Differential diagnosis of leg ulcers

Differentialdiagnosen des Ulcus cruris

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Keywords
- Chronic wound
- leg ulcer
- venous leg ulcer
- arterial leg ulcer
- Vasculitis

Summary
In Germany about 0.7 % of the adult population have a chronic leg ulcer. Although chronic venous insufficiency accounts for at least 80 % of all chronic leg ulcers, knowledge of the relevant differential diagnostic considerations is of crucial importance, in particular for patients who are refractory to therapy. In addition to vascular disease, other causes include neuropathic, metabolic, hematologic and exogenous factors as well as neoplasias, infections, drugs, genetic defects and some primary skin disorders. For the long-term successful treatment of patients with chronic leg ulcers, it is necessary to identify all relevant factors, in order to enable a pathogenesis-oriented, interdisciplinary therapeutic approach.

Schlüsselwörter
- Chronische Wunde
- Ulcus cruris
- Ulcus cruris venosum
- Ulcus cruris arteriosum
- Vasculitis

Zusammenfassung
Es wird geschätzt, dass in Deutschland etwa 0,7 % der erwachsenen Bevölkerung an einem Ulcus cruris unterschiedlichster Genese leidet. Auch wenn die chronische venöse Insuffizienz bei mindestens 80 % aller Patienten mit einem Ulcus cruris pathophysiologisch relevant ist, so ist doch die Kenntnis der relevanten Differentialdiagnosen insbesondere bei therapierefraktären Verläufen von entscheidender Bedeutung. Es existieren neben pathologischen vasculären Befunden auch neuropathische, metabolische, hämatologische und exogene Faktoren sowie Neoplasien, Infektionen, Medikamente, genetische Defekte und primäre Dermatosen, die ein Ulcus cruris verursachen können.
Für eine dauerhaft erfolgreiche Behandlung der Patienten mit einem Ulcus cruris ist es von entscheidender Bedeutung alle relevanten Faktoren der Genese eines Ulcus cruris zu diagnostizieren, um eine kausal ansetzende, interdisziplinäre Therapie zu ermöglichen.

Introduction

An estimated 0.7 % of the adult population in Germany suffers from leg ulcers (ulcus cruris) of various origins [1, 2]. Although patient history and clinical findings are often sufficient for a presumptive diagnosis of the cause of the ulcer, additional serologic tests and device-based diagnostic parameters are essential to objectifying the assessment [3]. Epidemiological data from cross-sectional general population studies are still lacking, but it is presumed that at least 70 % of all patients have a venous leg ulcer, 10 % have an arterial leg ulcer, 10 % have a leg ulcer of mixed arterio-venous origin, and about 10 % a leg ulcer with another pathogenesis (Figure 1) [2, 4]. In recent years, research in various areas of medicine has expanded our understanding of the diseases that cause leg ulcers and obstruct healing (Table 1). Knowledge of differential diagnoses and initiation of suitable interdisciplinary therapy are thus absolutely essential for ensuring lasting treatment success in patients with leg ulcers.

Diagnosis

During the initial examination of the patient, serologic testing of blood count and C-reactive protein (CRP) levels should be performed. Tests to determine HBA_1c, erythrocyte sedimentation rate (ESR), total protein, blood differential, coagulation parameters, and electrolytes

