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CME ARTICLE

Occlusive cutaneous vasculopathies as cause of chronic ulcers

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Summary

The term occluding vasculopathies covers a large number of different conditions. These often manifest as skin ulcers. Occluding vasculopathies should be considered in the differential diagnosis of leg ulcers. The term "occlusive vasculopathies" encompasses pathophysiologically related entities that share structural or thrombotic obliteration of small cutaneous vessels. In this article, we will focus on livedoid vasculopathy with and without antiphospholipid syndrome and calciphylaxis with differentiation from hypertonic leg ulcer as the most relevant differential diagnoses of leg ulcer. The term also includes vascular occlusion, for example due to oxalate or cholesterol embolism, and septic vasculopathy. This often leads to acral ulceration and is therefore not a differential diagnosis with classic leg ulcers. It will not be discussed in this article.

Occlusive vasculopathy may be suspected in the presence of the typical livedo racemosa or (non-inflammatory) retiform purpura as a sign of reduced cutaneous perfusion in the wound area. Inflammatory dermatoses, especially vasculitides, must be differentiated. This is achieved by histopathological evaluation of a tissue sample of sufficient size and depth taken at the appropriate time. In addition, specific laboratory parameters, particularly coagulation parameters, can support the diagnosis.

KEYWORDS
chronic wounds, vasculopathy, calciphylaxis, livedoid vasculopathy, Martorell's ulcer

INTRODUCTION

About 800,000 people in Germany suffer from chronic wounds, mostly on the lower legs. Due to the multitude of possible underlying causes, leg ulcers must always be investigated in regard of differential diagnoses. Basic vascular diagnostics including clinical examination, palpation of the foot pulses, measurement of the ankle-brachial index (ABI), and duplex sonography can detect the most common causes such as chronic venous insufficiency (CVI) and peripheral artery disease (PAD), which together account for about 80 % of all causes for chronic leg ulcers.[1] However, in primary care even these basic investigations are not sufficiently performed.[2]

Particularly in specialized wound centers, the percentage of rare causes for chronic ulcers may be markedly increased, which requires additional diagnostics supplementing the basic investigations.[3] These "atypical" wounds include ulcers caused by inflammatory diseases, ulcerated neoplasms, infections, hematological disorders, or occlusive vasculopathies.[4] Diagnostic procedures can be structured according to the ABCDE rule for the diagnostics of chronic wounds,[5] so treatment can be initiated according to the underlying cause. Table 1 shows the individual steps of the ABCDE rule.

Occlusive vasculopathies constitute an important group of differential diagnoses when investigating leg ulcers (Table 2). This article will therefore discuss the most common occlusive vasculopathies as possible underlying causes of chronic leg ulcers. It is important to differentiate primarily inflammatory *vasculitis* from occlusive *vasculopathy*.[6,7] The conditions are pathophysiologically

TABLE 1 Parameters of the ABCDE rule for standardized diagnosis of chronic wounds (according to Dissemond J. ABCDE rule of diagnosis of chronic wounds).[5]

Anamnesis (A)	Pre-existing diseases, medication, dynamics of the ulcerations, pain, travel history, family history, allergies
Bacteria (B)	Colonization, infection, wounds with typical infectious causes such as leishmaniasis, atypical mycobacterial disease
Clinical findings (C)	Location, skin disorders in the surrounding tissue (such as livedo, palpable purpura)
vascular status (D)	Foot pulse, ankle brachial index (ABI), duplex sonography
Extras (E)	Histology, coagulation parameters, auto-antibodies, genetic diagnostics

TABLE 2 Suspicious facts for the presence of occluding vasculopathy.

Clinical findings	Livedo racemosa, *atrophie blanche*, necrosis, ulcers with bizarre configuration
Associated diseases	Kidney failure, dialysis patients, arterial hypertension, rheumatological disease (such as SLE), known coagulopathies, thromboembolic events in the personal or family history, hematological disease, neoplasm

related and show clinical as well as histopathological overlaps. Clinical findings in both cases show retiform purpura: livid macules or plaques, non-blanching at the center, with irregular branches. Ulceration with surrounding livid patterns may sometimes appear. Some authors differentiate between inflammatory and non-inflammatory retiform purpura. Inflammatory retiform purpura is characterized by light erythema with emphasis of the margins and can be considered a sign of vessel wall inflammation. This is not the case in non-inflammatory retiform purpura which more strongly indicates coagulopathy. It is, however, important not to omit appropriate diagnostics in the one or the other direction since there are overlaps. Livedo reticularis, characterized by reticulate livid patterns on the skin, is the clinical correlate of limited blood flow and may be considered a precursor of retiform purpura. If blood flow gets even slower and (partial) occlusion of cutaneous vessels occurs, the pattern will be broken and becomes irregular. This is called livedo racemosa.

The primary event in vasculitis is inflammation of the vessel wall, which may be followed by thrombosis due to activation of the endothelium. In occlusive vasculopathy, thrombosis or embolism of the vessel is the primary event. Embolisms may be caused by cholesterol, oxalate, or microorganisms (septic embolism). Possible causes of thrombosis include platelet aggregation as in heparin-induced thrombocytopenia or myeloproliferative syndrome, erythrocyte aggregation as in reticulocyte crisis in sickle cell anemia, or cold-induced increases in viscosity. Inflammation may occur as a secondary event after occlusion. It is therefore plausible that the timing of diagnostic sampling decides its diagnostic value – indicating that biopsies should always be taken from fresh lesions.[8] Secondary thromboses may be found in histological samples of vaculitis, and secondary perivascular inflammatory infiltration may occur in vasculopathies, so the timing of biopsies is crucial for their diagnostic value. This article concentrates on occlusive vasculopathies. Ratzinger et al. have proposed a systematic classification of vasculopathies differentiating between small and medium-sized cutaneous vessels, in accordance with the Chapel-Hill classification of vasculitis.[9] If appropriate, larger vessels in more remote locations may also be included in the classification – especially in cases of peripheral arterial occlusive disease/peripheral artery disease (PAOD/PAD) which causes arterial leg ulcers. Pathophysiologically, these are also included in the group of vasculopathies.

