Effective treatment of severe forms of RSV and *Pneumocystis jiroveci* infections in a child with Down syndrome and acute lymphoblastic leukemia treated with chemotherapy

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ABSTRACT

There has been significant progress in acute lymphoblastic leukemia (ALL) treatment throughout the previous decades. However, infectious complications are still the main problem during cancer treatment. Literature reports show that treatment-related mortality is 2–4% and is mainly related to infection. Here, the authors report a 3-year-old patient with Down syndrome and ALL who was hospitalized in the Department of Pediatric Hematology, Oncology and Transplantology of the Medical University of Lublin. The patient was treated according to the AIEOP-BFM 2017 protocol and developed a severe co-infection of *Pneumocystis jiroveci* and respiratory syncytial virus during the induction phase of chemotherapy and *P. jiroveci* re-infection while receiving Protocol II. As a result, chemotherapy was interrupted for 51 and 31 days, respectively. The patient required the administration of broad-spectrum antibiotics, antiviral and antifungal therapy and passive oxygen therapy. Due to a severe clinical condition, the patient was also temporarily hospitalized in the intensive care unit.

Research revealed several risk factors for infectious complications in patients with ALL including intensive chemotherapy or Down syndrome. Therefore, despite anti-infective prophylaxis, increased medical vigilance is necessary. In the case of infectious symptoms, early diagnosis and prompt treatment should be implemented to enable the continuation of the ALL therapeutic protocol.

Key words: acute lymphoblastic leukemia, infection, respiratory syncytial virus, *Pneumocystis jiroveci*, Down syndrome

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy [1]. ALL is treated with steroid therapy and multi-agent chemotherapy [2]. There has been significant progress in ALL treatments throughout the previous decades. It contributed to an increase in the five-year survival rate to over 90% [3]. However, infectious complications are still the main problem during cancer treatment. Literature reports show that treatment-related mortality is 2–4% and is mainly related to infections [4].

Pneumocystis jiroveci pneumonia (PJP) is a fungal opportunistic infection that primarily affects patients with cellular immune suppression. PJP was the most common cause of infectious death in children with leukemia before the addition of PJP prophylaxis to standard therapy [5]. Currently, the European Conference on Infections in Leukemia (ECIL) recommends cotrimoxazole for primary prophylaxis of PJP in children during ALL treatments. It should be administered at a dose of 150 mg trimethoprim and 750 mg sulfamethoxazole per square meter of body surface area per day 2–3 times a week [6]. Nevertheless, despite prophylaxis, patients with hematological malignancies might still develop PJP pneumonia [7].

Respiratory syncytial virus (RSV) infections are common in immunocompromised children and have a wide range of

symptoms from mild cold symptoms to lower respiratory tract infections (LRTI) and higher hospitalization rates. It is worth noting that RSV infections are responsible for 44% of fever episodes in children with leukemia [8].

Here, the authors report a patient with relapsed ALL, in whom severe *Pneumocystis jiroveci* and RSV infection occurred during chemotherapy. Medical records of the patient were reviewed for clinical and laboratory data.

CASE REPORT

A 3-year-old male patient with Down syndrome (DS) was treated in the Department of Pediatric Hematology, Oncology and Transplantology of the Medical University of Lublin from 21 January 2020 due to precursor B-cell common (+) ALL. The child received treatment by the *Association* International Election Observation Program Berlin–Frankfurt––Munich Acute Lymphoblastic Leukemia (AIEOP-BFM ALL) 2017 therapeutic protocol. Cotrimoxazole and fluconazole were administered as anti-infective prophylaxis.