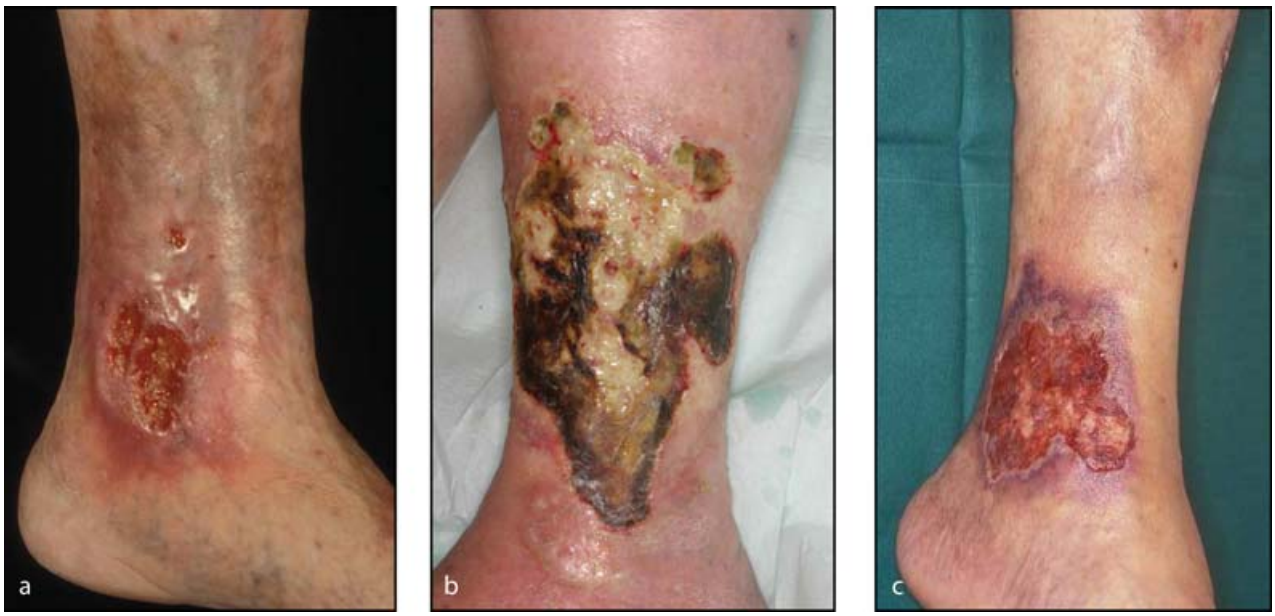

Figure 1: a) Venous leg ulcer. (b) Arterial leg ulcer. (c) Leg ulcer associated with allergic vasculitis.

are also advisable. A biopsy is recommended if there is clinical suspicion of neoplasia or vasculitis. Based on these findings, device-based diagnostic testing should be performed for further clarification. Bidirectional Doppler examination and an assessment of ankle-tibial index (ABI) belong to basic diagnostic procedures and should be performed on any patient with a leg ulcer. Findings of vascular abnormalities warrant color duplex sonography and light reflection rheography. Severe arterial disease states can be clarified with angiography, e.g., digital subtraction angiography (DSA) or, alternatively, nuclear magnetic resonance imaging (MR-angiography) [3]. There is still no consensus on the necessity of taking a bacteriological smear during the initial examination. A smear is essential if there are clinical signs of infection or if there is uncertainty concerning whether the patient has methicillin resistant Staphylococcus aureus (MRSA) (Table 2).

Venous leg ulcer (Ulcus cruris venosum)

The term chronic venous insufficiency (CVI) was coined in 1957 by Henrik van der Molen as the summation of clinical changes to the skin and subcutaneous tissue occurring in a chronic venous disease [5]. CVI usually arises from post-thrombotic syndrome (PTS), varicosis, or arteriovenous malformation. Varicose veins are caused by degenerative changes to the vessel wall and loss of elasticity. If changes lead to valve insufficiency, CVI can result. Predisposing factors include increasing age, genetic factors, pregnancy, and professions requiring prolonged standing. Although the etiology of primary varicosis remains unclear, secondary varicosis usually results from deep vein thrombosis involving the leg. Destruction of venous valves allows development of pathological reflux of blood which then leads to ambulatory venous hypertonia from walking and associated venous hypervolemia. Dilation, deformation, and loss of capillaries result with increased transendothelial protein transport leading to microlymphangiopathy. Increased venous pressure leads to reduced perfusion pressure, decreasing capillary flow velocity. Leukocytes come into contact with the endothelium, are activated, and induce an inflammatory reaction. It has been proposed that increased leakage of fibrinogen leads to formation of a fibrin cuff around the capillary, creating a functional barrier for permeability and diffusion, causing local hypoxia, and ultimately leading to development of venous leg ulcers. It is estimated that about 1–2 % of patients with CVI will develop a venous leg ulcer during their lifetime.

