Review

⧖ Thieme

Vasculitis allergica - a non-IgE-mediated hypersensitivity syndrome

Vasculitis allergica – ein nicht-IgE-vermitteltes Hypersensitivitätssyndrom

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ABSTRACT

The diagnosis "Vasculitis allergica" suggests a classical allergic IgE-mediated genesis. However, this is not the case; rather, it is a highly complex mechanism that often prevents the antigen that actually triggers the antigen from being detected.
The current nomenclature for this dermatological disease pattern is cutaneous IgM or IgG immunocomplex vasculitis, which is leukocytoclastic vasculitis of the post-capillary venules [3]. This new classification discards the association associated with the original name with a typically IgE-mediated allergic disease.

Vasculitides are immunologically associated with immune complex diseases, the so-called type III reaction according to Coombs and Gell [14, 15, 16]. They are classified as "non-IgE-mediated allergic hypersensitivity syndrome" according to the underlying immunological process [14, 15, 16]. Many vasculitides are clinically first noticeable on the skin, e. g. by acute, rapidly progressive ulcerations, often associated with severe pain. They are therefore important in the clarification of the causes of venous leg ulcers, but here they rank among the rare diagnoses.

The long-standing term "leukocytoclastic vasculitis" for this disease no longer stands for a single disease pattern but rather for a histological pattern of a group of vasculitides, the so-called immune complex vasculitides [3]. Most of the vascular calibres are small vessel vasculitis, which can occur as single organ vasculitis (SOV) with sole manifestation on the skin or as a cutaneous partial symptom of another multi organ vasculitis (MOV), for example in the context of systemic lupus erythematosus [1]. Cutaneous IgM or IgG immunocomplex vasculitis shows the classic sudden, rapidly progressive course for vasculitis and is clinically characterized by a typical primary fluorescence, the palpable purpura, with high inflammation [2]. In the therapy concept, the first priority is to identify and eliminate the triggering agent [2, 42, 44]. Usually this type of vasculitis shows a predominantly residueless healing with low risk of recurrence, provided that the triggering agent is identified and eliminated [2, 41, 42, 44].

ZUSAMMENFASSUNG

Die Diagnose „Vasculitis allergica" suggeriert eine klassisch allergische IgE-vermittelte Genese. Dies ist jedoch nicht der Fall, vielmehr handelt es sich um einen hochkomplex ablaufenden Mechanismus, der häufig das eigentlich auslösende Antigen vor der Detektion bewahrt.
Die aktuelle Nomenklatur für dieses dermatologische Erkrankungsbild lautet kutane IgM oder IgG Immunkomplex-Vaskulitis, es handelt sich um eine leukozytoklastische Vaskulitis der postkapillären Venolen [3]. Diese neue Einordnung legt die mit dem ursprünglichen Namen einhergehende Assoziation mit einer typisch IgE-vermittelten allergischen Erkrankung ab. Vaskulitiden werden immunologisch betrachtet den Immunkomplex-Erkrankungen, der sogenannten Typ III Reaktion nach Coombs und Gell, zugeordnet [14, 15, 16]. Sie werden als

entsprechend dem dahinter liegenden immunologischen Prozess als „non-IgE-mediated allergic hypersensitivity Syndrom" eingestuft [14, 15, 16]. Viele Vaskulitiden machen sich klinisch zuerst an der Haut u. a. durch akut auftretende, rasch progrediente Ulzerationen bemerkbar, häufig assoziiert mit starker Schmerzhaftigkeit. Sie sind damit in der Ursachenabklärung eines Ulcus cruris bedeutsam, rangieren hier aber unter den seltenen Diagnosen.

Der lange bestehende Begriff einer „leukozytoklastischen Vaskulitis" für diese Erkrankung steht entsprechend nicht länger für ein einzelnes Erkrankungsbild, sondern vielmehr für ein histologisches Muster einer Gruppe von Vaskulitiden, den sogenannten Immunkomplexvaskulitiden. [3] Hierbei handelt es sich von Gefäßkaliber überwiegend um „small vessel"

Vaskulitiden, diese können als „single organ vasculitis" (SOV) mit alleiniger Manifestation an der Haut oder auch als kutanes Teilsymptom einer anderen „multi organ vasculitis" (MOV) zum Beispiel im Rahmen eines systemischen Lupus erythematodes auftreten [1]. Die kutane IgM oder IgG Immunkomplex-Vaskulitis zeigt den für Vaskulitiden klassisch plötzlich auftretenden, rasch progredienten Verlauf und ist klinisch durch eine typische Primärefflorenz, die palpable Pupura, mit hoher Inflammation charakterisiert. [2] Im Therapiekonzept steht an erster Stelle das auslösende Agens zu identifizieren und zu eliminieren [2, 42, 44]. In der Regel zeigt dieser Typ von Vaskulitis eine überwiegend residuenfreie Abheilung mit niedrigem Rezidivrisiko unter der Voraussetzung, dass das auslösende Agens identifiziert und beseitigt ist [2, 41, 42, 44].

Classification of vasculitides as a disease group and categorisation of cutaneous IgM or IgG immune complex vasculitis

The 2012 revised International Chapel Hill Consensus Conference (CHCC) nomenclature of vasculitides demonstrates the diversity of this group of diseases and makes clear the importance of the medical history and a detailed clinical description for diagnosis. The CHCC classification integrates aetiology, pathogenesis, calibre of the vessel, the type of inflammation, the most-affected organs with clinical manifestation, genetic predisposition and demographic characteristics. The revision undertaken in 2012 brings greater clarity to the presentation of the group of vasculitides diseases, stipulates the name to be given to a specifically defined disease process and facilitates the handling of the disease in everyday clinical practice [1]. In 2018, a dermatological addendum was added to this existing CHCC classification of 2012. The aim of this addition was to standardise the nomenclature and definitions for cutaneous vasculitis [3].

The first categorisation level still refers to the calibre of the vessel affected by the inflammation. Vessels are subdivided into large, medium and small [1]. There is also a further group, variable vessel vasculitis, which can affect any calibre of vessel [1].

In addition to this size classification, the 2012 CHCC introduced a new term "single-organ vasculitis" where, by definition, only one organ is involved. In addition, there is a group of vasculitides associated with systemic diseases and one group whose representative is associated with a specific aetiology [1, 4, 7, 11].

The term "leukocytoclastic vasculitis" (LcV) that has long been used for the disease pattern of cutaneous IgM or IgG immune complex vasculitis, ultimately reflects the histological picture of a vasculitis subgroup and is used in the dermatological addendum to the CHCC classification as a synonym for this subgroup of immune complex vasculitides. This is the most common form of vasculitis with a cutaneous manifestation [3, 11].

Cutaneous IgM or IgG immune complex vasculitis therefore shows the histological pattern of leukocytoclastic vasculitis in the skin and is classified as small vessel vasculitis (SVV) and initially as single-organ vasculitis (SOV) that is manifested only in the skin. Ap-

propriate clinical observations will show whether this will still be the case in the future, or whether this type of vasculitis will also include other organ systems, consistent with multi-organ vasculitis (MOV) [1, 3, 7, 8, 9, 11].

Types of small vessel vasculitis (SVV)

Single-organ vasculitis (SOV)

IgM or IgG immune complex vasculitis is probably the most important representative of the SVV group. Cutaneous leukocytoclastic vasculitis (LcV, the term most commonly used in the current literature to describe this clinical picture) is one of the most frequent forms of vasculitis, with an incidence of 10–20/100 000 [1, 3, 19, 20, 21, 44].

Vasculitis that is manifested as LcV can also occur as a partial symptom of a systemic disease [5].

Leukocytoclastic vasculitis associated with systemic diseases

This variant, which is often also called secondary vasculitis, occurs classically in the context of collagen diseases, especially the typical lupus vasculitis of the skin, but also the ulcers in systemic scleroderma [5]. Ulcerations in connection with collagen diseases show the typical pattern and clinical course of vasculitis; they are highly acute and strongly inflammatory. The initial clinical picture is often that of classic LcV (▶ **Fig. 1**) and they are associated with severe pain (ischaemic pain).

Case histories of the disease

To illustrate the clinical course and causal relationships in the "fulfilment" of the pathophysiological mechanism of IgM or IgG immune complex vasculitis, the manuscript describes the course of 2 typical cases of the disease. For the sake of clarity, these passages are shown in italics.

