Poxviruses

General Concepts

Clinical Manifestations

Smallpox has been eradicated. The remaining poxviruses pathogenic for humans cause skin lesions with usually only limited constitutional involvement. Human cowpox and parapox infections are usually localized and relatively unimportant; human monkeypox is a severe generalized infection which involves organs such as the lungs.

Structure

Poxviruses are brick-shaped (240 nm by 300 nm) and have a complex internal structure including a double-stranded DNA genome (130–260 kb) and associated enzymes. Naturally released virions have an additional outer membrane not found on infective virions extracted artificially from infected cells. Parapoxviruses have a characteristic morphology.

Classification and Antigenic Types

Genera are identified by genetic and serologic properties. Species within genera are very closely related antigenically and are recognized by biologic and/or DNA characteristics. Some poxviruses, (from e.g. seals and crocodiles) are not yet formally classified.

Multiplication

Viral DNA is not infectious per se; virion-associated enzymes are important for replication. An important practical development is the production of recombinant poxvirus vectors (especially vaccinia and canarypox viruses) that express foreign genes and can be used for immunization against other pathogens.

Pathogenesis

Infection is usually caused by invasion through broken skin and in most cases remains localized. Human monkeypox is acquired by contact or by airborne transmission to the respiratory mucosa. Initial viremia during the incubation period spreads infection to internal organs; a second viremia then spreads the virus to the skin.

Host Defenses

The first line of defense is unbroken skin. The initial response after infection involves interferon and inflammation. Cell-mediated and humoral responses to viral antigens are important for recovery and subsequent immunity. The immune response to antigens on the membrane of naturally released virions is particularly important.

Epidemiology

With smallpox now eradicated, all natural human poxvirus infections except molluscum are zoonoses and are geographically restricted, except for molluscum and parapox infections. Despite their names, the reservoir hosts of cowpox and monkeypox viruses are not known with certainty.

Diagnosis

The diagnosis is often suggested by the presence of skin lesions and a history of contact with human or animal cases. Diagnosis is confirmed by electron microscopy and/or virus isolation.

Control

Vaccination is not appropriate for human infections. Some infections are occupational hazards and are probably unavoidable, despite care in handling infected animals.

Introduction

The last endemic case of smallpox occurred in 1977, total eradication was confirmed in 1980, and the official account of the disease and its eradication has appeared. Consequently, smallpox is not discussed below. However, its importance should not be forgotten. It helped to shape history, and it made history by being the first disease to be controlled by immunization and the first to be eradicated. A typical case is shown in Fig. 69-1, and Table 69-1 lists the features that made smallpox an ideal candidate for eradication. Features 10 and 11 meant that the disease spread slowly; features 3, 4, 12 and 13 meant that the source of infection of virtually all cases was another clinically ill individual. The disease was controlled and then eradicated by vigorous surveillance and containment, backed up by vaccination.

Figure 69-1

Smallpox in a child, demonstrating the characteristic centrifugal distribution of the lesions. [Courtesy of WHO Smallpox Eradication Unit.]

TABLE 69-1 Features of Smallpox that made it Eradicabl

Primary Features
1. Effective vaccine
2. One stable serotype
3. No animal reservoir
4. No persistent infection

Additional Features
5. Severe disease with high morbidity and mortality
6. Feasibility demonstrated by elimination from developed countries
7. Potential savings in developed nonendemic countries that are no longer required to vac
8. No cultural and social barriers to case tracing and control
9. Easily diagnosed
10. Long incubation period
11. Low communicability
12. Infectious only after incubation period
13. Subclinical infection rare and not a source of infection
14. Long-term immunity conferred by infection

Table 69-1

Features of Smallpox that made it Eradicable.

The remaining poxvirus infections of humans are relatively insignificant (Table 69-2). Furthermore, even such important animal diseases as sheeppox and camelpox are less important than animal infections caused by other pathogens.

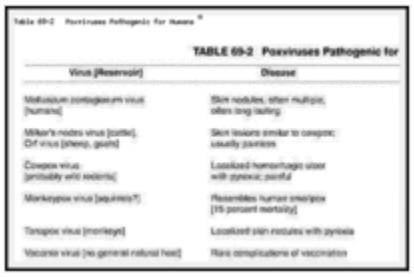

TABLE 69-2 Poxviruses Pathogenic for

Virus [Reservoir]	Disease
Molluscum contagiosum virus [humans]	Skin nodules, often multiple; often long lasting
Milker's nodes virus [cattle]; Orf virus [sheep, goats]	Skin lesions similar to cowpox; usually painless
Cowpox virus [probably wild rodents]	Localized hemorrhagic ulcer with pyrexia; painful
Monkeypox virus [squirrels?]	Resembles human smallpox [15 percent mortality]
Tanapox virus [monkeys]	Localized skin nodules with pyrexia
Vaccinia virus [no general natural host]	Rare complications of vaccination

Table 69-2

Poxviruses Pathogenic for Humans [a].