The child's clinical condition deteriorated on the 22nd day of induction chemotherapy. The physical examination revealed abnormalities, such as extensive rhonchi, crackles and rales, muted vesicular breath sound, tachypnoea (40 breaths/min) and decreased blood oxygen saturation level. In laboratory tests, profound neutropenia and increasing levels of inflammatory markers (C-reactive protein, procalcitonin) were found. Chest computed tomography (CT) showed bilateral massive areas of ground glass within pulmonary parenchyma, linear atelectasis and areas of increased density of consolidation (Figure 1). Numerous microbiological tests were performed. Positive results of laboratory tests revealed the presence of RSV (Table 1). Chemotherapy was discontinued 21 days after starting treatment. The doses of steroids were reduced. Broad-spectrum antibiotic (meropenem), antiviral (ribavirin) and antifungal therapy (liposomal amphotericin B), inhaled salbutamol, passive oxygen therapy and respiratory rehabilitation were used. The cotrimoxazole was administered in a prophylactic dose (Figure 2). After temporary improvement, the signs of respiratory failure worsened. The patient had a cough, difficulty expectorating secretions from the respiratory tract, tachypnoea (up to 70 breaths/min), tachycardia (periodically up to 140 beats/min), signs of respiratory distress, retraction of intercostal muscles and diaphragm. Lung auscultation revealed wheezes. Follow-up chest CT showed bilateral progression of inflammatory changes. Bronchoscopy was performed on the 12th day of infection. The result of bronchial aspirate culture was negative. At this time, positive test results for *Pneumocystis jiroveci* and *Candida* were also obtained. The intravenous cotrimoxazole therapy was intensified (90–120 mg/kg — therapeutic dose) and pentamidine by inhalation was administered. The antibiotic and antifungal therapy were continued (Figure 2). It was necessary to use passive oxygenation (up to 6 L/min) and pulmonary rehabilitation because oxygen blood saturation periodically reached only 80%. On the 23rd day after the first symptoms of infection and after numerous anesthesia consultations, the child was transferred to the intensive care unit (ICU). The antibiotic and oxygen therapies were continued and eventually, intubation was unnecessary. After 6 days, the clinical condition stabilized, and the patient returned to the Department of Hematology.

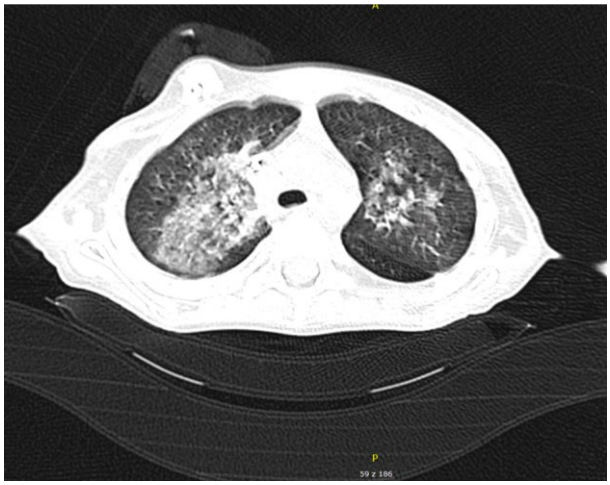

Figure 1. Computed tomography of the chest during the first infection

The features of respiratory failure and abnormal lung sounds gradually subsided. Follow-up chest CT (performed one month after the onset of infection symptoms) showed persistent diffuse irregular parenchyma consolidation. The entire interruption of chemotherapy was 51 days. Satisfactory laboratory test results allowed for its continuation. Because of complications, it was decided not to administer drugs on days 22nd and 29th of remission induction (vincristine, daunorubicin). The consolidation was completed without treatment interruptions. During the consolidation, after 42 days of a therapeutic dose of cotrimoxazole, it was also decided to return to prophylactic dosing.

During Protocol M, methotrexate was administered at reduced doses due to DS. Correct elimination of methotrexate and good treatment tolerance were observed.

The last phase of intensive therapy, reinduction, was started after the next three weeks. However, the microbiological blood tests (indirect immunofluorescence test) showed reactivated *Pneumocystis jirovecii* infection. The physical examination revealed abnormalities, such as: sharpened vesicular breath sound and extensive rhonchi over the lung fields. A chest CT scan revealed the recurrence of changes which were observed during the first infection. Chemotherapy was discontinued after 22 days of reinduction. Broad-spectrum antibiotic therapy, granulocyte colony-stimulating factor, intensive antifungal therapy and passive oxygen therapy were used. Due to a large amount of secretion retaining in the airways, inability to cough up mucus and muscle flaccidity, therapeutic bronchoscopy

