

Chapter 12 Collagen Diseases

Collagen diseases share certain similarities with autoimmune diseases, because autoantibodies specific to each collagen disease are produced. Multiple organs may be affected, and the site of the main lesion often differs from case to case: Diagnosis of collagen diseases is mainly based on the criteria established by the American College of Rheumatology, which include cutaneous lesions. Dermatologists play an important role in diagnosing and treating collagen diseases.

A. Lupus erythematosus (LE)

Definition, Classification

Lupus erythematosus (LE) is a diagnostic name for diseases that cause various systemic changes including those in the skin, such as systemic lupus erythematosus (SLE) and neonatal lupus erythematosus. The term is also used for localized cutaneous lesions such as those seen in discoid lupus erythematosus (DLE), lupus erythematosus profundus and subacute cutaneous lupus erythematosus. Cutaneous LE is subcategorized as acute, subacute or chronic, with each subcategory having characteristic features (Table 12.1). Since acute LE usually occurs as a manifestation of SLE, it is discussed in the SLE section. Subacute (cutaneous) LE and chronic LE are usually localized on skin, and most cases do not meet the diagnostic criteria of SLE. These two diseases are discussed in another section of this chapter.

1. Systemic lupus erythematosus (SLE) ★★

Outline

- Multiple organ failure occurs. The kidneys, heart, joints and central nervous system are affected. SLE is an autoimmune disease whose cause is unknown. Young women are most commonly affected.
- Typical mucocutaneous manifestations are butterfly rash,

Table 12.1 Lesions of cutaneous lupus erythematosus.

Acute	Progresses in a few days
	Butterfly rash, alopecia, palmar erythema, aphtha
Subacute (SCLE)	Progresses in a few weeks to a few months
	Papulosquamous and annular-polycyclic lesions
Chronic	Progresses over a long period of time
	DLE, lupus panniculitis, lupus profundus, nodular cutaneous lupus mucinosis

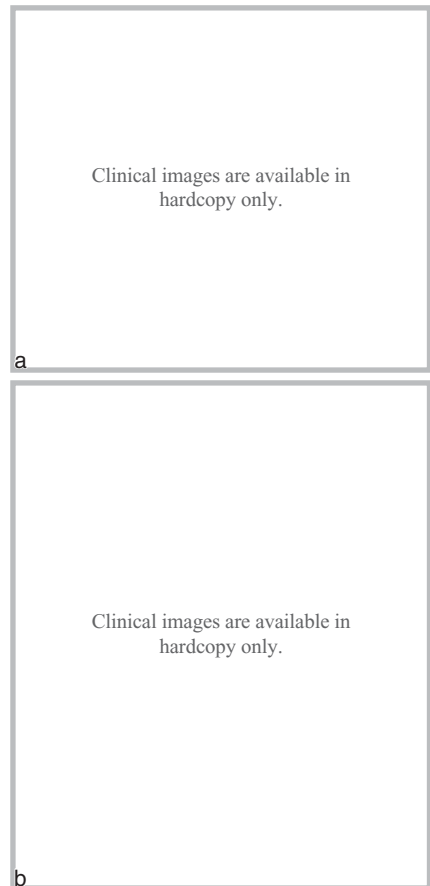


Fig. 12.1-1 Systemic lupus erythematosus (SLE).

a: Butterfly-shaped erythema and edematous erythema that is symmetrically spread from the dorsum of nose to the cheeks of a young woman in her teens. The skin lesion does not usually spread to the nasolabial groove and lips. b: “Butterfly rash” from the recurrence of SLE in a woman in her thirties. As SLE worsens, such rashes may recur.

