Original Review

Vasculitic Ulcers

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Abstract

Vasculitic ulcers are an emerging problem in wound care that needs to be well defined and adequately approached by caregivers. Cutaneous vasculitis includes several inflammatory disorders that compromise microvessels and specifically the cutaneous vascular system: arterioles, capillaries, postcapillary venules. The pathogenetic role of circulating immunocomplexes and autoantibodies (antineutrophil antibodies) in these diseases has been widely demonstrated in animal models and in humans. Vasculitis can be limited to the skin or represent the cutaneous signs in case of systemic vasculitis with visceral involvement. The injury of cutaneous microvessels may result in impairment of blood flow and consequent focal ischemia and formation of skin ulcers. The ulcers are often multiple and localized on the lower leg and foot where the microcirculatory anatomy and rheologic dynamics are predisposing factors. Approximately 3% to 5% of skin ulcers may be caused by a vasculitic disorder.

Keywords

cutaneous vasculitis, skin ulcers, inflammatory ulcers

Cutaneous ulcers are mainly diagnosed as being of macrovascular venous and arterial origin. However, a consistent number of patients do not demonstrate an underlying anatomical or functional disturbance of large vessels. A notable part of them may be supposed to be related to specific microvascular disorders[1] (Figure 1).

Pathogenetically, we can distinguish 2 main groups: ulcers due to inflammatory microangiopathy and ulcers due to occlusive microangiopathy. Occasionally, the 2 mechanisms may overlap as often seen in cryoprotein-mediated vessel injury.

The majority of "inflammatory" ulcers are the result of a cutaneous vasculitis (CV), a vessel damage mediated by an immunological process that causes inflammation and destruction of both the vessels and the perivascular tissue.

Although a lot of information has been obtained about the potential pathogenetic mechanisms and the clinical association of CV, the natural history of a CV is still unpredictable. The theory that each type of vasculitis has a unique etiopathogenesis is now increasingly supported.

Sais and colleagues[2] have indicated some potential "risk factors" for the systemic involvement and for the probability of a long-term course in case of CV.

In daily clinical practice, physicians have to face several problems with patients affected by these conditions.

One of the most frequent challenge is to clinically suspect, make diagnosis, and establish a precise role of the impairment of the cutaneous microcirculation as casual factor or secondary reason for clinically atypical or nonhealing wounds.

The ulcers' clinical features are the result of the size and the severity of the involved small vessels. In many cases the ulcers are multiple and localized on the legs and feet[3] (Figure 2).

Instrumental evaluation (risk for internal vasculopathies) and macrocirculatory examination (Doppler ultrasonography) are advisable, in order to state potential alteration of the large vessels.

Clinical suspicion should be confirmed by laboratory and/or instrumental tests. Anamnesis aimed to exclude trigger factors, immunological investigation for vasculitis and connective tissue diseases (CTDs), assessment of the coagulatory function, lesional biopsy, and histological examination are mandatory.

From Small Vessel Vasculitis to Cutaneous Ulcer

Vasculitis is the inflammatory diseases of the cutaneous small vessels, more often responsible for skin ulcers.

The term vasculitis includes anatomic-clinical features that appear in different forms and consist in immunologically

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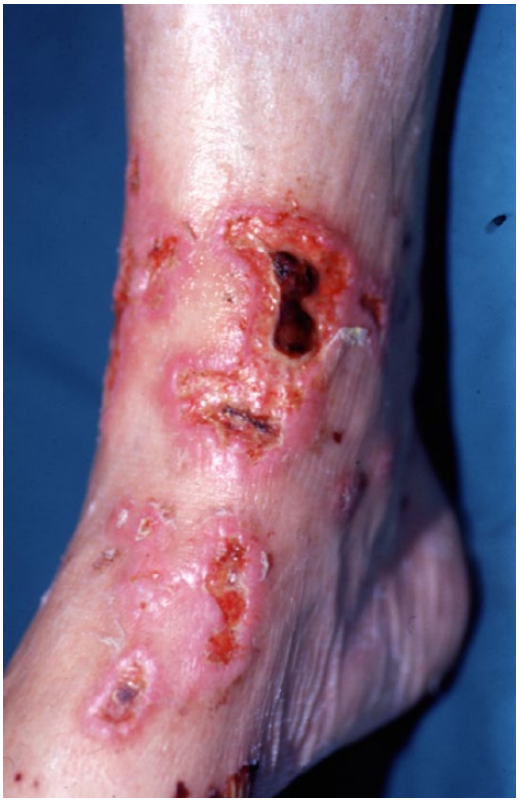


Figure 1. Leukocytoclastic vasculitis. A 51-year-old male with diffuse palpable purpura of the lower leg and multiple ulcerations. Histology: leukocytoclastic vasculitis.

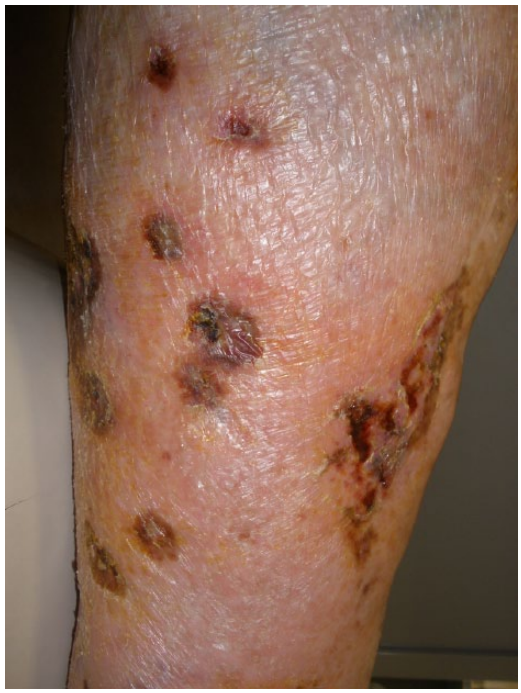


Figure 2. Several vasculitic necrotic lesions of the lower leg.

