Reactive arthritis following COVID-19 vaccination with BNT162b2

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INTRODUCTION

Reactive arthritis (RA) is a rare disease that is characterized by a triad of urethritis, conjunctivitis, and arthritis, typically secondary to an extraarticular infection of the genitourinary or gastrointestinal tract.[1] There is often significant variation in clinical features, and patients may present with mucocutaneous findings, such as oral lesions, circinate balanitis, keratoderma blenorrhagicum, and nail dystrophy.[1] Human leukocyte antigen (HLA) B27 positivity is strongly associated with this condition. Herein, we present a case of RA favored to be triggered by the Pfizer-BioNTech COVID-19 messenger RNA (mRNA) vaccine, BNT162b2.

CASE REPORT

A 49-year-old previously healthy man presented with progressively worsening skin lesions and arthritis. Roughly 1 week after receiving the first dose of the BNT162b2 vaccine, he developed a painful rash and swelling of the right foot, with progression of the rash to the left foot and penis. He did not have any preceding genitourinary or gastrointestinal symptoms. His primary care provider diagnosed a bacterial infection and prescribed a 2-week course of doxycycline 100 mg twice daily. He then received a 10-day course of prednisone 20 mg daily for joint pains. Over the next 2 weeks, he developed worsening arthritis of the shoulders, hands, and feet. At this time, he received prescriptions for gabapentin 600 mg and nifedipine 30 mg once daily for a presumed diagnosis of chilblains. The patient's cutaneous and systemic symptoms persisted, and he experienced an unintentional weight loss of approximately 20 pounds.

Abbreviations used:

HLA:	human leukocyte antigen
mRNA:	messenger RNA
RA:	reactive arthritis

The patient presented to our emergency department approximately 2 months after the onset of his rash. Physical examination revealed pink papulopustules and keratoderma on the plantar aspects of the feet (Fig 1, *A* and *B*), extensive onycholysis, nail thickening, and subungual debris of the toenails (Fig 1, *C*); tender edema of the right foot and joints of the right hand (Fig 1, *D* and *E*), and a scaly erythematous plaque on the penis (Fig 1, *F*). Laboratory workup showed an elevated erythrocyte sedimentation rate and an elevated level of C-reactive protein. Blood and urine cultures were negative. HLA-B27 testing by flow cytometry was indeterminate. Further HLA-B27 genotyping was not performed; a definitive result was therefore not obtained. Additionally, the patient tested negative for syphilis, HIV, chlamydia, and gonorrhea.

A punch biopsy of a pustule on the left foot showed psoriasiform epidermal hyperplasia, loss of the granular cell layer, neutrophilic infiltration of the epidermis, and entrapment of neutrophils in the stratum corneum; findings typical of a psoriasiform diathesis (Fig 2, *A* and *B*). Small-vessel vasculitis of the dermal papillary microvasculature was also observed. Additional immunologic stains revealed vascular deposits of complement factors C4d and C5b-9, representing classical complement pathway activation as seen in an Arthus type III immune

