Rare lymphomatoid reactions following SARS-CoV-2 vaccination

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INTRODUCTION

Cutaneous reactions following SARS-CoV-2 (COVID-19) vaccination, such as swelling, erythema, and local injection site reactions, are relatively common and largely self-limited.[1,2] Here, we describe 2

Abbreviations used:

CLH: cutaneous lymphoid hyperplasia
PLEVA: pityriasis lichenoides et varioliformis acuta

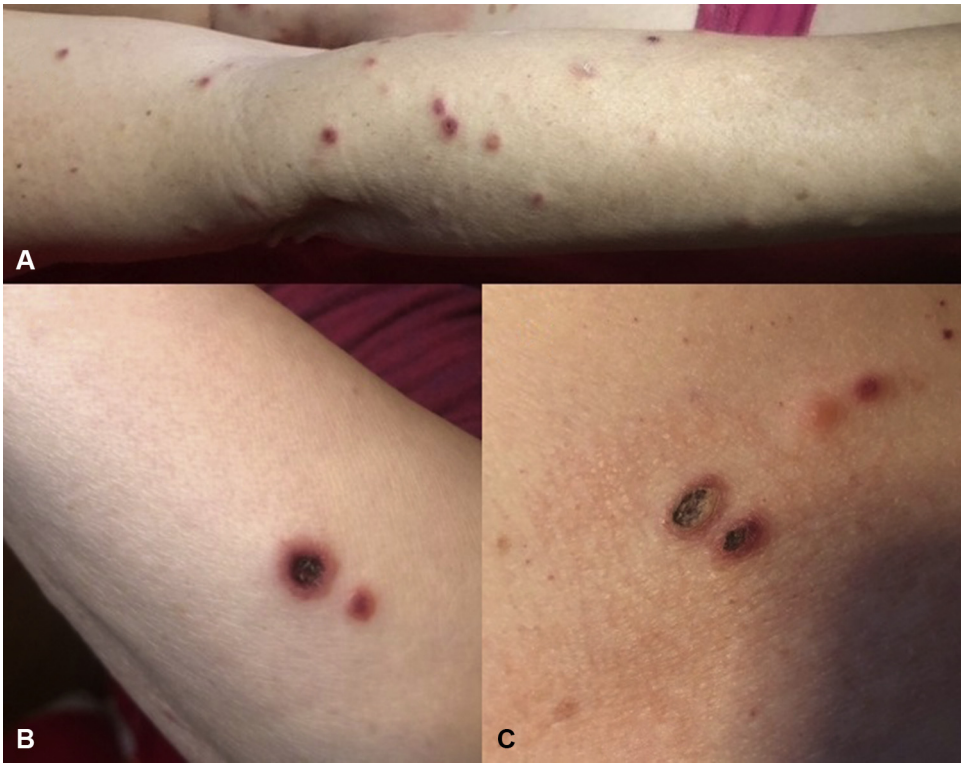

Fig 1. Ulcerated, pink papules with hemorrhagic, necrotic crust on the arms (**A**, **B**) and trunk (**C**).

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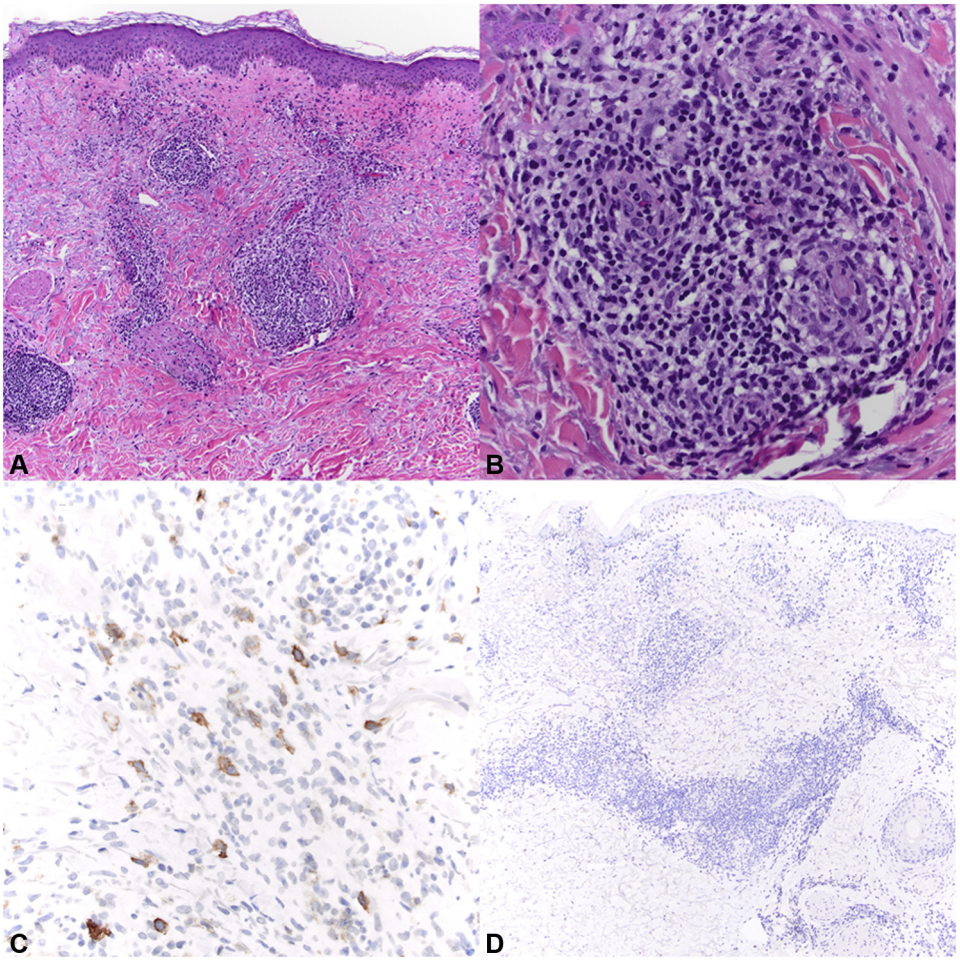