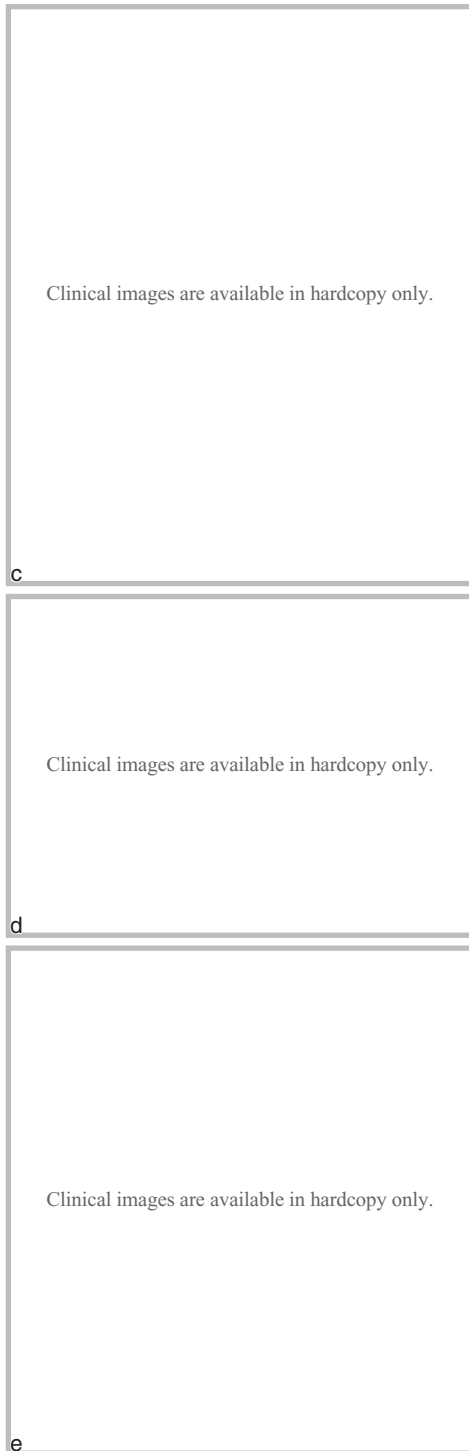


Fig. 12.1-2 Systemic lupus erythematosus (SLE).

c: Skin lesion on fingers caused by discoid lupus erythematosus. Tenderness may be present. d: Diffuse erythema on the sole and toes. e: A large ulcer in the pharyngeal region. Large oral mucosal ulcers may be caused by SLE.

DLE, oral ulceration, solar photosensitivity and alopecia.

- The laboratory findings are antinuclear antibody positive, anti-dsDNA antibody positive, anti-Sm antibody positive, LE cell positive, biological false positive serological reaction for syphilis, decreased complements, and pancytopenia.
- The diagnostic criteria are those published by the American College of Rheumatology.
- The main treatment is oral corticosteroids.

Epidemiology

The onset tends to be between the ages of 10 and 30. Women outnumber men 10 to 1. Therefore, the majority of patients are women of childbearing age.

Cutaneous features

Various cutaneous findings are observed in more than 80% of cases. The four main symptoms of SLE, which are included in the diagnostic criteria (**Table 12.2**), are erythema on the cheeks, chronic DLE, oral ulcers and photosensitivity (**Figs. 12.1-1 to 12.1-3**). The frequencies of occurrence of various symptoms in SLE are listed in **Fig. 12.2**.

Erythema on the cheeks (Fig. 12-1-1): Also called butterfly rash, this is the most characteristic eruption. It is seen in about 90% of cases. Edematous erythema spreads symmetrically on cheeks with the dorsal nose at the center, forming a butterfly pattern. Generally, it does not extend beneath the nasolabial groove. The margin of the erythema is relatively distinct, with slight elevation. Blistering is rarely present. The patients are asymptomatic or have mild subjective symptoms, such as a slight burning sensation. It heals without scarring.

DLE: Discoid lupus erythematosus is sharply margined discoidal erythema. It is seen in 30% of patients with SLE, occurring on exposed sites such as the face, lips and ears. Scales and crusts often form. It gradually progresses into scarring atrophic lesions and causes alopecia when the scalp is affected (described later).

Palmar erythema: This is seen in about 50% of SLE cases. Diffuse erythema occurs on the palms, the thenar and hypothenar in particular. The lesions are hyperkeratotic and often accompanied by scales.

Alopecia: It occurs rapidly and diffusely in the head hair. The occurrence of short, thin, broken hairs at the front edge of the scalp results in uneven hair length (lupus hair). The severity of the alopecia is considered to reflect the degree of SLE progression.

Enanthema: This is seen in about 40% of SLE cases. Small hemorrhagic lesions with a red halo and small ulcers appear on the lips, oral mucosa, pharynx and pharyngeal mucosa. They may be found in DLE of the mucous membranes.

