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VZV meningitis following varicella vaccine

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Abstract

Live attenuated varicella zoster virus is administered to prevent varicella in children and herpes zoster in the elderly. We report a case of disseminated herpes zoster in a previously healthy elderly woman hours after Oka strain vaccination. PCR and restriction enzyme analysis revealed that symptoms were caused by wild type virus.

Keywords

Varicella; Vaccine; Disseminated herpes zoster

1. Why this case is important

Reactivation of latent varicella zoster virus (VZV) within the dorsal root and cranial nerve ganglia results in herpes zoster (shingles). Herpes zoster is characterized by unilateral radicular pain and a vesicular rash that is usually limited to a single dermatome. Complications, most frequently postherpetic neuralgia, occur in almost half of older patients with herpes zoster.¹ With advancing age the incidence and severity of herpes zoster increases, with a cumulative lifetime incidence of approximately 10–20% of the population.^{2,3} The growing risk of herpes zoster with increasing age has been correlated with a decreased cell mediated immune response to varicella zoster in the aged.^{4–6} A live attenuated VZV vaccine has been developed, and was approved by the FDA for the prevention of herpes zoster in individuals aged 60 years or older.¹ The adverse effects of this vaccine that were reported in pre-marketing studies were relatively minor. We report the case of a woman who developed varicella meningitis/encephalitis coincident with vaccination. This case illustrates the diagnostic evaluation of a potential serious post-vaccine event.

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Conflict of interest statement

AG consults for Glaxo Smith Kline on varicella and zoster vaccines and receives research funding from Merck. PL and SS have a fee for service contract to perform VZV strain identification by PCR on clinical samples. DF, JJ, and PK have nothing to declare.

2. Case description

A 79-year-old woman in good health except for treated hyperlipidemia, hypertension, and osteoporosis received a single dose (0.65 ml, greater than 19,400 plaque forming units) of the live attenuated varicella virus vaccine Zostavax. Within 6 h she developed a dull pain behind her right eye and in the right side of her throat. The pain worsened over the next 72 h and she developed fever as high as 39.5 °C and productive cough. Within 96 h after vaccination she also developed scattered vesicular lesions on her right ear, left cheek, left lower quadrant and right lower back. At this point she was started on famciclovir 500 mg q8h. Despite the antiviral therapy her symptoms worsened and, on the seventh day after vaccination she was noted to be confused and sent to the emergency room.

On presentation to the hospital she was febrile to 39.5 °C, tachycardic and tachypneic. She was alert but confused. Her examination was notable for the skin lesions described above as well as vesicular lesions on the right side of her palate, and scattered pulmonary rales. Her complete blood count showed normal hemoglobin and platelet count. The white blood cell count was normal with a slight monocytosis and lymphopenia. Liver function tests and renal indices were normal. Oximetry showed an oxygen saturation of 91% on room air. Because of her fever and confusion, a lumbar puncture was performed. CSF analysis showed 32 red blood cells, 307 white blood cells/ml (91% lymphocytes), CSF glucose of 84 mg/dl (serum 178 mg/dl) and protein of 123 mg/dl. The Gram stain was negative for bacteria. CT scan and MRI of the brain, both without contrast, were normal for her age. A chest radiograph was normal, although non-contrast chest CT scan showed some ground glass opacities and scattered nodules in the right lung fields.

She was admitted to hospital with diagnosis of varicella meningoencephalitis. Famciclovir was discontinued and intravenous acyclovir was started. During the subsequent 3 days of hospitalization, she developed an additional vesicular lesion on the tip of her nose. She defervesced with hydration and antiviral therapy, and her mental status returned to normal.

When discharged from the hospital, she was weak, hoarse, and had a productive cough. She found it very difficult to swallow and eat. Direct laryngoscopy showed right vocal cord paralysis consistent with right vagal palsy. Repeat CT of the chest has shown resolution of ground glass opacities and scattered nodules in the right lung fields. Since discharge she has regained some strength and, with therapy, has been able to increase her oral intake. However she has not been able to regain weight and fatigues easily.