The first case was a 97-year-old multimorbid female patient. Diuretic treatment with torasemide 10 mg/day was started due to a clinically observed increase in calf oedema; heart and renal fail-
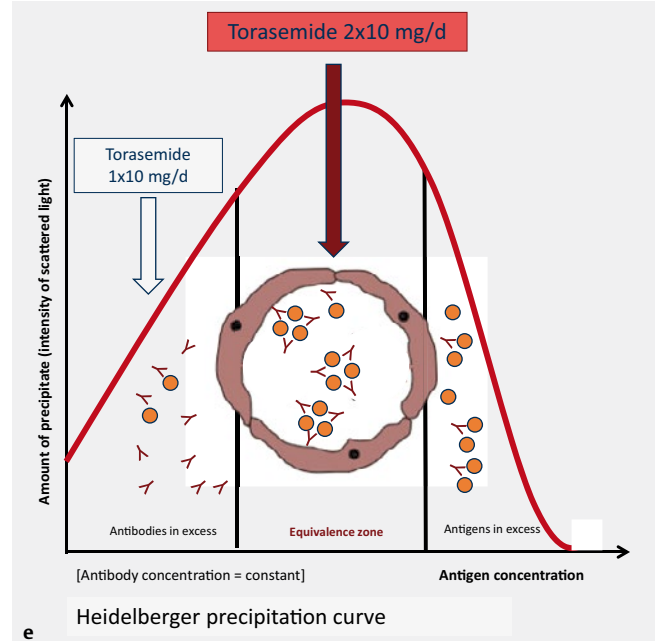
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▶**Fig. 1** Cutaneous manifestation of vasculitis with acral ulcers as components of systemic vasculitis within the framework of SLE.

▶**Fig. 2 a** Case 1 "Torasemide upward titration and acute kidney injury": at initial visit, individual efflorescences on the toes; **b** Case 1: 5 hours later, palpable petechiae had spread to the legs and up the trunk; **c** Case 1: Palpable purpura then spread to the hands as well; **d** Case 1: About 24 hours later, epidermolysis first occurred, rapidly followed by ulcerations; **e** Case 1: Another 24 hours later, areas of adherent necrosis.

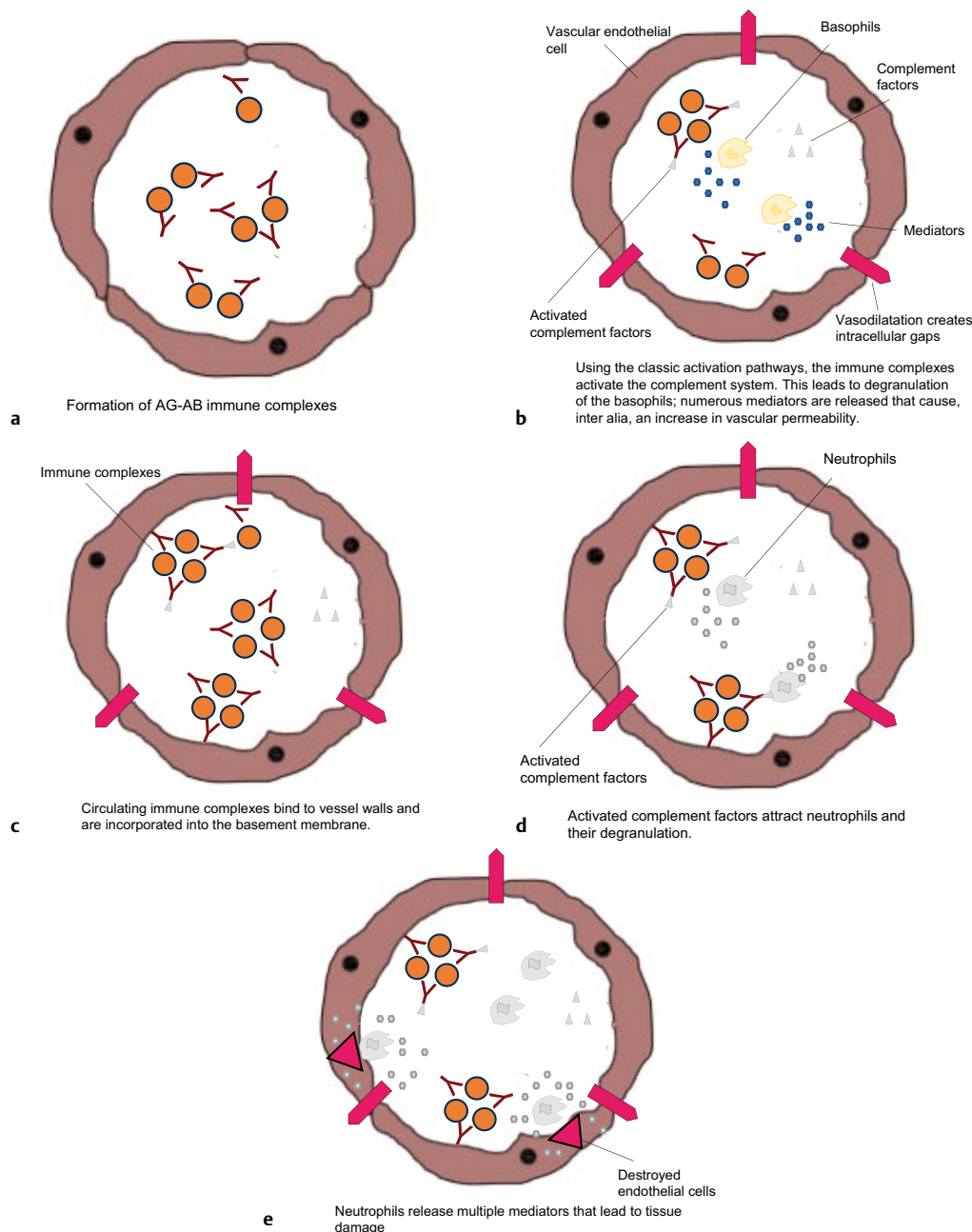▶**Fig. 3 a-b** Case 2 – First consultation of a patient via the cardiology ward showed zones of extensive necrosis on the right (▶**Fig. 3a**) and left (▶**Fig. 3b**) foot after cutaneous IgM or IgG immune complex vasculitis, most likely on recent upward titration of torasemide to 2x10 mg for heart failure; **c-d** Case 2 new fulminant exacerbation of the vasculitis (**c** left hand; **d** right hand) on renewed upward titration of torasemide to 2x10 mg after previous complete pause that had led to complete remission of the findings; **e** Achievement of equivalence zone with clinical formation of vasculitic foci with a dose of 2x10 mg torasemide.

ure were known to be present. The dose was titrated upwards to 2x10 mg/d 5 days after initiation because the improvement was inadequate; the first petechial skin changes occurred on the toes (▶Fig. 2a) a further 5 days later and were followed by rapid progression of the skin findings and acute presentation in the outpatient clinic of the Department of Dermatology at the Greifswald University Hospital, where both the skin changes as well as the overall condition of the patient deteriorated on an hourly basis (▶Fig. 2b-▶Fig. 2e). The second case was of a 65-year-old male patient. At the first consultation via the cardiology ward, there was a 6-week history of extensive areas of vasculitic changes over the entire integument, and associated necrosis on the feet and calves were present (▶Fig. 3a-▶Fig. 3b). History revealed that 5 days before the first skin changes occurred, the dose of torase-

mide – that had been 10 mg for many years – had been increased to 45 mg due to cardiac decompensation.

Immunological mechanism of the immune complex reaction – correlation with the clinical picture, histology and course

The earlier name for IgM or IgG immune complex vasculitis of "vasculitis allergica" stems from an erroneous interpretation of the disease genesis. Vasculitides are classified in immunological terms as a type III reaction according to Gell and Coombs. This implies an antigen-antibody aggregate mechanism, which has coined the term "immune complex disease". It is classified, in immunological

a — Formation of AG-AB immune complexes

b — Using the classic activation pathways, the immune complexes activate the complement system. This leads to degranulation of the basophils; numerous mediators are released that cause, inter alia, an increase in vascular permeability.

c — Circulating immune complexes bind to vessel walls and are incorporated into the basement membrane.

d — Activated complement factors attract neutrophils and their degranulation.

e — Neutrophils release multiple mediators that lead to tissue damage

▶ **Fig. 4 a-e** Coombs and Gell type III reaction – immune complex reaction – vasculitis.

terms, as a non-IgE-mediated allergic hypersensitivity syndrome. It is a humoral-mediated immune reaction carried by IgM or IgG [3, 13, 14, 15, 16, 45].

