VIA MEDICA

CASE REPORT

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Importance of genetic diagnosis for treatment and prognosis in acute lymphoblastic leukaemia (ALL) — a case report

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common malignancy among children. It originates from over-proliferating immature lymphoid cells called lymphoblasts. Modern genetic studies have shown that the aetiology of ALL is correlated with numerous chromosomal aberrations, including activating mutation of the JAK/STAT pathway. This pathway is responsible for regulating the transmission of signals from extracellular cytokines to the nucleus of cells, regulating their growth, differentiation and immune response. With proper patient diagnosis, it is possible to correctly classify the genetic subtypes of ALL, allowing more effective therapies to be introduced. The following study presents the importance of genetic diagnosis for the treatment of a paediatric patient with ALL with the above mutation in the genome.

Keywords: acute lymphoblastic leukaemia, children, JAK/STAT pathway

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Introduction

Acute lymphoblastic leukaemia (ALL) is the most common hematopoietic malignancy among paediatric patients and also the most common malignancy in children, as it accounts for up to 25% of all cases. The pathogenesis of ALL is based on the malignant transformation of normal precursor cells for B and T lymphocytes, resulting in excessive and uncontrolled proliferation of lymphoblasts, which causes neoplastic proliferation [1–3]. Among ALL, we can distinguish B-cell ALL (B-ALL), which accounts for about 80% of all cases among paediatric patients, and T-cell ALL (T-ALL), which accounts for 10–15% of cases [3]. The results of recent studies have shown that with appropriate therapy, the 5-year overall survival rate (OS) among paediatric patients has improved significantly and is estimated to be over 90%. Achieving treatment results at such a high level with conventional methods requires the use of chemotherapeutics in high doses [4]. Further advances in the treatment of ALL have been made possible by the increasingly common view of leukaemias from the genetic factors that promote the formation of hematopoietic malignancies. This view of ALL as well as other leukaemias enables the use of targeted treatment, which makes it possible to reduce the intensity of chemotherapy and toxicity of treatment while maximizing the effectiveness of therapy [3]. For this reason, early genetic diagnosis of a patient with ALL is extremely important. Many genetic abnormalities predispose to the development of ALL, one of which is an activating mutation of the JAK/STAT signalling pathway, which is what is found in the clinical case described below. The aforementioned genetic change occurs in 3–5% of B-ALL in children and 15% in adults [5]. The discovery of the impact of JAK/STAT pathway activating mutations on the development of leukaemia has allowed the introduction of treatment regimens containing JAK inhibitors, which have improved the efficacy of therapy [6]. The purpose of this paper is to determine the relevance of genetic diagnosis of patients with ALL based on the case report of a paediatric patient with a confirmed JAK/STAT mutation.

Case report

A 14-year-old boy was admitted to the Department of Paediatric Haematology, Oncology and Transplantology with suspected proliferative hematopoietic disease for diagnosis and treatment. In history, there were: weight loss of about 1.5 kg in a month, deterioration of mood, headaches and muscle pain, lack of appetite and periodic vomiting. The boy had been treated with an antibiotic with temporary improvement but there was a recurrence of the symptoms after a few days. The Complete Blood Count (CBC) performed on an outpatient basis showed hyperleukocytosis of 124.35 × $10^3/\mu$L.

On admission, the boy was in moderate general condition, with a fever. On physical examination doctors noticed pale, sallow skin, features of haemorrhagic diathesis in the form of punctate petechiae on the lower extremities, hepatomegaly and massive lymphadenopathy: right submandibular lymph nodes (approx. 3 × 5 cm), the same on the left side (2 × 4 cm), deep cervical and axillary lymph nodes bilaterally (on the right side — 2 cm in diameter, on the left side about 1.5 cm), numerous hard inguinal lymph nodes bilaterally (up to 2.5 cm in diameter). The results of some laboratory tests on the day of the patient's admission are shown in Table 1.

An abdominal ultrasound confirmed hepatomegaly and showed numerous irregular lymph nodes (with a short axis dimension of up to about 14 mm) in the hepatic portal area. Enlarged pancreas, splenomegaly and swollen peri-intestinal adipose tissue were also reported. A CT scan of the chest showed lesions that may correspond to fungal lesions.