Subcutaneous nodules: Nodules form on the face, hips and upper arms. This is from inflammation of fat tissue, also called

Table 12.2 1982 Revised criteria for classification of systemic lupus erythematosus.

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, but tending not to appear on the nasolabial folds
2. Discoid rash	Raised erythematous patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash from unusual reaction to sunlight, revealed by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	a) Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis—documented by ECG or rub or by evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 g per day or greater than 3+ if quantitation is not performed OR b) Cellular casts—may be red cells, hemoglobin, granules, tubules or mixed
8. Neurologic disorder	a) Seizures—in the absence of causative drugs or known metabolic disorder (e.g., uremia, ketoacidosis, electrolyte imbalance) OR b) Psychosis—in the absence of causative drugs or known metabolic disorder (e.g., uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder	a) Hemolytic anemia—with reticulocytosis OR b) Leukopenia—less than 4,000/mm ³ total on 2 or more occasions OR c) Lymphopenia—less than 1,500/mm ³ on 2 or more occasions OR d) Thrombocytopenia—less than 100,000/mm ³ in the absence of causative drugs
10. Immunologic disorder	a) Positive LE cell preparation OR b) Anti-DNA: antibody to native DNA in abnormal titer OR c) Anti-Sm: presence of antibody to Sm nuclear antigen OR d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

The proposed classification is based on 11 criteria. For clinical studies, a person is said to have systemic lupus erythematosus if any 4 of the 11 criteria are present, serially or simultaneously at any time during observation (Tan EM, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7).

lupus erythematosus profundus (described later).

Other cutaneous symptoms: These include palmoplantar keratosis, purpura, Raynaud’s phenomenon, erythema multiforme, and ulcers in the extremities.



Fig. 12.1-3 Systemic lupus erythematosus (SLE).

f: Diffuse alopecia caused by SLE. In this case, discoid lupus erythematosus (DLE) is present on the sites with alopecia.

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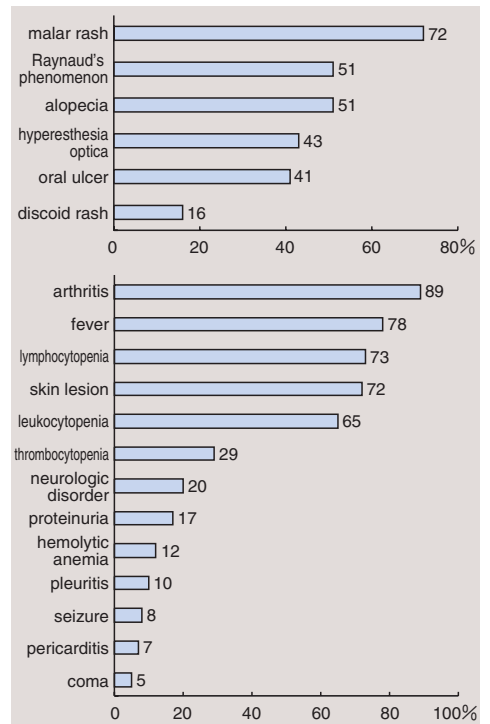
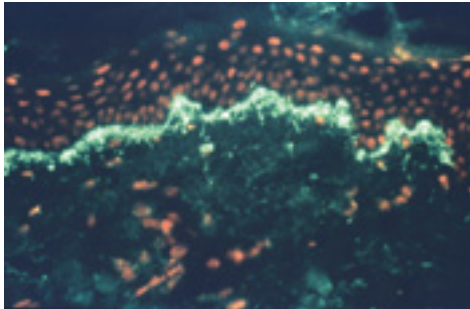


Fig. 12.2 Main eruptions caused by systemic lupus erythematosus (SLE) and their frequency (% of cases).

(Hashimoto H, Miyamoto A, editors. *Systemic lupus erythematosus. Clinical allergology*. 2nd ed. Nankodo; 1998).

Table 12.3 Factors associated with onset of SLE.