LIVEDOID VASCULOPATHY

Livedo vasculopathy (LV, Orphanet No. 542643) is a rare disease with an estimated prevalence of 1 : 100,000. Women are more frequently affected than men (ratio 3 : 1 to 3 : 2).[10] Its age range is 45 to 80 years, but age distribution differs according to ethnic factors.[11,12]

Clinical findings

Patients suffer from very painful, chronically recurrent ulcers. Quality of life is significantly impaired, especially by the severe pain.[13] At first, petechiae or purpura will appear in the area around the ankles, with subsequent ulceration. The ulcers are clearly delineated and frequently show bizarre configurations (Figure 1). In more than 80% of cases, the surrounding skin shows the livid-erythematous, forked-lightning patterns of livedo racemosa. While the ulcers are always found on the lower legs, livedo racemosa may not only occur in the surrounding areas but also on the arms and torso.[10] The ulcers will usually heal within a period of 3–4 months, with resulting *atrophie blanche*. The lesions have sometimes been described as "summer ulcerations", but they can actually occur year-round.[14,15] Both livedo racemosa and atrophie blanche are typical findings, but they are not pathognomonic for livedoid vasculopathy since they may also occur with other diseases.

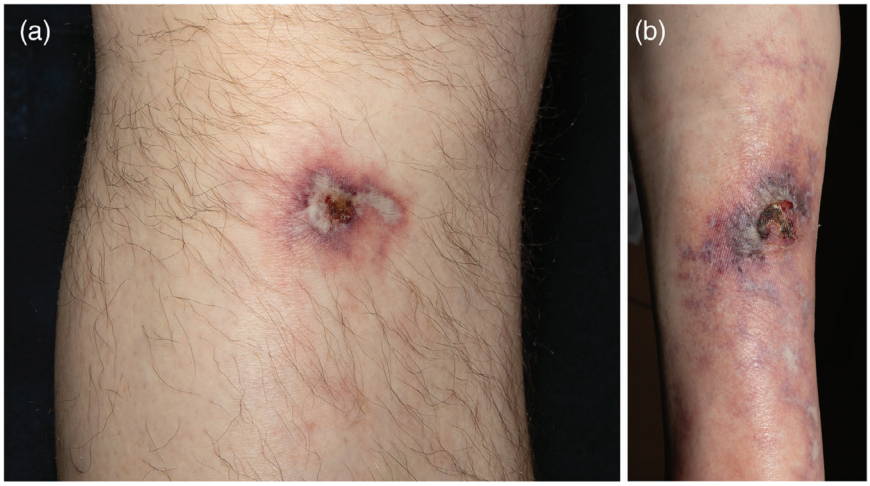

FIGURE 1 (a) Fresh lesion of a livedoid vasculopathy (LV) – the reduced blood flow originating centrally is clearly visible. (b) Livedoid vasculopathy on the dorsal lower leg with livedo racemosa of the surrounding skin. Cranial to the ulceration a whitish atrophic macula in the sense of atrophy blanche is visible.

Livedoid vasculopathy presents with the clinical triad of livedo racemosa, leg ulcers, and atrophie blanche. Quality of life is significantly impaired especially by the severe pain which is presumably caused by "skin infarction".

Pathophysiology

The exact pathogenesis of livedoid vasculopathy is still unknown. Skin infarction is caused by thrombosis in the vessels of the upper and intermediate layers of the dermis, which may explain the severe pain (cutaneous angina). Various coagulopathies such as antithrombin-III deficiency, protein-S deficiency, or protein-C deficiency may be associated with LV. Other pro-coagulatory factors which have been found in LV include hyperhomocysteinemia, increased concentrations of lipoprotein(a), detection of anti-cardiolipin antibodies and lupus coagulant, cryofibrinogenemia, and cold agglutinin disease. It should, however, be noted that coagulopathies can only be found in about 50 %of cases.[10] Livedo racemosa will develop in the area of (partially) thrombotic vessels. In case of complete occlusion, bleeding will result in retiform purpura with subsequent erosion/ulceration.[14]

Diagnostics

Diagnosis is made based on clinical findings and histology. A deep biopsy from the wound margin must be obtained during the acute stage of the disease to evaluate an appropriate vessel section. This can detect the changes typical for livedoid vasculopathy, and at the same time exclude differential diagnoses. Characteristic findings include intraluminal fibrin thrombi, subintimal hyaline deposits, and endothelial proliferation without primary inflammatory infiltrations. Direct immunofluorescence in some cases also shows (non-specific) granular deposits on the vessel walls, especially of C3, fibrinogen, and IgM.[16] The German S1 guideline lists leg ulcers, cutaneous angina, atrophie blanche, and livedo racemosa as the main clinical diagnostic criteria in addition to the histological findings. There is no validated score, however. Secondary criteria include detection of one or more prothrombotic parameters as listed above, female patient, obesity, arterial hypertension, therapeutic response to anticoagulation, and bilateral leg ulcers.[14] The guideline recommends an initial investigation of coagulation parameters including antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, beta2 glycoprotein-I antibodies), protein C, protein S, lipoprotein(a), and homocysteine (fasting). Investigation of the antiphospholipid antibodies has both diagnostic and therapeutic consequences, while investigation of homocysteine levels has therapeutic consequences (see "Treatment" below). A possible deficiency of protein-C or protein-S supports a decision in favor of anticoagulation but is not in itself an indication for initiating this treatment, so investigation may be dispensed with in the initial phase of diagnostics. Cardiovascular risk is increased in cases of elevated lipoprotein(a) concentration, so any risk factors should be more strictly controlled. However, isolated elevation of lipoprotein(a) concentration is not an indication for anticoagulation. Antithrombin-III deficiency, on the other hand, has been described in LV and is a relevant factor since heparin treatment would be less effective in these cases.[17]

If livedoid vasculopathy is suspected, initial coagulation diagnostics should include antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, beta2-glycoprotein-1 antibodies) and homocysteine.

