The clinical manifestations of cutaneous lupus erythematosus (CLE) include the subtypes acute CLE (ACLE); subacute CLE (SCLE); chronic CLE (CCLE), with its variants discoid LE (DLE), chilblain LE (CHLE), and LE profundus (LEP); and LE tumidus (LET), as well as bullous skin lesions associated with LE (BLE) (see Chap. 5).

**Acute Cutaneous Lupus Erythematosus**

The typical clinical manifestations of ACLE are characterized by a localized erythema known as the “malar rash” or “butterfly rash” on the central portion of the face or by a generalized, more widespread form (Fabbri et al. 2003, Sontheimer and Provost 2003). Localized ACLE may only affect the skin transiently, and the lesions may last for only several days up to a few weeks. Therefore, at the onset of disease, the patients may mistake this rash for sunburn and may seek medical advice only after the lesions have persisted for a longer period. Generalized ACLE, also known as “photosensitive lupus rash”, is a less common variety and may be located anywhere on the body; however, it has a predilection for sun-exposed areas of the face, extensor aspects of the arms and forearms, and the dorsal aspects of the hands. It generally presents as a maculopapular or exanthematous eruption with a pruritic component. In most of the patients, systemic manifestation is strongly associated with ACLE, preceding by weeks or months the onset of a multisystem disease along with the confirmatory serologic findings (Watanabe and Tsuchida 1995, Wysenbeek et al. 1992, Yung and Oakley 2000). Since dermatologists are not usually the primary managers of such patients, few data concerning this form are available in the dermatologic literature.

ACLE has been reported in 20%–60% of large lupus patient cohorts, and it is more common in women than in men (Cervera et al. 1993, Pistiner et al. 1991, Wysenbeek et al. 1992). In one study, women were found to be six times more often affected than men, and the patients were on average in their second or third decade of life (Ng et al. 2000). Ultraviolet (UV) exposure is a common exogenous factor to be capable of precipitating ACLE (Kuhn et al. 2001a, Wysenbeek et al. 1989), and photosensitive patients sometimes report an exacerbation of their systemic symptoms after sun exposure. Furthermore, infections, especially with subtle types of viruses, or certain drugs, e.g., hydralazine, isoniazide, and procainamide, have also been found to induce or aggravate this disease (Pramatarov 1998, Rubin 1999). A possible association with HLA-DR2 and -DR3 has been suspected, and familial associations or concordance in twins suggest a genetic component.
The localized form of ACLE usually begins with small, discrete erythematous macules and papules, occasionally associated with fine scales involving both the malar areas and the bridge of the nose while sparing the nasolabial folds (Fig. 6.1). This classic “malar rash” or “butterfly rash” can disappear without scarring and pigmentation or gradually becomes confluent and hyperkeratotic (Fig. 6.2), and facial swelling may be severe in some patients with this disease (Norden et al. 1993, Yell et al. 1996). Similar lesions have also been found to occur on the forehead, the V-area of the neck, the upper limbs, and the trunk. Furthermore, patients with ACLE may have diffuse thinning or a receding frontal hairline with broken hairs (lupus hair), telangiectasias and erythema of the proximal nail fold, and cuticular abnormalities (Patel and Werth 2002). Superficial ulcerations of the oral and/or nasal mucosa are frequently accompanied with ACLE and may cause extreme discomfort in some patients. The posterior areas of the hard palate are most commonly affected; however, the gingival, buccal, and lingual mucosa may also be involved. In general, ACLE lesions are nonscarring, and the simultaneous occurrence of ACLE and other variants of CLE, such as DLE, is uncommon.

Some patients experience an extremely acute, generalized form of ACLE that presents as a maculopapular rash and can develop a more prolonged disease activity (Fabbri et al. 2003, Sontheimer 1997). In the few existing reports in the literature, this form is characterized by a generalized eruption of symmetrically distributed small,
confluent erythematous macules and papules with a pruritic component. The color of the lesions is usually red or, less frequently, dull red or livid, and there have been reports of patients presenting with severe involvement of the oral mucosa or the palms and phalanges (Fig. 6.3) (Braverman 1981, McCauliffe 2001). In contrast to the classic malar erythema of ACLE, the generalized form is a rather uncommon cutaneous manifestation that may be located anywhere on the body, although the preferred sites are above the waistline (Sontheimer and Provost 2003, Yell et al. 1996). It may resemble a drug eruption or can simulate toxic epidermal necrolysis, and it frequently occurs after sun exposure. As with “malar rash” or “butterfly rash”, the onset of the generalized form usually coincides with exacerbation of systemic disease. Its incidence is estimated to be approximately 5%–10% of patients with SLE (Cardinali et al. 2000, Tan et al. 1982), but the sporadic observations published in the dermatologic literature probably underestimate the real prevalence of this form.

### Subacute Cutaneous Lupus Erythematosus

SCLE, a subset with specific clinical and serologic features occurring preferentially in white females, was first discussed as a distinct entity by Gilliam in 1977 (Gilliam 1977), with expanded descriptions in 1979 (Sontheimer et al. 1979), 1981 (Gilliam and Sontheimer 1981), and 1982 (Gilliam and Sontheimer 1982). This subtype shows a significant coincidence with HLA-DR2 or -DR3, and patients with overlapping manifestations of Sjögren’s syndrome or high levels of anti-Ro/SSA antibodies are more likely to have HLA-B8, -DR3, -DRw6, -DRw52, and -DQ2 (Sontheimer et al. 1981). Certain drugs, especially hydrochlorothiazide, angiotensin-converting enzyme inhibitors, and calcium channel blockers have been associated with the onset and/or exacerbation of this disease (Reed et al. 1985, Srivastava et al. 2003). In recent years, terbinafine has also been reported to induce SCLE with high titers of antinuclear antibodies (ANAs) and antihistone antibodies in genetically susceptible persons (Bonsmann et al. 2001, Callen et al. 2001). Furthermore, most patients with this subtype are sensitive to sunlight and exposure to UV irradiation can precipitate or aggravate SCLE lesions (Kuhn et al. 2001a). Patients with SCLE typically have prominent cutaneous and musculoskeletal complaints but generally do not develop a severe
systemic disease, and only half of them have four or more of the American Rheumatism Association (ARA) criteria for the diagnosis of systemic lupus erythematosus (SLE) (Cohen and Crosby 1994, Crowson and Magro 2001, Tan et al. 1982). Therefore, SCLE can be considered a relatively benign illness that is intermediate in severity between ACLE and CCLE (Sontheimer 1989).

