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CME

Clinical Manifestations of Cutaneous Lupus Erythematosus

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- Bullous LE
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Summary
Cutaneous lupus erythematosus (CLE) is a chronic inflammatory autoimmune disease with a broad spectrum of clinical manifestations and a variable course. In numerous investigations, it has been shown that exogenous factors, such as UV-light and drugs, can induce this disease. However, not all clinical aspects can be explained and therefore, the pathogenesis of CLE is currently under extensive research. The various cutaneous manifestations of LE are divided into LE-nonspecific and LE-specific skin disease based on histologic criteria. LE-nonspecific manifestations are mostly associated with systemic LE but can also occur in other diseases and include particularly vascular skin lesions such as periungual telangiectases. LE-specific skin disease includes the subtypes of CLE such as acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), chronic cutaneous LE (CCLE), and intermittent CLE (ICLE). The subdivision of these subtypes with different prognosis and course is supported by genetic, clinical, histologic, and immunoserologic findings. The subtypes of CLE require a specific morphological and clinical analysis, which is described in the first part of this review. In the second part of this review, further diagnostic procedures and therapeutic strategies in patients with CLE are discussed.

Introduction
Lupus erythematosus (LE) is a disease with a broad spectrum of cutaneous and systemic manifestations that has been the subject of clinical research for more than a century. The term “lupus” originated in ancient Greece. Surviving writings show that Hippocrates (460–375 B.C.) described cutaneous ulcers under the term “herpes esthiomenos.” This preliminary definition of skin lesions presumably also included the disease later known as “lupus”, which was first named during the Middle Ages. The term “lupus” (lat.: wolf) evolved from a very figurative description of skin changes that developed mutilations over the course of disease. John Manardus (1462–1536) and other physicians, compared the lesions to a “hungry wolf [who] is eating the flesh closest to it.” This broad definition of “lupus” was largely limited to the lower extremities and also included various other diseases such as leprosy, tuberculosis, and skin tumors. At the beginning of the 16th century, the physician and philosopher Paracelsus (1493–1541) distinguished malignant tumors from lupus and stated “Different is consolidia lupi, different are Esthiomenos, different are fistula, different are cancri”; however, this opinion was not initially accepted.

In 1851, the term "lupus érythémateux" was introduced by Alphée Cazenave (1795–1877) to distinguish between cutaneous tuberculosis and non-tubercular skin changes in LE. In 1845, Ferdinand von Hebra (1816–1880) described butterfly erythema of the face as "seborrhoea congestiva", but it was not until 1866 that the disease was named "lupus erythematosus". The new definition of the disease also received a great amount of attention in English-speaking countries, although the classification as "lupus" was initially viewed critically. Between 1875 and 1895, Moritz Kaposi, Jonathan Hutchinson, and William Osler presented initial ideas on the pathogenesis of LE suggesting that environmental factors such as exposure to sunlight could influence the disease. In these patients, involvement of various organ systems was also reported in conjunction with lupus erythematosus and "organ lupus" was distinguished from "skin lupus." Although the complex pathogenesis of LE has not yet been fully elucidated, the distinction between systemic LE (SLE) and cutaneous LE (CLE) remains.

Introduction of the term "lupus érythémateux" by Alphéi Cazenave 1851

Distinction of "organ lupus" from "skin lupus"

Definition and classification

The various skin manifestations of LE are divided by a classification system proposed by James N. Gilliam (1936–1984), who distinguished between LE-specific and LE-nonspecific cutaneous manifestations based on histological criteria (Table 1, 2). LE-nonspecific cutaneous disease, which is often associated with SLE, includes e.g. vascular skin changes such as periungual telangiectases, livedo racemosa, thrombophlebitis, Raynaud's syndrome, and acral occlusive vasculopathy. Leukocytoclastic vasculitis can occur as palpable purpura or urticarial vasculitis (especially hypocomplementemic urticarial vasculitis). Papular mucinosis, calcinosis cutis, nonscarring alopecia, and erythema multiforme are also found defined an LE-non-specific manifestations. LE-specific cutaneous disease includes the different subtypes of CLE and has been divided 2004 into four subtypes based on genetic, clinical, histological, and immunoserologic findings (Table 1): acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), chronic cutaneous LE (CCLE) and intermittent curtaneous LE (ICLE). Based on this revised classification, CCLE includes the variants discoid LE (DLE), LE profundus (LEP) and chilblain LE (CHLE). LE tumidus (LET) is listed as a separate entity (ICLE) on this basis of new clinical, histological, and photobiological findings as well as its benign, intermittent course. Other rare morphological or localized forms, especially in DLE, such as LE labialis and LE vermiculatus, are mentioned in the literature, but are no longer described as separate entities.

Systemic organ manifestation can occur, with varying probability, in any subtype of CLE. Fewer than 5 % of patients with DLE, the most common subtype of CCLE, develop SLE. In contrast, 10 % to 15 % of SCLE patients can have further, usually

Table 1: LE-specific skin disease – subtypes of cutaneous lupus erythematosus (CLE).

Acute cutaneous lupus erythematosus (ACLE)
Localized form
Generalized form
Subacute cutaneous lupus erythematosus (SCLE)
Annular form
Papulosquamous form
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Localized form
Disseminated form
Lupus erythematosus profundus (LEP; Synonym: LE panniculitis)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

Table 2: LE-nonspecific skin manifestations, particularly associated with systemic lupus erythematosus (SLE).

Leukocytoclastic vasculitis
Palpable purpura
Urticarial vasculitis
Livedo racemosa
Thrombophlebitis
Occlusive Vasculopathy
Raynaud's syndrome
Periungual telangiectases
Diffuse nonscarring alopecia ("lupus hair")
Calcinosis cutis
Papular mucinosis
Erythema multiforme

mild, organ manifestations such as arthritis. About 50 % of patients with SCLE meet the criteria of the American College of Rheumatology (ACR), although they do not suffer from SLE. According to the ACR criteria, which were established in 1982 and updated in 1997, a diagnosis of SLE is considered certain if four or more of the eleven criteria are fulfilled. Four of the criteria include dermatological signs: "butterfly erythema", discoid lesions, mucosal ulcers, and increased photosensitivity (see below). This results in overdiagnosing SLE in a number of patients who have mainly skin changes, but do not present with systemic disease. The overestimation of dermatological criteria in the diagnosis of SLE has been criticized and an interdisciplinary re-evaluation of the ACR criteria will include dermatological control groups.