Table 1. Microbiological diagnostics during the first infection

Day of material collection	The microorganism	Test method	Test result
1st	*Mycoplasma pneumoniae* IgM *Mycoplasma pneumoniae* IgG	Serum (blood), EUROIMMUN enzyme-linked immunosorbent assay (ELISA)	Negative Negative
1st	RSV antigen	Swab, Alere BinaxNow immunochromatographic screening test	Negative
1st	Bacterial flora Bacterial flora	Aerobic blood culture Anaerobic blood culture	Negative Negative
1st/5th*	*Chlamydia pneumoniae* IgM *Chlamydia pneumoniae* IgG	Serum (blood), EUROIMMUN enzyme-linked immunosorbent assay (ELISA)	Negative Negative
1st/14th*	*Pneumocystis jirovecii* IgM *Pneumocystis jirovecii* IgG	Serum (blood), indirect immunofluorescence assay	**Positive ++** **Positive +++**
2nd	Influenza A virus (RNA) Influenza B virus (RNA) RSV (RNA)	Swab, Xpert Xpress FLU/RSV test based on the RT-PCR reaction on the GeneXpert equipment	Negative Negative **Positive**
12th	Bacterial flora	Bronchial aspirate culture	Negative: • no pathogenic bacterial flora • only the physiological flora of the upper respiratory tract
13th/20th*	*Candida spp.* antigen	Serum (blood), Platelia Candida Ag immunoenzymatic assay	**Positive**
19th/25th*	Bacterial flora Bacterial flora	Aerobic blood culture Anaerobic blood culture	Negative Negative
33rd	Influenza A virus (RNA) Influenza B virus (RNA) RSV (RNA)	Swab, Xpert Xpress FLU/RSV test based on the RT-PCR reaction on the GeneXpert equipment	Negative Negative **Positive**
39th	Influenza A virus (RNA) Influenza B virus (RNA) RSV (RNA)	Swab, Xpert Xpress FLU/RSV test based on the RT-PCR reaction on the GeneXpert equipment	Negative Negative Negative
33rd/40th*	*Pneumocystis jirovecii* IgM *Pneumocystis jirovecii* IgG	Serum (blood), indirect immunofluorescence assay	Negative **Positive +++**
48th	Influenza A virus (RNA) Influenza B virus (RNA) RSV (RNA)	Swab, Xpert Xpress FLU/RSV test based on the RT-PCR reaction on the GeneXpert equipment	Negative Negative Negative

*Day of receiving the test result; Ig — immunoglobulin; RNA — ribonucleic acid; RSV — respiratory syncytial virus; RT-PCR — real-time polymerase chain reaction

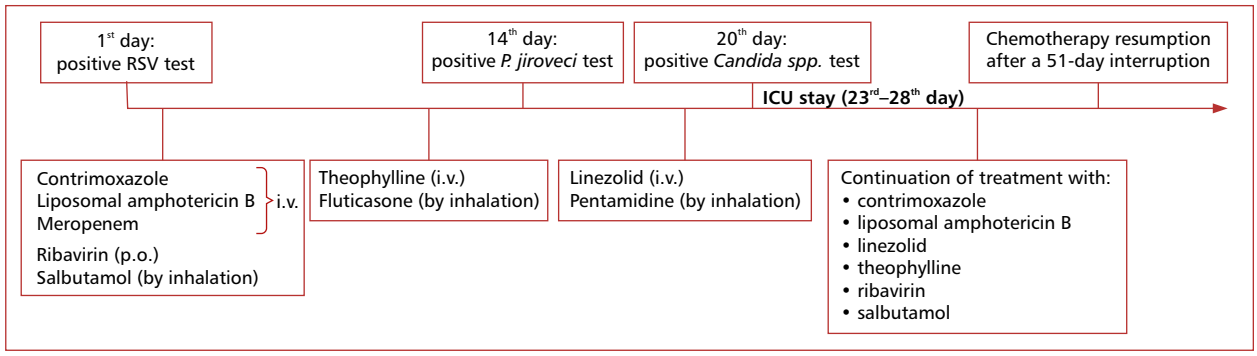

Figure 2. The main treatment regimen for the first infection; ICU — intensive care unit; i.v. — intravenous; p.o. — per os; RSV — respiratory syncytial virus

was performed twice. The results of the bronchial aspirate culture were negative (two times). The patient's clinical condition improved gradually. Chemotherapy was continued after a 31-day interruption. Currently, the patient is in good general condition and he is receiving maintenance therapy.

DISCUSSION

Infections are the main complications of leukemia therapy, causing interruptions during ALL treatments and increasing the risk of relapse and death [9]. Literature reports reveal that infection episodes occur more frequently during intensive chemotherapy [10]. In a retrospective observational study, Schmidt et al. analysed a cohort of 21 patients with DS and ALL comparing them to a group of 165 ALL patients without DS. The median age of the included patients was 5.3 years. Researchers reported that DS can increase the risk of infection and infection-related mortality in pediatric ALL patients treated with chemotherapy. Moreover, the study showed that in children with DS, it is difficult to find the dose of chemotherapy that is enough for complete remission and also minimizes treatment-related side effects [11].

