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Acute myeloid leukemia mimicking an Ewing's sarcoma family tumor: A clinical case

Relevance: M6 variant of acute myeloid leukemia is extremely rare in pediatric practice. The diverse clinical manifestations of erythroid leukemia complicate the timely diagnosis of this group of diseases.

Purpose: to describe a clinical case of congenital erythroid leukemia with multiple lesions of soft tissues and the skeletal system with complications in the form of the convulsive disorder, presented as a tumor of the Ewing's sarcoma family, diagnosed at the Research Center of Pediatrics and Pediatric Surgery (Almaty, the Republic of Kazakhstan).

Results: The presented clinical case demonstrated challenges in diagnosing and treating young patients with multiple life-threatening tumor lesions. The need to develop molecular genetic studies and expand diagnostic capabilities is an integral part of treating oncohematological diseases.

Conclusion: The presented clinical case is of great interest due to its rareness. This case confirms the need to conduct all diagnostic manipulations to assess the process prevalence and choose and conduct molecular genetic studies on all examination and treatment stages.

Keywords: clinical case, acute myeloid leukemia (AML) M6, acute erythroid leukemia (AEL), children, Ewing's sarcoma.

Introduction: Acute myeloid leukemia (AML) in children is a clinically and biologically heterogeneous group of diseases. It is caused by a malignant transformation of hematopoietic stem cells or myeloid progenitor cells. Acute leukemia has specific clinical manifestations in children below one year compared to elder children [1, 2]. Acute erythroid leukemia (AEL) (Di Guglielmo disease) is the rarest myeloid leukemia that occurs in 3-4% of all AML cases. There is almost always a very complex karyotype with multiple abnormalities, often including the loss of chromosomes 5 and/or 7, associated with a very aggressive clinical course and poor patient outcome [1, 3, 4]. Given these tumors' rarity, their extramedullary manifestations are extremely rare; in most cases, they are diagnosed by the classic picture of bone marrow lesions [4].

Tumors of the Ewing's sarcoma family are composed of small round blue tumor cells that affect both bone and soft tissue. Due to the variability of the clinical manifestations of AEL, the debut of this pathology is not dissimilar to the initial clinical manifestations of Ewing's sarcoma.

Purpose: The article describes a clinical case of diagnosing congenital erythroid leukemia with multiple lesions of soft tissues and the skeletal system, with a complication in the form of the convulsive disorder, presented as a tumor of the Ewing's sarcoma family, in the conditions of the Scientific Center of Pediatrics and Pediatric Surgery.

Patient information: Patient K., a six-months' boy, was admitted to the Scientific Center of Pediatrics and Pediatric Surgery (SCPPS, Almaty, Kazakhstan) through the air ambulance in October 2020 with a preliminary diagnosis: a tumor of the Ewing's sarcoma family of soft tissues of the back, left side, convulsive disorder.

Clinical information: According to the mother, the onset of the disease occurred at the age of 4 months, when a rounded mass of elastic consistency appeared in the area of the scapula on the left, which in dynamics grew to 8.0 cm in diameter, protruded above the level of the skin. The mass was cut out at the health care facility place in the home area. However, after a month, the parents noted the appearance of new masses in the subscapularis, axillary region on the left, increase in symptoms of intoxication, loginess, weakness, and hyperthermia. The patient was transferred to the SCPPS's specialized department for further examination and treatment.

From the patient's life history: The child was born from the 1st pregnancy and childbirth in the gestational age of 39 weeks with 8b according to the Apgar score, he cried out immediately. The birth weight – 3,510 g, height – 51 cm. According to his mother, he grew and developed according to his age. The first vaccinations were made at the maternity hospital according to the immunization schedule. The mother denies having had infectious diseases, negative family history.

