CASE REPORT

Fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient

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Accepted 11 April 2016

SUMMARY

A 79-year-old man with chronic lymphocytic leukaemia presented with fever and a widespread vesicular rash on 19 November 2014. The patient had not been under immunosuppressive regime for 6 months. He had received a shingles vaccine on 14th October and developed flu-like symptoms after 2 weeks. Intravenous antimicrobial therapy including aciclovir was started. He remained stable with no evidence of systemic involvement. On day 5, he developed respiratory and renal failure that required transfer to intensive care unit. Vesicle fluid, bronchoalveolar lavage and plasma were positive for varicella zoster virus by PCR. Slight clinical improvement allowed extubation on day 16. He subsequently deteriorated and died on day 25. Multiorgan failure was considered the immediate cause of death whereas disseminated varicella zoster infection was stated in the medical certificate as the other condition leading to this outcome. Varicella zoster Oka vaccine strain was detected in vesicle fluid, using PCR.

BACKGROUND

Protection against herpes zoster (HZ) infection affects a broad range of specialties. National guidance should help all medical practitioners in identifying both, indications and contraindications of HZ vaccine. This unfortunate case reinforces existing advice to not immunise individuals with haematological malignancies, who are nonetheless always considered previously exposed to VZV. Besides, it underpins the importance of not delaying antiviral treatment when a vesicular rash appears after inadvertent vaccination.

CASE PRESENTATION

On 19 November 2014, a 79-year-old man was admitted to a district general hospital, with a widespread vesicular rash clinically consistent with varicella zoster virus (VZV) infection. The patient had been diagnosed with chronic lymphocytic leukaemia in January 2012 and was no longer under immunosuppressive treatment after finishing first-line chemotherapy with six cycles of fludarabine, cyclophosphamide and rituximab, in April 2014. On 14th October, he received the live attenuated zoster vaccine as part of the regular UK immunisation catch up programme against shingles. Two weeks after vaccination, he gradually developed malaise, flu-like symptoms and lethargy. Besides, his right deltoid region showed inflammatory signs and subsequently some painful vesicular lesions

appeared around the site of injection, which then spread to his trunk and extremities. On admission on 19 November, the patient had a temperature of 41°C, rigors, and a general vesicular rash on trunk and limbs that did not seem to follow a dermatomal distribution. From the clinical examination, it was not possible to ascertain if the extensive rash represented early reactivation and dissemination of VZV or direct dissemination of the shingles vaccine strain. The patient showed no clinical signs of respiratory distress and a chest X-ray revealed no significant changes from previous records (figure 1A). His bloods demonstrated pancytopenia, with haemoglobin of 10⁹ g/L, white cell count of 1.3×10⁹/L (lymphocytes of 0.6×10⁹/L) and platelets of 55×10⁹/L. Of note, there was no information that he had been recently exposed to chicken pox. Also, there was no documented medical history of VZV infection.

INVESTIGATIONS

Vesicle fluid, bronchoalveolar lavage (BAL) and plasma were positive by PCR for VZV. BAL was negative by PCR for cytomegalovirus (CMV), herpes simplex virus type 1, herpes simplex virus type 2, influenza virus type A, influenza virus type B, respiratory syncytial virus, parainfluenza virus type 1, parainfluenza virus type 2, parainfluenza virus type 3, adenovirus, rhinovirus, *Mycoplasma pneumoniae* and *Pneumocystis jirovecii*, and culture for bacteria and fungi was also negative. VZV Oka (vOka) vaccine strain was detected in vesicle fluid, using a real-time PCR assay that targets single nucleotide polymorphism (SNP) 108111 in a 174 bp region of open reading frame 62. SNP 108111 has been shown to differentiate VZV vaccine and wild-type sequences.^{1 2} Briefly, reactions consisted of 0.7 µM each primer (VZV-F, 5' CGAAACAACTCACGACTCTT; VZV-R, 5' GATACCCGCCCCAAGGAAA) and 1.4 µM each probe (WT-Pr, 5' JOE-TTTcTCcAcTGGgCTGTCA; Oka-Pr, 5' FAM-TTTcTCcAcGGgCTGTCA, where DNA nucleotides are denoted in upper case, LNA nucleotides in lower case and the locked nucleic acid (LNA) nucleotide complementary to SNP 108111 is underlined), Quantifast Multiplex PCR mastermix (Qiagen), 5 µL purified DNA and water to make a 25 µL reaction volume. Cycling on an ABI 7500 Fast consisted of 95°C for 5 min followed by 45 cycles of 95°C for 30 s and 60°C for 30 s.

