

## Smallpox: New Mode of Old Disease

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### Abstract

Since last endemic smallpox in 1977, the variola virus can be detected only in some research institutes in the world. However, in fear of bioterrorism, the clinical manifestations that may be forgotten by emergency physicians have to be readdressed. Variola virus usually existed as two related strains: variola major with a mortality of 20 to 50%, and variola minor with a mortality of less than 1%. World Health Organization classification comprised another 3 additional types, that is, flat type, hemorrhagic type, and variola sine eruptione. The disease is highly contagious and spread by air droplets and direct contact with contaminants. Emergency reporting and pre-exposure vaccination are the most important steps in preventing epidemic, either from bioterrorism and the nature. (*Ann Disaster Med* 2002;1 Suppl 1: S36-S43)

**Key words:** smallpox; bioterrorism; vaccination; disaster medicine

### Introduction

Smallpox has vanished for more than 20 years. The variola virus has now existed only in research laboratories. The World Health Organization (WHO) tried to decrease the number of laboratories that still reserved the virus after global eradication of smallpox. Accordingly, there should be only two institutes retaining variola virus in the world; that is, the Centers for Disease Control (CDC) in Atlanta and the State Research Center of Virology and Biotechnology (the Vektor Institute) in Novosibirsk, Russia.<sup>1</sup> It will be a dilemma whether the variola virus should also be eradicated from the

laboratories. There is always an uncertainty that human beings may suffer from the threatening of natural smallpox as our ancestors did if the smallpox occurs again after we eradicate the residual variola virus in the laboratories. On the other hand, whether the virus will be used in wars or bioterrorism remains another concern. In addition, no one knows if there are still another laboratories that retain the virus beyond the two described above. An accidental or on-purpose release could cause a epidemic episode.<sup>2-4</sup> Because smallpox may become a lethal threatening as a bioterrorist weapon, we therein review the clinical

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manifestations of the disease and remind the emergency physicians for prompt recognition and actions if that do occur.

### **Pathogenesis**

Variola virus belongs to the family Poxviridae, which contain single, linear, double-stranded 130-to-375-kb DNA and replicate in cell cytoplasm. They are brick-like shaped with 200 x 250 x 300 nm in size. The virus enters human bodies via the respiratory tract, circulates rapidly into local lymph nodes, and causes viremia. There is then a latent period of 4 to 14 days, when the virus multiplies in the reticuloendothelial system. After another brief viremia period and the prodromal phase, the virus crosses the dermal capillary endothelium and causes the skin lesions.<sup>5</sup> Virus particles are abundant in oropharyngeal, skin lesions, spleen, lymph nodes, liver, bone marrow, kidneys, and other organs. They can also be detected in urine and conjunctival secretions.<sup>6,7</sup> The levels decrease gradually during convalescence phase. The immune response may limit the progression of the disease. Cytotoxic T cells and B cells increase during the early phase, followed by the peak of neutralizing antibodies in the first week, and then those of hemagglutination-inhibition antibodies and complement-fixation antibodies in the second week. Neutralizing antibodies are usually present for many years, whereas levels of hemagglutination-inhibition and

complement-fixation antibodies decline after one year.

### **Epidemiology**

Smallpox spreads primarily through air droplets, but contacts with contaminated clothing or bedding are potentially transmissible.<sup>8</sup> Although smallpox is less transmissible than measles, chickenpox, or influenza, the secondary attack rates among unvaccinated contacts are still high.<sup>1,9</sup> The infectivity is highest from the onset of the enanthema through the first 7 to 10 days of rash. Secondary cases are often limited to family members or health care personnel. Patients with severe disease or coughing can spread large amount of virus.

In Taiwan, none of the persons less than 30 years old have been vaccinated, and all of them are susceptible to smallpox. The persons who were vaccinated may still be partially protected; if exposed, they may have milder disease and may be less likely to transmit it to others.

### **Clinical Manifestations**

The incubation period lasts usually about 12 days (range 7-17).<sup>8</sup> It has been reported that the strains produced by the Russian biological warfare programme had much shorter incubation periods in primates.<sup>10</sup> Acute onset of fever, headache and backache may initially mimic influenza.<sup>8</sup> Enanthema over the tongue, mouth, and oropharynx precedes

the rash by one day. Non-specific erythematous rashes develop 1 to 2 days later. The rash begins as small, reddish macules, which become papules with a diameter of 2 to 3 mm over one or two days; after one or two more days, the papules become vesicles. The lesions occur first on the face and extremities but gradually spread over the body. Pustules that are 4 to 6 mm in diameter develop about four to seven days after the onset of the rash and remain for five to eight days, followed by umbilication and crusting. A second, less pronounced temperature spike may develop five to eight days after the onset of the rash, especially if the patient has a secondary bacterial infection.<sup>4</sup> Smallpox lesions have a peripheral or centrifugal distribution and are generally all at the same stage of development, which is different from chickenpox.<sup>1,4,8</sup> Lesions on the palms and soles persist the longest. This may be even the only skin manifestation in immunocompromised populations and not present as the indicator of the severity. There is no practical antiviral treatment. Although vaccination before exposure is effective, but it has numerous side effects and immunity does not last for life. Vaccination after exposure is moderately effective if it is given within four days. So it has potentially disastrous effects on the general population if smallpox were to be released because of high contagiousity.

