CASE REPORT

# COVID-associated non-vasculitic thrombotic retiform purpura of the face and extremities: A case report

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**Abstract**

SARS-CoV-2 infection can manifest many rashes. However, thrombotic retiform purpura rarely occurs during COVID-19 illness. Aggressive anti-COVID-19 therapy with a high-dose steroid regimen led to rapid recovery. This immuno-thrombotic phenomenon likely represents a poor type 1 interferon response and complement activation on the endothelial surface in response to acute infection.

**KEYWORDS**
acral lesions, chilblains, COVID-19, exanthema, purpura, SARS-CoV-2, vasculitis

## 1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) may manifest a variety of dermatologic findings. In one international registry of 171 patients with laboratory confirmed SARS-CoV-2 infection, the COVID-associated rashes were morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%).[1] Here, we present the case of a diffuse, violaceous, nonpalpable purpura initially thought to be a severe presentation of COVID pernio; however, this rash lacked the perivascular inflammatory infiltrates to corroborate the diagnosis.[2] Rather, this purpura of the face and all four extremities demonstrated a pauci-inflammatory infiltrate and microthrombosis of the skin microvasculature consistent with COVID-associated nonvasculitic thrombotic retiform purpura. Ultimately a good clinical outcome was achieved, and the rash resolved

completely at 6 weeks following the initial onset and treatment with a course of steroids. Inherent to COVID-associated rashes are an underpinning endotheliitis. The immunomodulators engaged in the endotheliitis differ, however, and thus produce distinct rashes. We contrast the pathophysiology and clinical presentation of COVID-associated thrombotic retiform purpura to that of COVID pernio. This case report was written in accordance with the CARE guidelines.[3]

