The Ocular Complications of Smallpox and Smallpox Immunization

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Although smallpox was eradicated worldwide, concerns have been raised about the use of smallpox as a biological weapon. Plans are being considered for smallpox immunization in the United States. Variola virus, the cause of smallpox, and vaccinia virus, used in smallpox immunization, are both orthopoxviruses that are associated with serious ocular complications, including eyelid and conjunctival infection, corneal ulceration, disciform keratitis, iritis, optic neuritis, and blindness. About 5% to 9% of patients with smallpox develop ocular complications, and case-fatality rates reach 20% to 35% among unvaccinated individuals. About 10 to 20 patients develop ocular complications per 1 million smallpox immunizations, usually through autoinoculation, in which the patient transfers vaccinia from the immunization site to the eye. The risk of ocular vaccinia infection may be reduced by instructing patients and individuals in close contact with the vaccinee to wash their hands often and avoid touching the immunization site and their eyes. Topical antiviral therapy, topical steroids, and topical and oral antibiotics have been used to reduce the ocular complications of smallpox immunization. In contrast, there has been little experience with the use of these therapies for the ocular complications of smallpox.

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Smallpox was known nearly worldwide by the late 18th century, when Edward Jenner discovered smallpox immunization. In the United States, smallpox immunization became compulsory in 1855, and by 1948, there were no further deaths reported from smallpox. Between 1948 and 1965, there were 200 to 300 deaths from smallpox immunization. Routine smallpox immunization for children was discontinued in the United States in 1971. The World Health Organization intensified efforts to eliminate smallpox in 1967, and the last naturally occurring case was found in Somalia in 1977. Remaining stocks of variola virus were reportedly destroyed or sent to either Atlanta, Georgia, or Moscow, Russia.

VIROLOGY

Variola and vaccinia are closely related members of Orthopoxvirus, a genus of viruses within the family Poxviridae. Poxviruses are large and complex brick-shaped viruses consisting of a core of viral DNA, lateral bodies, an outer membrane containing tubular-shaped lipoprotein subunits, and an envelope. Poxviruses use
their own set of enzymes to replicate the cytoplasm, and these sites of replication can be seen in histologic preparations as characteristic inclusions, or “Guarnieri bodies.” The host cell undergoes necrosis and ruptures, releasing infectious virions.

**EPIDEMIOLOGY**

**Smallpox**

Smallpox is spread from person to person through aerosolized droplets from respiratory discharges, direct skin contact, and through fomites. The incubation period is 10 to 14 days, and infected individuals can communicate the disease from 1 to 2 days prior to the onset of symptoms until the rash has resolved and all scabs and crusts have been shed. The case-fatality rates are about 20% to 35% among those who have not been vaccinated. Infants, pregnant women, and older adults are at higher risk of mortality from smallpox, and there is a lower risk of death among immunized individuals. Smallpox reportedly caused more than one third of the blindness in Europe prior to immunization, and even as late as the 1960s, smallpox remained a significant cause of blindness in Africa. Ocular complications have been reported in about 5% to 9% of patients with smallpox. During smallpox epidemics in Vienna, Italy, and France, the proportion of people with ocular complications was 9%, 7.2%, and 5.1%, respectively. During a smallpox epidemic in Cleveland in 1902, 1.8% of cases developed corneal ulcers. In a large series of smallpox cases in India, corneal ulceration developed in 1%, primarily in children younger than 14 years.

**Vaccinia**

The rate of ocular complications following smallpox immunization is about 10 to 20 patients per 1 million primary immunizations. In the United States in 1963, there were 115 accidental infections (85 after primary vaccination, 8 after revaccination, and 22 in contacts), of which 103 were caused by autoinoculation of the eye. Most cases occurred in children aged 1 to 4 years. The rate of accidental infections was 13.6 per 1 million primary vaccinations, and eye infections comprised nearly all of the cases of accidental infection. Higher complication rates occur with primary immunization compared with reimmunization. The rates of ocular complications with smallpox immunization in the United States are similar to that reported in Marseille, France (23.8 per 1 million immunizations), but higher than South Wales (10 per 1 million immunizations). Of 348 patients with ocular complications from immunization detected by the American Red Cross from 1963 to 1968, most were preschool children. Most had vaccinia of the eyelid or conjunctiva, and corneal involvement occurred in 6.3%.