Fig 2. Punch biopsy of the right forearm. **A**, Superficial and deep lymphohistiocytic infiltrate with central ulceration and hemorrhage observed at low power. **B**, Higher power revealed medium-sized lymphocytes with pleomorphism and slight atypia. **C**, Many scattered lymphocytes were $CD30^+$. **D**, CD21 staining was negative. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×10; **B**, ×40; **C**, CD30 stain; original magnification: ×40; and **D**, CD21 stain; original magnification: ×10.)

rare cutaneous lymphomatoid reactions following COVID-19 vaccination, including pityriasis lichenoides et varioliformis acuta (PLEVA) and T-cell–predominant cutaneous lymphoid hyperplasia (CLH).

CASE DESCRIPTIONS

Case 1

A 54-year-old, Caucasian woman with a history of psoriasis and transverse myelitis presented with a pruritic skin eruption of 3 weeks' duration. The rash was characterized by multiple 1- to 4- mm, ulcerated, pink papules with a hemorrhagic, necrotic crust on the trunk and extremities (Fig 1). Of note, the patient had received the first dose of the Pfizer/BioNTech COVID-19 vaccination 2 weeks prior to the eruption onset, with rapid and diffuse progression following the second dose 1 week later. She had no constitutional symptoms or symptoms of viral infection prior to or following vaccination.

Biopsies of the papules on the abdomen and forearm revealed a superficial and deep lymphohistiocytic infiltrate with central ulceration and hemorrhage (Fig 2, *A*). Lymphocytes were medium sized, with mild pleomorphism and atypia (Fig 2, *B*). Margination of neutrophils was noted, with karyorrhexis, fibrin, and lymphocytic vasculitis. Immunohistochemically, the lymphocytes were $CD3^+$ and $CD7^+$, with scattered $CD30^+$ cells (Fig 2, *C*). CD20 and CD21 failed to demonstrate a significant B-cell or follicular dendritic cell population (Fig 2, *D*). The CD4:CD8 ratio of the T-cell infiltrate was approximately 2:1. A tissue T-cell receptor gamma gene rearrangement assay was negative for T-cell clonality.

Based on clinical and histologic evidence, the differential diagnosis included lymphomatoid papulosis and PLEVA. We favored PLEVA due to the lack of large immunoblastic cells, limited CD30 expression, and lack of T-cell clonality within the infiltrate. Additionally, the clinical acuity and recent vaccination history also pointed to a reactive process. The patient had near-complete cessation of new lesions on doxycycline (200 mg daily) for 3 months. She developed a limited recurrence upon doxycycline discontinuation but quickly responded to medication reinitiation.

Case 2

A 78-year-old Caucasian woman presented with a new, intermittently pruritic, 6-mm pink papule on the upper portion of right arm (Fig 3). The lesion appeared a few days after she received the second dose of the Pfizer/BioNTech COVID-19 vaccination and approximately 6 months after herpes zoster vaccination (both in the affected arm). She reported no COVID-19 symptoms prior to vaccination and experienced mild constitutional symptoms following vaccination. The patient had no relevant medical history, and the review of systems was negative. A physical examination was negative for other skin findings. The patient opted for surgical excision.

