C. Other diseases related to vasculitis in small and medium-sized blood vessels

1. Behçet’s disease

Outline

- Recurrent oral aphtha, eye symptoms (uveitis), ulceration in the genitalia, and cutaneous symptoms (erythema-nodosum-like eruptions) typically occur.
- Behçet’s disease is an inflammatory disease with an unknown cause. It occurs mostly in middle-aged men. Severe thrombophlebitis is induced.
- A distinct, severe clinical type that involves nerves, intestines and blood vessels has been reported.
- Its occurrence correlates highly with HLA-B51. It occurs more frequently in ethnic Japanese than in people of other ethnicities.
- Needle reaction test is positive.
- Administration of colchicines and immunosuppressants are the main treatments.

Clinical features

Behçet’s disease first manifests in men and women in their 20s and progresses over a long period of time (Figs. 11.12-1 to 11.12-3). It occurs slightly more frequently in ethnic Japanese than in Caucasians, and in men more than women. The typical cutaneous symptoms are 1) erythema-nodosum-like eruptions, 2) thrombophlebitis, and 3) folliculitis and acne-like eruptions. The erythema-nodosum-like eruptions most commonly occur in the lower extremities and forearms and are accompanied by pressure pain. They subside in about 1 week; however, they tend to recur. Thrombophlebitis appears as palpable painful subcutaneous linear cord in the extremities, and it often migrates. Folliculitis and acne-like eruptions produce multiple follicular sterile pustules; they are presumably caused by increased irritability, and they produce a pustule where a needle has been inserted, 24 to 48 hours after insertion (needle reaction test).

The disease is also characterized by ulceration in the genitalia. Deep ulcers with sharp margins form in the scrotum in men and in the labia majora and minora in women. These are painful, and they leave scarring when they heal. Aphthae in the oral mucosa form sharply marginated ulcers that are persistently painful. They heal in about 10 days and then recur. More than 60% of patients with Behçet’s disease experience oral aphtha as an early symptom; this has diagnostic significance.

In addition, uveitis accompanied by hypopyon often occurs; there is a high risk of blindness. Fever, fatigue, arthritic symptoms, gastrointestinal symptoms (in the ileocecal region, in particular), epididymitis, vasculitis symptoms, and central nervous...
system damage may also occur.

**Pathogenesis**

The primary disease is thought to involve increased neutrophil activity; however, vasculitis plays a central role. Behçet’s disease is strongly correlated with the HLA-B51 allele, and abnormality in immunity is known to be associated with the occurrence of the disease. The involvement of bacterial allergy (especially hemolytic streptococcus) is suggested as an initiating factor. Antiphospholipid antibodies and autoimmunity are thought to be involved in the formation of thrombi.

**Pathology**

In erythema-nodosum-like eruptions, neutrophilic or lymphocytic cellular infiltration is found in the peripheral blood vessels in the deep dermal layer and subcutaneous fat tissues (septal panniculitis). Unlike in erythema nodosum, vasculitis may be found. In thrombophlebitis, thrombus tends to occur in the small veins of the subcutaneous fat tissues.

**Laboratory findings**

Needle reaction test is positive in 70% of cases, from enhanced irritability of the skin. Positive HLA-B51 is also an important finding in diagnosing Behçet’s disease. Increased erythrocyte sedimentation rate, positive CRP, increased immunoglobulins, and leukocytosis (particularly neutrophilic) are seen from inflammation. When the disease progresses, complement activity increases.

**Diagnosis**

Criteria for diagnosis of Behçet’s disease have been made by Health and Welfare Ministry of Japan (Table 11.3). When the four typical symptoms present during the course of the disease, it is called complete Behçet’s. In recent years, complete Behçet’s has rarely been seen; in incomplete Behçet’s there are three main symptoms or a combination of eye symptoms and one main symptom.

**Treatment**

Specific and severe types of Behçet’s disease and ocular symptoms, if any, are given priority in any treatment. When colchicines, which inhibit neutrophils and NSAIDs, are ineffective, immunosuppressants (cyclosporine A, tacrolimus) are useful. Anticoagulation therapy is performed on thrombosis.
2. Kawasaki disease

Synonyms: Mucocutaneous lymph node syndrome (MCLS), Acute febrile mucocutaneous lymph node syndrome

Outline

- The etiology is unknown. Kawasaki disease has six characteristics: ① fever continues for more than 5 days, ② edema, erythema and scaling occur in the distal fingers and toes, ③ eruptions of various shapes appear on the trunk, ④ hyperemia occurs in the bulbar conjunctivae, ⑤ reddening in the lips and oral cavity, flush, and strawberry tongue are present, and ⑥ non-purulent lymph nodes enlarge.
- It is most common in children age 4 and under (80% of cases).
- Aspirin and human immunoglobulins are the main treatments.

