Poxviruses

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Background

Poxviruses (members of the Poxviridae family) can infect both humans and animals. The orthopoxviruses include smallpox (variola), monkeypox, vaccinia, cowpox, buffalopox, cantagalo, and aracatuba viruses. The parapoxviruses include orf virus, bovine papular stomatitis virus, pseudocowpox virus, deerpox virus, and sealpox virus. Yatapoxviruses include tanapox virus and yabapoxviruses, which are found primarily in Africa. Molluscipoxviruses include the human poxvirus, molluscum contagiosum virus.

Smallpox and molluscum contagiosum are specific to humans. The other viruses cause rare zoonotic infections in humans. Vaccinia virus, which has been used for vaccination, can also infect humans.

Infections due to poxviruses have dated back to antiquity. The first evidence of smallpox was found in Egyptian mummies of the 18th Dynasty (1580-1350 BC). Variola became endemic in India in the first millennium BC and spread to Asia and ultimately to Europe in the eighth century. The introduction of smallpox to the New World in the 15th and 16th centuries decimated Native American populations. The British used smallpox as a biological weapon during the French-Indian wars. Smallpox continued to be a major worldwide problem well into the 20th century, accounting for up to a half million deaths per year in Europe. In the 20th century, through an intense program of vaccination, naturally occurring smallpox was eradicated.

The origins of immunization are grounded in the history of smallpox. The recognition that cutaneous exposure to the dried material of smallpox lesions caused a milder infection and induced permanent immunity led to the practice of variolization. Unfortunately, this practice frequently induced severe smallpox and death. In the 19th century, Jenner observed that inoculation with cowpox virus, a close relative of smallpox, conferred smallpox immunity. This observation established the practice of vaccination, although variolization continued into the 20th century.

The practice of vaccination with vaccinia virus began in the early 20th century. The origins of vaccinia virus remain unknown, but this virus is distinct from both variola and cowpox. Vaccinia virus has recently been shown to be closely related to the New World orthopoxviruses, cantagalo, and aracatuba viruses. Vaccination was standardized in the mid-20th century. An aggressive program of vaccination eradicated smallpox worldwide. In 1977, the last outbreak of smallpox occurred in Somalia, and the World Health Organization (WHO) certified eradication in 1980. Recently, concern has been raised over the potential of smallpox as an agent in bioterrorism. For an excellent discussion of the subject, refer to the article by Richard Preston, "The Demon in the Freezer."[1]

Following the WHO certification of smallpox eradication in 1980, only 2 known stocks of variola virus were permitted to exist. One is kept at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the other is kept in the former USSR. Evidence suggests that the former USSR expanded their stocks of variola and experimented with it for use as a biological weapon. Concern also exists that samples of these virus stocks have been transferred to other countries.

Molluscum contagiosum is also a poxvirus unique to humans. This virus is spread via close contact, often through sexual contact.

Other human poxvirus infections result from either zoonotic exposure to animal poxviruses or planned or accidental vaccinia administration. Notable examples of zoonotic spread to humans have recently been reported. In 2003, the first outbreak of monkeypox in North America occurred in the Midwest, with 81 cases. These infections were linked to skin exposure to pets, notably prairie dogs. The origin of the infection was ultimately traced to exotic rodents imported from Africa.[2]

Laboratory exposures that have led to infection with vaccinia and tanapox viruses, which are commonly used as vectors for experimental vaccines, have recently been documented. The smallpox vaccination program of civilian and military personnel resulted in numerous infections due to transfer to contacts.

For additional information, see Medscape's Emerging and Reemerging Infectious Diseases Resource Center.

Pathophysiology

Poxviruses are the largest and most complex viruses. They are linear double-

stranded DNA viruses of 130-300 kilobase pair.[3] The 200-400 nm virion is oval or brick-shaped and can be visualized on light microscopy. The extracellular virion possesses 2 envelopes, while the intracellular virus has only one envelope. The virion contains a large number of proteins, at least 10 of which possess enzymatic activity needed for genomic replication.