Initially, SCLE lesions present with erythematous macules and papules that evolve into scaly papulosquamous or annular/polycyclic plaques (Sontheimer et al. 1981). Approximately 50% of patients have predominantly papulosquamous or psoriasiform lesions (Fig. 6.4), and the other half have the annular/polycyclic type (Fig. 6.5); a few patients may develop both forms of lesions (Sontheimer 1985a, Sontheimer et al. 1979). However, some groups have observed a predominance of the papulosquamous lesions, whereas others have noted an abundance of the annular/polycyclic type (Callen and Klein 1988, Chlebus et al. 1998, Cohen and Crosby 1994, David-Bajar 1993, Fabbri et al. 1990, Herrero et al. 1988, Molad et al. 1987). One recent study found that 42% of the patients with SCLE studied exhibit the annular/polycyclic form, 39% had the papulosquamous form, and 16% showed both manifestations (Parodi et al. 2000). Generally, lesions of this subtype heal without scarring but can leave long-lasting and permanent vitiligo-like pigmentary changes as a “clue” for the clinical diagnosis (Fig. 6.6) (Milde and Goerz 1994). SCLE has a characteristic distribution of lesions in sun-exposed areas, in particular the upper chest and back, the deltoid aspect of the shoulders, the extensor surface of the arms, and less commonly the face or scalp. In the study by Parodi et al. (Parodi et al. 2000), the neck was affected in 83% of patients, with 66% exhibiting lesions on the face, 39% on the extensor arms, 21% on the dorsal hands, 16% on the lower limbs, and 12% on the scalp. Interestingly, 27%–100% of patients with SCLE have been reported to be abnormally photosensitive, and experimental studies showed positive phototest results in 63% after UVA or

Fig. 6.4. Papulosquamous subacute cutaneous lupus erythematosus (SCLE). Psoriasiform lesions with superficial scale and the tendency for individual lesions to merge into a vetiform pattern.
UVB irradiation (Kuhn et al. 2001a). However, some ethnic groups, such as Japanese and Chinese, seem to be less photosensitive (Nishikawa and Provost 1991, Shou-yi et al. 1987). A prevalence of polymorphous light eruption of 60%–70% has also been demonstrated in patients with SCLE, as well as phototoxic reactions when photosensitizing medications were prescribed (Millard et al. 2000).

Several other skin lesions that are not specific for LE have been described in patients with SCLE (Parodi et al. 2000, Sontheimer 1989). The most frequently encountered of these include nonscarring alopecia, painless mucous membrane lesions, livedo reticularis, periangual telangiectasias, and Raynaud’s phenomenon (Callen et al. 1986, Callen and Klein 1988, David et al. 1984, Herrero et al. 1988, Molad et al. 1987, Sanchez-Perez et al. 1993, Sontheimer 1985a). Cutaneous vasculitis of the lower extremities is a frequent finding in anti-Ro/SSA antibody-positive patients with SCLE also described under the rubric of Sjögren’s syndrome/LE overlap syndrome (Provost et al. 1988). Furthermore, cutaneous calcinosis may be seen rarely in patients with SCLE, and HPV-11-associated squamous cell carcinomas of the skin were noted in one patient with SCLE (Cohen et al. 1992). In one additional case, annular/polycyclic SCLE lesions were reported over time to progress to plaques of morphea (Rao et al. 1990).

Patients with SCLE may also develop localized facial ACLE, which has been seen in 7%–100% of patients (David et al. 1984, Fabbri et al. 2003, Molad et al. 1987, Shou-yi et al. 1987, Sontheimer 1985a). However, ACLE skin lesions tend to be more transient, to heal less often with pigmentary changes, and to be more edematous and less scaly than SCLE lesions. ACLE more commonly affects the malar areas of the face; in general, SCLE involves the face much less often. Several reports have also noted that up to 29% of patients with SCLE manifest DLE lesions during their clinical course and, interestingly, 19% of the original cohort of patients with SCLE had classical DLE

**Fig. 6.5.** Annular subacute cutaneous lupus erythematosus (SCLE). Polycyclic lesions with central hypopigmentation and inflamed erythematous borders on the extensor aspects of the arm
Callen and Klein 1988, David et al. 1984, Molad et al. 1987, Shou-yi et al. 1987, Sontheimer 1985a, Sontheimer et al. 1979). These lesions can predate the onset of SCLE lesions; however, DLE lesions are generally associated with a greater degree of pigmentary changes, may display atrophic dermal scarring, and are more characteristically associated with follicular plugging and adherent scaling than SCLE lesions. Furthermore, DLE lesions are characteristically indurated, whereas SCLE lesions are not (David-Bajar et al. 1992).

In addition to the common forms of SCLE, several unusual varieties of this subtype have been reported. Infrequently, SCLE lesions present initially with an appearance of erythema multiforme, which can simulate Rowell’s syndrome (erythema multiforme-like lesions occurring in patients with SLE in the presence of anti-La/SSB autoantibodies) (Rowell et al. 1963, Sontheimer 1985b). Lyon et al. (Lyon et al. 1998) reported two cases of delayed diagnosis of SCLE because of the clinical and histologic similarities between SCLE and erythema multiforme. Furthermore, lesions similar to erythema annulare centrifugum can be seen in some patients, and, as a result of hyperacute basal cell layer injury, on rare occasions, the active edge of annular SCLE lesions undergoes a vesicular change that breaks down to produce a striking crusted appearance (Grant 1981, Wechsler and Stavrides 1982). On at least one occasion such lesions have progressed to mimic toxic epidermal necrolysis (Bielsa et al. 1987), and in a study by Herrero et al. (Herrero et al. 1988), vesiculobullous changes were present in 38% of the SCLE population, which coincided histologically with focal areas of necrosis. In 1988, one patient with SCLE was reported to initially present exfoliative erythroderma (DeSpain and Clark 1988) and this was also noted more recently by Mutasim (Mutasim 2003). Other patients presented with a curious acral distribution of annular lesions (Scheinman 1994) or a form of SCLE with widespread plaques (Tsutsui et al. 1996). Pityriasisform (Caproni et al. 2001, Hymes et al. 1986) and exan-

![Fig. 6.6. Hypopigmentation in subacute cutaneous lupus erythematosus (SCLE). Permanent vitiligo-like depigmentation in the face of a patient with SCLE](image)
thematous (Sontheimer 1985b) variants of SCLE have been mentioned anecdotally on rare occasions. In addition, follicular erythematosus lesions are occasionally seen in patients with SCLE, and it has been reported to be associated with generalized poikiloderma (Pramatarov et al. 2000).

**Chronic Cutaneous Lupus Erythematosus**

Several different entities can be allocated to the group of CCLE, such as DLE, with its “hypertrophic/verrucous” and “telangiectoid” variants; and the more rare subtypes LEP and CHLE.

