

## CASE REPORT

# The impact of primary varicella zoster virus infection on delay in diagnosis and treatment of neoplastic diseases in children – case reports

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## ABSTRACT

Primary varicella zoster virus (VZV) infection is highly contagious and life-threatening in immunocompromised patients. Children treated for neoplastic disease are at increased risk of severe illness and fatal outcomes. Varicella zoster infection (VZI) may cause diagnostic difficulties and result in the delay in anticancer therapy. We present the cases of four children diagnosed with neoplastic diseases and chickenpox infection simultaneously. Two patients were diagnosed with acute lymphoblastic leukaemia (ALL), one with acute myeloblastic leukaemia (AML), and one with Wilms tumour. Initially all patients received targeted and symptomatic treatment against VZV infection, and then they were reassigned to chemotherapeutic treatment. Three children received intravenous acyclovir for seven days, and one received oral treatment. The patient diagnosed with Wilms tumour, after receiving actinomycin-D, developed veno-occlusive disease with a very acute course. Mean delay in chemotherapy due to VZI was eight days. None of the patients died as a result of the infection or oncological disease.

## KEY WORDS:

**chickenpox, acute leukaemia, childhood cancer, VZV.**

## INTRODUCTION

Chickenpox is one of the most common infectious diseases of childhood. It is caused by varicella zoster virus (VZV). After recovering from chickenpox, the virus remains latent in the ganglia of sensory nerves for many years [1]. As a result of the reactivation of the VZV virus, a secondary infection occurs in the form of zoster. The only reservoir of the virus is the human body. The virus is transmitted by droplet and through direct contact with a sick person. Lower rates of varicella are observed more often in equatorial populations compared to populations living in temperate climates. Moreover, in tropical countries a higher susceptibility to infection is observed among adults, which is associated with a more severe course of the disease [2].

Although chickenpox usually occurs in a mild form, it can lead to life-threatening complications. The most important include bacterial superinfection of skin lesions, interstitial pneumonitis, hepatitis, myocarditis, necrotising fasciitis, and neurological complications, such as aseptic meningitis, encephalitis, cerebellar ataxia syndrome, and cranial nerve palsy [3].

Immunodeficient patients (especially with congenital deficiency of cellular immunity), newborns, oncological patients, transplant recipients, as well as people treated with high doses of corticosteroids are at high risk of severe course of varicella zoster infection (VZI) [4].

Neonatal chickenpox is a disease with a mortality rate of up to 30% [5]. Newborns are at greater risk of developing severe illness than older children due to their immature immune system [6]. Varicella zoster infection occurs

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in this group via vertical transmission during pregnancy or delivery, and after that time chickenpox is acquired from infected individuals. Mortality due to neonatal varicella is more likely when the mother develops symptoms of varicella five or fewer than five days before until to two days after delivery [7]. This time is insufficient for the development of maternal antibodies that would diffuse through the placenta to the foetus.

Intensive chemotherapy of neoplastic diseases leads to myelosuppression, which results in a significant immune system insufficiency; thus, children who undergo oncological treatment are particularly prone to the severe course of VZI. Patients who suffer from acute lymphoblastic leukaemia (ALL) often develop a disseminated form of chickenpox, and mortality due to VZI in this group is increased [8, 9]. Steroid therapy during the VZV incubation period significantly increases the risk for developing severe varicella infection [10]. A high-dose steroid therapy in children with ALL, who also have documented varicella exposure, should be postponed after the incubation period, even if the patients were previously vaccinated or treated with varicella zoster-immunoglobulin (VZIG) [10].

We present four different clinical cases of children diagnosed with malignant disease, who also developed chickenpox. All the patients were treated in our department. We would like to draw particular attention to the diagnostic and therapeutic complications that VZV infection potentially causes in oncological patients.

## CASE REPORT 1

A 14-year-old boy was admitted to the Department of Pediatric Infectious Diseases of the University Children's Clinical Hospital in Białystok due to thrombocytopenia and multiform skin eruptions: spots, red papules, and vesicles that persisted for more than 14 days, and mild fever of 38°C. In addition, four weeks before hospitalisation the patient had experienced swelling of the dorsal part of the right foot, followed by the left foot, accompanied by an increase in body temperature.

