Review Article

Vitiligo after COVID-19 Vaccination: A Literature Review

Muhammad Mahbub ul Alam [1], Muhammad Shahidul Islam [2]

Abstract

The COVID-19 pandemic posed unprecedented challenges to global health systems, leading to the urgent development and deployment of vaccines to mitigate the spread of the virus and reduce morbidity and mortality. Vaccination programs were instrumental in controlling the pandemic, but they also sparked discussions about potential adverse events, particularly those related to autoimmune disorders. Vitiligo is a chronic autoimmune skin condition characterized by the destruction of melanocytes, resulting in the loss of skin pigmentation. While the exact etiology of vitiligo remained unclear, it is believed to involve a complex interplay of genetic, environmental, and immunological factors. Emerging reports raised questions about the potential association between COVID-19 vaccination and the onset or exacerbation of autoimmune conditions like vitiligo. This led to growing interest in understanding whether COVID-19 vaccines, which elicited robust immune responses, could potentially trigger or worsen vitiligo in predisposed individuals. Addressing these concerns was critical to ensuring vaccine confidence and providing comprehensive guidance to patients, particularly those with pre-existing autoimmune conditions or a family history of vitiligo. This article aimed to explore the relationship between COVID-19 vaccination and vitiligo, examining the evidence available at the time and its implications for clinical practice.

Keywords: *Vitiligo, COVID-19, Pandemic, Vaccination, Review.*

Date of received: *11.07.2024*

Date of acceptance: *29.09.2024*

DOI: https://doi.org/10.3329/kyamcj.v15i03.79712

KYAMC Journal. 2024; 15(03): 144-151.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), produced a worldwide pandemic.[1] The World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC) on 30 January 2020, and assessed the outbreak as having become a pandemic on 11 March. The pandemic continued till 05 May 2023. Clinical manifestations of COVID-19 infection are complex and diverse, and the whole systems may be affected, including the skin. Vitiligo is an acquired chronic depigmenting disorder of the skin resulting from selective destruction of melanocytes, and autoimmune abnormality is one of the main causes of vitiligo. Until now, there had been some case reports of new vitiligo or deterioration of original vitiligo after COVID-19 vaccination and infection, but largescale epidemiological data are lacking. In a recent study, the authors reported active vitiligo vulgaris following the administration of the Oxford-AstraZeneca (AZD1222) vaccine against SARS-CoV-2. They believe that immune activation during SARS-CoV-2 infection may increase vitiligo disease activity.[2] In another study, 15 cases (88.2%) had new-onset or worsening vitiligo after COVID-19 vaccination and two cases (11.8%) developed vitiligo following primary COVID-19 infection. Patients who have comorbid autoimmune diseases were more likely to develop vitiligo.[3]

Vaccinations was the most essential strategies for controlling and preventing the pandemic.[4] Various cutaneous adverse effects have been reported in COVID19 vaccinated patients. COVID19 vaccinations can cause a cytokine pathway imbalance, which can lead to autoimmunity and auto inflammation.[5]
Vitiligo is a pigmentary disorder that is manifested as the development of pale depigmented patches over any areas of the skin or mucous membrane. It affects 0.5%–2% of the world population. Vitiligo is classified as localized (segmental) or generalized (non-segmental) types.[6] This condition occurs as a result of progressive destruction of skin melanocytes. There are different opinions about the etiopathogenesis of vitiligo; however, no exact explanation has been found. Nevertheless, T-cell autoimmunity and prolonged cytokine release are believed to play an important role.[7]
Vitiligo is more common in the black people, those with genetic predisposition and those with psychological distress. Other risk factors include sunburn, cutaneous trauma, use of some chemicals such as phenolic compounds, pregnancy, and autoimmunity.[8]

01. Professor and HOD of Transfusion Medicine, Khwaja Yunus Ali Medical College and Hospital, Sirajgonj, Bangladesh.
02. Professor, Department of Transfusion Medicine, Khwaja Yunus Ali Medical College and Hospital, Sirajgonj, Bangladesh.

Corresponding author: Muhammad Mahbub ul Alam, Professor and HOD of Transfusion Medicine, Khwaja Yunus Ali Medical College and Hospital, Sirajgonj, Bangladesh. **Cell:** +880 1552-345448, **E-mail:** dr.mahbub19@gmail.com

Materials and Methods

This literature review inspects the relationship between vitiligo and COVID-19 vaccination. Relevant studies were identified through explorations in PubMed, Scopus, Web of Science, and Google Scholar, covering the period from December 2020 to December 2024. Keywords included 'Vitiligo,' 'COVID-19 vaccine,' and related terms. Inclusion criteria focused on articles discussing vitiligo onset or exacerbation after vaccination, while irrelevant or non-primary data studies were excluded. Data on patient demographics, vaccine type, timing, and clinical outcomes were extracted and analyzed. A narrative fusion was used to condense findings, emphasizing patterns and differences across cases.

