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REVIEW

Update on Cutaneous Small Vessel Vasculitis: Terminology, Morphology, Diagnostic Evaluation, and Management

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Abstract

Purpose of the Review Cutaneous small vessel vasculitis (CSVV) is the clinical presentation of the histologic entity of leukocytoclastic vasculitis (LCV); the vasculitis may be skin-limited, or also affect internal organ systems. Even when skin-limited, it may be a manifestation of a systemic illness. The etiologies and disease associations are broad, ranging from an uncomplicated, self-limited, immunological phenomenon to a harbinger of autoimmune disease, infection, or malignancy. It is a challenging entity for clinicians to provide a thoughtful and comprehensive evaluation for patients presenting with small vessel vasculitis.

Recent Findings A dermatologic addendum to the Chapel Hill Consensus Criteria proposed a logical framework to categorize cutaneous small vessel vasculitis into both skin-limited and systemic variants. Recent publications have demonstrated that branching morphology and systemic symptoms suggest a greater need for systemic work up, while cases presenting with non-branching, venule involvement with scant systemic symptoms may not require extensive evaluation. Moreover, radiological studies have demonstrated limited value.

Summary As cutaneous small vessel vasculitis is a heterogenous disease entity, an updated understanding of terminology, pathogenesis and lesion morphology will help to inform clinicians when to suspect systemic versus skin-limited disease and guide their evaluation accordingly.

Keywords Vasculitis · Small vessel vasculitis · Leukocytoclastic · LCV · Palpable purpura · Cutaneous

Introduction

Leukocytoclastic vasculitis (LCV) is a histology-derived description of a form of cutaneous small vessel vasculitis (CSVV). On histology, small vessels (arterioles, capillaries, post-capillary venules) are infiltrated by neutrophils with evidence of fibrinoid necrosis, neutrophilic disintegration and vessel destruction [1]. CSVV is the most common type of vasculitis [2], and etiologies range from a transient, skin-limited process to a manifestation of a systemic disease, with or without internal organ involvement. Associated systemic diseases are broad and include connective tissue disease, systemic vasculitides, infection, and rarely, malignancy. While the majority of CSVV is idiopathic and skin-limited, the multitude of etiologies can result in a broad differential diagnosis with extensive diagnostic testing. This paper aims to define CSVV and associated terminology, review associated systemic diseases and clarify the physician's diagnostic approach for a patient presenting with CSVV.

Definition and Terminology

The nomenclature and classification of vasculitis is challenging and is primarily based on two systems: The Chapel Hill Consensus Conference (CHCC) nomenclature system [3] and the American College of Rheumatology (ACR)

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classification system [4]. There are many descriptive terms that are used interchangeably, without clear consensus, and include leukocytoclastic vasculitis, cutaneous leukocytoclastic angiitis, hypersensitivity vasculitis, and small vessel vasculitis [5].

In 2018, a Dermatologic Addendum was added to the CHCC clarifying that CSVV could arise in one of three conditions:

1. A cutaneous component of a systemic vasculitis (e.g., IgA vasculitis/Henoch-Schönlein purpura, ANCA-associated vasculitis, polyarteritis nodosa, cryoglobulinemia, etc.)
2. A skin-limited expression of a systemic vasculitis (e.g., IgA vasculitis without renal/gastrointestinal manifestations, skin-limited manifestation of ANCA-associated vasculitis, small vessel vasculitis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), sarcoidosis, Crohn's disease, etc.)
3. A skin-limited CSVV which lacks clinical, laboratory, and pathologic features associated with a systemic disease or internal organ involvement [6••]

Clinical Presentation and Morphology

The clinical presentation of vasculitis is determined by two primary factors:

1. The size/type of involved vessel
2. The presence/absence of non-cutaneous symptoms

Distribution and Morphology

The most typical presentation of CSVV involves the postcapillary venules. This presents as clusters of pink to red papules or inflammatory purpura symmetrically distributed on the ankles and lower legs (Fig. 1). There is an accentuation of lesions in areas of dependence or pressure [1, 7, 8]. The purpura appear simultaneously or sequentially within 24–48 h, beginning on the distal legs and spreading proximally symmetrically. Wrists, hands, and hips are typically involved before the trunk, which is rare, and facial involvement is extremely uncommon. Lesions may begin as bright pink to red inflammatory papules in the very earliest stages and resolve to purpura subsequently. The classic term "palpable purpura" implies there is both inflammation and purpura formation concurrently although can be a misleading term as many cases, early in the presentation, exhibit only inflammatory papules rather than true purpura.

