SKIN

Clinical Management Recommendations

Mixed Connective Tissue Disease Onset in the Setting of COVID Vaccination - Case Report and Recommendations

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ABSTRACT

Background: As of 2024, the COVID-19 pandemic has infected over 700 million people resulting in over 7 million deaths worldwide. The vaccination has had significant controversy, partially implicated through a number of reported adverse events. Previous studies have suggested that vaccines can trigger autoimmune disease, and the COVID-19 vaccine has been no exception to this. This study presents a case report and literature review exploring the potential link between the COVID-19 vaccination and autoimmune reactions.
Case Report: We present a previously healthy 28-year-old male who developed a diffuse pruritic rash two weeks after receiving a booster Moderna vaccine for COVID-19. The patient, with a history of hypothyroidism and positive antinuclear antibody (ANA), exhibited pink erythematous, minimally scaly papules and plaques, predominantly on his hands, forearms, wrists, face, neck, and left shoulder. Subsequent workup revealed elevated anti-ribonucleoprotein (RNP) levels, leading to a diagnosis of mixed connective tissue disease (MCTD). This paper also features a review on cutaneous and systemic autoimmune conditions thought to be triggered by COVID-19 vaccines. Potential mechanisms are explored including molecular mimicry, bystander activation, and epitope spreading. Findings indicate that cutaneous reactions like dermatitis, urticaria, and morbilliform rashes are relatively common and can predispose more severe autoimmune conditions.
Conclusion: Implications of this study are the importance for medical professionals and patients to be wary of autoimmune reactions post-vaccination. Early recognition and management of these reactions is critical in ensuring patient safety, improving vaccination protocols, and maintaining public trust in vaccination programs and efforts.

INTRODUCTION

As of 2024 the COVID-19 pandemic has infected over 700 million people resulting in over 7 million deaths worldwide.[1] As of March 2023, there were 183 vaccines in clinical development and a further 199 in preclinical development.[2] The Moderna COVID vaccine also known as the mRNA-1273 vaccine is a messenger RNA (mRNA) based vaccine and has been administered in the United States since December of 2020.[3] Various side effects have been reported within seven days of receiving the vaccine with most people experiencing mild to moderate effects. Common side effects include chills, difficulty in moving, headache, joint pain, nausea, and vomiting.[4] A smaller number of people

reported more severe side effects that required hospitalization.[5]

Previous studies have suggested that vaccines can trigger autoimmunity and autoimmune diseases. The COVID-19 vaccine has been no exception to this concept as reports have emerged suggesting an association between COVID-19 vaccination and the development of rare autoimmune diseases including autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis.[6] The mechanisms through which this can occur are thought to be molecular mimicry, bystander activation, anti-idiotypic network, and epitope spreading.[6] This concept however has been formulated on the basis of anecdotal case reports with the existing studies being only observational.[7] There's a limited number of cases of autoimmune pathology that have been firmly associated with particular vaccines. For example, the 1976-1977 vaccination campaign against swine influenza was associated with a form of Guillain-Barre syndrome. Similarly, idiopathic thrombocytopenia may arise after administration of the measles-mumps-rubella vaccine.[7] In this case, we report a 28-year-old male developing a severe autoimmune disease in the setting of COVID vaccination, mixed connective tissue disease.

CASE PRESENTATION

A 28-year-old male with a past medical history of hypothyroidism, Raynaud's, and positive antinuclear antibody (ANA) presented to an outpatient dermatology clinic with a diffuse pruritic rash two weeks after receiving his first booster of the Moderna COVID vaccine series. The patient had no prior autoimmune diagnosis and denied any prior manifestations of autoimmune disease, other than an occasional Raynaud's flare. He denied any other accompanying symptoms such as fever or chills, as well as any similar rashes to prior doses of the Moderna COVID vaccine.

The rash consisted of pink erythematous minimally scaly papules, thin plaques and patches involving the left and right dorsal hands, forearms, wrists, face, neck, and left shoulder (**Figures 1, 2, 3, 4**). The remainder of the patient's skin including the bilateral lower extremities, the eyelids, conjunctiva, and oral mucosa was clear. The patient denied any similar rashes in the past.

The patient declined any allergies to medications, food, or environmental triggers. He did not endorse any notable contact allergen exposures, including to soaps, lotions, and cosmetic products. The patient also claimed no significant family or past surgical history. The patient was on Armour Thyroid for hypothyroidism and testosterone for low levels since age eighteen. The patient was started on cetirizine 10 mg once daily for the rash with minimal improvement noted.