TREATMENT

On admission, the patient started intravenous empirical antibiotic therapy with piperacillin/

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To cite: Costa E, Buxton J, Brown J, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212688

Figure 1 Chest X-ray evolution. (A) Day 0: admission to hospital. (B) Day 6: admission to intensive therapy unit. (C) Day 22: on extubation.

tazobactam and gentamicin, and high-dose intravenous aciclovir (ACV; 10 mg/kg three times a day). In addition, human normal immunoglobulin was added to the treatment regimen (400 mg/kg every other day for a total of five doses). Despite treatment, the patient continued to develop new vesicular lesions, mainly on his trunk. However, he remained stable with no clinical evidence of systemic involvement and unremarkable chest X-ray images. On day 5 after admission, he suffered abrupt clinical deterioration that required transfer to intensive care unit for mechanical ventilation, inotropic support and management of acute renal failure. A chest X-ray revealed patchy consolidation throughout both lungs and a slightly nodular area of consolidation peripherally in the right mid-to-upper zone (figure 1B). Given the rapidity of the radiological changes, pulmonary oedema was suspected, with a differential diagnosis of viral pneumonitis. Intravenous ACV was increased to 20 mg/kg three times a day and ganciclovir (GCV) 5 mg/kg twice daily was added in case of possible CMV pneumonitis. Both ACV and GCV dosages were adjusted for renal impairment. GCV was stopped after 24 h of treatment, as CMV PCR was negative on BAL and plasma.

OUTCOME AND FOLLOW-UP

Development of new vesicular lesions was no longer observed after day 8 of hospitalisation. VZV became undetectable by PCR in plasma on day 13 and in BAL on day 14 after hospitalisation. Follow-up chest X-ray studies were informed as stable or slightly improved on day 13 (figure 1C). Modest clinical improvement was briefly achieved and the patient was extubated on day 16 after hospitalisation. He subsequently presented unexplained acute liver failure on day 18 and developed multi-organ failure on day 20 following hospitalisation. The patient died 25 days after admission to the hospital despite treatment.

DISCUSSION

VZV is a ubiquitous α -herpesvirus that causes vesicular rash. HZ, or shingles, results from reactivation of latent VZV in nerve-root ganglia, usually many years after the primary VZV infection (varicella, also known as chicken pox). HZ is typically restricted to one or two contiguous dermatomes, but can be extensive in elderly and immunocompromised individuals. Life-threatening disseminated disease can occur in severely immunosuppressed patients. HZ complications include postherpetic neuralgia, HZ ophthalmicus, stroke and meningoencephalitis.¹ The zoster vaccine has been shown to be effective in preventing both zoster and postherpetic neuralgia. Consequently, immunisation programmes were introduced in the USA, in 2006, and thereafter in European countries.³ Zoster vaccine contains the same vOka live, attenuated strain in the varicella vaccine, formulated with a significantly higher dose.

Although varicella vaccine is well tolerated and safe, fatal outcome following varicella vaccination has been reported in immunosuppressed patients.^{4–6} The UK zoster immunisation programme started in September 2013, initially targeting people aged 70 (routine programme) and 78 or 79 (catch up programme) years. Medical history and current status of VZV IgG are not required prior to receiving the zoster vaccine. Coverage rates of around 60% have been reached in the target age groups. While varicella vaccine is licensed in some immunocompromised populations, recommendations for the use of zoster vaccine in the immunocompromised is mixed.^{3 7 8} Zoster vaccine has been extensively used in immunosuppressed persons in the USA and UK over the past several years without this lethal outcome.⁹ However, even where limited use in the immunocompromised is recommended, zoster vaccine is contraindicated for individuals with haematological malignancies.⁷ Confusingly, recommendations available at the time of this adverse event also suggested that zoster vaccine could be given 6 months after the end of chemotherapy or radiotherapy, as was the case for this patient.⁷ Investigational alternatives to zoster vaccine in older adults and in immunocompromised patients are currently being tested.^{10–12}

Learning points

- ▶ To the best of our knowledge, this is the first case of death following zoster vaccination.
- ▶ This case reinforces existing advice to not immunise individuals with haematological malignancies.
- ▶ Clear national and local guidance for herpes zoster immunisation in the immunocompromised setting is mandatory.
- ▶ If a varicella rash develops after inadvertent zoster vaccination, aciclovir should be instigated urgently.

Contributors EC and was involved in design, clinical data acquisition/interpretation, drafting and final approval. JBux was involved in design, clinical data acquisition/interpretation, draft revision and final approval. JBro and JBre were involved in design, specialist laboratory data acquisition/interpretation, draft revision and final approval. KET and IJ were involved in design, clinical and laboratory data acquisition/interpretation, draft revision, and final approval.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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