Literature Review

Coronavirus disease 2019 (COVID-19) has given rise to several new-onset or exacerbated dermatologic disorders.[9] Moreover, medications used in the settings of SARS-CoV2 infection, as well as various types of COVID vaccine, have also been followed by cutaneous adverse events.[10,11] The incidence and prevalence of vitiligo have increased considerably since the beginning of the COVID-19 pandemic. The reason could be the viral infection itself, medications used for the treatment, and vaccines introduced to prevent the disease as well as psychologic distress of pandemics.[12,13] There are many aspects on this issue that are to be discussed in this article.

COVID vaccine-related vitiligo: since vitiligo is a very common pigmentary disorder throughout the world, and because vaccination program is held universally with expectable adverse events, the onset of vitiligo after SARS-CoV-2 vaccination can be a mere incidence. Nonetheless, the temporal relationship between vaccination and development of vitiligo and the reports of various autoimmune phenomena following vaccination could raise the suspicion of the causal association between SARSCoV-2 vaccination and vitiligo.[14]

Besides the wide range of dermatologic manifestations and complications following SARS-CoV2 infection, COVID-19 vaccines have also given rise to a variety of cutaneous reactions and disorders.[15,16] Many post-COVID vaccine cutaneous reactions are mild and temporary and do not cause great morbidity or mortality; nevertheless, some adverse events such as vitiligo pose significant concerns due to their disfigurement and the subsequent stigma and psychological burden. The incidence of COVID vaccine-related cases of vitiligo has been quite higher than the one following SARS-CoV-2 infection. Several cases of hypo pigmentations have been reported after receiving COVID vaccines, resulting from cutaneous reactions such as toxic epidermal necrolysis (TEN), subacute cutaneous lupus erythematosus (SCLE), and pityriasis lichenoides.[17,18] However, vitiligo that is presented as skin depigmentation has also been common after SARS-CoV-2 vaccination including mRNA-1273 (Moderna) vaccine and mRNA BNT162/Comirnaty vaccine (Pfizer-BioNTech).[19,20]

Most cases of new-onset COVID vaccine-related vitiligo have been reported within 1 week following receiving the first vaccine dose, with progression after the second dose.[21,22] The probability of developing COVID vaccine-related vitiligo is higher in patients with pre-existing autoimmune diseases, such as ulcerative colitis[23] which might reflect the advantage of maintaining a minimal treatment in those cases with an autoimmune background to prevent development of another autoimmune phenomenon following COVID vaccination. Since the COVID vaccination will continue after cession of pandemic, a rigid surveillance for development of new autoimmune disorders including vitiligo in genetically predisposed patients and early treatment of them (but not too early which interfere with immunologic body response to vaccination) should be strongly considered by clinicians all over the world. As a matter of fact, the immune system is stimulated by vaccines to produce antibodies. Some of these antibodies harm the host, rather than having benefit as they may trigger autoimmune disorders in individuals with genetic susceptibility. The emergence of many autoimmune diseases such as multiple sclerosis, Guillain Barre syndrome, and immune thrombocytopenic purpura following COVID vaccination are some examples.[24,25]

Molecular mimicry and bystander activation are the most probable pathophysiologic mechanisms proposed for vaccine induced autoimmunity. However, vaccine adjuvants may play a role in bringing about autoimmune phenomena.[26,27] On the other hand, upregulation of Th1 response by the vaccines leads to an increase in inflammatory cytokines such as IL-2, IFN-γ, and TNF-α, thereby predisposing to skin autoimmune disorders including vitiligo.[28] Moreover, epitope spreading, polyclonal activation of B cells, and cytokine production might be other explanations for vaccine induced auto reactions which lead to autoimmune skin disorders.[29] Melanocytes can be affected like any other body component in vaccine-induced autoimmune phenomena, and since vitiligo results from destruction of melanocytes by T cells immune response, the robust cellmediated immune response induced by vaccines can give rise to the onset of vitiligo.[30,31] The secondary trauma imposed by vaccine injection can also be a trigger for vaccine induced vitiligo.[32]

In a study titled 'Sudden onset of vitiligo after COVID-19 vaccine', 314 patients with vitiligo participated among whom 47.5% were males, with an average age of 25.5±15.9 years and 266 (84.7%) patients received COVID-19 vaccination. About three fourth (70.3%) of the patients reported progression of vitiligo after vaccination, mostly within 3 months, 55.6% of the patients had disease progression after the second dose of vaccine, 270 patients experienced COVID-19 infection, and 30.7% of these patients had progression of vitiligo after infection, most of the progression occurred within 1–2 months. More than a half (68.2%) interrupted treatment. Analysis of the results indicated patients in active stage had a higher risk for vitiligo progression after COVID-19 infection and vaccination.[33]

The COVID-19 pandemic has swept the world, becoming the largest and most widespread public health event of this century. COVID-19 infection can cause damage to multiple organs throughout the body with complex and varied clinical presentations. Vaccination against COVID-19 is an important way to

prevent COVID-19 infection and reduce the percentage of severe cases in infected patients. Vitiligo is an acquired depigmentation skin disease. Autoimmune abnormalities play an important role in the pathogenesis of vitiligo. It is well-recognized that the skin-infiltration of melanocyte-specific CD8 + T cells mediates the progressive destruction of melanocytes and plays a key role in the pathogenesis of vitiligo.[34] There have been reports of vitiligo or vitiligo progression after COVID-19 vaccination or COVID-19 infection in some cases, but epidemiological investigations in large samples are lacking.