## 2 | CASE REPORT

A 55-year-old Caucasian female presented to her family physician with chief concern of worsening cough and shortness of breath. Her oxygen saturation on room air was purportedly 70%, and she was sent to the emergency room. Her symptoms began 6 days prior to presentation. She experienced chest pain with coughing, shortness of breath, myalgias, arthralgias, sore throat, anosmia, and dysgeusia. One day prior to emergency department presentation, she had started developing painful skin changes on the face and extremities that were continuing to spread and worsen in severity. The patient reported that the skin lesions were tender to palpation but not pruritic. She denied recent exposure to unusually cold or damp, nonfreezing weather. Interestingly, the patient was fully vaccinated against COVID-19 with the Pfizer two-dose series 6 months prior to admission (Figure 1). She did not drink alcohol or use illicit drugs and had not used tobacco for 11 years. Her comorbidities included hypertension, uncontrolled type 2 diabetes mellitus, hypercholesterolemia, anxiety, and depression. Her outpatient medication regimen included rosuvastatin (40 mg/day), lisinopril (20 mg/day), pioglitazone (30 mg/day), glipizide (10 mg/day), metformin (1000 mg/day), and empagliflozin (25 mg/day). She was not taking insulin. Index vital signs in the emergency room were remarkable for an oxygen saturation of 90% on room air, tachypnea of 20 breaths per minute, and systolic hypertension measuring 140/66. She was afebrile. The patient generally appeared nontoxic with nonlabored respirations. Lung auscultation demonstrated clear and vesicular breath sounds bilaterally without adventitial sounds. On skin examination, the patient had numerous purpura distributed haphazardly over her glabella, nose, cheeks, dorsal forearms, and shins. Similar lesions were noted much more minimally on the torso, upper arms, and thighs. Inspection of the fingertips and toes revealed confluent purpuric plaques encompassing the entirety
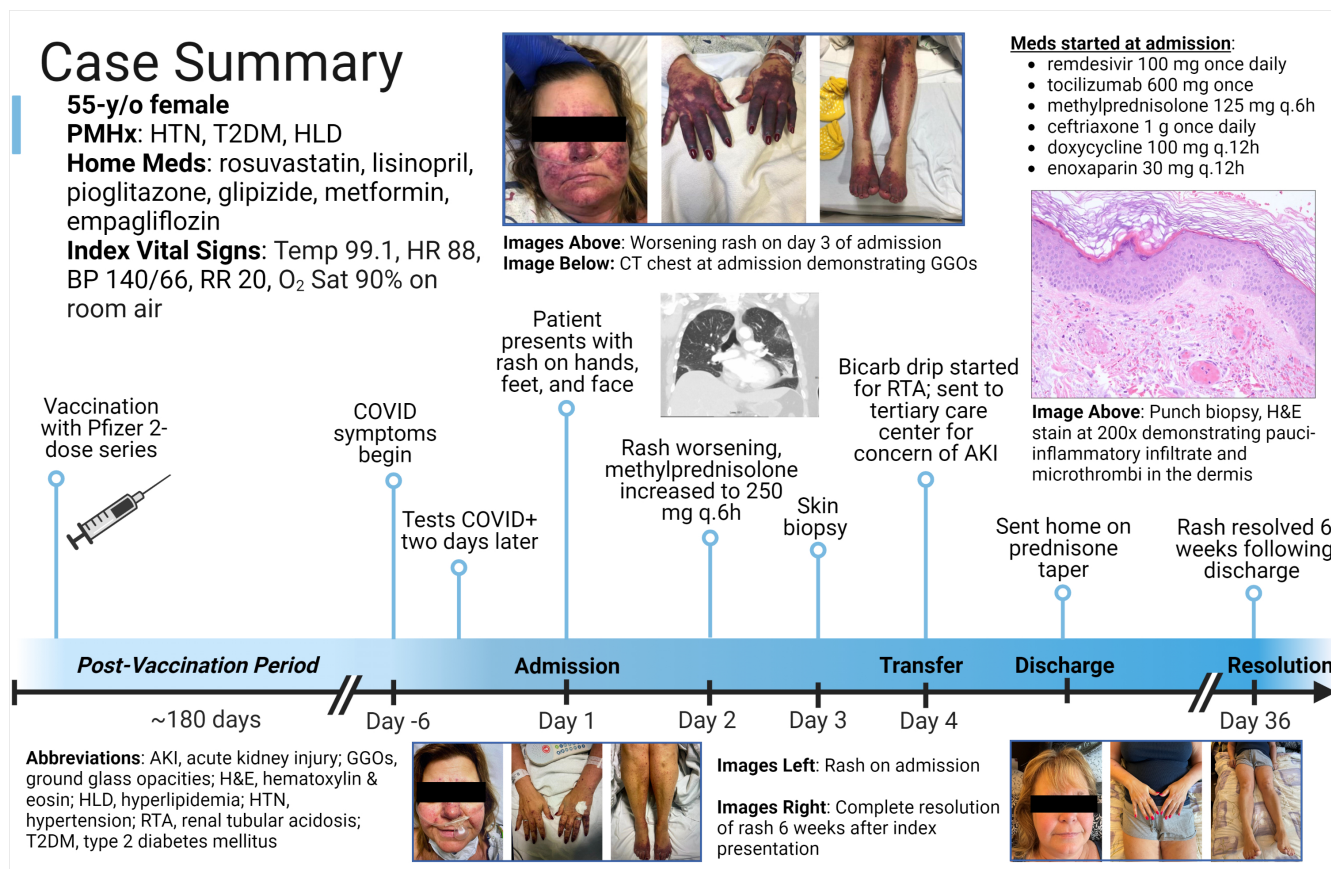


# Case Summary

**55-y/o female**
**PMHx**: HTN, T2DM, HLD
**Home Meds**: rosuvastatin, lisinopril, pioglitazone, glipizide, metformin, empagliflozin
**Index Vital Signs**: Temp 99.1, HR 88, BP 140/66, RR 20, O₂ Sat 90% on room air

**Images Above**: Worsening rash on day 3 of admission
**Image Below**: CT chest at admission demonstrating GGOs

**Meds started at admission**:
- remdesivir 100 mg once daily
- tocilizumab 600 mg once
- methylprednisolone 125 mg q.6h
- ceftriaxone 1 g once daily
- doxycycline 100 mg q.12h
- enoxaparin 30 mg q.12h

**Image Above**: Punch biopsy, H&E stain at 200x demonstrating pauci-inflammatory infiltrate and microthrombi in the dermis

Vaccination with Pfizer 2-dose series

COVID symptoms begin

Tests COVID+ two days later

Patient presents with rash on hands, feet, and face

Rash worsening, methylprednisolone increased to 250 mg q.6h

Skin biopsy

Bicarb drip started for RTA; sent to tertiary care center for concern of AKI

Sent home on prednisone taper

Rash resolved 6 weeks following discharge

*Post-Vaccination Period* — Admission — Transfer — Discharge — Resolution

~180 days | Day -6 | Day 1 | Day 2 | Day 3 | Day 4 | Day 36

**Abbreviations**: AKI, acute kidney injury; GGOs, ground glass opacities; H&E, hematoxylin & eosin; HLD, hyperlipidemia; HTN, hypertension; RTA, renal tubular acidosis; T2DM, type 2 diabetes mellitus

