Dermatology Practical & Conceptual

Localized Vitiligo and Post-Inflammatory Hypopigmentation at the Injection Site of a COVID-19 mRNA Vaccine

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Introduction

The COVID-19 pandemic has been a global emergency since January 2020. One of the most commonly used COVID-19 mRNA vaccines is Pfizer- BioNTech vaccine BNT162b2 [1]. In a registry-based study of 414 cutaneous reactions to mRNA COVID-19 vaccines, delayed and immediate injection site reactions were the most common [2]. Herein, we discuss two similar cutaneous reactions following COVID mRNA vaccination in order to further characterize dermatologic reactions.

Case Presentation

Case 1. A 38-year-old woman, Fitzpatrick type III, presented to our consultation after the second dose of Pfizer vaccine BNT162b2. After vaccine administration, the patient described an immediate local reaction on the injection site characterized by an erythematous and edematous plaque. This reaction evolved to a hypopigmented patch with irregular borders measuring 20 mm (Figure 1A). Wood lamp examination of the lesion (Figure 1B) revealed neither fluorescence nor accentuation, which is consistent with post-inflammatory hypopigmentation. This cutaneous lesion fainted after 2 months without treatment.

Case 2. A 30-year-old woman, Fitzpatrick type V, presented to our consultation after the first dose of Pfizer vaccine. Few hours after the vaccine, the patient noted an immediate local reaction characterized by an erythematous and edematous plaque with a central blister. Over two weeks, this reaction evolved to a hypopigmented patch with 25 mm of diameter and irregular borders, surrounded by

