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Clinicopathologic understanding and control of varicella-zoster virus infection☆

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ABSTRACT

As reflections by the recipient for the Japanese society for vaccinology Takahashi award, clinicopathologic understanding and control of varicella-zoster virus (VZV) infection was briefly reviewed. In 1974, a live varicella vaccine was developed by attenuating the Oka strain of VZV after the passages in non-human cells at a low temperature. The vaccine was immunogenic, well tolerated, and effective, and distributed worldwide so far. For post-exposure prophylaxis of varicella, the vaccine and acyclovir is effectively used in the incubation period of varicella. The delayed type hypersensitivity to VZV skin test antigen was applied for evaluation of cell-mediated immunity to VZV which is commercially available in Japan. The biphasic viremia during incubation period of varicella and airborne spread of VZV from varicella patients and from herpes zoster patients with localized lesions were shown by the virus isolation or by detection of the virus DNA.

1. Introduction

Varicella-zoster virus (VZV) causes two distinct diseases with varicella occurring after primary viral infection and zoster resulting from a secondary infection due to reactivation of latent VZV in the sensory ganglia. Varicella is generally believed to be a benign disease with occasional complications in immunocompetent individuals, but infection can be severe or fatal in immunocompromised hosts. More than 30 years ago there were no effective tools, such as a vaccine or acyclovir, to control primary VZV infection. In the early 1970s, I started clinicopathologic and virological research on VZV infection in order to understand the pathogenesis of primary VZV infection, to diagnose and treat the disease, as well as to prevent the disease. Over the past several decades, our understanding of this virus has greatly improved with new techniques for virological study and global implementation of a VZV vaccine. Reflections and results from these 30 years of research will be briefly introduced in this article.

2. Development of a live attenuated varicella vaccine

The vaccine virus was isolated from a vesicle of a 3-year-old otherwise healthy boy called Oka (his family name) who had typical varicella. This virus was passaged through human embryonic lung cells, guinea pig embryonic cells at a low temperature, and human diploid cells (WI-38). It was then adapted to MRC-5 human diploid cells for vaccine preparation. The vaccine contains cell-free virus with a minimum of 1000 plaque forming units per dose and suitable stabilizers [1]. In 1974 the vaccine was administered to hospitalized children immediately after the occurrence of an index varicella case because preventive methods, such as administration of VZV immune globulin, were unavailable at the time. The vaccine prevented the spread of varicella throughout the children's ward of the hospital. Subsequently, the vaccine was shown to be immunogenic, well tolerated, and efficacious even in high-risk children [2]. The vaccine has been studied extensively with largely favorable results as shown in Table 1 [3–16].

The vaccine was initially licensed in Japan in 1987 for high-risk children but was extended just after licensure to include normal children based on the needs of parents and physicians. Because varicella vaccination is not compulsory in Japan, only approximately 36% of Japanese children received the vaccine in 2006. This low level of coverage was not sufficient to alter the circulation of wild-type VZV, and the epidemiology of natural varicella has not changed since the vaccine was introduced. The most dramatic changes were reported in the USA after the introduction of a universal immunization strategy in 1996 [17–21], causing vaccine coverage to increase to 89% in 2006. As a result, there have been substantial declines among both children and adults in the incidence of varicella, hospitalizations and ambulatory visits for varicella, mortality due to varicella, varicella-related complications, and overall expenditures for varicella-related illnesses. The vaccine is now commercially available worldwide and was administered to approximately 14 million individuals in more than 100 countries in 2005.

☆ Reflections by the recipient for the Japanese society for vaccinology Takahashi award.

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Table 1
Properties of the live attenuated varicella vaccine (Oka strain)

1.	Causes little or no clinical reactions[a]
2.	Induces antibody (measurable by CF, NT, FAMA, IAHA tests)
3.	Induces CMI (delayed-type skin reaction, lymphocyte transformation)
4.	Lack of contact infection in most cases
5.	Induces long-term protective immunity
6.	Prevents disease when administered up to 3 days after exposure
7.	Does not enhance the incidence of herpes zoster

[a] Mild clinical reactions in 15–75% of leukemic children.

3. Development of VZV skin test antigen

Cell-mediated immunity (CMI) to VZV is important in order to recover from VZV infections. In 1977 Kamiya et al. developed a skin test antigen from virus-infected cells that was used to evaluate CMI to VZV [22]. This is a very convenient method and VZV immune status can be determined by measuring the diameter of erythema 24–48 h after intradermal inoculation of the skin test antigen. Subsequently, an improved VZV skin test antigen was developed from the supernatant of virus-infected cells, which has far less protein content than the former test that was prepared by sonicating infected cells [23]. The varicella vaccine is now administered to the elderly to enhance VZV CMI in order to prevent herpes zoster and postherpetic neuralgia with favorable results. The skin test antigen has been successfully used to evaluate CMI to VZV [24,25].

