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REVIEW ARTICLE

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SARS-CoV-2 vaccination-induced cutaneous vasculitis: Report of two new cases and literature review

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Abstract

Currently the most powerful tool in combating the COVID-19 pandemic is vaccination against SARS-CoV-2. A growing percentage of the world's population is being vaccinated. Various vaccines are worldwide on the market. Several adverse reactions have been reported as a part of post-marketing surveillance of COVID-19 vaccines. Among the possible adverse events, cutaneous vasculitis has occasionally been reported. We present a narrative review on cutaneous vasculitis related to COVID-19-vaccination to summarize clinical findings, histopathology, treatment and outcome. We searched for "COVID vaccine", "COVID vaccination" AND "cutaneous vasculitis" in PUBMED. Articles in English have been selected, from inception to December 2021, and analyzed for patient's characteristics, type of vaccine, time of appearance of cutaneous vasculitis and clinico-histopathologic type. Treatment and outcome have also been considered in this narrative review. Two new unpublished cases of ours were added. Cutaneous vasculitis is a rare adverse event to COVID-19 vaccination. It has been observed with mRNA and adenovirus-vector vaccines. IgA vasculitis, lymphocytic and ANCA-associated vasculitis, leukocytoclastic and urticarial vasculitis have been reported. This adverse event can occur after first or second shot. Most cases run a mild to moderate course. Cornerstone of medical treatment are systemic corticosteroids. Complete remission could be achieved in most patients. Vasculitis may not be considered as a contraindication of vaccination, being uncommonly reported and shows a favorable prognosis. The benefit of the vaccination remains high especially for immunocompromised patients. COVID-vaccine induced vasculitis is important in the differential diagnosis of purpuric and vasculitis disorders.

KEYWORDS
adverse events, COVID-19, cutaneous vasculitis, mRNA vaccine, SARS-CoV-2 vaccination, vector vaccine

1 | INTRODUCTION

Vasculitis represent a heterogeneous group of disorders with blood vessels inflammation. The classification of vasculitis based upon vessels affected, dominant cells of the inflammatory infiltrate and clinical characteristics. The ideal classification has yet to be found.[1] Vascular affection is common in COVID-19 disease. Thromboembolic and inflammatory reaction patterns have been observed.[2] Vaccination against SARS-CoV2 is currently the most powerful medical approach against the pandemic. Although the various vaccines are in general well-tolerated, adverse events have occasionally been reported including the appearance or re-activation of cutaneous vasculitis.[3] In