At the time of hospitalization, the patient's condition was assessed as very ill in terms of the underlying disease, symptoms of intoxication in the form of severe weakness, lethargy, convulsive disorder, secondary arterial hypertension, arterial tension was 122/65 mm Hg, manifestations of the anemic syndrome, bilateral polysegmental pneumonia. The skin and visible mucous membranes – pale pink, clean from rashes, without hemorrhagic rashes. No signs of bleeding. Peripheral lymph nodes not enlarged. Hyperthermia – up to febrile figures of 37.4-38.6°C. By auscultation

tion, breathing was weakened in the lower sections of the lungs, with multifarious rales, respiration rate – 44-46 per minute, StO_2 – 91-93%. On examination, masses were observed in the 6th rib area along the posterior axillary line at the lower edge of the scapula on the left; a 7 cm long scar visualized; a tissue mass of a densely elastic consistency of

2x3 cm, rising above the skin level by 0.5 cm, noted laterally, which was moderately mobile, moderately painful on palpation; the color of the skin over the mass unchanged. The liver was at the edge of the costal arch, the spleen unpalpable.

Timeline (Figure 1):

Figure 1 - Timeline of the clinical case: AML mimicking a tumor of the Ewing's sarcoma family

Diagnostics:

1. FBC: leukocytes - 10,020 thousand, erythrocytes - 3,240, hemoglobin - 75.2 g/l, hematocrit - 24.82%, MCV - 76.52 fL, MCH - 23.12 pg, MCHC - 30.22 g / L, platelets - 480 thousand, neutrophils - 21%, lymphocytes - 44%, monocytes - 9%, eosinophils - 4%, basophils - 1%, blasts - 11%, possibly tumor, myelocytes - 3, metamyelocytes - 3, stab - 4.

Myelography, immunophenotyping, and FISH examination were conducted due to the preliminary diagnosis of a tumor of Ewing's sarcoma family to exclude bone marrow metastatic lesion.

2. Myelogram: bone marrow aspirates (from 2 points) were completely infiltrated with blast cells - 90%. Blast elements were mesogenic, with a high nuclear-cytoplasmic ratio. Nuclear polymorphism with hyperchromatism, dendritic, breakthrough basophilia, and vacuolization of the cytoplasm noted. Cytochemistry: reaction to myeloperoxidase – 100% negative. PAS-reaction – 100% positive in granular form. Conclusion: Morphocytochemical picture of the bone marrow corresponded to acute lymphoblastic leukemia/Burkitt's lymphoma (L3). Acute lymphocytic leukemia (Figure 2). Myelogram suggested lymphoma with bone marrow involvement.

Figure 2 - (A) PAS-reaction, 100% positive, in granular form, (B) Blast elements – mesogenic, with a high nucleo-cytoplasmic ratio. Nuclear polymorphism, hyperchromatism with dendritic, breakthrough basophilia, and vacuolization of the cytoplasm

3. Bone marrow cells' immunophenotyping: the CD45 / SSC cytogram revealed a pathological population of cells, accounting for 27% of the total number of nucleated events. Transformed cells were negative for the general leukocyte antigen CD45, with high granularity. Differentiation clusters (CD10, 19, 22, 20, 79a, IgM, K / L, TdT, 117, 13, 33, 14, 15, 11c, 11b, MPO, 61, 42a, 41a, 38, 138, 7, 5, 3, 4, 8, 2, 1a, 34, HLA-DR, 56, GlyA) on the transformed cells not expressed. A bright expression of the myeloid antigen CD13 (94.5%) and a weaker expression of the erythroid antigen CD71 indicated AML-M6 - erythroblast variant.

4. The FISH test revealed no rearrangements of the C-Myc, EWSR, MLL, BCR/ABL genes.

5. Liquorogram: protein – 5289, glucose – 5.7, chlorides – 113, protein – 158, glucose – 1.89, chlorides – 106, leukocytes – 27 in 1 μ l. Erythrocytes – a few, blasts – 80%, lymphocytes – 15%, segmental-nuclear neutrophils – 3%, monocytes – 2%.

6. Karyotyping revealed a hyperploid 50 XY karyotype.

7. The histological blocks were reviewed from the materials received. The solid neoplastic structure was represented by small-size monomorphic cells with a high nuclear-cytoplasmic ratio; tumor elements formed no structures. IHC test showed an expression of CD13, Vimentin, INI1, weakly positive reaction with Fli1, dot-like reaction with CD99, partial positive reaction to CD45. Proliferative activity by Ki67 – 65-70%. The antibody reaction to CD34, Tdt, CD117, CD3, CD5, CD20, CD79a, CD10, CyclinD1, EMA, CK7, CK5, CK19, TLE1, MDM2, SatB2, WT1, Synaptophysin, Chromogranin, Desmin, and Myogenin – negative (Figure 3). Morphology and immunophenotype corresponded to an undifferentiated small round cell tumor NOS (not otherwise specified). A positive reaction with CD13, FLI1 did not exclude myeloid differentiation.