The presence of "branching," "stellate," "retiform," or necrotic purpura (Fig. 2B) is produced by the involvement of small vessels in deeper layers in the skin, often arterioles, and results from vessel destruction or occlusion. Such

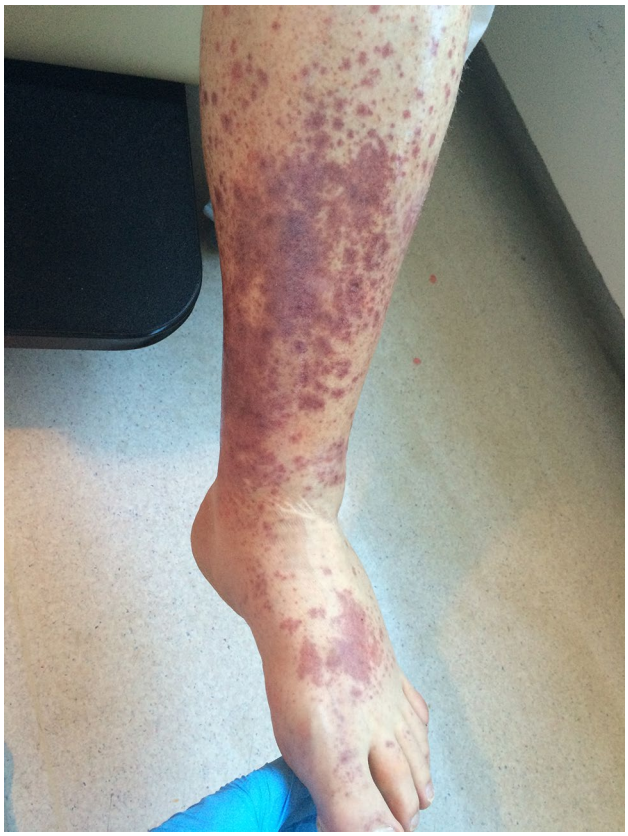
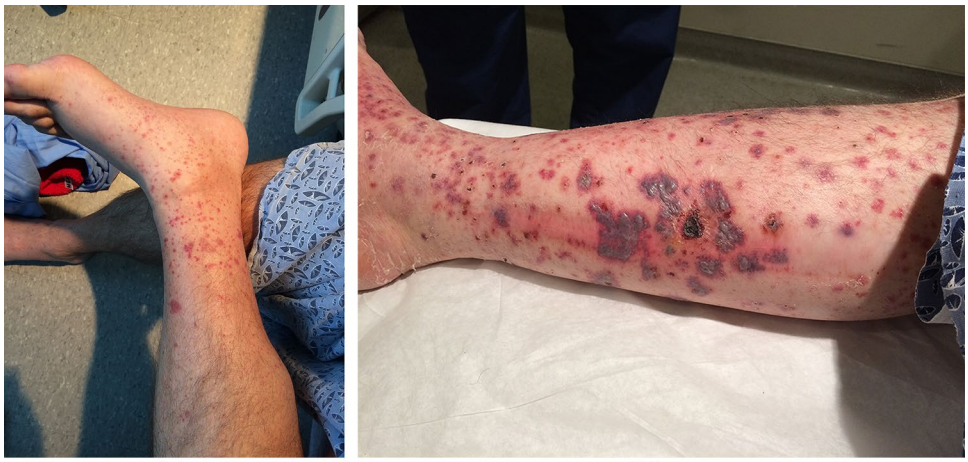


Fig. 1 Typical CSVV with involvement of bilateral lower extremities

morphology warrants evaluation of a broader range of etiologies as there is a higher likelihood for underlying systemic disease [6••, 9•]. Furthermore, if the vasculitis extends into medium-sized subcutaneous vessels, the patient may exhibit subcutaneous nodules, livedo, ulcerations, or digital necrosis. These findings are invariably associated with an underlying systemic disease [1, 8].

Signs and Symptoms: Cutaneous vs. Systemic Disease

Skin lesions in CSVV can range from asymptomatic, to pruritic or painful. Transient fevers or arthralgias are common but nonspecific findings. A detailed review of systems should be performed to assess for systemic disease, particularly of the gastrointestinal and pulmonary systems, as well as for constitutional systems. A review of medical history for connective tissue disease, malignancies, recent infections, medication exposure, illicit drug use, viral hepatitis, or other infectious exposures will help to understand the associated causes of the CSVV. It should also be established as to whether this is the patient's first episode or whether episodes have been recurrent, as recurrent disease raises concern for an associated underlying systemic illness.



(a) (b)

Fig. 2 Images of non-branching and branching purpura

Causes of Cutaneous Small Vessel Vasculitis

The causes of CSVV can be broadly divided into two primary categories: (1) immune complex vasculitis and (2) ANCA-associated vasculitis. Both categories can have either single-organ (i.e., skin-limited) or multi-organ (systemic) involvement (Table 1).

