Kowalczuk Maria, Lipińska Justyna, Lipiński Łukasz, Lejman Monika, Zawitkowska Joanna. Acute lymphoblastic leukemia (ALL) with KMT2A gene rearrangement in infants - characteristic clinical picture based on a case report. Journal of Education, Health and Sport. 2022;12(3):266-273. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.03.022
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.03.022
https://zenodo.org/record/6401312

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 10.03.2022. Revised: 16.03.2022. Accepted: 31.03.2022.

Acute lymphoblastic leukemia (ALL) with KMT2A gene rearrangement in infants - characteristic clinical picture based on a case report

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Key words: leukemia; leukemiainfant; infant KMT2A

Abstract

The most common malignancy affecting children is leukemia, which in infants refers to be diagnosed before 1 year of age and is relatively rare, but remains a problem for clinicians due to its aggressive clinical presentation, poor response to current treatments, and molecular biology. Infants with acute leukemia tend to present with aggressive features, including hyperleukocytosis, hepatosplenomegaly, central nervous system (CNS) involvement, and cutaneous infiltration. In infant leukemia, the KMT2A gene rearrangement at chromosome 11q23 is quite common. Infants diagnosed with acute leukemia harboring a 11q23 rearrangement have a particularly poor prognosis when compared to other children with acute leukemia.

A 10-month-old girl was admitted in December 2017 to the Department of Pediatric Hematology, Oncology and Transplantology in Lublin with the suspicion of leukemia. One week before hospitalization minor bruises began to appear on the skin, unrelated to an injury. The child was admitted to the hospital, and there a complete blood count showed anemia, hiperleukocytosis and thorombocytopenia. On the admission to the Clinic: the severe general condition of the patient, with features of cardiopulmonary insufficiency were confirmed. Due to the patient's age and the presence of the KMT2A/MLLT3-t(9;11) (p22;q23) gene rearrangement, the infant was stratified as a high-risk group (*HRG*) and chemotherapy was started in accordance with the therapeutic program.

Infant leukemia is one of the most difficult clinical situations encountered in pediatric oncology. Given the infant’s vulnerability and unique genetic rearrangements, there is a need to develop new protocols and therapies for infants.

Introduction

The most common malignancy affecting children is leukemia, which is a group of blood cancers that arise usually from blood marrow and account for about one-third of all cancers. Leukemia in infants refers to acute leukemia diagnosed before 1 year of age and is relatively rare, but remains a problem for clinicians due to its aggressive clinical presentation, poor response to current treatments, and molecular biology [1]. It is the second most common cancer in children less than 1 year of age, following neuroblastoma [1,2]. Acute lymphoblastic leukemia (ALL) is slightly more common than acute myeloid leukemia (AML) in infants and almost all lymphoid cases are B-lineage with <5% T-lineage. Infants represent 2 to 5% of pediatric ALL cases [3].The majority is shown in girls, compared to children older than 1 year of age, in whom leukemia is more common in boys [1].

Infants with acute leukemia tend to present with aggressive features, including hyperleukocytosis (300,000/μL), hepatosplenomegaly, central nervous system (CNS) involvement, and cutaneous infiltration. Confirmation of the diagnosis provides peripheral blood smear examination and bone marrow biopsy [4].

In infant leukemia, there is a high proportion of balanced chromosomal translocations, which involve the histone lysine methyltransferase 2A gene (KMT2A) at chromosome 11q23. This gene is formerly known as the mixed lineal leukemia (MLL) gene. The rearrangement occurs in 70% to 80% of ALL and in approximately 50% of AML in infants, and only about 5% and 15-20% in children older than 1 year of age. Infants diagnosed with acute leukemia

harboring a 11q23 rearrangement have a particularly poor prognosis when compared to other children with acute leukemia [2]. Clinically, the most common immunophenotype of infant leukemia is pro-B (CD34+, CD19+), CD10 negative, and sometimes with aberrant expression of monocytoid differentiation. This suggests that these leukemias originate from very early B-cell progenitors with both lymphoid and myeloid features [2, 3]. MLL rearrangement is associated with 90% of CD10- cases, but only with 20% of CD10+ cases [4].