Overestimation of the dermatological ACR criteria

Clinical symptoms

The various subtypes of CLE can be distinguished by genetic, clinical, histological, and immunoserologic characteristics (Table 3–10).

Acute cutaneous lupus erythematosus (ACLE) (Table 3)

ACLE can occur as localized or generalized disease. The more common localized form is characterized by "butterfly erythema" which usually spreads symmetrically over the bridge of the nose and the cheeks, typically sparing the nasolabial folds; the sharply bordered erythema is frequently mistaken by patients for sunburn (Figure 1a). Smaller erythematous lesions can initially appear which later merge and develop into papules and plaques, in addition, severe edema, scaling, erosions, and crusts may occur. The histological changes seen in ACLE are less pronounced than in other subtypes of CLE and usually show only a discrete interface dermatitis with minimal vacuolization of the basement membrane. Differential diagnosis includes rosacea, seborrheic eczema, perioral dermatitis, tinea faciei, and erysipelas.

Butterfly erythema

Generalized ACLE usually presents with morbilliform or maculopapular, sometimes pruritic, exanthema, consisting of multiple, erythematous confluent macules and

Generalized exanthema

Table 3: Acute cutaneous lupus erythematosus (ACLE).

Clinical signs

Localized form

- "Butterfly erythema": sharply and regularly bordered erythema, usually symmetrical pattern on the cheeks and bridge of the nose, sparing the nasolabial folds
- In 20–60 % of SLE, in 15 % of SCLE

Generalized form

- Exanthema: morbilliform or maculopapular affecting skin of entire body, palms/soles and interphalangeal extensor aspects of the fingers, erythema of nail fold and telangiectases, red lunula; rarely transformation into TEN
- Enanthema:
  - o Erythema, erosions, superficial ulcerations in 7–45 % with acute flare
  - o Localization: hard palate > gingiva and buccal mucosa
  - o Histology: LE-specific ("interface mucositis") or LE-nonspecific
- Erosive/crusty cheilitis

Specific features

- High photosensitivity
- Healing without scarring
- Temporary postinflammatory hyperpigmentation
- Diffuse thinning of the hair along the hairline ("lupus hair")
- Associated with high level of disease activity in SLE
- In 40–90 % antibodies to dsDNA and in 10–30 % anti-Sm antibodies

Differential diagnosis

- Localized form: rosacea, seborrheic eczema, perioral dermatitis, tinea faciei, erysipelas
- Generalized form: dermatomyositis, viral and drug-induced rash, erythema multiforme, TEN

Modified after Kuhn et al. 2006

papules (Figure 1b). The rash spreads out symmetrically over the entire body, often also involving the palmar and plantar surfaces as well as the backs of the hands and extensor surfaces of the fingers. On the distal phalanges of the fingers and toes there is patchy or diffuse erythema, sometimes with small hemorrhagic areas. The skin changes in ACLE typically do not affect the knuckles but, unlike dermatomyositis, involve the interphalangeal areas. At the nail fold periungual erythema and telangiectases can occur and are often associated with a red lunula on the nail. Usually, the generalized form of ACLE is associated with increased disease activity of SLE and is often accompanied by mucosal changes affecting the mouth (hard palate, buccal mucosa, gingiva, uvula), nose, pharynx, and vagina. Ulcerous/aphthous mucosal lesions are usually painful while erythematous mucosal lesions are often painless (Figure 1c). The lips may present with erosive, crusty cheilitis. In severely acute ACLE, even a toxic epidermal necrolysis (TEN)-like picture may even develop. Localized and generalized forms of ACLE both heal without scarring, although temporary postinflammatory hyperpigmentation is possible. Diffuse thinning of the hair ("lupus hair") can occur along the hairline. Differential diagnosis in generalized ACLE includes dermatomyositis, viral and drug rash, erythema multiforme, and TEN.

Subacute cutaneous lupus erythematosus (SCLE) (Table 4)
The most common extra-cutaneous symptoms associated with SCLE are arthritis and myalgia. Cutaneous manifestations show a symmetrical distribution: a) annular

Table 4: Subacute cutaneous lupus erythematosus (SCLE).

Clinical signs

Annular form
- Ring-like or oval, erythematous plaques with training scale and central clearing

Papulosquamous form
- Papulosquamous plaques, possibly transforming into clinical picture resembling psoriasis

Combination of both forms is possible

Special features
- High photosensitivity
- Polycyclic confluence of solitary lesions
- Predilection sites: symmetrical involvement of sun-exposed areas (V-shaped area of upper chest, back, extensor surfaces of arms, lateral and posterior neck, face less often affected
- No scarring; possible hyperpigmentation or – more often – vitiligo-like depigmentation
- Mild systemic symptoms (arthralgia, myalgia)
  Transformation into SLE with moderate disease activity in 10–15 % (ACR criteria formally met in 50 %)
- ANA in 60–80 %
- Anti-Ro/SSA antibodies 70–90 %; anti-La/SSB antibodies in 30–50 %
- Positive rheumatoid factor (> 30 %)
- Immunogenetic disposition: HLA-A1, -B8, -DR3
- Associated disorders: Sjögren's syndrome, autoimmune thyroiditis

Differential diagnosis
- Psoriasis vulgaris, tinea corporis, mycosis fungoides, erythema annulare centrifugum, dermatomyositis, pityriasis rubra pilaris, nummular eczema, drug-induced rash, seborrheic eczema, erythema multiforme /TEN, erythema gyratum repens

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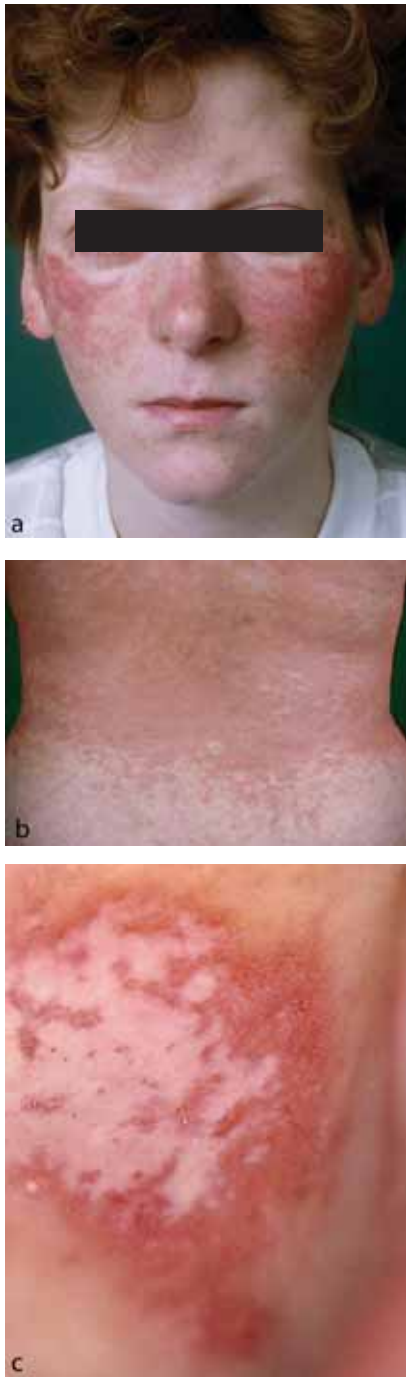

