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Systematic Review

Cutaneous small vessel vasculitis in the COVID-19 era: a systematic review

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Abstract

Background Dermatological adverse effects may occur after COVID-19 infection or vaccine administration. Since the beginning of the pandemic, several case reports and systematic reviews have been published on vasculitis associated with both COVID-19 infection and vaccination. Fever, malaise, urticaria, and rash are common symptoms of COVID-19. These symptoms can also occur as adverse reactions to COVID-19 vaccines. However, the occurrence of serious autoimmune reactions due to COVID-19 infection or its vaccine is rare. Cutaneous small vessel vasculitis (CSVV) is an autoimmune disorder that manifests with palpable purpura and petechiae involving the extremities. It results from neutrophilic inflammation within and around dermal vessels and is usually self-limited.

Objective We provide a thorough systematic review on CSVV occurring in the COVID-19 era.

Methods We followed the PRISMA 2020 checklist for systematic review, searching PubMed, Google Scholar, Cochrane, and Embase. We included case reports, case series, correspondence articles, and letters to the editor written in English. Characteristics of each were then summarized and analyzed.

Results 39 cases were included in our review – 27 due to the COVID-19 vaccine and 12 due to COVID-19 infection. Mean age of onset was similar, but mean time to onset was sooner in the vaccination group. Common treatments included systemic steroids, and almost all patients experienced complete recovery with the exception of a few patients in the COVID-19 infection cohort.

Conclusion While most cases are self-limiting and resolve with no long-term sequalae, the occurrence of more severe reactions appears to be associated with COVID-19 infection rather than with vaccination.

What is already known about this topic?

- Dermatological adverse effects may occur after COVID-19 infection or vaccine administration.
- Since the beginning of the pandemic, several case reports and systematic reviews have been published on vasculitis associated with COVID-19 infection and vaccination.

What does this study add?

- To the best of our knowledge, a comprehensive systemic review focusing on cutaneous small vessel vasculitis associated with COVID-19 infection and vaccination is lacking.
- We provide a thorough systematic review of CSVV occurring in the COVID-19 era.

COVID-19 infection may be asymptomatic or may cause a variety of symptoms such as rhinorrhoea, sore throat, loss of smell and taste, cough, myalgia and headache. The most serious manifestation of infection is pneumonia, which is characterized by cough, shortness of breath, fever and bilateral lung infiltrates on chest imaging.[1] COVID-19 can also cause various cutaneous manifestations, including morbilliform and papulovesicular rashes, as well as urticaria.[2] Additionally, there have been case reports of IgA vasculitis and Kawasaki vasculitis associated with COVID-19,[3] although development of cutaneous small vessel vasculitis (CSVV), also known as leucocytoclastic vasculitis, is rare.

Dermatological manifestations may also occur after COVID-19 vaccine administration. Erythematous local reactions, urticaria and morbilliform rash are frequently reported, and COVID-19 vaccine-associated exacerbation of systemic vasculitis has been described.[4] New-onset CSVV has

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been reported with many vaccines, including vaccinations against influenza virus, hepatitis A virus, hepatitis B virus, Bacillus Calmette-Guérin, human papillomavirus and rotavirus.[5] However, CSVV due to the COVID-19 vaccine is rare, despite widespread vaccination globally.[6]

CSVV may also occur as a cutaneous manifestation of inflammatory bowel disease (IBD), both in ulcerative colitis and Crohn disease. When present in patients with Crohn disease, CSVV often (but not always) occurs secondary to biologic use. IBD-induced CSVV may result in antineutrophil cytoplasm antibody positivity and is correlated with active disease.[7,8]

CSVV is an autoimmune disorder limited to the skin that results from immune complex deposition and neutrophilic infiltration within dermal arterioles, capillaries and venules.[9] It presents with nonblanching, erythematous and palpable macules, papules, petechiae and purpura involving the bilateral extremities. Infections, neoplasia, medications and autoimmune conditions are the most common causes of this condition, although often the cause remains idiopathic. A key histopathological feature of CSVV is neutrophilic infiltration within and around the vessel walls, as well as the presence of neutrophilic debris (leucocytoclasts) due to their subsequent destruction. The clinical course of CSVV is usually mild and resolves within a few weeks.