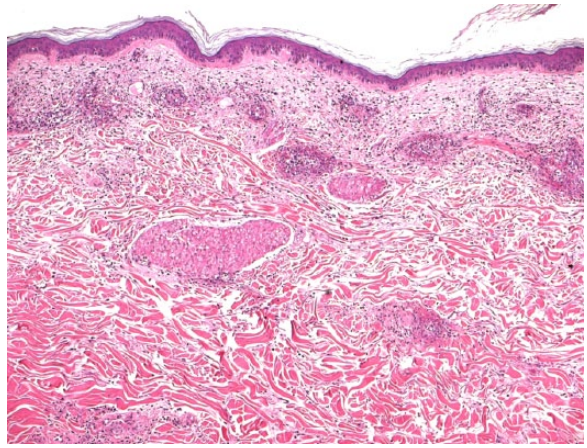


Figure3. Histology of leukocytoclastic vasculitis: fragmented neutrophil granulocytes (leukocytoclasia) that infiltrate the wall of the upper dermal small vessels and the perivasal tissues. Fibrinoid necrosis of the vessels wall.

mediated angiocentric inflammation, characterized by neutrophils (prevalent) and lympho-monocyte infiltration, fibrinoid necrosis of the vessel walls, and extravasation of red cells[4] (Figure 3). It may result in destruction, thrombosis, or fibrosis of the vessel, narrowing of the lumen and reduction of tissue blood supply, and focal ischemia (Table 1). Ischemia explains the tissue necrosis and subsequent cutaneous ulceration. It is a common complication during CV (Figures 4-6). The red blood cells' extravasation justifies the initial hemorrhagic aspect (palpable purpura) of many vasculitic lesions.

The skin is one of the target organs of vasculitis due to the anatomic features of the postcapillary venules and the microcirculation physiology influenced by the hydrostatic pressure. For these reasons, the majority of the vasculitic lesions localize in the lower half of the leg and in the foot.[5] The skin is often only seemingly the unique organ involved. It has been reported that the internal organs are involved in 20% of patients affected by CV.[2] Kidney, lung, and joints are the preferential site of internal organ involvement.

Theoretically, any type of CV can cause ulcerations. However, it is unlikely that this occurs if the vessels involved are very small as in case of Henoch-Schönlein purpura (IgA vasculitis).

The histological feature of the leukocytoclastic vasculitis (LV), in which the neutrophil granulocytes are predominant, is the hallmark of a large part of CV, as results from lesional biopsy.[6] The fibrinoid necrosis of the vessel wall is the histological sign that allows one to make a diagnosis

Table 1. Revised Nomenclature of Vasculitis: Chapel Hill Consensus Conference 2012.

Large vessel vasculitis
Temporal arteritis
Takayasu arteritis
Medium vessel vasculitis
Panarteritis nodosa
Kawasaky disease
Small vessel vasculitis
Immunecomplex-mediated
Cutaneous leukocytoclastic vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Urticarial vasculitis
ANCA-associated
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Microscopic polyangiitis

of vasculitis. Other less frequent histological aspects are the granulomatous vasculitis (polymorphic infiltrate with presence of histiocytes, lymphocytes, and neutrophils; Figure 7) and the lymphocytic vasculitis in which the lymphomonocytes are predominant. Histologically, the few patterns commonly shown in the cutaneous lesions (leukocytoclastic/lymphocytic vasculitis) do not usually permit to identify the etiologic factors and provide little evidence also on the pathogenetic mechanisms supporting the vasculitis.

The presence of associated symptoms and, above all, the laboratory, immunological, and instrumental investigation allow to diagnose specific subsets of cutaneous or cutaneous-systemic vasculitis.[7]

Classification

The widely accepted classification is based on the anatomical-topographic criterion that distinguishes large, medium, and small vessel vasculitis (Table 1).

In 2012 the new Chapel Hill Consensus Conference introduced in the classification of small vessel vasculitis also the pathogenetic concept of immunecomplex mediated and antineutrophil antibodies-associated vasculitis (ANCA-positive vasculitis).[8]

Clinical Features

The most frequent presenting sign is palpable purpura that is a common denominator of several CVs (Figure 8). The lesions have a diameter of less than 1 cm and begin as erythematous maculae that become purpuric papules, sometimes confluent, thus determining the formation of plaques or nodules that can ulcerate. A clinical polymorphism is frequent. This indicates the various degrees of vascular damage and depends on the caliber of the larger vessels involved, their anatomic site, and the composition of the inflammatory infiltrate.[11] Therefore, the lesions can vary from urticaria-like forms (very small vessel damages) to palpable purpura up to ecchymosis, hemorrhagic bullas, as well as infarctual lesions and ulcerations when tissue ischemia is severe.[9]