At the time of admission, the patient was in fair general condition. Abnormalities found in the physical examination were as follows: numerous symmetrical pleomorphic skin lesions in various stages of development like macules, papules, vesicles, and pustules distributed over the skin of the whole body (excluding the mouth and scalp), numerous follicular changes suggesting molluscum contagiosum, and slight symptoms of dehydration. Laboratory tests showed downward tendency in haemoglobin concentration (HGB on the day of admission – 13.3 g/dl, three days later a decrease to 10.9 g/dl), thrombocytopenia (platelet count [PLT]  $44 \times 10^3/\mu\text{l}$ , followed by three days of PLT  $13 \times 10^3/\mu\text{l}$ ), and white blood cell count within laboratory limits (WBC  $6.1 \times 10^3/\mu\text{l}$ ). Peripheral blood smear showed 40% of blast cells. In-

flammatory markers were slightly elevated – C-reactive protein (CRP) concentration was 6.3 mg/dl (laboratory norm 0–5 mg/dl). Antiviral therapy, antibiotic therapy, parenteral hydration, vascular endothelium sealing drugs, and allopurinol were administered. After haematological consultation, followed by resolving of the active skin lesions, the patient was referred to the Department of Pediatric Oncology and Hematology for further diagnosis and treatment.

The patient's myelogram showed the presence of 60% of blast cells with myeloblastic features. Based on the immunophenotype, acute myeloid leukaemia M2 was diagnosed, without Auer rods. The boy was classified to a high-risk group treatment protocol. After a one-day hospitalisation in the Department of Pediatric Oncology and Hematology, the boy was again transferred to the Department of Pediatric Infectious Diseases due to reoccurrence of chickenpox skin lesions in the lumbar region. The treatment included blood products, antiviral agents, antibiotics, immunoglobulins, vascular endothelial sealing drugs, parenteral hydration, and a probiotic. After a four-day stay, the patient was again transferred to the Oncology Unit for treatment of the underlying neoplastic disease. The patient received antineoplastic treatment according to the AML-BFM-2012 Interim protocol, based on chemotherapy and central nervous system prophylactic radiotherapy. During treatment no recurrence of VZV occurred. He remains in clinical and laboratory remission.

## CASE REPORT 2

A four-year-old girl suffering from chickenpox (eruptions lasting for more than four days) was admitted to the Department of Pediatric Infectious Diseases due to a fever higher than 41°C lasting for three days, pain localised in the left lower limb for over two weeks, and significantly reduced appetite. At the time of admission, she was in fair general condition but weak and apathetic. In the physical examination, several abnormalities were found: skin of the whole body covered with numerous efflorescence characteristic of chickenpox – spots, vesicles, and papules, also alveolar and erosive lesions on the oral mucosa and throat, enlarged cervical lymph nodes, and in the laryngological examination: inflamed palatine tonsils and mild features of dehydration. Laboratory tests revealed: anaemia (HGB 10.1 g/dl), thrombocytopenia (PLT  $96 \times 10^3/\mu\text{l}$ ), and leukocytosis ( $35.3 \times 10^3/\mu\text{l}$ ) with 69% blasts in peripheral blood smear. Due to the suspicion of a bone marrow proliferative process, a bone marrow biopsy was performed. In myelogram 91% of blast cells were found with the precursor B-lymphocyte phenotype. Pre-B lymphoblastic leukaemia (common-ALL) was diagnosed. During hospitalisation, parenteral hydration, antiviral drugs, antibiotics, allopurinol, and a probiotic were used. The girl was transferred to the Department of Pediatric Oncology

and Hematology. Antineoplastic treatment according to the ALLIC BFM 2009 protocol was started immediately after transfer to the Oncology Unit. During antineoplastic treatment no recurrence of VZV infection was observed. The child has now finished the treatment, and during the last four years of ambulatory observation she remains in clinical and laboratory remission of neoplastic disease.

### CASE REPORT 3

A five-year-old boy was sent from the District Hospital to the Children's Clinical Hospital due to chickenpox lesions (the last new lesion was spotted two days prior to admission) lasting for over two weeks and due to abnormalities in laboratory tests: leukocytosis – WBC  $16.8 \times 10^3/\mu\text{l}$ , anaemia – HGB 7 g/dl, and thrombocytopenia – PLT  $23 \times 10^3/\mu\text{l}$ . Joint and bone pain in the lower limbs lasting more than three days was also reported.

At the time of admission, the patient was in poor general condition. Physical examination showed: polymorphic chickenpox skin lesions over the whole body, enlarged submandibular lymph nodes, and hepatosplenomegaly. The deviations in laboratory tests were: leukocytosis (WBC  $16.4 \times 10^3/\mu\text{l}$ ), anaemia (HGB 6.9 g/dl), and thrombocytopenia (PLT  $20 \times 10^3/\mu\text{l}$ ). Due to the presence of 74% of blasts in the peripheral blood and poor general condition, bone marrow biopsy was abandoned. Based on the immunophenotyping of peripheral blood blast cells, acute lymphoblastic leukaemia “common” type with CD10 and CD19 expression was diagnosed. The child was hospitalised in the Department of Pediatric Infectious Diseases for seven days. After transfer to the Department of Pediatric Oncology and Hematology antineoplastic treatment according to the ALLIC BFM 2009 protocol was started. No recurrence or complications of VZI was observed during the treatment of ALL nor during post-treatment observation. The child remains in clinical and laboratory remission.