Since the beginning of the pandemic, several case reports and systematic reviews have been published on vasculitis associated with COVID-19 infection and vaccination. However, to the best of our knowledge, a comprehensive systemic review focusing on CSVV associated with these is lacking. To fill this void, we have collected the most up-to-date published data on the topic and summarized them below.

Materials and methods

Literature review

To conduct this review, we followed the PRISMA 2020 checklist for systematic reviews.[10] We searched PubMed, Google Scholar, Cochrane and Embase from 31 December 2019 to 31 December 2023 for articles written in English. Search terms included terms related to COVID-19 and cutaneous small vessel vasculitis, for example 'Cutaneous small vessel vasculitis' OR 'Leukocytoclastic vasculitis' AND 'Covid-19' OR 'Coronavirus' OR 'SARS-CoV-2' AND 'Skin manifestations' OR 'Dermatological manifestations' AND 'Covid-19 infection' OR 'Covid-19 vaccination'. The references of selected results were then searched to ensure comprehensive coverage of available articles.

Inclusion and exclusion criteria

We included case reports, case series, correspondence articles and letters to the editor written in English that reported on biopsy-proven cases of CSVV (also called leucocytoclastic vasculitis) in adults with either recent COVID-19 infection or vaccination. We eliminated duplicate articles, results that reported aggregate data and results in which other causes of vasculitis could not be ruled out.

Data extraction and statistical analysis

The preliminary title, abstract and full-text screening was completed by two reviewers. Any discrepancies between the two reviewers were resolved by a third reviewer.

We included descriptive data on patients' age, sex, cutaneous physical exam findings, comorbidities, diagnosis, treatment and outcomes in a table. We then calculated mean and median patient age for both infection-induced and vaccination-induced vasculitis. We further analysed the data on sex distribution, treatment received and response to treatment.

Quality assessment

The quality of each article was assessed according to the Joanna Briggs Institute (JBI) checklist.[11] A score of 1 point was assigned for each of the eight separate tools as per the checklist. Two independent reviewers reviewed each of the articles and any discrepancies were resolved by a third reviewer.

Results

After an extensive literature search, we included 39 cases of CSVV in our systematic review (Figure 1). Out of these, 27 were due to the COVID-19 vaccine and 12 were due to COVID-19 infection (Table 1). We then used the JBI guidelines to assess the quality of cases and assigned scores. The mean JBI scores of included cases was 6.89, with a low score of 5 and a high score of 8.

Demographic breakdown

Tables 1 and 2 detail the demographic and clinical characteristics of all the patients with CSVV that met the inclusion and exclusion criteria. Although the mean (SD) age in both groups was similar [53 (18) years in the vaccine-induced group and 52 (20) years in the infection-induced group], a higher proportion of individuals were ≥65 years of age in the infection-associated CSVV group (n=4/12; 33%) compared with the vaccine-associated CSVV group (n=8/27; 30%). The majority of patients in the infection group (n=8/12; 67%) were men, whereas there were more women in the vaccine group (n=16/27; 59%).

Patient characteristics

Almost all patients had lower extremity involvement. Mean time to onset was sooner in the vaccination group, although there was more variation among the infection group. Six out of 12 patients in the infection group and 21 out of 27 patients in the vaccine group received systemic steroids for treatment. Additionally, topical steroids and antihistamines were other common treatments prescribed.

Cases of deterioration

Clinical improvement or complete resolution was reported in all but three cases associated with COVID-19 infection; these patients demonstrated clinical worsening. In each of these cases, the patients had varying degrees of underlying

