1. Polyarteritis nodosa (PN)

**Synonym:** Periarteritis nodosa

**Outline**
- It affects muscular arteries the most severely. PN is classified into cutaneous (only the skin is affected), systemic (systemic symptoms occur), and microscopic (renal symptoms caused by affected arteries occur, and respiratory symptoms occur).
- Histopathologically, it is leukocytoclastic vasculitis in small and medium-size arteries.
- Cutaneous findings include subcutaneous nodules, livedo reticularis, and erythematous ulceration.

**Clinical features, Epidemiology**

Polyarteritis nodosa (PN) most frequently occurs in men and women in their 30s to 60s. There are no significant differences in cutaneous manifestations between systemic PN and cutaneous PN, and cutaneous symptoms are seen in 10% to 60% of systemic PN cases. Palpable subcutaneous nodules of 1 cm to 2 cm in diameter, purpura, livedo and ulceration occur mainly parallel to the superficial arteries (*Fig. 11.8*). Tenderness may be present. PN becomes chronic with repeated recurrences and regressions. Urticaria and transient erythema may also occur. Livedo reticularis (livedo racemosa) is commonly found.

Systemic PN may be accompanied by fever, fatigue, weight loss, arthralgia, and visceral symptoms such as renal failure, cardiac infarction, cardiac failure, pericarditis, high blood pressure, abdominal pain, neuritis and myalgia. The kidneys are the most commonly affected organs, and death from renal failure is possible. Patients with microscopic PN may develop acute progressive nephritis, interstitial pneumonia, and pulmonary hemorrhage. The disease is highly associated with MPO-ANCA.

**Pathogenesis**

The etiology is unknown. The hepatitis B virus, bacterial infectious diseases (e.g., streptococcus), and drug hypersensitivity are known to precede or induce PN.

**Pathology**

PN is leukocytoclastic vasculitis that is accompanied by swelling in the tunica media of small and medium-sized arterial walls, fibrinoid degeneration, and neutrophilic cellular infiltration (*Fig. 11.9*). As PN progresses, thromboembolism, aneurysm and bleeding occur, leading to the formation of epithelioid cell granuloma. In cutaneous PN, these symptoms occur in the arteries in
the deep dermal layer and subcutaneous fat tissue. Lesions occur in almost all the nutrient arteries in systemic PN; nevertheless, the lungs are rarely affected. The thickness of the blood vessels and the depth from the skin surface for PN and other vasculitides are compared in Fig. 11.2.

**Laboratory findings**

Immune complex deposition may be found in the area with eruptions. ANCA is generally positive in microscopic PN. Aneurysm is frequently observed by angiography.

**Diagnosis**

PN is diagnosed by the clinical features, laboratory findings and skin biopsy. It is necessary to differentiate it from systemic lupus erythematosus (SLE), cutaneous small-vessel vasculitis, erythema nodosum, erythema induratum and cryoglobulinemia.

**Treatment**

Cutaneous PN with mild clinical severity is treated by bed rest with the lower extremities raised, and administration of vasodilators, NSAIDs and DDS. Steroids are temporarily administered orally during acute aggravation. For systemic PN, steroids and immunosuppressive drugs are necessary in high doses.

**Prognosis**

Cutaneous PN has a good prognosis. The eruptions heal in several weeks; however, they are persistent and recur for years. In contrast, the prognosis of systemic PN is poor, because of various internal-organ disorders (e.g., renal failure, intracranial hemorrhage, cardiac infarction).

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**2. Allergic granulomatous angiitis (AGA)**

**Outline**

- AGA is a vasculitis syndrome. Allergic symptoms such as asthma, fever, and increase of eosinophils and IgE precede AGA.
- Necrotizing vasculitis in small and medium-sized arteries and the formation of granuloma are the primary diseases.
- Interstitial pneumonia and lung granuloma occur.
- P-ANCA is positive.
- Oral or pulse administration of steroids is the main treatment.

**Clinical features, Differential diagnosis**

In most cases intractable bronchitis and other allergic diseases occur for several months to several years before the onset of allergic granulomatous angiitis (AGA) (Fig. 11.10). Infiltrated
subcutaneous nodules, purpura and erythema frequently appear. Peripheral nerve disorder (usually mononeuropathy multiplex) and gastrointestinal lesions are also found. Lung involvement is common; migrating polymorphic interstitial pneumonia resembling Löffler syndrome is observed by chest X-ray. In comparison with PN, prodromes are common and renal dysfunction is rare in AGA. The typical symptoms of AGA are summarized in Table 11.1.

<table>
<thead>
<tr>
<th>Symptoms and findings</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial asthma</td>
<td>Expiratory wheezing or high-pitched rales</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Eosinophils accounting for 10% or more of the fraction of peripheral leukocytes</td>
</tr>
<tr>
<td>Neuropathy, mono or poly</td>
<td>Numbness accompanied by pain, with glove-stocking distribution</td>
</tr>
<tr>
<td>Pulmonary infiltrates, non-fixed</td>
<td>Migrating or transient pulmonary infiltration (X-ray)</td>
</tr>
<tr>
<td>Paranasal sinus abnormality</td>
<td>Sharp pain or tenderness in paranasal sinus, or abnormal findings in X-ray</td>
</tr>
<tr>
<td>Extravascular eosinophils</td>
<td>Extravascular eosinophils in the skin and lung, observed pathologically</td>
</tr>
</tbody>
</table>

Table 11.1 Main clinical symptoms and findings of Churg-Strauss syndrome (based on classification criteria proposed by the American College of Rheumatology).