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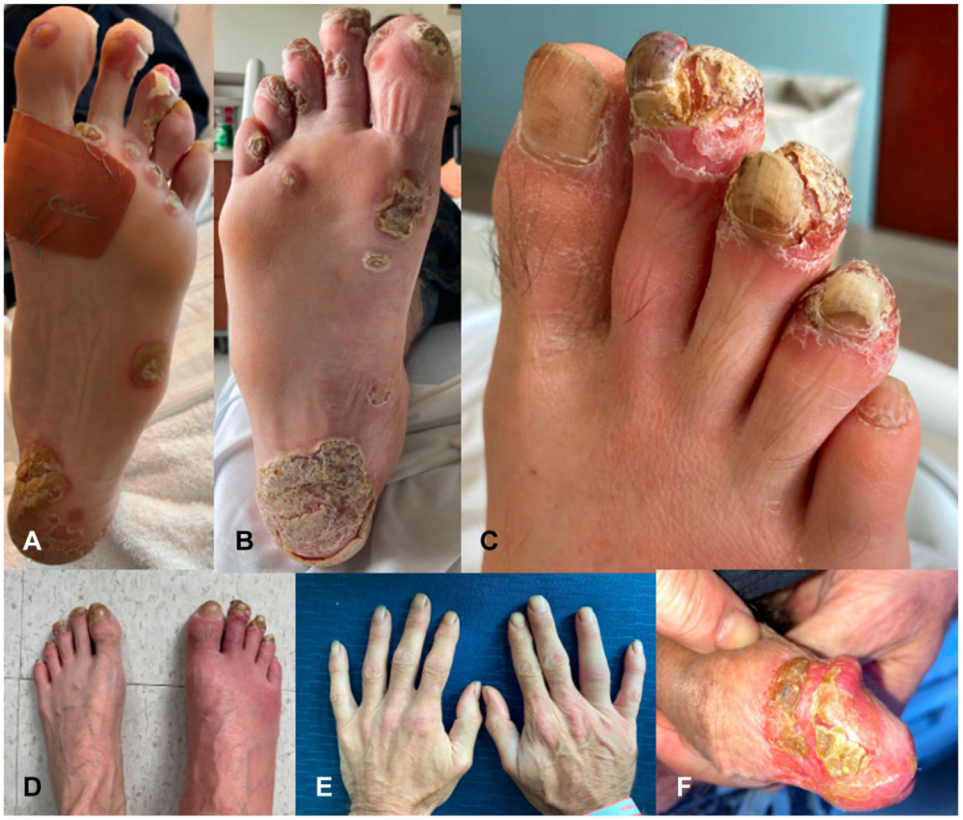

Fig 1. Clinical images taken upon admission to the hospital. **A** and **B,** Papulopustules and hyperkeratotic plaques on the plantar aspects of the feet. **C,** Onychodystrophy of the toenails. **D,** Erythema and edema of the right foot. **E,** Swelling of the proximal interphalangeal joint of the right ring finger. **F,** Scaly erythematous plaque on the glans penis.

complex reaction (Fig 2, *C* and *D*). Human-manufactured spike glycoprotein was identified within reticular dermal microvessels (Fig 3). These pathologic findings led to a diagnosis of keratoderma blenorrhagicum in the setting of RA triggered by the BNT162b2 vaccine.

The patient experienced symptomatic improvement after 2 days of intravenous methylprednisolone 32 mg. He was discharged on oral prednisone and ibuprofen. He follows with rheumatology and continues to experience improvement with weekly methotrexate.

DISCUSSION

Adverse cutaneous reactions to COVID-19 mRNA vaccination have been well-documented in recent literature.[2,3] Cutaneous morphologies purportedly vary, ranging from eczematous and psoriasiform rashes to vasculitic and bullous eruptions.[2-4] Cases of acute, new-onset arthritis following the COVID-19 vaccine have also been reported,[5,6] as have flares of rheumatoid arthritis in patients with previously well-controlled disease.[7] Given the temporal onset of our patient's symptoms and the unrevealing infectious and autoimmune workup, RA triggered by the COVID-19 vaccine was most favored in this case.

RA has been described as a form of arthritis in which a type III immune complex-mediated reaction results from an antigenic stimulus. Typically, this syndrome occurs within 4 weeks of infection caused by species of *Chlamydia, Salmonella, Shigella, Yersinia,* or *Campylobacter.*[1,8] In the present case, the histologic findings of a psoriasiform tissue reaction accompanied by leukocytoclastic vasculitis were consistent with a diagnosis of keratoderma blenorrhagicum—the characteristic cutaneous manifestation of RA.[8] The extensive complement deposition in the microvasculature also highlighted the role of complement pathway activation in the pathogenesis of this condition. Immune complex-mediated reactions have been described following infection with and vaccination against COVID-19,[9] and this case further illustrates the role of complement in these circumstances.

The pathogenesis of hypersensitivity reactions following COVID-19 mRNA vaccination has not been well established. The BNT162b2 vaccine