Autoimmune workup for the rash was notable for an elevated anti-RNP and as the patient's past medical history included Raynaud's phenomenon and ANA positivity for ten years, the patient was diagnosed with mixed connective tissue disease (MCTD). Autoimmune conditions can often have an indolent course, where symptoms progressively develop and worsen. MCTD is an autoimmune overlap syndrome that can consist of the following three connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis. The patient did not follow up and was not amenable to completing a thorough autoimmune workup with rheumatology.

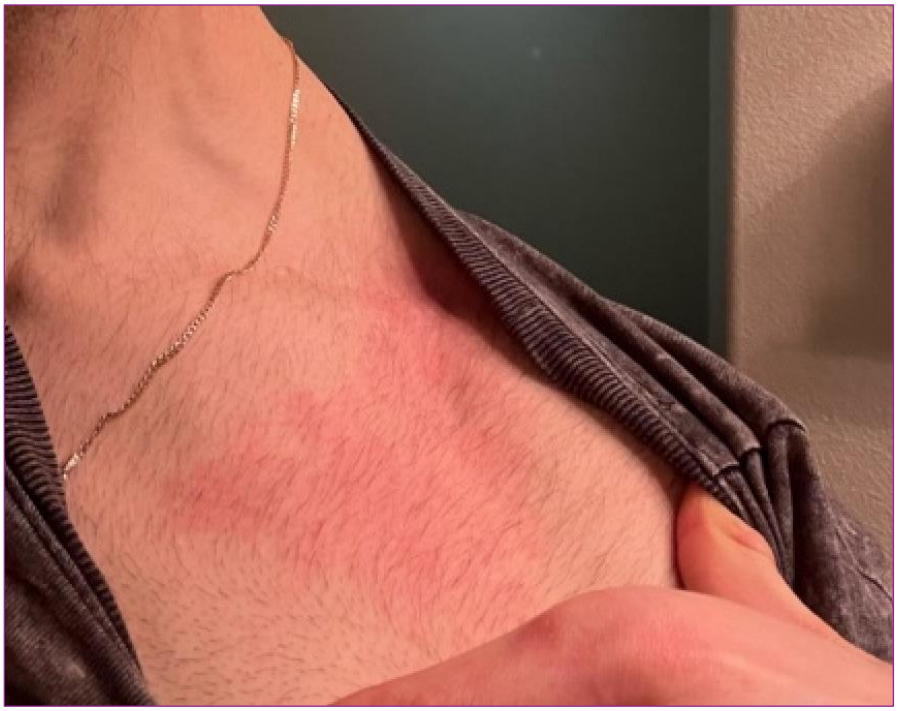

Figure 1. Pink erythematous minimally scaly papules, thin plaques and patches involving the left shoulder.

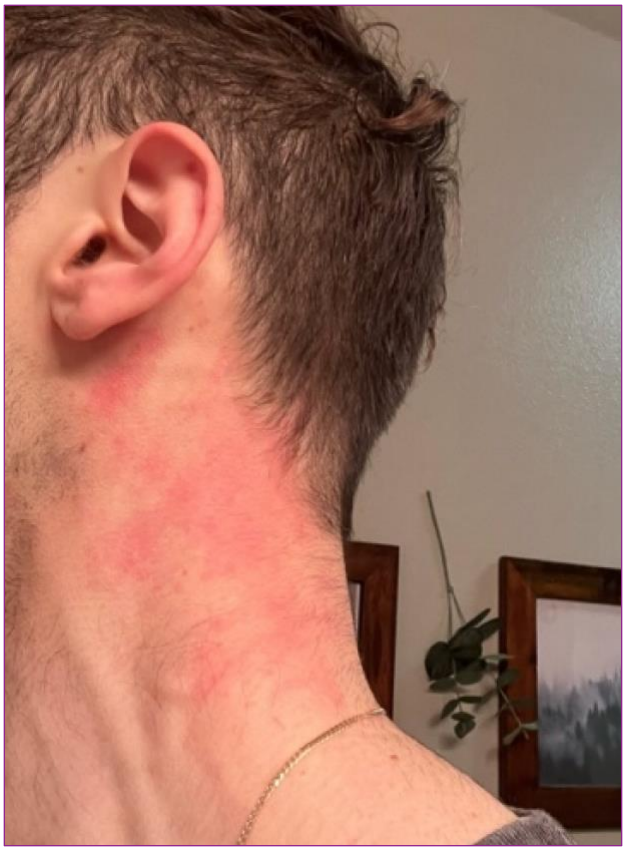

Figure 2. Pink erythematous minimally scaly papules, thin plaques and patches involving the left neck.