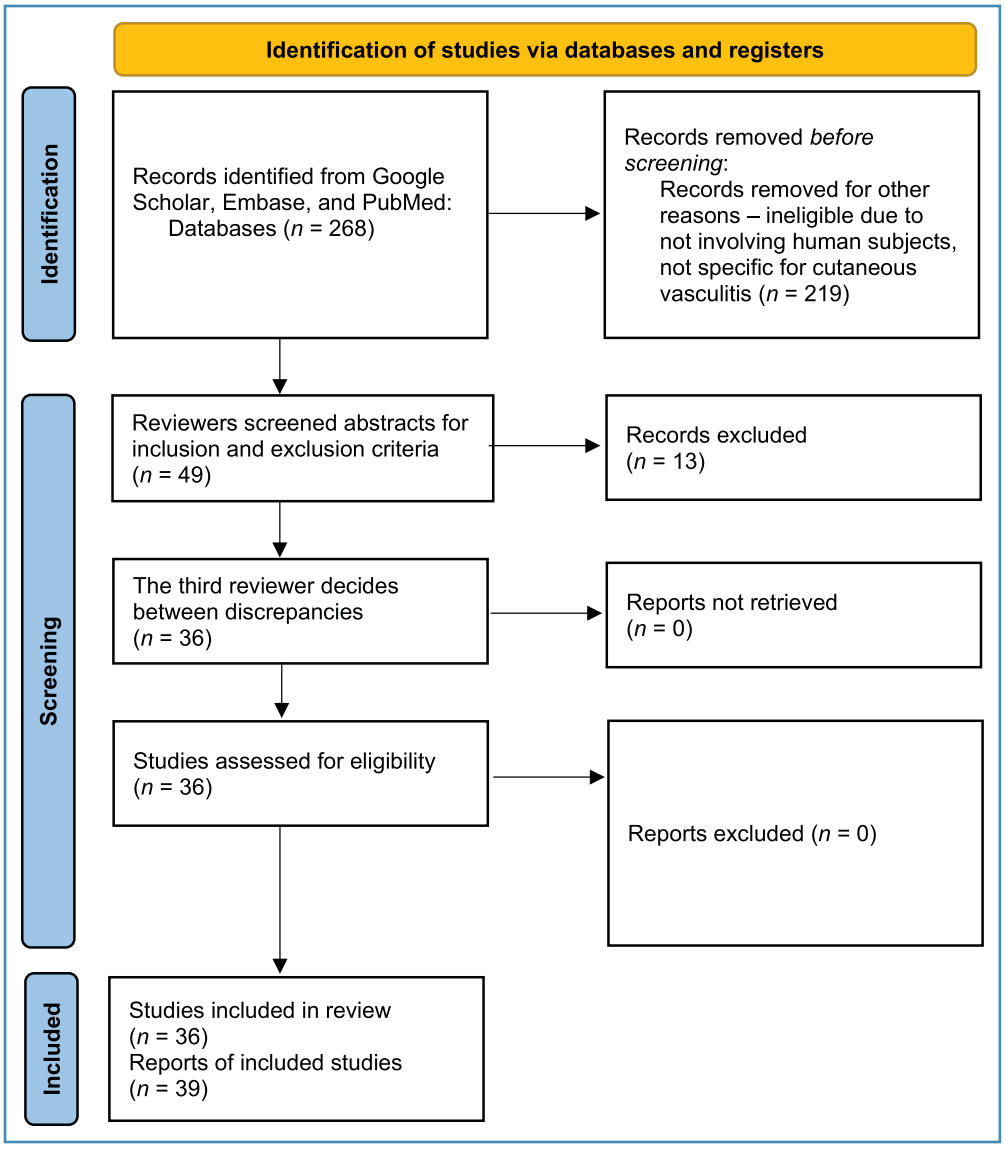

Figure 1 Schematic of the sequential steps in the selection of case reports for the systematic review.

comorbidities. One patient, a 93-year-old man who died due to CSVV, had underlying peripheral artery disease, chronic renal failure and arterial hypertension. Another patient, a 41-year-old man, had underlying type 2 diabetes mellitus and required eventual amputation of one digit. A third patient, a 47-year-old woman, required amputation of her right foot, debridement of the left foot and trochanteric regions, and bilateral mastectomy, and had only a past medical history of rheumatoid arthritis, which was in remission.

Discussion

CSVV is a single-organ vasculitis that primarily affects small blood vessels without involvement of noncutaneous organs.[33] It is defined by neutrophilic inflammation of the dermal capillaries and venules, causing fibrinoid necrosis. Finally, the neutrophils break down and die, resulting in leucocytoclasia, the histological hallmark of CSVV. While CSVV is idiopathic in 50% of cases, it can be triggered by numerous autoimmune disorders, infections, drugs, toxins and malignancies. Although rare, COVID-19 infection and COVID-19 vaccines have been associated with the development of CSVV through various mechanisms. Although most cases are self-limited and run a benign course, severe manifestations requiring systemic steroids can occur.

