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THE VALUE OF METHODS FOR DIAGNOSING ALVEOLAR RHABDOMYOSARCOMA: A CLINICAL CASE

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ABSTRACT

Relevance: *Rhabdomyosarcoma is extremely rare in practice. Clinical manifestations of rhabdomyosarcoma are diverse, which complicates the timely diagnosis of diseases of this group. The use of modern diagnostic methods in the complex will allow for accurate diagnosing and choosing proper treatment tactics.*

The study aimed to *evaluate the informativeness of various research methods in diagnosing alveolar rhabdomyosarcoma.*

Methods: *The article describes a clinical case of a male patient with the diagnosis: "Alveolar rhabdomyosarcoma with metastasis of the lungs, pleura, peripheral, subclavian, inguinal lymph nodes, pelvis, bone marrow" presented as a lymphoproliferative disease, diagnosed at the medical center of Marat Ospanov State Medical University (Aktobe, Kazakhstan).*

Results: *The immunohistochemistry results "The histological structure of the tumor and its immunophenotype correspond to alveolar rhabdomyosarcoma. The immunophenotype of the bone marrow sample:* ***CD45neg-CD56+CD7+CD2+CD3+CD38+CD34-*** *did not exclude a solid tumor.*

Conclusion: *This clinical case aroused great interest in our medical institution due to its rarity, thereby revealing difficulties in diagnosing a patient with multiple life-threatening tumor lesions. The clinical case again proves that alveolar rhabdomyosarcoma is characterized by an extremely aggressive course and an unfavorable prognosis. A long and accurate examination, including IHC, flow cytofluorometry, and morphological studies, was required to verify the diagnosis. These results should be considered in the differential diagnosis of neuroblastoma and rhabdomyosarcoma.*

Keywords: *clinical case, rhabdomyosarcoma, flow cytofluorimetry, immunohistochemistry.*

Introduction: Early cancer diagnostics is the key to adequate management of patients and improvement and outcome of the disease. Soft tissue sarcoma accounts for about 7% of cancers in children and 1% in adults [1]. Advances in molecular biology and genetics have also made it possible to better understand the pathogenesis of rhabdomyosarcoma. These approaches continue to provide a platform to improve diagnostics, disease classification, patient risk stratification, and management strategies. Although rare, rhabdomyosarcoma is a relatively common form of childhood cancer and is the most common soft tissue sarcoma in children. The overall incidence of rhabdomyosarcoma is approximately 4.5 patients per million people <20 years of age. In the United States, rhabdomyosarcoma is approximately 350 new cases per year. Based on data from the Surveillance, Epidemiology, and End Results (SEER) program, rhabdomyosarcoma's incidence varies by age and histology [2]. This article describes the immunophenotyping of the bone marrow by flow cytometry with the verification of the rhabdomyosarcoma diagnosis by immunohistochemistry (IHC).

Despite the advances in understanding this disease's biology, few clinical studies are specific to rhabdomyosarcoma. Therefore, several important questions remain unanswered regarding how and what diagnostic method to use to verify the rhabdomyosarcoma diagnosis.

This study aimed to evaluate the informativeness of various research methods in diagnosing alveolar rhabdomyosarcoma.

Materials and methods: The article presents a description of a clinical case of alveolar rhabdomyosarcoma with metastasis of the lungs, pleura, peripheral, subclavian, inguinal lymph nodes, small pelvis, bone marrow, presented as a lymphoproliferative disease, diagnosed at the Medical Center of West Kazakhstan Marat Ospanov Medical University (Aktobe, Kazakhstan).

Clinical case:

Patient information: Patient O., born in 2003, was admitted to the Department of Hematology of the Medical Center of West Kazakhstan Marat Ospanov Medical University with the suspected lymphoproliferative disease, acute leukemia.

Clinical data: Based on the anamnesis vitae, it is known that the debut of the disease took place in August 2022, after hypothermia of contact with cold water. The patient addressed a physician at the place of residence and was administered treatment but could not name the drugs or provide an extract from medical records. After treatment, there was no improvement, and myalgia increased, as well

as weakness in the upper limbs joined. Then a rheumatologist examined the patient, and a preliminary diagnosis was made: "Paraneoplastic inflammatory myopathy with a high degree of activity, damage to the reticuloendothelial system (lymphadenopathy of the para-aortic and external inguinal and cervical lymph nodes), retroperitoneal lymphoma, hepatosplenomegaly. Exclude blood disease (lymphoproliferative disease, leukemia)."