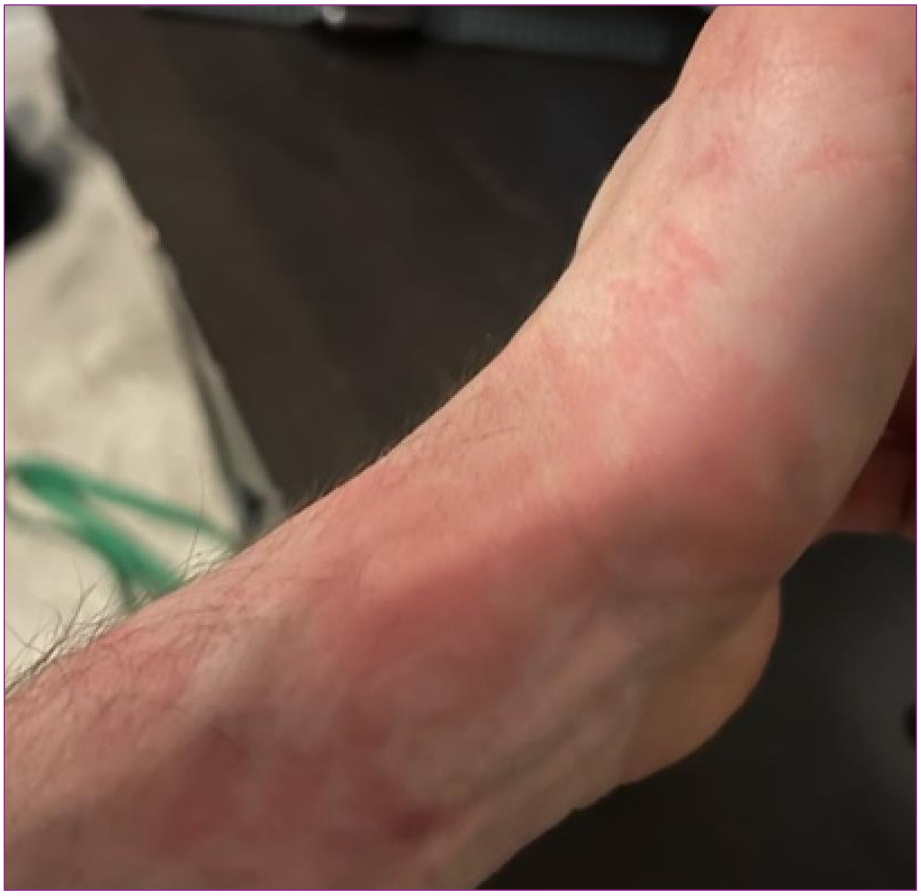

Figure 3. Pink erythematous minimally scaly papules, thin plaques and patches involving the left wrist.

Figure 4. Pink erythematous minimally scaly papules, thin plaques and patches involving the right wrist.

DISCUSSION

Overview of COVID-19 Vaccines and Autoimmune Reactions

The global rollout of COVID-19 vaccines has been crucial in managing the pandemic. However, there have been reports of autoimmune reactions post-vaccination, including skin reactions such as dermatitis. In patients with autoimmune conditions like MCTD, these reactions can be more complex and severe.[8,9]

Review of the Literature

Various studies have documented autoimmune reactions, including cutaneous reactions, following COVID-19 vaccination. Cutaneous reactions post-vaccination are not a new concept; immediate reactions to vaccines are generally caused by ingredients such as egg proteins, gelatin, and formaldehyde.[10] Specifically, with COVID-19 vaccines, polyethylene glycols (PEGs) and cross-reactive polysorbate 80 have been linked to immediate allergic reactions such as urticaria, angioedema, and even anaphylaxis.[10] Based on a review of 414 patient records, the most common cutaneous reactions for the Moderna vaccine were delayed large local reactions, local injection site reactions, urticaria, morbilliform, and erythromelalgia.[11] For the Pfizer vaccine, the same review indicated that the most common cutaneous manifestations were urticaria, local injection site reactions, and morbilliform rashes.[11]

