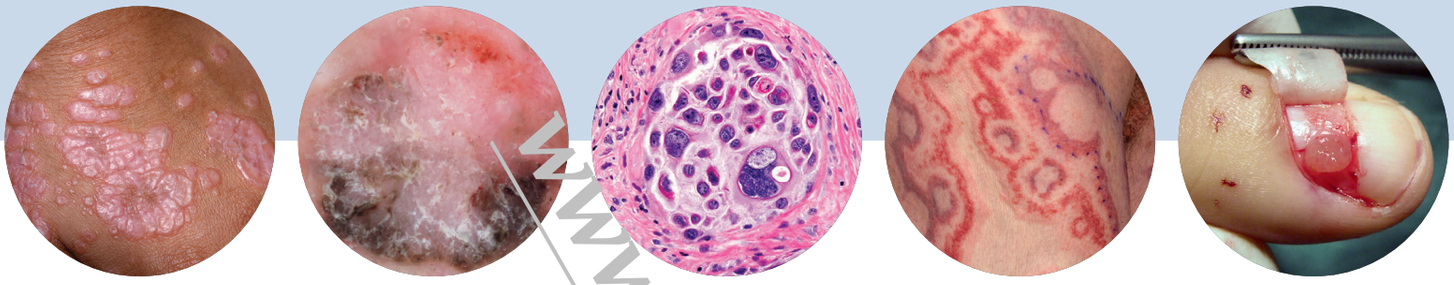
Fifth Edition

DERMATOLOGY



EDITED BY

Jean L. Bolognia MD
Professor of Dermatology
Yale School of Medicine
New Haven, CT, USA

Julie V. Schaffer MD
Professor of Pediatrics
Division of Pediatric Dermatology
Hackensack Meridian School of Medicine
Hackensack, NJ, USA

Lorenzo Cerroni MD
Associate Professor of Dermatology
Director, Dermatopathology Unit
Department of Dermatology
Medical University of Graz
Graz, Austria

ASSOCIATE EDITORS

Jeffrey P. Callen MD
Professor of Medicine (Dermatology)
Lafayette G. Owen Endowed Professor
Chief, Division of Dermatology
University of Louisville College of Medicine
Louisville, KY, USA

Edward W. Cowen MD MHSc
Diplomate, American Board of Dermatology
Newton, MA, USA;
Fellow, American Academy of Dermatology
Schaumburg, IL, USA;
Senior Clinician and Head, Dermatology Consultation Service
Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, MD, USA

Karynne O. Duncan MD
Private Practice
St. Helena, CA, USA

George J. Hruza MD MBA
Adjunct Professor of Dermatology
St. Louis University School of Medicine
St. Louis, MO, USA;
Medical Director
Laser & Dermatologic Surgery Center
Chesterfield, MO, USA

Jonathan Leventhal MD
Associate Professor of Dermatology
Yale School of Medicine
New Haven, CT, USA

Luis Requena MD PhD
Chairman, Department of Dermatology
Fundación Jiménez Díaz de Madrid
Professor of Dermatology
Universidad Autónoma de Madrid
Madrid, Spain

Antonio Torrelo MD PhD
Head, Department of Dermatology
Hospital Infantil Universitario Niño Jesús
Madrid, Spain

Thomas Wiesner MD
Professor
Department of Dermatology
Medical University of Vienna
Vienna, Austria

ELSEVIER

ELSEVIER

First edition 2003
Second edition 2007
Third edition 2012
Fourth edition 2018

Disclaimer
In 2015, under the Pregnancy and Lactation Labeling Rule (PLLR), the US Food and Drug Administration (FDA) abolished the letter rating system for drug safety in pregnant women and during lactation; the letters are to be replaced with narrative-based labeling. Drugs approved prior to 2015 have three years to comply with the new format while drugs approved thereafter must comply from the onset. Fed Regist 2014;79;72064-72103.

Dr Cowen's work as editor was performed outside of the scope of his employment as a US Government Employee. The views expressed are his own and do not necessarily represent the views of the National Institutes of Health or the US Government.

Notices

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-7020-8225-2
E-ISBN: 978-0-7020-8469-0
INTERNATIONAL EDITION: 978-0-7020-8468-9

Content Strategist: Charlotta Kryhl
Content Development Specialist: Jennifer Shreiner
Project Managers: Anne Collett, Joanna Souch
Design: Margaret Reid
Illustration Manager: Muthukumaran Thangaraj
Illustrator: MPS North America LLC
Marketing Manager: Mary McCabe-Dunn

Printed in Poland

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Contents

SECTION 11: Hair, Nails, and Mucous Membranes

Volume 2

SECTION 12: Infections, Infestations, and Bites

SECTION 13: Disorders Due to Physical Agents

SECTION 14: Disorders of Langerhans Cells and Macrophages

SECTION 15: Atrophies and Disorders of Dermal Connective Tissues

SECTION 16: Disorders of Subcutaneous Fat

SECTION 17: Vascular Disorders

SECTION 21: Surgery

SECTION 22: Cosmetic Surgery

EULAR/ACR classification for SLE

Entry criterion
Anti-nuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE; if present, apply additive criteria

Additive criteria
- Do not count a criterion if there is a more likely explanation than SLE
- Occurrence of a criterion on at least one occasion is sufficient
- SLE classification requires at least one clinical criterion and ≥10 points
- Criteria need not occur simultaneously
- Within each domain, only the highest weighted criterion is counted toward the total score*

Clinical domains and criteria	Weight
Constitutional	
Fever (>38.3°C)	2
Hematologic	
Leukopenia (WBC <4.0 x 10^9/L)	3
Thrombocytopenia (plts <100 x 10^9/L)	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous¶	
Non-scarring alopecia§	2
Oral ulcers§	2
Subacute cutaneous§ *OR* discoid lupus§	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria (>0.5 g/24 h)	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies† *OR*	
Anti-β2GP1 antibodies *OR*	
Lupus anticoagulant	2
Complement proteins	
Low C3 *OR* low C4	3
Low C3 *AND* low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody‡ *OR*	
Anti-Sm antibody	6

Total score:

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled

*Additional criteria items within the same domain will not be counted.
†Anti-cardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 units or >99th percentile).
‡In an assay with at least 90% specificity against relevant disease controls.
¶If skin biopsy is performed, typical changes must be present.
§Observed by a clinician on physical examination or via a photograph.