Factor	Finding
Genetic	Familial prevalence, especially in monozygotic twins
Viral infection	Type C viral particles are detected in the SLE patient's kidney, skin and lymph nodes. The virus is persistent and forms an immunocomplex, resulting in onset of SLE.
Sex hormone	SLE frequently occurs in women of child-bearing age. Endogenous estrogens and androgens are associated with the onset of SLE. The SLE symptoms in model mice are improved by androgen.
Extrinsic	Procainamide, hydralazine, isoniazid, hydantoin and other drugs may cause skin/systemic symptoms and serological findings that are similar to those of SLE. If these symptoms are improved by discontinuation of these drugs, the condition is called drug-induced lupus. Otherwise these symptoms are thought to be idiopathic SLE that was triggered by drugs.

**Fig. 12.3 Lupus band test.**

Normal skin in the unexposed area of a patient with SLE, observed by direct immunofluorescence. There is linear deposition of IgG (fluorescent green) in the epidermal basement membrane. The nuclei stain orange.

Differences between SLE and DLE MEMO

SLE is the diagnostic name of a condition in which various lesions appear on the whole body. DLE and LE profundus are the diagnostic names of eruptions. Therefore, DLE and LE profundus may occur in patients with SLE, or they may occur without underlying diseases associated with SLE.

Anti-ENA antibody MEMO

Nuclear proteins that are soluble in a buffer solution are called extractable nuclear antigens (ENA). Anti-ENA antibodies include anti-RNP antibodies, anti-Sm antibodies, anti-SS-A antibodies, and anti-SS-B antibodies.

Systemic symptoms

The symptoms of SLE are significantly various (**Fig. 12.2**). The onset is an attack of fever, systemic fatigue, arthralgia and edema, accompanied by the cutaneous symptoms described above.

Renal symptoms: Lupus nephritis is the most critical lesion. It relates closely to the prognosis. It affects various sites and causes proteinuria, hematuria, nephrosis syndrome and renal failure.

Arthralgia: This is seen in more than 90% of SLE cases. Multiple or single arthralgia occurs, transiently in many cases. Proximal interphalangeal joints, knees, legs, shoulders and elbow joints are most frequently affected.

Cardiac symptoms: Libman-Sacks endocarditis, pericardiac inflammation and cardiac tamponade occur.

Mental and neurological symptoms: Central nervous system (CNS) manifestations such as convulsions, impaired consciousness, depression, schizophrenia-like symptoms or cognitive deficit occur in about 20% of cases during the acute active period. It may be difficult to differentiate CNS lupus from similar symptoms caused as side effects by corticosteroids.

Blood abnormalities: Hemolytic anemia (mostly autoimmune hemolytic anemia), leukocytopenia and thrombocytopenia are present.

Pathogenesis

Hereditary predisposition, viral infection, sex hormones and other factors are thought to interact in complex ways to cause immune abnormality and SLE. However, the pathogenesis has not been identified (**Table 12.3**). It is known that antinuclear antibodies, anti-DNA antibodies and anti-Sm antibodies are produced and destroy tissues directly (type II allergy) or form immunocomplexes to destroy tissues by complement cascades (type III allergy), which results in inflammation in the systemic internal organs.

Complications

SLE may present symptoms that meet the diagnostic criteria for collagen diseases such as rheumatoid arthritis, scleroderma, Sjögren syndrome and dermatomyositis (overlap syndrome). Viral infection, such as by herpes zoster, and mycotic infection result from decreased cellular immunity.

Pathology

Pathological findings are various, and each eruption presents different cutaneous clinical features depending on its stage. Cutaneous atrophy, keratotic plug formation, vacuolar degeneration, edema in the upper dermis, mucin deposition, and perivascular and periadnexal inflammatory infiltration of lymphocytes are found. IgG, IgM and C3 may be found deposited in the basement membrane zone of eruptions in unexposed normal-looking skin, which can be identified by skin biopsy and immunofluorescence

(lupus band test; **Fig. 12.3**).

Laboratory findings

Anemia, leukocytopenia, lymphocytopenia and thrombocytopenia are found. The erythrocyte sedimentation rate is elevated as a result of the systemic inflammation; however, CRP is only slightly increased. Human immunoglobulins and IgG increase and complements (C3, C4, and CH₅₀) decrease. SLE is an autoimmune disease; various autoantibodies, such as anti-nuclear antibodies, anti-DNA antibodies (especially antidouble-stranded DNA antibodies; dsDNA) and anti-ENA antibodies are detected in the serum. When antiphospholipid antibodies are positive, biological false positive (BFP) is observed in serological reaction for syphilis.