Immune Complex Vasculitis

IgG/IgM Immune Complex Vasculitis

IgG/IgM immune complex vasculitis may occur idiopathically, or with an associated cause. The most commonly associated etiologies are connective tissue disease or as an immunologic response to a medication, infection or rarely, malignancy. It is therefore further denominated as immune complex vasculitis without probable etiology or immune complex vasculitis with probable etiology.

IgG/IgM Immune Complex Vasculitis Without Probable Etiology

Approximately 50% of cases of CSVV have no identifiable association, appear to occur idiopathically, and affect only the skin. The favored term for this type of CSVV is *IgG/IgM vasculitis or single organ cutaneous vasculitis without probable etiology (this is a provisional diagnosis as defined in the 2018 dermatologic addendum to vasculitis nomenclature)* [6••]. The clinical presentation is typically a vasculitis which affects only post-capillary venules with inflammatory papules symmetrically clustered in dependent areas with non-branching morphology (see Distribution and Morphology section). Associated systemic symptoms are mild and may include transient fevers or arthralgias but otherwise lack clinical or laboratory evidence of other organ involvement.

It should be noted that there are cases in which a DIF is not performed, or does not demonstrate immunoglobulin reactants. In the absence of extracutaneous involvement or associated systemic illnesses, such cases may be labeled as "cutaneous small vessel vasculitis without probable etiology" although the presentation, morphology, and disease course would otherwise be congruent with what is described above.

Immune Complex Vasculitis Associated with Probable Etiology: Systemic Disease, Medication, Infection, Cryoglobulinemia

When CSVV appears to be associated with an underlying systemic disease, medication, or infection, it then adopts naming based on the associated exposure, e.g., "rheumatoid small vessel vasculitis," or "Sjogren's small vessel vasculitis." The majority of these cases have only skin involvement; however, particularly in cases associated with autoimmune disease, more significant vessel involvement may occur and result in branching morphology, cutaneous ulcers, digital necrosis, and neuropathy [6••]. Cases associated with SLE may demonstrate nephritis.

When a medication, such as an antibiotic, is a suspected trigger, cases are typically milder, self-limited, resolve within weeks of discontinuation of the culprit medication, and follow a clinical presentation and course identical to that of IgG/IgM vasculitis without probable etiology (discussed above). Medications such as minocycline and levamisole can induce ANCA-associated vasculitis and are discussed in the "Medication-Induced ANCA-associated vasculitis" section below.

Cryoglobulinemic vasculitis demonstrates findings consistent with CSVV along with positive serum cryoglobulins. Type I cryoglobulinemia is not typically vasculitic and presents are vasocclusion, whereas type II and

Table 1 Causes, frequency, and presentation of systemic and non-systemic CSVV. Adapted and modified from 2018 dermatologic addendum of CHCC [1, 6••, 9•, 11]

Type and subtype of CSVV	CHCC* Definition (adapted from CHCC 2018 paper)	Findings as cutaneous component of systemic vasculitis	Findings as skin-limited variant	Branching morpholoy	Medium vessel involvement (livedo, ulceration, gangrene, large purpura)
Immune complex vasculitis					
IgG/IgM immune complex vasculitis	Vasculitis with moderate-to-marked vessel wall deposits of IgG or IgM immunoglobulin, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries)	See subtypes	IgG or IgM on DIF* (similar presentation to IgA vasculitis)	See subtypes	See subtypes
Without probable etiology	Idiopathic—no causative etiology identified	Lacks systemic disease association by definition	Typical non-branching morphology, post-capillary venule involvement	Unexpected	Unexpected—consider alternate diagnosis
Connective tissue disease	Vasculitis secondary to connective tissue disease (e.g., rheumatoid arthritis, SLE, Sjogren's, rarely sarcoidosis)	May result from flare of CTD* or systemic involvement of vasculitis (e.g. nephritis, cerebritis)	Skin-limited immune complex vasculitis	Variable—implies systemic involvement	Variable—highly suggestive of systemic involvement
Medication	Vasculitis presenting in a temporal association with inciting medications	Uncommon—typically presents as mild nephritis	Typical non-branching morphology, post-capillary venule involvement	Unexpected	Unexpected—consider medication-induced AAV or alternative diagnosis
Infection	Immunologic response to prior URI, viral infection (HBV/HCV/HIV) or chronic endocarditis or osteomyelitis	Uncommon—typically as mild nephritis	Typical non-branching morphology, post-capillary venule involvement	Uncommon	Rare—consider septic vasculitis or emerging coagulopathy
Neoplasm	Immune complexes derived from abnormal clonal proliferation (multiple myeloma/MGUS, lymphoma), cytokine dysregulation (leukemia, lymphoma), or as host immune response to solid malignancy	Uncommon	Typical non-branching morphology, post-capillary venule involvement	Uncommon	Unexpected
Cryoglobulinemia	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles); associated with serum cryoglobulins	Common—systemic symptoms may be attributed to underlying associated disease (typically HCV*, RA*, or clonal hematologic malignancies) or renal involvement of vasculitis.	Skin-limited cryoglobulinemic vasculitis without systemic vasculitis	Uncommon	Suggests type I cryoglobulinemia with cold precipitates—invariably associated with MGUS or malignancy Type II/III cryoglobulinemia presentation mimics typical IgM/IgG immune complex vasculitis