Table 41.5 The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE)[67]. plts, platelets. *Modified from Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 2019;71:1400–12.*

CUTANEOUS FINDINGS (NONSPECIFIC) THAT SUGGEST THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS
Diffuse non-scarring alopecia
Raynaud phenomenon
Nail-fold (periungual) telangiectasias and erythema
Vasculitis
• Urticarial vasculitis
• Small vessel vasculitis (e.g. palpable purpura)
• Polyarteritis nodosa-like lesions
• Ulcerations
Cutaneous signs of antiphospholipid syndrome
• Livedo reticularis
• Ulcerations
• Acrocyanosis
• Atrophie blanche-like lesions
• Degos-like lesions
• Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis
Sweet syndrome-like neutrophilic dermatosis and neutrophilic urticarial dermatosis

Table 41.6 Cutaneous findings (nonspecific) that suggest the diagnosis of systemic lupus erythematosus. These are in addition to skin signs of other autoimmune connective tissue diseases, which raise the possibility of an overlap syndrome.

the diagnosis of cutaneous LE, but a negative DIF does not exclude the diagnosis. It has been noted that DIF is most likely to be positive in well-established, active lesions. DIF is often negative or nonspecific in LE tumidus. In lupus panniculitis, DIF may show immunoreactants around dermal vessels, but granular deposits at the dermal–epidermal junction are not uniformly present.

Antibody Deposits Within Normal-Appearing Skin

In normal-appearing skin, the presence of antibody deposits at the dermal–epidermal junction correlates reasonably well with systemic disease. The antibody deposits are typically granular and are sometimes referred to as a "lupus band", with examination for the deposits referred to as the "lupus band test". The terminology is confusing, because some authors use the term "lupus band" to apply to the antibody deposits at the dermal–epidermal junction, whether the skin tested is normal-appearing or lesional, while other authors reserve the term "lupus band" to describe antibody deposits in normal-appearing skin. It has been proposed that, if this terminology is used, the investigator should modify the term "lupus band" by a preceding adjective of "lesional" or "non-lesional", so that the subject of discussion is clearly identified.

