Fatal visceral varicella in a child with newly diagnosed acute lymphoblastic leukemia

Paul Schnitzler¹, Julia Tabatabai², Neysan Rafat³, Hendrik Witt⁴, Andreas Sauerbrei⁵, and Roland Zell⁵

¹Universitätsklinikum Heidelberg Zentrum für Infektiologie
²UniversitätsKlinikum Heidelberg Zentrum für Kinder und Jugendmedizin
³Universität Heidelberg Medizinische Fakultät Mannheim
⁴Praxis für Kinder- und Jugendmedizin
⁵Friedrich Schiller Universität Jena Institut für Mikrobiologie

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Julia Tabatabai⁶, Neysan Rafat⁵, Hendrik Witt⁴, Andreas Sauerbrei⁵, Roland Zell⁵,
Paul Schnitzler⁶

⁶Center for Childhood and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany;
⁵Center for Infectious Diseases, Virology, University Hospital Heidelberg, Heidelberg, Germany;
⁴Department of Neonatology and Pediatric Critical Care, University Children’s Hospital, University of Heidelberg, Mannheim, Germany;
⁵Praxis für Kinder- und Jugendmedizin, Weinheim, Germany; "Section of Experimental Virology, Institute for Medical Microbiology, Jena University Hospital, Friedrich Schiller University of Jena, Jena, Germany

Corresponding author
Dr. med. Julia Tabatabai
Tel.: +49-6221-56 39149
E-mail address: julia.tabatabai@med.uni-heidelberg.de

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To the editor:

We report a 15-year-old boy with a high suspicion of ALL with leucocytosis, anaemia, thrombocytopenia and hyperuricaemia, see Table 1. The routine blood draw was performed by the paediatrician prior to discontinuation of testosterone injections in hypergonadotropic hypogonadism in the context of Klinefelter’s syndrome. The patient was admitted to our paediatric intensive care unit on suspicion of tumour lysis syndrome with
leucocytosis, blasts >83% and LDH of 1,600 U/l. Physical examination revealed hepatosplenomegaly and facial acne. After bone marrow biopsy and lumbar puncture with intrathecal administration of 12 mg methotrexate, treatment with prednisolone was started. Initially, the total leucocytes dropped to approximately 60/nl, while cell decay was controllable. On day 4, the leucocyte count rose, continuing the next day to 180/nl despite increasing the prednisolone dosage. LDH rose to 7,489 U/l and epigastric abdominal pain increased, which we treated empirically with pantoprazole suspecting corticosteroid-induced gastritis. There was also liver capsule pain and generalised pruritus, which improved only slightly after administration of an antihistamine. On day 5, the patient’s condition worsened with oxygen demand and dyspnoea. Cyclophosphamide was administered to improve cell decay and prednisolone was administered full dose. We also decided to start haemodialysis with increasing renal retention parameters and LDH of 13,636 U/l).

On day 6, we electively intubated and placed the boy on mechanical ventilation. Ubiquitous fluid-filled vesicles with brownish-reddish contents developed. The intravesicular fluid was tested positive for VZV DNA with a high viral load of 1,3 x10^9 copies/ml. Retrospective analysis showed rising viral loads of VZV DNA with a peak of 2.1 x 10^8 copies/ml on day 6 in peripheral blood. The causative pathogen was genotyped and revealed a variant of the VZV clade 3, European genotype E2 (Fig. 1). Retrospectively, serum samples from day 1 to day 6 were analysed for anti-VZV (IgG, IgM) antibodies, all with negative result. The patient was immediately started on acyclovir intravenously and blood exchange to reduce the leukostasis syndrome. Uncontrollable haemorrhages with diffuse bleeding from puncture sites and mucous membranes developed. Acute respiratory distress syndrome occurred with extremely high ventilation parameters and multiple cardiac arrests with ultimately unsuccessful resuscitation attempts. The patient died due to multi-organ failure.

The parents reported that the patient joined a school trip to Italy the week before he was hospitalised. Chickenpox cases had been observed in the meantime among other students of the school trip. There was no prior history of varicella or vaccination against varicella for the patient. This case is a tragic course of an initially undiagnosable primary varicella infection at the time of the manifestation of acute lymphoblastic leukaemia. Due to immunosuppression caused by the underlying disease in combination with the required corticosteroid treatment, a fulminant VZV sepsis with multi-organ failure occurred.

The standard treatment for organ VZV infection is acyclovir and should be started immediately upon suspicion of the diagnosis. Older age at ALL diagnosis, and VZV diagnosis during or within three weeks of prednisone therapy are independently associated with an increased risk for severe infection. Despite the varicella vaccine and a dropping incidence of primary infections, VZV remains a dangerous pathogen for paediatric patients with ALL. Patients who are on ALL therapy and are exposed to VZV should have steroid therapy delayed until after the VZV incubation period.

Organ failure in disseminated VZV infections is caused primarily by VZV-induced cell damage and cell lysis. Extensive visceral dissemination can occur several days before the skin lesions appear. Another fatal case of a child from Germany suffering from ALL with a VZV viral load of 7 x 10^6 copies/ml had been reported previously. The VZV viral load of 2.1 x 10^8 copies/ml in the peripheral blood of our case is extremely high compared to healthy children with primary varicella, ranging from 3 x 10^2 to 6 x 10^3 copies/ml. The clinical course of this disease is often so rapid, that the initiation of antiviral therapy may be too late. An unexplained liver dysfunction in immunocompromised children needs prompt consideration of visceral VZV infection, even in the absence of a history of VZV exposure and also in patients without skin involvement. The detection of VZV DNA in peripheral blood by PCR and prompt initiation of antiviral therapy are therefore recommended in such a clinical setting.

Recommendations for vaccination include seronegative people at special risk, such as children with leukaemia. These recommendations apply certainly to the patient of this report with no history of chickenpox, and vaccination against varicella prior to the immunosuppressive therapy might have prevented the fatal outcome of this primary VZV infection. A study of varicella vaccination in paediatric oncology patients without interruption of chemotherapy (no steroids) had been presented, where live-attenuated VZV vaccine was safely administered, and adaptive immunity was induced despite incomplete seroconversion.
In conclusion, immunocompromised patients without varicella history are at special risk to develop life-threatening complications of varicella. The most effective method to prevent severe varicella in immunocompromised patients is active immunization prior to the immnosuppressive therapy. However, severe VZV-related complications are rare in children with ALL and cannot be prevented in all cases, especially in newly diagnosed ALL.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES


Figure legend

**Fig 1.** Genotyping of the clinical VZV strain 202-14 (in bold). For the phylogenetic analysis, the ORF21-22 gene region (969 nt) of strain 202-14 and 35 VZV reference sequences representing five VZV clades were compiled and used for tree inference utilizing the neighbor-joining method implemented in MEGA X. Genetic distances were computed with the p-distance method; the bar indicates substitutions per site. Grey boxes indicate the five VZV clades.
Table 1.doc available at https://authorea.com/users/625473/articles/647469-fatal-visceral-varicella-in-a-child-with-newly-diagnosed-acute-lymphoblastic-leukemia