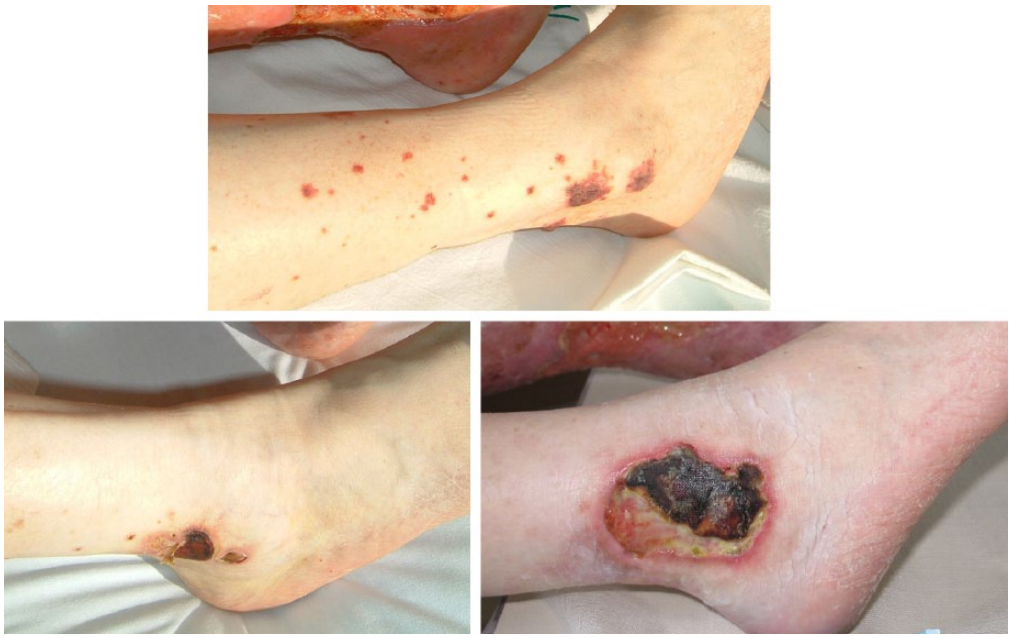
Skin ulcer is frequently the evolutionary complication of a CV. However, sometimes, it can constitute the initial sign of the process onset. It always occurs as a consequence of an ischemic phenomenon that follows a vessel occlusion or a condition of focal reduced perfusion due to the decreased efficiency of the cutaneous microvessels (Figure 9). Table 2 summarizes the main causes of occlusion or reduction of the cutaneous vessels' caliber in the course of CV.

In a clinical point of view, the ulcers are usually small, multiple, and tend to coalesce in greater polycyclic lesions. They mainly appear at the lower limbs at various levels, with particular incidence in the lower half of the leg and, rarely, the fingers of the hands.

When the deep cutaneous vessels are involved nodular lesions can be seen. The presence of livedoid aspects (tree like = livedo racemosa) is the expression of a severe damage of the cutaneous microvascular-tissue functional unit responsible for thrombotic and/or fibrotic vessel occlusion. It is typical of some CVs (ie, panarteritis nodosa) and can also be observed in some syndromes of difficult nosological definition (livedoid vasculopathy, antiphospholipid antibodies syndrome, calciphylaxis) at high risk of ulcerative complication.[10]

Sometimes the ulcers can become chronic, increase in dimension, and assume a nonspecific morphology. The contemporary presence of macrocirculatory disturbances or other concomitant factors (diabetes, CTDs, genetic polymorphism of some coagulation factors, such as MTHFR, PAI-1, and others, as well as the long-term assumption of cytostatic and immunosuppressive drugs) are factors that can enhance this evolution.

CVs can present together with a series of generally nonspecific signs and symptoms. Edema of the lower limbs, subjective feeling of lesion burn, and typical symptoms of serum disease (arthromyalgia, fever) are very frequent. The extension of the vasculitic damage to the internal organs must be suspected in the presence of neurologic manifestations (peripheral neuropathies), persistent polyarthritis, abdominal pains, thoracic pain of pleuritic and pericardial nature. In IgA vasculitis (Henoch-Schönlein purpura) the onset of abdominal pain and melena, associated to signs of nephropathy, is significant.



Figures 4, 5, 6. From small vessel vasculitis to cutaneous ulcer: A 63-year-old female with arterial hypertension and hyperglycemia properly controlled by diet and oral antidiabetic drugs, affected by phagedenic ulcer of the left leg for 4 years, resistant to therapies (inclusive of grafts of autologous skin). Following oral antibiotic therapy with piperacyllin tablets, she developed multiple lesions of palpable purpura of the legs. Histological examination disclosed a leukocytoclastic vasculitis. After a brief oral therapy with low dose of corticosteroids (prednisone 15 mg/day) the purpuric lesions disappeared with the exception of a purpuric-necrotic supramalleolar area that appeared enlarged and evolved with eschar and subsequent ulceration (Figure 5). After 1 month the ulcerative lesion was very large, painful, and did not respond to therapies. There is no doubt that the newly formed ulcer is of vasculitic origin; however, in the absence of other clinical (purpura) or anamnestic notes, the diagnosis may be very difficult.

Diagnostic Criteria (Table 3)

The histological examination must always confirm the clinical suspect of CV. Biopsy of recent lesions provides major indications due to the evolutionary character of the inflammatory infiltrate. The ulcer biopsy is more indicative at the active edge of the lesion where the tissue has not been destroyed by the necrotic process or in the periulcerative area when new lesions tend to develop. The direct immunofluorescence on skin lesions shows Ig, complement, and fibrin in the vessel walls and in the perivasal zone. It is useful to diagnose the type of vasculitis, and the detection of perivascular IgA is typical of IgA vasculitis. Decreased levels of the complementary fractions (C_3, C_4) are found in CVs associated to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome, hepatitis C virus (HCV)-related cryoglobulinemia, and Henoch-Schönlein disease. The alteration of the serum-protein feature can raise a suspicion of lymphoproliferative disorders and infections (especially viral), and it is strongly indicative of paraproteinemias (Waldenstrom's macroglobulinemia).

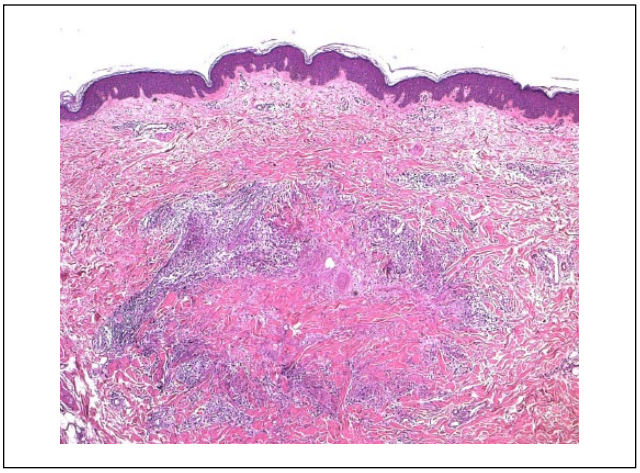


Figure 7. Granulomatous vasculitis in a male patient with Wegener's granulomatosis.