Anamnesis vitae: The patient grew and developed according to age and gender.

Objective data: The general condition of moderate severity due to the activity of the autoimmune process. Peripheral lymph nodes: an enlarged anterior cervical lymph node on the left, 3.5x3.0 cm in size, painless. Palpation: Pain in the inguinal region, enlarged lymph nodes on both sides. Body temperature: 36.8-37.0°C. There is no visible pathology from the side of the osteoarticular system, but the patient moves with difficulty due to severe myalgia. There are no swollen joints. Movement in the peripheral joints in complete, moderate pain in the knee joints. Palpation: pain in the lower and upper extremities' muscles on both sides.

Diagnostics:

Complete blood count, September 2022: leukocytes – 12.6x10^9/L, hemoglobin – 65 g/L, platelets -31x10^9/L,

Biochemical blood test, September 2022: creatinine – 401 μmol/L, urea – 18.2 mmol/L, ALT – 9.4 U/L, AST – 38.4 U/L, total bilirubin – 6.8 μmol/L, total protein – 48 g/L.

Myelography, bone marrow immunophenotyping (IPT), and lymph node IHC were performed to exclude hemoblastosis, given the preliminary diagnosis of lymphoproliferative disease and acute leukemia.

Myelogram, September (2022). Bone marrow is cellular, predominantly represented by cells of the lymphoid lineage. The remaining hematopoietic lineage is depressed. Megakaryocytes were not found. Blast cells in the blood (bone marrow) – 60.5%. Conclusion: Acute lymphoblastic leukemia (ALL) (Figure 1).

The rhabdomyosarcoma cells were mistaken for blast cells, and ALL was diagnosed accordingly.

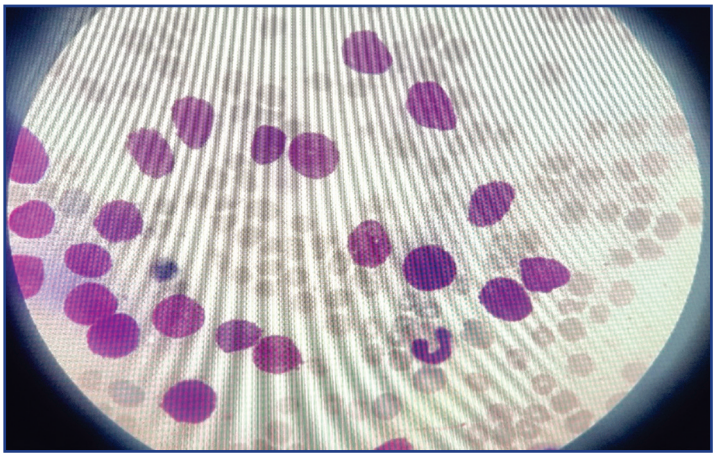

Figure 1 – Myelogram. Picture of acute lymphoblastic leukemia in patient O., 20 years old
(Olympus microscope, Olympus Corporation, Japan)

To identify the immunophenotype, we used the following:

Screening (verification) panel: CD45 KrO/ CD3 PB/ CD2 FITC /CD56 PE /CD19 ECD/ CD5 PC5.5/ CD34 PC7/ CD8 APC/ CD38 APC-A700.

All monoclonal antibodies available at the laboratory were added to the panel to clarify the immunophenotype of the CD45 neg CD56+ population and exclude neoplasia from mature lymphocytes.

IPT of bone marrow cells, September 2022: CD45neg CD56+, the resulting immunophenotype CD45neg-CD56+CD7+CD2+CD3+CD38+CD34- did not exclude a solid tumor (Figure 2).

The bone marrow trepanobiopsy histopathological preparations were sent for review at the UNIM reference laboratory (Moscow, RF). The conclusion was, "The morphological picture in the bone marrow and the identified immunophenotype characterize the metastasis of alveolar rhabdomyosarcoma (cranial-nasopharyngeal localization?). Data in favor of a tumor of a hematolymphoid nature, including acute leukemia, were not found".

The histological preparations were revised at the UNIM reference laboratory. The material from the lymph node from the inguinal region underwent an IHC study at the pathoanatomical laboratory of the Medical Center of West Kazakhstan Marat Ospanov Medical University. The conclusion was, "The histological structure of the tumor and its immunophenotype are consistent with alveolar rhabdomyosarcoma. ICD-10:C80.0 ICD-O: 8920/3; Alveolar rhabdomyosarcoma; ALVEOLAR RHABDOMYOSARCOMA; C809; UNKNOWN; considering the above data, a malignant process of a hematopoietic nature was excluded" (Figures 3, 4).