Clinical features

Kawasaki disease occurs in 3 boys for every 2 girls. Pro- dromes are not present. It begins with a fever of about 39 °C. Sharply margined erythema occurs in the fingers and toes. Reddening or blistering at the site of BCG immunization appears. Shortly after that, irregular eruptions occur on the whole body. The eruptions are mainly erythema, followed in frequency by urticaria and by scarlet-fever-like or rubella-like eruptions in some cases. So-called strawberry tongue is present. The distinctive facial features of strawberry tongue, and eruptions and firm edema on the hands and soles are seen 3 to 5 days after the onset of Kawasaki disease. Non-purulent cervical lymphadenopathy also occurs at this time. Scaling occurs in the tips of the fingers and toes 10 to 15 days after onset (Fig. 11.13). Joint pain and swelling, and nail deformation are found. Myocarditis, pericarditis and coronary vasculitis occur as complications in 70% to 80% of all cases.

Pathogenesis

It is unknown. There is a theory that superantigens of hemolytic streptococcus and chlamydia infection are involved.

Laboratory findings

In the peripheral blood, leukocytosis (increase in neutrophils and platelets, and left shift of white blood cells), platelet increase, elevated erythrocyte sedimentation rate, positive CRP, and increased α-2 microglobulins are seen. These findings are helpful for early diagnosis.

Diagnosis

Children with a persistent high fever that does not respond to antibiotics may have Kawasaki disease. The diagnostic criteria are those of the Kawasaki disease Research Group of the Health
and Welfare Ministry of Japan.

**Treatment**

Aspirin is administered orally, to prevent thrombus. Human immunoglobulin preparations given in large doses are effective in shrinking coronary artery aneurysm in the early stages (less than 7 days after onset).

### 3. Pyoderma gangrenosum

**Outline**

- Small pustules and papules rapidly appear to form ulcers with an elevated edge. These mostly occur in the lower body.
- The etiology is unknown. It is frequently associated with primary diseases such as chronic ulcerative colitis, aortitis syndrome and leukemia.
- Steroids and oral DDS are the main treatments.

**Clinical features**

Pyoderma gangrenosum occurs most commonly in the extremities, lumbar region, and abdomen of women from about age 10 to 60. The eruptions progress through four stages. In the first stage, blisters, pustules, and small hemorrhagic papules occur. In the second stage, many of them coalesce into ulcers that enlarge centrifugally. The periphery of the ulcer is elevated in a river-bank shape. The ulcers have undermined edges and are accompanied by palpable infiltration. The bottom of the ulcer contains brownish-yellow necrotic substances with mulberry pigmentation at the periphery. The ulcer is painful and secretes pus when pressed (Fig. 11.14). In the third stage, the center of the ulcer begins to heal and papillary granulation proliferates. In the fourth stage, the ulcer heals with scarring. The scars have the surface roughness of fabric. These eruptions recur chronically in a cycle of several months.

**Pathogenesis**

One theory is that vasculitis is the cause, with autoimmune response as the etiology. Another is that bacterial allergy is the cause. However, no definite cause has been identified. Injury, bruise, or skin biopsy may also induce pyoderma gangrenosum.

**Pathology**

Nonspecific neutrophilic infiltration and fibrin deposition are the major findings of pyoderma gangrenosum. Since necrotic vasculitis is not seen, it is thought that vasculitis is not involved.

**Complications**

Aortitis syndrome, ulcerative colitis, rheumatoid arthritis, leukemia, Crohn’s disease or IgA deficiency may appear as a