**Images Left**: Rash on admission

**Images Right**: Complete resolution of rash 6 weeks after index presentation

**FIGURE 1** Case timeline summary of COVID-associated nonvasculitic thrombotic retiform purpura. Created with BioRender.com.

of the distal digits with some extension proximally onto the bilateral distal feet. Lesions were nonscaly and nonpalpable. No erosions or ulcerations were noted in a complete dermatologic examination (Figure 2). Bilateral radial pulses and dorsalis pedis pulses were 2+. All four extremities were warm and had capillary refill of <3 s but had mild nonpitting edema.

On the day of admission, a nasopharyngeal swab sample was positive for SARS-CoV-2 messenger ribonucleic acid (mRNA) and negative for influenza A and B by a reverse transcription–polymerase chain reaction test. The laboratory results were remarkable for elevated white blood cell count, fibrinogen, D-dimer, erythrocyte sedimentation rate, C-reactive protein (CRP), interleukin-6, and lactate dehydrogenase. The serum bicarbonate was low while the electrolytes, blood urea nitrogen, creatinine, coagulation studies, and procalcitonin were within normal limits (Table 1). The electrocardiogram demonstrated normal sinus rhythm, and troponins were within normal limits. Blood cultures were obtained and ultimately negative. Urine analysis revealed trace proteinuria and 4+ glucose. Chest radiograph showed bilateral lower lung infiltrates. A computed axial tomography angiogram of the chest was negative for pulmonary embolism but demonstrated

bilateral peripheral ground-glass opacities. The patient was started on 100 mg/day of remdesivir, one 600 mg dose of tocilizumab, and 125 mg of methylprednisolone every 6 h (q6h) for COVID-19 pneumonitis. Ceftriaxone (1 g q24h) and doxycycline (100 mg q12h) were also administered prophylactically against superimposed bacterial pneumonia. Enoxaparin (30 mg q12h) was started for venous thromboembolism prophylaxis.

On the second day of admission, the patient's skin changes became more widespread and severe, with an increasing number of purpuric macules on the face and the development of confluent purpuric patches on the forearms and legs. Retiform purpura were present on the fingers, hands, toes, and distal feet. The patient reported less tenderness in her feet but more tenderness in the hands, especially when picking up items. Her oxygen saturation was 95% on 2 L/min oxygen via nasal cannula. CRP and D-dimer levels both notably increased, and white blood cell count decreased. Immunologic workup included anti-cardiolipin antibody, antinuclear antibodies (ANA), rheumatoid factor (RF), cytoplasmic antineutrophil cytoplasmic autoantibody (c-ANCA), and complement levels to rule out underlying lupus, systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis, and c-ANCA-associated
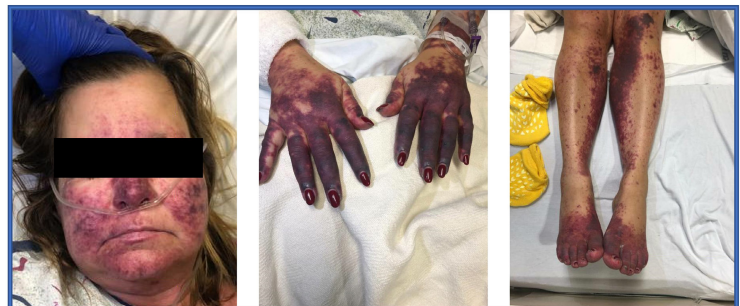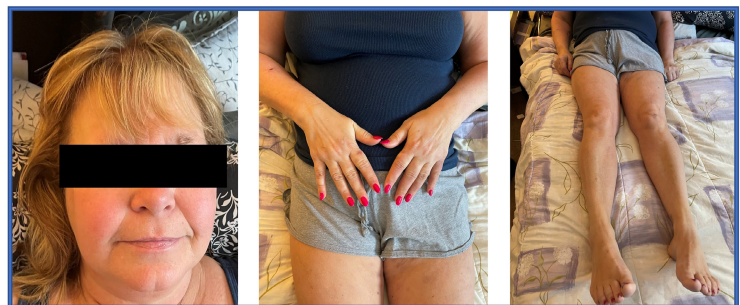


