistence of autoantibodies and the clinical criteria according to the 2013 American College of Rheumatology/European League Against Rheumatism classification. Due to the proximity of the two events, we hypothesized a cross-reaction between COVID-19 vaccination and, in genetically predisposed patients, an emergence of systemic sclerosis. Our case suggests a potential relationship between the mRNA COVID-19 vaccine and new-onset autoimmune diseases. Physicians should be aware of this possible association.

Keywords: COVID-19; mRNA-based vaccine; systemic sclerosis

1. Introduction

The SARS-CoV-2 virus, causing severe acute respiratory syndrome, started in December 2019 in the province of Wuhan, China [1]. In March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic, and since then it has had a far-reaching impact on worldwide health and the global economy [1–3]. In order to mitigate or control the COVID-19 pandemic a rapid response was needed, either in terms of a cure or preventative measure. With unprecedented collaboration within the global pharmaceutical industry, the first COVID-19 vaccine emerged in late 2020 and was delivered outside of a clinical trial setting given the global health emergency [4,5].

The history of vaccination dates to the year 1800 [6]. Since then, there has been a general recognition of the benefits to both individual and community health. As a result of the massification to at least 185 countries worldwide, the vaccine has been shown to substantially decrease COVID-19 severity, morbidity, and mortality [3,5,7]. However, within only two and a half years of COVID-19 vaccination, potential adverse effects were being described. Comparatively, previous vaccines have taken several years to recognize and achieve a safe vaccination status [4].

In literature, there is growing evidence suggesting that the mRNA COVID-19 vaccine may cause new-onset rare immune-mediated-diseases (IMD), such as rheumatic, glomerulonephritis and hepatitis in patients with underlying autoimmune disease or in those with no known history of autoimmune diseases [2,3]. It is hypothesized that molecular mimicry, resulting in similarities between vaccine components and specific human proteins could result in IMD [3,8,9].

Systemic sclerosis (SSc) is a rare, heterogeneous, multiorgan connective tissue disease of unknown etiology, characterized by microangiopathy, chronic immune response, and fibrosis of the skin and internal organs [9,10]. According to the 2013 American College of Rheumatology/European

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League Against Rheumatism (ACR/EULAR) classification of systemic sclerosis, patients with a total score of 9 or more are classified as having definite systemic sclerosis [10].

Having carried out the administration of the COVID-19 vaccine worldwide, in a very short time, new-onset sclerotic skin diseases were reported after inoculation with the mRNA COVID-19 vaccine. Herein, we report yet another case of a patient with no prior IMD skin disease with new-onset sclerotic skin disease post-COVID-19 vaccination.

2. Case report

A 56-year-old male with a history of COPD, and an episode of Deep Venous Thrombosis (DVT) associated with a single dose of mRNA COVID-19 vaccine (BioNTech Pfizer), was admitted to our inpatient department. He presented with a 16-month history of swollen fingers, Raynaud's phenomenon, digital ulcer, skin thickening of the limbs, weight loss, fatigue on exertion, difficulty in swallowing, regurgitation at bedtime, and abdominal pain. These symptoms started 4 weeks after his mRNA COVID-19 vaccination.

Physical examination revealed, microstomia, sclerodactyly, diffuse skin thickening (Modified Rodnan skin score [mRSS] 30/51 points), decreased breath sounds at 2/3 of the right lung, and abdominal tenderness.

Laboratory testing showed eosinophilia, ESR 97 mm, CK 1564 U/L (33-211 U/L). The autoimmune panel revealed positive nuclear fine speckled (AC 4; title 1/1280), positive Ac. Anti-SSA/Ro60, but no SSc autoantibodies (Table 1), and high-resolution chest CT revealed bilateral pleural effusions, predominantly in the right lung. Thoracocentesis drained 1800 mL of "milky" fluid, which was, according to Light's criteria, suggestive of exudate. Upper endoscopy revealed grade A peptic esophagitis. Nailfold capillaroscopy showed an extensive avascular area, and skin biopsy showed findings consistent with scleroderma (Table 2). Altogether, findings of physical examination, laboratory testing, and skin biopsy were consistent with new-onset scleroderma.

Combination therapy with oral prednisolone 20 mg/day, hydroxychloroquine 400 mg/day, methotrexate 7.5 mg/week, and folic acid 5mg/week was started.

Four weeks later, he showed dermal improvement (mRSS 20/51 points). Once clinical stability was achieved, the patient was discharged.