### CASE REPORT 4

A 15-month-old boy was referred from the District Hospital to the Children's Clinical Hospital in Białystok with the suspicion of abdominal tumour, fever of  $38.5^\circ\text{C}$  lasting for over two days, and paleness. Ultrasound of the abdomen confirmed the presence of tumour arising from the left kidney. Medical history revealed a three-week complaint of waking up at night, restlessness, and diarrhoea. Recently, the boy has remained in the incubation period of chickenpox (he had contact with his sister, who developed the first skin eruptions six days before his hospitalisation). At the time of admission, the patient was in good general condition. Physical examination revealed: paleness of the skin, multiple “café au lait” spots, and a palpable pathological hard mass in the left hypochondriac region. Laboratory tests revealed: normocytic anaemia

(HGB 8.9 g/dl), activity of neurospecific enolase (NSE) moderately elevated 30.2 ng/ml (norm 0–16.3 ng/ml), as well as elevated CRP – 31.84 mg/dl (norm 0–5 mg/dl). The  $\alpha$ -fetoprotein and  $\beta$ -HCG concentrations remained within laboratory norms. The presence of tumour arising from the left kidney with the characteristic radiological features of nephroblastoma was confirmed by ultrasound and computer tomography (CT) of the abdominal cavity. No regional and distant metastases were found. The administration of anticancer treatment was suspended until the end of the chickenpox incubation period. On the 21st day after contact with VZV, the patient presented a full-blown chickenpox skin infection. Numerous changes were observed with the character of reddened lumps, blisters, and scabs on the skin of the entire body. The patient was treated with parenteral hydration, an antiviral agent, antibiotics, and probiotics. After the anticipated period of chickenpox infectivity ended, the patient was referred to the Department of Pediatric Oncology and Hematology for the continuation of treatment. Preoperative chemotherapy was started according to the SIOP program for Wilms tumour. After a second week of treatment, having received one dose of vincristine and one dose of actinomycin-D in week one and a single second dose of vincristine in week two, the patient developed symptoms of veno-occlusive disease (VOD) with a very acute course, as a rare side effect of treatment with actinomycin-D. Increasing ascites with body weight gain of more than 5%, peripheral oedemas, and painful hepatomegaly with biochemical markers of liver failure were observed. The patient fulfilled modified Seattle and Baltimore Criteria for VOD diagnosis. Maximum bilirubin concentration was 2.73 mg/dl, maximum ALAT activity – 4603 IU/l, maximum ASPAT – 11042 IU/l, and ammonia 227.3  $\mu\text{mol/l}$ . Serious coagulation disorders were observed with elongation of prothrombin time (PT) to a maximal value of 29.5 sec, maximal INR – 2.51, kaolin-cephalin time (APTT) – maximal value 36.3 sec, maximal D-dimer concentration 23,599 ng/ml, and minimal antithrombin value – 65%. The patient received a few platelet transfusions because of thrombocytopenia with minimal number of  $7 \times 10^3/\mu\text{l}$ , due to high risk of bleeding, and red blood cell transfusion because of anaemia – minimal Hb concentration 7.4 g/dl. Ultrasound of the abdominal cavity demonstrated (as well as tumour of the left kidney) enlarged hyperechogenic liver, pleural fluid on the right side, and peritoneal fluid. USG using colour Doppler showed the portal system with features of fibrosis, very narrow diameter of hepatic veins, thickened, hyperechogenic right hepatic vein, and gallbladder with thickened wall. Due to worsening of the general condition, increasing concentration of inflammatory parameters, presence of pleural and peritoneal fluid, and developing multiorgan failure including respiratory failure, the patient was transferred to the Intensive Care Unit and required temporary mechanical

ventilation. The patient was given broad spectrum antibiotics, immunoglobulins, antifungal and antiviral drugs, albumins, hepatoprotective drugs, and diuretics. Defibrinogen was used for 21 days in a dose of 25 mg/kg divided into four doses a day. During the following 15 days after transfer to the Intensive Care Unit, the child's clinical condition and laboratory findings improved significantly and he could be retransferred to continue anticancer treatment.

## CASES SUMMARY

Table 1 presents a summary of cases with implications related to VZV infection and cancer: delay in chemotherapy, duration of acyclovir treatment, chickenpox organ involvement, and final outcome.

## DISCUSSION

For many years, chickenpox has been treated exclusively symptomatically. Antipyretic drugs and medicines to reduce pruritus of skin lesions have been used. Currently, widely available and well-tolerated antiviral drugs and vaccination have become applicable in everyday practice.