In a study the researchers investigated the correlation between COVID-19 vaccine and progression of vitiligo. Up to 70.3% of patients (187, 187/266) had disease progression after vaccination. Ahmed et al reported that a male had new- onset vitiligo after the administration of the first dose of the Oxford–Astra-Zeneca (AZD1222) vaccine.[35] Tsai et al conducted a systematic review and reported that 12 patients had new-onset vitiligo, while the other two had preexisting vitiligo that was exacerbated by COVID-19 vaccination.[36] Another study found that most patients (104, 55.6%) had disease progression within 3 months after the second dose. Patients who were in active stage (OR = 0.182, 95% CI: 0.099–0.336) had higher risk for further progression. Kaiqiao He et al described 35 patients had vitiligo progression within 1 month of vaccination, and 51.4% of these patients developed after the second dose of vaccination, which was consistent with our results.[37] COVID-19 vaccines require two partial vaccinations to achieve the highest possible immunity.[38] This may explain why most patients experience progression after the second dose of the vaccine. For those patients who were in active stage, delayed vaccination may prevent progression.

Up to 97% (182/187) of patients with vitiligo experienced disease progression after receiving inactivated vaccines, which may be related to the predominance of inactivated vaccines approved in China or similar to the survivor bias, in which patients with disease progression are more likely to go to the hospital. There is no clear explanation for the relationship between COVID-19 vaccination and disease progression, and we hypothesized an autoimmune link. The following are several hypotheses about the possible pathogenesis. First, it could be explained as molecular mimicry, which is a similarity between specific pathogenic elements contained in the vaccine or vaccine adjuvants and specific human proteins.[39] Moreover, vaccine components and adjuvants can induce potent innate immune responses that non-specifically activate self-reactive T and B cells. Through these mechanisms, vaccines stimulate the immune system to produce antibodies against viral proteins as well as unintended antibodies against melanocytes.[40]

COVID-19 infection has been documented to cause a variety of skin problems such as urticaria, bullous pemphigoid-like disease and psoriasis. Vitiligo or progression of vitiligo after COVID19 infection have also been reported. Pastukhova et. al. described a new onset of vitiligo postCOVID-19 infection.[41] Schmidt et al found a new onset of vitiligo post-COVID-19 infection and present a patient who developed both eruptive halo nevi and vitiligo after a confirmed COVID-19 infection.[42] In our study, 270 patients infected COVID-19, and 30.7% of them had progression of vitiligo. We found that patients in active stage (OR = 12.01, 95% CI: 5.54–26.04) had higher risk for vitiligo progression. And patients who interrupted treatment (OR = 1.707, 95% CI: 0.360–8.100) had higher risk for vitiligo progression, but no statistical significance. Xu et al conducted a retrospective study and determined treatment delays as the most important independent risk factor for disease progression and recurrence, and maintenance therapy (>2 years) as a protective factor against recurrence, during COVID-19 epidemic.[43] The following were possible causes of vitiligo progression due to COVID-19 infection. Firstly, COVID-19 disrupts immune tolerance, resulting in increased inflammation potentiated by increased interferon gamma (IFN-γ) signaling and consequent cytotoxic destruction of melanocytes.[44] Furthermore, Schmidt et al postulated a hyper stimulated CD8+ response and increased oxidative stress as catalysts.[45] Finally, based on the shift of the immune system in nonsegmental vitiligo toward adaptive type 1 (IFN-γ and CD8+T cells) and innate immune responses, immune activation during SARS-CoV-2 infection or COVID-19 disease may increase vitiligo disease activity.[46]

A 41year old man presented with a history of new onset light-coloured lesions on the fingertips of bilateral hands and palms, which developed 10 days after receiving the first dose of COVID 19 vaccination (COVAXIN), and the lesions progressed in number and size after receiving the second dose. There was a history of vitiligo in the mother. There was no history of frequent exposures to sanitizers or chemical and physical agents at the workplace or in the environment. His medical history for thyroid disease, autoimmune diseases, and pernicious anemia was unremarkable. No history of any topical or systemic treatment was found. General and systemic examinations were unremarkable. On examination, there were well demarcated depigmented macules over palms, fingertips, and nail folds [Figures- 1a]. Dermoscopy revealed white structureless areas with a glow and the absence of pigment network [Figure 1b]. Based on clinical and dermoscopic findings, a clinical diagnosis of vitiligo was made. The patient was screened for other autoimmune conditions: complete blood count, thyroglobulin, transglutaminase, and thyroid stimulating hormone, which were within normal ranges. In the absence of any additional risk factors, COVID 19 vaccination was identified as the most likely cause of vitiliginous skin changes. The patient was prescribed a potent topical corticosteroid. The patient is currently under follow up with no appearance of new lesions.

Vaccinations are generally safe with a low incidence of severe adverse reactions. Cutaneous reactions seen after COVID 19 vaccines are chilblain like lesions, pityriasis rosea like eruptions, local injection site reactions, morbilliform eruptions, urticaria, and erythromelalgia. These adverse effects are usually mild and self-limited.