The replication of poxviruses is equally complex.[4] Infection is initiated by attachment of the poxvirus to one of several cellular receptors. The virus can then enter the cell via numerous mechanisms. Unlike other DNA viruses, poxviruses replicate in the cytoplasm. The virus contains all the elements for genomic replication, but cellular functions appear necessary for complete viral maturation.

Smallpox infections are initiated by inhalational exposure of nasal, oral, or pharyngeal droplets. The incubation period is 10-14 days. Smallpox viruses replicate locally and spread to the local lymph nodes. An asymptomatic viremia ensues on day 3-4, with spread to the bone marrow and spleen. A secondary viremia begins on approximately day 8. This secondary viremia is associated with generalized symptoms of fever and a toxic appearance. The virus in leukocytes then becomes localized in the blood vessels of the dermis. The characteristic rash of smallpox then develops.

Maculopapular lesions appear on the buccal and pharyngeal mucosa and on the face and extremities and move to the trunk. Over several days, these lesions first form vesicles, which are firm and imbedded in the epidermis. They then slowly form pustules. Approximately 8 days after onset, the pustules umbilicate. Scab formation follows. At this stage, mucosal lesions ulcerate, with the release of infectious virus into secretions. The smallpox rash is characterized by skin lesions that are in the same stage of evolution. These lesions are in contrast to chickenpox, in which lesions appear in successive waves and various forms (ie, vesicles, pustules, scabs) that can develop simultaneously. In addition, smallpox causes a significantly worse fever and toxicity prior to the rash than chickenpox. The smallpox lesions then heal, although they characteristically lead to significant scarring.

Other poxviruses are introduced by cutaneous or ocular inoculation. Vaccinia virus used as a vaccine replicates at the site of inoculation, forming local erythematous maculopapules. These maculopapules then vesiculate (ie, jennerian vesicles), scar, and heal over 10-14 days. The virus also spreads to regional lymph nodes, which is often associated with tenderness and fever. Resolution of the lesions involves pustule formation followed by scabbing and healing. This resolution is associated with the development of immunity to variola infection that persists for up to 10 years.

Other poxviruses generally follow the same pattern of evolution, with primarily localized disease. An exception is monkeypox infection, which leads to a clinical syndrome similar to variola. Monkeypox infections can range from mild with few lesions, as in the North American outbreak, to severe systemic illness that resembles smallpox. Molluscum contagiosum virus also replicates at the site of inoculation, but the character of the skin lesions is distinct.

Epidemiology

Frequency

United States

The last reported cases of wild-type smallpox occurred in 1977 in Somalia. No reporting system exists for molluscum contagiosum, but its transmission as a sexually transmitted disease is fairly common. Infections involving the other poxviruses are rare. In 2003, a monkeypox outbreak occurred, involving 81 cases related to the importation of exotic animals from Africa and subsequent spread to prairie dogs that were purchased as pets.[2]

International

With the exception of molluscum contagiosum, poxvirus infections are uncommon. The last cases of smallpox occurred in the late 1970s. Infections with the other poxviruses are due to animal exposures, laboratory infections, or spread following vaccinia immunization.

Mortality/Morbidity

Variola major carries a mortality rate of 25-30%, while the fatality rate associated with variola minor is less than 1%. Morbidity and mortality due to vaccinia infections are uncommon, but infection can be spread by autoinoculation or by close contact with someone who is infected. Poxvirus infections tend to be more severe in persons with eczema and/or immunodeficiency (eg, leukemia). Molluscum contagiosum rarely causes morbidity, although persons with immunodeficiency who develop molluscum contagiosum tend to develop multiple skin lesions. Other poxvirus infections are rare and generally cause only localized scarring. The exception is monkeypox infection. Mortality rates in African monkeypox outbreaks have been as high as 17%. No deaths were reported in the 81 cases in the United States.

Race

Poxvirus infections have no racial predilection.

Sex

Poxvirus infections have no sexual predilection.

Age

Poxvirus infections have no age predilection.

Clinical Presentation

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