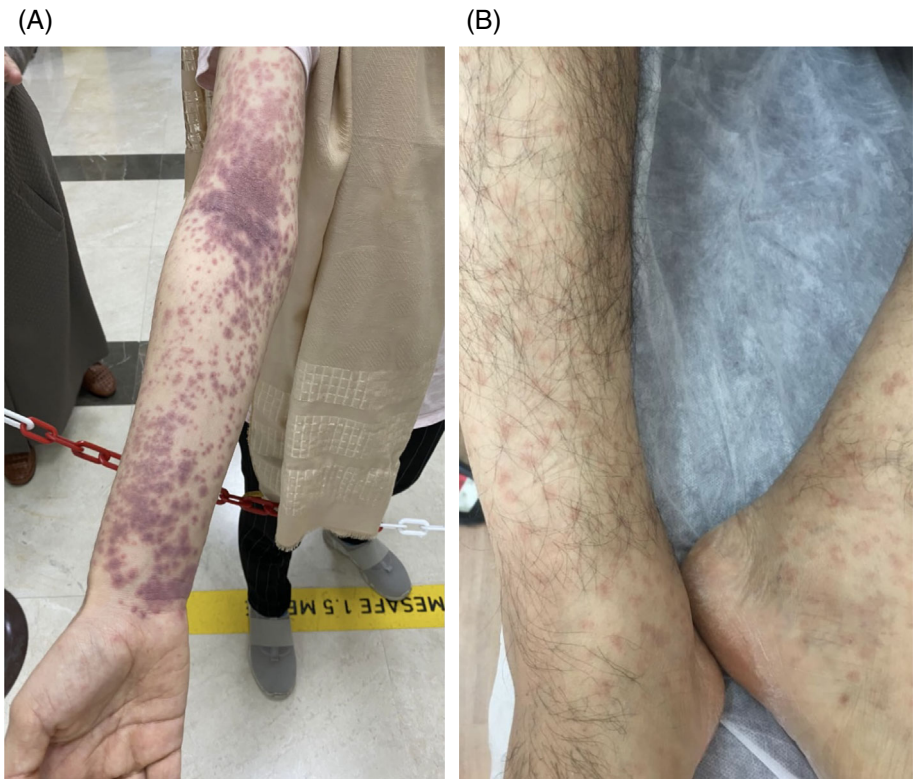

FIGURE 1 (A) A case of a 17-year-old female with IgA-vasculitis 10 days after the first dose of Pfizer-BioNTech BNT16B2b2 mRNA vaccine. (B) A case of 48-year-old man with LCV 4 days after the second dose of Pfizer-BioNTech BNT16B2b2 mRNA vaccine

this narrative review, we analyzed the available data in the English medical literature to better characterize these adverse events and discuss the treatment options. Two new unpublished cases of ours were added (Figure 1).

2 | MATERIAL AND METHODS

We searched for "COVID vaccine", "COVID vaccination" AND "cutaneous vasculitis" in PUBMED. Articles in English have been selected, from inception to December 2021, and analyzed for patient's characteristics, type of vaccine, time of appearance of cutaneous vasculitis and clinico-histopathologic type. Treatment and outcome have also been considered in this narrative review. The results of our research have been classified according to the subtype of vasculitis.

3 | RESULTS

Of the 38 cases, including ours, 52.6% (20 cases) had received the mRNA vaccine, 31.6% (12 cases) had received ChaAdOx1 nCoV-19 vaccine (vector), and 15.8% (6 cases) had received the inactivated SARS-CoV-2 vaccine. Vasculitis developed in 63.2% (24 cases) after the first dose. The mean age of the cases was 53. 65.8% (25 cases) of the cases were female. 55.3% (20 cases) were LCV, 23.7% (9 cases) were IgA vasculitis, 7.9% (3 cases) were lymphocytic vasculitis, 5.3% (2 cases) were ANCA-associated vasculitis, 5.3% (3 cases) was urticarial vasculitis, and 2.6% (1 cases) was Immune Complex Vasculitis. The average occurrences time was 6.2 days. The lesions in the cases disappeared in an average of 2.5 weeks. The average occurrences time was 6.2 days. The lesions in the cases disappeared in an average of 2.5 weeks. The following is an overview of the reviewed cases. Summary of the data is highlighted in Table 1.

3.1 | IgA vasculitis

IgA vasculitis is an of small vessel vasculitis caused by perivascular deposition of IgA1 and activation of neutrophils. It may present as systemic vasculitis (Henoch-Schönlein purpura) or as a skin-limited variant. IgA-vasculitis is the most common vasculitis type in infants.[39] IgA vasculitis has been observed after Pfizer-BioNTechBNT16B2b2 mRNA vaccine and Vaxzevria (ChAdOx1 nCoV-19 AZD1222) vaccine.[4–6,10–15] In case of appearance after first shot, a second shot of vaccination did not cause a relapse of the vasculitis symptoms. Treatment of choice was oral corticosteroids; however, spontaneous remission was occasionally reported. Interestingly, of the reviewed cases, two had history of COVID-19 infection; two had history of IgA vasculitis.[6,10–15]A favorable risk–benefit profile of BNT162b2 in rheumatoid arthritis patients, including those on biologics, has been noted.[15,40]

3.2 | Lymphocytic vasculitis

Lymphocytic vasculitis is a histologic reaction pattern with a dominant lymphocytic inflammatory infiltrate that correlates with broad clinical

TABLE 1 Cutaneous vasculitis reports related to SARS-CoV-2 vaccine in the literature, and two new cases