As far as we know, only six cases of vitiligo associated with COVID 19 vaccination are reported in the literature and this is the first due to COVAXIN. Multiple case reports imply a temporal relationship between COVID 19 vaccination and the development of vitiligo like lesions, according to the literature [Table 1] [47-50] The first occurred 1 week after the dose

of Pfizer BioNtech COVID19 vaccine in a man without a family history of vitiligo who was suffering from ulcerative colitis in 2021.[4] All the case reports suggested that the vitiligo lesions appeared within 1–3 weeks post vaccination, which was consistent with our case [Table 1].

The pathophysiology leading to vitiligo after COVID 19 vaccination remains unclear, but several hypotheses exist. Several studies suggest that vaccine components can trigger multiple autoimmune diseases in individuals who are genetically susceptible. Possible pathogenic mechanisms include molecular mimicry and bystander activation. Molecular mimicry occurs when a genetically susceptible individual is vaccinated by the agent that carries antigens that are immunologically similar to host antigens. This leads to the activation of T or B cells. There is a breakdown of tolerance to self-antigens, and an immune response is directed towards host antigens. Bystander activation occurs when viral agents induce the release of sequestered self antigens or modify self antigens that activate antigen presenting cells, leading to the clonal expansion of self-reactive T and B cells.[51,52]

Vaccine components may trigger a strong innate immune response, resulting in nonspecific activation of cluster of differentiation (CD)4+ or CD8+ T cells, causing adverse drug reactions. Another possible mechanism is vaccine induced stimulation of plasmacytoid dendritic cells (pDCs) that secrete type 1 interferon (IFN 1).[53,54] IFN 1 production and pDC recruitment are an important step in vitiligo pathogenesis.[55,56] Through all these proposed mechanisms, the vaccine may stimulate the immune system to produce antibodies against severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) spike protein and incidentally against melanocytes, which may become unintentional targets for antibodies and immune cells newly produced by the vaccine. These hypotheses may be plausible because vitiligo involves the destruction of melanocytes by autoreactive CD8+ T cells and successful vaccination also involves an extensive CD8+ T cell response.

Clinicians should be aware of these autoimmune cutaneous adverse reactions to vaccinations. Such adverse reactions are modest and manageable and possess a low risk compared with the deadly outcome of COVID 19 infection; thus, patients need to be encouraged to continue receiving vaccinations. In conclusion, this is the first case of vitiligo reported to develop after COVAXIN vaccination. We present this case to add to the mounting literature regarding COVID 19 vaccination, which may assist clinicians regarding the spectrum of possible cutaneous manifestations. This may also assist others to be vigilant of the association between COVID 19 vaccination and vitiligo. Thus, further and extensive case studies are needed to demonstrate a causal relationship between COVID 19 vaccination and vitiligo.

Case presentation

Figure 1: (a): Well-demarcated depigmented macules over palms and fingertips on bilateral hands. (b): Dermoscopy revealed white structure less areas with a glow and the absence of pigment network (Heine NC2, 10x)

Table I: A literature review of previous case reports of vitiligo after COVID19 vaccination [4-7]

Author, Year	Age, Sex	COVID 19 vaccine	Onset of vitiligo	Sites of lesion	(Personal and family history of autoimmune disorders)
Aktas et al .[4] 2021	58, male	Pfizer BioNtech vaccine	One week after the first dose	Face	Patient had a history of ulcerative colitis
Kaminetsky et al.[5] 2021	61, female	Moderna (mRNA1273) vaccine	Several days after the first dose, and macules progressed after three days after the second dose	Anterior neck; generalized after the second dose	No predisposing factors
Ciccarese et al.[6] 2021	33, female	Pfizer BioNtech vaccine	One week after the first dose	Trunk, neck back	Father had vitiligo
Uğurer et al .[5] 2022	47, male	Pfizer BioNtech vaccine	One week after the first dose	Bilateral axilla, forearm	History of ankylosing spondylitis
Militello et al.[7] 2022	67, female	Moderna vaccine	Two weeks after the first dose	Bilateral dorsal hands	No predisposing factors
Bukhari et al .[4] 2022	13, female	Pfizer BioNtech vaccine	Three weeks after the first dose	Extremities and trunk	Father and paternal uncle had vitiligo

Case study

1. Vitiligo typically presents as a sporadic condition with genetic and autoimmune influences. While viral infection has been implicated as triggers for vitiligo, the role of COVID-19 vaccination in its onset remains underexplored. A recent study presents a unique case of sudden-onset vitiligo following the COVID-19 vaccination, along with a systematic review of existing literature to shed light on the potential link between vaccination and vitiligo development.