**FIGURE 2** Top Row: Clinical images from the day of presentation showing purplish patches on the face, bilateral hands, forearms, feet, and legs. Middle Row: Clinical images from the third day of admission showing worsening purpura. Bottom Row: Images 6 weeks after index presentation demonstrating complete resolution of the rash.

causes of vasculitis. All tests were unremarkable including complement component 3 (C3) and total complement levels, except for a mild, nonspecific elevated C4 level (Table 1). Because of the worsening skin lesions, the methylprednisolone dose was increased to 250 mg q6h. Upper and lower extremity duplex ultrasound was negative for deep vein thrombosis, and another dose of tocilizumab was administered.

On the third day of admission, the patient's skin rash continued to intensify on the face, hands, and legs; however, the lesions on the soles of her feet began to fade. The patient was concerned about increased swelling in the digits. Her oxygen saturation remained 100% on 2 L/min nasal cannula. CRP decreased significantly to below the levels on the day of admission. ANA, RF, and c-ANCA resulted negative. A 4 mm punch biopsy of lesional skin on the right dorsal forearm was performed. Histologic review of hematoxylin and eosin (H&E) stained slides demonstrated a pauci-inflammatory vascular infiltrate with microvascular thrombosis and red cell extravasation consistent with an occlusive nonvasculitic vasculopathy (Figure 3).

On the fourth day of admission, the patient was started on a bicarbonate drip at a rate of 150 ml/h due to low bicarbonate and normal chloride levels. With concern of renal tubular acidosis (RTA) and acute kidney injury, the patient was transferred to a university hospital where she was followed by a rheumatology team for several days and subsequently discharged on a prednisone taper. Thirteen days after discharge, the patient followed up with her family physician. At that time, she reported residual mild cough and fatigue and that the rash was clearing. At a second follow-up 6 weeks following the initial rash onset, her skin lesions had completely resolved (Figure 2).

## 3 | DISCUSSION

Thrombotic retiform purpura occurs with thrombotic, embolic, or infectious impedance of blood flow in the dermal and hypodermal microvasculature leading to vessel engorgement and extravasation.[4] The differential diagnosis for occlusive nonvasculitic vasculopathies includes cryoglobulinemia, antiphospholipid antibody syndrome,

**TABLE 1** Laboratory results throughout hospital stay

| Lab test | Reference range* | First day of admission | Second day of admission | Third day of admission | Fourth day of admission | Six weeks after admission |
|---|---|---|---|---|---|---|
| White blood cell count (K/μl) | 4.0–11.0 | 10.0 | 6.4 | 11.4 | 7.3 | 8.0 |
| Fibrinogen (mg/dl) | 180–350 | 664 | – | 436 | 290 | – |
| D-dimer (μg/ml FEU) | 0.19–0.49 | 2.53 | 4.18 | 4.34 | 2.29 | – |
| Erythrocyte sedimentation rate (mm/h) | 0–29 | 68 | – | – | – | 12 |
| C-reactive protein (mg/L) | 0.0–3.0 | 65.9 | 106.0 | 46.6 | 24.1 | – |
| Interleukin-6 (pg/ml) | 0.0–13.0 | 63.8 | – | – | – | – |
| Lactate dehydrogenase (units/L) | 110–225 | 273 | 287 | 267 | 247 | 254 |
| Sodium (mmol/L) | 134–145 | 137 | 137 | 140 | 136 | 143 |
| Potassium (mmol/L) | 3.6–5.2 | 3.8 | 4.6 | 4.8 | 4.2 | 4.2 |
| Chloride (mmol/L) | 96–108 | 100 | 101 | 105 | 101 | 106 |
| Carbon dioxide (mmol/L) | 21–29 | 16 | 12 | 13 | 22 | 21 |
| Glucose (mg/dl) | 70–105 | 116 | 155 | 203 | 304 | 95 |
| Blood urea nitrogen (mg/dl) | 8–23 | 25 | 28 | 34 | 32 | 22 |
| bun/creatinine ratio | 12.0–20.0 | 31.3 | 36.8 | 52.3 | 58.2 | 29 |
| Procalcitonin (ng/ml) | 0.00–0.09 | 0.07 | – | – | – | – |
| Complement component 3 (mg/dl) | 82–167 | – | 143 | – | – | – |
| Complement component 4 (mg/dl) | 12–38 | – | 47 | – | – | – |
| Total complement (units/ml) | >41 | – | >60 | – | – | – |
| Rheumatoid factor (international units/ml) | 0.0–14.0 | 10.3 | – | – | – | – |

Abbreviation: FEU, fibrinogen equivalent units.