In the case of chickenpox infection, it is recommended to use paracetamol to reduce fever. Nonsteroidal anti-inflammatory drugs, e.g. ibuprofen, increase the risk of bacterial superinfection as a result of inhibiting phagocytosis [11]. Acetylsalicylic acid, in turn, increases risk of Reye syndrome [12]. Following guidelines, all four of our patients received paracetamol as an antipyretic drug.

Passive immunisation with varicella zoster-immunoglobulin (VZIG at a dose of 0.2–1 ml/kg), administered within 96 hours of exposure, is effective in preventing disease or in reducing severity of illness in immunocompromised

persons [13]. Unfortunately, this method needs to be repeated after every exposure and has some limitations. VZIG is expensive and in short supply in many countries. None of the described four patients received VZIG due to the time that passed from the exposition to VZV.

It is recommended that unimmunised parents and siblings of patients with acute leukaemia should be vaccinated against varicella to protect the patient against contraction of varicella from close contacts [14]. Parents, grandparents, siblings, and households of children with ALL and other neoplastic diseases, treated in our department, are strongly advised to vaccinate against VZV to provide herd immunity. Moreover, children over 12 months with malignancy and without a history of VZI or vaccination should be given two doses of vaccine six weeks apart, at least six months after the cessation of the anticancer treatment [14]. Patients with history of malignancies may receive vaccination against varicella if they are in full haematological remission; in addition, total lymphocyte count must be at least  $1.2 \times 10^3 \text{ mm}^{-3}$ , and other symptoms of cellular immunity disorders must be excluded [14]. Vaccination against chickenpox is guaranteed free of charge for children with oncological diseases up to 12 years old under the vaccination programme in Poland.

Studies suggest that post-exposure acyclovir prophylaxis in immunocompromised patients reduces the incidence of varicella and its severity [13]. It has been proven that their use reduces the risk of serious complications, as well as the risk of death among patients undergoing chemotherapy, especially among patients with acute lymphoblastic leukaemia [15].

Children up to 12 years of age with uncomplicated chickenpox course do not require causal treatment. It is recommended that antiviral treatment be used intravenously in immunocompromised patients and newborns

TABLE 1. Patients characteristics

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Female	Male	Male
Age	14 years	4 years 3 months	5 years	1 year 3 months
Delay in chemotherapy (days)	7	7	3	13
Duration of acyclovir treatment (days)	12	9	7	7
Dose of acyclovir treatment	3 × 500 i.v. (7 days) 5 × 400 mg p.o. (5 days)	3 × 160 mg i.v. (6 days) 4 × 300 mg p.o. (3 days)	32 × 200 mg p.o. (7 days)	3 × 300 mg i.v. (7 days)
Duration of occurrence of VZV skin lesions (days)	14	12	10	5
Organ involvement during VZV infection	Skin	Skin	Skin	Skin
Underlying disease	AML	ALL	ALL	Wilms tumour
Final outcome	In ambulatory observation	In ambulatory observation	In ambulatory observation	In ambulatory observation

VZV – varicella zoster virus, AML – acute myeloblastic leukaemia, ALL – acute lymphoblastic leukaemia

due to better bioavailability. Acyclovir, valaciclovir, or famciclovir should be administered from days 3 to 21 post exposure in therapeutic doses: acyclovir 600 mg/m<sup>2</sup> four times daily; valaciclovir 1000 mg three times daily; 500 mg three times daily for patients less than 40 kg body weight; or famciclovir 500 mg three times a day [13].

Among the patients presented above, no serious complications or deaths due to severe viral infection were observed, except for the VOD incident revealed in the 15-month-old boy. A connection between the VOD episode to the VZV infection cannot be confirmed or excluded due to lack of sufficient evidence, but it should be taken into account because of strong tropism of varicella virus to hepatic cells.

## CONCLUSIONS

The four demonstrated cases of patients with childhood malignancy and accompanying primary VZV infection proved that specialists are challenged with diagnostic and therapeutic difficulties regarding comprehensive and interdisciplinary patient care. In the described group attention is paid to a more severe, longer course of chickenpox. Overlapping systemic clinical signs of VZV infection are likely to cause a delay in the proliferative process diagnosis. The necessity to control and limit the acute phase of viral infection contributes to the prolongation of antiviral and symptomatic treatment, and thus to anticancer treatment postponement (Table 1). Consecutively, the delay in antineoplastic therapy might lead to worsened outcomes. All of the indicated factors substantiate that VZV infection in patients with newly diagnosed neoplasm can relevantly influence their treatment and long-term prognosis. There is a clear need for effective chickenpox prevention in cancer patients undergoing chemotherapy to ensure the best possible therapy outcome.

## DISCLOSURE

The authors declare no conflict of interest.

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