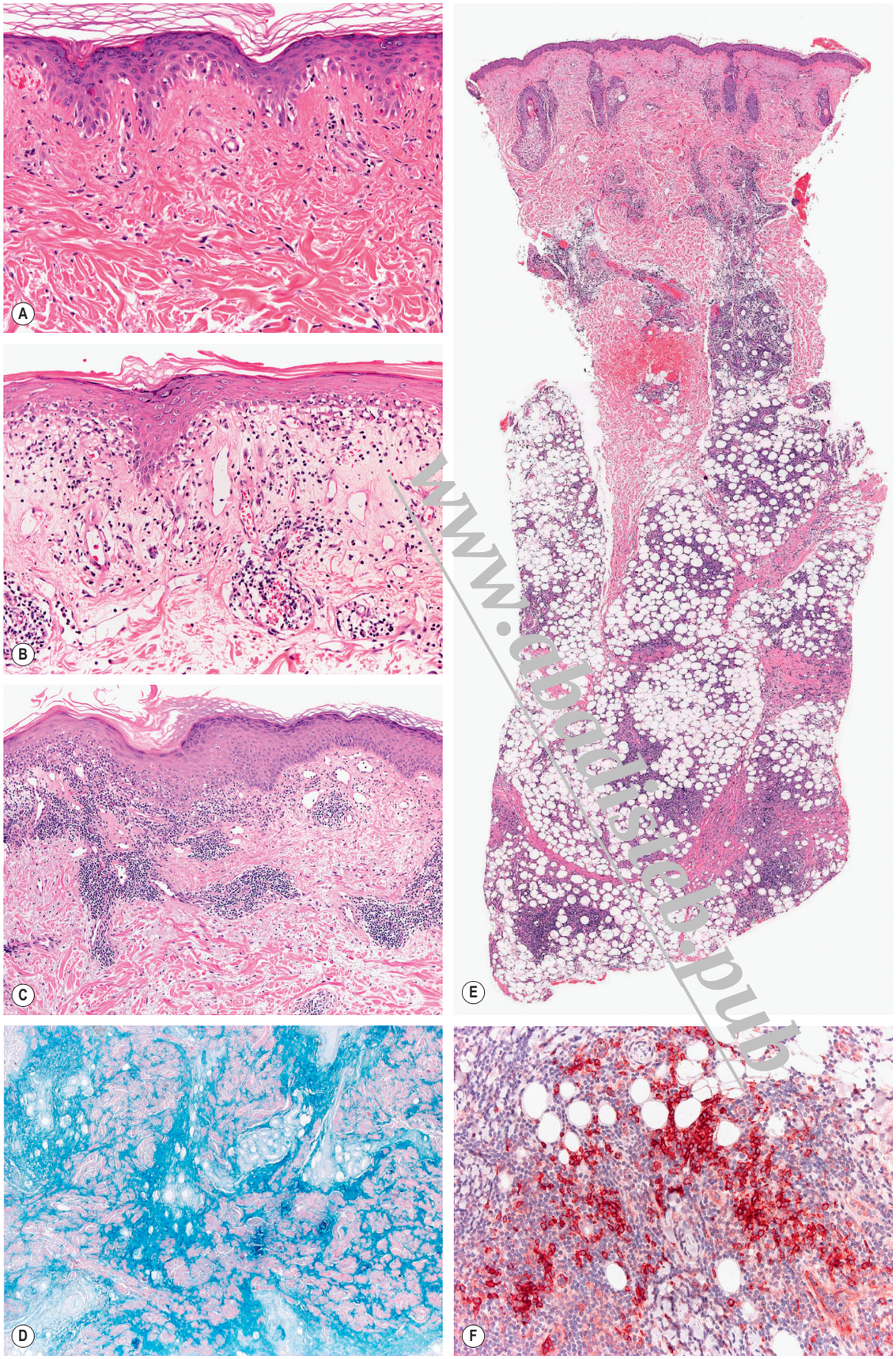


Fig. 41.17 Histopathologic features of cutaneous lupus erythematosus (LE). A Acute cutaneous LE showing mild interface dermatitis with vacuolization of basal keratinocytes and sparse superficial lymphoid infiltrates. **B** Subacute cutaneous LE with more obvious interface dermatitis and perivascular inflammation. **C** Discoid LE showing focal interface dermatitis and dense perivascular lymphoid infiltrates throughout the dermis. **D** Mucin deposition within the dermis highlighted by a colloidal iron stain. **E** Lupus panniculitis with prominent inflammatory infiltrates within the lobules of the subcutaneous fat. Perivascular and periadnexal lymphocytic infiltrates are also present in the dermis. **F** The pattern and intensity of immunohistochemical staining for CD123 (plasmacytoid dendritic cells) may help to distinguish cutaneous lupus, including lupus panniculitis, from other disorders. *Courtesy Lorenzo Cerroni, MD.*

Weak, discontinuous deposits may be seen in persons who do not have LE, including healthy adults, particularly when chronically sun-exposed skin is examined. For this reason, many investigators do not consider a non-lesional lupus band test to be positive unless the deposition of immunoreactants is strong and continuous. A true positive non-lesional lupus band test occurs in three-quarters or more of patients with SLE if sun-exposed skin is examined, and in about one-half of patients with SLE if sun-protected skin is examined[75]. A positive non-lesional lupus band test is unlikely to occur in patients who do not have SLE, but there are instances where the non-lesional lupus band test has been positive in patients with other autoimmune diseases.

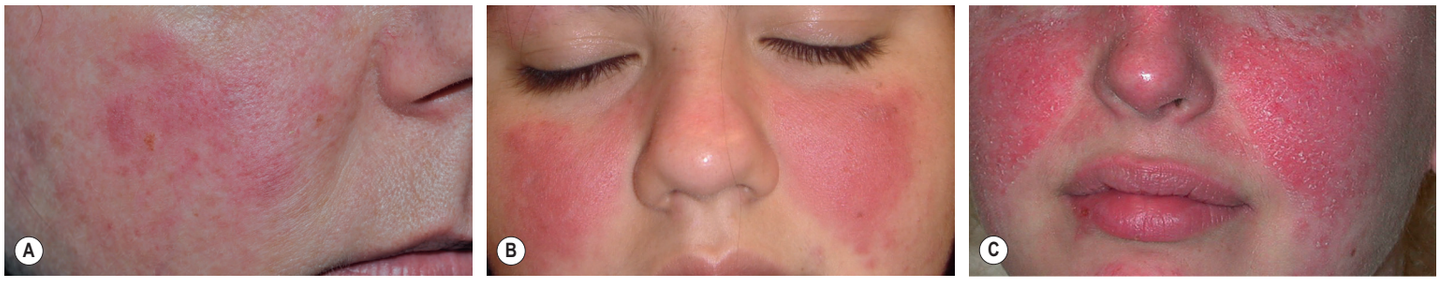


Fig. 41.9 Acute cutaneous lupus erythematosus (ACLE). The facial erythema, often referred to as a "butterfly rash" may be variable (**A**), edematous (**B**), or have associated scale (**C**). The presence of small erosions can aid in the clinical differential diagnosis. *A, Courtesy Kalman Watsky, MD.*

MEDICATIONS ASSOCIATED WITH DRUG-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS
More common/higher risk*
Terbinafine
Thiazide diuretics (e.g. hydrochlorothiazide)
TNF inhibitors (e.g. adalimumab, etanercept, golimumab, infliximab)
Proton pump inhibitors (e.g. lansoprazole, pantoprazole, omeprazole)
Calcium channel blockers (e.g. diltiazem, nifedipine, nitrendipine, verapamil)
Anti-epileptics (e.g. carbamazepine, phenytoin)
Chemotherapy (e.g. taxanes, capecitabine, gemcitabine > doxorubicin, 5-fluorouracil)
Immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab, atezolizumab)
ACE inhibitors (e.g. enalapril, lisinopril)
Less common*
β-blockers
Imiquimod (topical)
Interferon-α and -β
Other immunomodulators (e.g. abatacept, leflunomide, secukinumab, ustekinumab)
Palbociclib, abemaciclib
Ranitidine
HMG-CoA reductase inhibitors ("statins")
Tamoxifen
Thrombocyte inhibitors (e.g. ticlopidine)
VEGF/VEGFR inhibitors (e.g. bevacizumab, pazopanib)
*Medications are classified as being more common or having a higher risk if there were >10 cases reported in the literature as of 2023 or the relative risk in reference 48 was ≥2.0. Medications are classified as being less common if there have been 3–10 cases reported and the relative risk was <2.0.