The primary treatment in infants with ALL is chemotherapy and steroidtherapy [5]. Infants with ALL and KMT2A rearrangement are located to high-risk group. Compared to older children, infants with ALL usually are more likely to have chemotherapy-resistance cytogenetic features and high relapse rates. Allogeneic hematopoietic stem cell transplantation is reserved for patients with high-risk disease or persistent minimal residual disease [6].

Case report

A 10-month-old girl was admitted in December 2017 to the Department of Pediatric Hematology, Oncology and Transplantology in Lublin with the suspicion of leukemia.

The patient’s medical history was as follows: a child born at 37 weeks of pregnancy, APGAR score of 10, pregnancy complicated by infection of the mother's genital tract with intrauterine growth restriction (IUGR) diagnosis. No clinical symptoms were suggesting an infection. The infant was not vaccinated due to rhinitis. The grandfather had chronic lymphocytic leukemia. The child was treated with antibiotics 2 weeks before hospitalization because of blood in stool noticed by the mother, but to no avail. About a week later, minor bruises began to appear on the skin, unrelated to an injury. Due to the considerable pallor of the skin and a feverish state (37.2 Celsius degrees), the child was admitted to the hospital, where he lived. Complete blood count showed anemia, hiperleukocytosis and thorombocytopenia. On the admission to the Clinic: the severe general condition of the patient, with features of cardiopulmonary insufficiency. The patient was conscious, the position of the body was unrestricted, she sucked rather reluctantly. She had accelerated breathing, wheezes, prolonged exhalation, intercostal pain, tachycardia 140-180 / min, systolic murmur, waxy-pale skin, pale conjunctiva, numerous point-like ecchymoses on the skin and oral mucosa, and serum nasal discharge. The child did not lift his head, neonatal reflexes were symmetrically weakened.

The following abnormalities were observed in the laboratory tests: Hemoglobine (HGB) 4.1 g / l, White Blood Count (WBC) 142 000/ µl, percentage of undifferentiated cells 84%, Platelets 10,000 / µl, in biochemistry: increased uric acid level and lactate dehydrogenase (LDH). On the basis of complete blood count (Table 1), infant leukemia was suspected. The platelet concentrate and RBC were transfused without complications. Broad-spectrum antibiotic therapy and antifungal treatment were implemented. The allergic reaction to Mycamine occurred - the infusion was discontinued, and Fluconazole was administrated.

Laboratory results of blood morphology of patient

Parameters	**Diagnosis**
WBC/µl	142 000 (↑)
RBC/µl	1 230 000 (↓)
PLT/µl	10 000 (↓)
LDH [U/l]	2571 (↑)
Uric acid [mg/dl]	6,39 (↑)
CRP [mg/dl]	0,39 (N)
ALT [U/l]	22,0 (N)
AST [U/l]	87,0 (↑)

Tab. 1 Laboratory tests in the first day of the admission; WBC - white blood cells, RBC - red blood cells, PLT - platelets, LDH - lactate dehydrogenase, CRP - C-reactive protein, ALT - glutamic pyruvic transferase, AST - aspartate transaminase

Based on myelogram and bone marrow flow cytometry evaluation B-cell precursor acute Lymphoblastic Leukemia common negative BCR/ABL (-), KMT2A/MLLT3(+), ETV6/RUNX1(-), TCF3(-), IKZF1(-) was diagnosed. Examination of the cerebrospinal fluid revealed no central nervous system involvement. Due to the patient's age and the presence of the KMT2A/MLLT3-t(9;11) (p22;q23) gene rearrangement, the infant was stratified as a high-risk group (*HRG*) and chemotherapy was started in accordance with the therapeutic program. The child has no indication to stem cell transplantation. During

therapy, the patient presented many side-effects: massive ulcerations on the buttocks and anus, myelosupression, hipertriglicerydemia and hepatotoxicity.

Discussion

Leukemias diagnosed in under 1-year-old infants generally have an aggressive clinical nature and unique molecular biological characteristics. Acute lymphoblastic leukemia in infants is still intractable and difficult to treat as compared with other pediatric ALLs, for which considerable progress in treatment outcomes has been recently achieved.