A presumptive diagnosis of a venous leg ulcer can usually be made upon clinical inspection given that typical clinical stigmata above the medial malleolus and on the lower leg can often be detected (Table 3). Findings include "blow-out" veins, edema, corona phlebectatica paraplantaris, atrophie blanche, acroangiodermatitis (Mali disease), lipodermatosclerosis, brown discoloration of the skin, and stasis dermatitis (Figure 2) [6].

Arterial leg ulcer (Ulcus cruris arteriosum)

Arterial leg ulcers result from peripheral arterial occlusive disease (PAOD), the most common cause of which is arteriosclerosis, responsible for PAOD in more than 90 % of patients. Major risk factors include smoking, diabetes mellitus, arterial hypertension, and hypercholesterinemia. In Germany an estimated 20 % of the population over age 65 currently suffers from PAOD, although only one-third exhibit clinical symptoms [7]. Prior to ulceration, symptomatic patients tend to complain of intermittent claudication. Subjective complaints usually worsen with elevation of the legs. Ulcerations develop predominantly on the extremities. The surrounding skin is cool to the touch. Lower leg involvement generally affects the region about the lateral malleolus or the tibial margin [4]. Compared with patients with venous leg ulcers, patients with arterial leg ulcers more often experience severe pain.

Hypertensive leg ulcer (Ulcus Cruris hypertonicum Martorell)

Hypertensive leg ulcers (Ulcus Cruris hypertonicum Martorell) are extremely painful lesions that occur more frequently

Table 1: Factors in the pathogenesis of leg ulcers.

1. Vascular disease	
Veins	Chronic venous insufficiency: postthrombotic syndrome, varicose veins, dysplasia,
Arteries	Peripheral arterial occlusive disease, hypertension, arteriovenous fistulas, arterial thrombosis, embolism, dysplasia, thromboangiitis obliterans, aneurysm
Lymph buildup	Lymphedema, dysplasia
Vasculitis	Rheumatoid arthritis, leukocytoclastic vasculitis, polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome, erythema induratum of Bazin, systemic lupus erythematosus, Sjögren syndrome, scleroderma, Behçet disease
Microangiopathy	Diabetes mellitus, Livedoid vasculopathy
2. Neuropathic	
Peripheral	Diabetes mellitus, alcohol, medication
CNS	Tabes dorsalis, myelodysplasia, syringomyelia, spina bifida, poliomyelitis, multiple sclerosis
3. Metabolic	Diabetes mellitus, gout, prolidase deficiency, Gaucher disease, amyloidosis, calciphylaxis, porphyria, hyperhomocysteinemia
4. Hematologic	
Erythrocytes	Sickle-cell anemia, thalassemia, polycythemia vera
Leukocytes	Leukemia
Thrombocytes	Thrombocythemia
Dysproteinemia	Cryoglobulinemia, lymphoma
Coagulation	Clotting factors (Factors I-XIII) in plasma Coagulation inhibitors (antithrombin III, APC resistance, protein C and S) Fibrinolysis factors (t-PA, PAI, plasmin)
5. Exogenous	Heat, cold, pressure, ionizing radiation, artefacts, noxious chemicals, allergens
6. Neoplasia	
Primary cutaneous malignant	Basal cell carcinoma, squamous cell carcinoma (Marjolin ulcer), malignant melanoma, angiosarcoma, cutaneous lymphoma
benign Metastasis	Papillomatosis cutis carcinoides, keratoacanthoma
7. Infection	
Bacteria	Furuncles, ecthyma, mycobacterioses, syphilis, erysipelas, anthrax, diphtheria, chronic vegetative pyodermia, tropical ulcer
Viruses	Herpes, variola virus, cytomegaly
Fungi	Sporotrichosis, histoplasmosis, blastomycosis, coccidiomycosis
Protozoa	Leishmaniasis
8. Medication	Hydroxyurea, leflunomide, methotrexate, halogens, coumarin, vaccinations, ergotamine, extravasated cytostatic agents
9. Genetic defect	Klinefelter syndrome, Felty syndrome, TAP1 mutation, Leukocyte adhesion deficiency, factor V mutation
10. Skin disorder	Pyoderma gangrenosum, necrobiosis lipoidica, sarcoidosis, perforating dermatosis, Langerhans cell histiocytosis, papulosis maligna atrophicans, bullous skin diseases