**Discoid Lupus Erythematosus**

The most common form of all chronic cutaneous variants is DLE, which can be localized or generalized, both with and without systemic manifestations of LE. Typical DLE lesions may be present at the onset of SLE in about 5%–10% of patients, and approximately 30% of patients may develop DLE lesions, usually of the generalized type, during the course of SLE (Cervera et al. 1993, Hymes and Jordon 1989, Tebbe et al. 1997). The localized form presents with sharply demarcated, erythematokeratotic, atrophic or scarring lesions, and it is often seen on the face and scalp, whereas the generalized form also involves the regions below the neck (Fabbri et al. 2003, McCauliffe 2001, Patel and Werth 2002). DLE occurs mostly in the third to fourth decade of life; however, in two recent studies, more than 40 children with DLE ranging in age from 2 to 16 years have been described in the literature (Cherif et al. 2003, Moisés-Alfaro et al. 2003). Earlier reports indicated that DLE may be more prevalent in whites than in blacks, but epidemiologic studies showed that it can affect any race (Findlay and Lups 1967, Ng et al. 2000, Tebbe and Orfanos 1997). Besides the genetic predisposition, the clinical manifestations may often be provoked or aggravated by exogenous factors, such as UV irradiation, cold, mechanical trauma, and, in rare cases, infections or drugs (Djawari 1978, Kuhn et al. 2001a, Lodin 1963). Association with HLA-B7, -B8, -Cw7, -DR2, -DR3, and -DQw1 has been described in the literature (Fischer et al. 1994, Knop et al. 1990).

Most commonly, DLE begins unilaterally or bilaterally, with flat or slightly elevated, sharply demarcated, erythematous macules or papules with a scaly surface. Early lesions most commonly evolve into larger, coin-shaped (“discoid”), confluent, disfiguring plaques of varying size (from a few millimeters to approximately 15 cm) owing to peripheral growth demonstrating a prominent adherent scale formation (Fig. 6.7) (Crowson and Magro 2001). When the adherent scale is peeled back from more advanced lesions, follicle-sized keratotic spikes similar in appearance to carpet tacks can be seen to project from the undersurface of the scale (“the carpet tack sign”). Telangiectasia and hyperpigmentation can replace the active inflammation, and the patches may give a poikilodermatous appearance. Pigmentary changes are common, especially in dark-skinned people, with white hypopigmentation in the central area and a hyperpigmented zone at the active border. Furthermore, in some ethnic groups, such as Indians from the Asian subcontinent, DLE can also present as isolated areas of macular hyperpigmentation (George et al. 1992). The skin lesions are
generally progressive, and resolution of the lesions leaves more or less evident atrophy and scarring, depending on the duration and severity of the lesions during the active phase. This may result in considerable mutilations, particularly when present in acral regions on the face, such as the tip of the nose and the ears, or in irreversible scarring alopecia on the scalp. A characteristic pitted, acneiform scarring is also a common feature of the perioral area (Fig. 6.8).

Cutaneous lesions of DLE predominantly occur in light-exposed areas, such as the face, particularly the cheeks and ears, but the forehead, eyebrows, eyelids, nose, and lips can also be included (Fabbri et al. 2003, McCauliffe 2001, Patel and Werth 2002). Symmetrical, butterfly-shaped DLE plaques will occasionally be found over the malar areas and the bridge of the nose. Such lesions are not to be confused with the more transient, edematous erythema reactions that occur over the same distribution in patients with ACLE. As with ACLE, DLE usually spares the nasolabial folds. However, DLE lesions may further affect sun-protected areas, such as inguinal folds and palmar-plantar skin, and involvement of the scalp can be found in approximately 60% of patients with this subtype (Sontheimer and Provost 2003). At the latter location, DLE may even be the only cutaneous manifestation in 10% of cases and thus presents a classical differential diagnosis of scarring alopecia (Fig. 6.9) (Prystowsky and Gilliam 1975). In one series, irreversible scarring alopecia resulting from permanent follicular destruction occurred in more than 30% of patients (Wilson et al. 1992); in some patients, DLE on the scalp progresses to the point of total, irreversible scarring alopecia and may be accompanied by secondary bacterial superinfection (Fig. 6.10). The irreversible scarring alopecia that is the result of persistent DLE activity in localized areas differs from the more widespread, reversible, nonscarring alopecia that patients with SLE often develop during periods of systemic disease activity. There is also an increased incidence of alopecia areata in patients with DLE (Werth et al. 1992). Fur-
thermore, DLE lesions occurring below the neck are most commonly found on the extensor aspects of the arms and the V-area of the neck. However, in the generalized form, such lesions can occur at virtually any site on the body, although the presence of DLE lesions solely below the neck is extremely uncommon. Painful erosive palmar-plantar DLE involvement can predominate in some cases, producing significant disability and presenting an especially difficult management problem (Ashinoff et al. 1988, Parrish et al. 1967). Small, follicularly oriented erythematous papules of less than 1 cm in diameter present as follicular DLE at the elbows but may occur at any other part of the body as well. These lesions may also be more common in Chinese and other Asian patients (Wong 1969).

Mucous membrane involvement can be found in 25% of patients with DLE and other forms of CCLE (Andreasen and Poulsen 1964, Botella et al. 1999, Burge et al. 1989). It does not necessarily reflect systemic manifestation or high disease activity; however, it is included in the list of the 11 diagnostic ARA criteria for the diagnosis
of SLE (Tan et al. 1982). Urman et al. (Urman et al. 1978) extensively studied oral ulcerations in 47 (26%) of 182 patients with SLE and noted no significant correlation between the oral ulcerations and cutaneous manifestations. Interestingly, an increased frequency of these mucosal lesions was associated with increased overall clinical activity, but no detectable correlation was found between oral ulcerations and serologic parameters. Oral, mainly buccal, manifestations are most common, with the palate, alveolar processes, and tongue less frequently involved, but nasal, conjunctival, and anogenital mucous membranes may also be affected at times. Individual lesions begin as painful, erythematous patches, later maturing to a chronic plaque that has a sharply margined, irregularly scalloped white border with radiating white striae and telangiectasia (Fig. 6.11). The surface of these plaques overlying the palatal mucosa often have a well-defined meshwork of raised hyperkeratotic white strands that encircle zones of punctate erythema (Burge et al. 1989). The centers of older lesions cause atrophy and may become depressed and, occasionally, undergo painful ulceration. Sometimes mucosal DLE resembles lichen planus, with a honeycomb appearance, and squamous cell carcinoma as a long-term complication should be suspected and excluded in any case of chronic asymmetrical induration of either mucosal or cutaneous lesions (Miyagawa et al. 1996, Reichart 2003, Sherman et al. 1993, Voigtlander and Boonen 1990). Well-defined DLE plaques also can appear on the vermilion border of the lips or can present as a diffuse cheilitis, especially on the more sun-exposed lower lip, causing considerable discomfort and disfiguration (Fig. 6.12). Mucosal lesions of the nose may result in nasal septum perforation, especially in association with generalized DLE or SLE (Bach 1980, Rahman et al. 1999). Similarly, ocular affections that are mainly located at the palpebral conjunctiva and the lower margin of the eyelids can cause permanent loss of eye lashes, ectropion, and corneal stromal keratitis (Afshari et al. 2001, Raizman and Baum 1989). Conjunctival DLE lesions begin most commonly as small areas of nondescript inflammation producing considerable disability, and as the early lesions progress, scarring becomes more evident (Frith et al. 1990, Heiligenhaus et al. 1996, Meiusi et al. 1991).