Similar to the type 1 reaction, a sensitisation phenomenon can also occur with type III reactions that can also lead to recurrences on re-exposure. The average latency until the reaction after first exposure is 8–13 days, on re-exposure 6–12 hours [47].

The mechanism involved in an immune complex reaction starts with the diffusion of allergen-specific IgG and IgM antibodies from the blood vessels into the tissues, where they form immune complexes with the specific allergen. These immune complexes are deposited on the basement membrane of vascular endothelia (▶ **Fig. 4a**) and can be demonstrated in tissue sections using direct immunofluorescence. To enable differentiation from IgA-positive LcV, it is important to demonstrate the immunoglobulin subtypes IgG and IgM as part of the immune complex [3, 5, 13, 14, 15, 16]. The clinical picture is of initial petechial-appearing, slightly raised pinhead-sized papules that correlate with the histological picture of ectatic vessels with thickened walls (generally post-capillary venules, but also small veins and arterioles) [3, 6, 7, 8, 18, 20, 21, 42, 44] (▶ **Fig. 5a**, ▶ **Fig. 6a**). Dermatoscopy shows the vasodilatation as deep dark-red, sometimes livid dots and globules [46,

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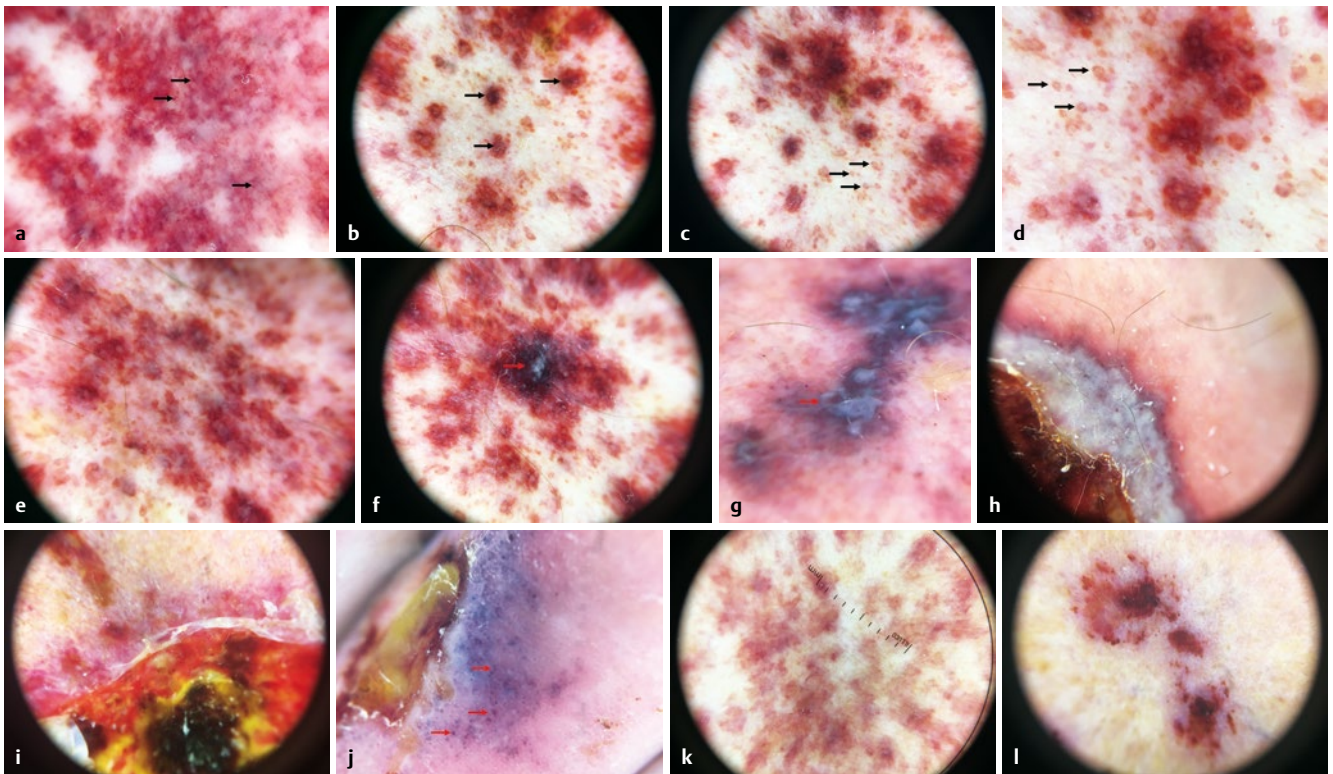
▶**Fig. 5** **a** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: in the centre of the efflorescences prominent vessels are visible as dots and globules (arrows) with surrounding haemorrhagic-purpuric spotted, indistinct background (= typical of a vasculitic event). The background correlates clinically with the livid-erythematous ground colour (▶**Fig. 7a-b**) and corresponds histologically with the extravasation of erythrocytes (▶**Fig. 6b**); **b** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: as the inflammatory process progresses, the perivascular infiltrate, oedema and extravasation of erythrocytes increase; this corresponds to the clinically observable palpable purpura (arrows) (▶**Fig. 7a-b**); **c-d** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: the follicular openings are typically visible as perifollicular purpuric haloes (arrows); **e** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: as the disease progresses, the individual efflorescences begin to coalesce to form large areas; **f** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: the initially bluish-white translucent areas later appear in the centre of the palpable purpura. These correspond histologically with the start of epidermolysis and clinically with vesicles (arrow); **g** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: with continued evolution of the disease, the bluish-white translucent areas coalesce to form clinical bullae. (arrow); **h** Dermatoscopic picture of cutaneous IgM or IgG immune complex vasculitis: thereafter, the bluish-white shiny bullae merge to form large areas; **i** Dermatoscopy: cutaneous IgM or IgG immune complex vasculitis: on further evolution, adherent necrosis and ulcerations caused by the lack of nutrient supply to the skin due to the vasculitis-induced thrombotic occlusion of blood vessels in the papillary dermis; **j** Dermatoscopy: vasculitis-induced ulcer: an ulcer with a noticeable highly-inflammatory margin is visible, bluish-white shiny surrounding skin interspersed with dots and globules (arrows) in the livid background as evidence of ongoing active vasculitis; **k** Dermatoscopy: the healing phase of cutaneous IgM or IgG immune complex vasculitis; dots and globules as signs of an active vasculitis are no longer present. The palpable purpura is now clinically absent. The existing livid-erythematous background (haemorrhage) is fading into a yellowish-brown spotted pattern (breakdown of erythrocytes); **l** Dermatoscopy: the healing phase of cutaneous IgM or IgG immune complex vasculitis; the vesicles and bullae have become haemorrhagic crusts.

48, 49] (▶**Fig. 5a**). The first lesions of the disease typically appear on the feet and calves. This is probably caused by stasis (vasodilatation). The vasodilatation promotes the deposition of immune complexes [2, 3, 21].