3. Results

Table 1. Autoimmune workup

Indirect immunofluorescence ANA	**Positive, 1:1280, nuclear fine speckled**
Ac.Anti- SSA/Ro60	Positive
Ac.Anti-SSB/La	Negative
A.Anti-Ro-52	Negative
Ac.Anti-CCP	Negative
Ac.Anti-dsDNA	Negative
Ac.Anti-Histone	Negative
Ac.Anti-Centromere	Negative
Ac.Anti-Scl 70	Negative
Ac.Anti-RNA Polimerase III	Negative
Ac.Anti-Smd	Negative
Ac.Anti-U1RNP	Negative
Ac.Anti-PM-Scl	Negative
Ac.Anti-Jo	Negative
Ac. Anti-Rib-P	Negative
ANCA	Negative
Antiphospholipid antibodies	Negative
Lupus anticoagulant	Negative

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Table 2. Anatomic-pathology report.

Anatomic-pathology report
It is observed under an epidermis without significant alterations, marked condensation, and thickening of the collagen fibers of the superficial and deep dermis. There is horizontalization of the collagen fibers and reduction of the interstitial space as well as of the perisudoriferous adipose tissue. The changes described are more marked in the middle and deep dermis. Conclusion: The set is scleroderma.

4. Discussion

Throughout history, vaccination has proven to be beneficial in the management of public health emergencies. Despite their high level of safety and efficacy, no vaccine is completely free of risk or adverse reaction [2,3,11]. Literature shows us examples of the association between vaccines and immune-mediated-disease. For example, Guillain-Barré syndrome following Influenza and Varicella-zoster, systemic lupus erythematosus after papilloma vaccine, morphea profunda after diphtheria-tetanus-pertussis vaccination, multiple inflammatory phenomena (uveitis, vasculitis, and myositis) after MMR vaccine, [2,11]. In summary, worldwide COVID-19 immunization, due to the COVID-19 pandemic, once more reminds us of the rare association between vaccines and the potential development of autoimmune disease [3,11,12]. For instance, new-onset IMD manifestations, such as systemic sclerosis, following COVID-19 vaccination and other relapse autoimmune diseases have been reported, most of them related to the mucocutaneous system [4,8,12,13].

It has been proposed that the mRNA COVID-19 vaccine may be a potential trigger or accelerator of an underlying autoimmune disease via two modes of action. Firstly, this could include molecular mimicry, triggering the cascade and perpetuation of the immune response, potentially inducing new-onset IMD through similarities between the vaccine components and human proteins [3,6,11,12]. Therefore, the inoculation may lead to the formation of cross-reactive antibodies, consequently responsible for the new onset of IMD [12,14]. Secondly, the mRNA vaccine is composed of mRNA encapsulated in lipid nanoparticles, and they are thought to cause a powerful immune response [12,15]. It has been shown, that both hypotheses can only occur in genetically predisposed patients, as evidenced by the epigenetic mechanism of underlying autoimmune diseases [13,16].

Herein, we present a case of rapid progressive new-onset systemic sclerosis (SSc) following mRNA COVID-19 vaccination. We cannot overlook the temporal association between the two phenomena. Because, days after his COVID-19 vaccination, our patient presented deep venous thrombosis, one of the well-known complications documented during SARS-CoV-2 infection or after COVID-19 vaccination [17,18]. We believe that the state of hypercoagulability of our patient, as well as the new onset of skin manifestations, resulted in a severe inflammatory response following COVID-19 vaccination.

Though its pathogenesis is not fully understood, SSc is the most commonly described IMD and cutaneous manifestation after COVID-19 vaccination, followed by dermatomyositis [7]. Like, other case reports found in the literature, we hypothesized that our patient showed cutaneous symptoms compatible with diffuse systemic sclerosis, because of the IMD within a plausible time frame between his only COVID-19 vaccination and the new onset of cutaneous symptoms [4,8,12,13].

According to Watad et al. (2021, p. 8-16) and Nguyen et al. (2022; p. e238), most of the patients who developed post-vaccine symptoms had pre-existing autoimmune disease; most of them flares. On the contrary, new diagnosis of IMD disease following COVID-19 vaccination was uncommon [4,7]. Our patient had no history of previous IMD, which means it is a rare phenomenon for those with no IMD and the COVID-19 vaccine is largely a safe vaccine.

Regarding to the AC/EULAR systemic sclerosis classification, our patient scored 11≥9 points consistent with the diagnosis (puffy fingers, sclerodactyly, digital tip ulcers, Raynaud´s phenomenon; abnormal nail fold capillaries). Besides this, he showed a persistently high level of antinuclear antibodies despite the absence of SSc-related autoantibodies (anti-Scl-70, anti-centromere, anti-RNA polymerase III) [10,14]. We hypothesized that the absent SSc-related autoantibodies could constitute a distinct subset of SSc. The score obtained using the ACR/EULAR classification system was sufficient

evidence to diagnose systemic sclerosis of the aforementioned patient, and furthermore, the skin biopsy results provided confirmatory diagnostic data.