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To differentiate LV from ANCA-associated vasculitis, investigation of ANCA (anti-neutrophilic cytoplasmatic antibodies) can be helpful. Their target structures are myeloperoxidase (MPO-ANCA/perinuclear, p-ANCA) and proteinase-3 (PR3-ANCA/cytoplasmatic, c-ANCA), respectively. ANCA are not only present in vasculitis but also

after infections or in other autoimmune diseases (such as rheumatoid arthritis or autoimmune hepatitis) but in these cases they usually target other perinuclear or cytoplasmatic antigens.[18,19] Additional recommended investigations include a differential blood count as well as antinuclear antibodies and cryoproteins (cryoglobulins, cryofibrinogen). Interpretation of any positive results should, however, consider the patient's individual medical history and may require an interdisciplinary approach. Hyperhomocysteinemia, for example, has also been described in patients with venous leg ulcers.[20] In addition, the diagnostic measures for calciphylaxis (or to exclude calciphylaxis) described below should be performed, depending on the clinical findings.

Treatment

The recommended first-line treatment for livedoid vasculopathy is low-molecular-weight heparin (LMWH) at the therapeutic dose used also for deep venous thrombosis or pulmonary embolism (for example enoxaparin 1 mg/kg body weight [BW] twice a day). In the further course, a switch to half this dose may be feasible once the clinical findings have stabilized.[14,21] The risk of heparin-induced thrombocytopenia (HIT) can be minimized by monitoring platelet counts twice a week during the first four weeks of treatment. The risk of antibody-mediated HIT is highest during this period. It should be noted, however, that the risk of HIT is markedly lower with LMWH than with unfractionated heparin. If the patient has a high risk of recurrence, treatment with LMWH should be continued. Alternatively, it is possible to switch to direct factor Xa antagonists such as rivaroxaban 20 mg once a day, or initiate treatment with this drug immediately. If the clinical findings improve and stabilize, the dose of rivaroxaban may be lowered to 10 mg/day, or discontinuation of treatment may be attempted (Figure 2).[14,22] These are off-label treatments.

Livedoid vasculopathy is treated with low-molecular-weight heparin or rivaroxaban as first-line treatments.

After anticoagulation is initiated, pain relief will typically be observed within 2–4 days. A pain diary can therefore also offer diagnostic suggestions. If antiphospholipid antibodies have been detected, the patients must not be treated with direct oral anticoagulants (DOAC) such as rivaroxaban, since increased rates of thrombosis have been described.[23] In these cases, vitamin K antagonists can be used as an alternative. Since the synthesis of the anticoagulatory factors protein S and protein C is vitamin K-dependent and these proteins have a shorter biological half-life than the vitamin K-dependent coagulation factors, there will be an increased tendency in favor of coagulation during the first few days after initiating treatment with vitamin K antagonists. The anticoagulatory effect will only start after 36–72 hours. Initiation of warfarin/marcumar must therefore be performed under effective parenteral anticoagulation. In patients with hyperhomocysteinemia, this risk factor can be treated as well. There is some evidence that supplementation of folic acid, vitamin B6, and vitamin B12 will lead to a decreased concentration of homocysteine and result in improved wound healing.[24–26] In treatment-refractory cases, intravenous immunoglobulins (IVIG) constitute an effective and safe, albeit expensive, treatment option. Reports have shown that previously treatment-refractory patients with or without known coagulation disorders have profited from IVIG at a dose of 2 g/kg BW, distributed over a period of five days. This treatment cycle is repeated every 25 to 28 days. Response will be observed within the first six months.[27–30] It has not yet been determined if (and when) treatment can be discontinued after the ulcers have healed.

Intravenous immunoglobulins elicit good responses in the treatment of livedoid vasculopathy.

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If a patient does not respond to IVIG, prostaglandin infusions are an option (for example 1–2 ng iloprost/kg BW/min i.v. over a period of 6 hours per day at 1–4-weekly intervals. The published case reports cover patients with and without coagulation disorders (lupus anticoagulant, heterozygous factor-V mutation).[31–33] At this point in time, controlled studies on either IVIG or prostaglandins are not available.

In contrast to previously disappointing results with anti-inflammatory medications (glucocorticoids or nonsteroidal anti-inflammatory drugs),[21] there have recently been encouraging reports on successful application of anti-TNF-α-treatments such as etanercept[34,35] and adalimumab[36]. Interestingly, Janus kinase (JAK) inhibitors such as tofacitinib and baricitinib have also been used successfully in individual, previously treatment-refractory patients.[37,38] This refashions our previous understanding of this disease as a form of coaguloathy and emphasizes the potential (secondary) inflammatory component. It should, however, be noted that not all patients had received anticoagulants beforehand, and any successful differentiation from cutaneous polyarteriitis nodosa or the recently described lymphocytic thrombophilic arteritis needs to be carefully scrutinized. In some cases, histological confirmation of the diagnosis was not reported. Data on the presence of coagulopathies are mostly lacking. The use of JAK inhibitors in livedoid vasculopathy is particularly interesting since the US Food and Drug Administration (FDA) has issued a warning regarding an increased risk of thrombosis with JAK inhibitors. There is currently no high-level evidence in favor of primary immunomodulatory or immunosuppressive treatment.