SARS-CoV-2 infects the host by using angiotensin-converting enzyme 2 (ACE-2) receptors found in the heart, lungs, kidney, intestine and endothelial cells.[4] High expression of ACE-2 receptors in endothelial cells may allow for SARS-CoV-2 binding, membrane fusion and entry, leading to infection and vascular injury.[1] This then leads to endothelial inflammation, cellular apoptosis, endothelial dysfunction and, ultimately, vasculitis in patients with COVID-19.[48,49] Elevated serum levels of interleukin (IL)-1, IL-6, IL-8 and tumour necrosis factor have been identified in patients with CSVV. COVID-19 infection may cause a cytokine storm, with high levels of IL-6 leading to immune complex-mediated inflammation and damage of cutaneous small vessels, resulting in CSVV.[3,33]

Table 1 Summary of characteristics of patients with COVID-19 vaccination- or infection-induced cutaneous small vessel vasculitis

Reference	Age (years), sex	Time to onset	Cutaneous findings	Comorbidities	Treatment	Diagnosis	Clinical course
Vaccine-induced (*n*=27)							
Fiorillo *et al.*[12]	71, F	4 days	Symmetrically distributed purpuric macules and papules on lower legs	Fibrocystic mastopathy, arterial hypertension	Oral prednisone 20 mg daily tapered over 14 days	CSVV associated with Vaxzevria COVID-19 vaccine	Complete clinical resolution of skin lesions
Kar *et al.*[13]	46, F	5 days	Palpable purpuric papules on the lower legs	None	Leg elevation, rest, antihistamines	CSVV secondary to COVAXIN COVID-19 vaccine	Complete clinical resolution in 15 days; continued resolution at 1 month
Kharkar *et al.*[14]	31, F	4 days	Painful palpable purpura primarily on the left leg	None	Rest, leg elevation, antihistamines	CSVV with eosinophil predominance secondary to COVAXIN COVID-19 vaccination	Clinical resolution in 1 week with residual hyperpigmentation, continued resolution with monthly follow-up
Pathak *et al.*[15]	55, F	2 days	Coalescing erythematous patches with palpable purpura on the bilateral upper and lower extremities with areas of desquamation	Chronic back pain	Topical steroids and hydroxyzine initially, then IV steroids followed by oral prednisone taper for 30 days	CSVV secondary to Moderna COVID-19 vaccination	Significant improvement 1 week after diagnosis with near-complete clinical resolution after 1 month
Sandhu *et al.*[16]	55, F	5 days	Palpable purpura on the bilateral ankles and lower legs	None	Oral prednisone 0.5 mg kg^{-1} daily tapered over 2 weeks	CSVV secondary to ChAd0x1 nCoC-19 (AstraZeneca) COVID-19 vaccination	Clinical resolution after 2 weeks
Sandhu *et al.*[16]	48, M	2 days	Symmetric bilateral palpable purpura on the hands, forearms, gluteal region and lower limbs	Hypertension	Oral prednisone 0.5 mg kg^{-1} daily tapered over 2 weeks	CSVV secondary to ChAd0x1 nCoV-19 (AstraZeneca) COVID-19 vaccination	Not reported
Larson *et al.*[17]	83, F	1 week	Bilateral palpable purpuric papules with erythema and oedema on the lower extremities	None given	Oral antibiotics and topical corticosteroids	CSVV secondary to Pfizer-BioNTech COVID-19 vaccination	Clinical improvement (timeline not provided)
Bencharattanaphakhi *et al.*[18]	23, F	36 h	Bilateral nonblanchable, discrete, erythematous plaques with pinpoint purpura on all extremities	None	IM dexamethasone followed by IV dexamethasone, followed by oral prednisolone (10 mg twice daily) for 5 days	CSVV secondary to Sinovac COVID-19 vaccination	Complete clinical resolution with residual hyperpigmentation after 4 weeks; continued clinical resolution at 3-month follow-up
Bencharattanaphakhi *et al.*[18]	26, F	4 h	Bilateral nonblanchable, discrete, erythematous plaques with pinpoint purpura on the upper and lower extremities	None	IM dexamethasone, followed by IV dexamethasone, followed by oral colchicine (0.6 mg twice daily) and naproxen (250 mg twice daily) for 4 weeks	CSVV secondary to Sinovac COVID-19 vaccination	Complete clinical resolution with residual hyperpigmentation after 4 weeks; continued clinical resolution at 3-month follow-up
Fritzen *et al.*[19]	60, F	11 days	Palpable purpura and multiple petechiae on the bilateral lower legs, leg pain	Chronic liver disease, portal hypertension, polycythaemia vera, hypothyroidism, type 2 diabetes mellitus	Prednisone (60 mg daily) for 7 days, discharged from hospital on 40 mg daily prednisone	LCV secondary to Oxford–AstraZeneca COVID-19 vaccination	Not reported
Oskay *et al.*[20]	77, M	2 weeks	Palpable, tender, non-blanching violaceous coalescent patches on the bilateral thighs, calves, feet and hands; haemorrhagic bullae bilaterally on the extensor sides of the lower legs and feet	None reported	Oral prednisone (0.5 mg kg^{-1} daily)	Cutaneous and gastrointestinal LCV secondary to COVID-19 vaccination	Complete clinical resolution at 14-day follow-up

