C. Perforating dermatosis

**Elastosis perforans serpiginosa**

**Clinical features**

Small, bilaterally symmetrical, reddish-brown keratotic papules with an atrophic and umbilicated center are produced in linear or circular arrangement on the neck region, extremities and upper trunk, giving the skin a serpentine appearance (Fig. 18.12). Köbner phenomenon tends to be positive.

**Pathogenesis**

Transepidermal elimination results from elimination of degenerated elastic fibers in the upper dermal layer through the epidermis. It may appear idiopathically in young men. In up to a third of cases, there is an associated systemic condition or connective tissue disorder. It tends to accompany abnormality of the dermis, such as Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum or dysostogenesis. It may be caused by prolonged intake of D-penicillamine.

**Pathology**

Degenerated elastic fibers accumulate in the dermal upper layer, on which the epidermis proliferates to enwrap the abnormal fibers into the dermis. Thickening of the epidermis and foreign-body granuloma in the dermis occur.

D. Granulomatous disorders

1. **Sarcoidosis**

**Outline**

- It is a systemic granuloma of unknown pathogenesis.
- The skin symptoms are granulomatous lesion (cutaneous sarcoidosis) and inflammatory reactive lesion (e.g., erythema nodosum).
- Extracutaneous lesions such as those of bilateral hilar lymphadenopathy (BHL) and uveitis occur.
- Angiotensin converting enzyme (ACE) activity is elevated, and hypercalcemia is present.
- Topical and oral steroids are the first-line treatments.
It is unknown.

Skin lesions are seen in 20% to 35% of cases of systemic sarcoidosis. Some cases demonstrate only skin lesions. The cutaneous symptoms of sarcoidosis vary widely depending on the location and severity of the infiltration of epithelioid cell granuloma (Figs. 18.13-1 and 18.13-2). The disease tends to be asymptomatic and is often classified into nodular, plaque, diffuse, infiltrative and subcutaneous types. More than one type of cutaneous symptom may be seen in one patient.

**Nodular sarcoidosis**: This is the most frequent type. The face, particularly around the nose, and the extremities and the center of the trunk are most commonly affected. Multiple, slightly elevated infiltrative erythema range in color from light pink to dark red and in diameter from 3 mm to 30 mm. There may be scaling. Small papules are often produced in the lower legs.

**Plaque sarcoidosis**: Relatively large, flat-topped infiltrative plaques with an elevated rim and an atrophic center occur, most frequently on the face (forehead, cheeks and nose in particular).

**Diffuse infiltrative sarcoidosis**: Dark red, diffuse, infiltrative plaques occur symmetrically, mainly on the nose, cheeks, fingers and toes. It is asymptomatic. Areas that are prone to frostbite are frequently involved (lupus pernio).

**Subcutaneous sarcoidosis**: It most commonly appears in the extremities, as palpable, elastic, subcutaneous induration of 1 cm to several centimeters in diameter.

**Scarring infiltrative sarcoidosis**: It tends to occur on areas that are prone to injury, such as knees and elbows. Epithelioid cell granuloma occurs on a preexisting scar that was caused by injury, for example. This is specific to sarcoidosis and has diagnostic value.

**Other cutaneous sarcoidoses**: ① **Erythema nodosum-like eruptions** resemble erythema nodosum, except that epithelioid cell granuloma is found histopathologically. They heal spontaneously in many cases. ② **Lichenoid sarcoidosis** is multiple, asymptomatic small papules on the trunk and extremities.

Other types of sarcoidosis are ichthyosis-like eruptions, and ulcerative, leukodermal, verrucous, psoriatic and erythematous types.

Besides the granulomatous lesions (cutaneous sarcoidoses) listed above, erythema nodosum may also occur as a nonspecific eruption (MEMO).

**Systemic symptoms**

Subjective symptoms are rarely present. Although various organs may be involved, the bilateral hilar lymph node (BHL), lungs (e.g., pulmonary fibrosis) and eyes (uveitis) are most frequently affected.

**Pulmonary lesion**: This is the most frequent sarcoidosis lesion.
Patients with chronic sarcoidosis are characterized by bilateral hilar lymphadenopathy (BHL). Subjective symptoms are rarely present. Emphysema and pulmonary heart disease may occur in the final stages.

**Eye lesion**: Uveitis and iridocyclitis occur.

**Cardiac lesion**: The condition is known as cardiac sarcoidosis. Heart block, arrhythmia and Adams-Stokes syndrome may cause unexpected death.

**Bone lesion**: Sausage-like swelling of occurs in the finger joints. Bone cysts are observed by osteal X-ray.

**Neural lesion**: The central nervous system and the peripheral nervous system are affected. Paralysis occurs in the facial nerve, glossopharyngeal nerve and vagus nerve.