5. Conclusions

Our case suggests a potential relationship between the mRNA COVID-19 vaccine and new-onset autoimmune diseases. Even though vaccinations against COVID-19 are proven to be effective and safe, there are genuine concerns about vaccine-induced adverse effects. However, the benefit of vaccination outweighs its potential side effects as evidenced by the thousands of millions of lives that have been saved worldwide since the emergence of COVID-19, whilst rarely new-onset autoimmune diseases have been reported. In conclusion, physicians should be aware of the potential association between the COVID-19 vaccine and new-onset skin symptoms.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Origin of SARS-CoV-2. World Health Organization (2020). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/origins-of-the-virus.
2. Ishay Y, Kenig A, Tsemach-Toren T, Amer R, Rubin L, Hershkovitz Y, Kharouf F. Autoimmune phenomena following SARS-CoV-2 vaccination. Int Immunopharmacol. 2021 Oct;99:107970. doi: 10.1016/j.intimp.2021.107970. Epub 2021 Jul 10.
3. Guo M, Liu X, Chen X, Li Q. Insights into new-onset autoimmune diseases after COVID-19 vaccination. Autoimmun Rev. 2023 Jul;22(7):103340. doi: 10.1016/j.autrev.2023.103340. Epub 2023 Apr 17.
4. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N, Haddad A, Elias M, Zisman D, Naffaa ME, Brodavka M, Cohen Y, Abu-Much A, Abu Elhija M, Bridgewood C, Langevitz P, McLorinan J, Bragazzi NL, Marzo-Ortega H, Lidar M, Calabrese C, Calabrese L, Vital E, Shoenfeld Y, Amital H, McGonagle D. 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. doi: 10.3390/vaccines9050435.
5. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modeling study. Lancet Infect Dis. 2022 Sep;22(9):1293-1302. doi: 10.1016/S1473-3099(22)00320-6.
6. Segal, Y., Shoenfeld, Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune cross-reaction. Cell Mol Immunol 15, 586–594 (2018). doi.org/10.1038/cmi.2017.151.
7. Nguyen B, Lalama MJ, Gamret AC, Elman SA. Cutaneous symptoms of connective tissue diseases after COVID-19 vaccination: a systematic review. Int J Dermatol. 2022 Jul;61(7): e238-e241. doi: 10.1111/ijd.16293.
8. Alhayaza R, Alhayaza G, Algarni A, Alhumidi A, AlHarithy R. Generalized morphea following COVID-19 vaccine: Case report and literature review. Clin Case Rep. 2023 Mar 30;11(4):e7133. doi: 10.1002/ccr3.7133. PMID: 37006851; PMCID: PMC10062313.
9. Kowalska-Kępczyńska A. Systemic Scleroderma-Definition, Clinical Picture, and Laboratory Diagnostics. J Clin Med. 2022 Apr 20;11(9):2299. doi: 10.3390/jcm11092299.
10. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Csuka ME, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J, Pope JE. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013 Nov;65(11):2737-47. doi: 10.1002/art.38098.

11. Olivieri B, Betterle C, Zanoni G. Vaccinations and Autoimmune Diseases. Vaccines. 2021; 9(8):815. doi.org/10.3390/vaccines9080815.
12. Sprow G, Dan J, Abbott J, Jiang A, Diaz D, Vazquez T, Kodali N, Werth VP. Sclerotic skin disease development following COVID-19 vaccination. JAAD Case Rep. 2022 Apr;22:74-77. doi: 10.1016/j.jdcr.2022.02.008.
13. Cole A, Thomas R, Goldman N, Howell K, Chakravarty K, Denton CP, Ong VH. Diffuse cutaneous systemic sclerosis following SARS-Co V-2 vaccination. J Autoimmun. 2022 Apr;128:102812. doi: 10.1016/j.jaut.2022.102812.
14. Fineschi S. Front. Immunol Case Rep June 2021. Systemic Sclerosis After Covid-19 Infection. Sec. Autoimmune and Autoinflammatory Disorders. Volume 12 - 2021 | doi.org/10.3389/fimmu.2021.686699.
15. Kondo M, Murakawa Y, Honda M, Moriyama M, Yoshioka Y. A flare of systemic sclerosis potentially triggered by anti-SARS-CoV-2 mRNA vaccination. Rheumatology Advances in Practice, Volume 6, Issue 3, 2022, rkac103, doi.org/10.1093/rap/rkac103.
16. Mazzone R, Zwerge C, Artico M, Taurone S, Ralli M, Greco A, Mai A. The emerging role of epigenetics in human autoimmune disordes. Clinical Epigenetics (2019);11:34. doi.org/10.1186/s13148-019-0632-2.
17. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020 Oct;194:101-115. doi: 10.1016/j.thromres.2020.06.029.
18. Campello E, Bulato C, Simion C, Spiezia L, Radu CM, Gavasso S, Sartorello F, Saggiorato G, Zerbinati P, Fadin M, Tormene D, Simioni P. Assessing Clinically Meaningful Hypercoagulability after COVID-19 Vaccination: A Longitudinal Study. Thromb Haemost. 2022 Aug;122(8):1352-1360. doi: 10.1055/a-1788-5206.