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EDITORIAL COMMENTARY

Varicella Zoster Virus and Giant Cell Arteritis

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(See the major article by Gilden et al on pages 1866–71.)

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When an effective vaccine is deployed in a population, the infectious agent ought to disappear or almost disappear, unless the vaccine is a live agent, which can become latent and subsequently reactivate. The live attenuated varicella zoster virus (VZV) vaccine, for example, has greatly reduced the prevalence of varicella; however, vOka, the vaccine virus, establishes latency and can reactivate to give rise to zoster [1]. The varicella vaccine was licensed in the United States in 1995. This event and the consequent near-universal administration of the vaccine caused the incidence of varicella to decline by >90% [2]; nevertheless, the incidence of zoster has not declined significantly over the same period [1]. Both wild-type (WT) VZV and vOka are now causes of zoster [3]. Fortunately, however, the reduction in both circulating VZV and the prevalence of varicella have not also caused a massive increase in the incidence of zoster that was feared on the basis of models that assumed that continuous contact with circulating VZV was necessary to maintain immunity [4]. In fact, the incidence of zoster had already been increasing as a result of the introduction of immunosuppressive therapeutic modalities in the 1950s, which preceded varicella vaccination, and the adoption of universal varicella vaccination did not alter the trajectory of this rise. It, thus, does not appear to be necessary to subject children continually to varicella to protect adults from zoster [5, 6]. The incidence of zoster is probably increasing as a function of many factors of modern life, including the aging of the population, and improved ascertainment, as well as a greater use of immunosuppressive therapy to treat individuals with cancer or autoimmune illnesses and recipients of organ transplants [5].

Although a live attenuated zoster vaccine that also uses vOka is available for healthy individuals aged >60 years, it is not widely used and is at best only 50%–60% effective in preventing zoster. Its protective efficacy, moreover, lasts only about 8 years [7]. The zoster vaccine shares the ability of the varicella vaccines to cause zoster, although the vaccine virus does so less frequently than WT VZV [3, 8, 9]. Despite the availability of effective vaccines against it, VZV continues to be, paradoxically, a serious pathogen with expensive outcomes, owing to the considerable morbidity and even some mortality it causes.

Recent discoveries have made it clear that VZV is a dangerous virus that does not deserve its reputation is a generally nonthreatening virus. Gilden, Nagel, and their colleagues have demonstrated that the reactivation of VZV can cause significant damage to the vascular system [10–13]. VZV famously establishes latency in dorsal root ganglia and cranial nerve ganglia and then, when it reactivates, transmits infection to the epidermis to give rise to the infectious rash of zoster [14]. Zoster occurs in a dermatomal distribution because the neurons within which it reactivates project to these regions of the skin. VZV, however, also establishes latency in ganglia that do not project to the skin, including neurons of the sympathetic, parasympathetic [15], and enteric nervous systems [16, 17]. When VZV reactivates in these neurons, a secondary infection (a form of zoster) will occur in sites to which these neurons project. Presence at those sites leads to occult infections, which are difficult to diagnose because they are not associated with the rash that is almost universally but erroneously expected to accompany zoster [18]. The arteries that sympathetic neurons innervate, and the gastrointestinal wall, which enteric neurons innervate, are, thus, targets for reactivating VZV to infect. The development of polymerase chain reaction analysis made diagnosis of VZV without rash possible because VZV DNA can be detected in cerebrospinal fluid, arterial walls, gut, and other infected tissues and fluids [16, 18].

About 20 years ago, Don Gilden and his colleagues became intrigued by the presence of giant cells in granulomatous arteritis, which suggested that the disorder might be due to a viral infection [19]. They studied cerebral arteries in a patient who had died from vasculitis and found both VZV DNA and VZV antigens in the tissue. There was no evidence of cytomegalovirus or herpes simplex virus infection in this patient. The Gilden group went on to find evidence of productive VZV infection, including identification of viral particles, in intracerebral vasculopathy, which can lead to

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strokes [10, 20]. The age of people in whom granulomatous arteritis syndromes (temporal arteritis, intracranial vasculopathy, giant cell arteritis, and Takayasu aortitis) occur is often >50 years, which is consistent with the idea that these syndromes are due to the reactivation of VZV in neurons that project to affected arteries [12, 21, 22].