Table 1 (continued)

Type and subtype of CSVV	CHCC* Definition (adapted from CHCC 2018 paper)	Findings as cutaneous component of systemic vasculitis	Findings as skin-limited variant	Branching morpholoy	Medium vessel involvement (livedo, ulceration, gangrene, large purpura)
IgA vasculitis	Vasculitis with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). May occur as post-infectious phenomenon or with medication trigger.	Common—associated systemic involvement includes arthralgias, abdominal pain or nephritis	IgA demonstrated on DIF*, most common with typical non-branching morphology, post-capillary venule involvement (similar presentation to IgG/IgM vasculitis)	Uncommon	Unexpected
Urticarial vasculitis (UV)					
Hypocomplementemic UV (HUV)	Vasculitis accompanied by urticaria and hypocomplementemia, affecting small vessels (i.e., capillaries, venules, or arterioles) and associated with anti-C1q antibodies	Less common—systemic findings include glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation	More common—skin-limited HUV with post-capillary venule involvement with vascular deposits of immunoglobulins, urticarial lesions without systemic vasculitis (but often associated with underlying connective tissue disease, e.g., SLE*)	Unexpected	Unexpected—consider associated coagulopathy
Normocomplementic UV (NUV)	Cutaneous small vessel vasculitis, accompanied by lasting urticarial lesions and associated with normocomplementemia and absence of anti-C1q antibodies	Uncommon	Most common (considered to be skin-limited vasculitis only) —cutaneous small vessel vasculitis, accompanied by lasting urticarial lesions and associated with normocomplementemia and absence of anti-C1q antibodies; may be part of a spectrum with neutrophilic urticarial dermatosis	Unexpected	
ANCA-associated vasculitis					
MedicationiInduced ANCA-associated vasculitis	ANCA vasculitis presenting in temporal association with inciting agent. Most commonly minocycline, hydralazine, propylthiouracil, and levamisole.	Rare—may have renal and pulmonary involvement	More common in medication-induced AAV—cutaneous findings include larger, stellate purpura with necrosis and ulceration	Common	Common

Table 1 (continued)

Type and subtype of CSVV	CHCC* Definition (adapted from CHCC 2018 paper)	Findings as cutaneous component of systemic vasculitis	Findings as skin-limited variant	Branching morpholoy	Medium vessel involvement (livedo, ulceration, gangrene, large purpura)
Autoimmune ANCA-associated vasculitis	Necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries); associated with ANCAs	Common—vasculitis of cutaneous post-capillary venules, small veins, arterioles, and small arteries; associated with ANCAs	ANCA-associated vasculitis limited to the skin (not further specified)	See below	See below
Granulomatosis with polyangiitis (GPA)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tracts, and necrotizing vasculitis affecting predominantly small-to-medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins)	Expected—the presence of cutaneous involvement is highly associated with multi-organ involvement	Rare—skin-limited GPA (including drug-induced skin-limited GPA); vasculitis of small vessels in the skin (spectrum as in MPA), with nonvasculitic extravascular dermal granulomatous inflammation but without eosinophilia, without a history of asthma, and without systemic vasculitis; associated with ANCAs	Expected	Common
Microscopic polyangiitis (MPA)	Necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles)	Expected—the presence of cutaneous involvement is highly associated with multi-organ involvement	Rare—skin-limited MPA (including drug-induced skin-limited MPA); vasculitis of small vessels in the skin (post-capillary venules, arterioles, venules, or small arteries), without cutaneous granulomatous inflammation and without systemic vasculitis; associated with ANCAs	Expected	Common
Eosinophilic granulomatosis with polyangiitis (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels and associated with a history of asthma and eosinophilia	Expected—the presence of cutaneous involvement is highly associated with multi-organ involvement	Rare—skin-limited EGPA (including drug-induced skin-limited EGPA); eosinophil-rich vasculitis of small vessels in the skin (spectrum as in MPA), with, e.g., nonvasculitic extravascular dermal granulomatous inflammation, and with a history of asthma, but without systemic vasculitis; associated with ANCAs	Expected	Common