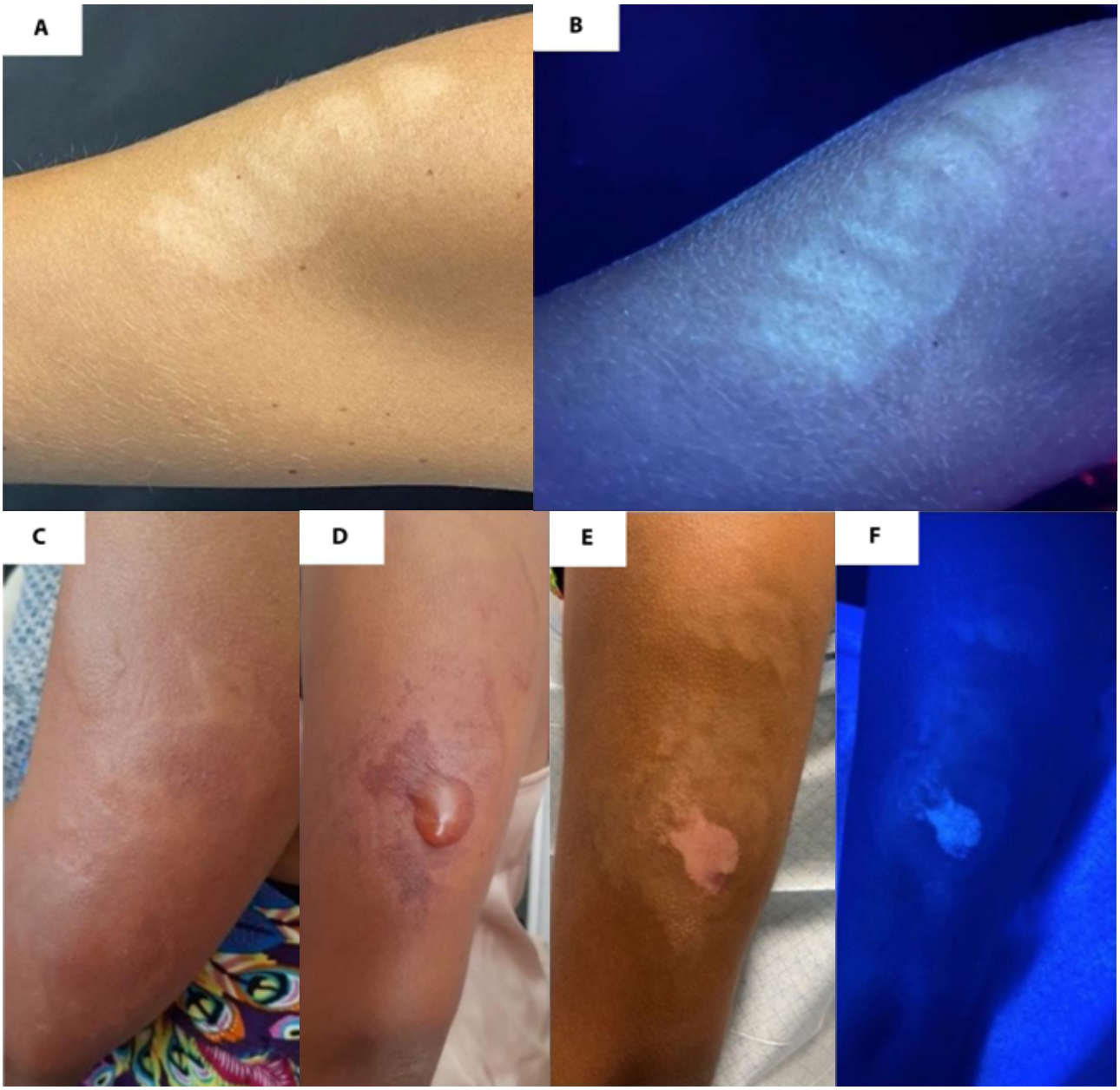

Figure 1. Skin hypopigmentation. Case 1. (A) Hypopigmented patch with irregular borders on the left arm at three weeks following the second dose of Pfizer vaccine. (B) Wood lamp examination revealed neither fluorescence nor accentuation. Case 2. (C-E) Site injection reaction on the left arm evolved from an erythematous and edematous plaque with a central blister to a hypopigmented patch over a period of hours to two weeks following the first dose of Pfizer vaccine. (F) Under Wood lamp examination the hypopigmented patch showed sharply demarcated bright blue-white fluorescence.

another patch with two shades of brown (Figure 1, C-E). Wood lamp examination demonstrated a sharply demarcated bright blue-white fluorescence (Figure 1F), consistent with vitiligo. Skin biopsy was also compatible with vitiligo (Figure 2) revealing a decrease or absence of melanin pigment in lesional skin with H&E and Masson-Fontana stains, respectively. Autoimmunity laboratory study (ANAs, ANA screening, anti-dsDNA, anti-thyroid antibodies) was negative and SARS-CoV2 anti-spike antibody titers were positive of (50.8 AU/mL). She was treated with topical tacrolimus twice daily with poor response. After the second dose of the vaccine, two months later, she had no skin reaction. At four months of follow-up only the vitiligo lesion remains, the brown patch is fading away.

Conclusions

Post-inflammatory hypopigmentation is an acquired partial or total loss of skin pigmentation occurring after cutaneous inflammation. There is limited information about the mechanism and pathogenesis. Melanogenesis is a complex process. It is controlled by multiple mediators (eg, growth factors, cytokines) acting on melanocytes, keratinocytes and fibroblasts. Through the release of these mediators, cutaneous