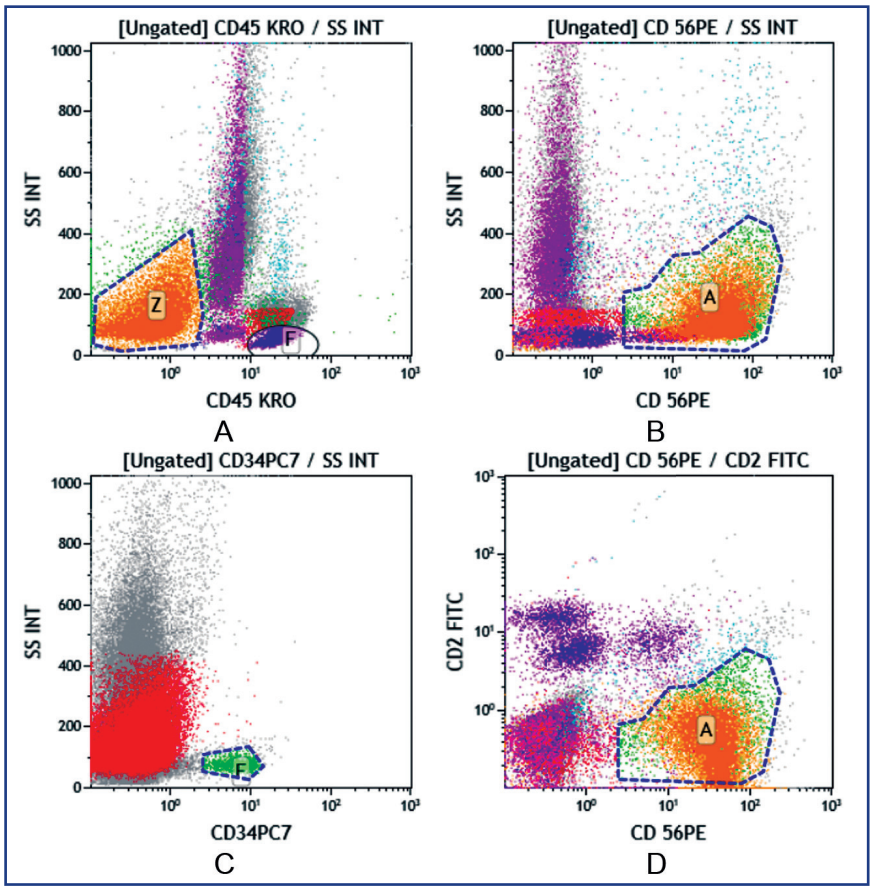

Figure 2 - Histogram of patient O., 20 years old, with a diagnosis of alveolar rhabdomyosarcoma:
A – CD45neg-, B – CD56+, C – CD34-, D – CD56+CD2+ (performed on Navios 10/3 flow cytometer, Beckman Coulter, USA)

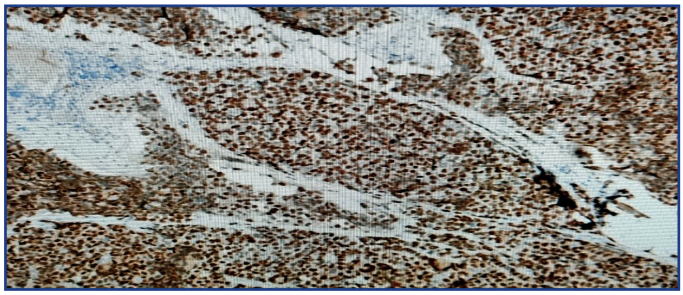

Figure 3 – Alveolar structures of the lymph node in alveolar rhabdomyosarcoma (analysis was performed on a digital slice scanner MAGSCANER KF-PRO-120, China)