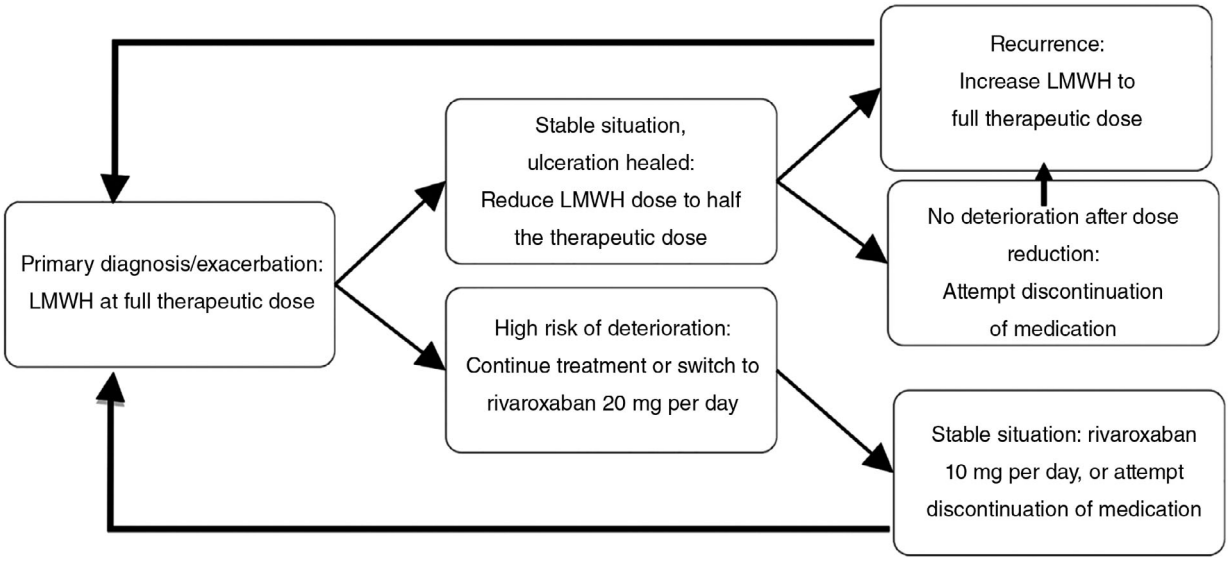

FIGURE 2 Treatment algorithm of livedoid vasculopathy according to the German S1 guideline Diagnostics and Therapy of livedoid vasculopathy.[14] All mentioned therapies are off-label for livedoid vasculopathy.

Important differential diagnoses for livedoid vasculopathy

The most important differential diagnosis for livedoid vasculopathy is a venous leg ulcer which is much more common than LV. This, as well as arterial leg ulcers, should be excluded via vascular diagnostics (palpation of the foot pulses, Doppler ultrasound, measurement of the ABI, and angiography if appropriate, Table 1). Neither venous nor arterial leg ulcers are however associated with livedo racemosa. Inflammatory diseases such as cutaneous polyarteritis nodosa (cPAN), lymphocytic thrombophilic arteritis, cutaneous vasculitis of small vessels, or secondary vasculitis in the context of Sjögren's Syndrome should also be considered as potential differential diagnoses. Lymphocytic thrombophilic arteritis has been described only recently and is related to cPAN. Histopathological and clinical criteria to differentiate the new entity from cPAN have recently been published after some discussion on whether it is a separate entity at all.[39] Other conditions that need to be considered include marcumar/warfarin-induced ulcers, antiphospholipid syndrome, Sneddon's Syndrome, and cryoglobulinemia type I.[14,40] Diagnoses with livedo racemosa as a leading symptom will be discussed in more detail below.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is characterized by thrombophilia caused by antibodies against phospholipid-protein complexes.[41] These include lupus anticoagulant, anti-β2 glycoprotein-I, and anti-cardiolipin antibodies. APS may occur as a primary disease or as a secondary event in underlying rheumatological disorders such as lupus erythematosus or rheumatoid arthritis, but also in cancer patients.

Clinical findings

Symptoms in APS can vary greatly. Apart from thromboembolic events, complications during pregnancy are the most important feature. Thromboses may occur in veins, arteries, or small vessels, and in all organs including the skin. Ulcerations (Figure 3a) may manifest at any location beyond the lower legs,[42] however they will occur in less than 10 % of APS cases.[41]

Pathophysiology

Disease mechanisms in APS are complex and not yet fully understood. Antiphospholipid antibodies bind to beta-2 glycoproteins in the plasma and on the cell surfaces and thus lead to activation of endothelial cells and monocytes which in turn express more adhesion molecules and tissue factor on their surface. Thrombocytes are activated as well, and increased numbers of prothrombotic molecules are formed. Together with activation of the complement cascade, this results in a sustained pro-coagulatory status as well as inflammation. At the same time, fibrinolysis is inhibited via interaction of the antiphospholipid antibodies with factors responsible for regulating coagulation, such as prothrombin, protein C, or plasmin. In spite of the existing thrombophilia, platelet counts are frequently decreased. This may be connected to thrombocyte activation and destruction and is associated with

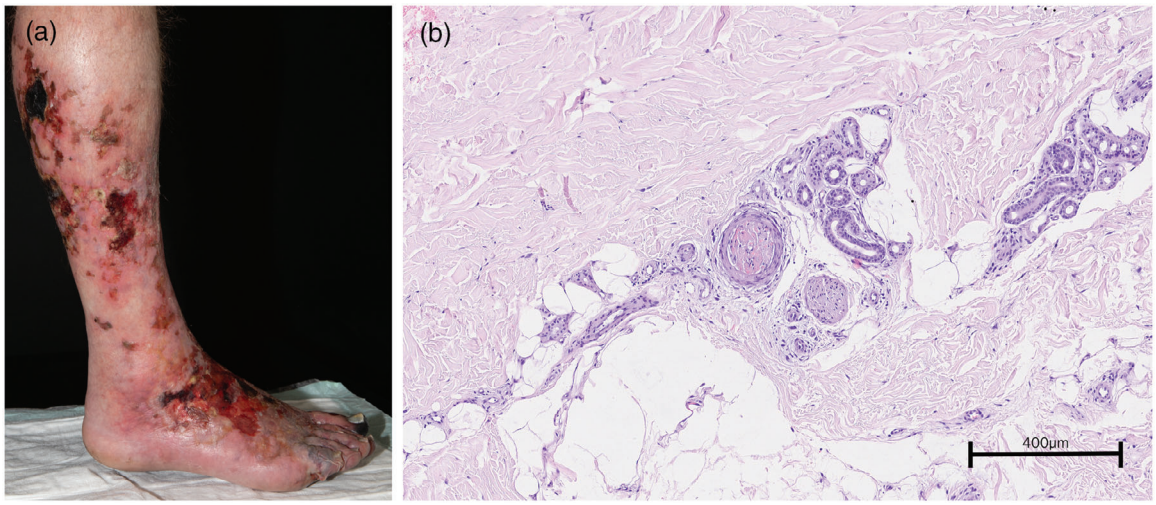

FIGURE 3 (a) Pronounced ulceration and necrosis in antiphospholipid syndrome (APS). (b) Skin biopsy from the knee of a patient with antiphospholipid syndrome. Thrombus in a small vessel in the mid dermis without accompanying inflammatory infiltrate (courtesy of Stefan Schliep, MD).

an increased risk of thrombosis.[43] Lifestyle factors such as smoking or hormonal contraceptives, or other cardiovascular risk factors may have a negative influence on disease processes.[41]