These complexes then activate the complement system, especially complement factors C3a and C5a. Complement-loaded immune complexes cause this activation by binding to various cell receptors of the immune cells circulating in the blood vessels (Fc receptors of mast cells, macrophages, granulocytes, T-lymphocytes) (▶**Fig. 4b**, ▶**Fig. 4c**). After the partial failure of phagocytosis (the immune complexes are too large to be completely phagocytosed), a variety of mediators are released (leukotrienes, prostaglandins and other cytokines) that result in a further increase in inflammation in the vessel walls (▶**Fig. 4b**-▶**Fig. 4d**). During the

mediator-triggered vasodilatation, the vessels become increasingly permeable and plasma proteins pass into the tissues, leading to perivascular spread of the inflammation [3, 5, 13, 14, 15, 16] (▶**Fig. 4b**-▶**Fig. 4d**). On histological examination, there are now small vessels in the stratum papillare of the dermis with markedly thickened walls, surrounded by a granulocyte-dominated infiltrate mixed with lymphocytes, eosinophils and clearly visible extravasation of erythrocytes as indirect evidence of the destruction of venules of the papillary plexus (▶**Fig. 6b**, ▶**Fig. 6c**). Classically, "disintegrating" granulocytes (leukocytoclasia) with visible nuclear dust (nuclear debris) now also present themselves, which ultimately led to the disease picture being given the name "leukocytoclastic vasculitis" [3, 6, 7, 8, 18, 20, 21, 42, 44] (▶**Fig. 6d**). This progression of the disease is clinically visible through the increase in inflamma-
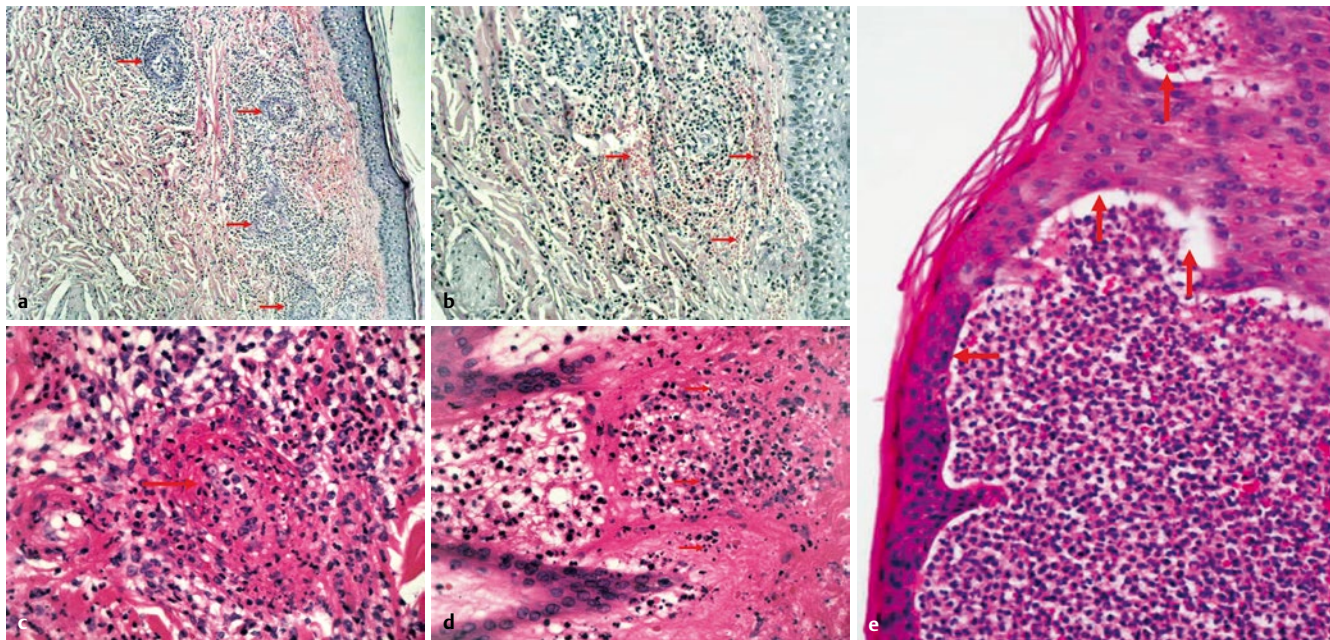
▶Fig. 6 **a** Histological picture of cutaneous leukocytoclastic vasculitis with ectatic, thickened-walled vessels (arrows) in the papillary plexus with surrounding granulocytic-lymphocytic infiltrates (HE staining, magnification 10x/0.25); **b** Histological picture of cutaneous leukocytoclastic vasculitis with ectatic, thickened-walled vessels (arrows) in the papillary plexus with surrounding granulocytic-lymphocytic infiltrates and substantial extravasation of erythrocytes (HE staining, magnification 20x/0.40); **c** Histological picture of cutaneous leukocytoclastic vasculitis with thrombosed, thickened-walled vessel (arrow) in the papillary plexus with surrounding granulocytic-lymphocytic infiltrates (HE staining, magnification 20x/0,40); **d** Visible nuclear dust as evidence of failed phagocytosis with resulting leukocytoclasia (arrows) (HE staining, magnification 40x/0.65); **e** Histology of advanced cutaneous leukocytoclastic vasculitis with ectatic, thickened-walled vessels in the papillary plexus with surrounding granulocytic-lymphocytic infiltrates, nuclear dust and substantial extravasation of erythrocytes. In addition, subepidermal clefts (arrows) and granulocytic infiltrates interspersed with red blood cells and substantial amounts of nuclear dust. This finding corresponds clinically to epidermolysis in the form of haemorrhagic vesicles and bullae. (▶Fig. 5f, ▶Fig. 5g, ▶Fig. 7c, ▶Fig. 7d,) (HE staining, magnification 20x/0.40).

tory components of the individual efflorescences. Haemorrhagic haloes with a centrifugal spread now appear around the palpable petechiae (▶Fig. 7a-▶Fig. 7b). Light microscopy now shows that the full picture of an LcV has been reached; besides the central dots or globules, there are haemorrhagic haloes that merge with each other and form the typical deep livid red-erythematous spotted indistinct background. The spotted pattern is typical of a vasculitic genesis of the purpuric changes (▶Fig. 5a, ▶Fig. 5b). The perifollicular purpuric halo shapes are also typical [46, 48, 49] (▶Fig. 5c, ▶Fig. 5d). The changes do not disappear on mechanical pressure because they are caused by bleeding and thromboembolic occluded vessels (dots, globules). The clinical Rumpel-Leede test (triggering of petechiae after application of 10 mmHg pressure using a blood pressure cuff for a period of 5 minutes) is positive, as a sign of the increased fragility of the inflamed vessels.

In terms of pathophysiology, the granulocytes and macrophages have started to phagocytose the immune complexes. Due to the size of the immune complexes, this phagocytosis fails, phagocytosing cells die, and this constitutes the histological picture of leukocytoclasia in the tissues [3, 18, 21] (▶Fig. 6d). Other immune cells diffuse into vessels that are still patent and transport immune complexes into the spleen and liver as classic breakdown organs of immune complexes. This mechanism can be exhausted by the relevant amount of immune complexes and/or the presence of other co-factors; this stage has been reached in clinically manifest vasculitis [13, 14, 15, 16].

If this immunological process continues, the epidermal tissue is destroyed because of the lack of supplied nutrients from vasculitic-thrombosed occluded vessels. The first clinical sign is epidermolysis in the form of vesicles and bullae, which then rapidly become necrotic (ischaemic death of tissue) [2, 20, 21, 44] (▶Fig. 6e, ▶Fig. 7c-▶Fig. 7g). These changes are visible with the dermatoscope as whitish-blue shiny patches (▶Fig. 5f, ▶Fig. 5g). This process is initially limited to the primary efflorescence – the palpable petechiae – but later extends into the periphery, bizarrely configured, sometimes lightning-like with highly inflammatory edges in the ongoing active and progressing process of vasculitis. (▶Fig. 5e, ▶Fig. 5h, ▶Fig. 7f) The full-blown disease shows a classic juxtaposition of fresh efflorescences, alongside necrosis, ulcerations and areas in the process of healing, that fade to yellowish-brown (siderophages) (▶Fig. 5k, ▶Fig. 5l).

The lesions generally start on the feet and lower legs (sometimes the hands), but without intervention they rapidly spread upwards over the thigh to the trunk. There are also a few individual case reports of facial involvement [2, 20, 21, 44] (▶Fig. 8).

The relative amounts of antigens and antibodies are crucial for the development of large pathological immune complexes. If both are present in similarly high concentrations, then the "equivalence zone" is reached and large numbers of antigen-antibody complexes (precipitates) are precipitated. If one of the two complex components predominates, only a few and small complexes are precipitated. This phenomenon is very important; it illustrates, for

▶**Fig. 7** Clinical picture of cutaneous IgM or IgG immune complex vasculitis with central raised purpura (palpable) and surrounding highly inflammatory-haemorrhagic halo (**a** Detailed image; **b** Overview); **c** Clinical picture of cutaneous IgM or IgG immune complex vasculitis: as the disease progresses, epidermolysis appears in the form of haemorrhagic vesicles and bullae on the foot; **d** Clinical picture of cutaneous IgM or IgG immune complex vasculitis; as the disease progresses, epidermolysis appears in the form of haemorrhagic vesicles and bullae on the hand; **e** Clinical picture of cutaneous IgM or IgG immune complex vasculitis; as the disease progresses, epidermolysis appears in the form of haemorrhagic vesicles and bullae also on the legs and then on the hands as well; **f** Vesicles and bullae become ulcerations with initially adherent necrosis and highly inflammatory margins as an expression of vasculitis progression; **g** Venous leg ulcer of vasculitis genesis with a dark red margin.

example, that the disease is often first triggered – and can also be causally treated – when the dose of a drug is changed or its metabolism is altered in the case of a drug-drug interaction [47] (▶**Fig. 9**).