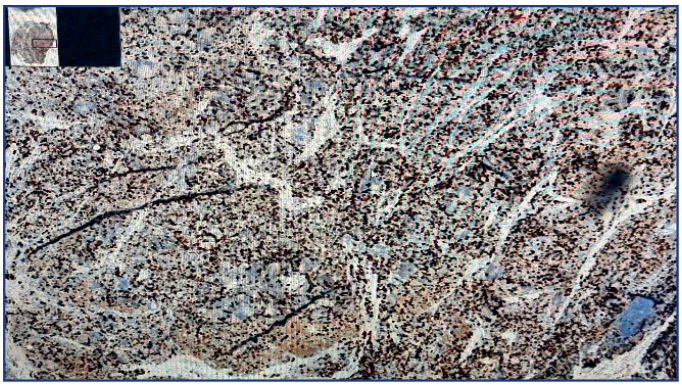

Figure 4 – CD56 (dot-like staining in part of the cells of the lymph node) in alveolar rhabdomyosarcoma (analysis was performed on a digital slice scanner MAGSCANER KF-PRO-120, China)

Treatment: The treatment was symptomatic and included blood transfusion therapy, sodium chloride, torasemide, metronidazole, levofloxacin, Mycosan, fluconazole orally, analgesic mixture, ketoprofen, tramadol, ursodeoxycholic acid, aminocaproic acid, etamsylate, tranexamic acid, metoclopramide, and furosemide. Against the background of symptomatic treatment, the effect was minimal. It was due to the severity of the patient's condition upon admission and generalized damage by tumor cells to all vital tissues, organs, and systems which led to death.

Figure 5 shows the timeline of this clinical case.