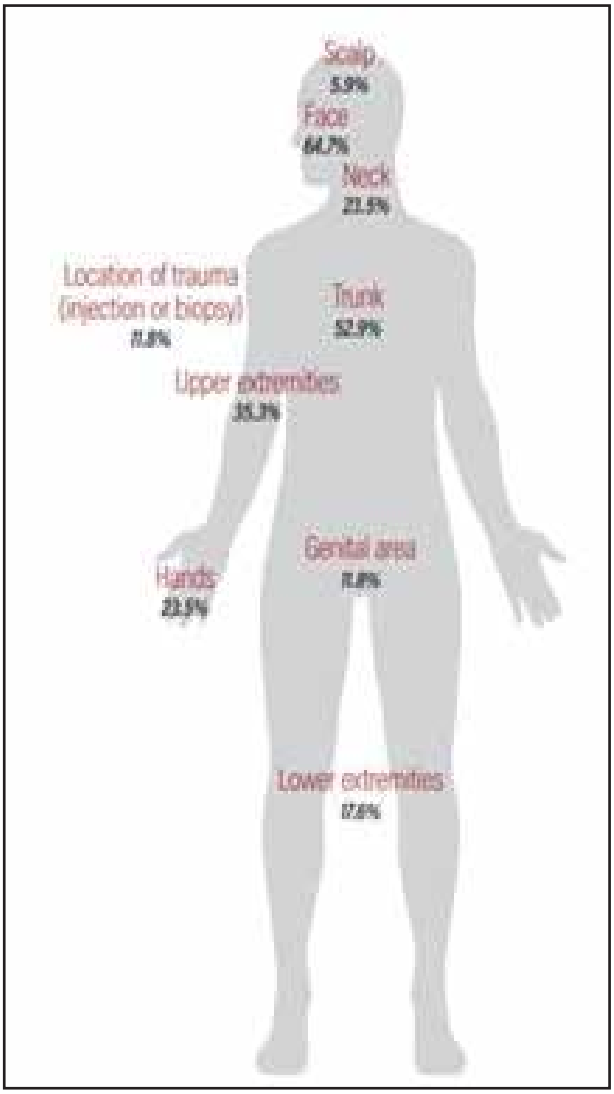

Figure 2: Locations of depigmentation among 17 patients with vitiligo post-COVID-19 vaccination, Percentage of patients (n=17)

In the cases following vaccination 53.3% described hypo pigmented lesions after the first dose and 40% reported onset after the second dose. only 23.5% of the total cases had a history of autoimmune disease.

2. Kasmilha I.C, Mansour M, Foodenow S, Kessler S, Appeal J. Vitiligo following COVID-19 Vaccination and primary infection: a case report and systematic review. Cureus 2023;15(9): e45546. doi: 10.7759/cureus45546.

A 62-year-old man with no history of autoimmune disease developed a depigmented rash within 24 hours of receiving his first Pfizer-BioNTech SARS-CoV-2 vaccination. The rash extend to his face, arms and chest and worsened after the second dose. Despite oral and topical steroid treatments, as well as tacrolimus cream, the patient reported only subjective improvement in his skin lesions. While vitiligo typically arises sporadically the temporal relationship between vaccination and depigmentation suggests a potential link, using clinicians to investigate and share similar cases.

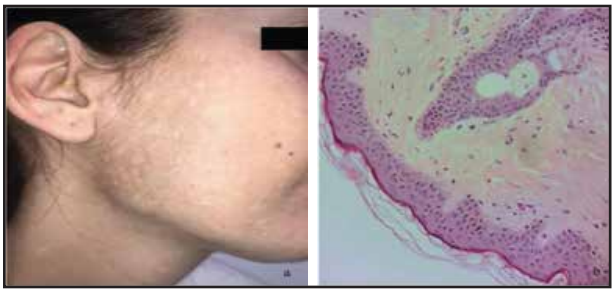

Figure 3a **Figure 3b**

3. A 39-year-old woman with no relevant past personal or family history presented with facial lesions of 10 days' duration and mild local pruritus. Physical examination showed depigmented, nonscaling lesions on the cheeks and neck (Fig 3a). No lesions were observed elsewhere. Direct microscopy with potassium hydroxide was negative and laboratory tests (complete blood count, biochemistry, and autoantibodies) were normal or negative. Histopathologic examination of 1 of the lesions showed an absence of melanocytes (Fig. 3b). The patient reported that the lesions had appeared 1 week after receiving the second dose of the mRNA BNT162/Comirnaty vaccine (PfizerBioNtech).

Several types of skin reactions associated with SARS-CoV-2 infection and COVID-19 vaccination have been reported, the latter mostly since vaccination of the wider population began. There has been just 1 previous report of vitiligo lesions on the face and it was related to the administration of an mRNA COVID-19 vaccine. We believe that this reaction might be linked to the innate and adaptive immune response, with a key role played by the production of interferon-γ, mainly by plasmacytoid dendritic cells. We also believe that these lesions may be a marker of better immune response to SARS-CoV-2 infection.

Figure 4: Appearance of the left antecubital fossa (a) and right antecubital fossa

(b) following second vaccination dose early in the disease course

A systemic review literature found in the PubMed, Embase, Scopus and web of science data bases focused on vitiligo onset post-COVID-19 infection or vaccination.