Sections revealed an acanthotic epidermis with reactive keratinocytes and fibrin (Fig 4, *A*). There was a dense dermal infiltrate, composed predominantly of medium-to-large pleomorphic lymphocytes (Fig 4, *B*). Vessel infiltration and hemorrhage were also noted. Immunohistochemistry revealed an infiltrate composed primarily of T-cells with a significant B-cell component (T:B ratio of approximately 2:1 [Fig 4, *D*]). The large, atypical cells were composed of mixed B- and T-cells, and CD30 (Ki-1) decorated numerous large, mononuclear cells (Fig 4, *C*). The CD4:CD8 ratio was approximately 10:1, with a predominance of CD4 cells within the atypical component. CD21 and Bcl6 stains failed to demonstrate follicular dendritic meshwork or clusters of centrocytes or centroblasts. Inducible T-cell costimulatory protein (CD278) and programmed cell death protein-1 (CD279) highlighted many large cells. Kappa and lambda *in situ* hybridization failed to demonstrate light chain restriction. T-cell receptor gamma gene and immunoglobulin H gene rearrangement assays were positive for T-cell clonality but negative for B-cell clonality.

Histologic evidence of prominent fibrin, edema, reactive keratinocytes, and syncytial dendritic cells may suggest a viral process with mixed reactive B- and T-cells, but viral cytopathic changes were not observed histologically, and Epstein-Barr virus-encoded small RNA-1 *in situ* hybridization was negative. Thus, despite pleomorphism, atypia, and T-cell clonality, a diagnosis of lymphoid reaction mimicking lymphomatoid papulosis was favored.

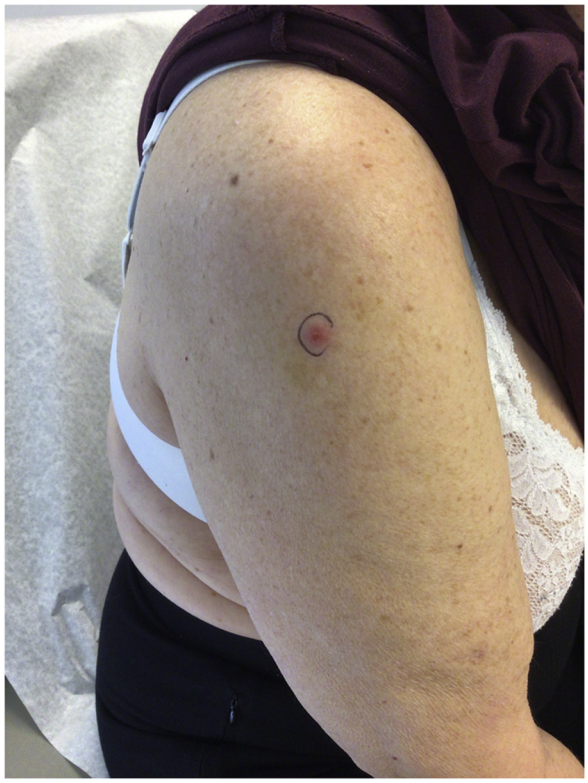

Fig 3. 6-mm, pink papule on the upper portion of the right arm at the site of COVID-19 vaccination.

DISCUSSION

The most commonly reported cutaneous reactions following messenger RNA COVID-19 vaccines include swelling, erythema, local injection site reactions, and delayed large local reactions. Less common reactions, such as urticaria, morbilliform eruptions, erythromelalgia, and flares of existing dermatologic conditions, have also been reported. The majority of cutaneous reactions have been described in healthy Caucasian females.[1]

Here, we present rare cutaneous reactions following the Pfizer/BioNTech COVID-19 vaccination. Both cases were referred to us for the evaluation of possible cutaneous lymphoma. Despite their differing clinical presentations (one generalized, one localized), both cases represent similar phenomena, including reactive lymphoid infiltrates with CD30 expression.

PLEVA is a rare, self-limited, inflammatory disorder characterized by the acute onset of erythematous macules that rapidly progress into hemorrhagic inflammatory papules or papulovesicles. Though

