

Chapter 23 Viral Infections

A virus is a particle of DNA or RNA enclosed by structural proteins. Viruses infect cells and proliferate to cause viral infections. Viral skin diseases are classified by clinical features into three types: ① degeneration of epidermal cells and blistering (e.g., in herpes simplex and herpes zoster), ② tumorous changes in epidermal cells (e.g., in verruca vulgaris), and ③ allergic eruptions on the whole body (e.g., in measles and rubella). The first two types are caused by viral infection in epidermal keratinocytes; the last type is caused by systemic viral infection (viremia). This chapter introduces various viral skin diseases, including HIV infection.

A. Viral infections whose main symptom is blistering

1. Herpes simplex ☆☆

Outline

- It is caused by infection or reactivation of herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2).
- HSV-1 causes herpes labialis, herpes gingivostomatitis and, Kaposi's varicelliform eruption.
- HSV-2 causes herpes genitalis. In recent years, the number of herpes genitalis cases caused by HSV-1 has been increasing.
- Detection of the viral antigen and Tzanck test are useful for diagnosis. The main treatment is administration of acyclovir.

Pathogenesis

Herpes simplex is caused by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). The oral cavity, eyes and genitalia are affected by HSV-1, whereas the genitalia are mainly involved in HSV-2. The infection pattern of HSV is shown in **Fig. 23.1**. The virus enters the skin through a minor external injury, or through the oral mucosa, eyes or genitalia. It travels along the sensory nerve axons to reach the trigeminal ganglia or lumbosacral spinal cord ganglia. In 90% of cases, primary infection does not progress beyond latency, however, symptoms may be apparent in infants or in people with immunodeficiency. After the symptoms subside, viral DNA remains in the gangliocytes and becomes reactivated by stress or a common cold. Some viruses may travel along the axons anterogradely to reach the skin and become reactivated.

Clinical features

The initial latency is between 2 and 10 days. Localized aggregation of small herpetic blisters occurs in primary infection. It

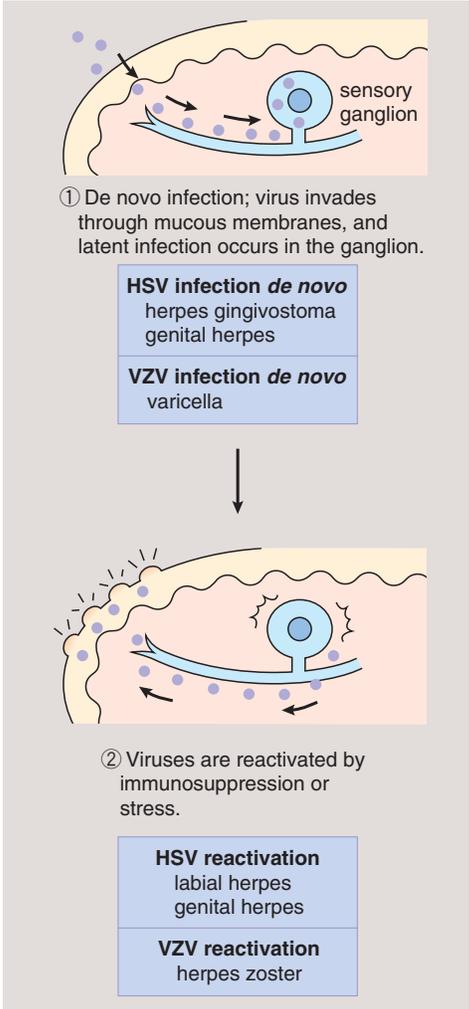


Fig. 23.1 Mechanism of infection by HSV and VZV.
 HSV: Herpes simplex virus. VZV: Varicella zoster virus.