Author year	A/G	Clinical findings	Histopathology /Vasculitis type	Time to reaction	Time to resolution	Which dose	Outcome	Treatment	Vaccine type
Hines et al., 2021[4]	40/F	Gluteal region rash	IgA Vasculitis	20 days	1 week	Second dose	Recovery	Only follow-up	Pfizer-BioNTech BNT16B2b2
Sirufo et al., 2021[5]	76/F	Maculopapular purpuric rash on gluteal and leg regions	IgA Vasculitis	7 days	3 weeks	First dose	Recovery	Deflazacort 30 mg/kg for ten days	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Naitlho et al., 2021[6]	62/M	Petechial purpuric rashinvolving both legs	IgA Vasculitis	8 days	1 week	First dose	Recovery	Prednisone 40 mg per day for 7 days	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Vassallo et al., 2021[7]	51/F	Maculopapular rash on upper limbs and trunk	Lymphocytic vasculitis	1 day	2 weeks	First dose	Recovery	Systemic antihistamine and local steroid	Pfizer-BioNTech BNT16B2b2
Kharkar et al., 2021[8]	31/F	Purpuric lesions on her legs	Lymphocytic vasculitis	1 day	2 weeks	Second dose	Recovery	Systemic antihistamine	Inactivated viral vaccineCOVAXIN®
Ungari et al., 2021[9]	64/M	Maculopapular rash on the limbs and trunk	Lymphocytic vasculitis	3 days	2 weeks	Second dose	Recovery	Only follow-up	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Badier et al., 2021[10]	72/M	Maculopapular rashlower limbs	IgA Vasculitis	15 days	3–4 weeks	First dose	Recovery	Prednisone 40 mg per day for 3 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Bostan et al., 2021[11]	33/M	Erythematous macules and palpable papules on the legs, forearms	Leukocytoclastic vasculitis	3 days	2 weeks	First dose	Partial resolution	Local steroid	Inactivated COVID-19 vaccine (CoronaVac)
Maye et al., 2021[12]	23/F	Palpable purpuric rash on the extremities and trunk	IgA Vasculitis	2 days	2 weeks	Second dose	Recovery	Prednisone 20 mg per day for 2 weeks	Pfizer-BioNTech BNT16B2b2
Obeid et al., 2021[13]	78/F	Palpable purpura on the hips and lower limbs	IgA Vasculitis	7 days	2 weeks	First dose	Recovery	Methylprednisolone 1 mg/kg for 2 weeks	mRNA-1273 (Moderna) vaccine
Grossmanet al., 2021[14]	94/M	Palpable purpura on the waist	IgA Vasculitis	10 days	3 weeks	Second dose	Recovery	Prednisone 60 mg/day for 3 weeks	mRNA-1273 (Moderna) vaccine
Iwata et al., 2021[15]	70/F	Palpable purpura on the feet	IgA Vasculitis	2 days	3 weeks	Second dose	Recovery	Only follow-up	Pfizer-BioNTech BNT16B2b2
HakroushandTampe., 2021[16]	79/F	Upper thigh pain	ANCA-associated vasculitis	14 days	4 weeks	Second dose	Partial resolution	Methylprednisolone 250 mg per day for 3 days	Pfizer-BioNTech BNT16B2b2
Okuda et al., 2021[17]	37/F	Erythema on her bilateral forearms, forehead, and thighs, and red and swollen left auricle	ANCA-associated vasculitis	12 days	3 weeks	First dose	Partial resolution	Prednisolone 30 mg/ day for 3 weeks	Pfizer-BioNTech BNT16B2b2
Fritzen et al., 2021[18]	60/F	Painful purpuric lesions and palpable papules on the lower limbs	Leukocytoclastic vasculitis	13 days	2 weeks	Second dose	Recovery	Prednisolone 60 mg/ day for 2 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Cohen et al., 2021[19]	46/F	Erythematous palpable papules on the legs	Leukocytoclastic vasculitis	2 days	2 weeks	Second dose	Recovery	Prednisolone 20 mg/ day for 2 weeks	Pfizer-BioNTech BNT16B2b2

(Continues)

TABLE 1 (Continued)