Additionally, Sjögren syndrome may occur. When facial nerve paralysis, uveitis and parotid bubo are caused, it is called Heerfordt syndrome.

**Pathology**

Noncaseating epithelioid cell granuloma is characteristically observed (Fig. 18.14). Slight lymphocytic filtration is seen at the periphery of granulomas (naked granuloma). There are inclusion bodies such as Schaumann bodies and asteroid bodies in the giant cells of granuloma, but these are not specific for sarcoidosis and they may occur in other granulomatous reactions. The Schaumann bodies have a basophilic round lamellar structure that is positive for alkaline phosphatase and calcium deposition. The asteroid bodies have a radiated, acicular structure with a central core. In addition to granulomatous lesion, foreign substances such as silica are found in scarring infiltration.

**Laboratory findings**

Sarcoidosis is diagnosed mainly from clinical and
Disorders of the Dermis and Subcutaneous Fat

Histopathological findings. Tuberculin test is negative and levels of angiotensin-converting enzyme (ACE) and calcium are elevated. Accumulation of $^{67}$Ga is observed by $^{67}$Ga scintigraphy. BHL revealed by chest X-ray or CT scan has diagnostic value.

**Treatment**

Oral steroids are effective; however, they are not usually necessary in the early stages because sarcoidosis tends to heal spontaneously and has a good prognosis. Oral steroids are used when sarcoidosis is progressive and extensive pulmonary lesions are causing clinical symptoms such as breathing difficulty, or when lesions occur in the heart, eyes or nervous system. Topical steroids are applied for cutaneous lesions.

### 2. Granuloma annulare (GA)

#### Outline

- It is a doughnut-shaped eruption with an elevated rim.
- Histopathologically, there is the formation of a palisading granuloma.
- When GA generalizes to the whole body, diabetes mellitus may be involved.

#### Classification

Granuloma annulare (GA) is classified by the clinical features into four subtypes: localized, generalized, perforating and subcutaneous (Figs. 18.15-1 and 18.15-2; MEMO).

#### Clinical features, Pathology

Small, firm, doughnut-shaped nodules with a concave center appear and spread centrifugally. Firm, small papules 2 mm to

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**Granuloma annulare classified by clinical features**

1) **Localized granuloma annulare**
   It occurs most commonly in young women and tends to be localized to the dorsal hands and finger joints. About half of cases heal spontaneously within 2 years after onset.

2) **Generalized granuloma annulare**
   Small contralateral or dispersed granuloma annulare occurs multiply, most frequently on the trunk and distal extremities of middle-aged women. In about half of cases, the disease is associated with diabetes mellitus. When generalized granuloma annulare is suspected, examination for diabetes mellitus is highly recommended.

3) **Perforating granuloma annulare**
   It is a papule with a centralized concavity that may ulcerate and crust. Dermal excretion of degenerated collagen fibers occurs. It often arises secondarily after localized granuloma annulare.

4) **Subcutaneous granuloma annulare**
   A palpable, subcutaneous nodule of normal skin color, it commonly occurs in early childhood. Bony sites that tend to be subject to pressure, such as the elbows, are easily affected.
Disorders of the dermis / D. Granulomatous disorders

4 mm in diameter form in circular arrangement. The papules are normal skin color to light pink and are asymptomatic. Histopathologically, degenerated collagen fibers at the center are radially surrounded by histiocytes, lymphocytes and giant cells (palisading granuloma) (Fig. 18.16). Acid mucopolysaccharides deposit in the lesion in the central area of incomplete necrosis.

Pathogenesis

The mechanism of GA has not been fully clarified. Impaired peripheral circulation, diabetes, insect bites, UV radiation and injury may induce GA.

Treatment

GA tends to heal spontaneously. After a skin biopsy, the biopsy lesion often disappears. As local therapies, topical steroids, PUVA therapy and cryotherapy are conducted. If diabetes mellitus is involved, it is treated.

3. Annular elastolytic giant cell granuloma (AEGCG)

Synonyms: Actinic granuloma, Elastophagic giant cell granuloma

A granulomatous lesion whose main components are elastic fiber-phagocytosing giant cells occurs, most frequently in middle-aged women. A large, circular erythematous eruption with an elevated rim and central depigmentation occurs on exposed areas, such as the face, neck region and extremities (Fig. 18.17). It may resemble annular erythema. The lesion heals spontaneously in many cases. AEGCG is widely known as a subtype of GA. It often accompanies diabetes mellitus.

4. Cheilitis granulomatosa

Synonym: Melkersson-Rosenthal syndrome

Clinical features

Men and women in their 20s are most frequently affected. When all three main symptoms are present together – swelling of the lips, fissured tongue (scrotal tongue, lingua plicata) and facial nerve palsy – it is called Melkersson-Rosenthal syndrome.