:

Clinical Manifestations

Poxvirus infections are characterized by the production of skin lesions. With most poxviruses there is typically just a primary lesion, but generalized lesions develop with human monkeypox and molluscum (Fig. 69-2). In human cowpox and parapox infections the lesion develops at the site of inoculation (usually the hand), and infection may be spread to other sites such as the face and/or genitals by scratching. When seen by the physician, cowpox and parapox lesions are usually hemorrhagic crusting ulcers, but early in infection the former are usually vesicular and the latter nodular. The lesions of molluscum, usually multiple, are firm, pearly, flesh-colored nodules.

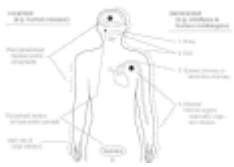

Figure 69-2

Localized and generalized poxvirus infections. Numbers indicate progression of infection.

Parapox and molluscum infections are relatively painless and cause very little constitutional disturbance. Human cowpox is very painful, particularly in young children, usually causes pyrexia and marked lymphadenopathy; patients often require hospitalization. Rare encephalitic complications of cowpox have been reported, and erythema multiforme is a complication of parapox infections. Infection in immunocompromised or eczematous individuals is more severe and usually results in generalized illness, and in cowpox has caused deaths.

Smallpox vaccination has been associated with serious complications. However, routine use of smallpox vaccine has been discontinued, and any future use of recombinant vaccinia virus vaccines will involve attenuated strains, thus reducing the chances of complications.

Although human monkeypox is rare and geographically localized, it is a serious generalized infection, which clinically resembles mild smallpox (Figs. 69-1 and 69-2). A febrile prodrome precedes the development of a vesicular or pustular rash, typically centrifugal in distribution. Detailed examination of more than 300 cases in Zaire showed an overall mortality of 10 percent, reaching 15 to 20 percent in unvaccinated children. Respiratory complications were seen in about 12 percent of unvaccinated patients.

Structure

Poxvirus virions are large and brick shaped. Orthopoxviruses are approximately 240 nm by 300 nm, with short surface tubules 10 nm wide. Parapoxviruses are narrower (160 nm) and have one long tubule that winds around the virion; in electron micrographs, superimposition of the top and bottom surfaces gives a characteristic criss-cross appearance (Fig 69-3). Virions extracted artificially from infected cells are infectious and are generally used in studies on poxviruses. However, virions released naturally from infected cells acquire an additional envelope, which is easily lost during manipulation (Fig. 69-4). These naturally released virions possess extra antibody neutralization sites not present on the artificially

extracted forms (Fig. 69-4). Internally, virions have a dumbbell-shaped core and two lateral bodies (Fig. 69-5). The genome consists of one molecule of double-stranded DNA, from 130 kb (parapox) to 260 kb (fowlpox), and the core contains enzymes for virus uncoating and genome replication. Linear maps of the genomes of various poxviruses have been prepared, and the entire genome of a strain of vaccinia virus has been sequenced.

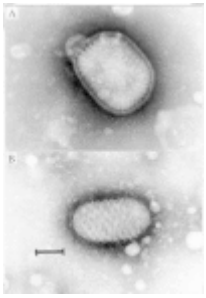

Figure 69-3

Electron micrographs of negatively stained, naturally released virions of (A) vaccinia virus and (B) parapoxvirus. The outer envelope is particularly obvious in (A). (bar = 100 nm)

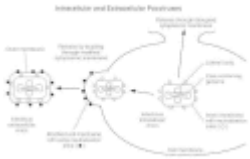

Figure 69-4

Intracellular and extracellular poxviruses.

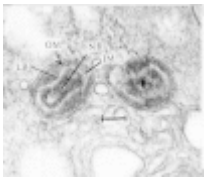

Figure 69-5

Thin section of intracellular vaccinia virus showing the core or nucleoid (N), lateral bodies (LB), inner membrane (IM), and outer membrane (OM). The outer element of OM is lost as the virion is released naturally from the cell.

Classification and Antigenic Types

Poxviruses are assigned to genera on the basis of close genetic and serologic relationships (Table 69-3). The viruses are antigenically complex. Surface and soluble antigens show extensive cross-reaction between species in a genus but not between genera. This means that antigenic typing, as used for other virus groups, is not appropriate. Poxviruses have traditionally been assigned to species on the basis of biologic criteria. Genome analysis is now used and has generally confirmed biologic work, although some strains (e.g., rabbitpox and buffalopox viruses) are now regarded as variants of vaccinia virus. Isolates of molluscum virus can be typed by DNA restriction enzyme analysis.