In the current issue of *The Journal of Infectious Diseases*, Gilden et al demonstrate that there is a strong correlation between the presence of VZV DNA and VZV antigens in aortas from humans with giant cell arteritis. Their approach was to study aortic specimens removed at autopsy from patients in whom granulomatous arteritis was diagnosed and from control individuals who lacked this diagnosis. All 30 specimens were subjected to polymerase chain reaction analysis to determine whether VZV DNA was present and then to immunocytochemical analysis for detection of VZV antigens. None of the individuals studied had manifested a zosteriform skin rash during life. An observer who was blinded to the data and the original diagnosis then evaluated 17 specimens that were found to have both VZV DNA and antigens for the presence of inflammatory cells, tissue necrosis, and giant cells (inflammation). Each of 11 patients who had this form of inflammation was found to have VZV antigens and VZV DNA in the aortic tissue; 9 of 11 also manifested aortic aneurysms. No evidence of inflammation was seen in 18 aortic specimens that were considered to be controls. Of these, 5 of 18 (28%) also turned out to contain VZV DNA and antigens, even though evidence of inflammation was lacking. The authors postulate that subclinical reactivation of VZV occurred in these individuals. If this is true, it means that reactivation can occur and deliver VZV to a target of innervation without clinical consequences. It is possible that the VZV DNA and antigens are resting benignly inside of macrophages or other immune effectors in the tissues of control subjects. An additional specimen that contained VZV DNA and antigen came from a patient with nongranulomatous aortitis. The difference between the patients with VZV and aortitis (11 of 11) and the controls with VZV and no aortitis (5 of 18) was highly significant. Remaining to be determined is why VZV DNA and antigen could be present in 28% of specimens without causing detectable inflammation. It seems possible that genetic predisposition and/or differences in immune responses to VZV determine whether the release of VZV into the aortic wall causes disease. This phenomenon requires further exploration. Whatever the cause of VZV DNA and antigens in controls, we are indebted to Gilden and his colleagues because if they had not reasoned that the presence of giant cells in arteries could be a sign of a viral infection, the trail of evidence implicating VZV in arteritis would not have been uncovered. These infections, as the Gilden group recognizes, have to follow from the reactivation of latent VZV in autonomic neurons, the axons of which innervate arteries but not the skin. Following reactivation, VZV infects all layers of the arterial wall, including the adventitia, media, and intima, which weakens the structure of the arteries and may lead to aneurysms and strokes [23].

Potentially serious occult VZV infections continue to occur despite the use of effective vaccines. In addition to those of the arterial wall, there are those of the gastrointestinal wall. VZV is, as noted above, latent in the enteric nervous system. No enteric neurons project to the skin, but they innervate the gastrointestinal mucosa in a manner analogous to the way dorsal root ganglia and cranial nerve ganglia neurons innervate the skin. Latent VZV in enteric neurons can reactivate just like that in other autonomic dorsal root ganglia neurons or in cranial nerve ganglia neurons. Reactivation of VZV in enteric neurons causes enteric zoster, the signs and symptoms of which include abdominal pain, gastrointestinal bleeding, perforation of the bowel, and chronic intestinal pseudo-obstruction [17, 24, 25]. It is possible to use the presence of salivary VZV DNA to screen for gastrointestinal VZV infections [17]. VZV DNA is not a normal constituent of saliva [26]. The observation that VZV DNA is present in saliva is, thus, strong evidence of a lytic VZV infection somewhere in the body [27, 28]. In the case of the gut, abdominal pain and salivary VZV DNA suggest VZV infection of the gastrointestinal tract. When arteritis is suspected, it is conceivable that salivary VZV DNA might make it possible to diagnose this condition as well during life. Because VZV can be treated with derivatives of acyclovir, the early discovery of VZV-evoked arteritis might allow a life-saving therapeutic intervention.

The new data from Gilden et al involving arterial infections cry out for formal testing of specific antivirals, such as acyclovir and/or valacyclovir, for treatment of patients with arteritis. Gilden's group has reported that several patients seemed to respond to treatment with open-label acyclovir or valacyclovir, with or without steroids [29]. They also reported another patient with giant cell arteritis and Takayasu aortitis who responded dramatically to long-term therapy with antivirals [22]. Based on the availability of diagnostic tests for VZV DNA and antigens, it will be important to determine whether antiviral therapy can improve the prognosis for these patients. This would require double-blinded placebo-controlled studies; the length of treatment would also have to be established. Whether antiviral therapy can begin in time to be effective in preventing fatal arterial damage is still to be determined. Perhaps salivary VZV DNA can now be used to select patients at risk of arterial damage to undergo a test of antiviral treatment. Certainly, such patients have a great deal to gain, although the data from the Gilden group will complicate the ethical use of a placebo in clinical trials.

It is a shibboleth that an ounce of prevention is worth a pound of cure. The newly developed subunit vaccine for the prevention of zoster may, however, offer

the best approach by prevention of VZV aortitis/vasculopathy by preventing clinical reactivation of VZV [30]. In contrast to the live attenuated zoster vaccine, this subunit vaccine dramatically prevents the development of zoster and, thus, its sequelae in about 95% of vaccinees, even when the vaccinated individuals are >70 years of age. The only notable adverse effects of the subunit vaccine appear to be transient reactions at the injection site and temporary malaise. The vaccine is composed of VZV glycoprotein E (the major target of immunity to VZV) and the adjuvant $AS01_B$, which promotes strong immune responses to recombinant proteins. This vaccine, in contrast to live attenuated zoster vaccine, cannot establish latency, is not infectious, and can, therefore, be administered safely to immunocompromised patients [31, 32]. Although additional studies are necessary, this vaccine could eventually be offered to most adults. If it continues to be as effective as initial studies indicate, the subunit vaccine may not only decrease the incidence of obvious cutaneous zoster but also the incidence of occult VZV reactivation disease, such as aortitis and enteric zoster.

The findings of Gilden, Nagel, and their colleagues are dramatic, exciting, and important. They further implicate VZV as a dangerous cause of vascular disease. They also expand the list of serious diseases that reactivation of VZV causes. With this knowledge, it should be possible, using enhanced diagnostic assays such as the examination of saliva for VZV DNA, to develop new vaccines and antiviral therapy to prevent and improve the prognosis for patients with occult VZV infections.

Note

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