Diagnostics

Diagnosis is made according to the revised Sapporo criteria, with at least one clinical and one laboratory criterion positive. The clinical criteria include thromboses (in veins or arteries or small vessels, in any organ) (Figure 3b) or pregnancy disorders (miscarriage in the 10th week of pregnancy or thereafter, premature birth before the 34th week due to eclampsia or placental insufficiency, three or more miscarriages before the 10th week of pregnancy without any maternal anatomical or hormonal disorders or parental chromosomal aberrations). Laboratory criteria include detection of lupus anticoagulant, anticardiolipin antibodies (IgM/IgG), and anti-Beta-2 glycoprotein-I antibodies (IgM/IgG) twice at least 12 weeks apart.[44]

Treatment

Prevention of thromboembolic events is the most important pillar of treatment. Risk assessment with consideration of additional risk factors and previous thromboses will determine the extent of anticoagulatory medication. Low-molecular weight heparins or vitamin K antagonists may be used. Direct oral anticoagulants, however, should be avoided as stated above, especially in triple-positive patients (detection of all three serological parameters).[23,45] Aspirin is used for secondary prevention after arterial thrombosis.

Direct oral anticoagulants should not be used for treating high-risk patients with antiphospholipid syndrome.

Patient management before and during pregnancy requires specific therapeutic approaches. In cases of secondary APS, adequate treatment of the underlying disease is also essential.[41]

Sneddon's Syndrome

If (additional) lesions apart from the lower legs occur, or neurological symptoms are present, differential diagnosis must include Sneddon's Syndrome. Sneddon's syndrome is a systemic thrombotic vasculopathy presenting with a triad of livedo racemosa, cerebral insults, and arterial hypertension. Necrotic ulcers may sometimes occur within the livedo racemosa lesions due to occlusion of the cutaneous vessels, but this is relatively rare.[46] Treatment mainly concentrates on anticoagulation such as platelet aggregation inhibitors, prostaglandins, and DOAC. Sneddon's Syndrome should only be diagnosed in the absence of antiphospholipid syndrome.

CALCIPHYLAXIS

Calciphylaxis (CP, Orphanet Nr. 280062) is also a rare disease found mainly in patients with terminal kidney failure. In this context, it is also termed calcific uremic arteriolopathy (CUA). Precise rates of incidence or prevalence are not available. Brandenburg et al. have proposed an incidence rate of 0.04 % CUA in dialysis patients.[47] The rate is probably somewhat higher, however.[48] In this vulnerable, frequently multimorbid patient population, CUA is a dreaded complication with high mortality due to septic disease progression

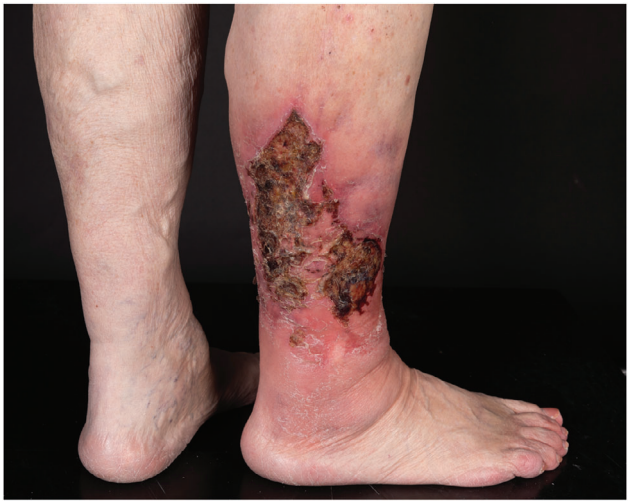

FIGURE 4 Bizarre-shaped ulceration on the laterodorsal lower leg with surrounding livedo racemosa in a patient with calciphylaxis.

and potential cardiovascular calcification. There have, however, also been reports of non-uremic calciphylaxis, sometimes associated with primary hyperparathyreoidism.[49,50] In the absence of any changes in the calcium-phosphate product, as occurs in kidney failure (or in primary hyperparathyreoidism), it is however difficult to differentiate these cases from hypertensive leg ulcers (see below). Hafner et al. have recently proposed that calciphylaxis and hypertensive leg ulcers should be summarized under the term of "ischemic subcutaneous arteriolopathy". In a pragmatic approach, they divided ulcerations in patients without terminal kidney failure into two groups with proximal or distal patterns. Proximal manifestation of non-uremic calciphylaxis is called proximal non-uremic calciphylaxis (or eutrophication in cases of morbid obesity), the distal manifestation is called hypertensive leg ulcer.[51] Using this approach, ulceration on the lower leg can only be diagnosed as calciphylaxis if the calcium-phosphate balance is impaired.

Clinical findings

Initial livedo reticularis is followed by retiform purpura and later manifest ulceration. The typical clinical findings with necrotic ulcerations in a forked-lightning pattern, mainly on the dorsal side of the lower legs and surrounded by livedo racemosa (Figure 4) indicate a potential case of calciphylaxis. Histology can confirm the diagnosis based on the triad of calcification of the tunica media in the cutaneous arterioles, hyperplasia of the tunica intima, and microthrombi.

Typical histological findings in calciphylaxis show a triad of calcification of the tunica media in the cutaneous arterioles, hyperplasia of the tunica intima, and microthrombi.

Unusual locations such as the abdomen or torso may make the diagnosis more difficult, as well as early subcutaneous induration (due to calcification in the fat and connective tissue) and hemorrhagic bleeding without necrosis.[52] Rare extracutaneous manifestations (for example affecting the muscles or eyes) have also been reported.[53,54] Table 3 offers a summary of the risk factors for calciphylaxis.