Swelling of lips: Swelling occurs suddenly in the lips (particularly the upper lip) as the earliest symptom in most cases of cheilitis granulomatosa. The buccal mucosa may also be involved. Although subjective symptoms such as pain are not present, the swelling persists for several hours to several days. It recurs, leading to rubber-like stiffness.

Lingua plicata: Swelling occurs in the tongue at the same time as the lips are affected. The folds in the surface of the tongue become marked.

Clinical images are available in hardcopy only.

Fig. 18.16 Histopathology of granuloma annulare.

Collagen fiber degeneration and the mucin deposition are observed at the center (★). Palisading epithelioid cell granuloma forms at the periphery.
Facial paralysis: At the same time or earlier than swelling of the cheeks, peripheral facial paralysis suddenly occurs on one cheek. Recurrences and remissions are repeated.

Other symptoms: Migraine, autonomic failure and mental deterioration may occur.

Pathogenesis, Pathology

The cause is unknown; however, dental metal allergy and sarcoidosis reaction are suspected. Lymphatic edema in the dermis, and lymphoid and histiocytic infiltration are pathologically found in the early stages. As it progresses, inflammatory granulomatous lesions consisting of lymphocytes, epithelioid cells and Langhans giant cells occur.

Treatment

Oral antihistamines and oral or locally injected steroids are useful as symptomatic therapies.

E. Hereditary connective tissue disease

1. Ehlers-Danlos syndrome (EDS)

Outline

- It is a congenital disease of the connective tissue. In most cases, it is autosomal dominant.
- Hyperextensible skin, fragility of the skin and blood vessels, and excessive mobility of joints are the main symptoms.

Clinical features

Ehlers-Danlos syndrome (EDS) is a common inherited disorder; the incidence is on the order of 1:5000 of the population. The skin is soft and stretches excessively, despite appearing normal; when stretched and released, the skin immediately returns to its former appearance. The skin is easily torn by extrinsic force or injury. Because injuries do not heal promptly, parchment-like scars form. At the terminal stages, the skin hangs saclike from the body. In areas subjected to strong extrinsic forces, such as the heels, subcutaneous fat enters the torn connective tissue and develops into lump tumors. The joints of the digits, elbows and knees hyperextend, exceeding 180 degrees of bending in the direction opposite the flexure direction. They become valgus (Fig. 18.18). Deformity and dislocation of the joints often occur. Congenital dislocation of the hip joints and gait disorder are present. Bleeding under the skin and in the ocular fundus, cardiac anomaly and valvular involvement, aneurysm, lens deviation and severe myopic astigmatism occur in the later stages of life, from fragility of the blood vessels.
Disorders of the dermis / E. Hereditary connective tissue disease

The causative genes vary according to disease type. Abnormality is found in collagen types I, III and V; the genetic mutations have been identified. EDS is classified by the clinical features, pattern of inheritance, causative gene and biochemical abnormality into more than ten subtypes (Table 18.1). The patterns of inheritance are various; however, EDS is autosomal dominant in many cases.

Pathogenesis

The causative genes vary according to disease type. Abnormality is found in collagen types I, III and V; the genetic mutations have been identified. EDS is classified by the clinical features, pattern of inheritance, causative gene and biochemical abnormality into more than ten subtypes (Table 18.1). The patterns of inheritance are various; however, EDS is autosomal dominant in many cases.

Laboratory findings, Diagnosis

The skin fibroblasts are cultured for detection of collagen abnormality. Genetic mutation is identified.

Treatment

There are no ultimate treatments for EDS, only symptomatic therapies. Pregnancy and delivery of the patients with EDS may cause uterine rupture or massive bleeding.

2. Marfan syndrome

Outline

● It is a congenital disease of the connective tissue. Skeletal abnormality, eye symptoms and cardiovascular impairment are the main symptoms.
● It is autosomal dominant, caused by mutation in the fibrillin-1 gene.
● Striae occur in the chest as a cutaneous symptom. Abnormal elastic fibers are eliminated from the epidermis.
● The major symptoms are arachnodactyly, skeletal deformity of the chest, annuloaortic ectasia and lens deviation.

Table 18.1 Types of Ehlers-Danlos syndrome (EDS).