Figure 3 - Figure 3 – Immune histochemical (IHC) test: (A) with antibody – CD71, total staining, (B) with Fli1 antibody – positive staining with negative control, (C) with CD13 antibody – positive staining of most cells, (D) hematoxylin-eosin staining (magnification 400) – small round cell infiltrate, (E) staining with hematoxylin-eosin (magnification 200) – infiltration by neoplastic cells from monomorphic small round cells

The immunophenotyping and IHC test results evidenced AEL, while the cytology results described a lymphoma with bone marrow involvement.

8. Brain CT performed due to the convulsive disorder showed the destruction of the parietal bone on the right, the occipital bone on both sides, and the lower jaw

on the left with a soft tissue component: a volumetric intracranial formation of the occipital region sized 59x24x-28mm, with heterogeneous structure and 45-51HU density (Figure 4).

A complication of neuroleukemia was diagnosed given a high blast content cell in the liquor.

9. Chest CT revealed multiple bone-destructive changes in the clavicle and scapula on the left, the proximal metaphysis of the humerus, the ribs' anterior branches, with a soft tissue component. Subpleural foci in the posterior

segments on both sides with a density of 46-48HU, accumulating contrast agent up to 59-74HU with a thickening of the costal pleura on the right, 5mm thick, with a density of 21HU.

Figure 4 – Brain CT: (A) frontal view, (B) sagittal view, (C) sagittal view: a mass of 59x24x28 mm

Thus, a bone marrow damage revealed by the lab and instrumental tests with 90% probability spoke of tumor cells' hematopoietic nature, though immunophenotyping revealed negative total leukocyte antigen CD45.

Treatment: Chemotherapy by AML protocol for children AML-BFM 2004, ADE section was performed for health reasons after repeated consultations with foreign specialists and taking into account the extremely serious condition of the patient, complicated by convulsive disorder and high blast infiltration of the bone marrow, brain with multiple osteolytic changes in the bones, and the respiratory system changes in the form of multiple subpleural foci of the posterior segments of both lungs of a tumor nature.

The treatment effect was minimal due to the severity of the patient's condition at admission. Generalized multifocal lesions of all vital tissues, organs, and systems by tumor erythroblast cells caused death.

Discussions: AML is characterized by progressive proliferation of a blast cells clone in the bone marrow and the presence of leukemoid infiltrates. However, according to the test results, this patient was additionally diagnosed with tumor masses both in soft tissues and in the skeletal system including in the back, occipital region, lower jaw on the left

with a solid component, with the destruction of the occipital, parietal, lower jaw on the left, ribs, humerus, scapula and clavicle on the left, which in turn extremely complicates the differential diagnostics. The simultaneous presentation of a solid small round cell tumor also could not be excluded. In this patient, AEL demonstrated aggressive growth due to diffuse damage to all systems and organs.

The literature describes rare cases of simultaneous detection of acute lymphocytic leukemia and Ewing's sarcoma [4]. AML-M6 clinical manifestations vary greatly: from general weakness, pallor of the skin, and hyperthermia syndrome to more serious complications such as bleeding, hepatosplenomegaly, anemia, and thrombocytopenia. Extramedullary involvement and lytic bone lesions are extremely rare in AML-M6. Several cases presented in the literature described enlarged lymph nodes, hemangioma, bilateral ovarian involvement in a 3.5-year-old child, and proptosis [1, 5]. AEL can disguise itself as small round-cell tumor masses such as acute sarcoma of Ewing's family or neuroblastoma [6].

Our case shows the necessity to distinguish AEL from small round cell tumors. According to the literature, the erythroid origin is difficult to identify using immunophe-

notyping since erythroid markers can be negative in true AEL due to its immaturity and insufficient differentiation. The world's most famous marker of AEL included glycoporphin A. However, glycoporphin A was completely negative in some AML variant M6 cases and probably indicated late erythroid, while CD71 was a nonspecific activation marker. Platelet CD41 antigen and myeloid markers like CD13 and CD33 can sometimes be positive [6].