Table 41.2 Medications associated with drug-induced subacute cutaneous lupus erythematosus (SCLE). ACE, angiotensin converting enzyme; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

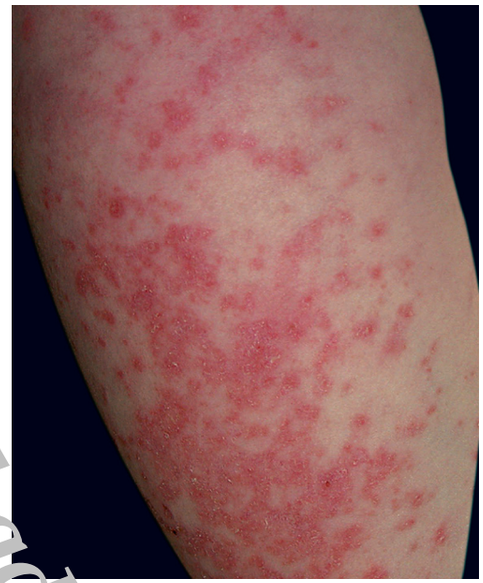


Fig. 41.10 Acute cutaneous lupus erythematosus (ACLE). This patient had ACLE lesions on the arms as well as the face.

Approximately half of patients presenting with SCLE fulfill classification criteria for SLE[51]. However, most do so on the basis of laboratory and mucocutaneous findings. In a study of 85 SCLE patients, only six had renal and three had neurologic disease[51]. Since anti-SSA/Ro autoantibodies are associated with Sjögren syndrome as well as SCLE, it is not surprising that some patients have features of both conditions, and some may have serious internal manifestations of Sjögren syndrome such as pulmonary or neurologic disease.

An important feature of SCLE, from the standpoint of understanding the pathogenesis of lupus, is its regular association with anti-SSA/Ro autoantibodies (see Ch. 40). Although investigators differ in their opinions as to the prevalence of anti-SSA/Ro autoantibodies in SCLE, it is likely that a substantial majority of patients with this condition (~70% in a large series, reported range of 60%–100%) have anti-SSA/Ro antibodies[46,52].

Acute cutaneous lupus erythematosus (ACLE)

The lesions of ACLE are exemplified by the development of bilateral malar erythema ("butterfly rash"; Fig. 41.9). These lesions tend to be transient, follow sun exposure, and resolve without scarring (but sometimes with dyspigmentation). An association with anti-dsDNA antibodies and lupus nephritis has been proposed and is plausible, although some patients with a malar rash have neither anti-dsDNA antibodies nor lupus nephritis. Patients presenting with this type of eruption must be evaluated carefully for evidence of internal disease.

The morphology of the lesions ranges from mild erythema to intense edema. The presence of telangiectasias, erosions, dyspigmentation and epidermal atrophy (i.e. poikiloderma) may help to distinguish the malar erythema of ACLE from that of common facial eruptions such as seborrheic dermatitis and the erythematotelangiectatic type of rosacea. Occasionally, there is a papular component, and occasionally lesions develop scaling (see Fig. 41.9C). The duration may range from a few hours to several weeks. The face, particularly the malar area, is most commonly affected, and there is often sparing of the nasolabial fold; sometimes lesions may be more widespread in distribution (Fig. 41.10; see Fig. 41.4). When lesions occur on the hands, the knuckles are typically spared. It is not unusual for patients with ACLE to also have oral ulcerations.

The presence of erythema multiforme-like lesions in lupus patients has been termed Rowell syndrome[53]. Rarely, patients develop an acute eruption clinically similar to toxic epidermal necrolysis or erythema multiforme major (see below). These lesions may represent a severe variant of ACLE or, in some cases, SCLE.

The three major types of cutaneous LE are not mutually exclusive. In a given patient, more than one type of cutaneous lesion may occur.

Cutaneous Lupus – Additional Variants (See Fig. 41.2)

Lupus erythematosus tumidus

Lesions are typically firm erythematous plaques that lack scale or follicular plugging. Although the epidermis appears to be uninvolved in the disease process, there is an intense perivascular and periadnexal inflammatory infiltrate within the dermis, as well as mucin deposition. LE tumidus lesions may be the same as the "urticarial plaques" described in lupus patients. However, these fixed plaques should not be confused with urticarial vasculitis (see Ch. 24). Some authors state that the lesions most commonly occur on the face, but they are often