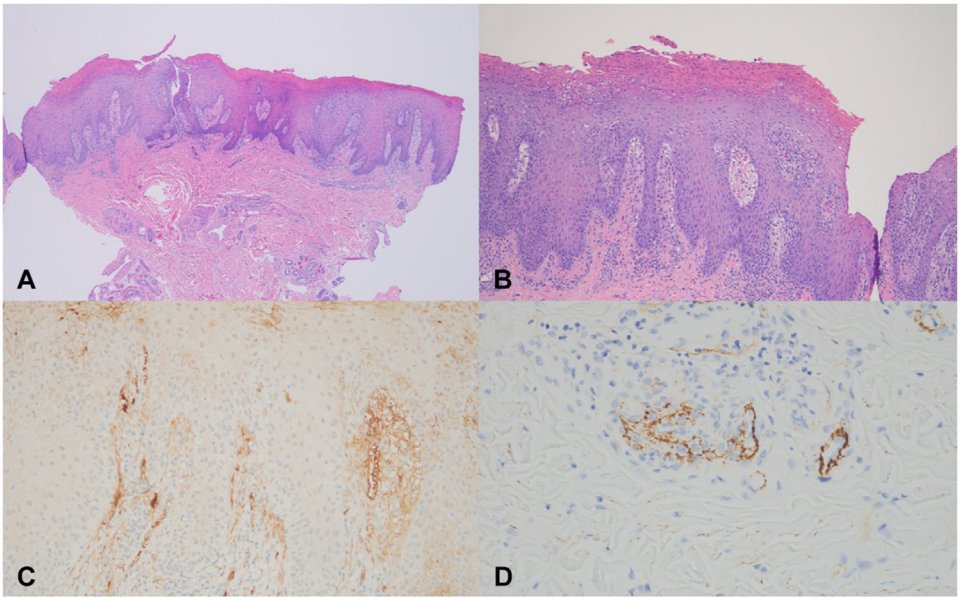

Fig 2. Histopathology of lesion tissue. **A** and **B,** Histopathologic image of a lesion specimen showed irregular psoriasiform epidermal hyperplasia, parakeratotic scale, and an absent granular cell layer, in addition to extensive neutrophilic infiltration of the stratum corneum. Inflammatory changes were also noted within the dermis (**A** and **B,** hematoxylin-eosin stain; original magnification: **A,** ×100; **B,** ×400). **C**, C4d stain revealed extensive highlighting of the microvessels, indicative of classic complement pathway activation triggered by immune complex deposition (C4d stain; original magnification: ×400). **D,** C5b-9 stain demonstrated a positive reaction in a granular array within microvessels. The endpoint of classic complement pathway activation is the formation of C5b-9 (C5b-9 stain; original magnification: ×400).

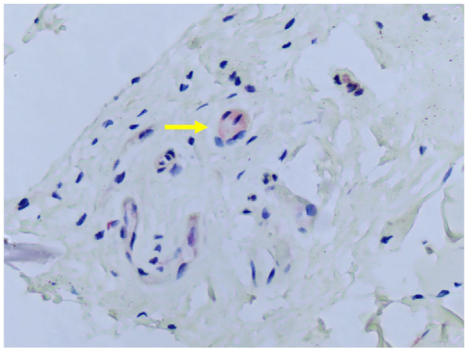

Fig 3. SARS-CoV-2 (COVID-19) Spike S1 Subunit Antibody. The *yellow arrow* points to human-manufactured spike glycoprotein localized to microvessels of the reticular dermis. In RA, immune complexes (in this case spike glycoprotein complexed to host-manufactured antibody) localize to the superficial microvessels of the skin. In this patient, since spike glycoprotein was already bound by host-manufactured antibody in the papillary dermis, the spike protein was not detected in the papillary dermal vasculature (red-chromagen stain; original magnification: ×400). Reproduced with permission from Gerard Nuovo, MD, Columbus, OH.

delivers mRNA that encodes the SARS-CoV-2 spike protein encapsulated in a lipid particle.[4] It is therefore possible that this spike glycoprotein, which is produced by myocytes upon vaccination, may act as an antigenic stimulus. In our case, spike glycoprotein was indeed identified in the deep cutaneous vessels (Fig 3). Another potential trigger is the polyethylene glycol vaccine additive, a polymer that is used to stabilize the lipid nanoparticle formulation. It has been suggested that this polymer, which is known to cause type I hypersensitivity reactions, may also cause delayed antibody-mediated responses.[3,4] A third possibility is that the vaccine may unmask a hypersensitivity reaction to an unidentified trigger, such as an asymptomatic infection. Though we cannot conclusively determine whether there was a causal relationship between the COVID-19 mRNA vaccine and the development of RA in our patient, further investigation of rare cases, such as this one, will ideally enhance our understanding of immune-mediated reactions to COVID-19 vaccination.

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Conflicts of interest

None disclosed.

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