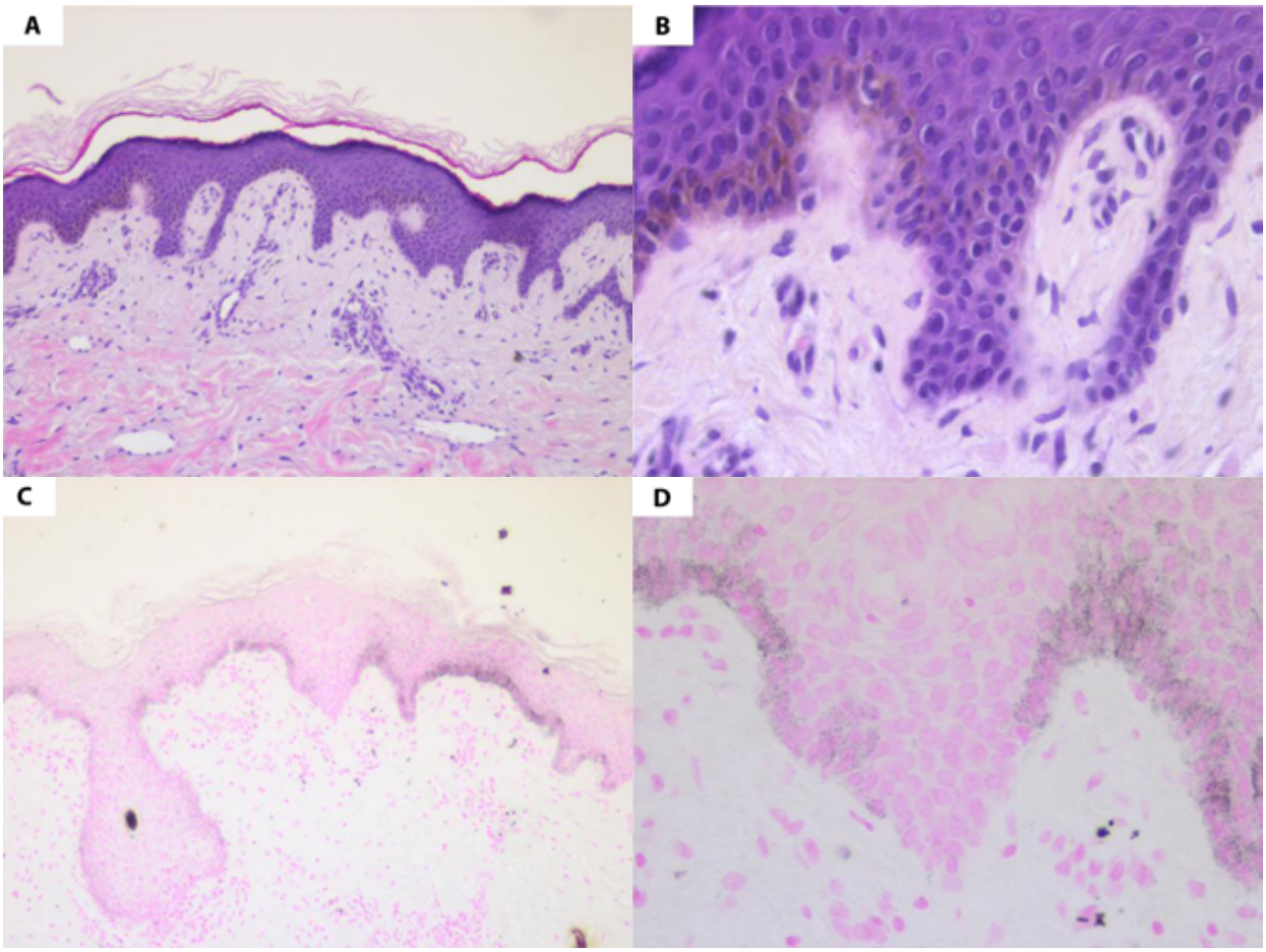

Figure 2. Vitiligo, Case 2. Skin biopsy performed on the edge of the hypopigmented patch. (A) Basal epidermal hyperpigmentation explained by the patient phototype. Scarce inflammatory infiltrate in the superficial dermis (H&E stain, magnification x100). (B) Slight Decrease in melanin pigment in lesional skin (H&E stain, magnification x400). (C,D) Masson-Fontana stain highlights loss of melanin on the left side of the biopsy (Fontana-Masson stain, magnification x100 and x400).

inflammation may cause aberration of melanogenesis leading to loss of melanocytes [3]. In Case 1, inflammation resulted in hypopigmented patches at the injection site. The hypopigmentation improved overtime after the inflammation ceased.

Vitiligo is an autoimmune disease. Cytotoxic CD8+ T cells are responsible for the destruction of melanocytes. The potential for vaccines to act as triggers of autoimmune reactions is well known [4,5]. The pathophysiology underlying the relationship between SARS- CoV-2 vaccination and vitiligo remains unclear.

mRNA vaccines encoding the SARS-CoV-2 spike protein encapsulated in lipid nanoparticles gain entry into dendritic cells (DCs) at the injection site. In addition, innate sensors are triggered resulting in production of type I interferon and multiple pro-inflammatory cytokines and chemokines. In particular, vaccine-driven production of type I interferon (IFN-1) promotes differentiation of CD4+ and CD8+ effector T cells producing inflammatory and cytotoxic mediators, and CD4+ T follicular helper cells, which promote B cell differentiation into antibody-secreting plasma cells [6]. In the pathogenesis of vitiligo, both IFN-1 and DCs were demonstrated to play a significant role. The activation of DCs and the release of IFN-1 seem to be key events in vitiligo following COVID-19 vaccination. Additionally, nonspecific activation of autoreactive CD8+/CD4+ T and B cells could stimulate the immune system to produce antibodies against SARS- CoV2 spike protein and incidentally against melanocytes [7-9].

On the other hand, studies with anti-melanoma vaccines demonstrated that vitiligo observed around the injection site does not occur unless autoreactive T cells are recruited into the skin by inflammatory stimuli, suggesting that vitiligo can be initiated by some form of trauma to the skin [10].

To date, there are only five reported cases of new-onset vitiligo following COVID-19 mRNA vaccine (Table 1). In case 1, the hypopigmented patch was a result of an inflammatory response that can occur in any patient and should be differentiated from vitiligo. Case 2 is the first report of site injection site vitiligo after an mRNA vaccine. Vaccines generate an immune response which can be a trigger to develop

Table 1. Literature review: reported cases of new-onset vitiligo following COVID-19 mRNA vaccine.

Authors/year	Age (years)	Sex	Vaccine	Local	Timing
Aktas H, Ertuğrul G [4] 2021	58	Male	Pfizer-BioNTech BNT162b2	Face	1 week after 1st dose
Kaminetsky J, Rudikoff D [7] 2021	61	Female	mRNA-1273 (Moderna)	Face, neck, chest, abdomen	Several days after 1st dose
Ciccarese G [9] 2022	33	Female	Pfizer-BioNTech BNT162b2	Trunk, neck, back	1 week after 1st dose
Militello et al. [5] 2022	67	Female	mRNA-1273 (Moderna)	Hands	2 weeks after the vaccine
Uğurer E et al. [8] 2022	47	Male	Pfizer-BioNTech BNT162b2	Axilla, forearms	1 week after 1st dose

vitiligo. We can hypothesize that in case 2, autoreactive T cells responses triggered by a local injection site inflammation along with activation of DCs and the release of IFN-1 might be responsible for the development of vaccine-induced vitiligo at injection site.

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