Pathophysiology

The exact pathophysiology of calciphylaxis is still unknown. Apart from deposits of calcium apatite in the tunica media of cutaneous vessels, associated with fibrosis of the tunica intima and subsequent stenosis, coagulation disorders and thrombotic stenosis are also thought to play a role in the pathophysiology.[55,56] A prothrombotic coagulation status appears to be associated with calciphylaxis.[57] Chronic inflammation is also considered a potential trigger of extraossary calcification.[55] Inhibitors of calcification in vessels and soft tissue, such as carboxylated matrix-Gla protein (MGP) and fetuin A[58], also play a role. For example: In patients with calciphylaxis, the ratio of carboxylated MPG to total MPG is decreased. Any decrease of the relative concentration of carboxylated MPG by 0.1 units more than doubles the risk of calciphylaxis.[59] Carboxylation is dependent on vitamin K.[60]

Diagnostics

If calciphylaxis is suspected, it is essential to analyze parathyreoid hormone and 25-hydroxy-cholecalciferol (Vitamin D) as well as creatinine, albumin, calcium, and phosphate (including calculation of the calcium-phosphate product) in serum. To exclude potential differential diagnoses, additional analyses of coagulation factors and auto-antibodies should be performed, depending on the suspected differential diagnosis. There have, however, been reports of an association between calciphylaxis and coagulation disorders; so this should be investigated.[61] More specific laboratory parameters include fetuin A, sclerostin, osteoprotegerin, TRAP5b, bone-specific alkaline phosphatase, serum cystatin C, globular arrest protein I, or fibroblast growth factor 23. These, however, mainly possess an experimental value and are not important for routine diagnostics.[61] Histological examination completes the diagnostic workup. This requires a deep, spindle-shaped skin biopsy. Ideally, the biopsy should include the transition zone from the ulceration to the intact skin, or it should be taken from the wider surroundings of the ulcer in the area of the livedo pattern, so an affected vessel section can be obtained. Calcification of the tunica media can be detected via von-Kossa staining.[62]

TABLE 3 Risk factors for the occurrence of calciphylaxis (after Gallo Marin et al. Calciphylaxis and Kidney Disease: A Review).[56]

Disorders of the calcium-phosphate metabolism (for example in the context of kidney disease, bone disease, tumors, or due to medication)
(Secondary) hyperparathyreoidism
Increase of alkaline phosphatase, calcium-phosphate product > 70 mg^2/dl^2, hypalbuminemia
Female patient
Obesity
Liver disease
Medication with vitamin-K antagonists
Coagulopathies

Treatment

Because this disease is so rare, there are no guidelines for treatment, especially for non-uremic cases. Physicians usually try to transfer the insights from CUA treatment to their non-uremic patients, as far as this may be possible in view of the frequently lacking alterations in calcium-phosphate metabolism. Underlying disease should be treated if at all possible; this usually means co-operation with a nephrology unit.

Local treatment should follow the standards of modern wound management, with special focus on debridement as well as prevention and treatment of infection since the risk of sepsis is high. The extent of debridement in calciphylaxis is currently being discussed. Surgical debridement is considered the most effective measure,[63,64] but due to severe pain and increased risk of anesthesia in multimorbid patients this should be considered very carefully. Some authors fear that excessive manipulation of the ulcerated lesions may cause a sort of pathergy phenomenon, so they even question the performance of biopsies.[65] There is one monocentric, retrospective study in 64 patients which offers a clear argument in favor of debridement: Patients with radical surgical debridement showed a significantly higher rate of survival after one year than patients without this intervention.[66] Any individual treatment decision needs to consider the patient's comorbidities. Successful alternative debridement methods, such as biosurgery with maggots, have been reported.[67]

Local wound management in calciphylaxis focuses on debridement and prevention of infection.

Local wound management in calciphylaxis focuses on debridement and prevention of infection.

In addition to optimized wound management, a diagnosis of calciphylaxis usually requires an interdisciplinary treatment decision regarding systemic medication. Especially in patients with non-uremic calciphylaxis, however, there is a lack of data on valid therapeutic approaches.[49] Since assoiations with certain medications have been reported, particularly vitamin K antagonists,[68] medication should be switched from vitamin K antagonists to heparin or DOAC.[69] Substitution of vitamin K is currently under discussion.

Medication should be switched from vitamin antagonists to heparin or DOAC in patients with calciphylaxis.

A plasminogen activator as adjuvant treatment for calciphylaxis has been reported in a case series of 15 patients.[70] Especially if an underlying coagulation disorder has been found, initiation of anticoagulation should be considered. In some individual cases, intake of calcium and vitamin D should be reduced. All of these treatment decisions must be taken in close collaboration with the nephrologists. It is possible to influence the calcium-phosphate metabolism either by increasing the frequency of dialysis, or via medication such as calcium-free phosphate binding compounds or cinacalcet, a calcimimetic[71] for the treatment of hyperparathyreoidism. If appropriate, the latter condition may also be treated surgically by removing the parathyreoid glands.[72] Bisphosphonates may also potentially inhibit calcification of the smooth muscle cells in the vessels by increasing the concentration of osteoprotegerin. Anti-inflammatory effects are also under discussion.[73] The effective use of bisphosphonates has been reported in case series of patients with uremic as well as with non-uremic calciphylaxis.[74–76] However, long-term use of bisphosphonates in dialysis patients is usually avoided because of their strong influence on bone metabolism, so any treatment with bisphosphonates should be discussed in an interdisciplinary setting. Another interesting compound for the treatment of calciphylaxis is sodium thiosulfate. This was originally developed for the treatment of acute cyanide poisoning, but there are several published case series on its successful use in calciphylaxis patients.[76,77]

Any treatment decision on medical intervention in the calcium metabolism in patients with calciphylaxis should be made in an interdisciplinary setting.

HYPERTENSIVE LEG ULCER (MARTORELL'S ULCER)

Arterial hypertension will lead to vessel damage in all organs (macroangiopathy and microangiopathy).[78] Hypertonic leg ulcers can be interpreted as end organ damage of the skin, caused by long-term hypertension. Affected

patients have usually had hypertension for many years. Other comorbidities include diabetes mellitus, obesity, and macroangiopathies such as coronary heart disease. Calciphylaxis as well as pyoderma gangrenosum constitute the most important differential diagnoses. A publication by Kolios et al. states that 50 % of patients with suspected pyoderma gangrenosum actually had hypertensive leg ulcers.[79] An incorrect diagnosis of pyoderma gangrenosum may result in immunosuppressive treatment which could prove fatal. However, these numbers are subject to some diagnostic uncertainty since diagnosis was mainly based on exclusion of differential diagnoses and treatment response. Nowadays, there are useful diagnostic scores particularly for pyoderma gangrenosum, so this disease is easier to differentiate.[80,81]

Clinical findings

Ulcerations develop mainly on the laterodorsal or anterolateral aspects of the calves, or in the area of Achilles' tendon, typically with a livid to black (necrotic) wound margin with bizarre configuration, and in a number of cases also with livedo reticularis/racemosa. Bilateral ulcerations occur in about 50 % of cases.[82,83] The ulcerations are very painful.[51] Their clinical appearance is extremely similar to the skin lesions seen in calciphylaxis. A hemorrhagic bulla precedes the ulcer in some cases.[84]

Pathophysiology

Arterial hypertension over years and decades will lead to calcification and intimal hyperplasia in the subcutaneous arterioles.[51] This increases vascular resistance, and decreased flow velocity leads to impairment of nutrient delivery to the tissue. At the same time, the vascular compensation mechanisms are also impaired[84], and capillary density is reduced. A comparison with other patient populations shows high vascular comorbidity, including an increased risk of pulmonaly hypertension.[79,85] This is a logical consequence of pathophysiology, since arterial hypertension affects all organs.