### Table 11.3 Diagnostic criteria of Behçet’s disease.

<table>
<thead>
<tr>
<th>1. Major symptoms</th>
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<tr>
<td>1. Recurrent aphthous ulceration in the oral mucosa</td>
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<td>2. Cutaneous symptoms</td>
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<tr>
<td>(a) Erythema-nodosum-like skin lesions</td>
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<tr>
<td>(b) Subcutaneous thrombophlebitis</td>
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<tr>
<td>(c) Folliculitis-like eruptions, acne-like eruptions; helpful finding: enhanced sensitivity of skin</td>
</tr>
<tr>
<td>3. Ocular symptoms</td>
</tr>
<tr>
<td>(a) Iridocyclitis</td>
</tr>
<tr>
<td>(b) Retinouveitis (chorioretinitis)</td>
</tr>
<tr>
<td>(c) Symptoms that suggest past occurrence of (a) and (b), such as posterior synchia of the iris, pigmentation on the lens, chorioretinal atrophy, optic atrophy, complicated cataract, secondary glaucoma, or phthisis of the eyeballs</td>
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<td>4. Genital ulceration</td>
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<th>2. Minor symptoms</th>
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<tbody>
<tr>
<td>1. Arthritis that is not accompanied by articular deformity or rigidity,</td>
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<tr>
<td>2. Epididymitis,</td>
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<td>3. Gastrointestinal lesions such as ileocecal ulcer,</td>
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<td>4. Vascular lesions,</td>
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<td>5. Moderate or severe central nervous symptoms</td>
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<th>3. Diagnostic criteria for types of Behçet’s disease</th>
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<tbody>
<tr>
<td>1. Complete Behçet’s disease</td>
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<tr>
<td>4 major symptoms during the course of the disease</td>
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<tr>
<td>2. Incomplete Behçet’s disease</td>
</tr>
<tr>
<td>(a) 3 major symptoms, or 2 major symptoms in combination with 2 minor symptoms</td>
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<tr>
<td>(b) A typical ocular symptom in combination with another major symptom, or a typical ocular symptom in combination with 2 minor symptoms</td>
</tr>
<tr>
<td>3. Possible Behçet’s disease</td>
</tr>
<tr>
<td>1 or more major symptoms that do not meet the criteria for incomplete Behçet’s disease, and recurrence or aggravation of typical minor symptoms.</td>
</tr>
<tr>
<td>4. Rare symptoms of Behçet’s disease</td>
</tr>
<tr>
<td>(a) Gastrointestinal Behçet’s disease: Abdominal pain should be investigated, and occult blood test should be conducted.</td>
</tr>
<tr>
<td>(b) Vascular Behçet’s disease: Impairment in large arteries, small arteries, or both large and small veins is noted.</td>
</tr>
<tr>
<td>(c) Neuro Behçet’s disease: headache, paralysis, and encephalomyelopathy. Investigation should be made for neurological symptoms.</td>
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<th>4. Helpful laboratory findings (not essential for diagnosis)</th>
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<tr>
<td>(1) Needle reaction of skin: negative/positive</td>
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<tr>
<td>(2) Skin prick testing (SPT) using Streptococcus vaccine: negative/positive</td>
</tr>
<tr>
<td>(3) Inflammatory response (enhanced ESR, serum CRP positive, increased WBC, and elevated complement titer)</td>
</tr>
<tr>
<td>(4) HLA-B51(B5) positive</td>
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</tbody>
</table>

From the Japan Intractable Diseases Information Center (http://www.nanbyou.or.jp/top.html).
complication. In pyoderma gangrenosum, various complications develop in 75% of cases.

**Laboratory findings, Diagnosis**

There are few specific diagnostic findings. As a result of inflammation, CRP is positive, the erythrocyte sedimentation rate is elevated, and there is an elevated level of neutrophils. As pyoderma gangrenosum is sterile pyoderma, bacteria are not detected in the lesions. Nevertheless, various bacteria are released by secondary infection during the course of pyoderma gangrenosum. Therefore, it is diagnosed by clinical features and complications. If pyoderma gangrenosum is suspected, there should be a thorough investigation for complications.

**Treatment**

Systemic administration of steroids and DDS are the main treatments. Pulse therapies of steroids or cyclophosphamide, and cyclosporine are administered in intractable cases.

4. Buerger’s disease

**Synonym:** Thromboangiitis obliterans (TAO)

**Clinical features**

Buerger’s disease most commonly occurs in male smokers in their 20s or older. It is caused by arterial obstruction and contraction of small arteries, and contractive ischemia. At onset, Raynaud’s phenomenon appears; that is, the skin color changes from white to purplish blue or red and sharp pain occurs in distal fingers and toes, cool sensation in fingers occur, and cyanosis is observed. Over time, a minor injury may trigger ulceration in the fingers, toes and peripheral nails. When a relatively large artery in the extremities is affected, weakened arterial pulse, intermittent claudication, and pain during rest may occur. It is accompanied by migrating thrombophlebitis in 20% to 30% of cases (Fig. 11.15).