*Reference ranges obtained from Saint Joseph Regional Medical Center.

disseminated intravascular coagulation, calciphylaxis, cholesterol embolization syndrome, heparin necrosis, warfarin necrosis, protein C and S deficiencies, thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, endocarditis, ecthyma gangrenosum, disseminated aspergillosis, visceral and hematologic malignancies, and cocaine use adulterated with levamisol; and now, SARS-CoV-2 infection.[4–6]

Here, we report a case of diffuse nonvasculitic thrombotic retiform purpura of the face, hands, forearms, feet, and legs with associated RTA in the setting of acute Delta variant COVID-19 pneumonitis, which occurred 6 months after receiving the BNT162b2 vaccine (Pfizer) two-dose series. This patient's proposed hyperimmune response required not only standard antiviral and immunologic
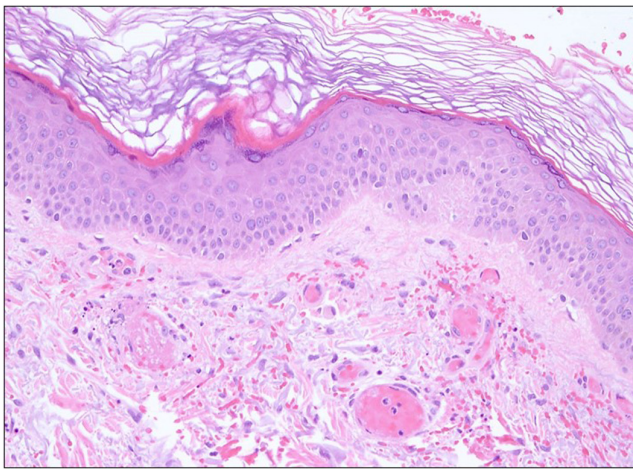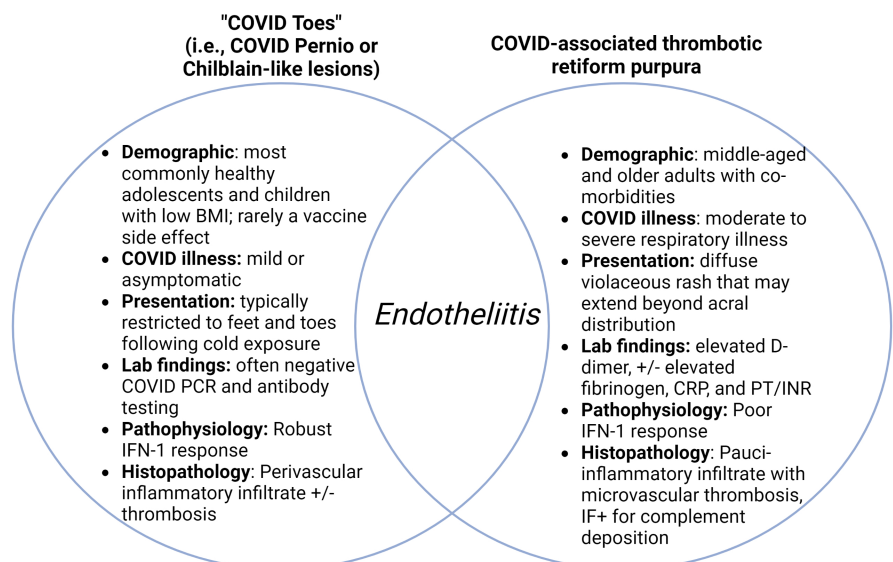


**FIGURE 3** Punch biopsy of right dorsal forearm, hematoxylin & eosin stain, 200× magnification. There is occlusion of postcapillary venules in the superficial dermis by platelet-fibrin thrombi. This is associated with red blood cell extravasation. No associated vasculitis is present.