Table 1 (continued)

Type and subtype of CSVV	CHCC* Definition (adapted from CHCC 2018 paper)	Findings as cutaneous component of systemic vasculitis	Findings as skin-limited variant	Branching morpholoy	Medium vessel involvement (livedo, ulceration, gangrene, large purpura)
Septic vasculitis	Not a true CSVV. Bacterial or fungal emboli lodge in the skin resulting in inflammation and vascular occlusion. Distribution is random. Lesion count is lower than CSVV and demonstrates mixed morphologies ranging from pustules, branching purpura to panniculitis based on the depth of cutaneous emboli.	Caused by bloodstream infection. May be spontaneous, associated with indwelling catheters or bacterial/fungal abscesses of other organ systems	N/A	Expected	Common, may imply larger emboli (ecthyma gangrenosum) or emerging DIC*

**CHCC* Chapel Hill Consensus Conference, *CTD* connective tissue disease, *DIF* direct immunofluorescence, *HCV* hepatitis C, *RA* rheumatoid arthritis, *CSVV* cutaneous small vessel vasculitis, *SLE* systemic lupus erythematous, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *ANCA* antineutrophilic antibodies

III cryoglobulinemia can present as cutaneous small vessel vasculitis. Cryoglobulins, rarely, if ever, develop without an underlying systemic disease; a diagnosis of cryoglobulinemia or cryoglobulinemic vasculitis should trigger investigation into associated conditions, namely viral infections (hepatitis B/C, HIV), connective tissue diseases (SLE, Sjogren's, RA), and clonal hematologic disease (multiple myeloma (MM), Waldenström macroglobulinemia, monoclonal gammopathy of unknown significance (MGUS)).

IgA Vasculitis

IgA vasculitis (formerly known as Henoch-Schönlein purpura) is characterized by IgA immune complex deposits in small vessels and presents classically with CSVV, arthritis, abdominal pain, and renal involvement. It occurs in both adult and pediatric populations and is the most common small vessel vasculitis in children 3–12 years of age [10]. It has been reported that 30–65% of cases of IgA vasculitis occurred following an upper respiratory infection (URI), and other causes include exposure to medications, vaccine antigens, or may be idiopathic [10]. In adults, an association with malignancy, particularly solid organ, has been observed [11]. There is a skin-limited variant, which demonstrates IgA deposits on direct immunofluorescence but does not demonstrate gastrointestinal or renal involvement. Such cases appear to be more common in adult populations, and may be idiopathic or triggered by preceding infections or medication exposures; these cases typically behave in the self-limited fashion as described for IgG/IgM vasculitis without probable etiology as described above.

Urticarial Vasculitis

There are two types of urticarial vasculitis (UV): normocomplementemic urticarial vasculitis (NUV) and hypocomplementemic urticarial vasculitis (HUV, or anti-C1q vasculitis). The presentation differs from other CSVV in that primary lesions are urticarial and fixed, lasting longer than 24 h and resolve with purpura or ecchymosis. Complement levels and anti-C1q antibodies should be investigated as HUV is strongly associated with an underlying connective tissue disorder (e.g., SLE) and systemic findings including glomerulonephritis, arthritis, pulmonary disease, and ocular inflammation [6••, 12•]. NUV has a milder presentation and clinical course similar to other skin-limited immune complex CSVV.

ANCA-associated Vasculitis

ANCA-associated vasculitis (AAV) may affect small vessels only or small-to-medium cutaneous vessels. The

presentation may be that of inflammatory non-branching purpura, in which there is leukocytoclastic vasculitis of the post-capillary venules, or, as in cases of mixed small and medium vasculitis, arteries and arterioles may be involved producing findings of branching purpura, subcutaneous nodules, digital infarction, or livedo racemose [6••].

Medication-Induced ANCA-Associated Vasculitis

Minocycline, hydralazine, propylthiouracil, and levamisole (usually as an adulterant in cocaine) are the most common medication triggers for AAV. While vasculitis may be multi-organ or skin-limited, skin-limited is more common for medication-induced AAV as compared to true autoimmune AAV. In both cases, the skin findings typically demonstrate larger, branching purpura resulting in cutaneous necrosis and ulceration. Medication-induced AAV is typically positive for MPO-ANCAs although PR3-ANCAs or mixed positivity can be seen. Cocaine adulterated with levamisole can produce large areas of necrosis over the face and ears. Anti-human neutrophil elastase antibodies may be positive in cases of cocaine abuse and can help to distinguish destructive lesions from cocaine abuse from those of classic AAVs [13, 14].