(*Continued*)

Table 1 (*Continued*)

Author	Age (years), sex	Time to onset	Cutaneous findings	Comorbidities	Treatment	Diagnosis	Clinical course
Ball-Burack *et al*.[21]	22, M	10 days	Scattered violaceous palpable purpura on the bilateral lower extremities; migratory arthritis of the ankles	None	None	LCV secondary to Johnson & Johnson COVID-19 vaccination	Improvement at follow-up (no timeline provided)
Sebastian *et al*.[22]	32, M	Same day	Bilateral lower limb oedema, reddish lesions and fluid-filled blisters	Unspecified seizure disorder, obesity	IV betamethasone, followed by oral steroid therapy and then topical steroids	LCV secondary to COVID-19 vaccination	Symptom improvement over hospital stay with discharge after 5 days
Gambichler *et al*.[23]	47, M	3 days	Disseminated symmetrically distributed purpuric papules on the legs and forearms	None reported	IV prednisolone taper starting at 1.5 mg kg^{-1}	LCV secondary to COMIRNATY® COVID-19 vaccination	Complete clinical resolution after 2 weeks
Dicks *et al*.[24]	65, M	2 days	Palpable purpuric lesions on the lower legs	Diabetes (type not specified), hypertension	One dose of IM triamcinolone (60 mg), oral prednisone (tapered from 60 mg daily to 10 mg daily), topical clobetasol, topical mupirocin	LCV secondary to Pfizer BioNTech COVID-19 vaccination	Not reported
Jin *et al*.[25]	68, F	7 days	Erythematous to purpuric nonblanching macules on bilateral lower extremities	None	Oral prednisolone (4 mg daily for 1 week, followed by 2 mg daily for 2 weeks), colchicine (1.2 mg daily) and topical methylprednisolone for 3 weeks	LCV secondary to ChAd0x1 nCoV-19 (AstraZeneca) COVID-19 vaccination	Resolution after treatment; lesions slightly recurred after second vaccination with spontaneous resolution
Liang *et al*.[26]	62, F	7 days	Bilateral lower limb nonblanching petechial rash	None reported	Rapid tapering course of oral prednisolone	LCV secondary to ChAd0x1 nCoV-19 (AstraZeneca) COVID-19 vaccination	Clinical resolution following treatment
Guzmán-Pérez *et al*.[27]	57, F	5 days	Confluent palpable purpuric lesions on the buttocks and in a splashed way on the arms and legs	Hypertension, hyperthyroidism	No treatment provided	LCV secondary to Oxford-AstraZeneca COVID-19 vaccination	Spontaneous resolution at 5-day follow-up with postinflammatory hyperpigmentation
Shahrigharahkoshan *et al*.[28]	77, F	10 days	Multiple palpable indurated purpuric papules along with erythematous plaques and bullae, some coalescing, on the bilateral lower extremities and pseudovesicles around the ankles; several purpuric lesions on the soft palate and tongue	None	Prednisolone 50 mg daily tapered by 5 mg every 3 days: dapsone 50 mg daily for 60 days	LCV secondary to ChAd0x1 nCoV-19 (AstraZeneca) COVID-19 vaccination	Symptomatic improvement with clinical resolution after treatment; limited residual blanching macules and patches on the previously affected sites
Erler *et al*.[29]	42, F	4 days	Rash on the bilateral legs extending up to the gluteal area 'with the typical appearance of cutaneous small vessel vasculitis'	Hypertension, obesity	Prednisolone 30 mg daily then increased to 60 mg daily	LCV secondary to Pfizer BioNTech COVID-19 vaccination	Resolution of rash over 5 days with 60 mg daily prednisolone treatment
Kim *et al*.[30]	59, M	7 days	Diffuse erythematous patches with multiple painful purpuric macules and papules on the bilateral lower legs	None	Topical steroid and oral prednisone with gradual dose tapering for 1 month	LCV secondary to Oxford-AstraZeneca COVID-19 vaccination	Near-complete resolution at 1-month follow-up
Kim *et al*.[30]	87, F	7 days	Multiple bilateral erythematous-to-violaceous painful palpable purpura and haemorrhagic crusts on the lower legs	Hypertension, hyperlipidaemia	Oral prednisone, colchicine and topical steroid	LCV secondary to Pfizer BioNTech COVID-19 vaccination	Skin lesions improved with residual hyperpigmentation after 5 weeks