among women than men, commonly involving the distal portion of the lower leg above the lateral malleolus. Most patients initially describe the appearance of livid macules surrounded by a highly inflammatory rim that may ulcerate with minimal trauma. The patient's arterial diastolic pressure is often continuously higher than 95 mmHg. Hypertensive leg ulcers may be caused by narrowing of the arteriole lumen due to subendothelial, intimal fibrosis, with subsequent reactive hyalinosis affecting the tunica media. Obliteration of supplying vessels need not be present [8]. Although a primary causal relationship between arterial hypertension and development of a leg ulcer has not yet been well established, antihypertensive therapy is nonetheless advisable for patients who have both conditions, despite ongoing controversy regarding hypertensive leg ulcers as a distinct entity.

Vasculitis

Vasculitis refers to inflammation of the vessel wall with subsequent damage. Primary systemic vasculitides can be subdivided using the classification scheme of the Chapel Hill Consensus Conference (Table 4) based largely on the anatomic diameter of affected vessels [9]. Secondary vasculitides are associated with underlying disease such as collagenosis, drug reactions, infections, or neoplasia. Leg ulcers

Table 2: Diagnosis of leg ulcers.

Diagnosis	Serology	Tests	Device-based tests
Minimum	Blood count, CRP	Microbiology	Doppler, ankle-tibial index
Standard	HBA1c, ESR, PT, PTT, total protein, blood differential, electrolytes	Epicutaneous tests	Duplex, light reflection rheography
Additional	Circulating immune complexes, cryoglobulins, homocysteine, AT III, PAI-1, APC resistance, vitamins, protein C, protein S, paraproteins, trace elements, ANA, ENA, ANCA, dsDNA, antiphospholipid antibodies, urea, creatinine, tetanus, blood lipids	Biopsy, Raynaud (cold stimulation) test, pathergy test	Angiography, partial pressure of oxygen, capillary microscopy, lymphography, X-ray/CT/MRI, phlebography, venous occlusion plethysmography, phlebodynamometry

presenting in patients with vasculitis are often highly painful and multilocular, with bizarre configurations and surrounded by livid erythema and petechia.

Cutaneous leukocytoclastic vasculitis

Cutaneous leukocytoclastic vasculitis (allergic vasculitis) is a term used to describe often episodic inflammation of cutaneous vessels. Vasculitis results from deposition of circulating immune complexes or bacterial endotoxins in vessel walls with subsequent complement activation, affecting almost exclusively postcapillary venules. Factors contributing to pathogenesis can vary and remain undetermined in up to 50 % of patients. Serologic parameters (ESR, CRP, leukocytosis, thrombocytosis) are frequently associated with the acuteness of disease. Women are affected 2–3 times more frequently than men. Appropriate tests should be performed to assess renal involvement and exclude internal manifestation [10]. The cardinal symptom of cutaneous leukocytoclastic vasculitis is palpable purpura, usually found on the lower legs. In more advanced stages of disease, vesiculae or bullae, hemorrhagic plaques, and ulcerations appear. A predilection exists for the extremities, especially the distal lower legs.