A thorough examination, including IHC, molecular and cytogenetic tests, is required for timely diagnosis verification [1, 3, 5]. Myeloblastomas can occur anywhere. They are present in the head's and neck's soft tissues in less than 5% of AML patients; bone lesions are practically not found in pediatric practice [1, 3].

Thus, AEL is a very rare childhood disease that can occur at any age and has extremely variable masks. Its onset and clinical presentation are not always idiosyncratic. Despite very intensive therapy, AEL treatment is challenging and does not always result in remission [5]. An extremely unfavorable prognosis for patients with AML-M6 due to a lack of standard protocol for this rare disease requires further research [6].

Conclusion: The presented clinical case is of great interest due to its rarity. It demonstrates the challenges in diagnosing and treating young patients with multiple life-threatening tumor lesions. Our clinical example proves again that AEL has an extremely aggressive course and un-

favorable prognosis. The examination findings should be considered in the differential diagnosis of small round blue cell tumors in infancy. The diagnosis required a thorough examination, including IHC, flow cytometry, molecular and cytogenetic studies.

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ТҰЖЫРЫМ

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Юинг саркомасы тұқымдасының ісігін имитациялайтын жіті миелоидты лейкоздың клиникалық жағдайы

Өзектілігі: педиатриялық практикада жіті миелоидты лейкозияның М6 нұсқасы өте сирек кездеседі. Эритробластыкалық лейкоздың клиникалық көрінісі әр түрлі, бұл осы топтың ауруларын уақтылы диагностикалауды қиындатады.

Мақсаты: Мақалада Педиатрия және балалар хирургиясы ғылыми орталығында Юинг саркомасы тұқымдасының ісігі ретінде ұсынылған конвульсиялық синдром түріндегі асқынулармен жұмсақ тіндердің және қаңқа жүйесінің көптеген зақымданумен туа біткен эритробластыкалық лейкозияны диагностикалаудың клиникалық жағдайы сипатталған.

Нәтижелері: Бұл клиникалық жағдай өмірге қауіп төндіретін ісік зақымдалуы бар осындай жас пациенттерді диагностикалау мен емдеудегі қиындықтарды көрсетеді. Молекулалық-генетикалық зерттеулерді дамыту және диагностикалық мүмкіндіктерді кеңейту қажеттілігі онкогематологиялық аурулардың ажырамас бөлігі болып табылады.

Қорытынды: ұсынылған клиникалық жағдай сирек кездесетіндігіне байланысты үлкен қызығушылық тудырады. Бұл жағдай процестің таралуын бағалау үшін барлық диагностикалық процедуралардың қажеттілігін растайды. Зерттеу мен емдеудің барлық кезеңдерінде молекулалық-генетикалық зерттеулерді анықтау және қолдану.

Түйінді сөздер: клиникалық жағдай, жіті миелоидты лейкозия М6, эритролейкемия, балалар, Юинг саркомасы.

АННОТАЦИЯ

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Актуальность: М6-вариант острого миелобластного лейкоза в детской практике встречается крайне редко. Клинические проявления эритробластного лейкоза многообразны, что затрудняет своевременную диагностику заболеваний данной группы.

Цель: описание клинического случая врожденного эритробластного лейкоза с множественными поражениями мягких тканей и костной системы, с осложнением в виде судорожного синдрома, презентующегося как опухоль семейства Саркомы Юинга, диагностированного Научного центра педиатрии и детской хирургии.

Результаты: Данный клинический случай демонстрирует трудности в диагностике, лечении таких юных пациентов с такими множественными жизнеугрожающими опухолевыми поражениями. Необходимость развития молекулярно-генетических исследований и расширения спектра диагностических возможностей является неотъемлемой частью лечения онкогематологических заболеваний.

Заключение: Представленный клинический случай вызывает огромный интерес в связи со своей редкостью возникновения. Данный случай подтверждает необходимость проведения всех диагностических манипуляций для оценки распространенности процесса, а также определения и проведения молекулярно-генетических исследований на всех этапах обследования и лечения.

Ключевые слова: клинический случай, острый миелобластный лейкоз М6, эритролейкоз, дети, Саркома Юинга.