

IMMUNE RESPONSES

Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term immunity (Fig. 229-1C). Early nonspecific (innate) immune responses during the prodromal phase include activation of natural killer cells and increased production of antiviral proteins. The adaptive immune responses consist of measles virus-specific antibody and cellular responses. The protective efficacy of antibodies to measles virus is illustrated by the immunity conferred to infants from passively acquired maternal antibodies and the protection of exposed, susceptible individuals after administration of anti-measles virus immunoglobulin. The first measles virus-specific antibodies produced after infection are of the IgM subtype, with a subsequent switch to predominantly IgG1 and IgG4 isotypes. The IgM antibody response is typically absent following reexposure or revaccination and serves as a marker of primary infection.

The importance of cellular immunity to measles virus is demonstrated by the ability of children with agammaglobulinemia (congenital inability to produce antibodies) to recover fully from measles and the contrasting picture for children with severe defects in T lymphocyte function, who often develop severe or fatal disease (Chap. 374). The initial predominant T_H1 response (characterized by interferon γ) is essential for viral clearance, and the later T_H2 response (characterized by interleukin 4) promotes the development of measles virus-specific antibodies that are critical for protection against reinfection.

The duration of protective immunity following wild-type measles virus infection is generally thought to be lifelong. Immunologic memory to measles virus includes both continued production of measles virus-specific antibodies and circulation of measles virus-specific $CD4^+$ and $CD8^+$ T lymphocytes.

However, the intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (non-measles virus) antigens, which persist for several weeks to months beyond resolution of the acute illness. This state of immune suppression enhances susceptibility to secondary infections with bacteria and viruses that cause pneumonia and diarrhea and is responsible for a substantial proportion of measles-related morbidity and deaths. Delayed-type hypersensitivity responses to recall antigens, such as tuberculin, are suppressed, and cellular and humoral responses to new antigens are impaired. Reactivation of tuberculosis and remission of autoimmune diseases after measles have been described and are attributed to this period of immune suppression.

APPROACH TO THE PATIENT:

Measles

Clinicians should consider measles in persons presenting with fever and generalized erythematous rash, particularly when measles virus is known to be circulating or the patient has a history of travel to endemic areas. Appropriate precautions must be taken to prevent nosocomial transmission. The diagnosis requires laboratory confirmation except during large outbreaks in which an epidemiologic link to a confirmed case can be established. Care is largely supportive and consists of the administration of vitamin A and antibiotics (see "Treatment," below). Complications of measles, including secondary bacterial infections and encephalitis, may occur after acute illness and require careful monitoring, particularly in immunocompromised persons.

CLINICAL MANIFESTATIONS

In most persons, the signs and symptoms of measles are highly characteristic (Fig. 229-1B). Fever and malaise beginning ~10 days after exposure are followed by cough, coryza, and conjunctivitis. These signs and symptoms increase in severity over 4 days. Koplik's spots (see Fig. 25e-2) develop on the buccal mucosa ~2 days before the rash appears. The characteristic rash of measles (see Fig. 25e-3) begins 2 weeks after infection, when the clinical manifestations are most

severe, and signal the host's immune response to the replicating virus. Headache, abdominal pain, vomiting, diarrhea, and myalgia may be present.

Koplik's spots (see Fig. 25e-2) are pathognomonic of measles and consist of bluish white dots ~1 mm in diameter surrounded by erythema. The lesions appear first on the buccal mucosa opposite the lower molars but rapidly increase in number to involve the entire buccal mucosa. They fade with the onset of rash.

The rash of measles begins as erythematous macules behind the ears and on the neck and hairline. The rash progresses to involve the face, trunk, and arms (see Fig. 25e-3), with involvement of the legs and feet by the end of the second day. Areas of confluent rash appear on the trunk and extremities, and petechiae may be present. The rash fades slowly in the same order of progression as it appeared, usually beginning on the third or fourth day after onset. Resolution of the rash may be followed by desquamation, particularly in undernourished children.

Because the characteristic rash of measles is a consequence of the cellular immune response, it may not develop in persons with impaired cellular immunity (e.g., those with AIDS; Chap. 226). These persons have a high case-fatality rate and frequently develop giant-cell pneumonitis caused by measles virus. T lymphocyte defects due to causes other than HIV-1 infection (e.g., cancer chemotherapy) also are associated with increased severity of measles.

A severe atypical measles syndrome was observed in recipients of a formalin-inactivated measles vaccine (used in the United States from 1963 to 1967 and in Canada until 1970) who were subsequently exposed to wild-type measles virus. The atypical rash began on the palms and soles and spread centripetally to the proximal extremities and trunk, sparing the face. The rash was initially erythematous and maculopapular but frequently progressed to vesicular, petechial, or purpuric lesions (see Fig. 25e-22).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of measles includes other causes of fever, rash, and conjunctivitis, including rubella, Kawasaki disease, infectious mononucleosis, roseola, scarlet fever, Rocky Mountain spotted fever, enterovirus or adenovirus infection, and drug sensitivity. Rubella is a milder illness without cough and with distinctive lymphadenopathy. The rash of roseola (exanthem subitum) (see Fig. 25e-5) appears after fever has subsided. The atypical lymphocytosis in infectious mononucleosis contrasts with the leukopenia commonly observed in children with measles.

DIAGNOSIS

Measles is readily diagnosed on clinical grounds by clinicians familiar with the disease, particularly during outbreaks. Koplik's spots (see Fig. 25e-2) are especially helpful because they appear early and are pathognomonic. Clinical diagnosis is more difficult (1) during the prodromal illness; (2) when the rash is attenuated by passively acquired antibodies or prior immunization; (3) when the rash is absent or delayed in immunocompromised children or severely undernourished children with impaired cellular immunity; and (4) in regions where the incidence of measles is low and other pathogens are responsible for the majority of illnesses with fever and rash. The CDC case definition for measles requires (1) a generalized maculopapular rash of at least 3 days' duration; (2) fever of at least 38.3°C (101°F); and (3) cough, coryza, or conjunctivitis.

Serology is the most common method of laboratory diagnosis. The detection of measles virus-specific IgM in a single specimen of serum or oral fluid is considered diagnostic of acute infection, as is a four-fold or greater increase in measles virus-specific IgG antibody levels between acute- and convalescent-phase serum specimens. Primary infection in the immunocompetent host results in antibodies that are detectable within 1–3 days of rash onset and reach peak levels in 2–4 weeks. Measles virus-specific IgM antibodies may not be detectable until 4–5 days or more after rash onset and usually fall to undetectable levels within 4–8 weeks of rash onset.

Several methods for measurement of antibodies to measles virus are available. Neutralization tests are sensitive and specific, and the results are highly correlated with protective immunity; however, these tests