The actual pathogenicity of the immune complexes depends on the solubility, the charge and the site of the deposition (skin or kidneys, for instance). The pathogenic process itself starts when the elimination capacity of the spleen and/or liver is exhausted. Only then does a clinically active deposition of the immune complexes in the kidneys, skin, joints, muscle, lungs and brain occur. This consists of positively charged immune complexes being deposited preferentially on negatively charged zones of basement membranes of the skin and glomeruli. Insoluble immune complexes are only weakly pathogenic in the tissue, whereas partially soluble ones lead to the local inflammatory reactions described above. In IgM or IgG immune complex vasculitis as SOV, generally only the skin is affected because hardly any IgM and IgG is deposited in the glomerular mesangium; both are considerably more rapidly broken down than IgA, which typically causes the IgA-mediated nephritis in IgA-positive vasculitis [2, 47].

At the advanced stage of the disease, there are rapidly progressing vasculitic ulcers on the legs that are characterised by highly inflammatory margins, quickly reach an impressive depth and are accompanied by severe pain due to the rapid ischaemic destruction of tissues and the high degree of tissue inflammation caused by the release of inflammatory mediators (▶**Fig. 7f**, ▶**Fig. 7g**, ▶**Fig. 5i**, ▶**Fig. 5j**).

Diagnosis

The diagnosis of IgM or IgG immune complex vasculitis is primarily based on the classic clinical features, patient history, course of the disease, histology and immunohistology and secondarily by

▶**Fig. 8 a-c** Clinical distribution pattern of cutaneous IgM or IgG immune complex vasculitis, beginning on the feet and lower legs and then spreading to the trunk.

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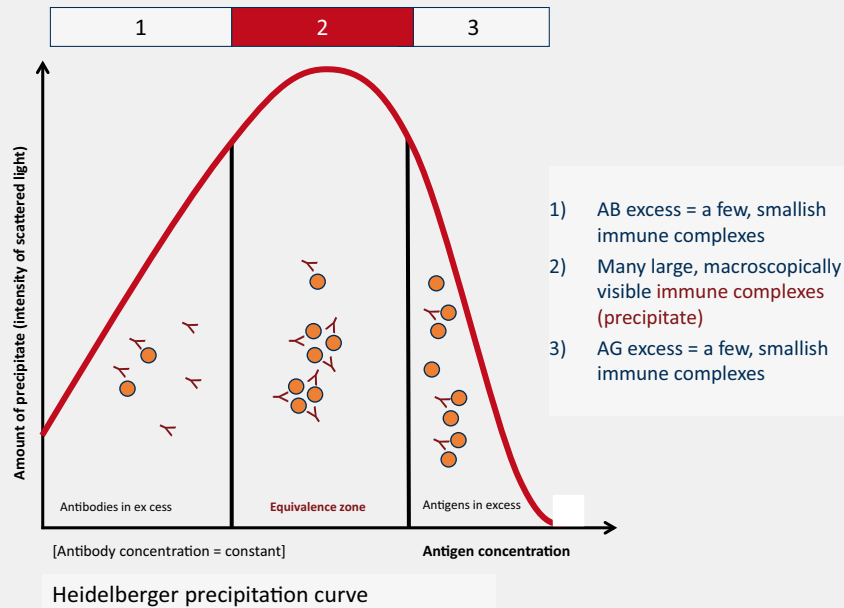
Fig. 9 Precipitation curve (Heidelberger curve) of the Coombs and Gell type III reaction.

the correspondingly negative serology for autoantibodies (ANA, ANCA), which excludes other types of small vessel vasculitis [2, 3, 4, 7, 8, 12, 42, 44].

When diagnosing vasculitis, it is always important whether it is an SOV or secondary vasculitis within the framework of a systemic disease, e. g. one of the collagen diseases. This question has a large influence on the treatment and prognosis.

Aetiology/causes

The genesis of IgM or IgG immune complex vasculitis is highly diverse. Infections and drugs are discussed most frequently, but a paraneoplastic genesis is also important in this context. In terms of an infectious genesis, predominantly infections of the upper airways caused by streptococci and adenoviruses can be considered. The possibility of viral hepatitis (hepatitis B and C), a parvovirus B19 infection and enteroviruses should also be investigated. Frequent triggering drugs are NSAID, sulfonamides, penicillins, cephaclor, diuretics such as HCT or furosemide, allopurinol, quinolones, hydralazine, MTX and also ovulation inhibitors [2, 3, 4, 7, 8, 12, 42, 44].

The drug history should not only include questions about new drugs but also about any dose changes, because the latter are particularly important. Enquiries should also be made about any other newly occurring diseases such as renal insufficiency or liver disease that can delay or completely prevent the elimination of drugs, as well as the breakdown of immune complexes that may have formed.

Furthermore, short-term interactions of drugs should be considered (delayed/accelerated metabolism), particularly NSAID, as they are often forgotten by the patient because these are classic "occasional" drugs. Because of this "usage mind-set", the probability of sensitisation by NSAID for all types of allergic reactions is likewise exceptionally high. Another group of causative drugs that are often

underestimated are the diuretics – both the thiazides as well as the loop diuretics. These drugs are often not immediately recalled by the patient because they are prescribed in combination products.

In both case histories, the loop diuretic torasemide could be identified as the causative agent. However in both cases, the drug should not be considered in isolation as a new drug; in one patient, acute kidney injury was also present and the increase in dose of the drug played the decisive role in the other. In the first case of the 97-year-old woman, an acute kidney injury was present on admission "grafted onto" the existing chronic kidney disease. This condition is most probably explained by diuretic-associated dehydration. The increase in dose of diuretic, coupled with the increasingly impaired renal function, was probably the trigger for the formation of pathologically-acting immune complexes once the equivalence zone of the antigen (torasemide) and antibody was reached.

The combination of an infection and a drug can also jointly induce cutaneous IgM or IgG immune complex vasculitis. The cause cannot be identified (idiopathic) in up to 50 % of cases of the disease [2, 42, 44].

The occurrence of the clinical picture of an IgM or IgG immune complex vasculitis as a partial symptom of an autoimmune disease (lupus erythematosus) needs to be urgently investigated and evaluated.

Differential diagnoses

The field of differential diagnoses for this disease is wide-ranging and can only be discussed as examples. When considering the differential diagnoses, it is advantageous to look at the two major

clinical courses of the disease separately, i. e. there are, on the one hand, diagnoses with clinically visible "palpable purpura" and, on the other, diagnoses with "necrosis and ulcerations" which must be excluded. However, as with LcV, there are also some diseases to be considered in the differential diagnosis in which two clinical courses occur in direct succession. In such a case, the diseases are classified according to the appearance often present at the first diagnosis (▶ Fig. 10).

Differential diagnoses for the clinical picture of "palpable purpura" (as an example)

This group consists of a whole range of vital, life-threatening diseases with a fulminant course, which makes differentiation enormously important.

The first and probably most significant representative is IgA-positive vasculitis, called Schoenlein-Henoch purpura after the first person to describe it. It is the most common type of vasculitis in children and typically occurs between the ages of 3 and 6; boys are distinctly more often affected than girls. The incidence is 15–25/100 000. There is also an adult variant, with a considerably lower incidence of 3/100 000. Irrespective of age, it is a multisystem disease with manifestations in the skin, joints, kidneys and intestines and less commonly in the CNS and testes. It typically and frequently occurs after a respiratory infection. The disease shows an episodic course and can last for up to 2 years, after which recurrences can also occur. Pathophysiological studies have identified immunoglobulins of the subtype IgA1 as the cause and here, too, the post-capillary venules are mainly affected, although small veins and arterioles can also be involved. Clinical examination shows an often reticular distribution pattern of the palpable petechiae. Once again, the skin changes are present especially on the lower leg. The disease also occurs in adults, where often only cutaneous manifestations are present [2, 10, 25, 26, 27, 29].