The variation of the renal function indexes such as creatinine clearance and the alteration of the urine tests

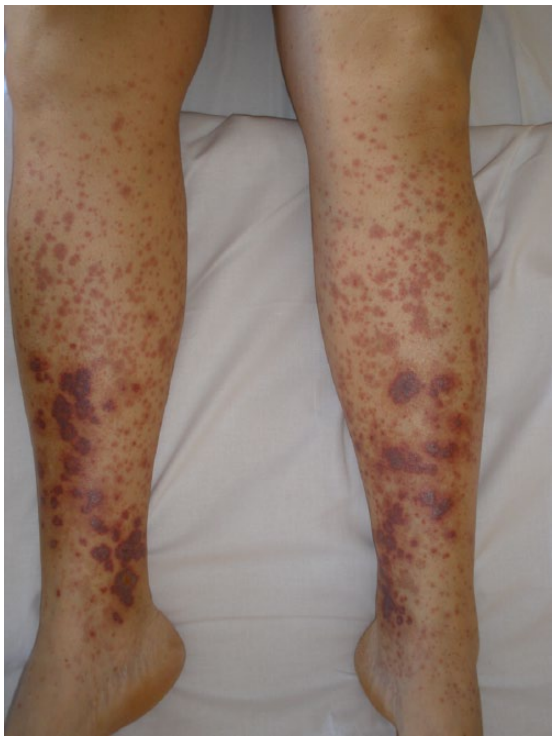


Figure 8. Palpable purpura of the legs.

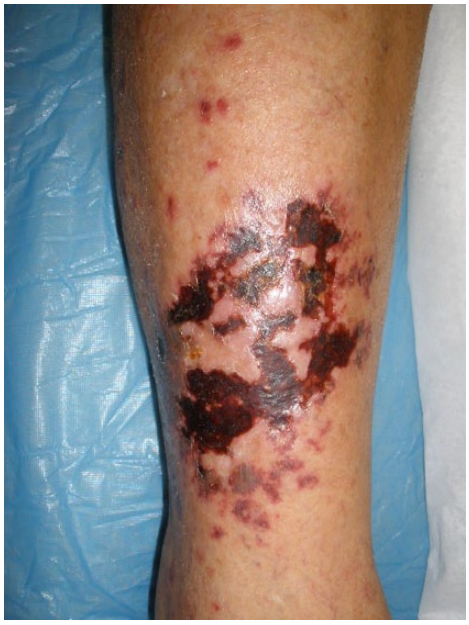


Figure 9. Leukocytoclastic vasculitis: 61-year-old diabetic patient. Severe necrotic-infarctual lesions associated with palpable purpura.

Table 2. Causes of Occlusion or Reduction of the Vessel Caliber in the Course of Vasculitis.

- Occlusion due to macromolecular or cold-predictable complexes (cryoproteins, paraproteins)
- Platelet thrombosis
- Fibrin thrombosis
- Intimal hyperplasia
- Postinflammatory fibrosis

Table 3. Basic Investigation Protocol in Case of Cutaneous Vasculitis or Vasculitic Ulcer.

Histological examination
Hemochrome
ESR, PCR, fibrinogen
Protein electrophoresis
Creatinine, urea blood test
GOT, GPT, alkaline phosphatase, γGT
PT, PPT
C_3, C_4, CH50
Antinuclear antibody
Extractable nuclear antigens antibodies (anti-ENA)
Antineutrophil cytoplasmic antibodies (c, p-ANCA)
Cryoglobulins
Rheuma-test
Antibodies anti–hepatitis B virus; antibodies anti–hepatitis C
Fecal research of occult blood
Urinalysis

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C reactive protein; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; γGT, glutamyl transferase; PT, prothrombin time; PTT, partial thromboplastin time.

(hematuria, proteinuria, cylindruria) may reveal renal damage related to systemic vasculitis.

The bacteriological and virological investigations (research of foci, screening for hepatitis B and C, HIV) are necessary in the case of relapsing CV.

Hematological tests and the markers of solid tumors must be performed if we suspect a paraneoplastic CV.

Erythrocyte sedimentation rate (ESR) values and acute phase proteins (polymerase chain reaction, fibrinogen, mucoproteins) are increased in two thirds of patients with CV, but can be very high in case of systemic vasculitis (PAN, Horton's arteritis, Wegener's syndrome).

Under the immunological aspect, antinuclear antibodies positivity, anti-ENA, anti-DS DNA antibodies, rheuma-test, and immunoglobulins serum levels can indicate an associated CTD.

Cryoglobulins, present in 90% of HCV+ patients and in several cases of CTDs, can explain many apparently "idiopathic" CVs or nonhealing wounds.

Table 4. Perspective Studies on the Associated Diseases and the Triggering Factors Identified in the Course of Cutaneous Small Vessel Vasculitis.

	Ekenstam and Callen[12]; 82 Patients	Papi et al[13]; 70 Patients
Connective tissue diseases	17	6
Viruses/bacteria	11	9
Drugs	8	14
Neoplasias		3
Others	2	1
Total	46%	47%

Circulating immunocomplexes can be detected during the active phases of the disease.

Clinical Aspects of the Main Cutaneous Vasculitis Associated With Ulcerations

Cutaneous Leukocytoclastic Vasculitis (CLV)

CLV can be classified as single organ or associated with visceral involvement. "Single organ" means that only the skin is apparently affected by vasculitis.

CLV is essentially a histopathological term and includes a heterogeneous group of small vessel vasculitis that may be a primary disorder or a clinical aspect of systemic vasculitis. A number of associated factors have been reported, some of them being strongly suspected to play an etiological role such as concomitant viral, microbial and mycotic infections, drug intake, CTDs, and malignancies[12,13] (Table 4). More than 50% of the patients do not present apparent association.