Diagnostics

A diagnosis of arterial leg ulcers is made as a synthesis of the medical history (long-term arterial hypertension), the clinical findings (location, necrosis, severe pain), and histopathology. Peripheral artery disease (PAD), as well as chronic venous insufficiency should be excluded; however, PAD can be present at the same time. A pathological ankle-brachial index (ABI) can neither support nor exclude a diagnosis of hypertensive leg ulcers. Due to the general vessel damage, the ABI of these patients is more frequently pathological than in healthy persons.[86] A deep biopsy reaching the fascia will show calcifications in subcutaneous arterioles, with particular affection of the tunica media and altered wall-to-lumen ratio. The most specific finding, however, is subendothelial hyalinosis. Lack of indications for other causes of ulceration can also be considered as histological diagnostic criteria. Pyoderma gangrenosum, for example, can be histologically differentiated due to lack of subcutaneous calcification, lack of calcification in the tunica media of the vessels, and the presence of neutrophilic infiltration.[87] Histological criteria that are identical with those for calciphylaxis pose the difficulty of differentiation between non-uremic calciphylaxis and hypertensive leg ulcers.[63] The only criterion for differentiation appears to be long-term arterial hypertension – however, this need not automatically to be absent in calciphylaxis. As stated above, hypertensive leg ulcer should therefore only be diagnosed if ulcerations on the lower legs are not associated with disorders of the calcium-phosphate metabolism.

Treatment

Apart from the best possible treatment of cardiovascular risk factors such as arterial hypertension, diabetes mellitus, and nicotin abuse as well as supportive measures, treatment of wounds >4 cm^2 mainly consists of radical debridement with excision of the affected tissue and subsequent split skin grafting, with additional topical negative pressure treatment if appropriate.[88] Hafner et al. proposed subsequent conservative treatment if more than two-thirds of the split skin grafts prove viable and pain is reduced at the same time; and if these conditions are not met, repeated split skin grafting.[51] Full-thickness skin grafting with several "punch grafts" is an alternative. In this case, small full-thickness skin grafts are obtained by punching, and then distributed over the wound area.[89] A small case series in nine patients with previous failure of skin grafting showed that treatment with iloprost (0.5–2 ng/kg BW/min during six hours per day over a period of 5 to 28 days) in combination with skin grafting was successful in seven out of nine patients.[90] A conservative treatment approach may be feasible for smaller wounds. Other treatments with sparse evidence are being discussed in the literature. These include anticoagulation with heparin or vitamin K antagonists, use of beta-sympathomimetics or chlorpromazine (a neuroleptic with inhibitory effects on α-adrenoreceptors), or lumbar sympathectomy to prevent vasospasms.[83,84]

OTHER DIFFERENTIAL DIAGNOSES

A multitude of diseases may lead to cutaneous vasculopathy. While the conditions described above are the most common differential diagnoses for chronic wounds, there are also other diseases with a more acute course which cause cutaneous ischemia, necroses, and subsequently also ulceration.[91] These include coagulation disorders in

rheumatological disease such as lupus erythematosus or rheumatoid arthritis, cryoglobulinemia, as well as paraneoplastic coagulation disorders. Acute embolic events such as fat embolism or oxalate embolism as well as emboli in the context of bacterial infection or foreign body emboli mostly present as vessel obstruction in the acral regions and do not always cause ulceration. Acute thrombotic vessel obstruction – called embolia cutis medicamentosa – has been described in various case reports as a complication after application of a number of drugs, particularly after intramuscular injection. Vasculopathies due to platelet aggregation have been reported both under heparin treatment (caused by heparin-induced thrombocytopenia), and as a complication after initiation of marcumar/warfarin treatment.[91]

BASIC WOUND MANAGEMENT AND SUPPORTIVE MEASURES

Once ulcerated lesions appear, at the very latest, the interdisciplinary team is encouraged to add a specialist for wound management. Any general treatment decisions should, if possible, be taken in specialized centers. Topical treatment must be supplemented by adequate pain relief since these patients often suffer severe pain. The choice of appropriate pain medication and dosage needs to respect any comorbidities. There are a number of measures that can be applied independent of the underlying disease; these will be described in detail below. In general, there are no special recommendations for topical wound management in vasculopathies even though individual case reports have been published for some treatment methods such as split skin grafting, negative pressure treatment, or hyperbaric oxygen therapy.[92,93]

The M.O.I.S.T. scheme offers a guide for topical treatment in chronic wounds.[94] The acronym covers several basic principles that can be utilized in topical wound management. Table 4 shows an overview of these principles.

Prevention of infection and early treatment of (local) wound infection are essential especially in conditions like calciphylaxis with its high mortality. The risk of infection needs to be assessed at regular intervals, for example with appropriate tools such as the TILI-Score 2.0[95] or the W.A.R.-Score[95]. According to the assessment, antiseptic rinsing solutions or antimicrobial wound dressings may be applied. If any relevant wound infection is detected, systemic antibiotics can be utilized in a targeted manner and according to the antibiogram. Until the resistogram is available, it is important that the initial calculated antibiotic treatment should be effective especially against *staphylococcus aureus*. The treatment should also cover gram-negative infectious agents if this is suspected. The guideline for skin and soft tissue infection offers more information.[97,98] Topical application of antibiotics to the wound is obsolete because of potential allergological sensitization, so other antimicrobial wound treatments are to be preferred (such as external therapeutics with silver dressings, or antiseptics). Re-evaluation is required at regular, fixed intervals (for example every two weeks).