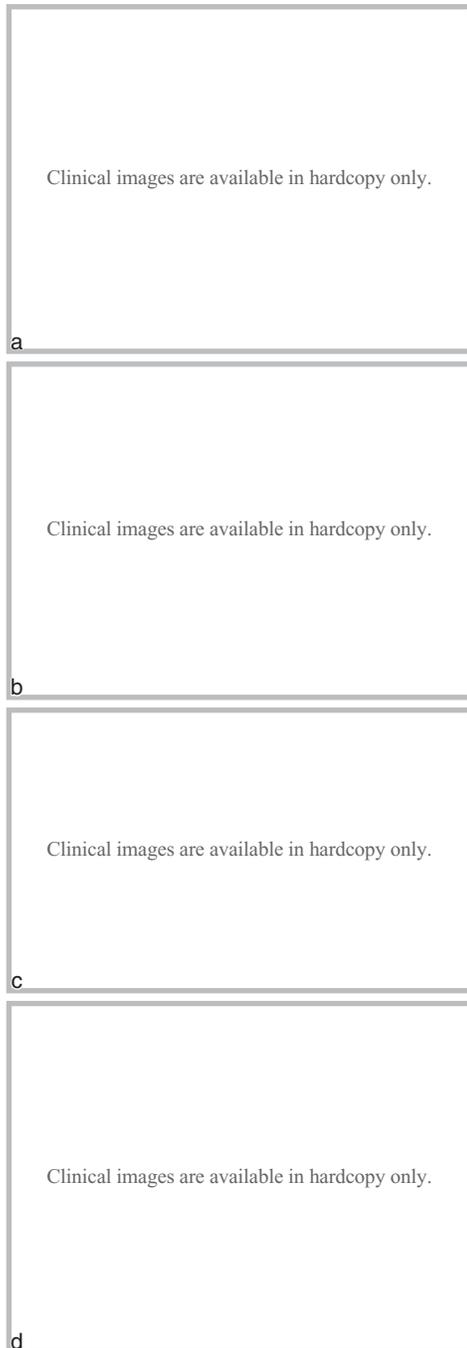


Fig. 23.2 Herpes simplex.
 a, b: Vesicles aggregated around the lips (herpes labialis) caused by herpes simplex. c: Affected eyebrow. d: Genital herpes.

may occur on any site of the body, particularly the lips, genitalia and fingers (**Fig. 23.2**). In severe cases, small blisters spread on the whole body. Recurrent herpes simplex may cause serious mental distress.

① Herpes labialis (cold sore)

This is the most common clinical form of herpes simplex seen in adults. Most cases are caused by reactivated HSV-1. It begins with prodromes such as itching and discomfort in the lips and their periphery, including the anterior naris cheeks and orbital region. After a day or two, edematous erythema appears and small blisters with central umbilication occur and aggregate, sometimes coalescing to form irregularly shaped blisters. The blisters soon form pustules, erosions and crusts. They heal in about 1 week.

② Herpes gingivostomatitis

This type occurs most frequently in initial infection of HSV-1 in infancy. It begins 2 to 10 days after infection, with discomfort, fever and pharyngeal pain. Accompanied by a high fever, multiple painful small blisters and erosions occur in the oral mucosa, tongue and lips.

③ Herpes genitalis (genital herpes)

This type occurs as an initial infection or recurrently. Herpes genitalis is often transmitted through sexual activity and can be regarded as a sexually transmitted disease (STD). Although men and women in adolescence and older are frequently affected, it may also occur in infants in rare cases. It may be transmitted to an infant by the hands of the mother or nurses. The causative virus in most cases is HSV-2; however, the number of cases caused by HSV-1 has been increasing in recent years. In initial infection, small blisters form in the glans penis or foreskin of adult men, or in the labia or perineal region of adult women. The blisters become severely painful small ulcers. The inguinal lymph node becomes painful and enlarged. The lesions usually disappear spontaneously in 2 to 4 weeks; however, when the sacral nervous root is involved it may leave urinary disturbance. The symptoms of recurrent cases are moderate.

④ Kaposi's varicelliform eruption

HSV-1 infection may spread widely on the face and over the whole body when the local skin is weak or damaged, especially in infants or atopic dermatitis patients. It is described in the next section.