Acute Lymphoblastic Leukemia in infants is characterized by an aggressive course. In a study Interfant-06, which assessed 651 infants with ALL, an overall survival (OS) was just 58% and 6-year event-free survival (EFS) was estimated at 46% [7]. Inaba et al. reported, that 5-year OS rates among children exceed 90% [8]. The factors that influence the prognosis include, first of all, KMT2A gene status, the age of the child at the time of diagnosis of ALL, white blood cell count, and initial response to prednisone. Wertheim also counted the presence of minimal residual disease after therapy as a strong independent prognostic variable in infant ALL. [7].

The clinical features of the infant ALL are characterized by hyperleukocytosis at diagnosis and resistance to glucocorticosteroids (almost 35% of patients). The most common clinical signs are hepatomegaly, splenomegaly, and skin lesions (leukemia cutis) [9]. Heikinheimo et al reported that the most consistent hematological feature of neonatal leukemia is hyperleukocytosis, with counts as high as 830 000/μL [10]. Pieters et al. showed that in study Interfant-06, 53% of 651 infants had a white blood cell count at diagnosis of 100,000 / μl or greater; more than 29% of patients had 300,000 / μl or greater WBC levels. Risk factors for worse prognosis in infant ALL include: rearrangements of the KMT2A gene, age less than 3 and 6 months of age, high leukocytosis at diagnosis, poor response to glucocorticoids (GCs) lack of CD10 antigen expression, co-expression of myeloid antigens on blasts, baseline central nervous system (CNS) involvement [11].

Infant leukemia cells frequently carry chromosome translocations involving the t(4;11) (q21.3;q23.3)/KMT2A-AFF1 gene rearrangement. A t(9;11) (p22;q23)KMT2A-AFF1 gene rearrangement is quite rare, usually occurs with AML, and is associated with

poorer outcomes than in AML [12]. A KMT2A-AFF1 fusion is characteristically observed in neonatal and infant ALL, representing a hallmark of poor prognosis. [13] In Interfant-99 study, 4-year event-free survival with KMT2A rearrangement in infants was only 37% [11]. Ishii et. al. have analyzed the association between age at onset and the presence of MLL gene rearrangements in infant leukemia from 162 patients. In the group of children with ALL, 24 patients (15% of patients) less than 2 months of age exhibited positive MLL gene rearrangements, whereas only two-thirds in late infancy (9–11 months of age) displayed this genetic rearrangement.

Dreyer et al. enrolled infants with ALL from 1996 to 2006. The study included 147 infants and the treatment was intensive chemotherapy for 46 weeks. In the results, the overall complete response (CR) rate was 92%, and 5-year EFS was only 42%. The main cause of treatment failure was relapse, and the main predictors of poor outcomes were KMT2A rearrangement, elevated white blood cell count, and age less than 90 days at diagnosis [14]. The study conclusion was that high-intensity chemotherapy is not sufficient for KMT2A-R infant ALL and novel approaches are needed.

A valid aspect of the treatment is the infant's unique vulnerability to complications and toxicities. Brown P reported, that in the Children's Oncology Group (COG) infant ALL protocol P9407, death from toxicity within the first 90 days of enrollment occurred in 25% of the first 68 patients [1]. Pieters et al. examined a group of 482 children treated by Interfant-99 protocol. During the intensification phase, 35 of 71 patients (49%) had infections, 21 (30%) patients had mucositis, 22 (31%) patients had toxic effects on the liver, and 2 (3%) presented neurotoxicity [15, 16]. As for the induction therapy complications, Salzer et al. reported, that the most common side effects included infectious toxicity and hematologic toxicity. Local skin toxicity was present in 13.9% of 209 infants [17].

Conclusions

Infant leukemia is one of the most difficult clinical situations encountered in pediatric oncology. Most treatment failures are due to relapse, treatment-related mortality, and late side effects. Standard protocols and treatments are not adapted for infants. Given the infant's vulnerability and unique genetic rearrangements, there is a need to develop new protocols and therapies for infants.

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