Varicella vaccination in a child with acute lymphoblastic leukaemia

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In July, 2003, during reinduction treatment 5 months after diagnosis of acute lymphoblastic leukaemia (ALL), a 4-year-old girl presented with generalised tonic-clonic seizures. She had been treated according to protocol ALL-BFM 2000. Cranial CT and analysis of cerebrospinal fluid showed no signs of cerebral haemorrhage. Ultrasonography showed an enlarged liver and no signs of ascites or veno-occlusive disease. Her skin appeared normal, with no vesicular rashes. Blood tests showed only raised concentrations of aminotransferases. During the next few hours, she developed respiratory insufficiency, petechiae, haematomas, and vesicular lesions of the oral and vaginal mucosal. On the assumption of an underlying infectious cause, intravenous treatment with piperacillin, sulbactam, tobramycin, IgG, and aciclovir was initiated. 48 h after the first seizure, her laboratory test results deteriorated, with aspartate and alanine aminotransferase concentrations increasing to 20 864 U/L and 16 029 U/L, respectively, and the full blood cell count indicated pancytopenia. Within 12 h, she developed multi-organ failure (liver, renal, and circulatory failure, and acute respiratory distress syndrome [ARDS]), necessitating artificial ventilation. Serostatus for varicella-zoster virus (VZV) was negative, but PCR for VZV was positive in peripheral blood samples (7×10^6 genome copies per mL). VZV was also isolated from a nasopharyngeal swab but not from cerebrospinal fluid. PCR analysis of peripheral blood was negative for hepatitis B and C viruses, herpes simplex virus 1 and 2, Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus, human herpes virus 6, and parvovirus B19. High doses of VZV-IgG were added to the treatment. Despite haemodialysis and ventilation, the child died of progressive ARDS and multi-organ failure 10 days after admission.

On receiving the positive VZV-PCR results, the mother recalled that her daughter had received live attenuated VZV vaccine (Varilrix) at another hospital 32 days before the onset of symptoms. Partial sequencing of VZV genes 38 and 54[1] isolated from the patient excluded a wild-type VZV infection and showed that viraemia was caused by the VZV vaccine strain OKA (figure). Vaccination was done 5 months after complete remission had been achieved; at that time lymphocyte count was more than $1\cdot5\times10^9$/L, and chemotherapy was interrupted for 1 week before and after vaccination.

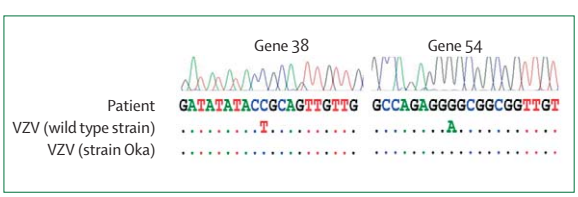

Figure: **Comparison of VZV sequences isolated from the patient with several fully sequenced VZV database entries including two VZV OKA vaccine strains**
Two genes (*orf38* and *orf54*) were sequenced and aligned to VZV sequences (accession numbers: DQ008354 and X04370) by use of the ClustalW-algorithm. Dots indicate homology to the patient's sequence.

Deaths after vaccinations with numerous attenuated viruses are well established. Fatal wild-type VZV infections have been reported in ALL patients during chemotherapy[2] and after bone-marrow cell transplantation.[3] Therefore, VZV vaccination is a useful, and generally accepted, therapeutic measure for patients with ALL in remission. Studies of VZV vaccination 3–4 months after autologous stem-cell transplantation,[4] and in early ALL maintenance therapy,[5] did not show fatal side-effects. However, any interruption of maintenance therapy in ALL can adversely affect outcome for the patient. In our patient, liver failure developed 5 weeks after VZV vaccination, which indicates longstanding replication of OKA strain in the liver. This suggestion accords with observations of late onset of complications (fever, vesicles, and severe hepatitis) in immunocompromised patients after VZV vaccination.[5] Therefore, although we cannot fully exclude that intensification of chemotherapy could have aggravated her symptoms, we suggest that VZV vaccination in seronegative children with leukaemia, who are in complete remission for at least 12 months, should not be undertaken until at least 9 months after the end of immunosuppressive treatment (including maintenance therapy) and not before a lymphocyte count of at least $1\cdot5\times10^9$/L has been ascertained. In addition, high-risk patients should remain under close surveillance in the critical phase (6 weeks after vaccination) so that immediate antiviral treatment with aciclovir can be initiated in symptomatic children.

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