⑤ Herpetic whitlow

HSV-1 (or HSV-2 in some cases) invades the body from a minor injury in the tip of a finger, leading to aggregated formation of painful blisters and pustules in fingers. The blisters on the fingers are not as fragile as those on other sites of the body. Infants who have a habit of finger-sucking and dentists may be infected. It is recurrent and heals in 2 to 4 weeks.

Pathology

Repetitive replication of viral DNA leads to ballooning degeneration and reticular degeneration of infected epidermal cells.

These degenerated epidermal cells are observed as ballooning cells containing intranuclear inclusion bodies by smear staining of the blister contents (Fig. 23.3).

Laboratory findings

Tzanck test, detection of the virus using monoclonal antibodies, and serological diagnosis are conducted. HSV-infected epidermal cells are easily and quickly observed by Tzanck test. Monoclonal antibody detection is conducted to differentiate between HSV-1, HSV-2 and varicella zoster virus (VZV). Serological diagnosis is made by ELISA.

Treatment

Antiviral drugs such as acyclovir are given topically, orally or intravenously, depending on the severity of the symptoms.

2. Kaposi's varicelliform eruption ★ ★

Synonym: Eczema herpeticum

Outline

- The cause in most cases is infection of herpes simplex virus type 1 (HSV-1). The virus infects a skin lesion, leading to severe blistering and erosion on the whole body.
- Infants are frequently affected. It is often induced by HSV reactivation in patients with atopic dermatitis.
- Oral or intravenous administration of antiviral drugs and systemic management are the main treatments.

Clinical features

Kaposi's varicelliform eruption occurs most frequently in infants with atopic dermatitis or eczema. In recent years, the number of recurrent cases of Kaposi's varicelliform eruption in adults with atopic dermatitis has been increasing. Acute high fever and swelling in systemic lymph nodes occur. Multiple blisters appear on eczematous plaques. Slightly larger than those in herpes simplex, the blisters rapidly disseminate. They are surrounded by red halo, coalesce, and form large erosions (Fig. 23.4-1 and 23.4-2). Pustules, bleeding, and secondary bacterial infection occur in many cases. The face and upper body are commonly involved; in breast-fed infants, the lesions often occur on the whole body. The eruptions usually form crusts in 4 to 5 days. Because eruptions occur successively, the course of Kaposi's varicelliform eruption may be from 10 days to more than 1 month.

Pathogenesis

Primary viral infection or reactivation affects localized areas of skin with deficient barrier function, such as areas affected by atopic dermatitis, eczema, Darier's disease or burns. Autoinoculation causes extensive lesions. The causative virus is usually HSV-1 but sometimes HSV-2.

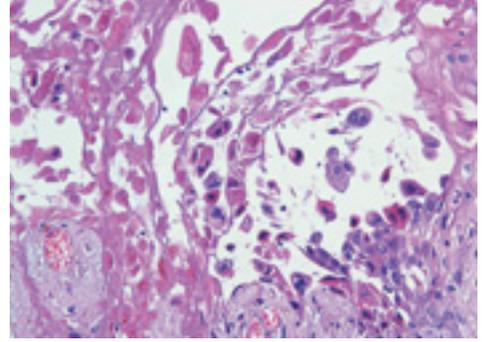


Fig. 23.3 Histopathology of herpes simplex. There is necrotic degeneration in epidermal cells. The giant cells contain inclusion bodies (ballooning cells).

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Fig. 23.4-1 Kaposi's varicelliform eruption. The eruptions are rimmed with a vivid red halo. The vesicles coalesce into a large erosion.