Due to hyperleukocytosis and the presence of 90% blast cells in the smear, a bone marrow biopsy was abandoned. Based on peripheral blood examination in flow cytometer (81.3% of blasts), a diagnosis of pre-B common(+) *BCR*/*ABL1*(—), *KMT2A*(—), *ETV6*/*RUNX1*(—), *PBX1*/*TCF3*(—), *HLF*/*TCF3*(—) ALL was made and chemotherapy was started according to the AIEOP-BFM ALL Poland 2017 — Protocol IA-Pred. Response to steroids on the 8th day was good (blasts count was 184 — the criterion for a good response is under 1000). On the 15th day, the percentage of blasts was 1.2%. However, due to the result of immunophenotyping (FCM-MRD — 11.98%), the boy was classified into the early high-risk (HR) group. The result of the genetic test showed the presence of deletions of the *IKZF1* and *PAX5* genes, as well as a deletion of the *CDKN2A* gene, meeting the criteria for the *IKZF1*(+) group, and a rearrangement in the *CRLF2* and *IGH* genes indicating activation of the JAK/STAT pathway. Therefore, chemotherapy was continued according to the Rux-cALL-Pol 2020 Program, in which ruxolitinib (a selective inhibitor of JAK1 and JAK2) was administered. On the 33rd day of treatment, the percentage of blasts in myelogram was 0% but MRD was positive (4 × 10^{-1}). The patient was classified into the HR group. Chemotherapy was continued as planned: after completion of Protocol IA-Pred, the boy received Consolidation A, followed by Consolidation B, during which, ruxolitinib (80 mg/m^2/day for 28 days) was administered. Treatment was complicated by aplasia, hypothyroidism, diabetes and polyneuropathy. The boy required transfusions of blood and blood products. Due to disorders in the haemostatic system, he received antithrombin III, cryoprecipitate and fresh frozen plasma. Due to increasing inflammatory markers, he required broad-spectrum antibiotic therapy and antifungal treatment. On the 64th day and 12th week (before the HR1 Block) of treatment, PCR-MDR was positive (2 × 10^{-2} and 4 × 10^{-1} respectively). Before the HR2 Block, MRD decreased to 1 × 10^{-1}, but the result remained positive. Later, before the HR3 Block, the MRD was 6 × 10^{-2}. Due to the failure to achieve remission, the coordinator of the Rux-cALL-Pol 2020 Program was consulted on further management. A decision was made to administer blinatumomab (anti-CD19 antibody). The patient's therapeutic plans include transplantation. Before the

Table 1. Results of some laboratory tests on the day of the admission

Parameter	Result	Reference range
Leukocytes [$10^3/\mu$L]	119.43	3.6–9.1
Erythrocytes [$10^6/\mu$L]	4.29	4.4–5.5
Haemoglobin [g/dL]	12.2	12.8–16
Platelets [$10^3/\mu$L]	51	140–420
Neutrophils [$10^3/\mu$L]	4.06	2.5–7
Lymphocytes [$10^3/\mu$L]	83.99	0.8–4
Monocytes [$10^3/\mu$L]	30.86	0.2–1.2
Eosinophils [$10^3/\mu$L]	0.31	0–0.1
Basophils [$10^3/\mu$L]	0.36	0–0.15
TSH [μIU/L]	3.2	0.51–4.3
LDH [U/L]	626	0–286
AST [U/L]	31	0–33
ALT [U/L]	12	0–26
CRP [mg/dL]	8.38	0–0.5
D-dimers [ng/mL]	4343	< 500
Creatinine [mg/dL]	1	0.57–0.87
Uric acid [mg/dL]	12.63	3.1–7
Urea [mg/dL]	33.4	18–45
Lipase [U/L]	206	0–46
Amylase [U/L]	199	28–100

TSH — thyrotropic hormone; LDH — lactate dehydrogenase; AST — aspartate aminotransferase; ALT — alanine aminotransferase; CRP — C-reactive protein

first infusion of the product, MRD was 4×10^{-2}, while after the infusion it was 1×10^{-4}. The expected result is below 5×10^{-4}, so the patient has achieved remission. Due to the lack of a compatible family donor, a compatible unrelated donor was selected for allogeneic bone marrow transplantation (allo-BMT). The procedure will be carried out after the administration of a second infusion of blinatumomab.