Another disease where the clinical picture involves petechial changes is purpura fulminans, also known as Waterhouse-Friderichsen syndrome. This is generally caused by an overwhelming acute meningococcal sepsis, though pneumococci and staphylococci have also been implicated. Disorders of the microcirculation occur during the sepsis and lead to disseminated intravasal coagulation (DIC), shock and acute adrenal failure due to haemorrhagic infarctions. In addition, the skin typically shows initial petechial changes that rapidly increase and turn into mummified necrosis, particularly of the fingers and toes. The condition is fatal in 15–20 % of cases [40].

Another differential diagnosis for the petechial stage of cutaneous immune complex vasculitis is purpura pigmentosa progressiva that is assumed to be associated with a type IV sensitisation to various drugs, (including diazepam and carbamides) [45, 47]. Notable clinical findings of the disease are symmetrical, brownish-red irregular spots with small cayenne pepper-like, non-blanching petechiae on the lower legs, sometimes also on the entire integument. It is important to note that this is generally a non-palpable, macular rash (▶ Fig. 11a-▶ Fig. 11b).

Pityriasis lichenoides et varioliformis acuta Mucha Habermann (PLEVA), as a dermatosis with an infectious-allergic-bacterial (haemolytic streptococci), drug-allergic or viral (Herpes zoster virus, Epstein-Barr virus) cause, must also be considered among dis-

▶ **Fig. 10** An irregularly demarcated, highly painful pretibial ulcer with inflammation of surrounding tissue, classic palpable petechiae in the periphery, with central, sometimes small vesicles as typical clinical manifestation of cutaneous LcV that is causally responsible for the ulcer.

eases of this type [2, 21]. A classic clinical finding is the "Heubner's star chart", that is characterised by the abrupt eruption of 0.2–0.4 cm-sized red or reddish-brown, initially lichenoid papules, that become eroded and ulcerated with haemorrhagic crusts (▶ Fig. 12a-▶ Fig. 12c).

In addition, there are many other diseases that display papular, petechial efflorescences, but often with clinically different courses and additional skin changes and symptoms that enable differentiation from cutaneous IgM or IgG immune complex vasculitis. For example, vasculitic Herpes zoster shows the classic efflorescences of LcV and also a comparable acute course. The unilateral and segmental nature of the findings enables a reliable clinical differentiation from LcV (▶ Fig. 13a-▶ Fig. 13c). Histological examination reveals intra-epidermal multilocular blistering due to reticular degeneration and acantholysis. There is also extensive necrosis of keratinocytes, and multinuclear ghost cells are present. A perivascular lymphocytic infiltrate, without the demonstration of vascular changes and leukocytoclasia, is seen in the upper dermis [2, 21] (▶ Fig. 13d-▶ Fig. 13e).

▶ **Fig. 11 a** Purpura pigmentosa progressiva on long-term treatment with mirtazapine; **b** Purpura pigmentosa progressiva on long-term treatment with mirtazapine.


▶ **Fig. 12** Pityriasis lichenoides et variolifomis acuta (PLEVA); **a** On the leg; **b** In the knee region; **c** Pectoral, detailed view.

Differential diagnoses from the clinical picture of "necrosis with subsequent ulceration"

A large variety of other diseases must be considered in the differential diagnosis also at this stage of the disease. Once again, it is mainly the group of vasculitides, specifically the group of small vessel vasculitides (SVV) that are among the most important differential diagnoses. On the one hand, the ANCA-associated vasculitides (AAV) need to be considered. This group of diseases can be manifested clinically principally as LcV. Since the diagnosis is often delayed, necrosis and ulcerations of the skin reminiscent of pyoderma gangrenosum are frequently present. A few AAV are skin-limited, but diseases in this group are generally systemic. As well as the manifestation on the skin, there are typical clinical patterns in other organs with corresponding symptoms and courses. These help to differentiate these vasculitides from cutaneous IgM or IgG immune complex vasculitis [2, 3, 4, 5, 6, 7, 9, 21, 43]. The pattern of involvement of AAV ranges from post-capillary venules to small arteries. The histological picture is often one of leukocytoclastic vasculitis alongside areas of granulomatous inflammation [2, 3, 18]. Drug-induced skin-limited AAV is particularly similar in its clinical pattern and course, but a positive ANCA titre can help the differ-
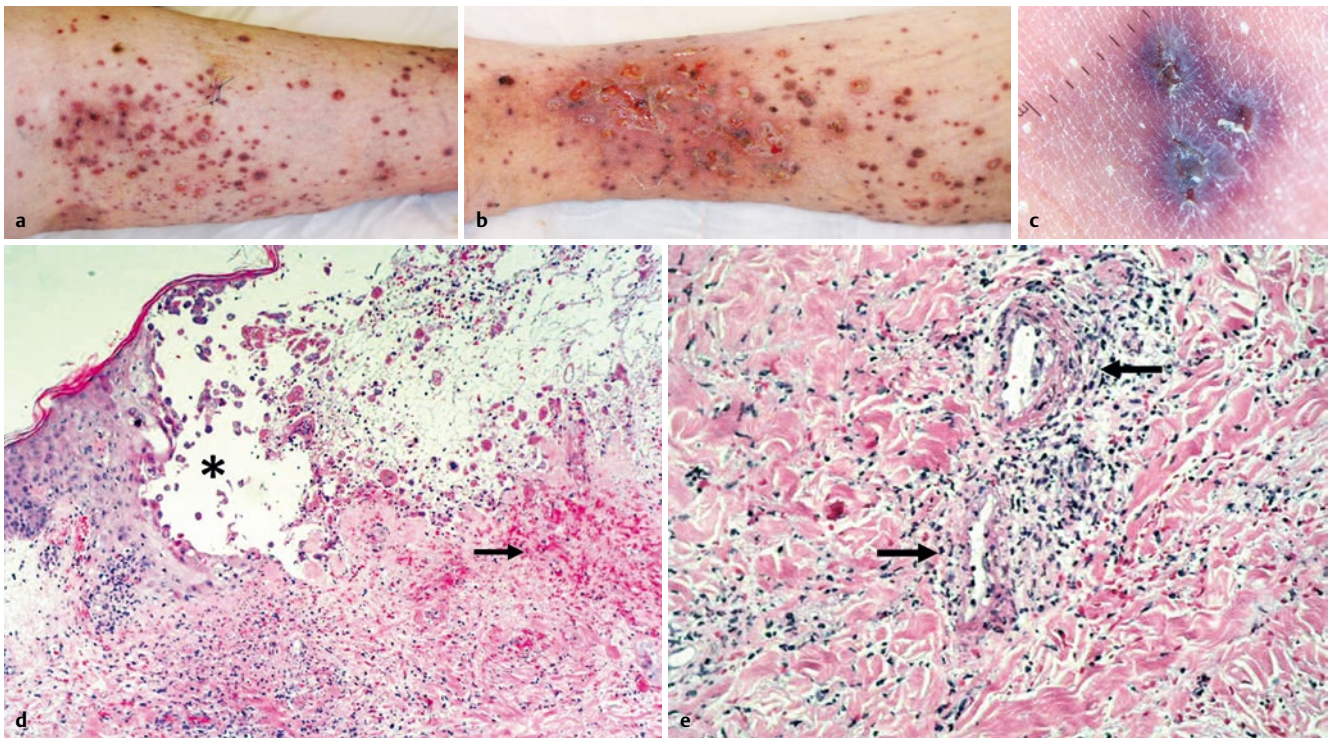
►**Fig. 13** Vasculitic multisegmental Herpes zoster of dermatomes L4-S2 right (**a** medial; **b** lateral) during ongoing immunosuppression with Cellcept after renal transplantation; **c** Dermatoscopy of vasculitic Herpes zoster; groups of the centrally umbilicated blisters, surrounded by haemorrhagic haloes. However, the typical dots and globules of LcV as an expression of the inflamed vessels are absent; **d** Histology of a clinical, vasculitic Herpes infection of the skin with visible intra-epidermal multilocular blisters, zones of acantholysis with single, rounded keratinocytes(*), some multinuclear ghost cells. Subepidermal substantial extravasated erythrocytes in the dermis (arrow), that are responsible for the clinical picture of vasculitis (►**Fig. 13a**). (HE staining, magnification 4x/0.10); **e** Histology of a clinical vasculitic Herpes infection of the skin; the vessels of the papillary dermis show a discrete perivascular infiltrate without morphological changes to the vessel walls; no evidence of neutrophils and corresponding leukocytoclasia (arrows) (HE staining, magnification10x/0.25).

entiation from cutaneous IgM or IgG immune complex vasculitis [28, 39] (►**Fig. 14a**-►**Fig. 14b**).