Diagnosis

Skin biopsy and direct immunofluorescence (IF) are necessary for diagnosis. The diagnosis of SLE can be made when four or more of the 11 diagnostic criteria are satisfied (**Table 12.2**). Even when four criteria are not met simultaneously, the other symptoms often appear later. Therefore, careful observation is required.

Treatment

The primary treatment is administration of immunosuppressants such as steroids, cyclophosphamides, azathioprine and cyclosporines. Steroid pulse therapy may be performed in intractable cases. Psychiatric treatments are also conducted for CNS lupus. Lifestyle guidance is important; stress caused by direct sunlight exposure, over-fatigue or the cold should be avoided as much as possible. It is known that SLE tends to become aggravated during pregnancy.

Prognosis

SLE progresses chronically with repeated aggravation and remission. It used to have great influence on the prognosis of renal disorders. However, the mortality rate has been reduced by dissemination of dialysis therapy (the 5-year survival rate now exceeds 90%). The number of deaths from central nervous system damage and cardiac failure has been increasing. Infection resulting from steroid treatment can be fatal.

2. Discoid lupus erythematosus (DLE) ★★

Definition

Discoid lupus erythematosus (DLE) is the name of an eruption, whereas SLE is the name of a clinical condition with systemic involvement. Some but not all patients with DLE may meet the criteria for SLE. In other words, in many cases of DLE, the skin is the only organ involved. Patients with SLE may have

Clinical images are available in hardcopy only.

a

Clinical images are available in hardcopy only.

b

Clinical images are available in hardcopy only.

c

Fig. 12.4-1 Discoid lupus erythematosus (DLE).

a: The affected dorsal nose of a man in his 20s. The skin lesion is a sharply demarcated macule with a reddish-pink center. The periphery is brownish and accompanied by scaling. b: A sharply margined skin lesion accompanied by dilated hair follicles on the cheek of a woman in her twenties. The lesion is partly erosive. c: A skin lesion spread on the whole of the right cheek of a woman in her thirties. Multiple DLE eruptions of 1 cm in diameter occur and gradually enlarge or coalesce into large plaques.

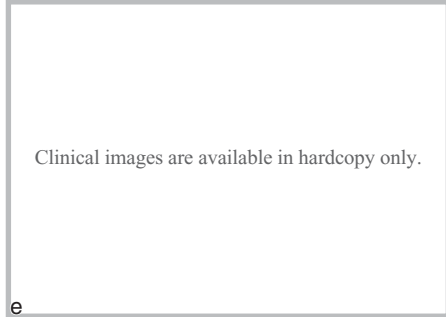
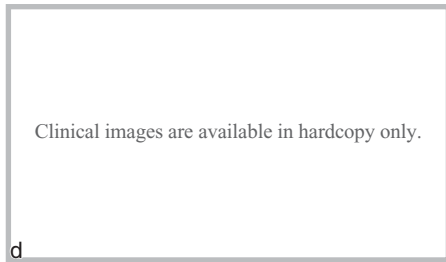


Fig. 12.4-2 Discoid lupus erythematosus (DLE).

d: DLE on the lips. Erythema and purple eruptions are present. It should be differentiated from lichen planus. DLE of the lips may induce squamous cell carcinoma. e: DLE on the dorsum of hand and fingers. There are thick scales and thickening of the skin.

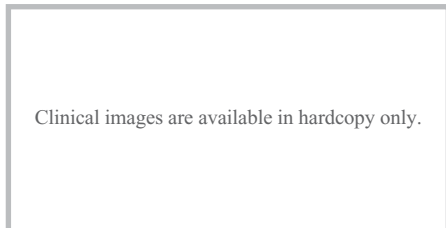
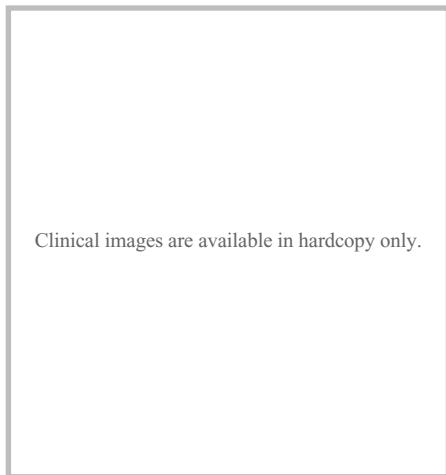


Fig. 12.5 Widespread discoid lupus erythematosus (DLE).