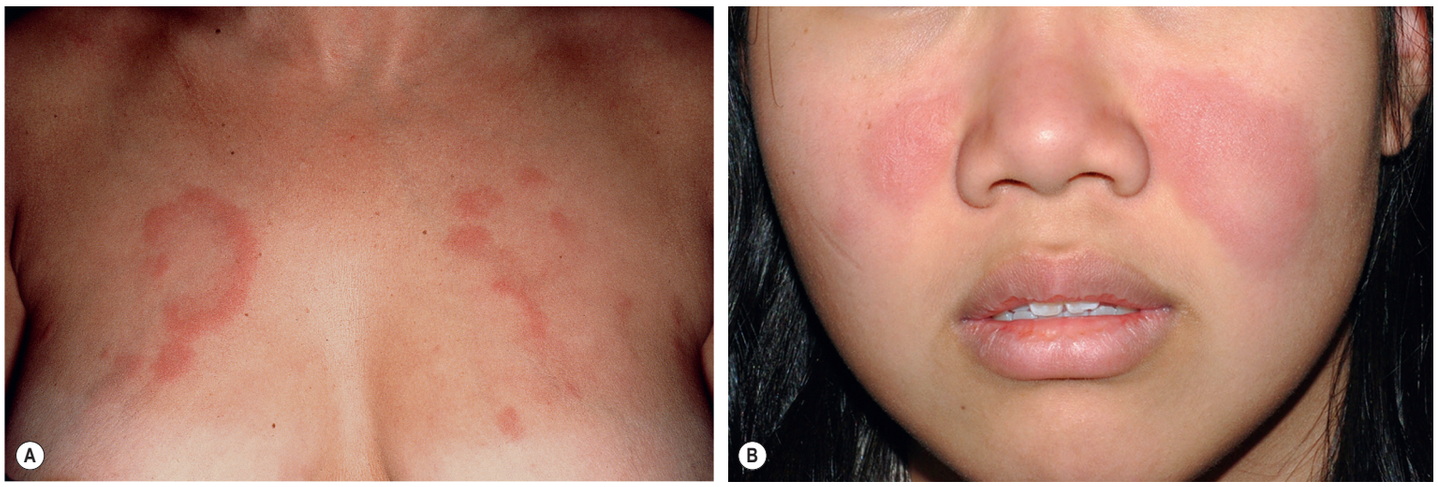


Fig. 41.11 Lupus erythematosus tumidus. Annular pink plaques on the chest (**A**) and pink–violet plaques on the face (**B**). None of the lesions have epidermal change. *B, Courtesy Julie V. Schaffer, MD.*

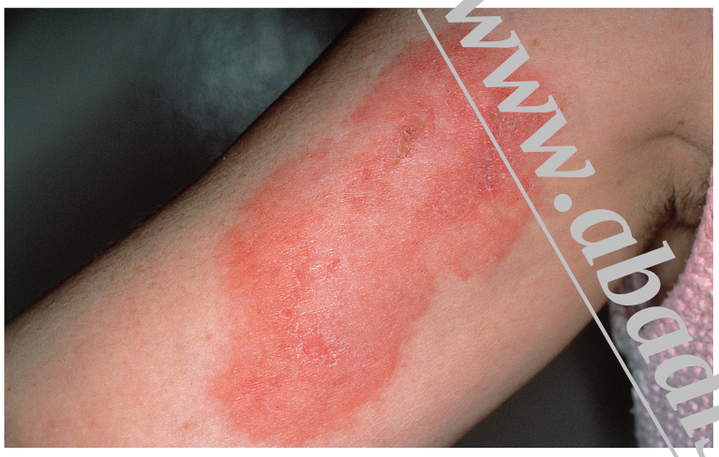


Fig. 41.12 Lupus panniculitis. Erythematous plaque on the upper arm. The lesions may resolve with lipoatrophy.

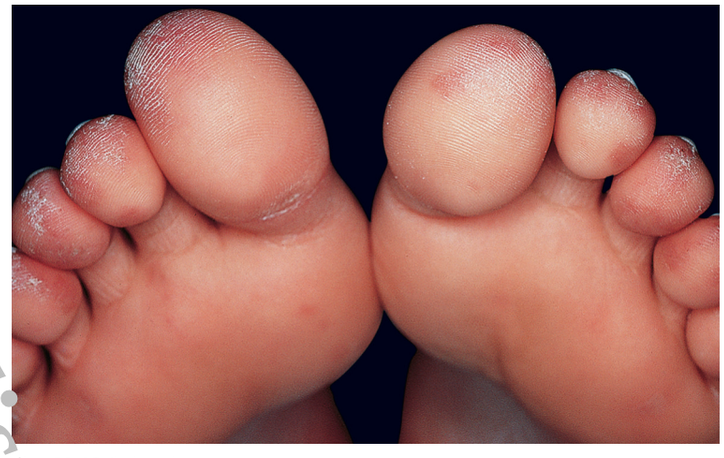


Fig. 41.13 Chilblain lupus. Violaceous plaques, some with scale, on toes. If there is a family history of this disorder, the possibility of mutations in *TREX1*, which encodes a DNA exonuclease, or *SAMHD1*, which encodes a host restriction nuclease that plays a role in the innate immune response, can be considered.

observed on the trunk as well (Fig. 41.11). Morphologically, the lesions are similar to those of lymphocytic infiltrate of Jessner and may have central clearing (see Ch. 121); some clinicians believe that lymphocytic infiltrate of Jessner and LE tumidus are either very closely related or exist along the same disease spectrum[54].

In patients reported to have LE tumidus, the very low prevalence of SLE, the relative lack of serologic abnormalities, and the very low prevalence of immunoglobulin deposition within the cutaneous lesions have made it difficult to determine whether LE tumidus is actually a variant of LE or an independent entity. However, the presence of LE tumidus lesions in patients with other specific types of cutaneous LE is evidence in favor of its being classified as a form of cutaneous LE. In the majority of patients, LE tumidus has been reported to be reproducible by phototesting[55]. The lesions tend to resolve without scarring, atrophy, or dyspigmentation.

Lupus panniculitis

Intense inflammation in the fat leads to indurated plaques that can evolve into disfiguring, depressed areas. Lesions of lupus panniculitis have a distinctive distribution, occurring predominantly on the upper arms (Fig. 41.12), face, scalp, upper trunk, thighs, buttocks, and breasts (see Fig. 41.4)[56]. Some patients may have discoid lesions overlying the panniculitis, and, in those cases, the condition is sometimes referred to as lupus profundus. For further discussion of lupus panniculitis, see Chapter 100.

Chilblain lupus

Chilblain lupus (SLE pernio; Fig. 41.13) consists of red or dusky purple papules and plaques on the toes, fingers, and sometimes the nose, elbows, knees, and lower legs. The lesions are brought on or exacerbated by cold, particularly moist cold climates. These lesions may represent the concurrence of ordinary chilblains in a patient with LE (see Ch. 88), although, with time, the lesions may develop a gross and microscopic appearance consistent with that of a discoid lesion.