The majority of the patients with single-organ CLV will experience only one episode that resolves in a few weeks, but 10% to 15% will suffer from periodic recurrences. The typical clinical feature is palpable purpura of the lower limbs, where the microvascular deposition of immune factors is a pathogenetic mediator. In some patients, necrotic-ulcerative lesions may present as an early sign of the vasculitis or, more often, complicate the natural evolution of palpable purpura (Figure 10).

A high number of ulcers are quite superficial, tend to regress in a short time, and leave only modest cutaneous dystrophic and/or pigmentary outcomes. However, sometimes, the ulcerative lesions persist for a long time and become resistant to the common therapies. This generally occurs as result of causal factors of delayed healing such as systemic treatments (immunosuppressive and chemotherapeutic drugs, especially if at high dosages).

A frequent association between CLV and ulcerative evolution has been related to positivity for thrombogenic biological risks.[14]

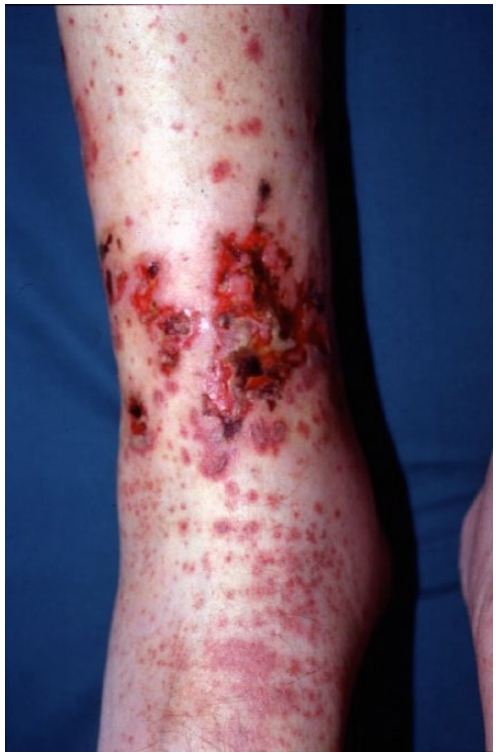


Figure 10. Drug-induced cutaneous leukocytoclastic vasculitis (amoxicillin).

Vasculitis in Course of Connective Tissue Diseases

- Rheumatoid arthritis (RA), systemic lupus erythematosus, Sjögren syndrome, systemic scleroderma
- Frequency of ulcers: 5% of cases of RA
- Often multiple and very painful ulcers

Among the cutaneous complications of CTDs, the ulcers of the lower limbs have a primary role, for both the chronic-relapsing progression of CTD-associated vasculitis and the resistance to conventional treatments. The initial cutaneous manifestations may be clinically identical to those of CLV and histologically characterized by the predominant aspect of LV. In many cases, a partial or complete occlusion of blood vessels as complication of the inflammatory event develops, due to thrombosis or late acellular fibrosis.

It has been calculated that 5% of patients with RA may develop ulcers of vasculitic origin and a higher incidence has been described for SLE[15] (Figure 11). The histologic findings show LV and clinical signs resembling panarteritis nodosa. It explains the polymorphous clinical aspects ranging from palpable purpura, necrotizing lesions, and nodules, to atypical ulcers and gangrene of the lower extremities. The lesions are often multiple, located on the lower limbs,

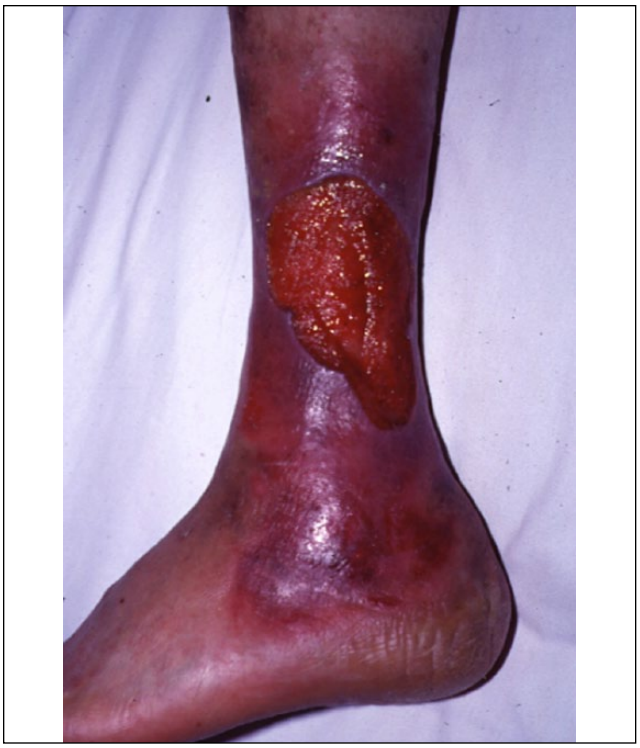


Figure 11. Chronic vasculitic ulcers in a female patient with SLE.

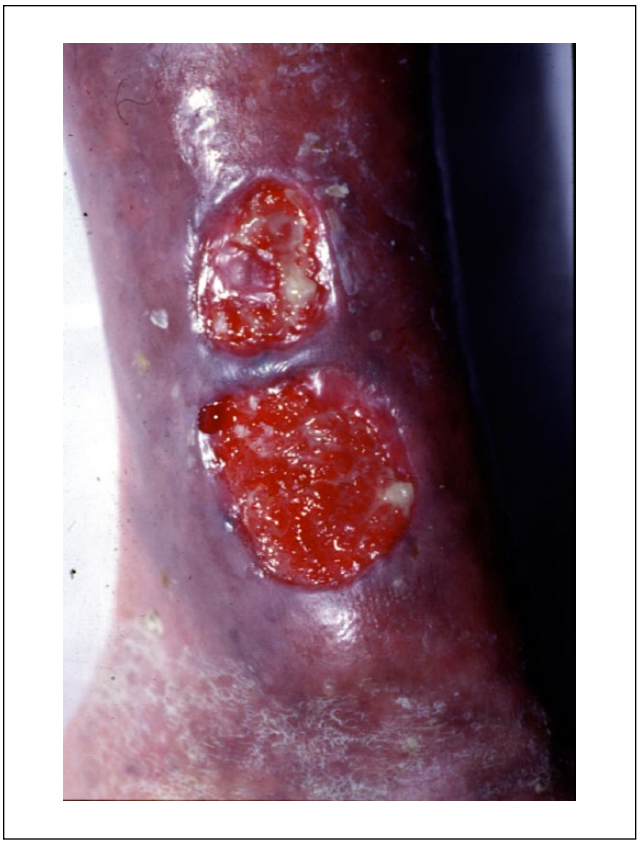


Figure 12. Long-lasting vasculitic ulcers in a 55-year-old female with Sjögren syndrome and recurrent leukocytoclastic vasculitis of the legs.

especially in the distal area. Small ulcers of the limbs (hands and feet) can frequently develop.

