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Sepsis caused by multidrug-resistant bacteria: *Pseudomonas aeruginosa*, as a complication of B-cell acute lymphoblastic leukemia treatment

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Recent years have seen huge progress in pediatric leukemia treatment [1]. Yet despite treatment progress, treatment-related toxicity is still common [2]. Infections are the predominant reason for treatment-related mortality in children with acute lymphoblastic leukemia (ALL). Some 4% of pediatric patients die from infections [3]. Sepsis is the main cause of patient death related to infections, and is defined as serious organ dysfunction caused by inappropriate response to an infectious agent [4]. Gram-negative bacteria are the most common cause of sepsis, followed by gram-positive bacteria, fungi and viruses [5]. Primary triggers among bacteria are *Klebsiella pneumoniae*, followed by *Escherichia coli* and *Pseudomonas aeruginosa*. Sepsis caused by *Pseudomonas aeruginosa* has been limited to only a few case reports in pediatric patients [6].

We present the case of an 8-year-old boy diagnosed with precursor B-cell acute lymphoblastic leukemia (BCP-ALL). In 2021, he was admitted to hospital with the following symptoms: entire body petechiae, enlarged peripheral lymph nodes, hepatosplenomegaly, and leukocytosis. Chemotherapy was started but was interrupted on day 22 due to severe treatment-related toxicity. Numerous complications, including acute pancreatitis, kidney failure, polyneuropathy, bowel obstruction and fungal infection of the lungs were reported during the

induction phase of leukemia treatment. The patient was receiving sulfamethoxazole–trimethoprim prophylaxis against *Pneumocystis jiroveci*, caspofungin for fungal lungs' infection, and meropenem. On the 36th day from the beginning of chemotherapy, the child developed the first symptoms of infection, which started with a fever. Moreover, he had a prolonged neutropenia episode. Laboratory examinations showed the gradual growth of inflammatory parameters: C-reactive protein and procalcitonin (Figure 1A). A first blood culture was performed, and *Pseudomonas aeruginosa* were detected. Therapy was modified by increasing the doses of meropenem from 20 mg/kg to 40 mg/kg (3-hour infusion), three times per day. Metronidazol was added as a preventative measure due to the bowel obstruction. However, the boy's condition started deteriorating. He developed necrosis of the right conch and anal ulceration, and presented consciousness disorders. Magnetic resonance imaging showed enlarged ventricles and cerebral sulci deepening. Further tests showed osmotic demyelination syndrome of the pons. The antibiogram was extended due to the lack of treatment effects. A swab was taken from the central venous catheter to detect the suspected source of infection. Subsequent blood cultures revealed that the bacteria were multi-drug resistant. Antibiotic therapy had to be constantly modified according to the current bacteria's sensitivity (Figure 1B, C). Additionally, the central venous catheter was removed. The patient required parenteral nutrition. Granulocyte colony-stimulating factor (G-CSF), immunoglobulin substitution, and clotting factor supplementation were administered.

The patient's condition, laboratory tests and complete blood count began to improve, and current treatment was continued. Blood culture was negative 29 days after the first sepsis symptoms.

Chemotherapy toxicity impacted the decision not to resume the treatment protocol, but instead to replace it with two cycles of blinatumomab immunotherapy. Then an allogeneic hematopoietic stem cell transplantation (HSCT) was performed. Currently, the boy is in remission and under the control of the hemato-oncology center.

We here describe the medical history of a pediatric patient who developed sepsis during the induction phase of ALL treatment. Eradication of infection was obtained by the properly selected antibiotics in accordance with antibiograms, removal of the central venous catheter, and G-CSF infusions.

Repeated interruptions in chemotherapy can result in worse leukemia treatment outcomes [7]. Patients in the induction phase are at the highest risk of contracting infections. This is due to intensive chemotherapy and high-dose steroids which cause immunosuppression. In addition, frequent hospitalizations and numerous invasive procedures contribute to the

occurrence of infections, for instance, in patients undergoing central catheter insertion, the use of which is an important factor contributing to nosocomial infections [8].

In a retrospective study, Inaba et al. conducted a trial on 409 ALL patients between 2000 and 2010. Of the 409 children, four died due to infection. The authors showed that the longest neutropenia episodes were observed during induction therapy. Through induction, this was strongly related to white race, being a low-risk patient, age at diagnosis (1–9.9 years), and B-lineage immunophenotype [8].