Heterozygous mutations in *TREX1* (see above) or *SAMHD1* can lead to a familial form of chilblain lupus with an onset during childhood[57]. Affected individuals may have arthralgias and a positive ANA, but otherwise do not develop internal disease. Mutations in these same genes, as well as *ADAR1*, *IFIH1*, and *RNASEH2A/B/C*, can result in the Aicardi–Goutières syndrome, a primarily autosomal recessive autoinflammatory disorder characterized by recurrent sterile fevers, progressive developmental delay, and chilblains (see Table 45.7, Type I interferonopathies). Mutations in these seven genes lead to an accumulation of nucleic acids, e.g. dsDNA, RNA:DNA duplexes.

Discoid lupus erythematosus/lichen planus overlap syndrome

A discoid lupus erythematosus/lichen planus overlap syndrome has been described, in which lesions with features of both conditions are present (see Ch. 11).

Neonatal lupus erythematosus (NLE)

A neonatal form of SCLE may occur in infants whose mothers have anti-SSA/Ro autoantibodies. In babies who have neonatal lupus erythematosus (NLE), the SCLE-like lesions are histologically identical to

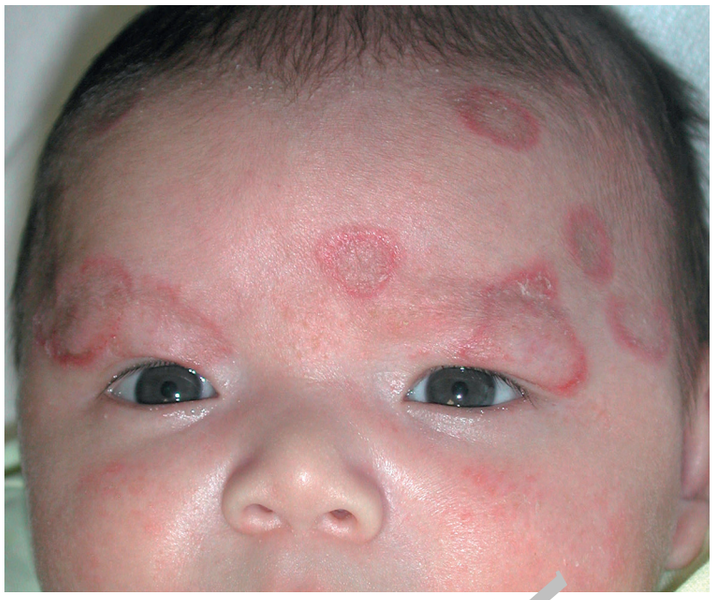


Fig. 41.14 Neonatal lupus erythematosus. Annular erythematous plaques on the forehead and scalp. Note the resemblance to the annular form of subacute cutaneous lupus erythematosus. *Courtesy Julie V. Schaffer, MD.*

SYSTEMIC EVALUATION OF AN INFANT WITH CUTANEOUS NEONATAL LUPUS ERYTHEMATOSUS
Initial and serial evaluations until 6–9 months of age
History, review of systems & physical examination: examination includes monitoring of growth and head circumference*; frequency depends upon degree of systemic involvement
Laboratory studies: electrocardiogram +/– echocardiogram, CBC with differential and platelet count, liver function tests; if tests are initially normal and infant without signs or symptoms, then tests repeated every 2–3 months × 2–3 (otherwise more frequently)
Family counseling and care coordination: risk for NLE in subsequent pregnancies, risk for development of AI-CTD in mother and, possibly, child
Preemptive treatment: for mothers of infants with cardiac NLE, consider hydroxychloroquine during subsequent pregnancies
Long-term considerations
History and physical examination: periodically per pediatrician
Laboratory studies: if normal or return to normal and the child remains healthy, further testing is not required
Risk of AI-CTD as adolescent/adult
*Macrocephaly/hydrocephalus and chondrodysplasia punctata (stippled epiphyses) have been reported as possible manifestations of NLE.

Table 41.3 Systemic evaluation of an infant with cutaneous neonatal lupus erythematosus (NLE). In the setting of characteristic skin lesions, the diagnosis is established via autoantibody testing in the mother (anti-SSA/Ro autoantibodies) +/– in the infant (anti-SSA/Ro, -RNP); if skin lesions are atypical, histologic examination may be required. AI-CTD, autoimmune connective tissue disease; CBC, complete blood count.

those of SCLE in adults, and there is a strong association with anti-SSA/Ro antibodies. Indeed, almost 100% of babies with NLE have anti-SSA/Ro antibodies[58], and less frequently anti-U_1RNP autoantibodies are present. Unlike SCLE in adults, lesions have a predilection for the face, especially the periorbital region and scalp (Fig. 41.14).

Photosensitivity is very common in NLE, but sun exposure is not required for lesions to form, as it is possible for lesions to be present at birth. Neonatal lupus skin lesions typically resolve completely, although perhaps one-fourth to one-third of children have cutaneous residua of telangiectasias, dyspigmentation, and/or atrophic scarring[59,60]. Atrophic scarring may be more likely in infants whose lesions began *in utero*[60].

Infants who have the cutaneous lesions of NLE may also exhibit internal manifestations. The major extracutaneous findings are congenital heart block (with or without cardiomyopathy), hepatobiliary disease, and cytopenias, in particular thrombocytopenia. The heart block is almost always present by birth, but on rare occasions has developed after birth. Clinically significant cardiomyopathy occurs concurrently in a small percentage of babies who have heart block. Usually, the cardiomyopathy is apparent during the neonatal period, but it is possible for it to become apparent only after several months have elapsed. Cardiac NLE has a mortality rate of approximately 20%, and approximately two-thirds of children require pacemakers[61].