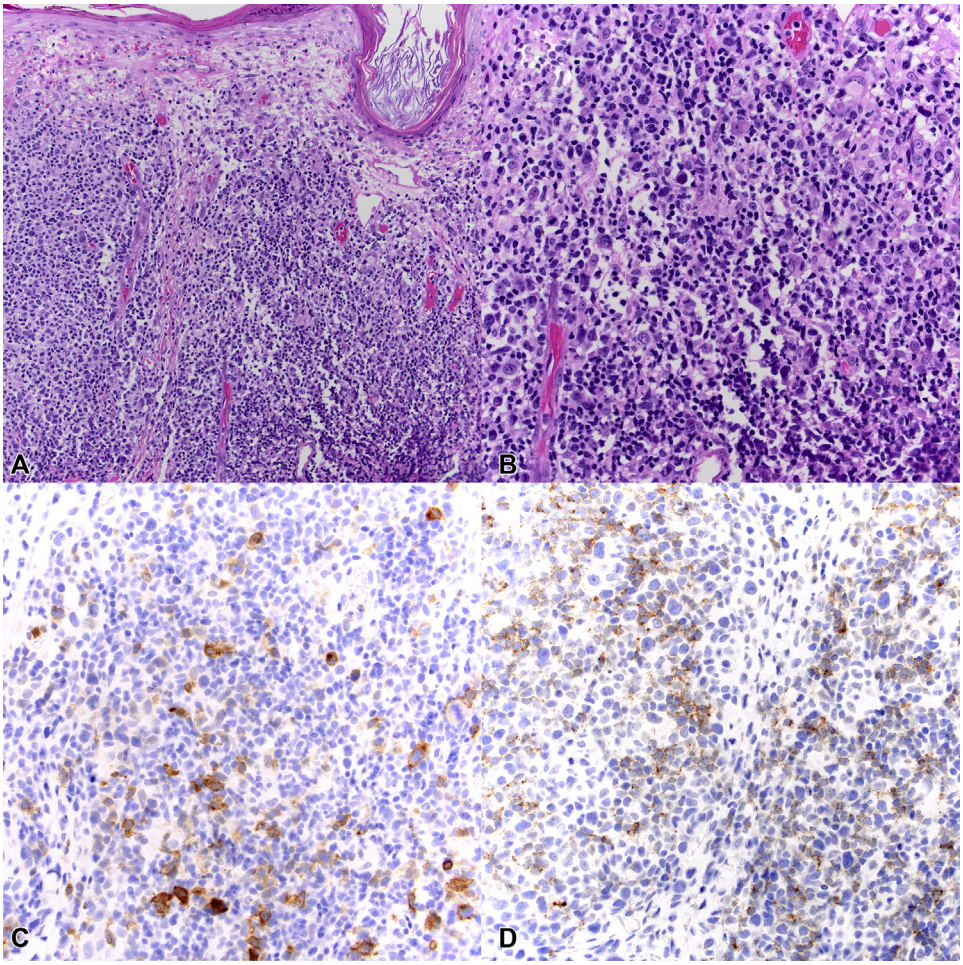

Fig 4. Punch biopsy of the right upper arm. **A**, On medium power, the epidermis is acanthotic, with a significant amount of fibrin. **B**, On higher power, there is a dense dermal infiltrate composed predominantly of medium-to-large pleomorphic lymphocytes. Vessel infiltration and hemorrhage were also noted. **C**, CD30 decorated numerous large, mononuclear cells. **D**, CD21 highlighted a significant component of the infiltrate. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×40; **C**, CD30 stain; original magnification: ×40; and **D**, CD21 stain; original magnification: ×40.)

the pathogenesis remains poorly understood, the best-supported theories suggest that PLEVA is a limited lymphoid proliferation secondary to viral reaction. This theory is supported by frequent reports of preceding or concurrent infection or vaccination (measles/mumps/rubella, antitetanus and antidiphtheria, and influenza).[2-5] Due to its resemblance to lymphomatoid papulosis and common clonality, PLEVA has also been theorized to be a primary lymphoproliferative disorder.[5] In case 1, we hypothesize that a robust immune response to the messenger RNA component of the COVID-19 vaccine may have triggered the patient's presentation. COVID-19 vaccines are thought to activate the immune system similarly to the virus itself.[6] This notion is supported by reports of pernio/chilblains, a relatively common manifestation of COVID-19 infection, following COVID-19 vaccination.[1,6]

CLH results from the infiltration of benign lymphocytes that can clinically and histologically resemble early primary cutaneous B-cell lymphoma. Four cases of CLH at the site of vaccination have been documented in the United Kingdom following Pfizer/BioNTech COVID-19 vaccination, but none have been reported in the medical literature.[7] In 2005, Maubec et al[8] reported 9 cases of CLH at the site of antihepatitis vaccination, with positive detection of aluminum hydroxide adjuvant in all cases.[9] Though there is no comparable adjuvant in COVID-19 vaccines, the CLH in case 2 likely represents a similar abnormal response to antigenic stimulation. Since CLH can be mistaken for primary cutaneous B-cell

lymphoma, and, in some cases, progress into low-grade primary cutaneous B-cell lymphoma, patients with this condition should be monitored.

Awareness of these reactions following COVID-19 vaccination, accompanied by a comprehensive histopathologic evaluation of skin biopsies, should be done to distinguish lymphomatoid reactions from true lymphoma.

Conflicts of interest

None disclosed.

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