In septic patients, empirical antibiotic administration is selected according to local epidemiology patterns. The therapy is started with broad-spectrum antibiotics followed by de-escalation when culture results are available [9]. It is important to detect the patient’s current infection at an early stage and to use effective antibiotic treatment to limit the number of chemotherapy interruptions.

In this patient’s case, sepsis and multi-organ complications forced the standard chemotherapy to be abandoned. A new therapeutic approach, intended for treatment-resistant or high-risk groups of patients, proved to be the treatment of choice for this patient.

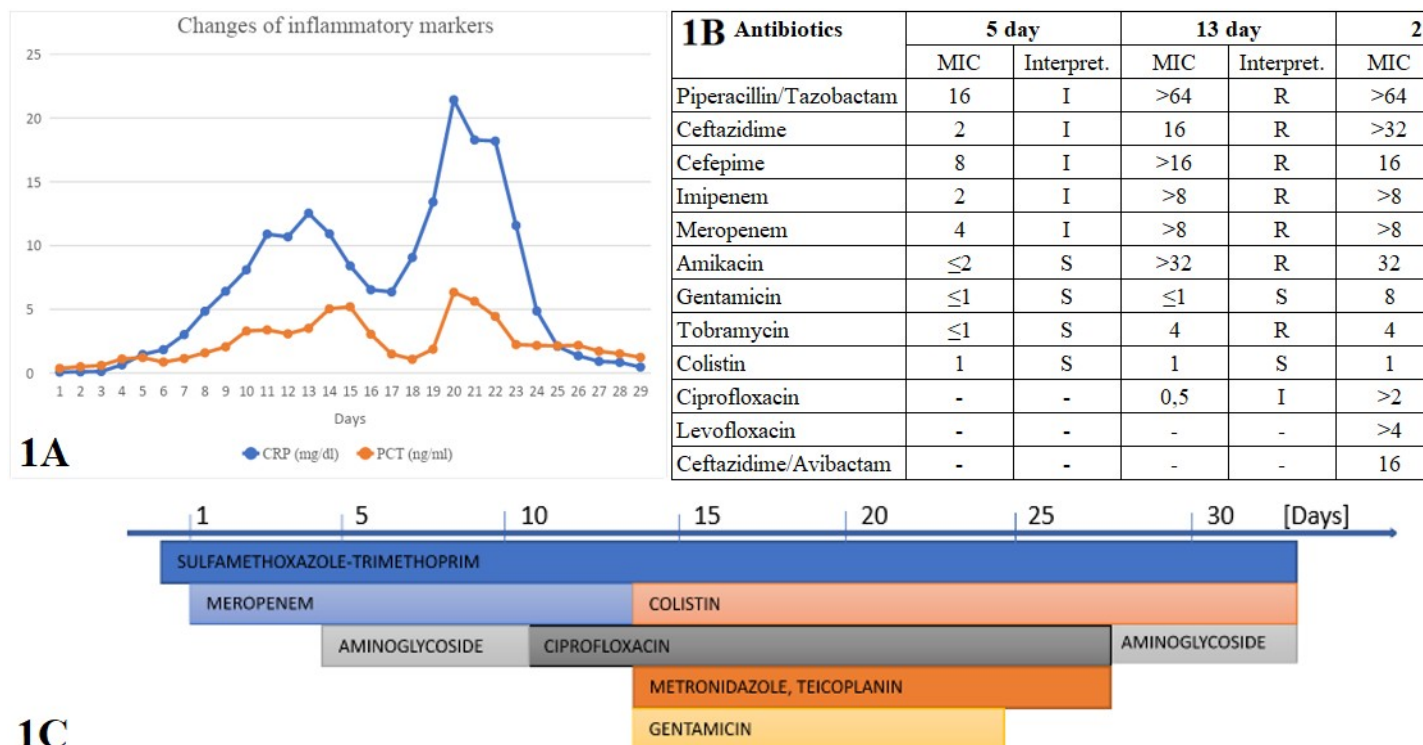


Figure 1A. Changes of inflammatory markers during sepsis from first day of sepsis to negative blood culture result; C-reactive protein (CRP); procalcitonin (PCT); **B.** Results of antibiograms

on particular dates; C. Antibiotic therapy during sepsis from first day of sepsis; MIC — minimum inhibitory concentration; interpret. — interpretation; I — intermediate; R — resistant; S — susceptible

Authors' contributions

JZ, KK — conceptualization. NZ, MJ — methodology. PM, MJ, NZ — writing, original draft preparation. JZ, KK — review and editing. All authors have read and agreed to published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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