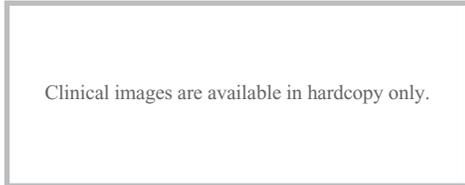
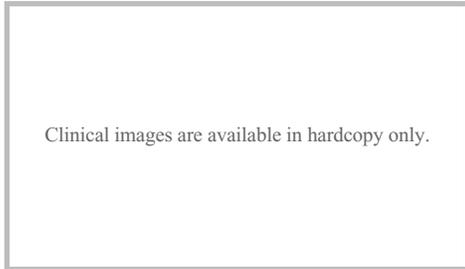


Fig. 23.4-2 Kaposi's varicelliform eruption.

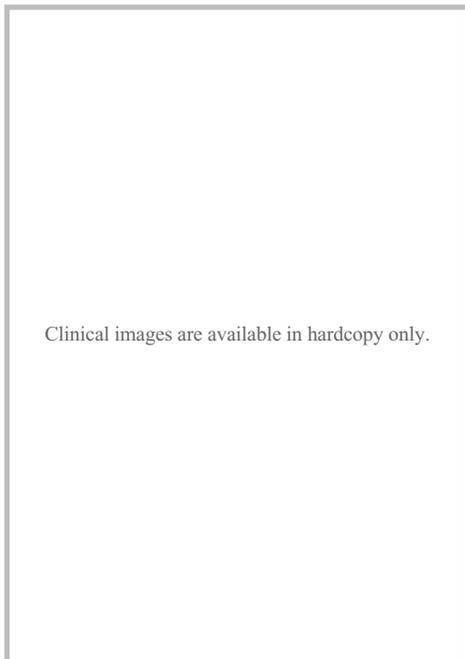


Fig. 23.5-1 Varicella in an adult.

Treatment

Antiviral drugs are given orally or intravenously.

Prognosis

Kaposi's varicelliform eruption responds well to treatment. Nevertheless, dehydration and multiple organ failure accompanying high fever may be fatal.

3. Varicella



Synonym: Chickenpox

Outline

- It is commonly known as chickenpox. Infants are most frequently affected.
- It is caused by primary infection of varicellazoster virus (VZV) and is highly infectious.
- A fever emerges concurrently with erythematous papules on the whole body. Eruptions progress in the course of vesicles, pustules and crusts, and healing. New eruptions continue to occur such that preexisting eruptions appear together with new eruptions.
- It heals in 7 to 10 days.
- Symptomatic treatments are helpful. Aspirin is contraindicated.

Clinical features

After a latency of 2 to 3 weeks, erythematous papules appear on the whole body, accompanied by fever (37 to 38°C) and systemic fatigue. The eruptions are accompanied by itching. They progress in the order of erythema, papules, blisters, pustules and crusts, over the course of several days. Varicella is characterized by small blisters that resemble insect bites and blisters that form on the scalp. Because the eruptions continue to appear, preexisting eruptions are found together with newly formed ones (**Figs. 23.5-1** and **23.5-2**). Blistering also occurs in the oral mucosa and palpebral conjunctiva. Varicella heals in 7 to 10 days, without scarring (**Fig. 23.6**). If the eruptions are scratched or secondarily infected, they heal with moderate scarring.

The main complications are pneumonia, encephalitis, unilateral high-frequency deafness (thought to be a symptom of Ramsay-Hunt syndrome), and Reye's syndrome (cerebritis and fatty liver).

Pathogenesis, Epidemiology

Varicella is caused by infection of the varicella zoster virus (VZV). This virus enters the upper respiratory tract by droplet infection or contact infection and proliferates in the regional lymph nodes, inducing primary viremia. The virus further proliferates in the liver and spleen, leading to secondary viremia, and reaches the skin, resulting in blistering. Varicella occurs most frequently between weaning and early childhood. Ninety-five