Figure 1: ACLE: Malar/butterfly rash in SLE (a); confluent, maculo-papular exanthema in SLE (back) (b); aphthoid ulceration with peripheral erythema on hard palate in SLE (c).

Annular plaques

Papulosquamous plaques

Sun-exposed areas

In 10–15 % of patients SCLE develops into a mild form of systemic lupus erythematosus

Anti-Ro/SSA and/or anti-La/SSB antibodies

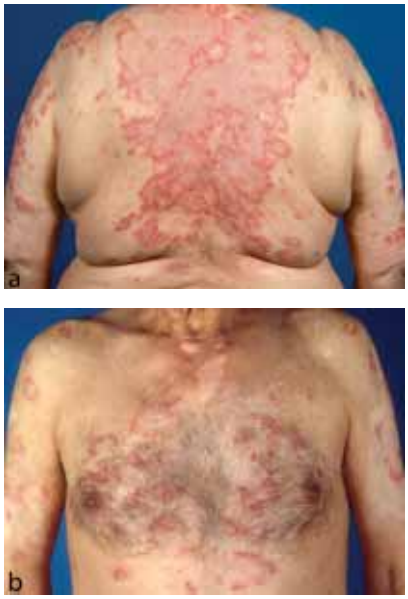

Figure 2: SCLE: Annular subtype with polycyclic confluence in sun-exposed areas (a); annular subtype with active plaques and vitiligo-like hypopigmentation after resolution (b).

Discoid plaques

Scarring alopecia

Köbner phenomenon

erythematous plaques with trailing scale and central clearing or b) papulosquamous, confluent plaques, which may mimic psoriasis. Both forms may be found in the same patient. SCLE is characterized by polycyclic merging of annular lesions resulting in a garland-like appearance (Figure 2a). Patients with SCLE have marked photosensitivity, and cutaneous changes are typically located in sun-exposed areas such as the lateral and posterior neck, the V-area of the upper trunk, and the extensor surfaces of the upper arms and forearms. Facial lesions are rare, and the "chin shadow" is typically spared. The cutaneous lesions heal without scarring and may result in vitiligo-like hypopigmentation, which may persist in particular when therapy is delayed (Figure 2b). Similar to ACLE, a TEN-like picture can develop, especially after UV exposure. In rare instances, there are bullous changes in the margins of SCLE lesions. In the majority of patients, SCLE shows recurrent episodes; in 10 to 15 % it develops into a moderate form of SLE. SCLE may also be associated with DLE or ACLE. LE-nonspecific cutaneous skin changes sometimes occur in SCLE, and lichen planus and morphea have also been reported. SCLE is characterized by certain immunogenetic factors (HLA-A1, -B8, -DR3), the presence of anti-Ro/SSA and/or anti-La/SSB antibodies, and an association with positive rheumatoid factor in more than 30 % of patients. Rowell's syndrome, with skin changes resembling erythema multiforme, ANA with speckled fluorescence, anti-Ro/SSA antibodies, and positive rheumatoid factor, is probably not a distinct entity. Since Rowell's syndrome shares many clinical and serological features, it is now widely considered to be a variant of SCLE. Unlike other subtypes of CLE, SCLE is more often induced by drugs, e.g., including hydrochlorothiazide, ACE inhibitors, and terbinafine. In drug-induced SCLE, skin lesions can be more widespread with extension to the lower extremities; anti-histone antibodies may be detected in serological testing. SCLE has also been described as a paraneoplastic syndrome, and therefore a search should be made in patients who do not respond to conventional therapy for underlying malignancies (most commonly bronchial or breast carcinoma, although stomach, uterine, liver and laryngeal carcinoma as well as lymphoma are reported). In addition to typical HLA predisposition, SCLE shows a significant association with a single nucleotide polymorphism in the TNF-alpha gene promoter (-308A) that causes high levels of TNF-alpha expression.

Differential diagnosis in SCLE includes psoriasis vulgaris, tinea corporis, mycosis fungoides, erythema annulare centrifugum, dermatomyositis, pityriasis rubra pilaris, nummular eczema, drug-induced rash, seborrheic eczema, erythema multiforme, and erythema gyratum repens.

Chronic cutaneous lupus erythematosus (CCLE)

CCLE includes three different forms of disease: discoid LE (DLE), LE profundus (LEP), and chilblain LE (CHLE).

Discoid lupus erythematosus (DLE) (Table 5)

DLE is the most common form of CCLE. Characteristic lesions are sharply-bordered, erythematous, keratotic plaques that grow peripherally and show a coin-shaped ("discoid") appearance. The center of the lesion often contains firmly attached areas of white, follicular hyperkeratosis with hyperesthesia; these are painful if lifted manually (the "carpet tack sign"). Over the course of disease, DLE plaques become atrophic and scar with central depigmentation and peripheral hyperpigmentation. Hair follicles are irreversibly damaged and hair-bearing areas such as the scalp, eyebrows, and bearded region of the face develop scarring alopecia (Figure 3a). The sites of predilection of DLE are the face and scalp (localized form), especially the cheeks, forehead, ears, nose, and upper lip. Characteristic pitting scars can result perioorally. Especially in men with involvement of the nose or ears scarring can lead to mutilation with considerable disfigurement. DLE, involving the upper part of the trunk and the extensor surfaces of the extremities (disseminated form) (Figure 3b) is less common. Involvement of palmar and plantar regions in DLE causes heavy pain. Painful lesions of the oral mucosa, especially the buccal mucosa, are relatively uncommon. Often lesions of the buccal mucosa resemble lichen planus, but tend to have a radial, brush-like appearance and usually radiate from a central inflammatory erythema or erosion. Exposure to the sun or irritating stimuli (Köbner phenomenon) can provoke or exacerbate disease. DLE can co-exist with all other subtypes of CLE.