The nails can be involved as a very uncommon site of occurrence; however, periungual telangiectasias and erythema of the proximal nail fold are significant cutaneous features that can occur in patients with DLE prone to developing systemic disease. Furthermore, focal lesions of DLE occurring over the nail fold can produce nail

**Fig. 6.10.** Total irreversible alopecia in discoid lupus erythematosus (DLE). In this patient, the disease process has progressed to the point of total irreversible scarring alopecia with secondary bacterial superinfection
plate dystrophy (Kanwar et al. 1993). The nail unit can also be impacted by other forms of CLE as well as SLE, producing red lunulae, clubbing, paronychia, pitting, leukonychia striata, and onycholysis (Costner et al. 2003).

The appearance of DLE lesions or other forms of CLE in unusual locations and on completely sun-protected areas may be evidence that these lesions can follow in the wake of any form of trauma to the skin (Koebner’s phenomenon or isomorphic response) (Ueki 1994). Rowell and Goodfield (Rowell and Goodfield 1992) stated that in their series, DLE lesions were initiated by trauma in 11% of patients, sunburn in 5%, infection in 3%, and exposure to cold in 2%. Furthermore, DLE lesions have been noted to occur following exposure to x-ray, diathermy, and chemical burns and have arisen in scars associated with herpes zoster. DLE lesions have also been reported to occur in the scars of smallpox vaccination (Lupton 1987). It has long been observed that DLE lesions develop mainly during the summer and can be precipitated by sun exposure; however, this occurs less frequently than with ACLE, SCLE, or LET (Lehmann 1996). Photosensitivity in DLE can manifest in several ways: discoid lesions may themselves be specifically induced and exacerbated by UV radiation, but the development of polymorphous light eruption (PLE) can also be seen. A prevalence of PLE has been reported in 50% of patients with DLE by Millard et al. (Millard et al. 2000). However, in contrast to PLE, it is predominantly UVB that aggravates DLE lesions, although longer UVA lengths can also be deleterious in some patients.
(Lehmann et al. 1990, Nived et al. 1993, Walchner et al. 1997, Wolska et al. 1989). In experimental studies, characteristic skin lesions have been induced by UV irradiation in 42% of patients with DLE. Approximately 50% of these patients reacted to both UVB and UVA irradiation, 33% to UVB only, and 14% to UVA only (Kuhn et al. 2001a). Interestingly, in more than 50% of patients, sun exposure does not seem to be related to the cause of their disease, and DLE lesions in the hair-bearing scalp, external auditory canal, or perineal areas are examples where this form of CCLE is not related to light exposure.

Hypertrophic/Verrucous Variant of Discoid Lupus Erythematosus

Hypertrophic/verrucous lesions in association with CLE were first described by Bechet in 1940 (Bechet 1940); in this very rare variant, the hyperkeratosis that is usually present in DLE lesions is greatly exaggerated. Classic DLE lesions are often present elsewhere on the body, aiding in diagnosis (Callen 1985, Santa Cruz et al. 1983) and, recently, a patient with SLE and hypertrophic lesions has also been reported (Cardinali et al. 2004). However, only approximately 2% of patients with DLE show a hyperkeratotic type of lesion (Mascaro et al. 1997, Sontheimer and Provost 2003).

Clinically, hypertrophic DLE consists of dull, red, and indurated lesions that can appear as unique or multiple papulonodular elements covered by keratotic scale, as larger plaques covered by an adherent multilayered oosaceous horny white or yellowish material, or as regionally diffuse hyperkeratosis that looks like a chalky dust applied over the skin (Fig. 6.13) (Daldon et al. 2003). The entity “lupus erythematosus hypertrophicus et profundus” seems to represent a further very rare variant affecting the face, associated with the additional features of violaceus or dull red, indurated, rolled borders, and striking central, crateriform atrophy (Dammert 1971, Otani 1977, Winkelmann 1983). Nevertheless, the name of this entity is somewhat ambiguous because its pathology does not include a significant degree of LEP.

The verrucous, indurated, hyperkeratotic plaques can occur at any site where classical DLE lesions develop, although the extensor aspects of the arms and limbs, the upper back, and the face are the most frequently areas affected (Daldon et al. 2003, Mascaro et al. 1997). Recently, conjunctival hypertrophic lesions have been reported in a patient with a history of chronic blepharoconjunctivitis (Uy et al. 1999). When the palms and soles are involved, hypertrophic DLE produces localized or partially diffuse keratoderma, up to 1- to 3-mm thick, that makes finger mobility more difficult (Rothfield 1993).

Differential diagnosis must take into consideration verrucous psoriasis, hyperkeratotic lichen planus, prurigo nodularis, keratoacanthoma, and squamous cell carcinoma (Daldon et al. 2003, Perniciaro et al. 1995, Romero et al. 1977, Vinciullo 1986). Squamous cell carcinoma needs special consideration because it is well known that it can develop on chronic lesions of DLE, and until date, more than 100 cases of squamous cell carcinoma arising on scars of CCLE have been reported in white and African American patients (Caruso et al. 1987, De Berker et al. 1992, Sherman et al. 1993). In most cases, a male predominance, long evolution of previous CCLE lesions (mean time for development of squamous cell carcinoma over CCLE is 30.8 years), and high metastatic tendency (40%), especially when in labial location, was found (Millard and Barker 1978).
Patients with hypertrophic DLE rarely develop systemic disease; however, the clinical course is characterized by chronicity and resistance to treatment (Daldon et al. 2003, Spann et al. 1988). The lesions may respond, in some cases, to local cryotherapy (with carbon dioxide or liquid nitrogen), topical glucocorticosteroid application, and systemic antimalarial drug therapy. Topical tretinoin and systemic isotretinoin therapy have also been found to be effective (Green and Piette 1987, Seiger et al. 1991).

**Telangiectoid Variant of Discoid Lupus Erythematosus**

The telangiectoid variant of DLE is extremely rare, consisting of purplish plaques or blotchy reticulate telangiectasia that may develop on the face, neck, ears, dorsal aspects of the hands, breast, front of the knees, and back of the heels or sides of feet (Fig. 6.14) (Bechet and Elizabeth 1948, Mascaro et al. 1997). The lesions are mostly associated with further CCLE lesions or can replace active inflammation in patients with DLE developing a poikilodermatous appearance and prominent atrophic scarring. Efficient management of telangiectoid lesions can be difficult; however, argon laser treatment has been reported to yield an excellent cosmetic result without any short-term side effects (Kuhn et al. 2000d).