## WHO Classification

WHO ever proposed a classification that encompasses five types of smallpox.<sup>1,7,8</sup> In that classification, the "ordinary" type of smallpox, variola major (as described above), comprised nearly 90 percent of cases with 20% to 50% mortality. The second "modified" type, variola minor, accounted for 2 percent of cases in unvaccinated persons and for 25 percent in previously vaccinated persons. They were rarely fatal; the lesions were fewer, smaller, and more superficial than those in patients with the ordinary type with more rapid evolution. The third type is the flat lesion that evolved more slowly than those of variola major and that coalesced; the cases comprised about 7% with fatality rate of 97% if unvaccinated. Hemorrhagic smallpox, the fourth type, accounted for less than 3 percent of cases. The diagnosis is difficult. Almost all patients with this type of smallpox died within the first seven days of illness. The last type of smallpox, variola sine eruptione,<sup>11</sup> occurs in previously vaccinated persons or in infants with maternal antibodies. Affected persons are asymptomatic or have only brief fever, headache, and influenza-like symptoms. The transmission of this type has not been documented. In cases of variola minor, which occurs mainly in the Americas and parts of Africa, the disease is mild, causing death in less than 1 percent of patients.

## Diagnosis

The diagnosis depends upon clinical judgments.<sup>1,4</sup> However, there are many eruptive illnesses to be differentiated. Severe chickenpox is one of the examples. The prodrome of chickenpox lasts for one or two days, fever occurs with the onset of the rash, and the eruption is concentrated over the trunk. Various lesions are present at different stages, progress from vesicles, and become crusting within 24 hours. Human monkeypox, a zoonotic disease, is another example. However, it has never occurred outside the Africa. In spite of similar rashes, the patients with monkeypox often have lymphadenopathy, and rarely have human-to-human transmission.

For confirmation, specimens such as scrapings or secretions can be examined directly for the presence of virions by electron microscopy, and for viral antigen by immunohistochemical studies.<sup>12,13</sup> The brick-shape characteristics of the variola virus are completely different from varicella-zoster virus. Polymerase chain reaction promises to be more useful than the above methods for confirming variola or other poxvirus infections.<sup>14-17</sup> Confirmatory tests are isolation of the virus on live-cell cultures and nucleic acid identification. The serologic testing does not differentiate among orthopoxvirus species. Paired serum samples are required to distinguish recent infection from vaccination in the past. The levels

of IgM are of help in increasing the sensitivity and specificity of serologic tests. The above confirmatory tests are especially important for identification of bioterrorist attack.

## Treatment

The suspected cases should be isolated in a negative-pressure room as possible, and be vaccinated especially in an early stage. An isolation hospital or other facility should be designated for endemic or epidemic smallpox. Supportive treatment such as adequate hydration and nutrition is still the most essential part. Penicillinase-resistant antibiotics should be used if secondary infected lesions or ophthalmic infections are present, if bacterial infection endangers the eyes.<sup>4</sup> Topical idoxuridine should be considered for the treatment of corneal lesions, although its efficacy is not proven. Cidofovir decreases pulmonary viral levels and pneumonitis in animals with vaccinia or cowpox. In the event of a smallpox outbreak, the drug could be made available under an investigational-new-drug protocol for smallpox or adverse effects of vaccine.<sup>17</sup> Vaccinia immune globulin has no benefit in patients with clinical smallpox, and has not proven to have survival advantages when combined with vaccination for prophylaxis.

## Alerting and Response

Smallpox eruption is an international health emergency.<sup>18</sup> Confir-

matory diagnostic tests should be performed as soon as possible in a Biological Safety Level 4 laboratory where staff members have been vaccinated. Any suspected cases should be reported immediately to CDC. The patient should be isolated; interviews should be conducted to identify contacts. The contacts should be vaccinated as soon as possible and not more than two or three days after exposure. All health care providers, regardless of their immunization status, should use universal precautions.<sup>18</sup> Scrapings of skin lesions, vesicular or pustular fluid, crusts, blood samples, and tonsillar swabbings must be sent to the CDC after notification or alerting.<sup>18</sup>

The CDC has released the guidelines for the release of vaccine in bioterrorism. Preexposure vaccination is not advised, except for clinical or laboratory personnel. If the risk of deliberate release increased, preexposure vaccination should be expanded. Accordingly, in the case of an international release of variola virus, the following groups would be vaccinated firstly:<sup>18</sup> 1) persons directly exposed to the release; 2) persons with face-to-face or household contact with an infected patient or in close proximity (within 2 m); 3) personnel directly involved in the management of infected patients; 4) laboratory personnel involved in processing specimens and others likely to have contact with infectious materials. Those vaccinated in the past might have

an accelerated immune response after revaccination or exposure. A detailed contact history within a period starting three weeks before the onset of the illness should be obtained as soon as possible to apply ring vaccination and containment strategy.

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## 浴火重生的天花

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### 摘要

自 1977 年的天花大流行之後，天花病毒現在只能在某些研究機構裡才存在。然而，由於對於生化戰的疑慮，這些早已為急診醫師遺忘的臨床症狀及表現，有必要再重新教育。天花病毒通常存在兩種發病型態：即死亡率 20%到 50%的主型和小於 1%之副型。世界衛生組織的分類包括其它三種型態：平坦型、出血型及出疹（如火山爆發）型。天花是高度接觸傳染且藉著空氣微粒散播和接觸污染源而致病。不管是生化戰或自然流行，急診的通報及暴露前的疫苗均是防止大流行的最重要方法。(Ann Disaster Med 2002;1 Suppl 1: S36-S43)

**關鍵詞：**天花；生物戰；預防注射；災難醫學

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