**Pathogenesis**

Most patients with Buerger’s disease are male smokers; the disease is strongly associated with cigarette smoking.

**Laboratory findings**

Multiple segmental blockages are found in the main peripheral arteries of the lower extremities (popliteal arteries) by arteriography.

**Pathology**

Thickening and inflammation are seen in the tunica intima of arterial walls in the medium-sized and large arteries. Accordingly, stenosis and blockage are caused by thrombosis. Necrotizing of the vascular walls does not occur.

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**Fig. 11.14 Pyoderma gangrenosum.**

a: Ulcer with inflammation is seen (2nd stage). b: These ulcers are replaced by blood crusts and granulomatous tissue (3rd stage). c: The lesions heal with scarring (4th stage). d: 4th stage (scarring stage).
Differentiation from arteriosclerosis obliterans is important. In general, Buerger’s disease is differentiated by the age of onset, sex and other factors (Table 11.4).

Treatment

Smoking should be discontinued immediately. It is important to keep the body warm, to maintain blood circulation in the affected sites, and to avoid external injury. Vasodilators, anticoagulants, and prostaglandins are administered. Revascularization or sympathetic nerve block is performed as a surgical treatment.

5. Mondor disease

Clinical features, Epidemiology

Subcutaneous linear cord with a diameter of 3 mm to 10 mm appears on the chest, upper abdomen and upper extremities (Fig. 11.16). Mondor disease is usually characterized by obliteratorive phlebitis, and it most frequently occurs in women between the ages of 30 and 60. However, it may also occur in men at the root of the penis and in the coronal sulcus. The primary disease is thrombophlebitis or lymphangitis in the subcutaneous fat tissues. It is induced by external injury or operation in the upper chest, or by infection. It may be accompanied by spontaneous pain. There may be some tenderness or discomfort, but there are often no symptoms until the patient discovers a red linear cord running from the lateral margin of the breast.

Pathology

The lumens of the vascular channels in the lesion are narrow and blocked by new connective tissue. Both the inner and outer membranes become thickened and fibrotic. Cellular infiltration is not seen (Fig. 11.17).

Treatment

The disease usually resolves naturally in several weeks. Clinical follow-up is fundamental.

6. Malignant atrophic papulosis

Synonym: Degos’ disease

Multiple rose-pink papules occur in the upper extremities. Several days after onset, they form peculiar eruptions with atrophy or telangiectasia at the center. Pathologically, lymphocytic infiltration is seen in the periphery of the blood vessels. Malignant atrophic papulosis has a poor prognosis, and it is known to cause cerebral infarction or perforative peritonitis several years after onset. Since eruptions that are pathologically similar to malignant atrophic papulosis are seen in SLE, systemic sclerosis, rheumatoid arthritis, dermatomyositis and Crohn’s disease, it is neces-
sary to examine the eruptions thoroughly to determine whether there is an underlying disease. There is controversy over whether malignant atrophic papulosis is an independent disease.

7. Thrombophlebitis

Concept
Thrombophlebitis is a disease in which thrombi form in the small and deep veins as a result of various factors.

Pathogenesis
Most cases of superficial venous inflammation treated by dermatologists result from damage to the veins by IV line placement, or from administration of vasodilators or antibiotics. Thrombophlebitis often develops in the lower extremities when there is infectious disease (e.g., tuberculosis), Behçet’s disease or chronic venous insufficiency including stasis varicose vein.

Clinical features
Thrombophlebitis occurs mostly where IV lines are placed and in the lower legs. Cord-like induration parallel to the veins occurs, accompanied by tenderness and itching. Reddening is often present. Ulceration may occur in severe cases. The lesion may change by the week depending on the pathogenesis. It may progress and recur.

Diagnosis, Differential diagnosis
Thrombophlebitis is easily diagnosed by the distinctive clinical symptoms. History-taking on drug administration and detection of Behçet’s disease and tuberculosis may be necessary. Particular care in differentiation should be taken for diseases in which there is linear cord, such as Mondor disease and gnathostomiasis.

Treatment
Bed rest is most important, followed by cooling of the affected sites. NSAIDs are necessary in many cases. When the symptoms are severe, oral steroids may be administered.

Fig. 11.16 Mondor disease.
Subcutaneous, cordlike induration is observed.

Fig. 11.17 Histopathology of Mondor disease.