(*Continued*)

Table 1 (*Continued*)

Author	Age (years), sex	Time to onset	Cutaneous findings	Comorbidities	Treatment	Diagnosis	Clinical course
Shakoei *et al*.[31]	45, M	2 days	Papular lesions on upper and lower limbs	None	Prednisolone	COVID-19 vaccination-induced CSVV (Sinopharm)	Improvement with postinflammatory hyperpigmentation at 3-month follow-up
Erol *et al*.[32]	38, M	4 days	Purpuric rash on the lower extremities	None	24 mg methylprednisolone	LCV secondary to Pfizer BioNTech COVID-19 vaccination	Complete resolution after 1 week
McGourty *et al*.[33]	58, M	1 day	Purpuric rash on both lower limbs	Psoriasis; psoriatic arthritis	Topical steroids	LCV secondary to Pfizer BioNTech COVID-19 vaccination	Clinical improvement
Betetto *et al*.[34]	30, M	17 days	Purpuric and haemorrhagic nonblanching papules and vesicles, some with central erosions, on both soles the dorsum of the feet and distal part of the legs; some haemorrhagic vesicles on the elbows	None	Topical corticosteroids	CSVV secondary to Ad26.COV2.S COVID-19 vaccination	Regression over several weeks
Uh *et al*.[35]	67, F	20 days	Violaceous indurated papules on the lower limbs; erosions on the gingiva	Hypertension	Oral methylprednisolone (4 mg daily), pentoxifylline (800 mg daily), antihistamines, topical steroids	LCV secondary to ChAd0x1 COVID-19 vaccination	Nearly complete resolution within 2 weeks
Infection-induced (*n* = 12)							
Dominguez-Santas *et al*.[36]	71, F	7 days	Bilateral purpuric macules and papules from the ankles to the thigh with Koebner phenomenon on the right knee	None given	Betamethasone dipropionate 0.05% cream twice daily	CSVV secondary to COVID-19 infection	Complete clinical resolution at week 3 with residual hyperpigmentation
Mayor-Ibarguren *et al*.[37]	83, F	1 month	Bilateral palpable purple papules and serohaematic blisters on the lower legs, feet and toes	Hypertension, transient ischaemic attack, atrial fibrillation, chronic renal impairment	30 mg prednisone daily, tapered after 10 days	CSVV secondary to COVID-19 infection	Clinical improvement after 10 days
Capoferri *et al*.[38]	93, M	8 days	Livid–erythematous, partly purpuric macules and papules on the bilateral legs, hands and periumbilical area, progressing to sharply demarcated haemorrhagic papules with interspersed blisters	Peripheral artery disease, chronic renal failure, arterial hypertension	IV methylprednisolone (250 mg daily) for 1 day followed by oral prednisone (1 mg kg^{-1} daily) for 5 days, then returned to IV methylprednisolone (125 mg daily) for 3 days, followed by a steroid taper over 10 weeks	LCV secondary to COVID-19 infection	Clinical worsening with extensive necrosis of the legs following initiation of oral steroids. Development of extensive dry gangrene of the legs and feet but declined amputation. Continued to decline with renal failure and death at 7 weeks post-COVID-19 diagnosis
Alattar *et al*.[39]	41, M	Concurrently	Bilateral swollen, erythematous upper limbs; multiple petechiae, palpable purpura and necrotic ulcers on the distal fingertips, bilaterally swollen, erythematous lower limbs with multiple dark, necrotic, painless ulcers and patches; petechial rash on the lower back	Type 2 diabetes mellitus	No vasculitis-specific therapy; surgical debridement and wound dressing as needed	LCV secondary to COVID-19 infection	Worsening of the rash throughout hospitalization with secondary infection. Eventual amputation of the left great toe. Eventual healing and discharge from the hospital in stable condition