Table 5: Discoid lupus erythematosus (DLE).

Clinical signs

Localized form (ca. 80 %)
- Face and scalp

Disseminated form (ca. 20 %)
- Also upper trunk and arms

DLE of oral mucosa
- Buccal mucosa > palate

Special Features
- Most common form of CCLE
- Discoid erythematous plaques with firmly adherent follicular hyperkeratoses and hyperesthesia
- Active border with erythema and hyperpigmentation
- Scarring with central atrophy and hypopigmentation, scarring alopecia in hair-bearing areas
- Discoid lesions about vermillion border > buccal mucosa
- Mutilation around nose and mouth, perioral pitted scars
- Provocation by irritative stimuli (Köbner phenomenon) possible
- High-titer ANA in about 5 %, generally no anti-dsDNA antibodies, rarely antibodies to Ro/SSA or U1-RNP
- Possible association with SLE and all subtypes of CLE

Differential diagnosis
- Actinic keratosis, tinea faciei, sarcoidosis, lupus vulgaris

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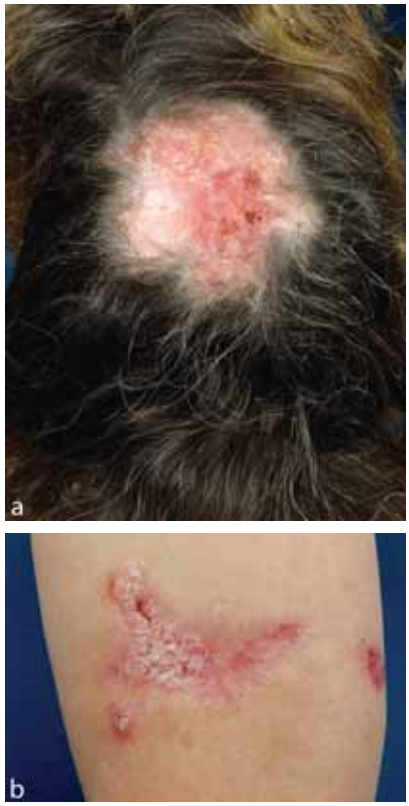

Figure 3: DLE: Erythema, hyperkeratosis, and scarring alopecia (a); peripheral erythema, central hyperkeratosis and scarring (upper arm) (b).

Since discoid skin lesions are also found in SLE, systemic disease should be ruled out during the initial visit. Although the possibility of drug-induced DLE is not widely accepted in the literature, Japanese studies have reported skin changes mimicking DLE arising from fluorouracil therapy; these observations have been confirmed in a mouse model. Recently, skin changes resembling DLE were reported after infliximab therapy in a patient with rheumatoid arthritis.
Differential diagnosis in DLE includes actinic keratosis, tinea faciei, sarcoidosis, and lupus vulgaris.
Two additional special forms of DLE are distinguished: LE hypertrophicus/verrucosus (LEHV), which involves severe hyperkeratosis, has a chronic course and is often resistant to treatment; and the extremely rare LE telangiectodes with reticular telangiectases that may merge to form large purpura-like plaques.

Subcutaneous nodules and plaques

Lupus erythematosus profundus (LEP) (Table 6)

Lobular panniculitis

LEP (synonym: lupus panniculitis) is characterized clinically by painful (later asymptomatic) subcutaneous, nodules and plaques that may later adhere to the overlying skin. Histology shows lobular panniculitis with a dense inflammatory infiltrate of lymphocytes and plasma cells as well as mucin deposits between fat cells. The sites of predilection in LEP are the gluteal region and thighs as well as the upper extremities. The face, scalp, and chest can also be affected; rarely, the salivary glands are involved. Occasionally, periorbital edema is an initial presenting symptom before typical skin changes appear. The nodules resolve with deep lipatrophy over the course of disease (Figure 4); they can ulcerate and form deeply indented scars that can be a major cosmetic concern to patients. Calcification may occur in older lesions. Irritative stimuli (but not UV exposure) can induce LEP. In about 70 % of patients, LEP can be associated with DLE. In 35–50%, ACR criteria are formally met in patients with LEP, but an association with SLE is common.
Differential diagnosis includes various forms of panniculitis, malignant lymphoma (especially subcutaneous panniculitic T-cell lymphoma), subcutaneous sarcoidosis, panarteritis nodosa, morphea profunda, as well as subcutaneous granuloma annulare.

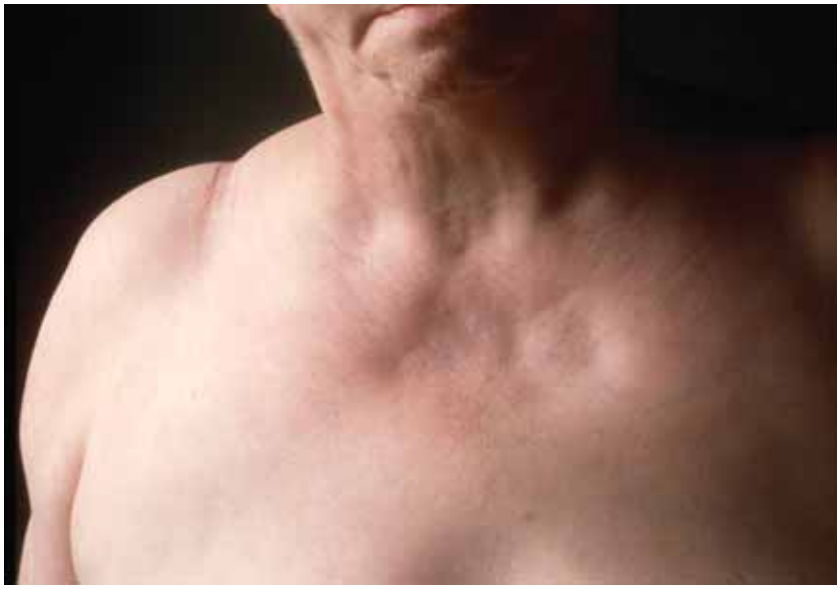

Figure 4: LEP: Lipatrophy after resolution (chin, neck, upper chest).

Table 6: Lupus erythematodes profundus (LEP).

