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Pure erythroid leukemia in four month old infant – case report

Białaczka czystoczerwonokrwinkowa u 4-miesięcznego niemowlęcia – opis przypadku

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Słowa kluczowe
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Summary

Acute myeloid leukemias (AMLs) in children represent a clinically and biologically heterogeneous group of diseases. Pure erythroid leukemia (PEL) is a very rare disease and represents fewer than 1% of all AML cases. The most common sites of extramedullary leukemia in children with AML include skin, gingival, central nervous system (CNS) and myeloblastomas in the head and neck area. In the studied clinical case, neuroblastoma was initially suspected, due to the patient's very young age (four months old) and the dominant clinical picture – the exophthalmos of an eye. The diagnostics was extended to include bone marrow biopsy performed. Cytometry was characteristic of cells belonging to the erythroid line. Current regimens for treating pediatric AML consist of aggressive induction therapy based on a combination of cytarabine and anthracycline to achieve complete remission, followed by consolidation with high-dose cytarabine-based blocks of chemotherapy or stem cell transplant. The beginning of the disease and its clinical picture may not be idiosyncratic and, despite very intensive therapy, the treatment may be very difficult and not always leading to remission.

Streszczenie

Ostra białaczka szpikowa (AML) u dzieci stanowi klinicznie i biologicznie niejednorodną grupę chorób. Białaczka czystoczerwonokrwinkowa (ang. *pure erythroid leukemia* – PEL) jest bardzo rzadką chorobą i stanowi mniej niż 1% wszystkich przypadków ostrej białaczki szpikowej. Najczęstszymi pozaszpikowymi lokalizacjami ostrej białaczki szpikowej u dzieci są: skóra, dziąsła, ośrodkowy układ nerwowy (OUN) oraz występowanie mieloloblastomy w obszarze głowy i szyi. W badanym przypadku klinicznym ze względu na bardzo młody wiek (cztery miesiące) i dominujący obraz kliniczny pacjenta – wytrzeszcz gałki ocznej, pierwotnie podejrzewano nerwiaka zarodkowego. Diagnoza została poszerzona o wykonanie biopsji szpiku kostnego. W cytometrii obecne były charakterystyczne komórki należące do linii erytroidalnej. Aktualne schematy leczenia AML składają się z agresywnego leczenia indukcyjnego w oparciu o kombinację cytarabiny i antracyklin do osiągnięcia całkowitej remisji, a następnie konsolidacji opartej na blokach dużych dawek cytarabiny lub przeszczep szpiku. Początek choroby i obraz kliniczny mogą być niecharakterystyczne, a leczenie mimo bardzo intensywnej terapii trudne i nie zawsze doprowadzające do remisji.

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

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INTRODUCTION

Acute myeloid leukemias (AMLs) in children represent a clinically and biologically heterogeneous group of diseases. It is caused by the malignant transformation of a hematopoietic stem cell or myeloid progenitor cell (1). According to new WHO classification (2008), 2 subtypes of acute erythroid leukemia are recognized based on the presence or absence of a significant myeloid (granulocytic) component: pure erythroid leukemia (PEL) erythroleukemia, erythroid/myeloid (AEL) (2, 3). Infants with AML comprise 6 to 20% of pediatric AML cases (4). PEL comprises only 3 to 14% of all acute erythroid leukemia cases and thus represents fewer than 1% of all AML cases (5, 6). Almost always shows a highly complex karyotype with multiple abnormalities, often including

losses of chromosomes 5 and/or 7, associated with a highly aggressive clinical course and poor patient outcome (5). Current regimens for treating pediatric AML consist of aggressive induction therapy based on a combination of cytarabine and anthracycline to achieve complete remission, followed by consolidation with high-dose cytarabine-based blocks of chemotherapy or stem cell transplant (1).

CASE DESCRIPTION

M.G. (second pregnancy, second birth), born in the 40th week of gestation; birth: natural; weight: 3800 grams; Apgar score: 10 points. The child was born with a flat angioma located close to the upper left eyelid and the left eyebrow. There were no complications in the neonatal period.

When the child was 4 months old, the parents noticed increasing exophthalmos of the child's left eye. The child was admitted to the University Children Hospital of Lublin, Poland. On the admission, infant was found to be in a good general condition, cardiovascularly and respiratorily stable. The physical examination revealed the following: a flat angioma size 2 x 3 cm; exophthalmos of the left eye; palpebral fissure asymmetry – wider on the left side; head circumference of more than 97 percentiles; a large and tense frontal fontanelle, size 4 x 3 cm; and hepatomegaly. The results of the laboratory tests showed upon the admission are presented in table 1. The ultrasound examination of the abdomen was performed with the following results: liver with a mildly heterogeneous echotexture and numerous hypoechogenic areas of up to 5 mm in diameter; enlarged. A CT scan of the head revealed a hyperdense tumor measuring 40 x 30 mm, located in the area above the left eye socket, surrounding the sphenoid bone (the greater wing), penetrating the left eye socket, left side of the middle cranial fossa and the left temporal area. Numerous osteolytic regions were observed in the bones of the base of skull. On the basis of the clinical picture, laboratory tests and the results of the imaging study, the presence of neuroblastoma was suspected. The diagnostics was extended to include bone marrow biopsy performed. The PAS reaction was positive in 96% of blast cells, the POX reaction in blasts was negative. Cytometry: the immunophenotype of leukemic cells CD45-/CD235a+/CD71+/CD36+/MPO- is characteristic of cells belonging to the erythroid line. The analysis of the patient's genetic material of the bone marrow with the use of FISH method gave the following results: no N-MYC amplification; no MLL rearrangement; no internal tandem duplication (ITD) within the FTL3 gene; finally, the transcripts of fusion genes AML1-ETO, CBFβ-MYH11, PML-RARA (bcr1 and bcr3) were not detected, either. Because of the diagnosis and a change in her CNS, the girl was classified as a high-risk patient and began to be treated according to the AML-BFM 2004 INTERIM treatment plan. It was decided that bone marrow transplant would be performed from a related donor (brother, compatible 10/10 loci HLA).