Large areas on the trunk and arms are involved.

DLE eruptions.

Clinical features

Multiple, round to oval, sharply demarcated rose-pink lesions accompanied by scaling and follicular dilation occur on sun-exposed sites (Figs. 12.4-1 and 12.4-2). These tend to occur on the face, scalp and auricular region and, rarely, as individual eruptions at sites lower than the neck. Scaling and ulcerative lesions may occur on the lips of the mouth. When DLE is produced in the head region, scarring alopecia may result from the destruction of hair follicles. These eruptions are aggravated by sun exposure, and they heal with scarring and pigmentation at the center. Multiple DLE eruptions that occur at sites lower than the neck region are called widespread DLE (Fig. 12.5), and these may progress to SLE accompanied by systemic symptoms.

Pathology

The characteristic findings are ① formation of horny follicular plugs, ② flat atrophy of the epidermis, ③ vacuolar degeneration of the basal layer, ④ dense focal infiltration in the periphery of the appendages and blood vessels, and ⑤ mucin deposition in the dermis (Fig. 12.6). Linear deposition of immunoglobulins is found in the skin basement membranes of the lesion in most cases (lupus band test is positive; Fig. 12.3).

Laboratory findings

Lesions tend not to occur in organs other than the skin. General laboratory findings are normal. However, in some cases (widespread DLE in particular), antinuclear antibodies and anti-DNA antibodies may appear, accompanied by hypocomplementemia with progression to SLE.

Table 12.4 Differential diagnosis between DLE and SLE.

	Patients with DLE eruption only	SLE patients with DLE eruption
Difference between sexes	Almost none	Women outnumber men
Common site of eruption	The face, head and auricles	The whole body surface
Clinical features of eruption	Discoidal	Exudative erythema, disseminated plaques
Subjective symptoms	None	Various systemic symptoms
Course of disease	Healing with scarring in several years to several decades	Accompanied by various systemic symptoms
Prognosis	Good	Poor, sometimes fatal
Lupus erythematosus cells	Negative in most cases	Positive in most cases
WBC count	Normal or decreased	Markedly decreased

Differential diagnosis

Patients with DLE eruptions only are compared to those with SLE accompanied by DLE eruptions in **Table 12.4**. Other eruptions that should be distinguished from DLE are polymorphous light eruptions, lichen planus and cutaneous sarcoidosis.

Treatment

Patients with DLE should avoid sunlight, which tends to aggravate the condition. Topical application of steroids and tacrolimus are effective.

3. Lupus erythematosus profundus ★★

Synonym: Lupus panniculitis

Definition

Lupus erythematosus (LE) profundus is a subtype with major lesions in the subcutaneous tissues. It is characterized by nonspecific inflammation of fat tissue.

Clinical features

Lesions occur as subcutaneous induration of normal color or rose pink, most frequently on the face, shoulders and hips (**Fig. 12.7**). DLE may be produced at sites with those lesions. Concave lesions may form in the course of LE profundus, and these heal with concave scarring. LE profundus may occur independently; however, more than half of all cases are accompanied by SLE and DLE.

Pathology

Perivascular infiltration of lymphocytes, mucin deposition and dense lymphocytic infiltration are found in the subcutaneous tissues. Interlobular inflammation gradually becomes fibrotic. Deposition of immunoglobulins and complements may be seen on the blood vessel walls and at dermo-epidermal junctions.

Treatment

Topical or oral corticosteroids are the main treatments.

4. Subacute cutaneous lupus erythematosus (SCLE) ★★**Definition**

Subacute cutaneous lupus erythematosus (SCLE) is characterized by eruptions whose course and duration are intermediate between those of chronic DLE and those of the acute LE seen in SLE.