Wegener granulomatosis

Wegener granulomatosis is a rare form of necrotizing, granulomatous vasculitis that often manifests with the classical triad of lung, ENT, and renal involvement. The exact etiology of disease remains unknown. One possibility is that a hypersensitivity reaction activates neutrophils, initiating a reactive inflammatory cascade. Cutaneous manifestations, including leg ulcers, tend to occur in later stages of disease in about 40 % of patients [11]. Detection of cANCA, which has a specificity of 95 %, is one main test used to diagnose Wegener granulomatosis.

Table 3: Classification of chronic venous insufficiency based on Widmer.

Grade I	Corona phlebectatica paraplantaris, edema
Grade II	Trophic skin changes • Capillaritis alba/atrophie blanche • Brown discoloration (purpura jaune d'ocre) • Venous stasis dermatitis • Lipodermatosclerosis • Acroangiodermatitis (Mali disease)
Grade III	Leg ulcer a) healed b) florid

Polyarteritis nodosa

Polyarteritis nodosa describes a rare necrotizing form of vasculitis, peaking in persons 65–75 years of age. The etiology of polyarteritis nodosa is only partially understood. In the literature, purely cutaneous manifestations of benign cutaneous polyarteritis nodosa and microscopic polyarteritis are both described as either independent entities or as forms of polyarteritis nodosa. During the prodromal stage of disease, patients often exhibit nonspecific signs such as fatigue, weight loss, low-grade fever, myalgia, and arthralgia which can be followed by changes involving multiple organs. The lower extremities in particular are affected by the sudden onset of discrete, painful, cutaneous or subcutaneous papules and nodules, usually following the path of an artery, which in the course of disease may ulcerate. Livedo racemosa is one main clinical symptom reflecting polyarteritis nodosa (Figure 3) [12].

Rheumatoid arthritis

With a prevalence of 0.4–12 %, rheumatoid arthritis is the most common inflammatory rheumatic disease affecting Caucasians. As many as 10 % of all