<table>
<thead>
<tr>
<th>Newly established</th>
<th>Traditional</th>
<th>Causative molecule</th>
<th>Inheritance pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Gravis (EDS type I)</td>
<td>Type V collagen</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Mitis (EDS type II)</td>
<td>Type V collagen</td>
<td>AD</td>
</tr>
<tr>
<td>Hypermobility</td>
<td>EDS type III</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Vascular</td>
<td>Arterial-ecchymotic (EDS type IV)</td>
<td>Type III collagen</td>
<td>AD</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>Ocular-Scoliotic (EDS type VI)</td>
<td>Procollagen lysine hydroxylase</td>
<td>AR</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>Arthrochalasis multiplex congenita (EDS type VII A, VII B)</td>
<td>Type I collagen</td>
<td>AD</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>Human dermatosparaxis (EDS type VII C)</td>
<td>ADAMTS2</td>
<td>AR</td>
</tr>
<tr>
<td>Other</td>
<td>X-linked EDS (EDS type V)</td>
<td></td>
<td>XR</td>
</tr>
<tr>
<td></td>
<td>Periodontitis (EDS type VIII)</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Progeroid EDS</td>
<td>XGPT1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenascin X</td>
<td>Tenascin X</td>
<td>AR</td>
</tr>
</tbody>
</table>

AD: autosomal dominant, AR: autosomal recessive, XR: X-linked recessive
Striae distens appear in the chest and thighs. Abnormal elastic fibers produced in the patient’s upper dermal layer are eliminated (elastosis perforans serpiginosa, described previously) in some cases. When this phenomenon occurs, small, keratotic, reddish-brown papules appear in a serpentine or circular pattern with an atrophic center. The patients are abnormally tall, with a markedly elongated lower body relative to the upper body. The extremities and digits are thin and long (arachnodactyly). Deformities occur in the chest (funnel chest or pigeon breast) and spine, and hypertension and dislocation of the joints occur. Mitral valve prolapse often occurs, as a result of reduced elasticity of the cardiovascular system. Incompetence of the aortal valve and dissecting aortic aneurysm are easily caused by annulo-aortic ectasia. Death may result.

Since Marfan syndrome is caused by abnormality in the fibrillin-1 gene, deviation occurs in the crystalline lens, because the zonules of Zinn, which support that lens, are composed of fibrillin. Severe myopia may be caused by elongation of the eyeball in the anteroposterior direction.

**Pathogenesis**

Marfan syndrome is caused by mutation in the fibrillin-1 gene on chromosome 15. Fibrillin-1, a protein component of the extracellular matrix, is essential to elastic fiber synthesis. The condition is autosomal dominant; however, it is caused by sporadic mutation in about 30% of cases.

**Diagnosis, Differential diagnosis, Treatment**

Marfan syndrome can be diagnosed easily by the clinical features. Genetic examination is necessary for differential diagnosis.

## 3. Pseudoxanthoma elasticum (PXE)

### Outline
- It is a hereditary disease caused by mutation in the ABCC6 gene. This gene encodes the multidrug-resistant protein MRP6. Abnormality occurs in the elastic fibers.
- Yellow or orange papules aggregate on the neck region and flexor surfaces of joints. Dermal laxity progresses with age. It is asymptomatic.
- Eye symptoms and vasoconstriction occur.

### Clinical features

Slightly yellowish papules aggregate and form reticular plaques with an orange-peel-like appearance, most frequently on the lateral region of the neck, axillary fossae and flexor surfaces of joints. The skin is soft and saggy. Skin wrinkling becomes marked with age (Fig. 18.19). It is asymptomatic.

Visual impairment or blindness results from formation of...
angioid streaks caused by degeneration of the Bruch’s membrane, which exists between the retina and choroids and contains abundant elastic fibers. It is at this point that many patients with pseudoxanthoma elasticum (PXE) first see a doctor. Fibrosis and calcinosis occur in the aortic tunica media, leading to constriction of the blood vessels and bleeding. This results in high blood pressure in renal arteries, claudication in the lower legs, cardiac attack, cardiac infarction, coldness of the limbs and gastrointestinal bleeding. Women outnumber men by two to one, but male cases tend to be more severe.

**Pathogenesis**

Mutation in ABCC6 on chromosome 16, a member of the ATP binding cassette (ABC), has been associated with the occurrence of PXE. This gene encodes multidrug-resistant protein MRP6. Although both dominant and recessive inheritance patterns are known, recent studies support the leading theory that PXE is autosomal recessive.

**Pathology**

Swelling and disruption occur in the elastic fibers in the middle-dermal to deeper-dermal layers, accompanied by calcium deposition and changes in the vascular walls (Fig. 18.20).

**Treatment, Prognosis**

The prognosis is good, as long as the cardiovascular symptoms are not severe. Eye symptoms should be treated.

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**Disorders of subcutaneous fat**

**A. Panniculitis**

Inflammatory lesions of the subcutaneous fat can be classified into three distinct categories.

1. Septal panniculitis
2. Lobular panniculitis
3. Panniculitis associated with vasculitis

**1. Erythema nodosum (EN)**

- Red nodules accompanied by tenderness occur, most commonly on the extensor surfaces of the lower extremities. They do not ulcerate.
- It is an inflammatory reaction whose inductive factors include upper respiratory infection, drug eruption, Behçet’s disease and sarcoidosis.
- Inflammation is histopathologically found in the subcuta-