In a prospective study, Patrick et al. observed 3,126 ALL patients aged 1–23 (median age of 4.5 years) including 86 patients with DS. Serious adverse events associated with infections occurred more frequently in ALL patients with DS than in the group without this chromosome abnormality (39.5% vs. 16.4%). In addition, all deaths of DS patients (n = 25) were due to infections, particularly bacterial sepsis (75%) and viral pneumonitis (25%) [12]. In another prospective study, O'Connor et al. [4] analysed 3,126 cases of ALL patients aged 1–24. They noticed that the deaths of these patients were mainly infection-related, with the predominant bacterial (68%) and fungal (20%) etiology of the observed infections. DS was the most common risk factor for infection-related mortality, in particular during maintenance therapy [4]. The increased susceptibility to infectious complications observed in ALL patients with DS can be the result of the presence of a genetic disease that causes functional impairments of B-cells, T-cells and phagocytic cells leading to immunodeficiency [13].

In a retrospective study, Hakim et al. analysed a cohort of 223 ALL patients aged 0–18. 95 out of them were diagnosed with 133 episodes of acute viral respiratory infections (caused by influenza virus and/or RSV). About 80% of children with viral infection required chemotherapy interruption and 26% had a severe clinical course. As expected, complications were more frequent and chemotherapy interruptions were longer in patients with viral LRTI than in those with upper respiratory tract infections. The infection-related mortality rate was low. There was only one case of an 11-month-old girl who had an RSV infection during the reinduction II phase of chemotherapy and developed a secondary bacterial infection. The child received vancomycin, meropenem, azithromycin, voriconazole, palivizumab and ribavirin, but she died 2 months later due to respiratory and hemodynamic failure [14].

Zhu et al. [15] evaluated 4,080 ALL patients aged 0–18 of whom 527 developed sepsis. Identified risk factors for sepsis included: the intermediate- or high-risk ALL and the induction phase of intensive chemotherapy. About 20.5% of infections were caused by multidrug-resistant organisms. Mortality among patients with sepsis was 3.4% and was associated with the female sex, coexisting complications, comorbidities and fungal infections [15].

Despite the use of recommended prophylaxis, the study patient developed two severe infections which resulted in two chemotherapy interruptions. It could be related to the presence of risk factors, such as DS, a younger age of the patient, associated immaturity of the immune system, the use of intensive chemotherapy and immunocompromised status. The impact of these factors on the risk of infection was confirmed in a retrospective study by Inaba et al. who analysed 409 ALL patients *under 18 years* of age [10]. In addition, in the case of *Pneumocystis jiroveci*, an active infection can be the result of the reactivation of a latent infection [5]. It should be mentioned that the patient's medical history revealed congenital pneumonia and pneumonia of unknown etiology two months before ALL diagnosis.

The time to the treatment initiation has an important impact on the clinical course of each infection. In the study patient, antiviral treatment against RSV was started in the first days of infection thanks to the rapid identification of the pathogen in microbiological tests. In the first infection, the bronchial aspirate was collected on the 12th day of infection, but the results of the cultures were negative. Whereas the positive indirect immunofluorescence test result for *Pneumocystis jiroveci* was obtained 2 weeks after the onset of symptoms and collection of a blood sample. The type of diagnostic method and the need to deliver the diagnostic material to another laboratory centre were the reasons for the long wait for the result. Once the diagnosis of PJP was made, cotrimoxazole therapy was intensified and pentamidine inhalation was added to the treatment.

In the diagnosis of *Pneumocystis jiroveci* infection, various diagnostic materials are used, especially blood/ /serum, sputum, nasopharyngeal aspirate and bronchoalveolar lavage fluid. *Pneumocystis jiroveci* can be detected with conventional and immunofluorescent staining. But there are also many novel methods such as polymerase chain reaction, loop-mediated isothermal amplification, flow cytometry, antibody assays (enzyme-linked immunosorbent assay [ELISA]) and antigen assays. These methods have higher sensitivities and specificities than conventional stains and can detect infections at an early stage reducing the time to initiate appropriate anti-infective treatment [16].

CONCLUSIONS

In conclusion, despite ongoing therapy improvements, infectious complications continue to be a major burden on pediatric ALL patients, especially those with Down syndrome who have fewer opportunities to adapt to infection. This is the result of genetic disorders and the associated susceptibility to multimorbidity. The described case shows the importance of early diagnosis and prompt treatment of infection, which will enable the continuation of the ALL therapeutic protocol. In addition, despite anti-infective prophylaxis, increased medical vigilance is a key element in the care of pediatric patients with ALL, particularly when the risk factors for infections are present and during periods of intensive chemotherapy.

Article information

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