The research revealed a total of 17 reported case. Of these 15 cases (88.2%) were associated with vaccination and 2 cases (11.8) followed primary COVID-19 infection. Most patients experienced a new onset of vitiligo (88.2%) while 2 cases reported worsening of preexisting vitiligo. The pigmentation varied in location with 64.7% reporting generalized vitiligo and 35.3% presenting with local vitiligo Locations of depigmentation varied among the 17 patients and many reported pigment changes in more than one region of their bodies.
In the cases following vaccination 53.3% described hypo pigmented lesions after the first dose. only 23.5% of the total cases had a history of autoimmune disease. Diagnostic methods included Wood's lamp examination (76.5%), biopsy (5.9%) or clinical diagnosis alone (5.9%).
Treatment outcomes were variable with no complete improvement reported 23.5% reporting some improvement, 11.8% showing on improvement and 64.7% lacking follow-up data.

Pearls from Past Research

Vitiligo's pathogenesis involves the destruction of melanocytes and while its exact cause remains unknown, proposed triggers include physical injury, emotional stress and autoimmune conditions. In the presented case and others in the literatures the temporal relationship between COVID-19 vaccination and vitiligo onset raises questions about a potential causal link.
The prevailing autoimmune theory suggest the involvement of cytotoxic T cells in the destruction of melanocytes. Biopsies in vitiligo cases have shown infiltrating cytotoxic CD8+ lymphocytes leading to melanocytes apoptosis. Additionally, elevated cells of cytokines like tumor necrosis factor alpha (TNF-α) interferon gamma and interleukin IL-10 and IL-17 have been implicated in melanocyte destruction. Notably, the Pfizer-BioNTech vaccine has been associated with inflammatory response involving upregulation of Type-I helper T cells and increased levels of IL-2 interferon Gamma and TNF-α suggesting a potential link to vitiligo development.

The literatures also report new-onset autoimmune disease following COVID-19 vaccination including lichen planus, Gullain-Barre syndrome, Systemic Lupus erythromatasus and immune thrombotic thrombocytopenia. "Notably, one case included in our study described an eruption of lichen planus after the first dose of the COVID-19 vaccine which worsen after the second dose, Additionally the patient developed vitiligo macules in several areas after the second dose" study authors wrote.

Molecular mimicry where autoantibodies or vaccine adjuvants contribute to autoimmunity has been proposed as a potential mechanism.

Conclusion

Up to 70.3% of the vitiligo patients had disease progression after COVID-19 vaccination and 30.7% of them had disease progression after COVID-19 infection. Active stage of vitiligo is a risk factor of vitiligo progression after COVID-19 vaccination and infection. Further investigations are required to clarify the relationship between COVID-19 infection or its associated vaccines and vitiligo progression.

Further research needed

While the reported cases of vitiligo following COVID-19 vaccination are rare the temporal relationship observed in this and other case s prompts consideration of a potential link between the vaccine and the onset of vitiligo. It is crucial for clinicians to be aware of the possibility of developing or worsening skin disease post vaccination or infection. Despite the limited sample size and heterogeneity of reported data the potential risk of skin disease should be weighed against the substantial benefits of COVID-19 vaccination.

Further research is necessary to stablish a definitive causal relationship between COVID-19 vaccination and vitiligo onset. In the interim clinicians should remain vigilant for similar reaction and treat them appropriately. The benefits of COVID-19 vaccination in preventing severe infection and its associated risks outweigh the rare occurrences of skin conditions. Continued monitoring and investigation will contribute to our understanding of the complex interplay between vaccination autoimmune responses and dermatological outcomes.

Acknowledgments

The authors would like to thanks Prof. Dr. Md. Zulfikar Ali (MBBS, DSM, MACG, PhD, FRCP), Professor of Medicine Khwaja Yunus Ali Medical College and Hospital for his continuous inspiration to write this review article.

Reference

1. Bukhari AE. New onset of vitiligo in a child following COVID 19 vaccination. JAAD Case Rep 2022;22:68 9.

2. Uğurer E, Sivaz O, Kıvanç Altunay İ. Newly developed vitiligo following COVID 19 mRNA vaccine. J Cosmet Dermatol 2022;21:1350 1.

3. Aktas H, Ertuğrul G. Vitiligo in a COVID 19 vaccinated patient with ulcerative colitis: Coincidence? Clin Exp Dermatol 2022;47:143 4.

4. Militello M, Ambur AB, Steffes W. Vitiligo possibly triggered by COVID 19 vaccination. Cureus 2022;14: e20902.

5. Flores-Terry M.Á, García-Arpa M, Santiago-Sánchez J.L, Mateoy G, Romero Aguilera. Facial Vitiligo After SARS-CoV-2 Vaccination, ACTAS Dermo-Sifiliográficas 113 (2022) 721

6. Bukhari AE. New onset of vitiligo in a child following COVID 19 vaccination. JAAD Case Rep 2022;22:68 9.

7. Uğurer E, Sivaz O, Kıvanç Altunay İ. Newly developed vitiligo following COVID 19 mRNA vaccine. J Cosmet Dermatol 2022;21:1350 1.

8. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, et al. Cutaneous reactions reported after Moderna and Pfizer COVID 19 vaccination: A registry based study of 414 cases. J Am Acad Dermatol 2021;85:46 55.

9. Aktas H, Ertuğrul G. Vitiligo in a COVID 19 vaccinated patient with ulcerative colitis: Coincidence? Clin Exp Dermatol 2022;47:143 4.