**Chilblain Lupus Erythematosus**

CHLE, a rare manifestation of CCLE distinguished by Hutchinson in 1888 (Hutchinson 1888), is strongly influenced by environmental factors (Breathnach and Wells 1979, Doutre et al. 1992, Helm and Jones 2002, Rowell 1987, Uter et al. 1988). This subtype seems to be more frequent in women and, interestingly, very uncommon in the United States, as Tuffanelli and Dubois (Tuffanelli and Dubois 1964) failed to detect such lesions among 520 patients; however, these patients were collected for the most part from the warm Southern California area. In contrast, Millard and Rowell (Millard and Rowell 1978) detected 17 cases with this subtype in a review of 150 patients with CLE (11.3%). Four of these patients demonstrated erythema multiforme-like lesions, and 3 of these 17 patients subsequently developed features of SLE. One further reported case of CHLE was induced by pregnancy and disappeared after delivery (Stainforth et al. 1993). The pathogenesis is unknown, but microvascular injury secondary to exposure to cold, damp weather or a drop in temperature and possible
hyperviscosity from immunologic abnormalities may play a role (Mascaro et al. 1997, Yell et al. 1996). In most reported cases, patients with CHLE present a polyclonal hypergammaglobulinemia, increased serum immunoglobulin levels, and a positive rheumatoid factor. In addition, anti-double-stranded DNA or anti-Ro/SSA antibodies have often been detected, but laboratory examinations usually fail to reveal evidence of cryoglobulins, cryofibrinogens, or cold agglutinins (Su et al. 1994). In a few patients, CHLE has been described in association with antiphospholipid syndrome (Allegue et al. 1988, De Argila Fernandez-Auran et al. 1996). The evolution of lesions in patients with CHLE is usually chronic, and sometimes these lesions precede other manifestations of SLE (Doutre et al. 1992). The risk of developing SLE is estimated to be approximately 20%, but in this rare form of CCLE, only a few studies have been reported; nevertheless, long-term follow-up of these patients is warranted (Viguier et al. 2001). Most patients progressing to SLE have arthralgia, manic depressive psychoses, or a reduced creatinine clearance, presumably from renal involvement. Furthermore, most patients with CHLE have or have had typical DLE lesions on the face; however, the evolution of both types of lesions is different, and chilblain manifestations usually persist when classic DLE disappears.

Clinically, CHLE is characterized by symmetrically distributed, circumscribed, sometimes infiltrated, pruriginous or painful areas of livid and purple plaques that appear and exacerbate during cold, damp weather periods (Fig. 6.15). There is only a slight tendency to central regression, and the lesions, in their evolution, may ulcerate or present firmly adherent hyperkeratosis (Kuhn et al. 2000c, Sontheimer and Provost 2003). The lesions of CHLE involve mostly the dorsal and lateral parts of the hands and feet, the ears, the nose, the elbows, the knees, or the calves (Helm and Jones 2002, Su et al. 1994). On toes and fingers, the lesions develop on the back or on the pads (Doutre et al. 1992, Fisher and Everett 1996), and fissuring of the knuckles as well as

![Fig. 6.14. Telangiectoid variant of discoid lupus erythematosus (DLE). Multiple erythematous plaques and reticulate telangiectasia on the face that produce large areas of disfigurement on confluence](image-url)
accompanying hyperhidrosis are common, producing a great deal of discomfort (Costner et al. 2003). Ulceration is frequent in digital pulp lesions, and they easily become necrotic on the soles (Mascaro et al. 1997). When located in the periungual zone, the nail plate may develop mild to severe dystrophy.

Because CHLE lesions are highly reminiscent of simple chilblains or pernio lesions (Viguier et al. 2001), one could question whether such patients have simple pernio that in the predisposed individual produces a Koebner’s phenomenon resulting in DLE. The terms “chilblain lupus” and “perniotic lupus” have been used to describe such lesions. Unfortunately, the term “lupus pernio” has also been used for such lesions, although this term is more properly used to designate a form of cutaneous sarcoidosis (James 1992). For a positive diagnosis of CHLE, it has been proposed to establish two groups of major and minor criteria (Su et al. 1994). Major criteria include (a) cold-induced or cold-aggravated lesions in acral locations and (b) evidence of LE on histopathology or direct immunofluorescence. Minor criteria include (a) the coexistence of SLE or other manifestations of CLE, (b) positive response to LE therapy, and (c) negative results of cryoglobulin and cold agglutinin studies. The diagnosis of CHLE may be affirmed if the patient fulfills both major criteria and at least one of the minor criteria. A chronic form of CHLE occurs especially in older persons who have underlying vascular abnormalities, such as acrocyanosis, Raynaud’s phenomenon, atherosclerosis, or erythrocytosis. In such patients, this subtype of CCLE can last for several months and tends to recur annually, sometimes with hemorrhagic blisters, erosions, or ulcers.
Lupus Erythematosus Profundus

LEP, historically referred to as “Kaposi-Irgang disease” or also known as “lupus panniculitis”, is a rare variant of CCLE in which pathologic changes occur primarily in the lower dermis and subcutaneous tissue. In 1883, subcutaneous nodules associated with LE were first described by Kaposi (Kaposi 1883), but the term “lupus profundus” was coined by Irgang (Irgang 1940) in 1940. Subsequently, different authors reported new cases and contributed to define the clinical and histopathologic characteristics of this disease (Arnold 1956, Sanchez et al. 1981, Tuffanelli 1971, Winkelmann 1970). Middle-aged women are predominantly affected; however, in a recent study it has been shown that LEP in Asian patients is more frequent in a younger age group compared with the Caucasian population (Ng et al. 2002). The course of this subtype of CCLE is usually chronic and characterized by periods of remission and exacerbation. The major morbidity is usually disfigurement and disability related to pain, and the lesions finally resolve, leaving deep atrophic scars (Kuhn et al. 2000c, Mascaro et al. 1997). LEP can be found in approximately 2%–10% of patients with SLE and other autoimmune diseases; however, patients with LEP present more commonly without further or only mild signs of systemic manifestations. In some extensive cases, association of LEP with serious systemic disease or a lethal outcome has been reported, although there is a relatively low incidence of renal involvement (Grossberg et al. 2001). Serologically, ANAs may be found to be low in titer or nonexistent, and hypergammaglobulinemia has been reported in some cases of LEP along with low total complement and C4 levels (Martens et al. 1999). Approximately 70% of patients with LEP also have other lesions of CLE, particularly discoid or hypertrophic lesions, often overlying the panniculitis lesions (Balabanova et al. 1992, Suss et al. 1994). When LEP exists in the absence of other LE-specific lesions, the diagnosis has been questioned. Therefore, it is important to obtain biopsy specimens to confirm the diagnosis because a number of cases of subcutaneous lymphoma have given a clinical appearance of lupus profundus (Magro et al. 1997, Ng et al. 2002). Physical factors, such as trauma, may often be directly related to the lesions of LEP (Tuffanelli 1971); however, the relevance of photosensitivity in this rare subtype of CCLE is unknown (Fabbri et al. 2003).