Hepatobiliary disease and cytopenias, especially thrombocytopenia, may be present at birth, or they may develop within the first few months of life[62]. Hepatobiliary disease can vary in severity and may present as liver failure during gestation or in the neonatal period, conjugated hyperbilirubinemia during the first few weeks of life, or mild elevations of aminotransferases at 2–3 months of life. There are also reports of hydrocephalus, microangiopathic hemolysis, and disseminated intravascular coagulation.

Although most children with cutaneous NLE do not have significant internal involvement, a systemic evaluation and counseling is recommended (Table 41.3). Mothers who have had a baby with cutaneous NLE have an increased likelihood of having a subsequent pregnancy complicated by NLE, including cardiac involvement. When pregnant, these women should be cared for by a perinatologist who has specialized training in high-risk prenatal care.

Bullous lesions

In the clinical setting of lupus, bullous lesions may appear for several reasons. On occasion, bullous or crusted lesions occur simply as a result of the intensity of the basal cell damage in lesions of ACLE or SCLE (see Fig. 41.8A) or, possibly, DLE. Rarely, a dramatic, acute eruption similar to erythema multiforme major or toxic epidermal necrolysis (TEN) may occur in patients with preexisting ACLE or SCLE, or it may appear *de novo* (Fig. 41.15). Blisters occurring within ACLE and SCLE lesions and erythema multiforme-like and TEN-like cutaneous lupus fit within the category of lupus-specific skin lesions.

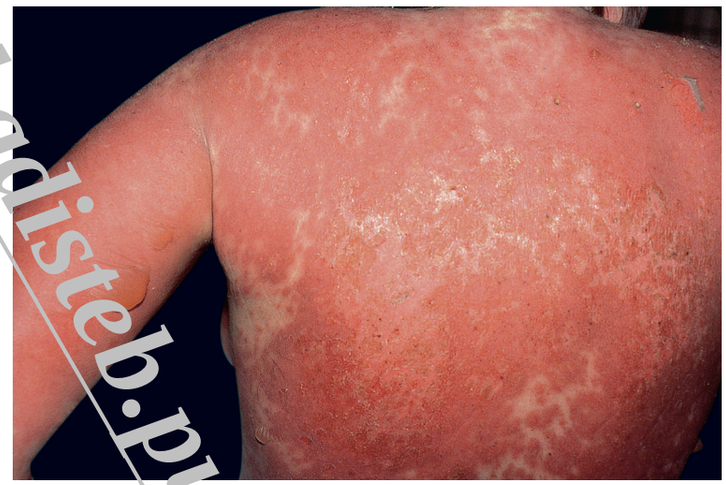


Fig. 41.15 Toxic epidermal necrolysis-like eruption of acute lupus erythematosus. This presentation has also been referred to as a form of *a*cute *s*yndrome of *a*poptotic *p*an-epidermolysis (ASAP).

The term bullous eruption of SLE, or bullous SLE, has been used to describe an acquired blistering eruption in patients who fulfill the criteria for SLE. It consists of vesicles and bullae whose histopathology often resembles dermatitis herpetiformis, with a primarily neutrophilic infiltrate and microabscesses within the dermal papillae (Fig. 41.16)[63]. In some patients, the clinical and histopathologic features may resemble neutrophil-rich bullous pemphigoid or epidermolysis bullosa acquisita. Immunoreactants are often found at the basement membrane zone and antibodies to type VII collagen have been detected in several patients[64]. This eruption may represent the concurrence of lupus with an autoimmune blistering disease due to autoantibodies to a component of the basement membrane zone. There are also a number of case reports of other autoimmune bullous diseases appearing in patients with lupus (reviewed in reference 65).

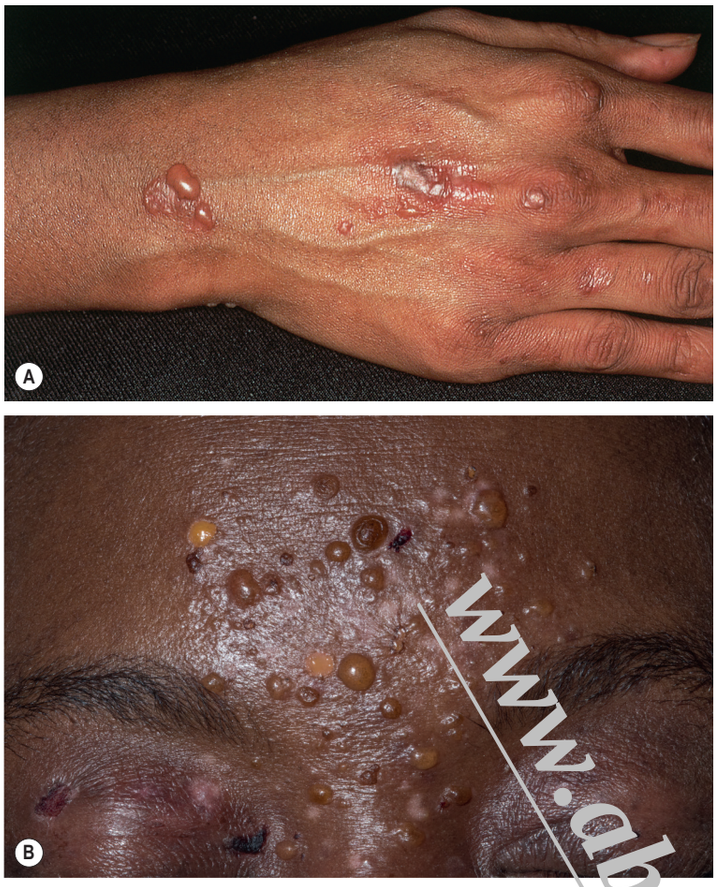


Fig. 41.16 Bullous eruption of systemic lupus erythematosus. A Vesicles and bullae due to autoantibodies against type VII collagen can develop in patients with systemic disease. **B** Multiple vesicles and bullae as well as erosions and hypopigmentation at sites of previous lesions in a woman with SLE. *B, Courtesy Edward Cowen, MD.*

Systemic Lupus Erythematosus

Lupus erythematosus is potentially a multi-organ disease, although in individual patients often only one or a few organs are significantly involved. Organ systems most commonly affected are joints, skin, hematologic, renal, and CNS as well as pleural and pericardial serosal surfaces. Nonspecific signs and symptoms such as fever, weight loss, fatigue, myalgias, and lymphadenopathy are also common in SLE. Additional less common manifestations are quite varied and include sensorineural hearing loss and vision loss. Although ACLE is the cutaneous phenotype with the strongest association with systemic disease, patients with any type of cutaneous LE may develop internal involvement.