10. Kaminetsky J, Rudikoff D. New onset vitiligo following mRNA 1273 (Moderna) COVID 19 vaccination. Clin Case Rep 2021;9:e04865.

11. Ciccarese G, Drago F, Boldrin S, Pattaro M, Parodi A. Sudden onset of vitiligo after COVID 19 vaccine. Dermatol Ther 2022;35:e15196.

12. Militello M, Ambur AB, Steffes W. Vitiligo possibly triggered by COVID 19 vaccination. Cureus 2022;14: e20902.

13. Abdullah L, Awada B, Kurban M, Abbas O. Comment on 'Vitiligo in a COVID 19 vaccinated patient with ulcerative colitis: Coincidence?' Type I interferons as possible link between COVID 19 vaccine and vitiligo. Clin Exp Dermatol 2022;47:436 7.

14. Bertolotti A, Boniface K, Vergier B, Mossalayi D, Taieb A, Ezzedine K, et al. Type I interferon signature in the initiation of the immune response in vitiligo. Pigment Cell Melanoma Res 2014;27:398 407.

15. Bertolani M, Rodighiero E, Del Giudice MB, Lotti T, Feliciani C, Satolli F. Vitiligo: What's old, what's new. Dermatol Rep 2021;13:9142

16. Schmidt AF, Rubin A, Milgraum D, Wassef C: Vitiligo following COVID-19: a case report and review of pathophysiology. JAAD Case Rep. 2022, 22:47-9. 10.1016/j.jdcr.2022.01.030

17. Kaminetsky J, Rudikoff D: New-onset vitiligo following mRNA-1273 (Moderna) COVID-19 vaccination . Clin Case Rep. 2021, 9:e04865. 10.1002/ccr3.4865

18. Bukhari AE: New-onset of vitiligo in a child following COVID-19 vaccination . JAAD Case Rep. 2022, 22:68-9. 10.1016/j.jdcr.2022.02.021

19. Flores-Terry MÁ , García-Arpa M, Santiago-Sánchez Mateo JL, Romero Aguilera G: Facial vitiligo after SARS-CoV-2 vaccination (Article in Spanish). Actas Dermosifiliogr. 2022, 113:721. 10.1016/j.ad.2022.01.030

20. Aktas H, Ertuğrul G: Vitiligo in a COVID-19-vaccinated patient with ulcerative colitis: coincidence? . Clin Exp Dermatol. 2022, 47:143-4. 10.1111/ced.14842

21. Koç Yıldırım S: A new-onset vitiligo following the inactivated COVID-19 vaccine J Cosmet Dermatol. 2022, 21:429-30. 10.1111/jocd.14677

22. Singh R, Cohen JL, Astudillo M, Harris JE, Freeman EE: Vitiligo of the arm after COVID-19 vaccination . JAAD Case Rep. 2022, 28:142-4. 10.1016/j.jdcr.2022.06.003

23. Nicolaidou E, Vavouli C, Koumprentziotis I, Gerochristou M, Stratigos A: Newonset vitiligo after COVID-19 mRNA vaccination: a causal association?. J Eur Acad Dermatol Venereol. 2022, 10.1111/jdv.18513. 10.1111/jdv.18513

24. López Riquelme I, Fernández Ballesteros MD, Serrano Ordoñez A, Godoy Díaz DJ: COVID-19 and autoimmune phenomena: vitiligo after Astrazeneca vaccine. Dermatol Ther. 2022, 35:e15502. 10.1111/dth.15502

25. Uğurer E, Sivaz O, Kıvanç Altunay İ: Newly-developed vitiligo following COVID-19 mRNA vaccine . J Cosmet Dermatol. 2022, 21:1350-1. 10.1111/jocd.14843

26. Ciccarese G, Drago F, Boldrin S, Pattaro M, Parodi A: Sudden onset of vitiligo after COVID-19 vaccine . Dermatol Ther. 2022, 35:e15196. 10.1111/dth.15196

27. Militello M, Ambur AB, Steffes W: Vitiligo possibly triggered by COVID-19 vaccination . Cureus. 2022, 14:e20902. 10.7759/cureus.20902

28. Macca L, Peterle L, Ceccarelli M, Ingrasciotta Y, Nunnari G, Guarneri C: Vitiligolike lesions and COVID-19: case report and review of vaccination- and infection-associated vitiligo. Vaccines (Basel). 2022, 10:1647. 10.3390/vaccines10101647

29. Caroppo F, Deotto ML, Tartaglia J, Belloni Fortina A: Vitiligo worsened following the second dose of mRNA SARS-CoV-2 vaccine. Dermatol Ther. 2022, 35:e15434. 10.1111/dth.15434

30. Okan G, Vural P: Worsening of the vitiligo following the second dose of the BNT162B2 mRNA COVID-19 vaccine. Dermatol Ther. 2022, 35:e15280. 10.1111/dth.15280

31. Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, Pan HF: New-onset autoimmune phenomena post-COVID- 19 vaccination. Immunology. 2022, 165:386-401. 10.1111/imm.13443

32. Caroppo F, Deotto ML, Tartaglia J, Belloni Fortina A. Vitiligo wors- ened following the second dose of mRNA SARS-CoV-2 vaccine. Dermatol Ther. 2022;36(6):e15434.