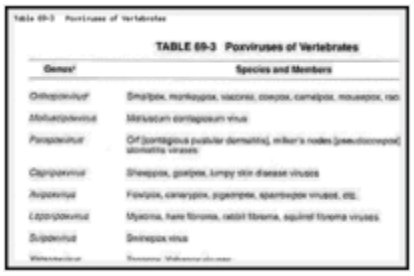

TABLE 69-3 Poxviruses of Vertebrates

Genus[1]	Species and Members
Orthopoxvirus[2]	Smallpox, monkeypox, vaccinia, cowpox, camelpox, mousepox, rat
Molluscipoxvirus	Molluscum contagiosum virus
Parapoxvirus	Orf (contagious pustular dermatitis), milker's nodes (pseudocowpox), pseudocowpox viruses
Capripoxvirus	Sheeppox, goatpox, lumpy skin disease viruses
Avipoxvirus	Fowlpox, canarypox, pigeonpox, sparrowpox viruses, etc.
Leporipoxvirus	Myxoma, hare fibroma, rabbit fibroma, squirrel fibroma viruses
Suipoxvirus	Swinepox virus
Yatapoxvirus	Tanapox, Yaba monkey tumor viruses

Table 69-3

Poxviruses of Vertebrates.

Multiplication

Poxvirus replication takes place in cytoplasmic inclusions. Infecting virions are partly uncoated by cellular enzymes and then fully uncoated by viral enzymes released from the virion core. The viral DNA is not infectious per se, and other core enzymes (including a DNA-dependent RNA polymerase) play essential roles in the replication cycle. The replication cycle can be divided into functions controlled by early (prereplicative) gene products and those controlled by late (postreplicative) gene products. Most virions (80 to 90 percent) remain within cells and therefore lack the outer envelope found on naturally released virions (Fig. 69-4).

Knowledge of the molecular biology of poxvirus replication has led to the development of recombinant vaccinia virus strains that code for the products of foreign genes inserted into the vaccinia virus genome (Fig. 69-6). Such recombinants are infectious and are being widely used to study gene expression, as candidate vaccines (e.g., against rabies and rinderpest), and for the production of biopharmaceuticals such as factor VIII. An extension of these studies has led to the development of canarypox recombinants which express foreign genes in mammals without causing productive infection. The use of such non-replicating vectors may overcome objections to the use of vaccinia virus as a vector.

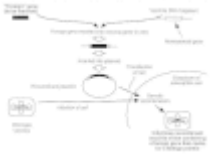

Figure 69-6

Strategy for the production of recombinant vaccinia virus strains.

Pathogenesis

The pathogenesis of localized poxvirus infections is simple. Virus invades through broken skin, replicates at the site of inoculation, and causes dermal hyperplasia and leukocyte infiltration. With cowpox, and to a lesser extent with parapox, there is limited lymphatic spread; this causes lymphadenopathy and elicits an immune response. The lesion of molluscum is circumscribed by a connective tissue capsule, and the dermis, although distorted, is not usually broken. Some poxviruses express an epidermal growth factor and host range genes which play a role in pathogenesis and cell tropism.

Human monkeypox is usually acquired via the respiratory tract, and during a 12-day incubation period viremia distributes infection to internal organs, which are damaged by virus infection. Spread to the skin initiates the clinical phase, and the lesions progress

through the classic stages of macule to papule to vesicle to pustule to crust. Lymphadenopathy, usually involving the cervical and inguinal areas, is often marked.

Host Defenses

With the exception of human monkey pox, which is usually acquired via the respiratory route, human poxvirus infections are acquired by inoculation into the skin or contact with broken skin (Fig. 69-2). Consequently, unbroken skin presents the first line of defense. Interferon, nonspecific inflammation, and probably pyrexia play a role in limiting infection during the early stages.

Infection induces humoral and cellular immune responses to naturally released virions and to viral antigens on the surface of virus-infected cells. Responses to the extra antigens on the envelope of naturally released virions (Fig. 69-4) are particularly important, determining the speed and extent of recovery and the prevention or attenuation of future infection.

In general, the immune response is related to the severity of infection; the immunity elicited by a mild infection may be insufficient to prevent reinfection, as is often the case with human parapox infections.

:

Epidemiology

With the exception of molluscum, which is a specifically human disease, human poxvirus infections are acquired from animal reservoirs (Table 69-2). In some cases the reservoir is known and distributed worldwide, as in the case of ovine and bovine parapoxviruses. Human infection with these viruses is an occupational hazard of those working with the infected reservoir hosts.

Monkeypox is restricted to West Africa, and squirrels are more important as reservoir hosts than monkeys. Cowpox virus is restricted to Europe and western parts of the former USSR. Bovine cowpox is rare, and the domestic cat is the most commonly reported host. Conclusive information about the reservoir host of cowpox virus is lacking, but it is probably small wild rodents. Cases occur without known contact with cats or cattle, and indirect spread via barbed wire or brambles is possible.