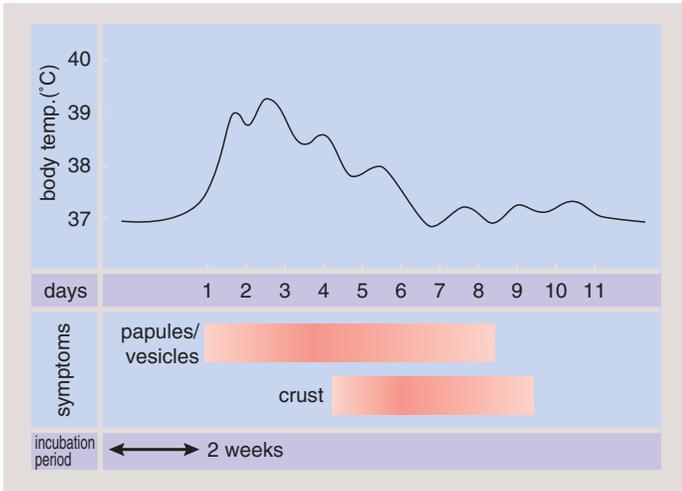


Fig. 23.6 The clinical course of varicella/chickenpox.

percent of children aged 9 have the antibodies. The age of initial infection has risen in recent years; varicella in adults is increasing. In adult cases, varicella is often accompanied by encephalitis and pneumonia, and it can easily become severe.

Laboratory findings, Diagnosis

Tzanck test is useful for early diagnosis. Varicella is characterized by balloon cells, the epidermal cells that are infected by VZV.

Treatment

Symptomatic therapies such as oral antihistamines against itching, and topical petrolatum or antibiotic ointments for eruptions are the main treatments for infants. In recent years, oral antiviral drugs have been used increasingly to keep the infection from worsening. Aspirin is contraindicated because of the danger of Reye’s syndrome. Antiviral drugs are administered intravenously to adults, patients with immunodeficiency, and newborns.

Prevention

Within 72 hours after infection, the onset can be inhibited by varicella vaccine in 60% to 80% of cases. Oral antiviral drugs may reduce the symptomatic severity in patients who have had contact with an affected individual within the previous week. Varicella can be fatal in patients with immunodeficiency; human immunoglobulin containing high anti-VZV antibody titer is used in some cases.