33. Ciccarese G, Drago F, Boldrin S, Pattaro M, Parodi A. Sudden onset of vitiligo after COVID19 vaccine. Dermatol Ther. 2021;35(1):e15196-e.

34. Mohseni Afshar Z, Babazadeh A, Janbakhsh A, et al. Vaccine- induced immune thrombotic thrombocytopenia after vaccination against Covid-19: a clinical dilemma for clinicians and patients. Rev Med Virol. 2022;32(2):e2273.

35. Havla J, Schultz Y, Zimmermann H, Hohlfeld R, Danek A, Kümpfel T. First manifestation of multiple sclerosis after immunization with the Pfizer-BioNTech COVID-19 vaccine. J Neurol. 2022;269(1):55-58.

36. Trimboli M, Zoleo P, Arabia G, Gambardella A. Guillain-Barré syndrome following BNT162b2 COVID-19 vaccine. Neurol Sci. 2021;42(11):4401-4402.

37. Chen Y, Xu Z, Wang P, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology. 2022;165(4):386-401.

38. Herzum A, Burlando M, Molle MF, Micalizzi C, Cozzani E, Parodi A. Lichen planus flare following COVID-19 vaccination: a case report. Clin Case Rep. 2021;9(12):e05092.

39. Velikova T, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int. 2021;41(3):509-518.

40. Riding RL, Harris JE. The role of memory CD8+ T cells in vitiligo. J Immunol. 2019;203(1):11-19.

41. Lane C, Leitch J, Tan X, Hadjati J, Bramson JL, Wan Y. Vaccination- induced autoimmune vitiligo is a consequence of secondary trauma to the skin. Cancer Res. 2004;64(4):1509-1514.

42. Nada HR, El Sharkawy DA, Elmasry MF, Rashed LA, Mamdouh S. Expression of Janus kinase 1 in Vitiligo & Psoriasis before and after narrow band UVB: a case-control study. Arch Dermatol Res. 2018;310(1):39-46. doi:10.1007/s00403-017-1792-6

43. Qi F, Liu F, Gao L. Janus kinase inhibitors in the treatment of vit- iligo: a review. Front Immunol. 2021; 18 (12): 790125. doi:10.3389/ fimmu. 2021. 790125

44. Gatti M, Turrini E, Raschi E, Sestili P, Fimognari C. Janus kinase inhibitors and coronavirus disease (COVID)-19: rationale, Clinical Evidence and Safety Issues. Pharmaceuticals (Basel). 2021;14:738. doi:10.3390/ph14080738

45. Levy G, Guglielmelli P, Langmuir P, Constantinescu S. JAK inhib- itors and COVID-19. J Immunother Cancer. 2022;10(4):e002838. doi:10.1136/jitc-2021-002838

46. Stebbing J, Sánchez Nievas G, Falcone M, et al. Jak inhibition reduces SARS-CoV-2 liver infectivity and modulates inflam- matory responses to reduce morbidity and mortality. Sci Adv. 2021;7:eabe4724.

47. Seror R, Camus M, Salmon J-H, et al. Do JAK inhibitors affect im- mune response to COVID- 19 vaccination? Data from the MAJIKSFR registry. Lancet Rheumatol. 2022;4:e8-e11.

48. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE, Group VW. New discoveries in the pathogenesis and classification of vitil- igo. J Am Acad Dermatol. 2017;77(1):1-13.

49. Mohseni Afshar Z, Babazadeh A, Hasanpour A, et al. Dermatological manifestations associated with COVID-19: a comprehensive review of the current knowledge. J Med Virol. 2021;93(10):5756-5767.

50. Mohaghegh F, Hatami P, Aryanian Z, Fatemi F, Mohseni Afshar Z. Acute generalized Exanthematous Pustulosis following SARS- CoV-2 virus: Remdesivir as a suspected culprit. Case Rep Med. 2022;10(2022):9880827. doi:10.1155/2022/9880827

51. Aryanian Z, Balighi K, Hatami P, Afshar ZM, Mohandesi NA. The role of SARS-CoV-2 infection and its vaccines in various types of hair loss. Dermatol Ther. 2022;35(6):e15433. doi:10.1111/ dth.15433

52. Richardson VL, Garcia-Albea VR, Bort NL, Mayne SL, Nolen ME, Bobonich MA. Reflections of COVID-19 on dermatology prac- tice. J Dermatol Nurses Assoc. 2021;13(1):49-53. doi:10.1097/ JDN.0000000000000586

53. Xu X, Zhang C, Jiang M, Xiang LF. Impact of treatment delays on vitiligo during the COVID19 pandemic: a retrospective study. Dermatol Ther. 2021;34(4):e15014.

54. Rodrigues M, Pandya AG, Hamzavi I, Ezzedine K, Bekkenk MW, Harris JE. Treatment recommendations for patients with vitiligo during COVID-19. Australas J Dermatol. 2021;62(3):e481-e482. doi:10.1111/ajd.13610