Since SLE is complex and variable, classification criteria have been developed to ensure that patients in clinical studies have SLE rather than other conditions that may mimic it. Historically, the American College of Rheumatology (ACR) criteria, developed in 1982 and modified in 1997, have been most commonly used. In 2012, a new set of criteria from the Systemic Lupus International Collaborating Clinics (SLICC) aimed to improve the sensitivity of the ACR criteria[66] (Table 41.4). In 2019, the ACR, in concert with the European League Against Rheumatism (EULAR), released a new classification system[67] (Table 41.5). Some of its notable features are as follows:

1. Presence of ANA (titer ≥1 : 80) is an entry criterion. Patients with persistently negative ANA tests are excluded.
2. Individual criteria have different weights and need not occur simultaneously.
3. Within a particular domain (e.g. renal), only the highest weighted criterion counts.
4. A criterion is counted only if SLE is the most likely explanation for the finding.

Nonspecific Cutaneous Lesions

Vascular lesions are common in patients with LE, particularly in those who have systemic disease (Table 41.6). These lesions include Raynaud phenomenon (see Ch. 43), livedo reticularis, palmar erythema, and nail-fold telangiectasia. Purpura, urticarial papules, or ulcerations due to vasculitis may occur, as well as cutaneous infarctions resembling Degos disease or atrophie blanche. Patients with cutaneous LE who have any of these findings should be evaluated for systemic disease. Livedo reticularis, thromboses, ulcerations, and lesions resembling Degos disease have each been associated with antiphospholipid antibodies[68] (see Ch. 23). The association of livedo reticularis with ischemic CNS disease has been called Sneddon syndrome (see Ch. 23), and the phenotype of the antiphospholipid syndrome has been called Hughes syndrome[69].

Alopecia often occurs as a result of scarring discoid lesions. However, non-scarring diffuse alopecia can appear in patients with systemic disease. It has been reported that patients with lupus have an increased likelihood of alopecia areata compared with the general population.

Sclerodactyly, calcinosis, and rheumatoid nodules, findings more consistent with systemic sclerosis or rheumatoid arthritis, have been observed in some patients with lupus, although many of the patients with these findings may have overlap syndromes rather than classic lupus. Other skin findings reported to occur in patients who have lupus include erythromelalgia, papulonodular mucinosis (of Gold; see Ch. 46), and anetoderma (see Ch. 99). Of note, ~75% of the patients with papulonodular mucinosis have SLE. Rarely, significant periorbital edema can develop secondary to dermal mucin. A Sweet syndrome-like presentation can also be seen in patients with SLE and this has been given several names including neutrophilic dermatosis in conjunction with LE and non-bullous neutrophilic LE as well as simply Sweet syndrome in association with SLE.

Patients with SLE have more subtle nail-fold capillary abnormalities than do patients with systemic sclerosis or dermatomyositis. Prominent large, tortuous capillaries and areas of marked avascularity are not characteristic of SLE.

PATHOLOGY

Histopathology

Histologic findings in cutaneous LE depend in large part on the subtype (Fig. 41.17; see Fig. 41.3). Characteristic findings in ACLE, SCLE, discoid lesions, LE tumidus, and lupus panniculitis are outlined in Table 41.7. However, in practice, an overlap in histologic findings occurs among the various clinical phenotypes, particularly ACLE, SCLE, and discoid lesions. Some of the more distinctive histologic features of cutaneous LE are basal cell damage (also referred to as vacuolar degeneration, hydropic change, or interface dermatitis), lymphohistiocytic inflammatory infiltrates admixed with $CD123^+$ plasmacytoid dendritic cells, and, primarily in discoid lesions, periadnexal inflammation, follicular plugging, and scarring. In lesions of ACLE, dermal changes can be relatively subtle although basal cell damage may be pronounced. In SCLE, epidermal changes and a superficial lymphocytic infiltrate are common. In contrast to discoid lesions, SCLE lesions tend to have little or no hyperkeratosis, basement membrane thickening, periadnexal infiltrate, follicular plugging, deep dermal infiltrate, or scarring[70,71]. LE tumidus has prominent dermal mucin deposition and dermal perivascular and periadnexal lymphocytic infiltrates with a lack of epidermal change. While changes of lupus panniculitis are most prominent in the subcutis, there may be overlying changes of DLE[72]. Occasionally, cutaneous LE presents with a neutrophil-rich infiltrate mimicking that of a neutrophilic dermatosis.

The inflammatory infiltrates of cutaneous lupus typically contain plasmacytoid dendritic cells that produce interferons and may play a role in the induction of lesions. Immunohistochemical staining for CD123, a marker for plasmacytoid dendritic cells, has been explored as a means to distinguish cutaneous lupus from other inflammatory diseases (e.g. lichen planopilaris, polymorphous light eruption) and from cutaneous lymphoma. Although positive CD123-staining is not specific for lupus and its sensitivity and specificity remain to be definitively established[73], the pattern and intensity of staining may help to distinguish lupus from other conditions.