Autoimmune ANCA-Associated Vasculitis: GPA, MPA, EGPA

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) presents with CSVV with positive ANCA testing. Skin findings are present in 30% of GPA/MPA and 50% of EGPA, although these findings include livedo, ulceration, gangrene, and not exclusively the purpuric lesions of CSVV [12•].

GPA, EGPA, and MPA typically present with significant constitutional symptoms (e.g., fevers, anorexia, weight loss, myalgias, arthralgias, fatigue) which have been occurring for weeks, if not months. Additionally:

- GPA typically involves the ENT and pulmonary systems and manifests with nasal crusting or ulceration, sinusitis, dyspnea, hemoptysis, or cough. Approximately 90% of patients are positive for ANCAs, typically c-ANCAs with anti-PR3 antibodies on ELISA testing.
- EGPA most commonly manifests with asthma (often 8–10 years before other manifestations), mononeuritis multiplex, eosinophilia, and cutaneous vasculitis. P-ANCA immunofluorescence (IF) is more common in this disease, with anti-MPO antibodies on ELISA testing although it should be noted that up to 50% of patients with EGPA may not demonstrate ANCAs, and so ANCA positivity is not a requirement for this, or other ANCA vasculitides.
- MPA presents similarly to GPA, but renal manifestations are more common, while ENT involvement is less common than GPA. Like GPA, 90% of patients are ANCA-positive; however, they are more typically positive for anti-MPO which is more likely to produce a p-ANCA pattern on IF.

Septic Vasculitis

The typical presentation of septic vasculitis is that of randomly scattered purpuric papules, most often with branching purpura or necrosis. These findings can be the result of septic emboli resulting in vessel occlusion or by direct infection of endothelial cells, resulting in vessel destruction and subsequent inflammation. As opposed to CSVV, skin findings are not symmetrical or dependent but rather are distributed randomly, and patients typically exhibit fewer lesions than in CSVV. Morphologies may differ within the same patient, ranging from pustules, branching purpura, or panniculitis depending on the depth of cutaneous emboli.

Diagnostic Approach to Cutaneous Small Vessel Vasculitis

1. A diagnostic approach to CSVV can be oriented around three primary features (Table 2):
2. Physical examination:
    (a) Typical vs. atypical distribution
    (b) Morphology:
        (i) Non-branching lesions: round, inflammatory purpura associated with a more superficial and non-occlusive processes
        (ii) Branching morphology: typically deeper, more significant small-to-medium vessels of the skin, associated with complete occlusion or destruction of the vessel walls
        (iii) Involvement of subcutaneous medium-sized vessels: digital necrosis, livedo, panniculitis
3. First episode of CSVV or a recurrent episode
4. The patient's known medical history combined with the absence or presence of other signs/symptoms on review of systems.

Based on the evaluation of these features, the clinician can then determine which further diagnostic evaluation is

Table 2 Diagnostic considerations for workup of CSVV

Diagnostic features	Categories	Features	Indications
Physical examination—morphology	*Branching morphology*	Branching pattern either entirely or solely at the border of a solid area, centers of branching lesions may be solid purple to black, but the lesion border retains jagged linearity, resembles part of a maple leaf. May present as bullous or necrotic.	Indicates arteriole involvement. Concerning for systemic disease. Random distribution and varying morphology (pustule, purpura, panniculitis) is concerning for septic vasculitis
	Non-branching morphology	Solid circular lesions that could appear flat (macular), raised (papular) or overlap to create larger patches or plaques.	Most commonly associated with immune complex CSVV
Timing of episode	*Recurrent episodes*		Even if skin-limited, recurrence suggests potential underlying associated disease, such as connective tissue disease, chronic infection or rarely, malignancy.
Past medical history and review of systems	*Clear inciting factor*	Skin manifestations 7–10 days after commonly associated trigger (medications, recent illness)	Basic laboratory investigation: CBC/differential and BMP +/− urinanalysis—primarly to rule out nephritis
	Presence of known illness	Connective tissue disorders, autoimmune disease, cancer, HCV*, HBV*, and HIV*	Testing for organ-relevant organ involvement, disease flare or infectious complication due to treatment. Consider: ANA*, dsDNA*, C3/C4, RF*, HCV*/HBV*/HIV* antibodies, cryoglobulins, serum protein electrophoresis (SPEP), and blood cultures
	Symptoms	Constitutional: fever, fatigue, weight loss, or appetite changes	Generalized systemic involvement or neoplasm—requires further testing
		Lower and upper respiratory symptoms (e.g., dyspnea, cough, hemoptysis, sinusitis), renal symptoms (e.g., hematuria)	ANCA-associated vasculitis—check for presence of ANCAs*
		GI symptoms (e.g., abdominal pain, melena), arthralgias, nephritis	DIF for IgA vasculitis.
		Ocular findings (e.g., uveitis)	Urticarial vasculitis, CTD, ANCA-associated vasculitis
		Neurologic symptoms (e.g., neuropathy, paresthesia, and wrist/foot drop), joint symptoms (e.g., arthralgias), constitutional symptoms,	ANCA-associated vasculitis, cryoglobulinemic vasculitis, immune complex vasculitis, rheumatoid vasculitis