(*Continued*)

Table 1 (*Continued*)

Author	Age (years), sex	Time to onset	Cutaneous findings	Comorbidities	Treatment	Diagnosis	Clinical course
Nassani *et al.*[40]	32, F	2 weeks	Erythematous-to-violaceous macules and papules on the bilateral extremities and the dorsum of the feet	Refractory cutaneous Crohn disease	IV immunoglobulin	LCV post-COVID-19 infection	Complete resolution of symptoms and improvement of cutaneous Crohn disease
Abdelrahman *et al.*[41]	41, M	2 weeks prior to COVID-19 symptom onset	Confluent macules, papules and petechiae of the bilateral legs, extending from the ankles to the thighs and lower back; involvement of palmar and plantar surfaces; ulceration of some macules; acral ischaemic haemorrhagic dots and papules of the fingers	Diabetes (type not specified)	Positive COVID-19 skin antigen test. No vasculitis-specific treatment	LCV secondary to COVID-19 infection	Clinical resolution with some residual hypo- and hyperpigmentation after 4 weeks
Tahir *et al.*[42]	47, M	Concurrently	Targetoid papules and plaques with central necrosis and peripheral erythema distributed symmetrically on extremities, buttocks and lower trunk; palpable purpura and areas of vesiculation	None	Topical betamethasone valerate 0.12% twice daily	CSVV secondary to COVID-19 infection	Not provided
Gouveia *et al.*[43]	27, M	7 days	Painful purpuric papules and vesiculobullous lesions on the lower limbs, back and upper limbs	None	Prednisone 1 mg kg^{-1} daily and prophylactic enoxaparin	CSVV secondary to COVID-19 infection	Improvement of lesions and discharge from the hospital after 5 days
Öztürk *et al.*[44]	47, F	3 days	'Bruising' on feet, bilateral breasts, hips and back	Rheumatoid arthritis	Piperacillin-tazobactam (3×4.5 g), methylprednisolone (250 mg daily) and enoxaparin (1×0.6 mL); after 3 days methylprednisolone increased to 1 g daily for 3 days and tapered	LCV secondary to COVID-19 infection	Superinfection and necrotic progression necessitating amputation of the right foot, debridement of the left foot and trochanteric regions, and bilateral mastectomy
Fatima *et al.*[45]	30, M	2 weeks	Nonblanchable erythematous papules and plaques over thighs and legs in a linear arrangement	None reported	Topical corticosteroid and oral antihistamine	CSVV secondary to COVID-19 infection	Not reported
Yıldırım Bay *et al.*[46]	66, M	15 days	Numerous palpable purpuric papules, some with a necrotic centre, and erythematous maculopapular on the bilateral legs and forearms	Type 2 diabetes mellitus, hypertension, coronary artery disease	Systemic corticosteroids (1 mg kg^{-1} daily) and antihistamines	LCV secondary to COVID-19 infection	Complete resolution of lesions within 2 weeks
Renuka *et al.*[47]	50, M	3 weeks	Erythematous macules, papules, plaques and a few purpuric lesions on the posterior trunk and upper limbs	None reported	IV dexamethasone (6 mg daily), enoxaparin (40 mg SC daily), and doxycycline (100 mg orally twice daily)	LCV secondary to COVID-19 infection	Complete resolution at 1-month follow-up

CSVV, cutaneous small vessel vasculitis; F, female; IM, intramuscular; IV, intravenous; LCV, leukocytoclastic vasculitis; M, male; SC, subcutaneous.