Additional laboratory studies became available after discharge. PCR done on varicella zoster virus gene 19 from the CSF was positive at 42,400 copies/ml (Viracor). Repeat assay of CSF showed 30,000 copies/ml. CSF PCR for herpes simplex virus was negative. Since VZV gene 19 contains no type specific polymorphisms, a frozen sample of CSF was evaluated in a research laboratory where techniques have been developed to distinguish wild type from vaccine strain VZV.⁷ On two separate occasions, it was possible to amplify a 222 bp segment of varicella gene 54. The 222 bp band migrated properly and was not digested by BgL-1, consistent with wild type strain. The 350 bp fragment of gene 38 described in prior studies⁸ could not be amplified. Three weeks after vaccination, serum and saliva samples

were obtained from the patient. Varicella zoster PCR amplification of these samples revealed beta-globin DNA and 10–100 copies/ml of wild type VZV-DNA. Analysis of serum obtained 3 weeks after vaccination showed elevated levels of both varicella IgM (8) and IgG (256) levels by FAMA.

3. Other similar and contrasting cases in the literature

Prelicensure adverse events preceding approval of the live attenuated varicella zoster virus vaccine to prevent herpes zoster and postherpetic neuralgia in the elderly were minimal.¹ In the clinical phase III study that enrolled 38,546 adults of 60 years or older, the vaccine reduced the incidence of herpes zoster by 51.3% and the incidence of postherpetic neuralgia by 66.5% in a time period of 5 years after the vaccination. In the vaccine group the most frequent adverse events at the injection site were erythema (35.8%), pain or tenderness (34.5%), swelling (26.2%) and pruritus (7.1%). There were 7 (<0.1%) cases of confirmed herpes zoster in the first 42 days after vaccination compared to 24 (0.1%) in the placebo control group. Only two cases of serious adverse vaccine related events were reported in the vaccine group; a 64-year-old woman had an exacerbation of asthma 2 days after receiving the vaccination and an 80-year-old man developed symptoms of polymyalgia rheumatica on day 3.¹ These results imply that the live attenuated Oka strain can safely be used in elderly patients.

4. Discussion and references

To the best of our knowledge, disseminated varicella zoster infection with CNS involvement directly following vaccine administration has not been previously reported. While our patient had presumed loss of cell mediated immunity due to her age, she had no other known predisposition to disseminated infection. The presence of varicella DNA in CSF alone is not sufficient to diagnose VZV meningitis or encephalitis, based on extrapolation of data from HIV positive patients showing that only a minority of patients with VZV DNA-positive CSF had neurological illness clearly attributable to VZV.⁹ However, the high CSF VZV copy number in combination with confusion, fever, and disseminated vesicles, along with negative HSV CSF PCR, do argue in favor of VZV encephalitis. Molecular analysis of the varicella DNA in CSF revealed the presence of wild type varicella only, and not the vaccine (Oka) strain. The incidence of herpes zoster in non vaccinated persons 70 years of age and above is 11.5 per 1000 person years,¹ translating to a daily risk of 0.00003 of developing herpes zoster. Despite the low probability of an individual developing reactivated varicella zoster infection on the day of vaccination, the occurrence of that coincidence is probable given the high attack rate of zoster among the elderly. In addition, the rapid onset of our patient's symptoms (6 h after vaccine administration) is not consistent with a likely association between the vaccine and her clinical course. It is highly likely that this patient would have developed zoster had she not been vaccinated. Coincidental incidences of severe illnesses and vaccination in young children are well described in the literature and have led to confusion regarding correlation and causality, such as the idea that vaccines cause autism in children.¹⁰ When patients develop apparent adverse events after immunization, it is important to analyze them as scientifically as possible to determine if vaccines really caused an illness that is temporally related.

Because of the availability of molecular methods to distinguish between vaccine and wild type VZV, it was possible to determine that this patient did not have an adverse event due to the vaccination. This is consistent with the large clinical trial indicating that injection of vaccine does not reactivate VZV.¹ In all probability the patient in this report would have developed zoster with meningitis had she not been immunized. This patient illustrates the utility and importance of the availability of molecular diagnostic procedures in differentiating between adverse events that appear to be vaccine related, in contrast to those which are not. Had Oka strain been identified as causing meningitis in this patient, the meningitis would somehow have had to be ascribed to immunization, even with an onset of only 6 h after the vaccine had been given. Further research on the unknown factors related to varicella reactivation may help us better understand cases such as the one we have reported.

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