Clinical features

Multiple eruptions appear symmetrically on sun-exposed sites

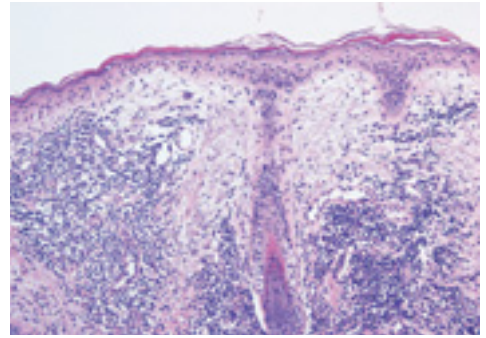


Fig. 12.6 Histopathology of discoid lupus erythematosus (DLE).

There is vacuolar degeneration in the basal cell layer, lymphocytic infiltration in the blood vessels and peripheral skin appendages, and severe edema and mucin deposition in the dermis. Neutrophils and eosinophils are rarely seen.

Clinical images are available in hardcopy only.

Fig. 12.7 Lupus erythematosus profundus.

Large panniculitis in the skin of a patient with SLE. DLE eruptions are present on the skin surface.

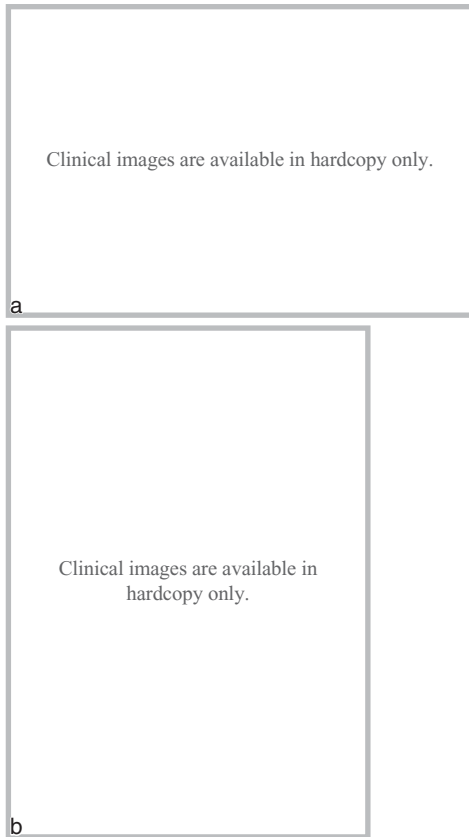


Fig. 12.8 Subacute cutaneous lupus erythematosus (SCLE).

a: Annular polycyclic SCLE on the back. The center of the lesion is healing centrifugally. This condition resembles the annular erythema of Sjögren syndrome. b: Papulosquamous SCLE. Psoriasis-like papules and scaling are present.

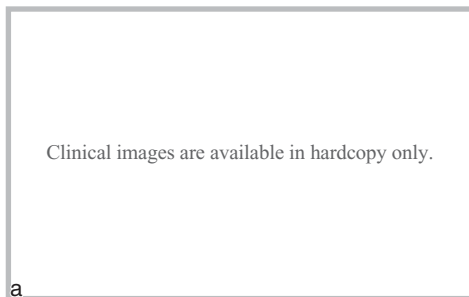


Fig. 12.9-1 Annular erythema in neonatal lupus erythematosus.

a: Annular erythema on the cheek of an infant with neonatal lupus erythematosus. It begins as erythema of 5 mm to 10 mm in diameter and gradually enlarges. The center of the lesion tends to regress; however, marked edema and elevation occur at the periphery.

of the body. There are two types of SCLE: annular-polycyclic SCLE, with erythema whose center tends to have color degradation (**Fig. 12.8**), and papulosquamous (psoriasisiform) SCLE, with eruptions resembling psoriasis. Both types heal without scarring and are recurrent. About half of patients with SCLE meet the diagnostic criteria of SLE. The disease may be accompanied by mild systemic symptoms, such as arthralgia and fever. Severe renal symptoms and central nervous system manifestations are rare.

Pathology

Characteristic findings of lupus erythematosus include epidermal atrophy, vacuolar degeneration in the basal layers, and perivascular and adnexal lymphocytic infiltration.

Laboratory findings

Antinuclear antibodies are positive in more than half of all cases. Since anti-SS-A antibodies and anti-SS-B antibodies are frequently found, a correlation has been reported between SCLE and HLA-B8 or HLA-DR3.