Tab. 1. The results of laboratory tests on the child's admission to hospital

Laboratory test		Result	The normal range
Peripheral blood morphology	RBC	2.20 x 10^6/ul	3.10-4.50
	Hemoglobin	6.5 g/dl	10.0-14.0
	Hematocrit	18.3%	28.0-42.0
	WBC	9.61 x 10^3/ul	5.00-15.00
	Neutrocytes	11.9%	10.0-35.0
	Lymphocytes	68.9%	45.0-70.0
	Monocytes	17.1%	2.0-15.0
	Eosinocytes	1.4%	0.0-7.0
	Basocytes	0.7%	0.0-2.0
	PLT	140 x 10^3/ul	150-450
Biochemistry	LDH	1118 U/L	< 764
	NSE	40.39 ug/l	< 18.3

DISCUSSION

The pure erythroleukemia is very rare cancer, especially among children. It represents fewer than 1% of all acute myeloid leukemias, each year there are diagnosed isolated cases of this disease in Poland (6). The rarity of this disease causes the fact, that in the medical literature can be found only a few descriptions of PEL in childhood. In the Memorial Sloan Kettering Cancer Center in New York City during 16 years of research, there has been reported only one case of child's PEL out of 46 analyzed erythroleukemia (7). Vineeta et al. in All India Institute of Medical Sciences, New Delhi, in the period from January 1990 to December 1998 had analyzed 297 cases of patients with acute myeloid leukemia, among whom there were 21 cases of erythroleukemia, and only 4 of them were pediatric patients (8). In another research, Deepak et al. during the 3-year follow-up had reported 5 cases of erythroleukemia which one of them was a 11-year-old boy (9). Day et al. published a report of two cases of erythroleukemia in childhood- infant and a 4-year old child, and Bubała et al. reported a case of PEL in a 7-month-old boy (10, 11).

There are various factors increasing the risk of AML: inheritance, infectious, environmental factors, chemicals and the influence of parent's lifestyle (12-15). Father's behavior, which may have an impact on the development of leukemia are smoking, exposure to pesticides and drug-taking (14, 16). A child is more likely to develop leukemia if there has been a prior miscarriage, the birth order has been higher or the child's weight at birth exceeded 4 kg (4). In the clinical case described above, the girl's parents are farmers, who had prolonged contact with pesticides in food, drinking water and air. A large birth weight of the child – 3800 g is drawing attention. As for other factors mentioned above, they were not involved in this case; however, if the correlation between the inhibitor of a DNA repair enzyme and leukemia, reported in numerous studies, had been taken into account, many other carcinogenic substances which parents had

contact with, would be identified. These substances are characterized by the activity of DNA topoisomerase inhibitor and are able to damage DNA, more specifically, to rearrange MLL gene in human's hematopoietic stem cells. They are not only in some cytostatics, but also in nature in certain foodstuffs (a component of green tea, cocoa, vegetables, fruits, caffeine, wine, chocolate, etc.) (17-20). Probably infants that were born by mothers who consume a lot of food containing mentioned above substances, have a higher risk of developing leukemia.

Diagnostics of our patient initially was based on the differentiation in the neuroblastoma due to her age and the clinical course of the disease. 90% of cases of neuroblastoma are diagnosed before the age of 5, in the average age of 22 months, its first manifestation often is exophthalmos of an eye caused by metastasis of tumor cells into the eye socket and complications incidental to involvement bone marrow (21). In addition, among the children with AML, the most frequently leukemia develops in skin, gingival and central nervous system. Myleoblastomas which is built from blasts, may occur anywhere, but usually presents in bones and soft tissues of the head, neck and they constitute less than 5% of patients who have been diagnosed with AML (1).

After the diagnosis, the child began treatment at therapeutic program AML-BFM 2004 INTERIM, accordingly she was qualified for the high-risk group. There are used in the induction of cytarabine and an anthracycline in order to achieve a complete remission, and then high-dose of cytarabine blocks or stem cell transplant after consolidation. The decision about HSCT among infants should be taken carefully. Patrick et al. recommend to consider a transplant, depending on prognostic factors – monosomy 7, mutation of FLT, and the availability of suitable donor (4). In our patient's case after 3 cycles of chemotherapy is not achieved remission, in the control biopsy, blasts constituted 14% of all cells. Thus, it was decided that HSCT would be performed, especially as the girl's brother is a fully compatible donor (10/10 loci HLA).

Summing up, PEL is very rare childhood disease. The beginning of the disease and its clinical picture may not be idiosyncratic and, despite very intensive therapy, the treatment may be very difficult and not always leading to remission.

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