In the course of scleroderma, acral ulcers are common, very painful and difficult to treat. For some of them, a pathogenic mechanism related to "sclerodermic vasculitis" can be hypothesized. Five percent of patients with Sjögren syndrome will develop skin ulcerations due to recurrent CV[16] (Figure 12).

HCV-Related Cryoglobulinemia

- Frequent diagnose of CV in the last 20 years
- Frequency of ulcers: high
- Pain and tendency to relapse
- Risk of organic involvement (kidney)

Cryoglobulins are circulating macromolecules that precipitate in vitro at temperatures below 37°C. They cause tissue damages promoting vascular sludging (hyperviscosity syndrome, mainly in type I cryoglobulinemia) and inflammation through an immune-mediated mechanisms (principally vasculitis, in mixed cryoglobulinemia).

Cryoglobulinemic vasculitis is caused by the deposition of mixed cryoglobulins in the walls of venules, capillaries, and arterioles. In the past decades a growing rate of association between HCV infection, HCV-related mixed cryoglobulinemia (MC), and CV has been pointed out. Ferri et al[17] found that about 90% of HCV-RNA-positive patients have MC and a large percentage of them manifest CV. The most frequent manifestations are purpura, arthralgias, and nephritis. The purpuric lesions are commonly recurrent. They may associate with necrosis and ulcerations or induce skin ulcers due to the repeated severe microcirculatory injuries. The ulcers may be multiple, extremely painful, and highly resistant to the therapy (Figure 13). Cutaneous ulcers and digital necrosis signify a high risk of infection, sepsis, and death.[18] A recent Italian multicenter study reported that among 126 patients affected with cryoglobulinemic vasculitis, 36 individuals (29%) experienced at least one episode of skin ulcers, more commonly localized at the lower limbs.[19]

HCV plays a major role in the pathogenesis of CLV in these patients, and this evidence supports the rationale for antiviral associated to immunosuppressive therapy.

Panarteritis Nodosa (PAN)

- Skin-limited form and cutaneous-systemic form
- Risk of polyvisceral involvement (kidney and lung)
- Nodules, livedo racemosa → ulcers (frequent)
- Local and systemic therapy

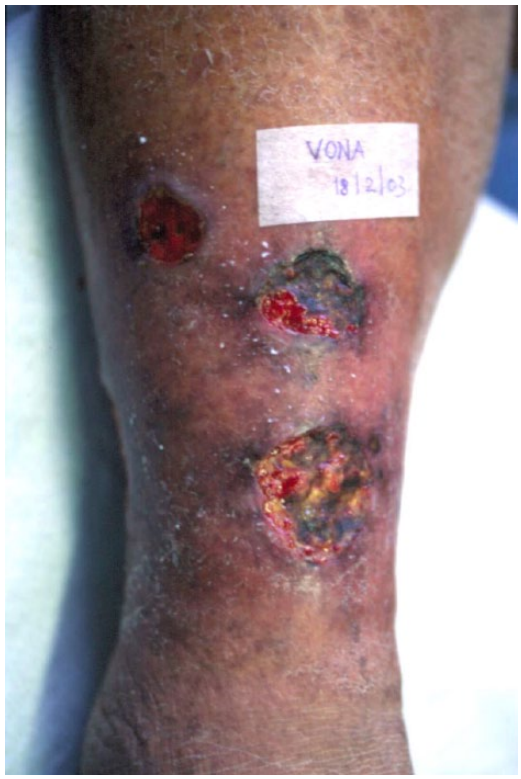


Figure 13. Cryoglobulinemic vasculitic ulcers in a 55-year-ole female patient. HCV+ and chronic hepatitis.

PAN is a multisystem vasculitis that compromises small to medium-sized arteries with wall necrosis, formation of inflammatory granulomas, and evolutive fibrosis. The systemic form involves electively the kidney, but presents with cutaneous lesions in an elevated number of patients. They include livedo racemosa, painful often ulcerating cutaneous nodules (Figure 14), and digital gangrene.

In some cases it has been repeatedly correlated with hepatitis B and C virus infections.[20]

A cutaneous benign form has been described. Clinical features of livedo racemosa associated to nodules with evolving in ulcerations are commonly seen in the lower extremities. No visceral involvement is observed, although the patients may refer fever, arthralgias, and symptoms due to peripheral neuropathy. An accurate follow-up of these patients is strongly recommended in order to check the risk of internal involvement.

Vasculitis Associated to Antineutrophil Cytoplasmic Antibodies (ANCA)

Vasculitis associated to circulating c- and p-ANCA constitute the most important group of the primary systemic vasculitis of the adult population. It includes the 3 main features reported in Table 1. Primarily, they affect adult people with an incidence peak between 50 and 60 years. ANCA positivity and dosing help confirm the diagnosis and, often, monitor the disease evolution and the response to therapy. Such antibodies could also have a pathogenetic role and constitute a very accurate marker of systemic vasculitis (c-ANCA in particular) and are very rarely detectable in the isolated CV.