**ANA* antinuclear antibodies, *RF* rheumatoid factor, *HCV* hepatitis C, *HBV* hepatitis B, *HIV* human immunodeficiency virus, *ANCA* antinuclear cytoplastic antibodies

necessary, including skin biopsy for H&E, skin biopsy for direct immunofluorescence, and further laboratory testing.

Physical Examination

CSVV is most likely to be skin-limited when it presents with < 1 cm, non-branching papules in a typical distribution. A review of systems will have no pertinent findings aside from possible mild fevers and arthalgias. In such cases, basic testing including CBC with differential, liver function testing, and basic metabolic panel may be the only testing necessary, primarily to rule out evidence of underlying infection (leukocytosis, hepatitis) or nephritis. A skin biopsy may not be necessary in these cases.

Branching morphology, atypical distributions, and positive review of systems, in combination with the patient's comorbidities and medical history, dictate further evaluation. Acral lesions are not typical and may imply underlying systemic disease or an embolic phenomenon. Randomly distributed purpura implies septic vasculitis for which skin biopsy; tissue culture and blood cultures should be performed. Ulceration, eschars, digital necrosis, livedo, or panniculitis implies medium vessel disease or a hypercoagulopathy such as DIC, heparin-induced thrombocytopenia and thrombosis (HITT), or antiphospholipid antibody syndrome (APLAS) among others [9•]. Urticarial lesions should lead to complement testing and associated connective tissue diseases.

Single vs. Recurrent Episodes of CSVV

For a patient with a single, initial episode of typical CSVV, immune complex disease is more likely and statistically most likely to be attributed to recent infection, medication exposure, or may be idiopathic. Recurrent episodes, even if only skin-limited, warrant further investigation into undiagnosed chronic processes such as CTD, IgA vasculitis, occult infections (hepatitis, CTD, osteomyelitis, subacute endocarditis), or malignancies (typically plasma cell dyscrasias, lymphoma, or leukemias) with clinical suspicion dictated by findings on review of systems.

Presenting Symptoms

A thorough but targeted review of systems and physical exam will help reveal systemic symptoms and identify underlying organ involvement. Constitutional symptoms like fever, fatigue, weight loss, or appetite changes imply generalized systemic involvement requiring further diagnostic testing, or neoplasm as an underlying etiology. ANCA-associated vasculitides present with both lower respiratory/pulmonary symptoms including dyspnea, hemoptysis, and cough as well as upper respiratory symptoms including sinusitis. They can also cause renal dysfunction including hematuria [15]. IgA vasculitis classically presents with gastrointestinal symptoms including abdominal pain, melena, and intussusception. IgA vasculitis can also present with arthralgias, though, joint pain may also indicate SLE or RA as underlying causes. Ocular findings, such as scleritis or uveitis, can be seen in AAV or UV [17]. Neurologic symptoms like neuropathy, paresthesia, and wrist/foot drop can be seen in a variety of systemic vasculitides including ANCA-associated, immune complex vasculitis, cryoglobulinemia, and rheumatoid vasculitis [15, 18, 19]. Importantly, identification of any symptoms that indicate systemic involvement prompts further diagnostic testing.

Skin Biopsy

A skin biopsy can be performed for typical evaluation with hematoxylin and eosin (H&E) or direct immunofluorescence (DIF). When performing a skin biopsy, lesion selection, location, and timing of the biopsy are important as the histologic changes vary depending on the timeframe within which the biopsy is taken. Skin biopsy should be performed on an early purpuric or inflammatory lesion which has developed within 48 h. For DIF, the yield is said to be highest within the first 24 h, as immunoglobulin deposition is among the first pathological changes within the vessels [20]. A 4–10-mm punch biopsy can be used; it is the authors' practice to select a size which fully removes the target lesion, selecting one for H&E and, if needed, a different, similar lesion for DIF. Lesions with ulceration or eschar may be more clinically striking but may not be the ideal diagnostic lesion as these findings are more associated with lesions that are > 48 h in duration.