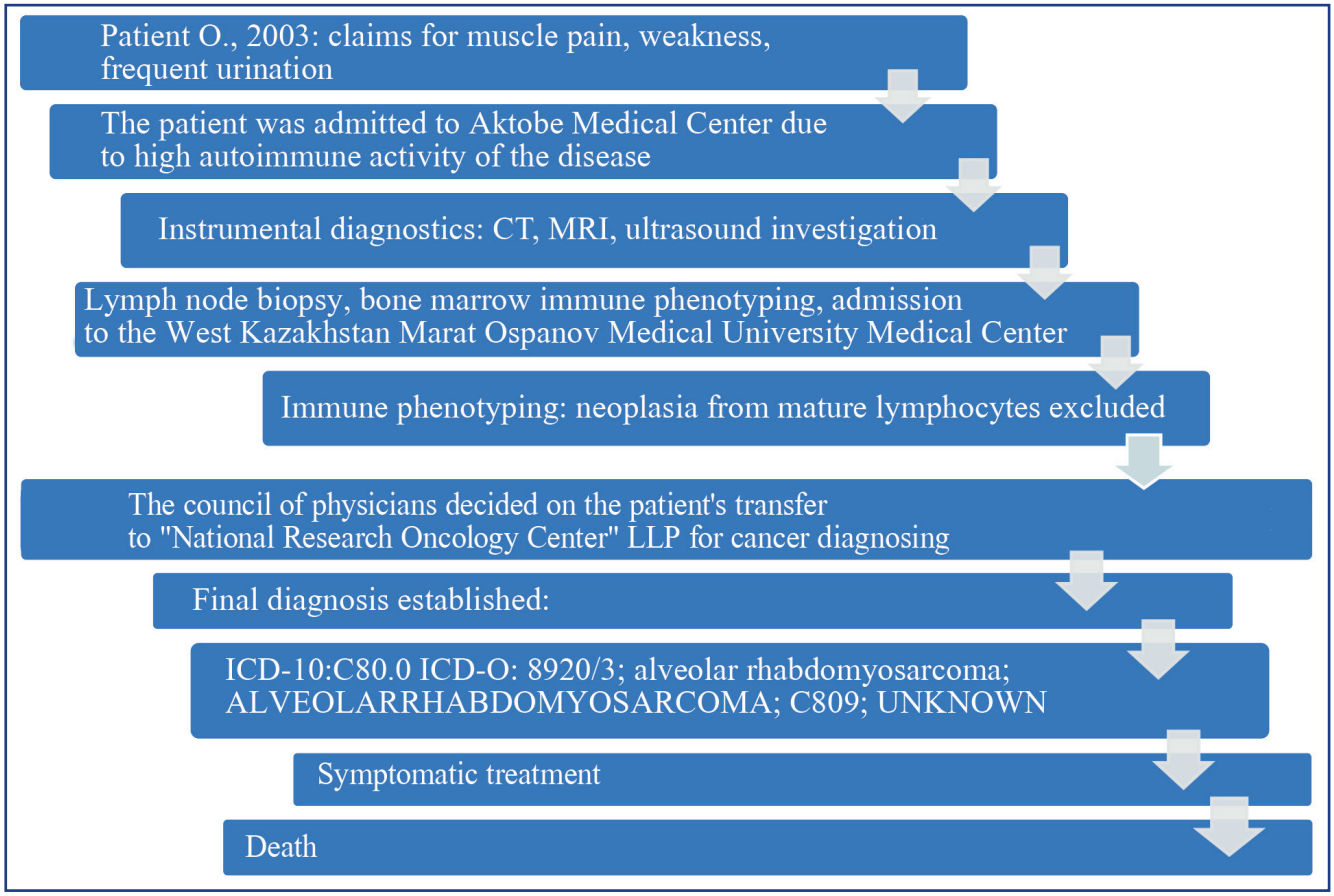

Figure 5 – Timeline of the clinical case of alveolar rhabdomyosarcoma in patient O., 20 years

Discussion: Patients with rhabdomyosarcoma have a poor prognosis. Detecting rhabdomyosarcoma tumor cells in the bone marrow is essential for clinical staging and risk assessment. In the presented clinical case, the histological and IHC opinion was made after comparing with the conclusion of the reference laboratory in Moscow. However, according to the conclusion of the myelogram, ALL was diagnosed, which made differential diagnosis extremely difficult. Simultaneous manifestation of a solid tumor was also not excluded.

Currently, leukemia/lymphoma and other hematopoietic malignancies' diagnosing relies mainly on immunophenotyping results [1, 2], in addition to cytomorphological/histopathological and molecular data [3, 4]. In contrast, the definitive diagnosis of non-hematopoietic (solid) tumors is based on histopathological examination of tissue samples followed by IHC staining for relatively broad panels of markers and further molecular studies in specific diagnostic tumor subtypes [5]. This approach, used for diagnostic screening of solid tumors in general, is time-consuming, resulting in a delay in the final diagnosis in a significant proportion of patients [1-4].

Multiparametric flow cytometry (MFC) is a key method for the immunophenotypic diagnosis of acute leukemia and chronic lymphoproliferative diseases. MFC can simultaneously assess several tumor cells [6]. Nevertheless, MFC is not part of routine diagnostics of solid tumors [4-6]. It is mainly due to the need to obtain (fresh) suspensions of individual cells and that, unlike IHC, MFC does not provide information on the structure and location of tumor cells in tissues [7]. Therefore, early studies on the use of MFC in solid tumors mainly focused on detecting disseminated disease in the bone marrow [8, 9]. Those studies revealed different antigen expression profiles among metastatic non-hematopoietic bone marrow tumor cells. Some profiles are closely associated (or even specific) with some diagnostic subtypes of solid tumors [10]. For example, the expression of $CD90^{+}$, $CD56^{+}$, and $CD57^{-/+}$ in the absence of CD45 is most often observed in rhabdomyosarcoma tumor cells [11].

A single combination of antibodies has been developed and validated for rapid and accurate diagnostic screening, targeting, and classification of solid tumors in children and adolescents. In addition, monoclonal antibodies can be used as an additional tool to conventional histopathology for diagnosing and classifying childhood cancer [12].

Further multicentre validation of the Solid Tumor Orientation Tube (STOT) classification of solid tumors is ongoing in the EuroFlow consortium, with particular attention to the detection of blast cells and other rare non-hematopoietic tumor types [9]. This clinical case demonstrates the difficulties in diagnosing patients with multiple life-threatening tumor lesions. The need to develop molecular genetic studies and expand the range of diagnostic capabilities of flow cytometry is an integral part of treating oncohematological diseases [13, 14].

Conclusion: This clinical case aroused great interest among the specialists of our medical institution due to its rarity. It revealed difficulties in diagnosing an early-age patient with multiple life-threatening tumor lesions. An extremely aggressive course and an unfavorable prognosis of alveolar rhabdomyosarcoma have been proven again. Verifying this diagnosis required a long and comprehensive examination, including IHC, flow cytometry, and morphological studies. The results should be considered in the differential diagnostics of neuroblastoma and rhabdomyosarcoma.