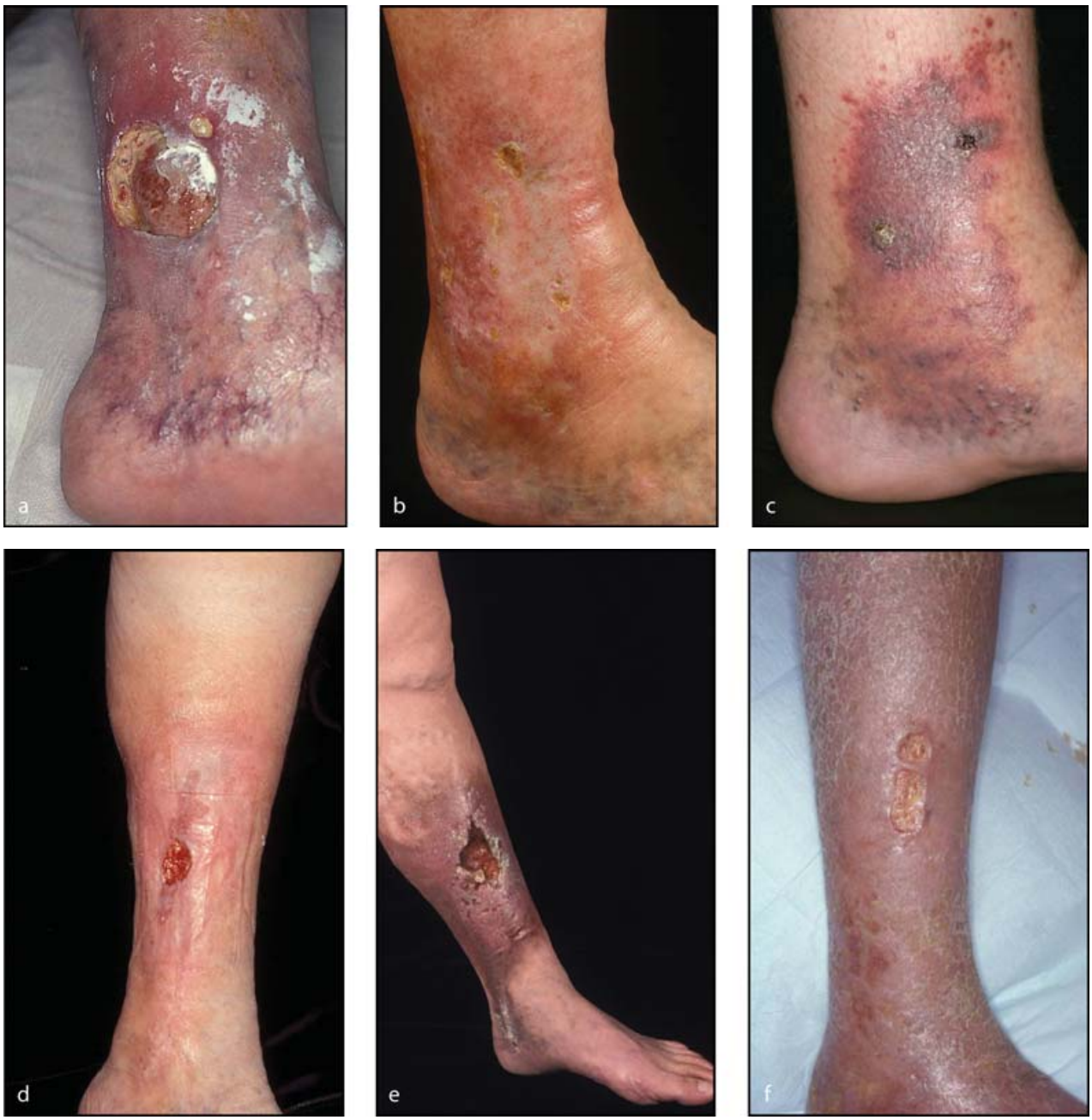

Figure 2: Pathological findings in patients with CVI. (a) Corona phlebectatica paraplantaris with reticular veins below the malleoli. (b) Atrophie blanche (capillaritis alba) reflects the loss of cutaneous capillaries and can be the starting point of an ulcer. (c) Acroangiodermatitis (Mali disease or pseudo- Kaposi sarcoma) is a benign vascular proliferation that presents clinically with livid, red papules and plaques involving the distal portion of the lower leg. (d) Lipodermatosclerosis resulting from chronic inflammation of the dermis, subcutaneous tissues and possibly also fascia with painful induration. An inverted "bottle neck" deformity of the lower leg results (e) Brown discoloration of the skin (purpura jaune d'ocre) describes hyperpigmentation caused by hemosiderin deposits from erythrocytes in perivascular spaces in the lower leg. (f) Venous stasis dermatitis describes eczema involving the lower leg in patients with CVI. Differential diagnosis must especially exclude the presence of allergic contact eczema.

patients with rheumatoid arthritis develop a leg ulcer during the course of disease. Against the background that such patients are disproportionately affected by CVI and/or PAOD, presentation of a leg ulcer warrants thorough differential diagnosis [13]. The choice of an appropriate systemic agent for the treatment of rheumatoid arthritis is often difficult as the majority of drugs potentially inhibit wound healing or induce vasculitides.

Livedoid vasculopathy

Livedoid vasculopathy is a thrombotic vasculopathy affecting small vessels that leads to secondary, refractory ulcers. Disease generally occurs in young adults without familial predisposition, affecting women three times as frequently as men. Predilection sites include the lower extremities as far as the knee and particularly tend to involve the malleolar region. Livedo vasculopathy is a chronic episodic disorder in which healing phases and recurrent ulcerations may overlap. The clinical picture is characterized by three nonspecific cardinal symptoms: livedo

Table 4: Chapel Hill classification of primary vasculitides.