In cases in which IgA vasculitis is suspected, a DIF helps to identify the presence of IgA deposits. IgG and/or IgM deposition is seen in other forms of immune complex vasculitis, connective tissue disease-associated vasculitis, and type II/III cryoglobulinemic vasculitis, although it should be noted that the diagnostic importance of identifying IgG or IgM deposits is unclear and may be unlikely to provide crucial information that would otherwise alter diagnosis of management of the patient. As such, a DIF does not have to be performed for every presentation of CSVV. Similarly, cases in which a patient presents with uncomplicated CSVV lacks concerning findings or has a clear etiology for CSVV, a skin biopsy may not be necessary to confirm an otherwise obvious clinical diagnosis. A skin biopsy aids in diagnosis for cases in which a diagnosis of CSVV is uncertain, there is a possibility for septic vasculitis, the caliber of blood vessel involvement needs to be investigated, or a DIF needs to be performed.

Laboratory Testing/Imaging Studies

Diagnostic laboratory testing and imaging depend on the findings from the history, review of symptoms, and physical exam. For all suspected cases of CSVV, a complete blood count (CBC), chemistry panel including basic metabolic panel (BMP) and liver function tests (LFTs), and urinalysis (UA) with sedimentation should be performed to rule out sub-clinical systemic involvement, particularly nephritis. In cases that are idiopathic and single episode, with no apparent signs or symptoms of systemic involvement, these laboratory tests are sufficient. If this initial assessment yields no presence of systemic involvement, then CSVV may be described as skin-limited or single-organ.

However, if systemic signs and symptoms have been identified or if the initial tests show abnormalities, other diagnostic tests are appropriate to determine the etiology. Based on the patient's presentation, these tests include immunological screening to identify the presence of ANCAs, serum complement levels of C3 and C4, cryoglobulins, rheumatoid factor, antinuclear antibodies, anti C1-q antibodies, HCV/HBV/HIV antibodies, serum and urine protein electrophoresis with serum free light chains (SPEP/UPEP/SFLC), and blood cultures (Table 2). Additionally, if indicated by the history and physical exam, imaging studies including chest X-ray and CT scan may be ordered. However, routine imaging in all cases is not recommended as it has low diagnostic utility in identifying underlying organ involvement, introduces the potential of false positives, and incurs increased healthcare costs [21•].

Treatment

Treatment varies based on the etiology and severity of CSVV (Table 1). For skin-limited or single-episode idiopathic cases, treatment is supportive with a focus on symptomatic relief. Supportive treatment includes rest, elevation of the lower extremities, use of compression stockings, and NSAIDs for pain. In cases with a clearly identified inciting medication or infection, discontinuation of the drug or resolution of the infection is sufficient for resolving the CSVV. If cutaneous findings are severe or extensive, a short course of corticosteroids may be warranted.

In cases that are chronic or recurrent, alternatives to corticosteroid treatment for long-term management may be considered with agents such as dapsone, colchicine, hydroxychloroquine, and NSAIDs. Colchicine and dapsone have both demonstrated efficacy in resolution of cutaneous vasculitis; however, their use may be limited by side effects of GI upset in colchicine and contraindication in patients with glucose 6-phosphate dehydrogenase deficiency with dapsone [22, 23].

Corticosteroids are also used as first-line treatment of underlying systemic vasculitis. Although most cases of IgA vasculitis are self-limited, corticosteroids are first-line treatment for IgA vasculitis in which there is abdominal pain refractory to acetaminophen/NSAIDs or changes in creatinine clearance or proteinuria greater than 0.5–1 g per day [16]. For UV, steroids are also used to reduce immune complex formation.

When the underlying etiology of CSVV is attributed to a chronic systemic vasculitis or autoimmune disease, or there is a continued lack of resolution with corticosteroids, immunosuppressive agents such as azathioprine, methotrexate, and mycophenolate mofetil are employed [24–29]. Hydroxychloroquine has also been utilized in cases of CTD-associated CSVV and UV. Lastly, the use of anti-CD20 agents like rituximab is commonly used for ANCA-associated vasculitis, CV, UV, and adults with IgA vasculitis [26, 30–32].

Conclusion

Because of the range of causes of CSVV, physicians should be aware of the importance in determining if there is underlying systemic involvement. This paper creates a framework for clinicians to identify and correctly diagnose CSVV, without failing to recognize potentially severe underlying causes. While there are specific symptoms and exam findings associated with systemic vasculitides and autoimmune diseases, the presence of any subcutaneous or multi-organ disease requires further diagnostic studies. Treatment varies on the etiology of the CSVV as well as the severity of cutaneous and systemic findings. Tables 1 and 2 aim to simplify the complex topic of vasculitis, and help physicians begin to diagnose CSVV in an outpatient dermatology setting.

Compliance with Ethical Standards

Conflict of Interest None of the authors (SRH, LD, ACW) have any conflicts of interest or competing interests to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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