Molecular mimicry has been identified as a potential trigger for autoimmune diseases post-vaccination. This can be seen with how the COVID-19 virus SARS-CoV-2 spike protein shares genetic similarities with human proteins. In five patients who received the SARS-CoV-2 vaccination, subacute thyroiditis or Graves' disease developed, phenomena categorized under autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[10] Thrombotic and vasculitic complications have also been documented, including the reactivation of leukocytoclastic vasculitis and the emergence of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). These conditions, resembling heparin-induced thrombocytopenia but occurring without prior heparin exposure, were noted following virus vector-based vaccinations. One study reported that by the end of February 2021, a new syndrome characterized by cerebral venous sinus thrombosis and/or splanchnic venous thrombosis combined with thrombocytopenia was observed in several patients.[10] Another study described five patients who developed venous thrombosis and thrombocytopenia between seven and ten days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine.[12] These patients had high titers of antibodies to platelet factor 4-polyanion complexes, similar to heparin-induced thrombocytopenia, but without prior heparin exposure, leading to the diagnosis of vaccine-induced thrombotic thrombocytopenia (VITT).

Neurological autoimmune diseases have been another significant concern, with 21 cases reported shortly after SARS-CoV-2 vaccinations. These cases included new-onset conditions as well as flares of existing diseases. One study detailed that these neurological conditions encompassed VITT with cerebral venous sinus thrombosis, central nervous system demyelinating diseases, inflammatory peripheral neuropathies, myositis, myasthenia, limbic encephalitis, and giant cell arteritis.[7] The median time to diagnosis was 11 days post-vaccination, with a predominance in female

patients. A systematic review published in December 2021 identified 276 cases of new-onset autoimmune syndromes post-COVID-19 vaccination, with Guillain-Barré syndrome being the most common (151 cases), followed by VITT (93 cases). Less commonly, the review reported the onset of conditions including autoimmune liver diseases, immune thrombocytopenic purpura, IgA nephropathy, autoimmune polyarthritis, rheumatoid arthritis, Graves' disease, and systemic lupus erythematosus.[7] These findings underscore the diverse and sometimes severe autoimmune responses that can occur following COVID-19 vaccination.

Case studies have detailed specific instances of leukocytoclastic vasculitis and other autoimmune syndromes, emphasizing the need for continued vigilance. For example, a study by Oskay et al. (2021) described a case of a 77-year-old male developing acute eruptive skin disorder, bloody diarrhea, and abdominal pain following the third dose of the CoronaVac vaccine.[13] The patient's dermatologic examination revealed diffuse palpable, tender, non-blanching violaceous macules and bullous hemorrhagic lesions, with a skin biopsy confirming small-vessel leukocytoclastic vasculitis. Similarly, another study reported a 62-year-old Asian female presenting with bilateral lower-limb non-blanching petechial rash, headache, myalgia, and arthralgias seven days after receiving the first dose of the ChAdOx1 vaccine.[14] Elevated C-reactive protein (CRP) and positive ANA were noted, with skin biopsy findings consistent with leukocytoclastic vasculitis.

Multicenter studies have provided further insight into disease flares post-vaccination in patients with autoimmune rheumatic diseases. For instance, data from Italy and China highlighted a manageable frequency of such events, underscoring the overall tolerability of COVID-19 vaccines in these populations.[15] In Italy, a study involving 71 patients with a previous diagnosis of cryoglobulinemia found that 9.5% experienced vaccination-related flares, with flares being more frequent in patients with essential mixed cryoglobulinemia compared to those with hepatitis C virus-cured mixed cryoglobulinemia or mixed cryoglobulinemia complicated by low-grade non-Hodgkin lymphoma. In China, a study of 1507 patients with autoimmune rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis, Behcet's disease, psoriatic arthritis/psoriasis, and primary Sjögren's syndrome, reported a 10.5% flare rate post-vaccination, with no fatal flares, indicating excellent tolerability of inactivated COVID-19 vaccines in this population. Additionally, the EULAR-supported study reported that 37% of patients experienced vaccine-related adverse events, and 4.4% reported disease flares.[15] Although these studies found there to be increased flares, these flares were shown to still be overwhelmingly tolerable.