Large vessels	Giant cell arteritis Takayasu disease
Medium-sized vessels	Polyarteritis nodosa Kawasaki arteritis
Small vessels	Wegener granulomatosis* Churg-Strauss syndrome* Microscopic polyarteritis* Henoch-Schönlein purpura Essential cryoglobulinemia Cutaneous leukocytoclastic vasculitis

* ANCA positive

racemosa, ulcers, and atrophie blanche. The usually highly painful ulcerations have bizarre configurations and are surrounded by an inflammatory, hemorrhagic rim [14].

Pyoderma gangrenosum

Pyoderma gangrenosum is an ulcerative disease of unexplained etiology involving circumscribed tissue destruction. Patient history frequently includes trauma. Pyoderma gangrenosum is a neutrophilic dermatosis that is commonly associated with chronic diseases such as ulcerative colitis, Crohn disease, or myeloproliferative disorders. Still, 30–50 % of patients do not have underlying diseases. Clinical presentation of pyoderma gangrenosum is characterized by initial erythematous nodules that are tender to palpation, ulcerate, and are surrounded by hemorrhagic, sterile pustules. Ulcerations are usually polycyclic and exhibit a painful, dark, livid, and sometimes undermined border. Disease is often self-limiting, resolving after several weeks or months [15]. Diagnosis of pyoderma gangrenosum is made based on clinical picture as precise serologic and histologic criteria are still lacking.

Leg ulcers in metabolic disease (Ulcus cruris metabolicum)

A number of metabolic disorders exist that can lead to leg ulcers. Disrupted methionine metabolism, for instance, results in *hyperhomocysteinemia*, which induces an endothelial dysfunction and thus presents a risk factor for development of atherothrombotic vascular disease. Activation of factor V and inhibition protein C also result. Patients with hyperhomocysteinemia thus frequently exhibit venous thromboses and arterial embolisms. Leg ulcers usually reflect an underlying postthrombotic syndrome. Other clinical signs include retardation, ectopia lentis, and skeletal anomalies [16].

Calciphylaxis is an uncommon, potentially fatal disease. Its pathogenesis is not well understood, though disrupted calcium-phosphate metabolism appears to play an important role. Almost all patients are on dialysis for terminal renal insufficiency. Between 1–4 % of all chronic dialysis patients develop calciphylaxis. The disrupted renal endocrine function leads to reduced vitamin D3 synthesis and a compensatory increase in parathormone. This can disrupt regulation of calcium-phosphate metabolism with an increase in the calcium-phosphate product. If the solubility threshold is exceeded, calcification of the vessel walls and subcutaneous fatty tissue occurs with subsequent tissue ischemia. Histopathologically, there is calcification of the tunica media of small vessels and intima proliferation. Initial clinical presentation includes livid areas of erythema that develop into excruciatingly painful ulcerations [17].

Leg ulcers in hematologic disease (Ulcus cruris haematopathogenicum)

Various blood constituents can play a role in the development of a leg ulcer in patients with hematologic disease. Hematologic disease disrupts microcirculation, sometimes with thromboembolic complications. This can lead to development of a leg ulcer, usually as a result of postthrombotic syndrome (PTS). In *sickle-cell anemia,* an autosomal recessive disorder, substitution of an amino acid causes qualitative changes to the hemoglobin. Generally only patients who are homozygous for sickle-cell anemia become symptomatic, with disease predominantly affecting non-white groups. As oxygen tension decreases, the erythrocytes assume an elongated sickle shape, resulting in increased blood viscosity [18].

Individual hypersensitivity to cold can be mediated by anti-erythrocyte antibodies in cold agglutinin disease. The term *cryoproteinemia* collectively describes various disorders that involve the presence of cold agglutinins, cryoglobulins, cryofibrinogen, or cold hemolysins in the plasma or serum of affected individuals which precipitate at temperatures below 37°C and become soluble again when temperature rises. Cryoproteinemia can occur after an infection such as hepatitis C, or neoplasia with an associated clinical picture of secondary ulcerative leukocytoclastic vasculitis [9].