Clinical signs and special features

- Subcutaneous nodules and plaques, later adhering to overlying skin
- Lesional surface: reddened with inflammation, unchanged or concomitant DLE
- Predilection sites: face, shoulders, upper arms, chest, buttocks, thighs, hips
- Possible calcification
- Healing results in scarring and lipatrophy of deep tissues
- ANA positive in up to 75 %; generally no anti-dsDNA antibodies
- ACR criteria formally met in 35–50 %, an association with SLE is less common

Differential diagnosis

- Various forms of panniculitis, malignant lymphoma (especially subcutaneous panniculitic T-cell lymphoma), subcutaneous sarcoidosis, panarteritis nodosa, morphea profunda, subcutaneous granuloma annulare

Modified after Kuhn et al. 2006

Deep lipatrophy after resolution of LEP

Chilblain lupus erythematosus (CHLE) (Table 7)

Livid plaques and puffy nodules in acral areas

Chilblain LE (CHLE) is characterized by tender, bluish plaques and nodules in cold-exposed areas (Figure 5). Edematous skin and nodules may have central erosions or ulcerations affecting the acral surfaces, especially the fingers, toes, heels, nose, and ears. CHLE appears during cold and damp times of the year or after a critical drop in temperature, and is often difficult to distinguish clinically and histologically from pernio ("chilblains"). Serological parameters, such as the presence of ANA and anti-Ro/SSA antibodies as well as a positive rheumatoid factor and a positive lesional direct immunofluorescence can support the diagnosis of CHLE.

Often difficult to distinguish CHLE histologically from pernio ("chilblains")

Differential diagnosis includes pernio, lupus pernio (chronic form of cutaneous sarcoidosis affecting acral surfaces) and acral vasculitis/vasculopathy.

A new genodermatosis has recently been described under the name "familial chilblain lupus." The gene locus for this disease is mapped on the short arm of chromosome 3. In a large German, non-consanguineous family, "chilblain lupus" was found in 18

Table 7: Chilblain lupus erythematosus (CHLE).

Clinical signs and special features
• Tender, bright red edema and puffy nodules sometimes with central erosion and ulceration
• Predilection sites: cold-exposed acral areas (dorsal and marginal areas of the fingers, tips of the toes, heels, ears, nose)
• ANA, anti-Ro/SSA antibodies and positive rheumatoid factor are variable, usually no anti-dsDNA antibodies
• Associated with SLE in ca. 20 %
Differential diagnosis
• Pernio (chilblains), lupus pernio (chronic form of skin sarcoidosis of the acral regions), acral vasculitis/vasculopathy

Modified after Kuhn et al. 2006

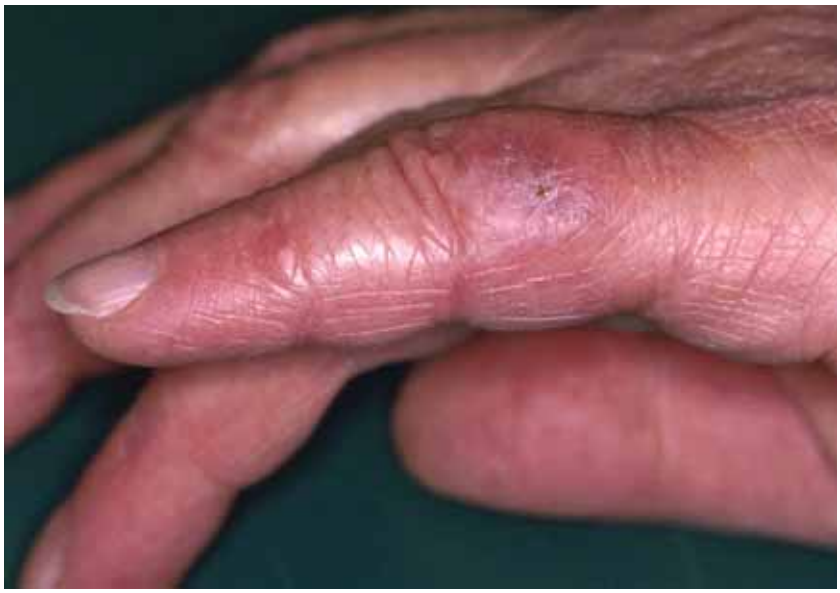

Figure 5: CHLE: Livid infiltration with central crusting (Dig. II).

family members (men and women) spanning 5 generations with manifestation in early childhood. Aicardi-Goutières syndrome – characterized by progressive encephalopathy – along with signs of SLE often also presents with skin changes resembling those found in chilblain lupus, and is also mapped on the short arm of chromosome 3. In Aicardi-Goutières syndrome, mutations on the TREX-1 gene are described; this gene apparently also plays a role in "familial chilblain lupus." "Familial chilblain lupus" is the first description of a monogenic hereditary form of CLE.

"Familial chilblain lupus"

Intermittent cutaneous lupus erythematosus (ICLE) (Table 8)

In 2004, LET was distinguished from CCLE on the basis of new clinical and scientific findings that could identify specific clinical, histological, and photobiological criteria. Also due to its benign, intermittent course, LET was distinguished from CCLE and described as the separate entity ICLE. Clinically, LET is characterized by sharply-bordered, "succulent", urticaria-like erythematous papules and plaques with a smooth surface and without epidermal involvement that occur as solitary lesions or in groups. LET lesions are usually found on sun-exposed areas (face, upper back, upper chest, extensor surfaces of the upper arms) and may be annular, centrifugal, or crescent-shaped (Figure 6). In very rare instances, they can also spread along the Blaschko's lines. LET heals without scarring, hypopigmentation, or hyperpigmentation; rarely, patients may also present with DLE. The course of the disease is

Succulent, urticaria-like papules and plaques

No epidermal involvement

Table 8: Lupus erythematosus tumidus (LET).

Clinical signs
- Succulent, urticaria-like, erythematous plaques with a smooth surface and no epidermal involvement
- Predilection sites: sun-exposed areas (especially the face, upper trunk, and extensor surfaces of the arms)
- Lesions often in annular arrangement or sometimes semilunar pattern
- Heals without scarring or pigmentary changes

Special features
- High photosensitivity (in > 70 % positive photo-provocation test)
- ANA positive in 10–30 %, anti-Ro/SSA and anti-La/SSB antibodies in ca. 5 %
- Variable course with very good prognosis, possible spontaneous resolution

Differential diagnosis
- Lymphocytic infiltration Jessner-Kanof or erythema arciforme et palpabile (see text), polymorphic light eruption, pseudolymphoma, B-cell lymphoma, plaque-like cutaneous mucinosis, solar urticaria

Modified after Kuhn et al. 2006

intermittent as individual lesions may persist for months or resolve spontaneously without residual defects. Histologically, there is a dense perivascular and periadnexal lymphocytic infiltrate. In contrast to other subtypes of CLE, the dermoepidermal junction is not affected in LET. Abundant mucin deposition is found between collagen fibers in the subepidermal tissue and is visibile with colloidal iron stain. Occasionally, edema is also visible in the papillary dermis.