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АҢДАТПА

АЛЬВЕОЛЯРЛЫ РАБДОМИОСАРКОМАНЫ ДИАГНОСТИКАЛАУ ӘДІСТЕРІНІҢ МАҢЫЗЫ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Рабдомиосаркома іс жүзінде өте сирек кездеседі. Рабдомиосаркоманың клиникалық көріністері әртүрлі, бұл осы топтың ауруларын уақтылы диагностикалауды қиындатады. Кешенде диагностиканың заманауи әдістерін қолдану дәл диагнозға және одан әрі емдеу тактикасына қол жеткізуге мүмкіндік береді.*

Зерттеудің мақсаты *– альвеолярлы рабдомиосаркоманы диагностикалаудағы әртүрлі зерттеу әдістерінің ақпараттылығын бағалау.*

Әдістері: *мақалада Марат Оспанов атындағы БҚМУ медициналық орталығында (Ақтөбе, Қазақстан) диагноз қойылған лимфопролиферативті ауру ретінде ұсынылатын "өкпе, плевра, перифериялық, субклавиялық, шап лимфа түйіндері, кіші жамбас, сүйек кемігінің метастазы бар альвеолярлы рабдомиосаркома" диагнозы қойылған Ер пациенттің клиникалық жағдайы сипатталған.*

Нәтижелері: *Иммуногистохимияға сәйкес: "ісіктің гистологиялық құрылымы және оның иммунофенотипі альвеолярлы рабдомиосаркомаға сәйкес келеді.*

Сүйек кемігі үлгісінің иммунофенотипі: ***Cd45neg-CD56+CD7+CD2+CD3+CD38+CD34-****қатты ісікті жоққа шығармады.*

Қорытынды: *Бұл клиникалық жағдай біздің медициналық мекемеде сирек кездесетіндігіне байланысты үлкен қызығушылық тудырды және осылайша көптеген өмірге қауіп төндіретін ісік зақымдануы бар науқасты диагностикалаудағы қиындықтарды анықтады. Клиникалық жағдай альвеолярлы рабдомиосаркоманың өте агрессивті ағыммен және қолайсыз болжаммен сипатталатынын тағы бір рет дәлелдейді. Диагнозды тексеру үшін IGH, ағынды цитофлуориметрия және морфологиялық зерттеулерді қоса, ұзақ және дәл тексеру қажет болды. Алынған нәтижелер нейробластома мен рабдомиосаркоманың дифференциалды диагностикасында ескерілуі керек.*

Түйінді сөздер: *клиникалық жағдай, рабдомиосаркома, ағынды цитофлуориметрия, иммуногистохимия.*

АННОТАЦИЯ

ЦЕННОСТЬ МЕТОДОВ ДИАГНОСТИКИ АЛЬВЕОЛЯРНОЙ РАБДОМИОСАРКОМЫ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Рабдомиосаркома на практике встречается крайне редко. Клинические проявления рабдомиосаркомы многообразны, что затрудняет своевременную диагностику заболеваний данной группы. Использование современных методов диагностики в комплексе позволит добиться постановки точного диагноза и выбора корректной тактики лечения.*

Цель исследования *– оценить информативность различных методов исследования в диагностике альвеолярной рабдомиосаркомы.*

Методы: *В статье описан клинический случай пациента мужского пола с альвеолярной рабдомиосаркомой с метастазом легких, плевры, периферических, подключичных, паховых лимфоузлов, малого таза, костного мозга, презентируемой как лимфопролиферативное заболевание и диагностированной в медицинском центре ЗКМУ имени Марата Оспанова (Актобе, Казахстан).*

Результаты: *По данным иммуногистохимии: «Гистологическая структура опухоли и ее иммунофенотип соответствуют альвеолярной рабдомиосаркоме.*

Иммунофенотип образца костного мозга: ***CD45neg-CD56+CD7+CD2+CD3+CD38+CD34-*** *не исключал солидную опухоль.*

Заключение: *Данный клинический случай вызвал в нашем медицинском учреждении огромный интерес в связи со своей редкостью и тем самым выявил трудности в диагностике пациента с множественным жизнеугрожающим опухолевым поражением. Клинический случай еще раз доказывает, что альвеолярная рабдомиосаркома характеризуется крайне агрессивным течением и неблагоприятным прогнозом. Для верификации диагноза требовалось длительное и точное обследование, включая ИГХ, проточную цитофлуориметрию и морфологические исследования. Полученные результаты необходимо учитывать при дифференциальной диагностике нейробластомы и рабдомиосаркомы в подростковом возрасте.*

Ключевые слова: *клинический случай, рабдомиосаркома, проточная цитофлуориметрия, иммуногистохимия (ИГХ).*

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