**OCULAR COMPLICATIONS OF SMALLPOX: CLINICAL FINDINGS**

The eyelids are usually involved in the generalized pustular rash, and the edema, discharges, and dried secretions may be severe enough to prevent the eyelids from opening for a few days. Conjunctival pustules can occur and are accompanied by pain, photophobia, and lacrimation. Conjunctival phlyctenules are occasionally reported. The smallpox virus is actively secreted in tears during conjunctivitis. Corneal involvement usually occurs through contiguous spread of a pustule at the limbus. Prior to the onset of the rash, corneal infiltrates may appear that do not stain with fluorescein. Corneal ulceration is the most common serious complication of smallpox and may involve any part of the cornea and result in perforation, iris prolapse, hypopyon, staphyloma, and/or endophthalmitis. Bacterial superinfection may occur with the corneal ulceration, leading to widespread destruction of the cornea. Disciform keratitis can occur late in the rash or 1 to 2 weeks after the patient has been released from quarantine and may last for months. A corneal leukoma may follow corneal ulceration or disciform keratitis as shown in Figure 1.
Eyelid vaccinia is characterized by umbilicated, white, pustules that may arise in a clear cornea or adjacent to a conjunctival pustule and can result in perforation and hypopyon. Disciform keratitis may occur as late as 2 to 3 months after immunization. Other complications include interstitial keratitis with vestibulocutaneous symptoms, central retinal artery occlusion, pigmentary retinopathy, retrobulbar neuritis with encephalomyelitis, transient strabismus, and orbital involvement with ptosis, reduced ocular motility, and optic atrophy. Entropion, symblepharon, eyelid margin defects, and loss of eyelashes are some long-term sequelae of eyelid involvement.

Diagnosis

The diagnosis of ocular vaccinia is made on the basis of a history of smallpox immunization or recent close contact with a vaccinee and the clinical appearance of pustules on the eyelid or conjunctiva. Laboratory confirmation is seldom needed, but scrapings of lesions may demonstrate the virus in chick chorioallantoic membrane cultures or show Guarnieri bodies on staining. The differential diagnosis of vaccinia of the eyelids includes herpetic lesions, preseptal and orbital cellulitis, atypical herpes simplex, and acute dacyrocystitis. Vaccinia keratitis may sometimes resemble herpes simplex keratitis.

Treatment

Topical antivirals, such as idoxuridine, trifluuridine, and vidarabine, are used to treat vaccinia of the cornea and conjunctiva or to prevent conjunctival and cutaneous involvement in patients with eyelid lesions. Topical antiviral drops or ointments are given every 4 hours for 7 to 10 days. Vaccinia immune globulin is recommended for ocular vaccinia at doses of 0.3 to 0.5 mL/kg of body weight and repeated in 48 hours if there is no improvement. Topical vaccinia immune globulin (100 mg/mL) may be used every 4 hours but is contraindicated if the corneal epithelium is not intact, as it may worsen corneal clouding and edema, presumably through precipitation of antigen-antibody complexes in the cornea.

Topical steroid therapy may be combined with antiviral therapy for treatment of disciform keratitis if the cornea is intact and the active infection has cleared. Topical and/or oral antibiotics have been used as treatment against bacterial superinfection of the conjunctiva or cornea or as prophylactic therapy against preseptal cellulitis in patients with severe eyelid involvement.

Prevention

The risk of ocular complications may be reduced by instructing patients and individuals in close contact with the vaccinee to wash their hands often and to avoid touching the im...
munization site and their eyes. Individuals who have been immunized against smallpox should probably avoid contact lens use until the scab on their immunization site has resolved. Relative ophthalmologic contraindications to smallpox immunization include allergic conjunctivitis, eyelid eczema, and other pruritic eye diseases in which there may be a greater likelihood of autoinoculation or altered immunity.

CONCLUSIONS

Smallpox is characterized by frequent and severe ocular complications. The ocular complications of smallpox vaccination are relatively rare, but in a hypothetical situation involving mass vaccination of 100 million individuals, about 1000 to 2000 cases of ocular vaccinia might be anticipated. The risks of ocular vaccinia may be reduced by careful patient education and appropriate prophylactic therapy. Although there are few published data on newer therapies for the ocular complications of smallpox, antiviral agents used to treat ocular vaccinia may prove beneficial should smallpox become an emerging medical problem.

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