Anti-Ro/SSA and anti-La/SSB antibodies are detected in about 5 % of patients with LET. There are only isolated case reports in the literature of an association with SLE. Due to its high photosensitivity, the detection of ANA in about 10–30% of patients, and occasional arthritis, it is possible that LET patients meet four ACR criteria for SLE (see above). In the majority of patients, LET has a very good prognosis with a variable course. Recently, there was a report of infliximab-induced LET in a woman with rheumatoid arthritis.

High photosensitivity

Very good prognosis

Differential diagnosis includes polymorphic light eruption, pseudolymphoma, B-cell lymphoma, plaque-like cutaneous mucinosis, and solar urticaria. It is currently being

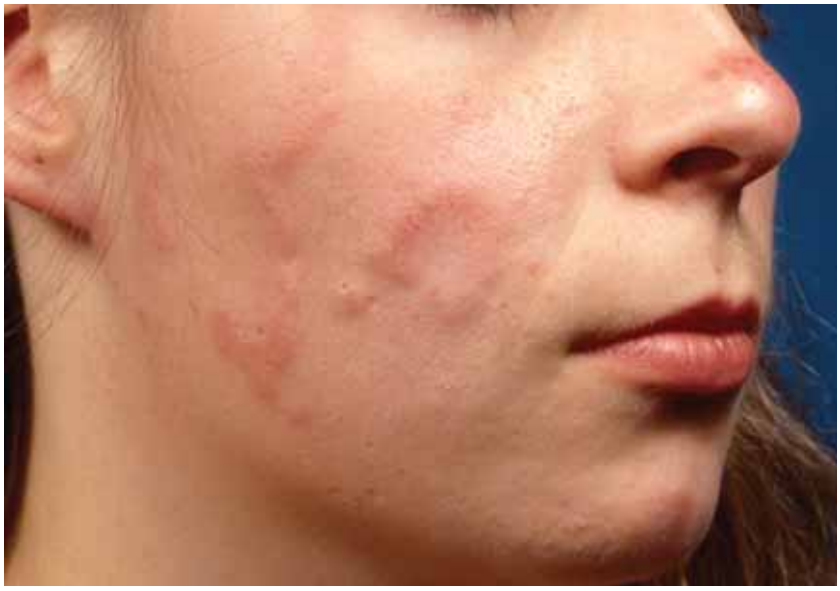

Figure 6: LET: Succulent, erythematous papules and plaques in semilunar and annular distribution.

discussed whether lymphocytic infiltration (Jessner-Kanof) and its variant, erythema arciforme et palpabile, is a separate entity or should be classified as LET.

Bullous lupus erythematosus (BLE) (Table 9)

Bullous LE (BLE) is is a rare subepidermal bullous disorder that is usually associated with acute and severe forms of SLE. Clinically, BLE lesions may appear as solitary small vesicles or groups of vesicles, or as large tense blisters on erythematous or normal skin (Figure 7). Over the course of disease hyperpigmentation, milia, and scarring can occur. Histology shows a subepidermal blister and neutrophilic microabscesses in the papillae. Various tests (direct and indirect immunofluorescence, immunoelectron microscopy) may reveal granular or linear deposits of IgG, and less often IgM and IgA as well as complement components (C3, C4) along the basement membrane zone or lamina densa. In part of the patients, autoantibodies against type VII collagen are detected.

Association with high disease activity of SLE

BLE should be distinguished from bullous disorders arising from pre-existing skin lesions in ACLE or at the margins of SCLE lesions, which show characteristic histological changes (interface dermatitis) of CLE.

Recently, vesiculobullous skin changes have been described as "TEN-like" ACLE and "TEN-like" SCLE corresponding clinically to classic TEN. However, they are not drug-induced, rather they may be triggered, for example by UV exposure. The name "Acute Syndrome of Apoptotic Pan-Epidermolysis (ASAP)" has been suggested to describe them. UV exposure leads to accumulation of apoptotic keratinocytes in the skin of patients with CLE, possibly as a result of abnormal clearance.

"TEN-like" ACLE and "TEN-like" SCLE

Table 9: Bullous lupus erythematosus (BLE).

Clinical signs and special features
• Solitary small vesicles or groups of vesicles, or larger, firm subepidermal blisters on erythematous or normal skin
• Healing with hyperpigmentation, milia, possible scarring
• Granular or linear deposits of IgG, IgM, IgA and complement along the basement membrane zone
• Antibodies to type VII collagen usually present
• Association with high disease activity of SLE
Differential diagnosis
• Epidermolysis bullosa acquisita, dermatitis herpetiformis (Duhring's disease), bullous pemphigoid, linear IgA-dermatosis, drug-induced bullous disorder, porphyria cutanea tarda

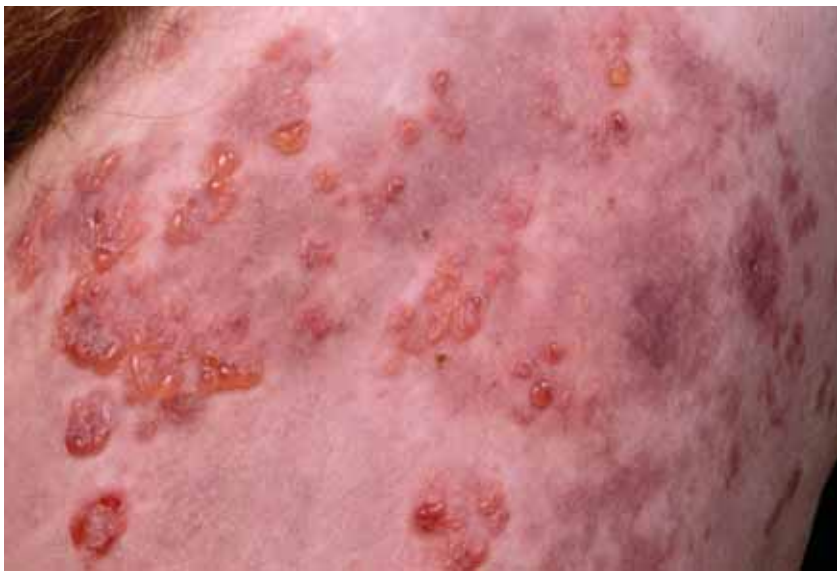

Figure 7: BLE: Tense grouped blisters on livid skin, partly annular arranged, in SLE (upper leg).