treatment specific for COVID-19 in the form of remdesivir and the anti-interleukin-6 monoclonal antibody tocilizumab but also high-dose bolus steroids normally reserved for systemic autoimmune diseases such as severe leukocytoclastic vasculitis (LCV) or lupus nephritis.[7,8] On the second day of admission, an attempt was made to attenuate the immunothrombotic response by increasing her steroid therapy to 250 mg of methylprednisolone every 6 h. A review of the literature reveals that high-dose steroids can be used in the treatment of COVID-19 pneumonia.[9,10]

We propose that a spectrum of immunothrombotic coagulopathy occurs in patients with COVID-associated rashes. Acral cutaneous lesions associated with coronavirus disease 2019 (COVID-19) have largely been described in the pediatric, adolescent, and young adult populations who have minimal systemic disease with the presence of cutaneous LCV on the toes following cold exposure.[11] Colloquially referred to as "COVID toes", COVID pernio or chilblain-like lesions most often associates with a mild or indolent infection with the SARS-CoV-2 virus.[11,12] In those with indolent or mild illness such as the healthy youth, the predominant mechanism is a robust type 1 interferon (IFN-1) response.[13] Interestingly, the majority of COVID toes cases have negative PCR results and antibody testing for SARS-CoV-2.[11] This finding mechanistically supports the robust IFN-1 response that may suppress humoral antibody production and accentuate cell-mediated clearance of the virus at the endothelium, causing the vasculitic endotheliopathy.[2,13] IFN-I behaves as a bridge between adaptive and innate immunity with direct influence on immunomodulation. The robust production of IFN-I in the pediatric population may explain the lower rates of respiratory and systemic symptoms. This is significant since these COVID-19 perniosis-like lesions are like those described in patients with interferonopathies where

**FIGURE 4** Venn diagram comparing the salient features of the "COVID toes" rash and COVID-associated thrombotic retiform purpura.[2,11–13] Created with BioRender.com. BMI, body mass index; CRP, C-reactive protein; IF, immunofluorescence; IFN, interferon; INR, international normalized ratio; PCR, polymerase chain reaction; PT, prothrombin time



**"COVID Toes" (i.e., COVID Pernio or Chilblain-like lesions)**

- **Demographic**: most commonly healthy adolescents and children with low BMI; rarely a vaccine side effect
- **COVID illness**: mild or asymptomatic
- **Presentation**: typically restricted to feet and toes following cold exposure
- **Lab findings**: often negative COVID PCR and antibody testing
- **Pathophysiology**: Robust IFN-1 response
- **Histopathology**: Perivascular inflammatory infiltrate +/- thrombosis

*Endotheliitis*

**COVID-associated thrombotic retiform purpura**

- **Demographic**: middle-aged and older adults with co-morbidities
- **COVID illness**: moderate to severe respiratory illness
- **Presentation**: diffuse violaceous rash that may extend beyond acral distribution
- **Lab findings**: elevated D-dimer, +/- elevated fibrinogen, CRP, and PT/INR
- **Pathophysiology**: Poor IFN-1 response
- **Histopathology**: Pauci-inflammatory infiltrate with microvascular thrombosis, IF+ for complement deposition

there is a defective regulation that causes excess production of interferons.[14–17] The mechanisms are comparable of the interferon-mediated, pre-COVID-19 era pernio-like rashes; specifically, there is an activation of the angiotensin II pathway–mediated proinflammatory and prothrombotic activity as well as increased vasospasm associated with increased release of IFN-I.[17–19] Thrombotic microangiopathy is a common histopathological marker of interferonopathies that is known to cause chilblain-like lesions.[20]

However, at the opposite end of the coagulopathic spectrum lies those patients with COVID-associated purpuric rashes with a predominate microthrombotic and pauci-inflammatory histologic pattern which reflects the underlying severity of the COVID-19 systemic illness and hypercoagulopathic state of these older, comorbid patients. In these sicker patients, prior evidence demonstrates a weaker IFN-1 response and increased complement activation by both the lectin and alternative pathways on the endothelial surface.[2] Complement factors C3d and C4d have been identified in subendothelial and dermal deposits of these patients, as well as the membrane attack complex C5b-9 on the endothelial surface.[2,12,21] Figure 4 contrasts the prevailing clinical presentations and pathophysiology between COVID-associated thrombotic retiform purpura and COVID toes.