Another representative of the group of small vessel vasculitides is cryoglobulinaemic vasculitis. Cryoglobulins are immunoglobulins that precipitate at or below 37.0°C. Cryoglobulinaemia can be monoclonal (type I, IgM or IgG) or mixed (type II-IgM and III-IgM). Mixed signifies that they contain other proteins such as rheumatoid factor as well as IgM. 80% of the diseases, especially the mixed forms, are associated with a hepatitis C infection [2, 3, 22, 23, 24]. Type II cryoglobulins are the most common type in patients with cutaneous cryoglobulinaemic vasculitis but type I and type III also show corresponding pictures. This vasculitis starts on the skin with the classic efflorescences of LcV, but these early skin changes are rarely observed clinically because they rapidly coalesce to form large purpuric areas and undergo extensive necrosis. These initially mild inflammatory skin changes then become highly inflammatory ulcerations, which is when the patient often first presents. Here too, immunohistology shows perivascular deposition of IgM and C3. The key differential diagnostic pointers are the vessels occluded by eosinophilic transparent structures (= cryoglobulin-antibody complexes). Post-capillary venules are predominantly affected, and occasionally arterioles and medium-sized vessels.

A further group of diseases that often first show petechial-appearing changes as a type of premonitory efflorescence be-fore necrosis and ulcerations are, on the one hand, the antiphospholipid syndrome (►**Fig. 15a**–►**Fig. 15b**, ►**Fig. 15f**) – both the primary and also the secondary form in the context of lupus erythematosus – and, on the other, livedoid vasculopathy (►**Fig. 16a**–►**Fig. 16b**) as vasculopathies. The clinical picture in both diseases can sometimes show highly inflammatory ulcerations with a petechial-appearing margin and pattern. In both diseases, dermatoscopic examination shows the porcelain-coloured bizarrely shaped areas of atrophy accompanied and/or surrounded by linear, predominantly helically (corkscrew-like) configured as well as glomerular vascular patterns [50] (►**Fig. 13b**–►**Fig. 13d** new, ►**Fig. 15c**-►**Fig. 15e**, ►**Fig. 14b**, ►**Fig. 14c** new, ►**Fig. 16c**–►**Fig. 16d**). Classic inflammatory changes are not visible (punctate vascular pattern) and there are no haemorrhages. Additional history (thrombophilia), clinical (the classic triad of livedoid vasculopathy – sequential occurrence of livedoid racemosa, very painful ulcerations and atrophie blanche) and/or paraclinical markers (antiphospholipid antibodies, histology) enable differentiation from vasculitis [30, 31, 32, 33, 34, 35, 36, 37, 38].

The rapid course, the highly inflammatory, bizarrely-shaped margins and the painfulness of the lesions in the context of a necrotising ulcer are indicative of a vasculitic process. The palpable petechiae are often visible alongside the ulcerations and necrosis in

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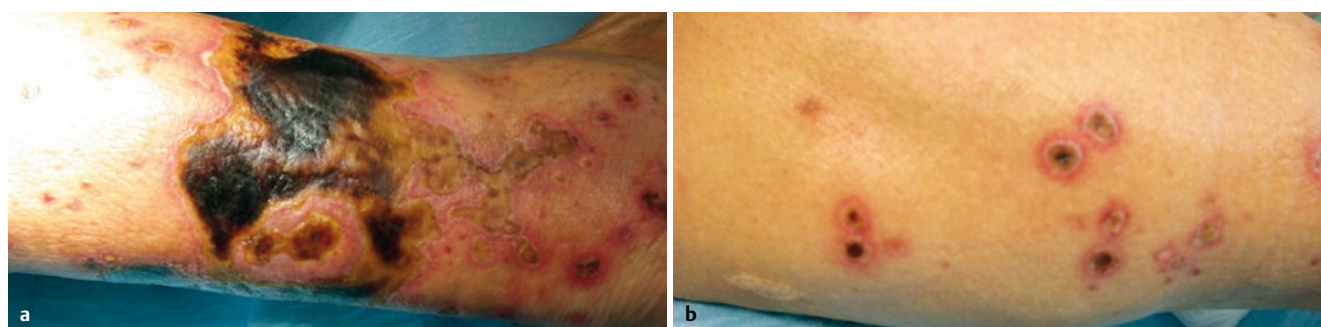
▶ **Fig. 14** Drug-associated immune complex vasculitis after ingestion of Arcoxia® (etericoxib) (a: lateral lower leg b: over the knee joint).
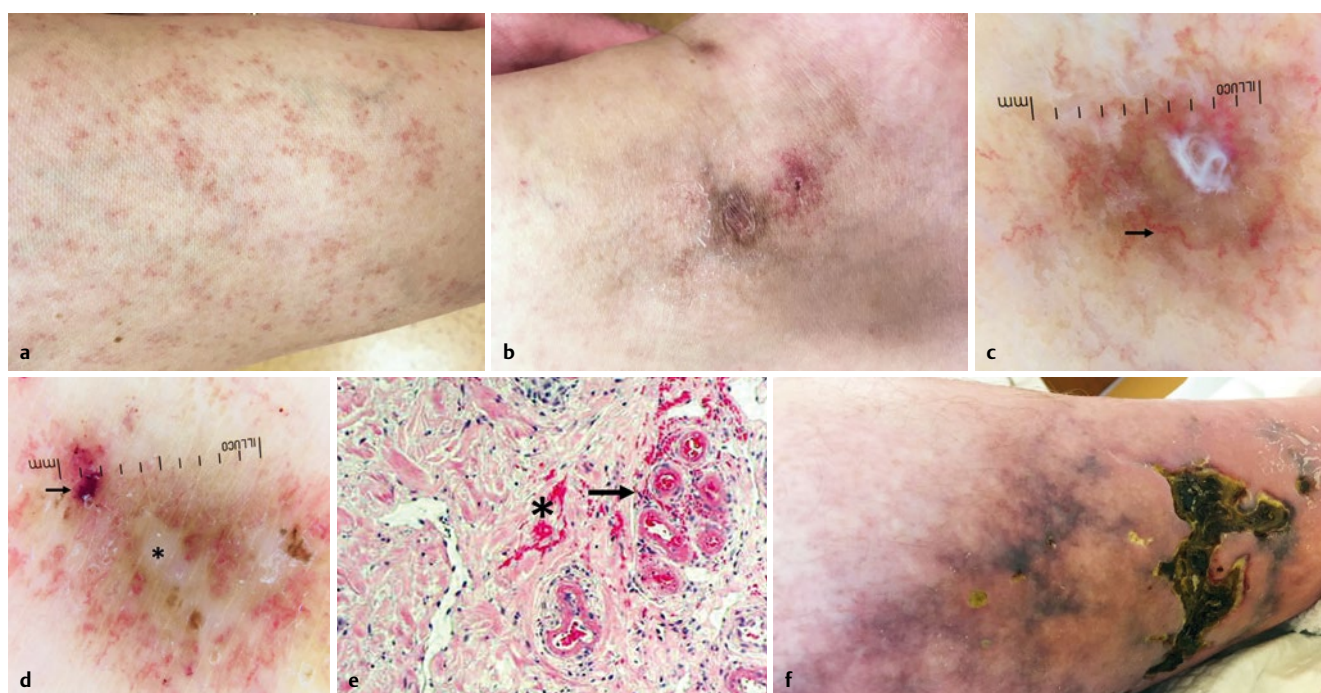
▶ **Fig. 15** Antiphospholipid syndrome (IgA type) with clinical petechial changes on the lower leg with the smallest inflammatory ulcerations, in addition to foci of atrophie blanche with hyperpigmented borders (**a** overall view, **b** detail); **c** Dermatoscopy antiphospholipid syndrome IgA subtype; a small ulcer with superimposed cream residue surrounded by linear, helical (corkscrew-like) configured vessels (arrow); **d** Dermatoscopy antiphospholipid syndrome IgA subtype; healed, porcelain-coloured areas (*), surrounded by pigment deposits and ectatic, sometimes freshly thrombosed vessels (arrow); **e** Histological picture of a vasculopathy; many small vessels in the subepidermis, arranged in groups (arrow) (corresponds to the clinical correlate of the helical (corkscrew-like) pattern with hyaline-thickened walls without perivascular infiltrate, with extravasated erythrocytes alongside them (*) (HE staining, 10x/0.25); **f** Image of the cutaneous clinical manifestation of an antiphospholipid syndrome with a haemorrhagic livid dark-red livedoid pattern in addition to bizarrely-configured, infarct-appearing ulcers with adherent necrosis.

the margin areas. If these petechiae are detected, then vasculitis should be considered as the cause of the ulceration.