Single or multiple sharply defined, persistent, asymptomatic or sometimes painful subcutaneous plaques or nodules of varying sizes are the typical lesions of LEP (Costner et al. 2003, Peters and Su 1989). The overlying skin ultimately becomes attached to the firm lesions, producing a deep depression into the subcutis with a normal or erythematous, inflammatory surface (Fig. 6.16). Dystrophic calcifications or ulcerations within older lesions of LEP, leaving atrophic scars or sometimes resembling lipatrophy, may occur and at times can be a prominent clinical feature of the disease requiring surgical excision. In addition, LEP may produce breast nodules that can mimic carcinoma, clinically and radiologically (Holland et al. 1995, Peters 2000), and linear involvement of the extremities or the scalp has also been observed (Nagai et al. 2003, Tada et al. 1991). Most lesions of LEP are usually found in areas of increased fat deposition, such as the trunk, buttocks, and proximal upper and lower extremities, but the shoulders and thighs are further sites of predominant involvement (Martens et al. 1999). LEP may also develop on the scalp clinically simulating alopecia areata (Kossard 2002) and in unusual zones on the face, such as the parotid
region. Interestingly, periorbital edema as an initial symptom of LEP has been described in several patients as the only clinical manifestation of the disease (Franke et al. 1999, Lodi et al. 1993, Magee et al. 1991).

**Lupus Erythematosus Tumidus**

In 1909, the term “lupus erythematosus tumidus” was first used by Hoffmann (Hoffmann 1909) at a meeting of the Berlin Dermatological Society, and, in 1930, five further patients were reported by Gougerot and Burnier (Gougerot and Burnier 1930, 1931, 1932) to describe a disease with erythematous, indurated, nonscarring lesions on the face with minimal or absent surface changes. However, the next case reports of LET were not mentioned until 1965 in the German and French literature (Bazex et al. 1965, Casala et al. 1971, De Graciansky et al. 1965), and in the following years, only a few further cases were reported (Dekle et al. 1999, Mosquera Vieitez et al. 1984, Ruiz and Sanchez 1999). This might be due to the fact that other authors have not considered LET as a separate entity different from other variants of CLE, and it is likely that skin lesions described under different designations, such as “urticarial plaque lupus erythematosus,” represent the same disease entity (Sontheimer and Provost 1996). Because some skin conditions share a variety of similar features, a correct diagnosis demands attention to rather subtle details and appreciation of the characteristic signs as well as the course of the disease. In 2000, our group (Kuhn et al. 2000a) analyzed 40 patients with LET and defined diagnostic criteria for the classification of this disease. Meanwhile, there is no doubt about LET being a separate entity, and further reports by other groups have been published indicating that the incidence of LET seems to be higher than found in earlier studies (Alexiades-Armenakas et al. 2003, Hsu et al. 2002, Hsu et al. 2002, Hsu et al. 2002).
Jolly et al. 2004, Pacheco et al. 2002). Interestingly, most case reports of LET in the literature are published by European countries indicating that many more patients are seen in the Caucasian population (Sontheimer 2000).

The importance of reevaluating this form lies in the characteristic clinical and histopathologic picture, in its remarkable photosensitivity, and in the course of the disease (Kuhn 2003). In several aspects, the cutaneous manifestations of LET differ from other variants of CLE. Scarring, the hallmark of DLE, does not occur in LET, even in patients with recurrent skin lesions at the same site for many years, and epidermal atrophy has not developed in any case. Follicular plugging and adherent hyperkeratotic scaling, which are further features of DLE, also have not been seen in any of the patients with LET. Hypopigmentation, frequently evident in patients with SCLE after the active phase with erythema and scaling, has never been detected in LET (David-Bajar and Davis 1997). Because some of the patients with LET present with annular skin lesions, there might be a possibility of developing annular erythema associated with Sjögren’s syndrome; however, this rare entity has only been reported for Asian patients (Kuhn et al. 2000b). Furthermore, association with systemic disease seems to be very rare in patients with LET (Alexiades-Armenakas et al. 2003, Jolly et al. 2004); however, none of our patients fulfilled four or more ARA criteria for the diagnosis of SLE (Kuhn et al. 2000, Tan et al. 1982). Although joint symptoms occurred temporarily, no signs of inflammatory joint disease or rheumatoid arthritis have been detected, and further systemic manifestations, such as renal, central nervous system, or lung involvement, have not yet been appreciated in any of the patients. Therefore, the prognosis in patients with LET is generally more favorable than in those with other forms of CLE and several patients who had been followed for more than 15 years showed no recurrence after local or systemic treatment. However, this would need to be confirmed by long-term investigations in a greater number of patients.

LET is mostly found in males, and the mean onset of the disease is nearly the same as that described for DLE; therefore, compared with SCLE or SLE, patients with LET are older when the disease begins (Bangert et al. 1984). However, even children may be affected, and, interestingly, one boy had already developed LET skin lesions when he was 9 months old (Kuhn et al. 1997). LET in childhood seems similar to the adult form of the disease, with the same clinical and histologic features, but, to date, only three children with LET have been published in the literature (two boys and one girl aged 9 months to 3 years at disease onset) (Sonntag et al. 2003). Interestingly, photoprovocation tests, which had been performed in two of the young patients, demonstrated no characteristic skin lesions after UV irradiation, although the patients had a positive history of photosensitivity, and ANAs were not detectable. During 6-year follow-up, no signs of systemic involvement had developed in any of the three children.

Clinically, LET is characterized by succulent, urticaria-like, single or multiple plaques with a bright reddish or violaceous, smooth surface on sun-exposed areas, such as the face, upper back, V-area of the neck, extensor aspects of the arms, and shoulders (Fig. 6.17); the lesions spare the knuckles, inner aspect of the arms, and axillae, and have never been detected below the waist (Kuhn et al. 2000a). The swollen appearance of the lesions and the absence of clinically visible epidermal involvement are the most important clinical features of this subtype. The borders are sharply limited, and, in some cases, there is a tendency for the lesions to coalesce in the periphery,
producing a gyrate configuration, or to swell in the periphery and flatten in the center (Fig. 6.18) (Mascaro et al. 1997). Some patients develop erythematous, annular lesions on the cheeks and upper extremities imitating the annular type of SCLE, and, recently, a patient with LET following the lines of Blaschko has been reported (Pacheco et al. 2002). LET lesions can also coexist with DLE lesions (Ruiz and Sanchez 1999) and have been reported to mimic alopecia areata when present on the scalp (Werth et al. 1992). However, other nonspecific LE lesions, such as hypopigmentation, mucous membrane ulcers, diffuse alopecia, livedo reticularis, and vasculitis, have never been seen in any patient.