Limited natural person-to-person spread of monkeypox has been observed, but not further than four or five generations. Parapox and cowpox infections rarely, if ever, spread from person to person. Person-to-person spread of molluscum is traditionally associated with physical contact sports (e.g., wrestling) and the sharing of towels. There is increasing evidence, however, that sexual transmission of molluscum is important.

Vaccinia virus is traditionally regarded as a laboratory virus with no natural reservoir. However, buffalopox virus, now considered a variant of vaccinia virus, appears to have established itself in India, although information about its reservoir host is lacking. Because of the potential use of recombinant vaccinia virus vaccines, it is important to remember that such strains may become established in animal populations and/or interact with genetically related viruses circulating in them.

Diagnosis

In many cases, the nature of the lesions and a careful history that establishes contact with an infected reservoir animal or another infected person will permit a satisfactory diagnosis; difficulties may arise if no such contact is established. This is perhaps most common with human cowpox, since most cases are not traced to a particular source and a clinical diagnosis of anthrax is sometimes made.

Electron microscopy of vesicle or scab material is an effective means of rapid diagnosis; poxviruses and herpesviruses are readily distinguished, and the characteristic morphology of

parapoxviruses can be recognized (Fig. 69-4). Cowpox was diagnosed in this way in 23/24 cases where suitable material was available. Immunofluorescence of infected cell cultures will differentiate morphologically similar poxviruses from different genera (e.g. *Orthopoxvirus* and *Yatapoxvirus*). Although molluscum virus has yet to be cultivated, the other poxviruses are easily isolated in tissue culture and/or chicken embryos. Cultivation then allows identification by biologic and serum neutralization tests. Precise identification by antibody detection is compromised by close antigenic relationships within genera, but knowledge of host and geographic range will help to confirm a presumptive diagnosis.

Control

Control of the common human poxvirus infections depends on knowledge of their epidemiology. In particular, persons caring for sick livestock should take precautions, but the extent of occupational exposure is such that infection and reinfection are inevitable. Control of infections such as cowpox which has an unknown reservoir, is virtually impossible. Person-to-person transmission is reduced by improving hygiene. Monkeypox is a special case. The World Health Organization considers that the benefits of vaccination do not outweigh the risks and expense. Control of this disease depends on health education and on breaking the link with the animal reservoir; this last should be achieved by the use of forest land near villages for agriculture.

In conclusion, it is significant that the strategies used for smallpox eradication are being assessed for the control and eradication of other diseases such as measles and that smallpox recombinant poxviruses may play an important role in the control of other infections.

References

1. Baxby D, Poxvirus infections in domestic animals. p.17. In Darai GM (ed): Virus Diseases in Laboratory and Captive Animals. Martinus Nijhoff, Boston, 1988.

2. Baxby D, Bennett M, Getty B. Human cowpox 1969–93: a review based on 54 cases. Br J Derm. 1994;131:598. [PubMed]

3. Bennett M, Gaskell CJ, Baxby D. et al. Feline cowpox virus infection. J Sm Anim Pract. 1990;31:167.

4. Binns M, Smith G L (eds): Recombinant Poxviruses. CRC Press, Boca Raton, FL, 1992.

5. Brown ST, Nalley JF, Kraus SJ. Molluscum contagiosum. Sex Transm Dis. 1981;8:227. [PubMed]

6. Cadoz M, Strady A, Meignier B. et al. Immunization with canarypox virus expressing rabies glycoprotein. Lancet. 1992;339:1429. [PubMed]

7. Goebel SJ, Johnson GP, Perkus M. et al. The complete DNA sequence of vaccinia virus. Virology. 1990;179:247, 517. [PubMed]

8. Esposito JJ, Knight JC. Orthopoxvirus DNA: a comparison of restriction profiles and maps. Virology. 1985;143:230. [PubMed]

9. Fenner F, Henderson DA, Arita I et al: Smallpox and Its Eradication. World Health Organization, Geneva, 1988.

10. Fenner F, Wittek R, Dumbell KR: The Orthopoxviruses. Academic Press, San Diego 1989.

11. Jezek Z, Arita I, Szczeniowski M. et al. Human tanapox in Zaire: clinical and epidemiological observations on cases confirmed by laboratory studies. Bull WHO. 1985;63:1027. [PMC free article] [PubMed]

12. Jezek Z, Fenner F: Human Monkeypox. Karger, Basel, 1988.

13. Johanneson JV, Krogh HK, Solberg I. et al. Human orf. J Cutaneous Pathol. 1975;2:265. [PubMed]

14. Scholz J, Rosen-Wolff A, Bugert J. et al. Epidemiology of molluscum contagiosum using genetic analysis of the viral DNA. J Med Virol. 1989;27:87. [PubMed]