4. Herpes zoster ★
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Outline

- Latent VZV in the ganglia reactivate to form band-like

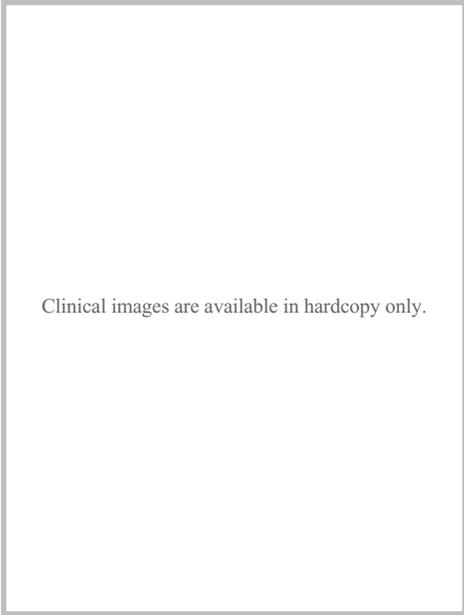
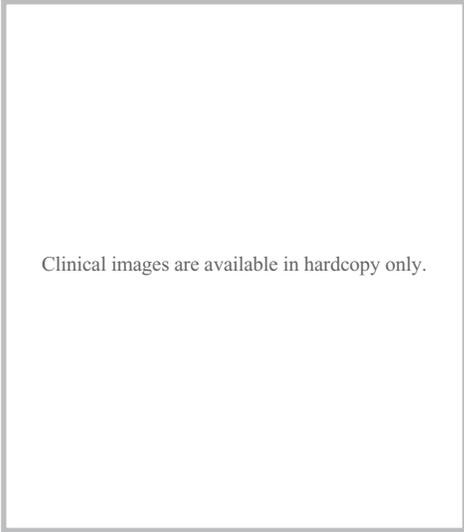
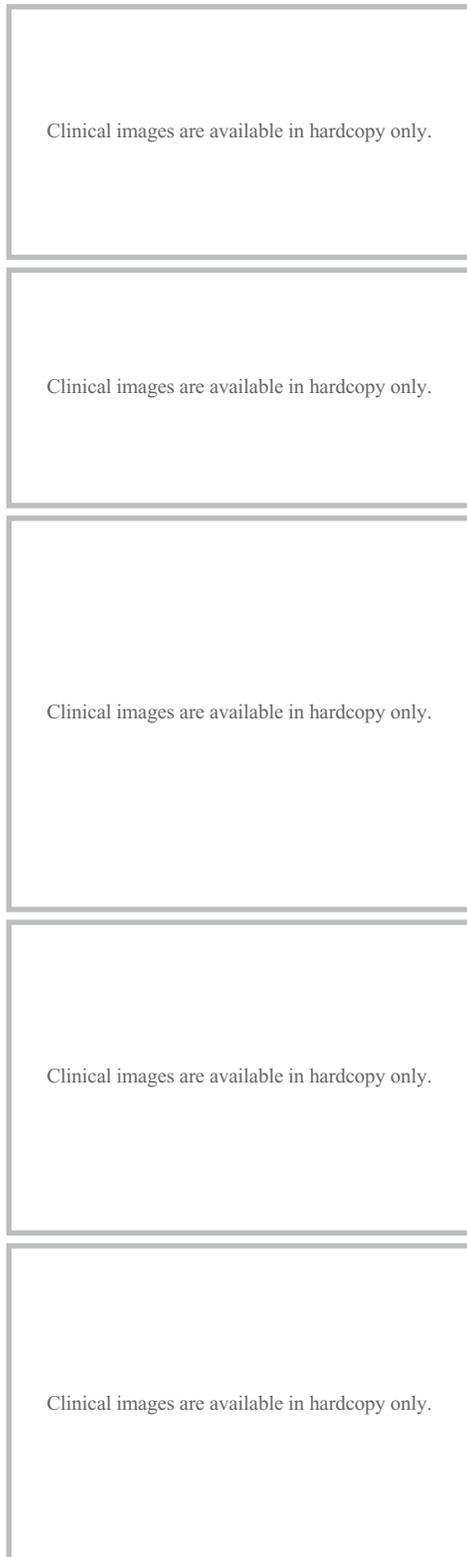


Fig. 23.5-2 Varicella.



herpetic aggregations of small blisters on certain innervated regions. Pain is present in areas over the involved nerves. It occurs in individuals with history of varicella infection.

- The blisters may disseminate on the whole body in cases with immunodeficiency, such as when there is malignant tumor, regardless of the affected nervous regions.
- The main examinations are Tzanck test, detection of viral antigens, and evaluation of the antibody titer in the blood. There is permanent immunity after the first infection.
- The pain that persists after healing is called post-herpetic neuralgia (PHN). When the ears and the peripheral regions are involved, hearing loss and peripheral facial paralysis may occur (Ramsay-Hunt syndrome).

Clinical features

Herpes zoster symptoms are divided into cutaneous and nervous. There are several specific types of herpes zoster.

① Mucocutaneous symptoms

Multiple herpetic vesicles appear in band-like patterns over certain innervated regions. The skin over the intercostal nerve is most frequently involved, followed in frequency by the trigeminal area of the face (Figs. 23.7-1 and 23.7-2). Prodromes such as neuralgic pain and abnormal paresthesia occur several days before the eruptions manifest. Later, edematous erythema and papules occur and transform into blisters. All these blisters progress in the same course; this differs from varicella, in which preexisting blisters are found concurrently with newly formed ones. The blisters soon rupture and become erosions. They heal after crust formation in 2 to 3 weeks.

② Nervous symptoms

Neuralgic pain is often present several days before the onset of eruptions. The pain is severest 7 to 10 days after the eruptions occur. The severity of pain ranges from moderate to intense, causing sensory disturbance, insomnia or paralysis. The pain in most cases subsides with remission of the eruptions.