It has long been suggested that this subset of CLE is characterized by a remarkable photosensitivity (Goerz et al. 1990). Provocative phototesting according to a standardized protocol revealed that patients with LET are more photosensitive than those with other forms of CLE. In a study by our group (Kuhn et al. 2001b), characteristic
skin lesions were induced by UV irradiation in 43 (72%) of the 60 patients; 30 patients 
(50%) reacted to UVA and 29 (48%) to UVB irradiation. Combined UVA and UVB 
irradiation has been used in 30 patients; 19 of these patients (63%) reacted to this 
testing regimen. Interestingly, 19 (32%) of the 60 patients with LET reacted to more 
than one wavelength of UV irradiation. However, because of the latency period in 
developing positive phototest reactions, it may be difficult for patients to link sun 
exposure to their skin lesions. In contrast to the studies by Kind et al. (Kind et al. 
1993) in 1993, our data further showed a positive photoprovocation test reaction in 
all 10% of the ANA-positive patients, and all 15% of the patients who had moderate 
ANA titers also developed skin lesions after UV irradiation. In addition, our data 
revealed a positive correlation of anti-Ro/SSA and anti-La/SSB antibodies and posi-
tive provocative phototest reactions, as has been described for patients with SCLE 
and neonatal LE.

Histologic analysis of skin lesions is necessary to confirm the diagnosis of LET, 
and, therefore, it represents one of the major criteria of this disease (Kuhn et al. 2003). 
The most frequent features in biopsy specimens from LET lesions are a moderate to 
dense, fairly well-circumscribed lymphocytic dermal infiltrate in a perivascular and 
periadnexal pattern and abundant interstitial mucin deposition. Occasionally, some 
neutrophils are present, and, in a few cases the dermis shows edema in its upper part; 
however, in contrast to other forms of CLE, epidermal changes, such as atrophy and 
follicular plugging, as well as vacuolar degeneration of the dermoepidermal junction 
or basement membrane thickening are absent. Skin biopsy specimens from UV-
induced lesions of LET taken after provocative phototesting present with a similar 
pattern compared with primary lesions, but a more dense infiltrate of lymphocytes is 
seen, and interstitial mucin deposition is less prominent. Direct immunofluorescence 
staining of lesional skin specimens of LET has mostly been negative for 
immunoglobulin or complement components (Kind and Goerz 1988). In our recent 
study (Kuhn et al. 2003), biopsy specimens from primary skin lesions demonstrated 
immunoglobulin deposits (IgG, IgM) along the dermoepidermal junction in 24% of 
patients with LET, but IgA as well as complement components were not identified in 
any specimen from primary or UV-induced lesions.

In the past years, immunohistologic studies helped characterize the skin lesions of 
patients with LET and supported the clinical findings that LET represents a distinct 
subset of CLE with a similar immunopathomechanism rather than a different disease 
(Alexiades-Armenakas et al. 2003, Kuhn et al. 2002a, b). Epidermal surface molecules, 
such as intercellular adhesion molecule-1 (ICAM-1), histocompatibility class II 
molecule (HLA-DR), and 27E10, a distinct marker for cell activation and differentia-
tion, were equally up-regulated in primary and UV-induced lesions of patients with 
LET, DLE, and SCLE (Kuhn et al. 2002b). Furthermore, skin specimens from patients 
with LET demonstrated an inflammatory infiltrate composed of more than 75% 
CD4+, CD8+, and HLA-DR+ cells; interestingly, CD45RO+ cells in contrast to CD45RA+ 
cells were the prevailing inflammatory cell population. Compared with skin speci-
mens from patients with DLE and SCLE, the mean expression of CD4+ and CD8+ cells 
was higher (but not significant) in LET, and no differences were observed with the 
other three antibodies (Kuhn et al. 2002a). In contrast to controls, ICAM-1, vascular 
adhesion molecule-1, E-selectin, and P-selectin showed the same expression pattern 
in skin specimens from patients with DLE, SCLE, and LET.
LET bears striking similarities to PLE, Jessner’s lymphocytic infiltration of the skin, reticular erythematous mucinosis (REM), and pseudolymphoma (Ruhdorfer et al. 1998). The clinical distinction between PLE and LET can be difficult; however, LET shows a much more delayed reaction after sun exposure, and healing of skin lesions takes much longer, even when sun exposure is avoided and a sun block is applied daily (Holze et al. 1987, Lehmann et al. 1986). Furthermore, in contrast to LET, desensitization phototherapy or photochemotherapy are the most effective forms of preventive treatment in PLE (Bilsland et al. 1993, Ortel et al. 1986). Histologic investigations provide further criteria to differentiate PLE from LET, both showing a superficial and deep lymphocytic infiltration and no changes at the dermoepidermal junction (Ackerman 1997). However, in contrast to LET, a marked edema is seen in the papillary dermis and interstitial mucin deposition is not detectable, which is best accomplished by colloidal iron staining. Interestingly, in two studies determining ANAs in patients with PLE, 10%-14% also showed titers of 1:80 or higher, correlating positively in one study with a longer duration of skin lesions (Murphy and Hawk 1991, Petzelbauer et al. 1992).

Jessner’s lymphocytic infiltration of the skin is a relatively uncommon disorder with asymptomatic, papulonodular, nonscarring lesions most often located on the face that has not always been considered a specific disease entity. Until today, no unanimity exists concerning its nosology (Weyers et al. 1998). Several studies demonstrated that clinical and histopathologic criteria are insufficient to distinguish Jessner’s lymphocytic infiltration of the skin from different subtypes of CLE (Aksu et al. 1992, Bonczkowitz and Weyers 1996). In a more recent report (O’Toole et al. 1999), the occurrence of these two conditions in one family further supports the theory that Jessner’s lymphocytic infiltration of the skin is in the same disease spectrum as CLE. In addition, Weber et al. (Weber et al. 2001) supposed by provocative phototesting that Jessner’s lymphocytic infiltration of the skin might be a photosensitive variant of LET. Histologically, Jessner’s lymphocytic infiltration of the skin shows a patchy perivascular and sometimes periadnexal infiltrate consisting of lymphocytes, few histiocytes, and plasma cells. The infiltrate often shows a tendency to arrange itself around cutaneous appendages and blood vessels, and it may extend into subcutaneous fat (Ashworth and Morley 1988, Bonczkowitz and Weyers 1996). However, in contrast to LET, mucin deposition seems not to be a major histologic criteria in patients with Jessner’s lymphocytic infiltration of the skin and was not described in the original report by Jessner and Kanof in 1953 (Jessner and Kanof 1953).