Differential diagnosis in BLE includes epidermolysis bullosa acquisita, dermatitis herpetiformis (Duhring's disease), bullous pemphigoid, linear IgA-dermatosis, drug-induced bullous disorder, and porphyria cutanea tarda.

Neonatal lupus erythematosus (NLE) (Table 10)

Neonatal LE (NLE) is caused by transplacental transmission of maternal antibodies to the fetus. A characteristic and diagnostically relevant feature is the presence of anti-Ro/SSA and/or anti-La/SSB antibodies in the mother and fetus. Rarely, anti-U1-RNP antibodies are also found. Furthermore, antibodies to calreticulin, alpha-fodrin, type M1 muscarinic receptors, serotonin receptors (5-HT4 subtype), a 57kDa protein, and a 75kDa phosphoprotein have also been described in NLE.

Annular plaques as in SCLE

NLE presents with erythematous macules and papules and, similar to SCLE, annular plaques with a trailing scale, mainly on sun-exposed areas such as face, scalp, trunk and extremities (Figure 8). Skin lesions usually appear during the first weeks of life, although they may be present at birth. Spontaneous resolution occurs within six months, along with the disappearance of the antibodies. In rare circumstances, resolution of the NLE skin rash may be followed by postinflammatory hyperpigmentation, telangiectases or scarring.

Anti-Ro/SSA autoantibodies have a distinct affinity for the conduction system of the fetal heart and can directly damage it, resulting in congenital atrioventricular (AV) block. Congenital AV block may occur as early as in the second or third trimester of pregnancy and is an irreversible condition potentially requiring the implantation of

Table 10: Neonatal lupus erythematosus (NLE).

Clinical signs and special featues
• Transmission of maternal anti-Ro/SSA and/or anti-La/SSB antibodies through the placenta to the fetus
• Erythematous macules, papules, and annular plaques as in SCLE
• Skin changes at birth or in first weeks of life
• Resolution of NLE skin lesions within 6 months parallel to disappearance of antibodies
• Irreversible cardiac damage possible (congenital AV block, lethal in ca. 14 %) as well as hematological and hepatic abnormalities
• Mothers with anti-Ro/SSA antibodies: development of NLE in ca. 2 %; mothers are asymptomatic or have SCLE, Sjögren's syndrome, or undifferentiated connective tissue disease
• 25 % risk of second child with NLE, if one child already born with NLE
• Serial echocardiographic studies to rule out fetal bradyarrhythmia, especially in weeks 16–24 of pregnancy

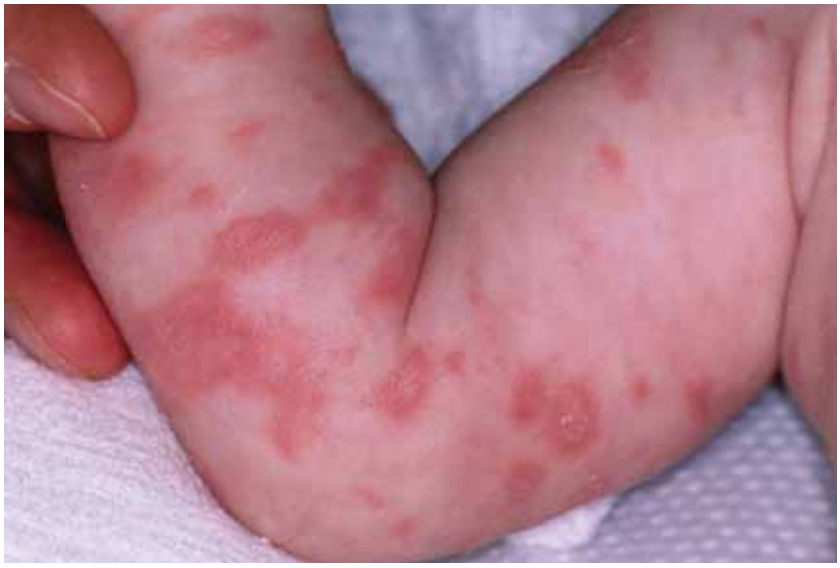

Figure 8: NLE: Annular erythema with central scaling (upper arm) as in SCLE.

a pacemaker. 14 % of children with congenital AV block die within the first three months of life. Most children who survive the neonatal period have normal lives without related health problems. However, children with NLE can develop other autoimmune diseases; follow-up observation is necessary. During pregnancy, women with anti-Ro/SSA antibodies should be carefully monitored (preferably in a risk consultation). Regular serial echocardiographic studies are necessary to rule out fetal bradyarrhythmia also at later stages of the disease. Hematologic (thrombocytopenia, leukopenia) and hepatic (transaminase elevation, hyperbilirubinemia, acute liver failure) abnormalities are less common than heart and dermatological symptoms.

The risk of NLE is about 2 % in children born to mothers with anti-Ro/SSA antibodies. In women, who have given birth to one child with NLE, the risk of a second child with NLE increases to 25 %. The mother may be clinically healthy or may have an autoimmune disease (e.g., SCLE, Sjögren's syndrome, mixed connective tissue disease, undifferentiated connective tissue disease); the risk of having a child with NLE is greater in women who exhibit clinical signs of disease.

In addition to NLE, any subtype of CLE can appear during childhood; however, all subtypes of CLE are extremely rare in childhood and are not distinguishable clinically or histologically from adult forms of the disease.