Author year	A/G	Clinical findings	Histopathology /Vasculitis type	Time to reaction	Time to resolution	Which dose	Outcome	Treatment	Vaccine type
Ball-Burack et al., 2021[20]	22/M	Palpable purpura on the dorsal feet and the both lower extremities	Leukocytoclastic vasculitis	10 days	3 weeks	First dose	Recovery	Systemic antihistamine and local steroid	Johnson & Johnson SARS-CoV-2 vaccine
Nastroet al., 2021[21]	84/M	Palpable purpura on the legs	Leukocytoclastic vasculitis	2 days	2 weeks	First dose	Recovery	Systemic antihistamine and local steroid	Pfizer-BioNTech BNT16B2b2
Sandhu et al., 2021[22]	55/F 48/M	Palpable purpura over both ankles, that progressed to the lower limb	Leukocytoclastic vasculitis	5 days	2 weeks	First dose	Recovery	Prednisolone 0.5 mg/kg/day, for 2 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Bostan et al., 2021[23]	57/F	Widespread erythematous eruption involving the trunk and extremities	Leukocytoclastic vasculitis	7 days	1 week	First dose	Recovery	Prednisolone 20 mg/day for 1 week	Pfizer-BioNTech BNT16B2b2
Dickset al., 2021[24]	65/M	Palpable purpuric lesions on the legs	Leukocytoclastic vasculitis	2 days	3 weeks	Third dose	Recovery	Prednisolone 60 mg/day for 1 week	Pfizer-BioNTech BNT16B2b2
Bencharattanaphakhi et al., 2021[25]	23/F 26/F	Erythematous pinpoint purpura on the lower and upper extremities	Leukocytoclastic vasculitis	2 days	4 weeks	First dose	Recovery	Prednisolone 20 mg/day for 5 days in patient A and oral colchicine 0.6 mg twice a day in patient B	Inactivated COVID-19 vaccine (CoronaVac)
Kar et al., 2021[26]	46/F	Purpuric papules on the legs	Leukocytoclastic vasculitis	5 days	2 weeks	First dose	Recovery	Systemic antihistamine and local steroid	Inactivated viral vaccine COVAXIN®
Jin et al., 2021[27]	68/F	Erythematous macules on both lower extremities	Leukocytoclastic vasculitis	2 days	3 weeks	First dose	Recovery	Oral colchicine 1.2 mg/day and topical steroid for 3 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Cavalliet al., 2021[28]	57/M	Erythematous macules on both lower extremities	Leukocytoclastic vasculitis	6 days	3 weeks	First dose	Recovery	Prednisolone 1 mg/kg/day for 3 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Liang et al., 2021[29]	62/F	Petechial rash on the bilateral lower limb	Leukocytoclastic vasculitis	7 days	3 weeks	First dose	Recovery	Prednisolone 1 mg/kg/day for 3 weeks	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Guzmán-Pérez et al., 2021[30]	57/F	Palpable purpura lesions on the buttocks	Leukocytoclastic vasculitis	1 day	1 week	First dose	Recovery	Only follow-up	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Shahrigharahkoshanet al., 2021[31]	77/F	Palpable papules on the lower limb and the hands	Leukocytoclastic vasculitis	10 days	5 weeks	First dose	Recovery	Dapsone 50 mg daily was prescribed for 60 days	Oxford-AstraZenecaCOVID19 = ChaAdOx1 nCoV-19
Erler et al., 2021[32]	42/F	Progressive rash on the lower legs and the gluteal region	Leukocytoclastic vasculitis	4 days	1 week	First dose	Recovery	Only follow-up	Pfizer-BioNTech BNT16B2b2

TABLE 1 (Continued)

Author year	A/G	Clinical findings	Histopathology /Vasculitis type	Time to reaction	Time to resolution	Which dose	Outcome	Treatment	Vaccine type
Colia et al., 2021[33]	22/F	Purpuric rash on the legs	Leukocytoclastic vasculitis	7 days	3 weeks	Second dose	Recovery	Prednisolone 25 mg/day for 1 week	Pfizer-BioNTech BNT16B2b2
Dash et al., 2021[34]	27/M	Urticarial plaques over the trunk and extremities	Urticarial vasculitis	7 days	1 week	Second dose	Recovery	Oral indomethacin 75 mg once daily	Inactivated COVID-19 vaccine (CoronaVac)
Mückeet al., 2021[35]	76/M	Purpuric rash with palpable purpura on both hands, legs and thighs	Immune Complex Vasculitis	12 days	3 weeks	Second dose	Recovery	Prednisolone 40 mg/day for 2 weeks	Pfizer-BioNTech BNT16B2b2
Larson et al., 2021[36]	83/F	Palpable purpura on both hands, legs and thighs	Leukocytoclastic vasculitis	7 days	2 weeks	Second dose	Recovery	Oral antibiotic and topical corticosteroids	Pfizer-BioNTech BNT16B2b2
Larson et al., 2021[36]	35/F	Palpable purpura on both hands, legs and thighs	Urticarial vasculitis	1 day	4 weeks	First dose	Recovery	Systemic antihistamines, methylprednisolone, and dapsone	mRNA-1273 (Moderna) vaccine
Altun et al., 2021[37]	38/M	Palpable purpura on legs	Leukocytoclastic vasculitis	4 days	2 weeks	First dose	Recovery	Systemic antihistamines, methylprednisolone	Pfizer-BioNTech BNT16B2b2
Nazzaro et al., 2021[38]	27/F	Maculopapular rash on both hands, legs and trunk	Urticarial vasculitis	10 days	3 weeks	First dose	Recovery	Systemic methylprednisolone	mRNA-1273 (Moderna) vaccine
Our Cases	17/F 48/M	Palpable purpura on both arms and legs Palpable purpura on both legs	IgA Vasculitis Leukocytoclastic vasculitis	10 days 4 days	4 weeks 3 weeks	First dose Second dose	Recovery	Systemic antihistamine and local steroid	Pfizer-BioNTech BNT16B2b2