③ Types of herpes zoster

Generalized herpes zoster: In patients who are immunocompromised as a result of steroid or immuno-suppressant intake or a primary disease, small widespread blisters resembling varicella may spread on the whole body 4 to 5 days after manifestation of typical eruptions of herpes zoster.

Eye symptoms (Hutchinson's sign): Complications involving the eyes, such as conjunctivitis and keratitis, may occur in herpes zoster at the first division of the trigeminal area (ophthalmic nerve). Herpes zoster on the nasal dorsum is called Hutchinson's sign. It often induces eye complications. In rare cases, a severe complication called acute retinal necrosis occurs.

Ramsay-Hunt syndrome: The external auditory canal and auricle are involved. Peripheral facial palsy and acoustic nerve impairment are present. The pathogenesis is thought to be

Fig. 23.7-1 Herpes zoster on various sites of the body.

pressure exerted on the facial nerve by genicular ganglia. In some cases, facial palsy is the only symptom and there is no blistering.

Post-herpetic neuralgia (PHN): Neuralgia may persist after the eruptions disappear. The pathogenesis is thought to be irreversible nerve degeneration. It often occurs after the onset of herpes zoster in the elderly and is often accompanied by sharp pain. Antidepressants and nerve block are administered. It may be treated at a pain clinic.

Pathogenesis, Epidemiology

Herpes zoster is caused by reactivation of latent VZV. During the course of varicella, VZV travels to the sensory nerves to reach the ganglia, whose dorsal-root cells remain latently infected after varicella heals and the anti-VZV antibodies increase. Stress, aging, malignant tumor and immunodeficiency can trigger re-proliferation of VZV (Fig. 23.1). Herpes zoster occurs most frequently in persons between the ages of 10 and 30 and over 50.

Pathology

Ballooning cells are observed by Tzanck test, as in herpes simplex (Fig. 23.8).

Diagnosis, Examination

Tzanck test, detection of viral antigens, and serological diagnosis are conducted, as in the cases of herpes simplex and varicella. Cases in the elderly or with generalized herpes zoster should be carefully observed, because there is the possibility of malignant tumor immunodeficiency as an underlying disease. Ophthalmologic examination is conducted on any lesions involved in the first division of the trigeminal area.

Treatment

As a basic treatment, antiviral drugs are administered, orally at the early stages and intravenously in severe cases. The main purpose of treatment is to alleviate the sharp pain in the acute stages to prevent sequelae that may include post-herpetic neuralgia and motor palsy. NSAIDs are used as a symptomatic therapy. The prognosis tends to be good. After first infection, patients obtain permanent immunity due to reactivated cell-mediated immunity.

Variola (Synonym: Smallpox)



Variola is caused by infection of the upper respiratory mucosa by the *Orthopoxvirus variola* virus. Infection is by droplet or contact. This pathogen is so virulent that it used to be fatal in many cases; however, Jenner's cowpox vaccine made prevention possible. A smallpox eradication program was developed in 1958 by WHO, and no cases of variola have occurred since 1977. In 1980, WHO declared the disease eradicated. The virus is kept at secure institutions in biosafety level 4 labs in the U.S. and Russia.

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Fig. 23.7-2 Herpes zoster on the first division of the trigeminal nerve.

Eye symptoms such as conjunctivitis and keratitis occur as complications in some cases.

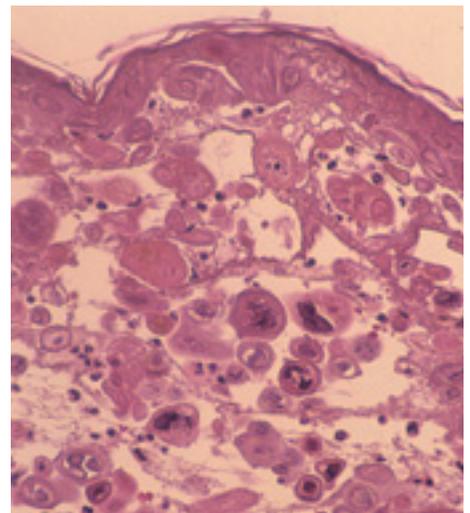


Fig. 23.8 Histopathology of herpes zoster.