Granulomatosis With Polyangiitis (Wegener's)

- Ulcer frequency: high, anomalous sites (upper limbs, face, oral cavity)
- c-ANCA associated
- Renal and pulmonary damages
- Response to cortisone, cyclophosphamide and anti-IFN-α drugs

It is a necrotizing vasculitis of the small arteries and veins, associated with the formation of intra- and extravascular granulomas.

The vasculitic process damages lower and upper respiratory tract, while precociously a segmentary or focal glomerulonephritis appears, possibly evolving in rapidly progressive glomerulonephritis with formation of crescents. More than 80% of the cases present an involvement of the paranasal sinuses and kidneys. About 50% to 60% of patients have eyes, joints, ears disorders and a nasopharynx damage. The most common clinical manifestations are cough, hemoptysis, sinusitis disorders, arthralgias, fever, otitis, and ocular damages (sclerouveitis).

The cutaneous lesions (30% to 40% of cases) are due to papules, nodular purpura, ulcers, and subcutaneous nodules[21,22] (Figure 15). Signs of renal involvement are almost constant, and if not treated, it is the most frequent cause of death.

ESR is very high (>80 mm/h) and anemia, leukocytos, and hypergammaglobulinemia can be present. About one third of the patients present nose granulomas with an ulcerative and obstructive involvement also of the nasal septum.

Temporal Arteritis (Giant Cell Horton's Disease)

- Ulcer frequency: low
- Localization in the forehead and scalp

Temporal arteritis is a granulomatous panarteritis that can affect medium and large sized arteries and that more often involves the temporal artery. The typical lesion is the cutaneous nonpulsatile nodule just next to the temporal area and thickness of the artery. It is a disease of the elderly and manifests with recurrent headache, visual impairment, and fever. In more than 50% of patients a condition of rheumatic polymyalgia is associated. ESR and C-reactive protein can be very high.

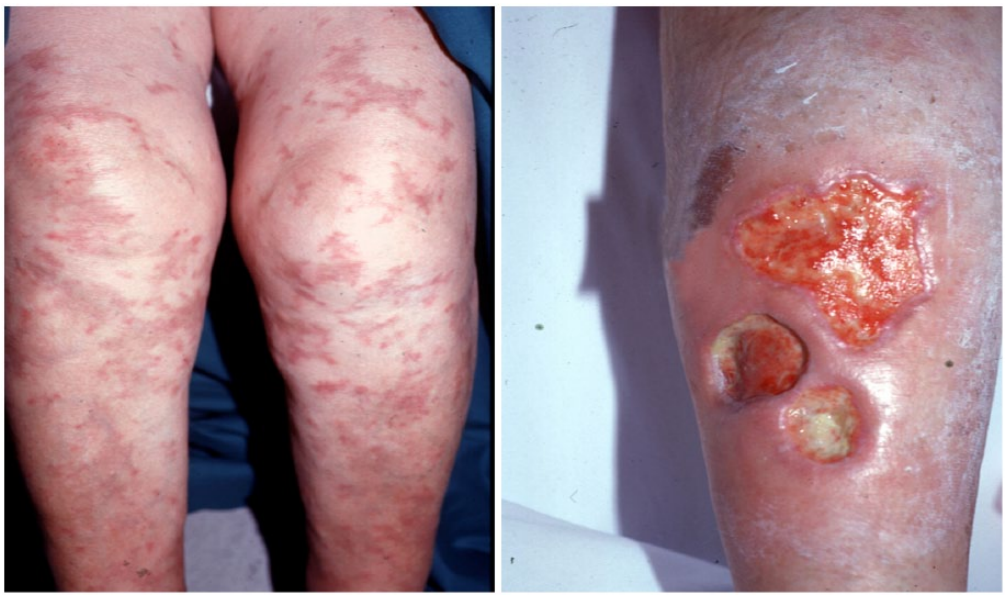
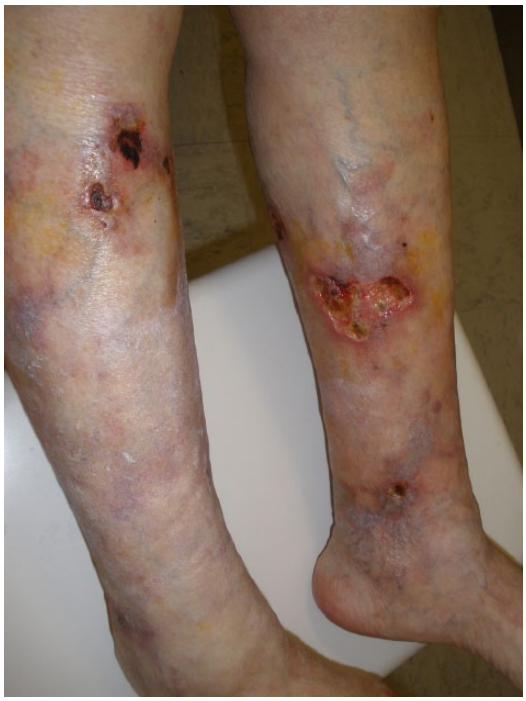


Figure 14. Panarteritis nodosa. Generalized livedo racemosa and nodules of the lower limbs in a 67-year-old woman with PAN. Complication with multiple leg ulcers after 3 years.



Figures 15. Granulomatosis with polyangiitis. Multiple ulcerative lesions of the legs during Wegener's granulomatosis. The disease commonly starts with lesions of the upper respiratory tract and nose.

Necrosis and cutaneous ulceration are rare: they involve the temporal area and the superior district of the scalp (Figure 16).

Long-term steroidal cortisone therapy is the first choice treatment.

Principles of Therapy

The basic therapy of the vasculitis is essential in the care of a vasculitic ulcer. The balance between anti-inflammatory and immunosuppressive drugs and their effect on renewing cells, in the phase of active proliferation, should be carefully monitored.

Ulcers due to vasculitis do not substantially differ from the ones of other origin and are subject to well-known complications, including infection. It is extremely useful to comply with the rules of "preparation of the ulcer bed" and the care recently defined by the acronym TIME (time infection medication epidermis).