Abbreviations: A, Age; F, Female; G, Gender; M, Male.

differential diagnosis from lichenoid, infectious, neoplastic to autoimmune connective tissue disorders.[41] Only three cases have been reported so far.[7–9] Kharkar et al.[8] reported a 31-year-old woman with painful purpuric lesions on her legs with pedal edema, one day after her second dose of inactivated viral vaccine (COVAXIN®; Bharat Biotech, Hyderabad, India). RT-PCR for SARS-CoV-2 infection was negative. The lesions improved over 10 days on antihistaminic. Eosinophils were reported in some of histology-confirmed cutaneous manifestations associated with COVID-19. Cinottiet al.[42] reported a case of eosinophilic cellulitis after the first dose of AstraZeneca vaccination in an elderly man. In a biopsy-proven study on cutaneous reactions after mRNA-based COVID-19 vaccines, Tihyet al.[43] noted that most of the COVID-19-vaccine induced reactions cases have the features of drug reaction-like such as epidermal keratinocyte necrosis associated with a perivascular lymphocytic infiltrate in the superficial and mid dermis, and a variable number of eosinophils and sometimes neutrophils. Interestingly, in a recent study, purpura on the lower legs was mostly seen in patients with severe "Drug-induced hypersensitivity syndrome."[44]

3.3 | ANCA-associated vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is an autoimmune vasculitis type which affects small- to medium-sized vessels. ANCA-associated vasculitis includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.[45] Only 2 cases of ANCA-associated vasculitispresented with associated cutaneous findings post-COVID-19 vaccination.[16,17] Kidney biopsy of one cases confirmed severe acute tubular injury with pauci-immune crescentic GN and interstitial nephritis. The kidney function then normalized following intravenous cyclophosphamide (initiated at 10 mg/kg).[16]

3.4 | Leukocytoclastic vasculitis

Leukocytoclastic vasculitis(LCV) represents a type of small vessel vasculitis, characterized by presence of neutrophil infiltrates, leukocytoclasis, fibrinoid necrosis, resulting in vessel walls damage.[46] Twenty cases of COVID-19-vaccine triggered-LCV were noted; three with an elevated anti-Spike SARS CoV-2 Antibody titer, two of them had no history of COVID-19.Oral mucosal involvement was noted in one case. Only one had cryoglobulinemia.[7,18–33,36,37] Nastro et al.[21] reported an 84-year-old woman, with history of chronic kidney disease and depressive disorder, developed burning pain on the distal part of right leg and foot, followed by ipsilateral multiple non-confluent purpuric papules and vesicles few hours after she received the first dose of Pfizer-BioNTech COVID-19 vaccine. PCR of a skin swab for varicella-zoster virus (VZV) resulted positive, and VZV IgM and IgG antibodies were positive. Skin biopsy of right lower leg consisted with LCV. Direct immunofluorescence test was negative. Atypical herpes zoster associated with cutaneous vasculitis was considered. Famciclovir 500 mg orally every 8 h for 10 days was started. Complete resolution of the lesion 2 weeks later with the persistence of local pain was noted. Because of the persistence of local pain and elevated liver enzymes, she refused the second dose of vaccine. Ibuchiet al.[47] recently reported a series of 14 patients with VZV reactivation after BNT162b2 vaccination. The majority of them where female, who developed herpes zoster (HZ) after the first dose. None had immunosuppressive or immunomodulatory treatment, except one. No recurrence was noted with the second dose.