COVID-associated rashes, predominately COVID pernio, has also been well-documented as a side effect of COVID-19 vaccination.[22–28] Another suggested mechanism for the COVID-19 vaccination–associated rashes is a delayed hypersensitivity reaction. It has been proposed that the autoimmune reactions following both innate and adaptive immune responses that cause LCV and associated functional angiopathies such as chilblains are mediated by a molecular mimicry due to the genetic similarities between the SARS-CoV-2 spike protein and endogenous cross-reactive human antigens. A COVID-19-mediated hyperactivation of the immune system is caused by a similar molecular mimicry between the virus and self-antigens which has been shown to trigger autoimmune responses such as myocarditis, immune-mediated myositis, antiphospholipid syndrome, and vasculitis with associated histopathologic manifestation of immunothrombosis.[29–32]

In adults, it has been shown that these COVID-associated vaso-occlusive lesions occur predominantly in hospitalized patients.[12,33] The presence of a COVID-associated rash in an adult suggested that our patient was at a higher risk for severe COVID-19 illness. Her previous immunization may have contributed to the hyperimmune and hyperthrombotic state that manifested with a purpuric rash that required immunomodulation with high dose corticosteroids, monoclonal antibody treatment, and specific antiviral therapy.

Although the purpuric rash initially was felt to be COVID pernio or chilblain-like rash, her moderately severe disease with involvement of the lung and kidney and diffuse nature of the rash corresponded to a COVID toes mimic, manifested by the preponderance of a microthrombotic and pauci-inflammatory histologic appearance. It has been proposed that a spectrum of coagulopathy based on severity of COVID-19 disease underlies the varied presentations of the COVID-associated rashes in patients with COVID-19 illness, and this case represents a preponderance of thrombosis along the immunothrombotic spectrum.

Ultimately, the patient experienced a full resolution of the rash at 6 weeks following its onset. However, she was experiencing some post-acute sequelae of COVID-19 in the form of fatigue and persistent cough. One limitation of this case report is the lack of immunofluorescent testing of the biopsy specimen to corroborate prior studies demonstrating complement deposition.

## 4 | CONCLUSIONS

This case represents a severe manifestation of an immunothrombotic response to both acute infection by COVID-19 and adaptive response to prior COVID-19 immunization. The patient's hyperimmune response required aggressive treatment with immunomodulatory therapy of monoclonal antibodies, high-dose corticosteroids, and antiviral treatment. The quick response to this regimen resulted in full clearing of the rash, which supports the hypothesis that this patient's clinical manifestation was caused by both coagulopathy and autoimmune disease.

**AUTHOR CONTRIBUTIONS**
**Connor M. Bunch:** Conceptualization; project administration; visualization; writing – original draft; writing – review and editing. **Nuha Zackariya:** Conceptualization; project administration; writing – review and editing. **Anthony V. Thomas:** Conceptualization; project administration; writing – original draft; writing – review and editing. **Jack H. Langford:** Writing – original draft; writing – review and editing. **Michael Aboukhaled:** Writing – review and editing. **Samuel J. Thomas:** Writing – original draft; writing – review and editing. **Aida Ansari:** Writing – review and editing. **Shivani S. Patel:** Writing – review and editing. **Hallie Buckner:** Writing – review and editing. **Joseph B. Miller:** Conceptualization; project administration; writing – original draft; writing – review and editing. **Christy L. Annis:** Writing – original draft; writing – review and editing. **Margaret A. Quate-Operacz:** Writing – original draft; writing – review and editing. **Leslie A. Schmitz:** Writing sss– original draft; writing – review and editing. **Joseph J.**

**Pulvirenti:** Writing – review and editing. **Jonathan C. Konopinski:** Writing – original draft; writing – review and editing. **Kathleen M. Kelley:** Conceptualization; project administration; writing – original draft; writing – review and editing. **Samer Hassna:** Writing – original draft; writing – review and editing. **Luke G. Nelligan:** Writing – original draft; writing – review and editing. **Mark M. Walsh:** Conceptualization; data curation; funding acquisition; project administration; visualization; writing – original draft; writing – review and editing.

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## CONFLICT OF INTEREST

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## DATA AVAILABILITY STATEMENT

All relevant data are presented in the case. Any other data or inquiries about the case are available from the corresponding author upon request.

## CONSENT

Written informed consent was obtained from the patient to publish the clinical course and photographs.

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