Treatment

The therapeutic concept is based principally on breaking the causal chain of the disease. In most cases, this includes withdrawal of possible causative drugs [21, 42, 44]. In addition to entirely new drugs, those where the dose had been altered 14 days prior to the appearance of the skin changes should, in particular, be thoroughly considered. It is also necessary to consider comorbidities that affect the

elimination of drugs (e. g. hepatic and renal dysfunction) and interacting drugs that change the concentration of the causative drug.

It is also expedient to consider the treatment of corresponding pathogen-associated diseases.

Alongside causative treatment, symptomatic treatments such as systemic antihistamines to reduce symptom-causing mediators can be given – and particularly in cases with a foreseeable severe course (formation of haemorrhagic epidermolysis – bullae – necrosis), the use of corticosteroids as well. One of the aims of such steroid treatment is to reduce cell-borne inflammation. Local measures with steroid-containing topical products and complex decon-
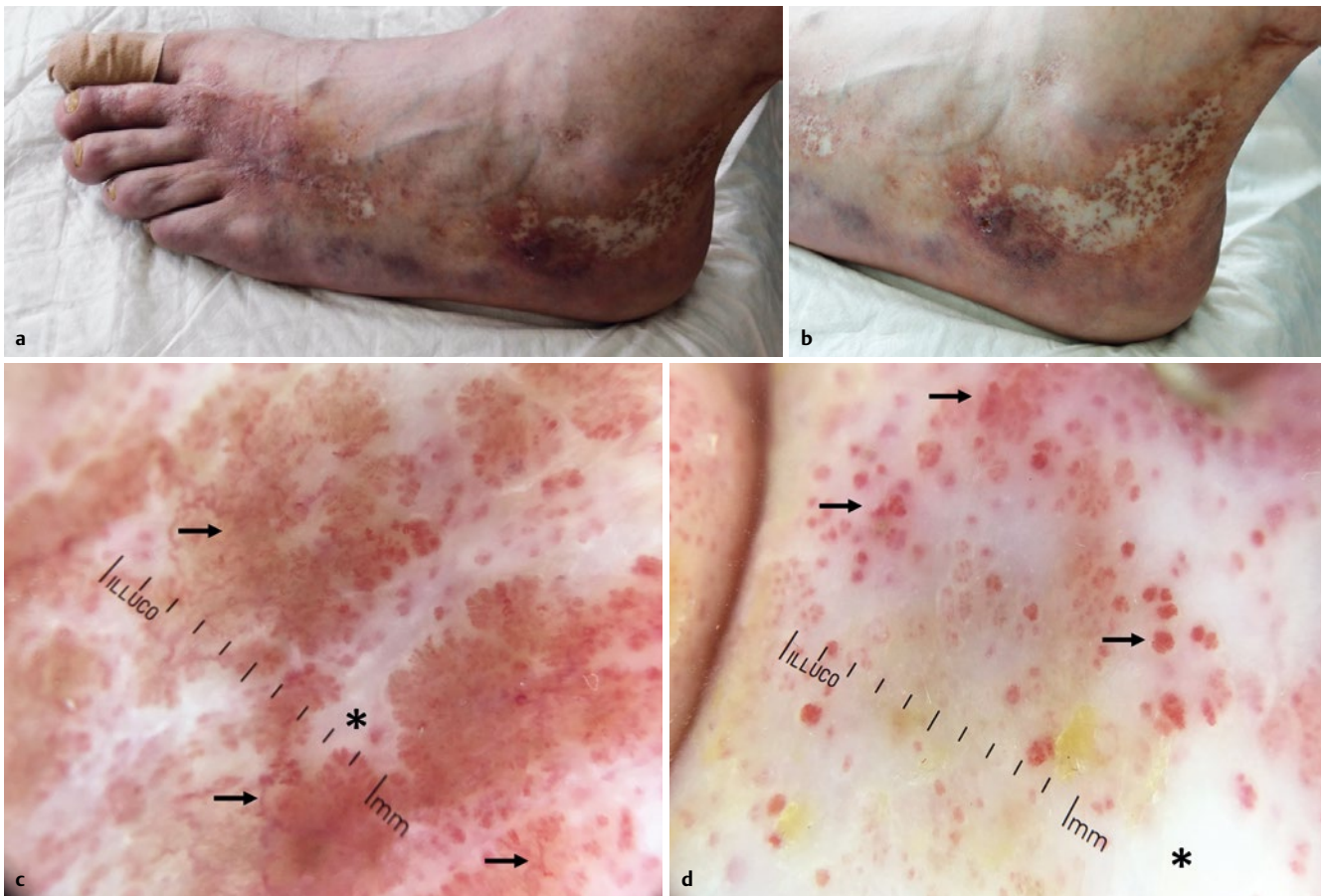
►**Fig. 16** Clinical livedoid vasculopathy with extensive foci of atrophie blanche and small, highly painful ulcerations in the forefoot-ankle region and livid-erythematous areas (**a** overall view; **b** detail); **c** Dermatoscopy livedoid vasculopathy; central porcelain-coloured atrophic areas (*), a few teleangiectatic linear vessels in the surroundings (arrows) in addition to predominantly glomerular vascular patterns. No punctate vascular patterns as evidence of an inflammatory genesis of the disease; **d** Dermatoscopy livedoid vasculopathy; disseminated glomerular vascular patterns (arrows) both in the porcelain-coloured atrophic areas (*) as well as in the surroundings.

gestion (compression, lymphatic drainage) can have a positive influence on the course [2, 19, 21, 41, 42, 44].

Recurrences are possible in the drug-associated variants of cutaneous IgM or IgG immune complex vasculitis, due to a sensitisation mechanism. Appropriate documentation should be undertaken and the patient and physicians involved in the further treatment must be informed.

In the case of the 97-year-old female patient, torasemide was discontinued and replaced by diuretics of another class. In addition, acute haemofiltration (dialysis) was carried out and corticosteroids initiated. Under this treatment, the vasculitis was halted and the skin changes began to heal, albeit very slowly.

After the initially complete withdrawal of torasemide, the vasculitis also stopped in the second case. But the drug was then cautiously re-started for an urgent cardiac indication. New vasculitic efflorescences appeared once the dose reached 2x10 mg for 2 days (►Fig. 3c–►Fig. 3d). Subsequent to this effect observed on increasing the dose, enquiry of her family doctor revealed a history of a similar event 1 year earlier. Inspection of the medical records of the first event showed a probable triggering dose of 2×10 mg/d torasemide, after which the drug had been consistent-

ly withdrawn until the second event (►Fig. 3e). This second case clearly illustrates the pure effect of reaching the equivalence zone without other influencing factors.

Discussion

Cutaneous IgM or IgG immune complex vasculitis is a vasculitis of the small vessels that, since it is skin-limited without manifestation in other organs, is described in the current classification as single-organ vasculitis (SOV). The histological picture is one of leukocytoclastic vasculitis. It is a typical immune complex disease, the cause of which is most often based on an association with a drug or an infection. The disease course shows two typical successive clinical phases, first the phase of palpable petechiae and then – if it is not stopped at this time – followed by epidermolysis in the form of vesicles and bullae and necrosis that can then become highly inflammatory ulcers. This clinical course makes the choice of differential diagnoses very wide and hence a detailed history, a painstaking clinical examination and the corresponding diagnosis are all the more important. The potential treatment depends on clarification of the cause – if causal, probably discontinuation of the causative agent or treatment of an underlying infection. The dis-

ease often subsides spontaneously even without the use of systemic corticosteroids. The prognosis is generally good; recurrences are possible, but rare.

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