4. Viremia during varicella

An understanding of the pathophysiology of VZV infection has been limited because there is no suitable experimental animal model to produce clinical varicella [26,27]. Asymptomatic viremia preceding the onset of a varicella skin rash is assumed to be a distinct phase of varicella [28]. Using sensitive culture techniques, the virus was isolated from peripheral blood mononuclear cells 1 day after disease onset [29]. This viremia could be detected between 5 days before varicella onset and 1 day after disease [30,31], with the most frequent detections occurring just before disease onset, which probably corresponds to secondary viremia in the logical schema by Grose [28]. The viremia disappeared 2 days after disease onset and was undetectable thereafter when specific immunity to VZV developed [31,32]. However, viral DNA was detected for a longer period after the introduction of polymerase chain reaction (PCR) amplification [33]. Although virus could not be isolated from the blood early in the incubation period, viral DNA was detected at the same stage by PCR amplification and was assumed to represent primary viremia [33]. After primary viremia, the virus replicates in the internal organs even in immunocompetent children with varicella [34]. The number of vesicular skin rashes on the body correlates with the maximum body temperature, duration of fever, and degree of viremia (the number of infected cells in the blood) [35]. The virus was not isolated from the blood of vaccine recipients at any time after immunization using the same technique [31]; however, viral DNA was occasionally detected in the blood of vaccine recipients from days 7 to 28 after immunization [36]. Our understanding of the pathophysiology of primary VZV infection is summarized in Fig. 1.

5. Virus spread from varicella and herpes zoster

Varicella is one of the most contagious infectious human diseases. Several observations suggest that infection occurs after exposure to aerosolized VZV from patients with varicella or herpes zoster, although the mechanism by which the virus is shed and the sites of viral shedding are unknown. It is generally accepted that typical varicella is infectious for 1–2 days before disease onset and for 4–5 days thereafter. However, it is difficult to isolate VZV from throat swabs just after the onset of disease [37], although viral DNA can be frequently detected [38]. Viral DNA has been detected on several environmental surfaces, including an air conditional filter, occasionally, intermittently or persistently just after disease onset and thereafter [38]. In the case of the viral DNA positive air conditional filter, this contaminated surface could not be directly touched by the family members, suggesting the airborne spread of VZV. Varicella patients, even when routinely treated with oral acyclovir for 5 days, excreted the virus from their respiratory tract or vesicles and disseminated the virus to the environment via an aerosol route [39].

After primary infection with VZV, the virus becomes latent in cells of the dorsal root ganglia and can be reactivated to produce herpes zoster. It is generally accepted that patients with localized herpes zoster are less contagious than those with varicella or

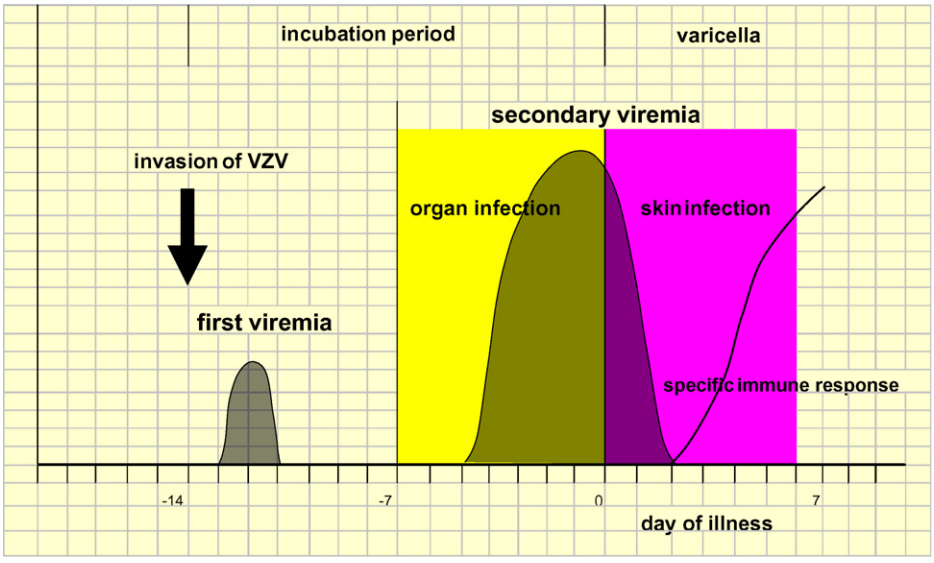

Fig. 1. Viral replication between invasion of VZV and clinical signs of varicella. *Note*: Biphasic viremia during the varicella incubation period and two stages of organ and skin infections.