TABLE 4 M.O.I.S.T. scheme for systematic local wound care (after Dissemond et al. M.O.I.S.T. – a concept for the topical treatment of chronic wounds).[94]

M – Moisture Balance	Management of exudation by choosing appropriate dressing materials, and searching for the cause of increased exudation, such as infection, edema, etcetera
O – Oxygenation	Improvement of local oxygen supply, for example via anticoagulation, use of specific procedures such as hyperbaric oxygen therapy (if available)
I – Infection control	Prevention or stage-appropriate treatment of localized/systemic wound infection
S – Support (of the healing process)	Wound bed optimization via application of interactive dressings that offer active wound healing support, or instrumental procedures such as negative pressure treatment
T – Tissue management	Various debridement methods

In the presence of topical infection, wound management requires antiseptic measures. Systemic antibiotics should be administered in a targeted manner depending on any systemic signs of infection and the patient's individual risk profile.

Debridement measures can reduce the bacterial burden even further. Appropriate methods for wound cleaning need to be chosen depending on the individual disease activity, the underlying disease, and the patient's general condition.[99] Atraumatic wound management with non-adhesive wound dressings is recommended, not least because of pain reduction. Mechanic wound cleaning can be supported by appropriate rinsing solutions. Supportive measures such as adequate pain relief, appropriate professional care at home, and availability of necessary medical aids must also be ensured to provide optimum wound management.

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[[CME QUESTIONS / LERNERFOLGSKONTROLLE]]

1. Hinter dem Akronym der ABCDE-Regel zur Diagnostik chronischer Wunden verbergen sich verschiedene Maßnahmen. Welche Zuordnung ist richtig?
   a. A steht für Durchführung einer Angiografie
   b. B steht für bildgebende Maßnahmen
   c. C steht für Farbe des Wundrandes (color)
   d. D steht für Prüfen der Durchblutungssituation
   e. E steht für Erheben eines neurologischen Status

2. Was gehört zu den typischen klinischen Verdachtsmomenten für eine Vaskulopathie?
   a. Vorliegen einer Leberinsuffizienz
   b. Eine Livedo racemosa in der Wundumgebung
   c. Auftreten von Beinödemen
   d. Entzündlich geröteter Wundrand
   e. Erhöhter HbA1c-Wert

3. Was gehört zu den typischen klinischen Symptomen einer Livedovaskulopathie?
   a. Atrophie blanche
   b. Ulzera an den Händen und Armen
   c. Wenig bis keine Schmerzen
   d. Livedo reticularis
   e. Abheilung innerhalb weniger Tage

4. Welche Aussage zur Livedovaskulopathie ist richtig?
   a. Histologisch findet man eine Kalzifizierung der Intima kutaner Arteriolen.
   b. Zu den diagnostischen Nebenkriterien gehören männliches Geschlecht und Untergewicht.
   c. Zur initialen Labor-Diagnostik gehört die Bestimmung von Antiphospholipid-Antikörpern.
   d. Der Nachweis einer Hyperhomocysteinämie ist pathognomonisch.
   e. Die Ulzera treten immer streng einseitig auf.

5. Welche Aussage zur Therapie der Livedovaskulopathie ist richtig?
   a. Direkte orale Antikoagulanzien sind wirkungslos.
   b. Niedermolekulares Heparin wird als Erstlinientherapie eingesetzt.
   c. Topische Steroide zeigen ein gutes Ansprechen.
   d. Intravenöse Immunglobuline sind wirkungslos.
   e. Rituximab ist zur Behandlung der Livedovaskulopathie empfohlen.

6. Welche Aussage ist richtig?
   a. Bei der Livedovaskulopathie treten typischerweise auch Schwangerschaftskomplikationen auf.
   b. Beim Sneddon-Syndrom treten zusätzlich neurologische Symptome auf.
   c. Die Diagnose des Antiphospholipid-Syndroms wird anhand der Chapel-Hill-Kriterien gestellt.
   d. Direkte orale Antikoagulantien sollten insbesondere beim Tripel-positiven APS therapeutisch eingesetzt werden.
   e. In Assoziation zu COVID-19 Erkrankungen sind hauptsächlich Vaskulopathien und keine Vaskulitiden beschrieben.

7. Welche Aussage ist richtig?
   a. Patienten mit Calciphylaxie zeigen eine niedrige Mortalität.
   b. Calciphylaxie tritt nur bei Patienten mit dialysepflichtiger Niereninsuffizienz auf.
   c. Ulzerationen bei Calciphylaxie lassen sich klinisch eindeutig vom Ulcus cruris hypertonicum abgrenzen
   d. Histologisch finden sich bei der Calciphylaxie eine Kalzifikation der Media, eine Intimahyperplasie und Mikrothromben.
   e. Die Calciphylaxie tritt nur an den Unterschenkeln auf.

8. Was zählt zu den Risikofaktoren für eine Calciphylaxie?
   a. Hyperalbuminämie
   b. Männliches Geschlecht
   c. Untergewicht
   d. Gabe von niedermolekularem Heparin
   e. Lebererkrankungen

9. Welche Untersuchung gehört zur diagnostischen Abklärung einer Calciphylaxie?
   a. Bestimmung des Parathormons
   b. Bestimmung des Vitamin-C-Spiegels im Serum
   c. Eine 3 mm Stanzbiopsie vom Wundgrund
   d. Eine Angiografie der großen Beinarterien
   e. PAS-Färbung des Biopsiematerials

10. Welche Aussage ist richtig?
    a. Zur Therapie der urämischen Calciphylaxie kann das Calcimimetikum Cinacalcet eingesetzt werden.
    b. Bei Vorliegen eines Hyperparathyreoidismus ist

eine Parathyreoidektomie immer erforderlich.

c. Bisphosphonate sind bei urämischer Calciphylaxie streng kontraindiziert.
d. Bei urämischer Calciphylaxie sollten Vitamin-K-Antagonisten therapeutisch eingesetzt werden.
e. Die Dialysefrequenz hat keinen Einfluss auf die Calciphylaxie.

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 30.Juni 2024.

Die richtige Lösung zum Thema "Pockenvirusinfektionen in der Dermatologie" in Heft 1/2024:
1d, 2d, 3c, 4a, 5d, 6b, 7b, 8c, 9d, 10e

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