Discussion

ALL is a disease originating from the clonal proliferation of precursor lymphoid cells (lymphoblasts) derived from the B or T lineage. It is the most common childhood cancer accounting for about 75% of all leukaemias, with a peak incidence between the ages of 1 and 5. The disease occurs in 4 out of 100,000 children between the ages of 0 and 14 with an incidence of 1 out of 100 000 in patients over the age of 15. However, ALL is not only a problem among paediatric patients, its second peak incidence affects adults in the sixth decade of life [7–10]. One of the subtypes of B-ALL is Philadelphia chromosome-like ALL (Ph-like ALL), identified in 2009. This ALL subtype has gene expression with a profile similar to Ph-ALL, but lacks the typical *BCR*/*ABL1* fusion gene due to t(9;22)(q34.1;q11.2). The most common mutations causing Ph-like ALL in children include changes in *IKZF1* (70–80%). Additionally, alterations in the JAK/STAT pathway (*CRLF2*, *JAK2*, *EPOR*), ABL (*ABL1*, *ABL2*, *CSF1R*, *PDGFR*) or RAS (*KRAS*, *NRAS*, *NF1*, *PTPN11*) are frequently observed [11]. Ph-like ALL occurs in 10% of standard-risk (SR) children with B-ALL and 15% of high-risk (HR) children. Ph-like ALL is characterized by significantly worse treatment outcomes (failure of induction, high MRD) and prognosis compared to other B-ALL (event-free survival rate (EFS) 63% in Ph-like ALL *vs.* 86% in others B-ALL). For this reason, such a diagnosis is an unfavourable prognostic factor [12]. The symptoms of ALL can appear suddenly or develop insidiously for several months. In many cases, they are nonspecific, which contributes to delayed diagnosis resulting in decreased chances of successful treatment. The most common symptoms include fever, weakness and lethargy, shortness of breath caused by anaemia, bleeding and excessive bruising arising as a result of thrombocytopenia. Neoplasm cells can infiltrate other organs: the meninges, tonsils, testes, liver, spleen, lymph nodes or orbits [9, 10]. The most common laboratory abnormalities among paediatric patients include anaemia, thrombocytopenia, neutropenia, leukopenia or leucocytosis $> 100 \times 10^3/\mu$L. Interestingly, hyperleukocytosis is more characteristic of T-ALL but was also found in Ph-like B-ALL patients. Rarer but also occurring changes in laboratory tests are elevated levels of uric acid and lactate dehydrogenase arising from the lysis of tumour cells [9]. The above clinical and laboratory symptoms were also presented by the study patient.

The primary treatment for ALL in paediatric patients is intensive, four-step chemotherapy (induction, consolidation, reinduction, maintenance treatment) according to the AIEOP-2017 Poland Program. This treatment is based on the administration of chemotherapeutics, such as vincristine, anthracyclines, asparaginase, cyclophosphamide, 6-mercaptopurine and methotrexate, for example. The effective doses of these drugs are often very high, which is associated with frequent side effects [13]. However, the discovery of new signalling pathways has enabled a shift in the treatment of ALL according to the principles of targeted therapy.

The effectiveness of ALL treatment is closely correlated with the selection of the appropriate therapy for a given genetic subtype of ALL, which is why it is so important to identify the specific mutations present in a given patient. Patients with *BCR*/*ABL* fusion were found to show a good response to tyrosine kinase inhibitors and cells with *ABL1*, *ABL2*, *CSF1R* and *PDGFRB* mutations were found to be sensitive to dasatinib, *BCL2* to venetoclax, *EPOR* and *JAK2* to ruxolitinib, and those with *ETV6-NTRK3* fusion to crizotinib. Epigenetic changes such as histone modifications susceptible to histone deacetylase inhibitor (HDACi) therapy — vorinostat — are also important [14]. The problem of Ph-like ALL is so important that a separate therapeutic program — the Rux-cALL-Pol 2020 Program — has been developed for patients with mutations that activate the JAK/STAT pathway. It includes ruxolitinib in addition to classical chemotherapy. It is a product that selectively inhibits JAK1 and JAK2 kinases and inhibits STAT3 and STAT5 phosphorylation. It is administered at a dose of 40 mg/m^2 for 28 days. Patients on this regimen show a significant decrease in MRD [15]. Thanks to the development of ALL treatment, complete remission occurs in 95% of patients and 55% of complete remission persists for five years [16].