Table 2 Comparison of vaccine-induced vs. infection-induced patient characteristics

	Vaccine-induced ($n=27$)	Infection-induced ($n=12$)
Sex		
Male	11	8
Female	16	4
Age (years), mean (SD)	53 (18)	52 (20)
Age (years), median (range)	55 (22–87)	47 (27–93)
Time to onset (days), mean (SD)	6.0 (4.9)	9.9 (8.8)
Predominant PE findings	Palpable purpura on the lower extremity	Palpable purpura, erythematous macules and papules, areas of necrosis and haemorrhage
Most common comorbidity	None, HTN, diabetes	None, HTN, diabetes
Most common treatment	Oral corticosteroids	Variable; included topical, oral and IV corticosteroids, as well as supportive therapy
Outcomes	Most commonly complete resolution	Most commonly complete resolution
Complications	PIH	Death, amputation, PIH

HTN, hypertension; IV, intravenous; PE, physical exam; PIH, postinflammatory hyperpigmentation.

Interestingly, CSVV is also the most common cutaneous vasculitis described following COVID-19 vaccination.[50] Although vaccination is widespread globally, CSVV due to COVID-19 vaccines is rare. Vasculitis has been reported following various vaccines, including influenza, hepatitis B and human papillomavirus.[15] While a causative link between the COVID-19 vaccine and vasculitis remains unclear, proposed mechanisms include the generation of autoimmunity due to cross-reactivity between the vaccine product and self-antigen.[33] This may be due to mRNA-containing lipid nanoparticles found in some COVID-19 vaccines, which are thought to have inflammatory effects. COVID-19 vaccines specifically target the antigenic spike protein of the SARS-CoV-2. The similarity in the skin reactions seen after COVID-19 infection and vaccination may suggest a trigger from the spike protein in the pathogenesis of CSVV.[51] Other suggested mechanisms include activation of autoreactive lymphocytes, molecular mimicry between the vaccine's viral spike protein component and endothelium, and immune complex deposition leading to complement-mediated leucocyte infiltration.[15]

CSVV presents clinically as palpable purpura or petechiae, usually affecting the bilateral lower extremities in a symmetrical pattern. Haemorrhagic macules, blisters, vesicles and ulcerations may sometimes be observed. Typically, skin lesions manifest within 7–10 days of the inciting event (i.e. infection or exposure to a drug). Sometimes a prodrome of arthralgias, myalgias, malaise and fever may either precede or accompany the cutaneous vasculitis.[15] Most cases of CSVV are self-limited, usually resolving within 3–4 weeks with supportive treatment.[52] In patients with more severe presentations, a 4–6-week tapering course of systemic corticosteroids may be employed.

In our review, the type of skin lesions and mean time to onset of CSVV in the infection and vaccine groups were consistent with CSVV described to be due to other causes. Moreover, 6 out of 12 patients in the COVID-19 infection group and 21 out of 27 patients in the vaccine group were treated with systemic steroids. Other options for more resistant and severe cases include immunosuppressive steroid-sparing agents like colchicine, dapsone, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide and intravenous immunoglobulin; however, need for these medications is rare.[3,52] While wound care is important to manage and heal these skin ulcers, they will not resolve unless the underlying vascular insult is cured.[53]

Over the course of the pandemic, COVID-19 diagnostic modalities have evolved. Because of this, there was some heterogeneity in how the diagnosis of COVID-19 was made in the studies included in our review. As the prevalence of COVID-19 infection and the coverage of its vaccination increased, it became more difficult to establish a clear cause–effect relationship between them and CSVV, which may add a limitation to our systematic review. As the total number of cases was low, it was difficult to perform statistical comparison between the two groups. Despite these limitations, this study provides a clear indication that both COVID-19 infection and vaccination have contributed to the incidence of CSVV since the beginning of the pandemic.

CSVV is a relatively uncommonly reported cutaneous adverse reaction to COVID-19 infection and vaccination. While most cases are self-limiting and resolve with no long-term sequalae, the occurrence of more severe reactions seems to be associated with COVID-19 infection rather than with vaccination. Physicians should be aware of these possible adverse reactions when educating their patients and participating in shared decision-making regarding vaccination options.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

Not applicable.

Patient consent

Not applicable.

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