For what concerns the strictly vasculitic lesions, local therapy is based on the use of corticosteroids, zinc oxide creams, and diluted antiseptics in case of exudative areas. We have recently noted good results for what concerns the inflammatory lesions and healing of some nonhealing vasculitic ulcer, treated with tacrolimus ointment 0.1% twice a day.

The use of compression therapy with bandage or elastic stockings is advisable, when the macrocirculatory conditions allow it.

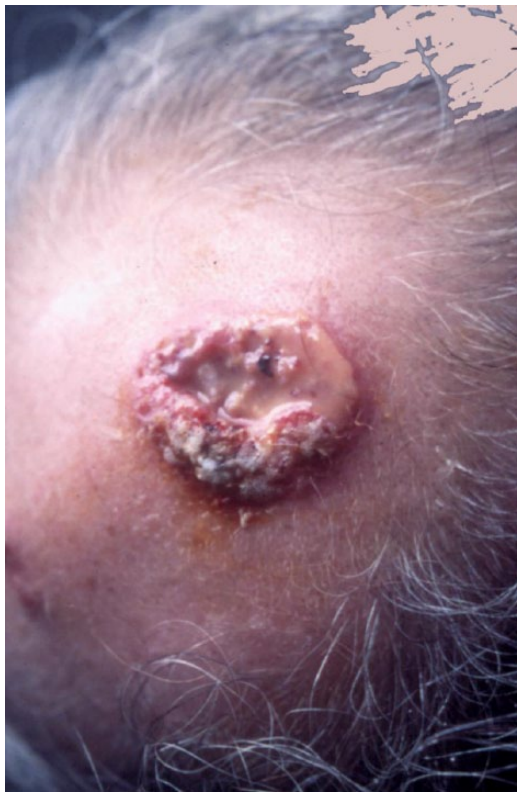


Figure 16. Temporal arteritis. Ulcer of the temporal area consequent to Horton's disease in a 76-year-old male patient.

Our group obtained excellent results in apparently nonhealing ulcers in PAN and cryoglobulinemic ulcer suggesting the use of short-stretching bandages.

Surgical debridement should be done with care under the circumstances of active phase of the vasculitis, in which new lesions tend to develop and there is a worsening of the preexistent ones. The risk is to induce a "pathergy" phenomenon that usually consists in the formation of severe necrotic or undermined lesions in the areas that have been debrided.

Intravenous treatment with iloprost (a stable prostacyclin analogue) can be useful in nonhealing vasculitic ulcers.[23]

The prognosis of systemic vasculitis has markedly improved since when corticosteroid have been combined with cytotoxic drugs, most commonly cyclophosphamide. In recent years, rituximab has been used with very good results in many systemic vasculitis.[17,24]

Discussion: The Ulcerative Risk in the Various Forms of Vasculitis

A question arises: Do all the CVs present the same risk of causing chronic ulcers?

The possibility that a CV tends to develop skin ulcers is rather high. However, it is likely that it is proportional to the anatomical site, typology, and size of the vessel injured. The patient's basic conditions such as preexistent macrocirculatory disorders, diabetes, or uncontrolled arterial hypertension represent another aspect to be considered, as preexistent vascular disorders may contribute to more severe damages.

The type of vasculitis can also condition the "risk of ulcer" not only in relation to the vessels gauge but also to the evolutionary characteristics (thrombotic complications, fibrosis, etc). We have already underlined that in IgA vasculitis involving very small postcapillary venules, such circumstance is very rare. However, the onset of necrotic-ulcerative lesions is possible in the single organ CLV. In our experience of more than 200 patients affected by such pathology, we have observed vasculitis-related skin ulcers in approximately 15%. The laboratory tests of some of our patients showed also the presence of lupus anticoagulant and other coagulation alterations that could support the suspect of an action favoring the microthrombotic complications. Mekkes et al reported an increased risk of hypercoagulability in patients with vasculitic ulcers, suggesting a strong pathologic relationship between clotting disorders and ulcerative complication in CLV.[14]

The "risk of ulcer" progressively increases if we consider the cryoproteins-related vasculitis and the more severe form of PAN. Both these pathologies are at high incidence of cutaneous ulcers, but differ substantially for their clinic manifestation and course.

In the cryoglobulinemic vasculitis a 2-fold microvessel damage can occur, either inflammatory and occlusive, due to molecular macrocomplexes (cryoproteins) that may occlude the small cutaneous vessels. Moreover, the chronicity of this disorder and the repeated skin damages caused by the purpuric eruptions determine a reduced structural resistance to possible microtraumatic injuries.

In PAN the ulcers are frequent, often as an evolution of the initial nodular lesions. These ulcers can become chronic, are very painful, and are resistant to therapies. The anatomic damage causing the ulcer in PAN is mainly the postinflammatory fibrosis that severely reduces the circulation and causes skin infarction.

Under the clinical and histological aspects, the vasculitis that appears in course of rheumatoid arthritis (rheumatoid vasculitis) is similar to panarteritis. The "risk of ulcer" is high also for this reason.

In the course of SLE and SS vasculitis with ulcerative evolution can also be observed. In SLE a careful and continuous study of the antiphospholipid immunity is always necessary.

In ANCA-positive vasculitis, cutaneous ulcers are not frequent but can develop in unusual areas (eg, nose, upper

limbs in Wegener's granulomatosis and are related to the dimensions of the involved vessel).

Very rare, but possible, are the forehead ulcers in course of temporal arteritis.

The following points should be kept in mind:

- All the vasculitis can potentially cause skin ulcers.
- The patient's basic circulatory disturbances are important and may condition the clinical features and duration.
- The associated presence of hypercoagulable disorders are predisposing factors to skin ulcers in CLV.
- Cryoprotein-related vasculitis and PAN are at higher "risk of ulcer formation."
- Histological confirmation of vasculitis is mandatory.
- Treatment is similar to other types of ulcers. Surgical debridement must be performed with great attention due to the risk of "pathergy phenomenon."

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