Conclusions

Chromosomal aberrations resulting in JAK/STAT activating mutation can cause ALL. The above mutation affects the more difficult course of the disease and worsens the prognosis and the effectiveness of therapy. It is extremely important to diagnose patients with hematopoietic malignancies from a genetic point of view. With these tests, it is possible to classify leukaemia into genetic subtypes, which allows patients to be included in targeted treatment regimens, enables more effective treatment, and allows patients to achieve long-term remission thus increasing their chances of survival.

Article information

Ethics statement: *Not applicable.*

Author contributions: *All authors — design of the study, MML — provision of clinical data, all authors — analysis of clinical data, KB, MR — literature review, KB, MR, MD, AD — writing manuscript, MML — critical review, all authors — final approval.*

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References

1. Lejman M, Chałupnik A, Chilimoniuk Z, et al. Genetic biomarkers and their clinical implications in b-cell acute lymphoblastic leukemia in children. Int J Mol Sci. 2022; 23(5), doi: 10.3390/ijms23052755, indexed in Pubmed: 35269896.
2. Nordlund J, Syvänen AC. Epigenetics in pediatric acute lymphoblastic leukemia. Semin Cancer Biol. 2018; 51: 129–138, doi: 10.1016/j.semcancer.2017.09.001, indexed in Pubmed: 28887175.
3. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am. 2015; 62(1): 47–60, doi: 10.1016/j.pcl.2014.09.004, indexed in Pubmed: 25435111.
4. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica. 2020; 105(11): 2524–2539, doi: 10.3324/haematol.2020.247031, indexed in Pubmed: 33054110.
5. Norvilas R, Dirse V, Semaskeviciene R, et al. Low incidence of ABL-class and JAK-STAT signaling pathway alterations in uniformly treated pediatric and adult B-cell acute lymphoblastic leukemia patients using MRD risk-directed approach - a population-based study. BMC Cancer. 2021; 21(1): 326, doi: 10.1186/s12885-020-07781-6, indexed in Pubmed: 33781217.
6. Hu X, Li J, Fu M, et al. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021; 6(1): 402, doi: 10.1038/s41392-021-00791-1, indexed in Pubmed: 34824210.
7. Chiaretti S, Messina M, Foà R. BCR/ABL1-like acute lymphoblastic leukemia: How to diagnose and treat? Cancer. 2019; 125(2): 194–204, doi: 10.1002/cncr.31848, indexed in Pubmed: 30561755.
8. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet. 2020; 395(10230): 1146–1162, doi: 10.1016/S0140-6736(19)33018-1, indexed in Pubmed: 32247396.
9. Leak Bryant A, Lee Walton A, Shaw-Kokot J, et al. Patient-reported symptoms and quality of life in adults with acute leukemia: a systematic review. Oncol Nurs Forum. 2015; 42(2): E91–E9E101, doi: 10.1188/15.ONF.E91-E101, indexed in Pubmed: 25806895.
10. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet. 2020; 395(10230): 1146–1162, doi: 10.1016/S0140-6736(19)33018-1, indexed in Pubmed: 32247396.
11. Pui CH, Roberts KG, Yang JJ, et al. Philadelphia chromosome-like acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2017; 17(8): 464–470, doi: 10.1016/j.clml.2017.03.299, indexed in Pubmed: 28842136.
12. Tran TH, Loh ML. Ph-like acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016; 2016(1): 561–566, doi: 10.1182/asheducation-2016.1.561, indexed in Pubmed: 27913529.
13. Ostra białaczka limfoblastyczna (ALL) – objawy, diagnostyka, leczenie. https://przyladeknadziei.pl/ostra-bialaczka-limfoblastyczna-all-objawy-diagnostyka-leczenie/ (13.08.2023).
14. Xu H, Yu H, Jin R, et al. Genetic and epigenetic targeting therapy for pediatric acute lymphoblastic leukemia. Cells. 2021; 10(12): 3349, doi: 10.3390/cells10123349, indexed in Pubmed: 34943855.
15. Hu M, Liu R, Li J, et al. Clinical features and prognosis of pediatric acute lymphocytic leukemia with JAK-STAT pathway genetic abnormalities: a case series. Ann Hematol. 2023; 102(9): 2445–2457, doi: 10.1007/s00277-023-05245-y, indexed in Pubmed: 37209119.
16. Diamond CA, Matthay KK. Childhood acute lymphoblastic leukemia. Pediatr Ann. 1988; 17(3): 156–161; 164–170, doi: 10.3928/0090-4481-19880301-06, indexed in Pubmed: 3281103.