Treatment

The main treatments are corticosteroids applied topically or administered orally in small doses.

5. Neonatal lupus erythematosus ★

Definition

Annular erythema occurs in newborns whose mothers have SLE or Sjögren syndrome with anti-SS-A and/or SS-B antibodies, even when the mother is asymptomatic for both diseases. The face is most frequently involved. Neonatal lupus erythematosus is a specific type of lupus erythematosus.

Clinical features

Neonatal lupus erythematosus resembles the annular erythema that accompanies Sjögren syndrome, or DLE-like annular eruptions in newborns in the first month after birth (**Figs. 12.9-1** and **12.9-2**), and it heals with abnormal pigmentation within 6 months. In addition to systemic symptoms associated with SLE (fever, hepatosplenomegaly, anemia, thrombocytopenia), congenital cardiac block is found in some cases. As cardiac block is irreversible, it requires full attention.

Pathogenesis

Placentally transmitted anti-SS-A antibodies and anti-SS-B antibodies in newborns are thought to lead to neonatal lupus erythematosus. An anti-SS-A antibody against 52kD antigen is strongly suspected of being involved. The cutaneous symptoms subside in 6 months, when placentally transmitted antibodies disappear from the newborns, which implies the involvement of the

antibodies.

Treatment

Symptomatic therapies for the eruptions and the systemic symptoms are the main treatments. A pacemaker may be implanted in patients with cardiac block.

6. Nodular cutaneous lupus mucinosis ★

Papules and nodules occur on the back and upper arms. Nodular cutaneous lupus mucinosis is a subtype of cutaneous LE. These lesions are caused by deposition of mucin in large amounts in the dermis, and they often accompany SLE.

7. Bullous lupus erythematosus ★

Bullous lupus erythematosus is a specific subtype of cutaneous LE in which blisters form. Antinuclear antibodies in the serum and autoimmune antibodies against type VII collagen in the basement membranes are thought to cause blistering. Blisters may form on normal skin or on LE erythematous lesions (**Fig. 12.10**).

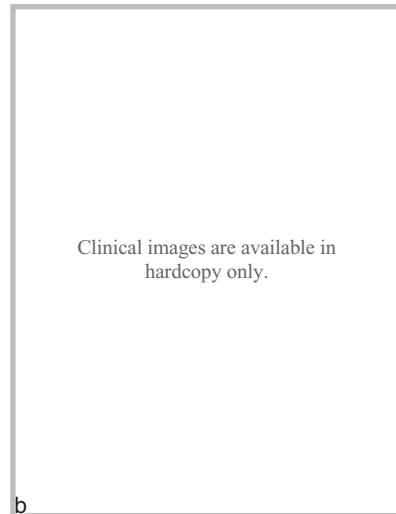


Fig. 12.9-2 Annular erythema in neonatal lupus erythematosus.

b: Two annular erythema on the face.

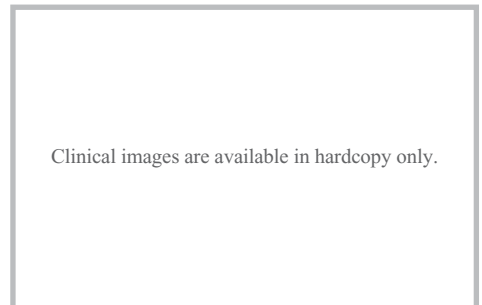


Fig. 12.10 Bullous lupus erythematosus.

Bullous LE in a patient with SLE. Vesicles form not only on the LE erythema but also on the normal looking skin.

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B. Scleroderma

Scleroderma is characterized by sclerosis of the skin that follows a course of edema, sclerosis and atrophy. It is divided into systemic sclerosis (SSc) and localized scleroderma. In SSc various lesions occur in the internal organs, whereas in localized scleroderma the internal organs are not involved.

1. Systemic sclerosis (SSc) ★★

Synonym: Progressive systemic sclerosis (PSS)

Outline

- Generalized cutaneous sclerosis, fibrosis in the synovium and small arteries, and Raynaud’s phenomenon are found.

Renaming from PSS to SSc

MEMO

Because progressive systemic sclerosis (PSS) is not necessarily progressive, the disease has come to be called systemic sclerosis (SSc).