3.5 | Urticarial vasculitis

Urticarial vasculitis is an uncommon clinic-pathologic entity that is characterized by chronic or recurrent episodes of urticarial lesions and LCV.[48] Three cases were published in association with COVID-19 vaccination. Two after the first dose of *Moderna* vaccine.[34,38,48]

3.6 | Immune complex vasculitis

Mücke et al.[35] reporteda 76-year old man, presented with a purpuric non-blanchable rash both hands, legs and thighs, and lower abdomen 12 days after the second mRNA-based vaccination for COVID-19 with BNT162b2.He has a history of compensated alcoholic liver cirrhosis. However, he reported of melena and diarrhea the day before. Workup revealed; elevated inflammatory biomarkers, micro-erythruria and leukocyturia, positive occult blood and moderately elevated stool calprotectin levels. Oral prednisolone, 40 mg, once daily, was started with resolution of all symptoms.

4 | DISCUSSION

Vasculitis post-COVID19 vaccination is a rare adverse event. The mean age of the patients was 53 years. 65.8% (25 cases) of the cases were female. Both induction and reactivation have been observed-either after first or second shot. Vasculitis developed in 63.2% (24 cases) after the first dose. In case of occurrence of vasculitis after first shot, the second vaccination was uncomplicated. Generally, vasculitis is not an absolute contraindication to receive the second dose of the vaccine. The most common subtypes of vasculitis reported are IgA and LCV; 55.3% (20 cases) were LCV, 23.7% (9 cases) were IgA vasculitis, 7.9% (3 cases) were lymphocytic vasculitis, 5.3% (2 cases) were ANCA-associated vasculitis, 5.3% (3 cases) was urticarial vasculitis, and 2.6% (1 cases) was immune complex vasculitis. The average occurrence time was 6.2 days after vaccination. The lesions disappeared on average after 2.5 weeks. Most cases have been reported with mRNA vaccines being the most worldwide-distributed COVID-19 vaccines. However, vasculitis was also reported after inactivated virus vaccines and others. Of the 38 cases, including ours, 52.6% (20 cases) had received the mRNA vaccine, 31.6% (12 cases) had received ChaAdOx1 nCoV-19 vaccine (vector), and 15.8% (6 cases)

had received the inactivated SARS-CoV-2 vaccine. The most frequent causes of vasculitis in the reviewed cases have been reasonably ruled out, that means exposure to the vaccines could be the potential trigger. An inflammatory response to vaccine component/antigen encoding SARS-CoV-2 spike glycoprotein, depositing in micro-vessels, targeting vascular endothelium and resulting in a neutrophil-rich inflammatory reaction, could be hypothesized. Type I adverse events have in part be related to non-viral vaccine constituents, such as polyethylene glycol. However, without testing the various components of the vaccines, it would be difficult to elucidate the antigenic trigger. Molecular mimicry between SARS-CoV-2 and vaccine components such the spike-protein sequences may contribute to adverse reactions to COVID-19 vaccination.[49] Nevertheless, seems unlikely, that only one pathway is responsible. Further studies are warranted to reach the precise pathogenesis of these reactions. Treatment of vasculitis depends on type of the disease, severity, age, and comorbidities. First line therapy in more advanced cases is oral prednisolone. Mild cases may show a spontaneous remission. It is important to exclude involvement of internal organs such as kidney, intestine, and central nervous system, but fortunately, most patients had a cutaneous vasculitis only.

5 | CONCLUSIONS

Vasculitis are a heterogeneous group of diseases, which share the common feature of endothelial damage secondary to inflammation. Cutaneous vasculitis is a possible adverse event associated with vaccination against SARS-CoV-2. Hypersensitivity vasculitis and antigen–antibody complex deposition (type III hypersensitivity reaction) in the small vessels with potential internal organs involvement, such as the kidney and intestines, are the most common subtypes. However, as most of other post-COVID-19 vaccination cutaneous reactions, cutaneous vasculitis is not part of a multiorgan adverse hypersensitivity response triggered by the vaccine but mostlya skin-limited inflammation. The pathogenesis of vaccination-associated vasculitis is not well understood. There seems to be regional differences in frequency and presentation of vasculitis. The knowledge of (cutaneous) vasculitis adverse events is important for patient safety and in the differential diagnosis of vasculitis and purpuric skin disorders in general. We think this review will aid the dermatologists in daily practice. It also provides an overlook for international agencies to guide the manufacturers about vasculitis as one of the important reactions to COVID-19 vaccines.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ayman Abdelmaksoud reviewed the literature and submitted the final draft. Uwe Wollina shared in reviewing the literature, reviewed and edited the final draft. Selami Aykut Temiz shared in literature review and data analysis. Abdulkarim Hasan reviewed the pathology of our cases. All the authors approved the final draft for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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