Exogenous causes of leg ulcers (Ulcus cruris exogenicum)

Numerous exogenous factors can directly or indirectly lead to development of a leg ulcer [3]. Multicausal development of *allergic contact eczema* is frequently observed in patients with leg ulcers. Contact sensitization has been found in 40–82.5 % of affected patients [20]. In rare cases, a contact allergy can cause a leg ulcer [21].

Congelatio (frostbite), which cools the body or specific body parts to temperatures below 0°C, leads to induction of tissue destruction. The severity of tissue damage mainly depends on the intensity and duration of exposure to cold as well as humidity. Prolonged exposure, or exposure to intense cold, lead to formation of intracutaneous ice crystals and necrosis at skin temperatures of –2°C and below. Clinical symptoms usually begin with ischemia of the extremities, which less commonly includes involvement of the lower legs [19].

Infectious causes of leg ulcers (Ulcus cruris infectiosum)

Numerous infectious diseases caused by bacteria, viruses, fungi, or protozoa can lead to leg ulcers. *Ecthyma* (*simplex*) is the term used to denote ulcerative pyoderma. The disorder initially involves a

Table 5: Typical clinical findings in patients with leg ulcers.

Pathogenesis	Localization	Margin	Surrounding area
CVI	Above or behind medial malleolus	Indistinct border, undermined	Edema, pigmentation, sclerosis, eczema
PAOD	Tibia, lateral malleolus	Sharply marginated, necrosis	Lightened, hair loss, atrophy
Vasculitis	Multifocal, otherwise "atypical" areas	Sharply marginated, bizarre configuration	Purpura, erythema

bacterial superinfection of a pre-existing injury, often a result of insignificant trauma, insect sting, or excoriation. A pustule appears on an erythematous background at the site where the cutaneous barrier was penetrated by bacteria. A secondary, deep, sharply marginated necrosis forms in the center of the pustule and later ulcerates. These highly refractory and usually multiple ulcers predominantly affect the lower leg.

Chronic vegetative pyoderma results from use of an unsuitable topical remedy to treat initially insignificant trauma (e.g., "wound ointment"). A chronic, persistent ulcer develops and is later surrounded by a papillomatous or verruciform margin. The elevated margin, sometimes bearing nodules of several centimeters, is often undermined and has a tendency to form fistulas which leak pus under pressure [22].

Genetic defects

Of the numerous genetic disorders that are potentially linked with the development of a leg ulcer, *Klinefelter syndrome*, with a prevalence of 1:590 male newborns is the best described. Characteristics of Klinefelter syndrome include gynecomastia, testicular hypoplasia, azoospermia with normal Leydig cell function, elevated FSH levels, gigantism, adipositas, diminished intelligence, or premature osteoporosis. The incidence of phlebothromboses is up to 20 times higher in patients with Klinefelter syndrome than in the normal population. Leg ulcers related to PTS are reported in 6–13 % of affected patients. Proposed causal factors include various thrombogenic factors such as vascular deformities, increased thrombocyte aggregation, increased factor VIII activity, or elevation of plasminogen activator-inhibitor (PAI)-1 in patient serum [23, 24].

Leg ulcers of mixed etiology (Ulcus cruris mixtum)

The notion of mixed leg ulcers accurately describes the fact that often at the conclusion of diagnostic testing a number of causal factors have been identified. In clinical practice, the term usually refers to the presence of both PAOD and CVI in a patient with a leg ulcer.

Conclusion

Despite findings that CVI constitutes a key pathophysiologic factor in at least 80 % of all patients with leg ulcers, relevant differential diagnoses (Table 5), especially for refractory ulcers, should be excluded by means of interdisciplinary diagnostics. <<<

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