The exact mechanisms behind these autoimmune responses remain under investigation. Proposed theories include the role of age-associated B cells (ABC) and the activation of Toll-like receptors (TLR7/8 and TLR9), which may trigger autoreactive antibody-secreting plasmablasts. ABCs, characterized by generating immunoglobulin G and increasing antigen presentation to T cells, are expanded with age and in autoimmune diseases like systemic lupus erythematosus. The activation of TLR7 and TLR9, used as adjuvants in mRNA/DNA SARS-CoV-2 vaccines, can lead to the production of interferon I, essential for the development of autoimmune diseases. Other candidates include anti-spike antibodies stimulating anti-idiotype antibodies and lipid

nanoparticles in the vaccine formulation. Understanding these mechanisms is crucial for developing strategies to mitigate such risks while maintaining the benefits of vaccination.

Proposed Theories

Molecular Mimicry:

Molecular mimicry is a well-established mechanism in which structural similarities between pathogen antigens and host tissues lead to an immune response that inadvertently targets the host's own tissues. This mechanism has been suggested in the context of COVID-19 vaccines. For instance, antibodies generated against the SARS-CoV-2 spike protein may cross-react with similar human proteins, potentially triggering autoimmune reactions. Studies have highlighted that such mimicry might involve interleukin-7 and alveolar surfactant proteins, suggesting that individuals with genetic predispositions could experience exacerbated autoimmune responses post-vaccination.[16,17]

Bystander Activation:

Bystander activation refers to the activation of autoreactive immune cells that were not initially targeted by the pathogen. This can occur due to the release of cytokines and other inflammatory signals during an immune response, leading to a broader activation of the immune system, including autoreactive cells. This mechanism has been implicated in vaccine-induced autoimmunity as the inflammatory environment post-vaccination could activate these dormant autoreactive cells, leading to conditions such as autoimmune hepatitis or dermatitis.[17,18]

Epitope Spreading:

Epitope spreading is a process where the immune response initially targets a specific antigen but gradually extends to other antigens, including self-antigens. This can occur when tissue damage releases a variety of antigens that the immune system then targets. This theory has been proposed to explain the prolonged and chronic nature of some autoimmune conditions following vaccination, as initial immune activation could lead to a cascading effect where multiple self-antigens become targets of the immune system.[17]

Pre-existing Autoimmune Predisposition:

Patients with pre-existing autoimmune diseases, such as MCTD, may have an inherently dysregulated immune system that makes them more susceptible to developing vaccine-induced autoimmunity. The immunogenic components of the vaccine might act as triggers in these patients.[19]

Clinical Management and Recommendations

Monitoring and Early Detection:

Regular monitoring of patients with MCTD before and after COVID-19 vaccination is crucial. Early detection of symptoms can allow for prompt management and prevent severe complications.

Adjusting Immunosuppressive Therapies:

For patients experiencing severe reactions, adjustments in immunosuppressive therapy might be necessary. This includes temporarily increasing doses of corticosteroids or other immunosuppressive agents to control the autoimmune response.

Patient Education:

Educating patients about the potential risks and symptoms of vaccine-induced reactions is essential. Patients should be encouraged to report any new or worsening symptoms immediately. Foster a relationship with patients to increase patient comfort in bringing up concerns early on.

Vaccination Benefits vs. Risks:

Despite the potential for autoimmune reactions, the benefits of COVID-19 vaccination in preventing severe disease generally outweigh the risks, especially in patients with autoimmune conditions who are at higher risk for severe COVID-19 complications.

Next Steps:

Long-term studies are needed to better understand the incidence and mechanisms of vaccine-induced autoimmune reactions. Tracking patients over time will provide valuable insights into the natural history, progression, and management of these reactions. Research into the molecular mechanisms underlying these reactions can help in developing targeted therapies to prevent and manage vaccine-induced autoimmunity. Expanding registries to include detailed data on autoimmune reactions post-vaccination will help in identifying patterns and risk factors. This data can guide clinical practice and patient management strategies, and better individualize care to patients. In conclusion, while COVID-19 vaccine-induced dermatitis and other autoimmune reactions in MCTD patients are concerning, they remain rare. Continued research, vigilant monitoring, and tailored clinical management are essential to optimizing outcomes for our patients.

CONCLUSION

Millions of individuals across the world are receiving COVID vaccines to protect themselves and members of their community, and it is of utmost importance that we continue to investigate adverse events. Although of low incidence, these rare effects have the ability to impact large numbers of people within both healthy and immunocompromised populations. It is critical that we examine and document adverse events in a rigorous manner, to ensure safe vaccine delivery and reassure the public about vaccine safety overall. While the benefits of COVID-19 vaccination may outweigh the risks, especially in preventing severe disease and mortality, it is essential to continue monitoring and researching vaccine-induced autoimmunity to ensure the safety and efficacy of vaccination programs.

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