Conclusion

Cutaneous manifestations are seen in 72–85 % of patients with SLE, can occur at any stage of the disease, irrespective of disease activity, and indeed are the first sign of disease in 23–28 %. In addition to characteristic discoid lesions, which are included in the ACR criteria for diagnosing SLE, there are a variety of other LE-specific skin manifestations known as CLE and its subtypes ACLE, SCLE, CCLE, and ICLE. CCLE is further divided in the subtypes DLE, LEP, and CHLE. The subtypes of CLE are often not distinguished by any other medical specialty and thus not defined as distinct disorders. CLE is therefore a dermatological domain, even though close interdisciplinary cooperation is needed at the time of diagnosis as well as over the course of disease to exclude any progression to SLE. The 11 criteria developed by the ACR in 1982 can be helpful in distinguishing CLE from SLE, but considering the overestimation of dermatological criteria (butterfly rash, photosensitivity, discoid lesions, and oral ulcers) 4 criteria for a diagnosis of SLE are fulfilled too often. The recent report of a monogenic inherited "familial chilblain lupus" raises hope that future research will help further elucidate the genetic factors that predispose individuals to various forms of CLE as well as SLE. Novel therapeutic strategies that are now available such as biologics have shown promising results of i.e. lupus nephritis in isolated case reports and provide hope of improved disease management also in CLE. Part 2 of this review will address the diagnosis and management of CLE.

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Conflict of interest

None.

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Fragen zur Zertifizierung durch die DDA

1. Welche Aussage trifft nicht zu?

a) Die diffuse Ausdünnung der Haare am Haaransatz beim ACLE wird als „Lupus-Haar" bezeichnet.
b) Photosensitivität ist ein charakteristisches Merkmal des ACLE.
c) Der ACLE heilt ohne Narben ab.
d) Eine typische Lokalisation des ACLE sind die Fingerknöchel.
e) Beim ACLE ist die Schleimhaut des harten Gaumens häufiger als die Wangenschleimhaut befallen.

2. Welche Aussage trifft nicht zu?

a) Der kongenitale AV-Block ist beim NLE reversibel.
b) Die Hautveränderungen des NLE bilden sich innerhalb von 6 Monaten zurück.
c) Beim NLE ist das Vorhandensein von anti-Ro/SSA Antikörpern charakteristisch.
d) Die anti-Ro/SSA Antikörper des NLE bilden sich innerhalb von 6 Monaten zurück.
e) Beim NLE können Blutbildveränderungen und Erhöhungen der Leberwerte auftreten.

3. Welche Aussage trifft nicht zu?

Bei einer Patientin bestehen seit 3 Monaten ringförmige, schuppende Hautveränderungen, die vom Hausarzt mit einer antimykotischen Salbe behandelt worden sind. Der Dermatologe äußerte die Verdachtsdiagnose eines SCLE. Folgende Befunde würden die Diagnose unterstützen:

a) ein positiver Rheumafaktor
b) ein positives Tapeziernagelphänomen
c) Nachweis von anti-Ro/SSA Antikörpern
d) der Kinnschatten ist ausgespart
e) eine hohe Photosensitivität

4. Welche Aussage trifft nicht zu?

a) Die Psoriasis ist eine Differenzialdiagnose des SCLE.
b) Der SCLE geht in 50 % in einen SLE über.
c) Das Gesicht ist beim SCLE häufig befallen.
d) Der SCLE zeigt eine charakteristische HLA-Assoziation.
e) LE-unspezifische Hautveränderungen können beim SCLE vorkommen.

5. Welche Aussage trifft nicht zu?

a) Der DLE verursacht an Palmae und Plantae oft sehr starke Schmerzen.
b) Mutilationen sind ein charakteristisches Zeichen des DLE.
c) Ein „Köbner-Phänomen" kann zum Auftreten eines DLE führen.
d) Beim DLE wird die Wangenschleimhaut häufiger als der Gaumen befallen.
e) Der DLE führt zu vitiligoartigen Hypopigmentierungen im V-Areal von Brust und Rücken und Streckseiten der Arme.

6. Welche Aussage trifft zu?

a) Eine „Interface-Dermatitis" ist charakteristisch für den LET.
b) Beim LET finden sich dichte Muzinablagerungen in der Dermis.
c) Die Hautläsionen des LET weisen eine Schuppung auf.
d) Der LET heilt mit Hyperpigmentierungen ab.
e) Bei der Mehrzahl der Patienten mit LET werden anti-Ro/SSA Antikörper nachgewiesen.

7. Welche Aussage trifft nicht zu?

a) Der „familiäre Chilblain-Lupus" ist eine polygen vererbbare Erkrankung.
b) Der CHLE lässt sich nicht leicht von Perniones abgrenzen.
c) Der Lupus pernio ist eine Differenzialdiagnose des CHLE.
d) Der Nachweis von anti-Ro/SSA Antikörpern unterstützt die Diagnose des CHLE.
e) Eine positive läsionale direkte Immunofluoreszenz unterstützt die Diagnose des CHLE.

8. Welche Aussage trifft nicht zu?

a) Periorbitale Ödeme können beim LEP auftreten.
b) In ca. 70 % tritt der LEP in Assoziation mit einem DLE auf.
c) Eine Kalzifizierung kommt nicht beim LEP vor.
d) Beim LEP findet man histologisch eine Pannikulitis.
e) Klinische Differenzialdiagnose des LEP ist das subkutane pannikulitische T-Zell Lymphom.

9. Welche Aussage trifft nicht zu?

a) Beim BLE lassen sich Antikörper gegen Typ-VII-Kollagen nachweisen.
b) Als Differenzialdiagnose ist beim BLE eine lineare IgA-Dermatose abzugrenzen.
c) Der BLE ist durch eine subepidermale Blasenbildung charakterisiert.
d) Das Risiko eines NLE liegt bei ca. 2 % für Kinder von Müttern mit anti-Ro/SSA Antikörpern.
e) Das Wiederholungsrisiko eines NLE liegt bei > 75 %, wenn die Mutter bereits ein Kind mit NLE geboren hat.

10. Welche Aussage trifft nicht zu?

a) Die Hautveränderungen des LE werden in LE-spezifische und LE-unspezifische Manifestationen unterteilt.
b) Ca. 50 % der Patienten mit SCLE erfüllen formal die ACR-Kriterien.
c) Das Auftreten des SCLE ist mit einem singulären Nukleotidpolymorphismus im TNF-alpha-Genpromotor (-308A) assoziiert.
d) Der SCLE kann nicht durch Medikamente ausgelöst werden.
e) UV-Exposition führt zur Akkumulation apoptotischer Keratinozyten bei Patienten mit CLE.

Liebe Leserinnen und Leser,

der Einsendeschluss an die DDA für diese Ausgabe ist der 18. Januar 2008.
Die richtige Lösung zum Thema „Evidenzbasierte Medizin: Literaturbewertung" in Heft 9 (September 2007) ist:
1d, 2c, 3b, 4b, 5e, 6d, 7d, 8a, 9c, 10e.
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