(Adapted from: http://www.rheumatology.org/publications/classification/churg.asp?aud=mcm)

Pathology

In AGA, as in PN, there is leukocytoclastic vasculitis in small and medium-sized arteries and small veins. Granuloma occurs in the vascular or perivascular walls, and there is marked eosinophilic infiltrate in the tissue.

Laboratory findings

Notable increase of leukocytes, eosinophils and serum IgE are seen. The patient often tests positive for P-ANCA (MPO-ANCA), a kind of anti-neutrophil cytoplasmic antibody (ANCA).

Treatment

With systemic high-dose application of steroids in the early stages, AGA subsides in a relatively short time. Their use in combination with immunosuppressants is recommended in intractable cases.

3. Wegener’s granulomatosis

Outline

- This rare vasculitis syndrome is preceded by upper respiratory symptoms such as paranasal sinusitis. It is accompanied by fever and systemic fatigue.
- Leukocytoclastic vasculitis and granuloma are found in the upper respiratory tract, lungs and kidneys.
- Cutaneous symptoms are the same as in PN.
- C-ANCA is positive. Multiple lung lesions are observed by chest X-ray.
- The prognosis is improved by combined use of steroids and cyclophosphamide.

Clinical features, Epidemiology

Wegener’s granulomatosis most commonly occurs in men and women between the ages of about 25 and 55 years. Necrotizing granuloma lesions in the upper and lower respiratory tracts cause foul-smelling rhinorrhea, mucosal erosion in the upper respiratory tract, nasal hemorrhage, paranasal sinusitis, ocular proptosis, hemosputum and breathing disruption. As the lesions progress, saddle nose may be caused. The lesion gradually spreads to the kidneys, leading to rapidly progressive renal failure.

Cutaneous symptoms are found in approximately half of all
cases. Various eruptions, such as gangrenous papules, blisters, erythema, purpura, pustules, nodules and ulcers, are produced symmetrically in the extremities and buttocks. In the early stages, a skin lesion resembling pyoderma gangrenosum may be found; it may be useful for early diagnosis (Fig. 11.11).

**Pathogenesis**

The etiology of Wegener’s granulomatosi is unknown; however, an autoimmune mechanism is suspected. Autoantibodies called C-ANCA (PR3-ANCA), which are anti-neutrophil cytoplasmic autoantibodies, are thought to activate neutrophils and monocytes, causing Wegener’s granulomatosis.

**Pathology**

Leukocytoclastic vasculitis in the upper dermal layer and granuloma formation in the periphery are found.

**Laboratory findings**

Elevated erythrocyte sedimentation rate, increases in leukocytes and platelets, and elevated levels of human immunoglobulins are found. Skull fracture may be observed by head X-ray. In a chest X-ray, there is shading that closely resembles that of pulmonary tuberculosis and pulmonary metastatic tumor, and cavitary circular shading with a thin wall is seen in 30% to 50% of cases. C-ANCA is useful for diagnosis as a specific antibody and is associated with disease severity. The antibody titer decreases during the course of successful treatment.

**Differential findings**

It is necessary to differentiate Wegener’s granulomatosis from sarcoidosis, lymphoma, Goodpasture syndrome, malignant tumor, PN, AGA and cutaneous small-vessel vasculitis. Diagnosis follows the diagnostic criteria of the American College of Rheumatology (Table 11.2).

**Treatment, Prognosis**

Systemic steroids and immunosuppressants (cyclophosphamide in particular) are used. Wegener’s granulomatosis was once regarded as having a poor prognosis and usually leading to death from renal failure or other disorder within a year after onset. Currently, it may subside as long as it is treated in the early stages.

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**4. Temporal arteritis (TA)**

**Synonym:** Giant-cell arteritis

**Outline**

- TA is a vasculitis syndrome. The superficial temporal arteries and ophthalmic arteries are affected.
- It occurs in elderly women. The typical symptoms are
unexplained fever, throbbing headache, and visual impairment.
- Cord-like induration occurs in the temporal region, and muscular pain develops (polymyalgia rheumatica).
- Oral steroids are the main treatment.

**Clinical features, Pathogenesis**

Temporal arteritis (TA) most frequently occurs in persons over age 50, with a ratio of 1 male to 3 females. Temporal arteries are mainly affected. Cord-like thickening of the temporal arteries, reddening, pain and swelling are present. Throbbing headache, difficulty of opening the mouth, blistering, ulceration, necrosis in the scalp, and hair loss occur. When the lingual artery is affected, the tongue becomes red, swollen and erosive. When the ophthalmic artery is affected, visual impairment results, with blindness following in 10% of cases. A temporary visual disorder (amaurosis fugax) may also occur. When an artery in the brain is affected, bulbar palsy and dementia occur as well.

The pathogenesis of TA is unknown; however, the involvement of viral or bacterial infection, or drug allergy is suspected. Since HLA-DR4 is associated with TA, genetic factors may be involved in the occurrence of TA.

**Laboratory findings**

Elevated erythrocyte sedimentation rate and increased CRP are observed. Autoantibodies are absent. The serum complement titer and myogenic enzyme are normal. By biopsy, TA appears as granulomatous inflammation accompanied by cellular infiltrate mainly caused by mononuclear cells and production of giant cells.

**Treatment**

To prevent visual impairment, steroids are used systemically in the early stages of TA. If the symptoms subside, the medication may be discontinued.