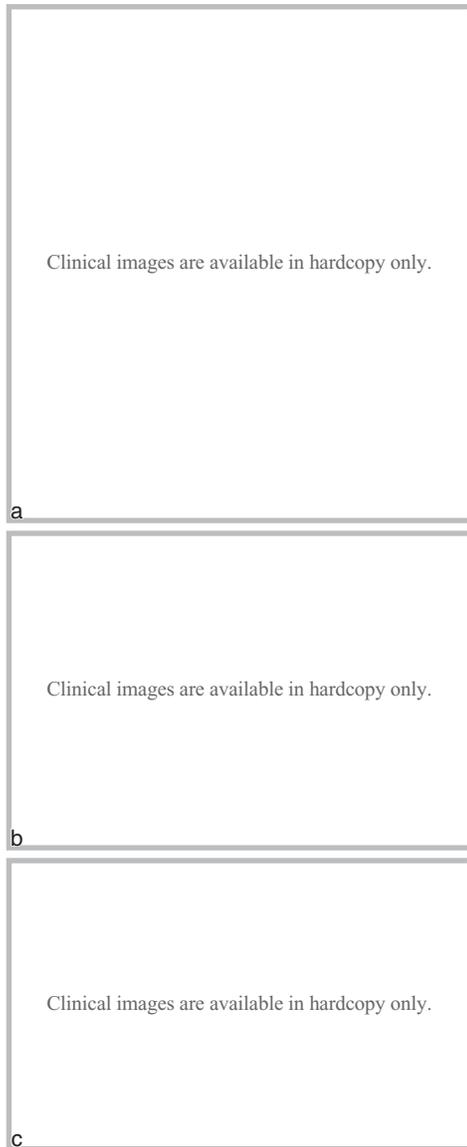


Fig. 23.9 Hand, foot and mouth disease.
 a: Vesicles accompanied by red halo and slight tenderness. b: Eruptions on the knees. c: Vesicles accompanied by sharp pain and aphtha in oral mucosa .

5. Hand, foot and mouth disease (HFMD) ★ ★

Outline

- An eruption is caused by coxsackievirus A16 or enterovirus 71. Breast-fed infants are most frequently affected.
- Blistering is present in the distal portions of the extremities and oral mucosa. It disappears in 4 to 7 days. Oral enanthema occurs on the buccal mucosa and tongue. Erythema or aphtha-like eruptions may also occur.
- The only treatment that is usually necessary is oral hydration.

Clinical features

Hand, foot and mouth disease (HFMD) occurs suddenly after 2 to 5 days of latency. In about half of cases, slight fever is present for 1 or 2 days. Dispersed small blisters with red halos appear on the hands, soles, knee joints and buttocks (**Fig. 23.9**). The blisters are oval, and their long axis is often parallel to the dermatoglyphic line. Some degree of tenderness, but not itching, may accompany these. The blisters disappear in 4 to 7 days without rupturing. Painful erythema, blisters, or aphtha-like erosions that number from a few to several dozen occur on the buccal mucosa and tongue. They resolve in several days. When caused by enterovirus 71, HFMD may be accompanied by aseptic meningitis.

Pathogenesis, Epidemiology

The main causative viruses are coxsackievirus A16 and enterovirus 71. These proliferate in the intestinal tract and are found in stool and in pharyngeal secretions. The viruses are spread by droplet and oral infection. The infectiousness is so high that widespread outbreaks sometimes occur in hospitals. HFMD occurs most commonly in 1- to 2-year-old breast-fed infants and in summer epidemics.

Treatment

No treatment is necessary. Symptomatic therapy is performed only in cases with severe symptoms.

B. Viral infections whose main symptom is verruca

1. Verruca vulgaris ★ ★

Outline

- It is caused by human papillomavirus (HPV) infection.
- It occurs most frequently on the fingers, toes, soles and