Reticular erythematous mucinosis is a further rare disease with skin lesions ranging from erythematous, indurated papules to reticulated, macular erythema on the central chest or upper back. In contrast to LET, young to middle-aged women are mostly affected. Interestingly, some authors also consider REM to be a variant of CLE because antimalarial agents have been reported to be the most effective therapy, and patients with REM have shown aggravation of the rash on exposure to sunlight (Braddock et al. 1993, Cohen et al. 1990). However, only a few attempts have been made to quantify the light intolerance or to provoke the skin by phototesting in this disease (McFadden and Larsen 1988), and, in addition, treatment of REM with a large dose of UVB radiation has even been suggested (Yamazaki et al. 1999). Histologic analysis of REM shows no or minimal vacuolar degeneration at the dermoepidermal junction.
and a mild to dense perivascular and perifollicular infiltrate of lymphocytes with abundant mucin deposition in the dermis (Vanuytrecht-Henderickx et al. 1984). Furthermore, pseudolymphoma can also clinically simulate LET; however, in most cases, histologic analysis shows a top-heavy, usually wedge-shaped infiltrate of small lymphocytes as well as plasma cells and eosinophils and no interstitial mucin deposition (Ploysangam et al. 1998, Weinberg et al. 1993).

In summary, LET is a distinct subset of CLE with characteristic clinical features requiring correlation with photobiologic, serologic, histologic, and immunohistologic findings because, taken in isolation, other diagnoses can be indicated. The reported data emphasize the importance of defining LET as a separate entity with an intermittent course and demonstrate that this disease has been neglected in the literature since first mentioned in 1909.

Bullous Lesions in Lupus Erythematosus

The frequency of bullous lesions associated with LE (BLE) is low, and it has been reported that less than 5% of patients with SLE and skin changes had chronic vesiculobullous lesions (Gammon and Briggaman 1993, Yell and Wojnarowska 1997). Confusion has always existed concerning the nosology and classification of the bullous skin changes that can occur in patients with LE, and there has been no consensus in this area for a long time. In 1997, Sontheimer (Sontheimer 1997) divided the various types of vesicular and bullous skin lesions that can be encountered in patients with LE into those that have or do not have LE-specific pathology and proposed the following classification scheme:

1. Bullae may develop in LE-specific skin lesions such as ACLE or other cutaneous forms of LE as a direct extension of the vacuolar degeneration of the epidermal basal layer. Skin cleavage occurs as a result of dissolution of the basal cell layer, resulting in subepidermal cleavage that may have the clinical appearance of toxic epidermal necrolysis. Anti-Ro/SSA antibody-positive patients seem to be at increased risk of developing this complication following UV light exposure (Gilliam et al. 1985, Kulick et al. 1983). Documentation of LE as the causal factor in this type of bullous skin change can be difficult because such patients are also frequently taking systemic medication and toxic epidermal necrolysis, therefore, also commonly develops as a result of drug hypersensitivity reaction. In patients with SCLE, vesiculobullous changes may also occur at the active advancing edge of annular lesions (Grant 1981, Sontheimer 1985b, Wechsler and Stavrides 1982), and subepidermal bullous changes have also been reported to be present in DLE lesions; however, these changes seem to be extremely rare (Nagy and Balogh 1961).

2. On unusual occasions, bullous eruptions or vesiculobullous lesions, unassociated with LE skin lesions, occur in patients with SLE (Bacman et al. 2004, Camisa and Sharma 1983, Gammon et al. 1985, Hall et al. 1982, Olansky et al. 1982, Penneys and Wiley 1979). These lesions predominantly involve flexural or extensor skin (Fig. 6.19), the upper trunk, and the supraclavicular regions, but the face and the mucosal membranes are also predilection sites. The bullae arise on erythematous or normal skin, tend to be tense, and may approach the size of blisters in
bullous pemphigoid or may resemble the vesiculobullous lesions of dermatitis herpetiformis. If the bullous lesions rupture, they leave erosions, crusts, and pigmentary changes, and when they regress, scars, milium cysts, or calcinosis cutis can remain (Eckman and Mutasim 2002). In this form of bullous skin lesions, the activity of blistering may or may not coincide with the activity of the patient’s systemic disease, and occasionally, mild and serious cases associated with organ-threatening disease have been reported (Gammon and Briggaman 1993, Sontheimer 1997). An important and interesting feature of these patients is also the dramatic response to treatment with dapsone even with very small doses (Hall et al. 1982, Yung and Oakley 2000). However, the drug could not be tapered and discontinued without rapid recurrence of the lesions. In a recent study, the efficacy of methotrexate in bullous SLE has also been reported in one patient (Malcangi et al. 2003). Histologically, the subepidermal blisters demonstrate neutrophilic microabscesses in dermal papillae along with a perivascular and periadnexal infiltration consisting of lymphocytes and neutrophils (Megahed 2004). Direct immunofluorescence shows linear or granular deposits of IgG, IgA, and/or IgM and complement along the basement membrane zone, and immunoelectron microscopic studies demonstrate IgG deposits at or below the lamina densa (Gammon and Briggaman 1993, Yell and Wojnarowska 1997). Furthermore, indirect immunofluorescent studies are positive using a 1 M NaCl split skin demonstrating mostly dermal binding (Gammon et al. 1985), and Western blot analysis showed that these autoantibodies bind to the noncollagenous portion of type VII collagen (Shirahama et al. 1998). These data further demonstrated that the autoantibodies in this bullous form of LE bind to the same epitopes as described in epidermolysis bullosa (Barton et al. 1986, Lapiere et al. 1993). Prior to these studies, two other groups had performed acid elution studies on skin of patients

![Bullous skin lesions associated with lupus erythematosus (BLE). Firm bullous lesions on the extensor aspect of the lower arm in a patient with SLE.](image)
with SLE, demonstrating autoantibodies reactive against human skin (Landry and Sams 1974, Nicholas and Gilliam 1981, 1982). It is highly likely that these investigators were dealing with autoantibodies reactive against type VII collagen. In more recent studies, Chan et al. (Chan et al. 1999) concluded that patients with bullous SLE may have autoantibodies to multiple basement membrane components, such as bullous pemphigoid antigen-1, laminin-5, and laminin-6. Furthermore, Yell and Wojnarowska (Yell and Wojnarowska 1997) demonstrated that two of seven patients also showed epidermal binding and, in one case, this was also associated with dermal binding.

In addition, a variety of primarily blistering diseases have been anecdotally reported to occur in patients with cutaneous and systemic manifestations of LE, in particular, dermatitis herpetiformis (Davies et al. 1976), bullous pemphigoid (Miller et al. 1978), pemphigus erythematosus (Chorzelski et al. 1968), pemphigus foliaceus (Blanchet et al. 1981), epidermolysis bullosa acquisita (Dotson et al. 1981), and linear IgA dermatoses (Lau et al. 1991). A non-autoimmune blistering skin disease, porphyria cutanea tarda, has also been reported in patients with different forms of LE (Gibson and McEvoy 1998, Weatherhead and Adam 1985); however, this association could also be merely fortuitous.

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