

## **ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) IN CHILDREN: CLINICAL DIAGNOSTIC CRITERIA**

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### **ABSTRACT**

The aim of the study is to assess the distribution of various options, identify risk groups and determine the most significant clinical and diagnostic criteria for Anaplastic large cell lymphoma (ALCL) in children in Uzbekistan.

The object of our study was statistics on all cases of NHL in children aged 2-17 years in the Republic of Uzbekistan according to information provided by oncological institutions, according to the accepted form of accounting and reporting documentation of the Ministry of Health of the Republic of Uzbekistan - 7SSV for 2011-2015. (for 5 years). Case studies of non-Hodgkin lymphomas (NHL) are grouped according to the International Classification of Diseases (ICD-10). An in-depth study of the incidence of NHL among the children of the Republic of Uzbekistan was conducted. The results of the study showed that the most characteristic localization for ACCL is damage to the soft tissues (58.3%) and peripheral lymph nodes (1 / y) (50.0%). Also characteristic is the presence of tumor conglomerates and damage to the lung tissue, skin and bones, which can be considered a prognostic criterion.

**KEY WORDS:** anaplastic large cell lymphoma (ALCL), children, Non-Hodgkin lymphomas (NHL), lymph nodes (l/n), tumor conglomerates

### **INTRODUCTION**

One of the well-known and insufficiently studied variants of non-Hodgkin lymphomas is anaplastic large cell lymphoma [9; 5, 199-207]. Anaplastic large cell lymphoma was first described just over a quarter century ago. Over the past period, the morphohistological picture and its cytogenetic features were studied and described [1, p. 3-9]. naplastic large cell lymphoma is characterized by a variety of disease options that differ in clinical, morphological, immunological, cytogenetic, and molecular biological characteristics [5, p. 199-207].

The clinical picture of anaplastic large cell lymphoma is diverse and is characterized by the presence of nodal and extranodal lesions of organs and systems [1, p. 3-9]. In adults, anaplastic large cell lymphoma makes up about 8% of all non-Hodgkin lymphomas, while in childhood this indicator is about 15% [1, p. 3-9]. Despite the achievements of modern oncology, the problem of complications and relapses of anaplastic large cell lymphoma, and in particular, their timely diagnosis, prognosis, and treatment, remains unresolved. According to the authors, relapse of the disease can reach from 10% to 40% [12, p. 31-41; 15, c. 153-160]. The success of treatment in these cases may depend on the identified initial stage of the disease, prognostic signs and the chosen method of induction therapy [21, p. 18-23]. As a rule, relapses of anaplastic large cell lymphoma are divided into early ones that

develop after a short remission, lasting no more than 12 months of remission and late ones that occur after remission lasting more than a year. Moreover, according to Ptushkina V.V. 2007, the results of treatment of the first category of patients with early relapses are significantly less effective than after late relapses [14, p. 18-23]. At the same time, one should take into account the fact that each subsequent relapse will reduce the patient's chances of long-term survival. At the same time, repeated chemotherapy, including repeated antitumor therapy, can lead to the development of complications that significantly worsen the quality and duration of life [14, p. 18-23].

According to the revised classification of the World Health Organization (WHO) of hematopoietic and lymphoid tissue tumors - anaplastic large-cell lymphoma is represented by classical, lymphohistiocytic, small-cell and similar Hodgkin's lymphoma histological variants [24a, p. 59-65; 4, p. 43-49]. Of these, children usually have the first three options.

One of the important criteria for non-Hodgkin lymphomas and anaplastic large cell lymphomas, including the measurement of lactate dehydrogenase levels available for research in a clinical laboratory. According to the recommendations at 3, 6, 12 and 24 months of observation, it is recommended to conduct a detailed blood test with the obligatory determination of the level of lactate dehydrogenase. [6, p. 50-55].

About 100 genetically determined syndromes are known that predispose to the development of neoplastic processes in childhood [6, p. 455-462]. Despite a fairly long history of research in the field of a comprehensive study of anaplastic large cell lymphoma in pediatrics, the results of the treatment leave much to be desired. To date, it has not been possible to achieve sufficiently high therapy results for this nosology. There is a need to continue research and identify the most significant prognostic and diagnostic criteria. It is also necessary to determine the modern and most optimal treatment strategy for children with anaplastic large cell lymphoma [5, p. 199-207]

Objective is to assess the distribution of various options, identify risk groups and determine the most significant clinical and diagnostic criteria for anaplastic large cell lymphoma in children in Uzbekistan.

## MATERIALS AND METHODS

The object of our study was the statistical data on all cases of non-Hodgkin lymphomas in children aged 2-17 years in the Republic of Uzbekistan according to information provided by oncological institutions, according to the accepted form of accounting and reporting documentation of the Ministry of Health of the Republic of Uzbekistan - 7SSV for 2011-2015. (5 years). An assessment of a comprehensive examination based on 126 selected case histories of patients with a verified diagnosis of Nekhodzhkinsky lymphomas of children who were treated in the Department of Pediatric Oncology of the Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology (RSNMTSOiR) and the Tashkent city branch of RSNMTSOiR for the period from 2011-2015 was evaluated.

The studied cases of Non-Hodgkin lymphomas are grouped according to the International Classification of Diseases (ICD-10) [8, p. 81-85]. An in-depth study of the incidence of Non-Hodgkin lymphomas among the children of the Republic of Uzbekistan was conducted.

All patients underwent clinical (medical history, general examination), and laboratory (general and biochemical blood tests, morphological and cytochemical studies of bone marrow (myelograms), morphological and immunological studies of tumor tissue were performed to clarify the diagnosis and

differential diagnosis. [20, p. 539-540; 25, p. 249-256]. The clinical stage of the disease was determined on the basis of chest x-ray, CT, ultrasound of the abdominal cavity and extraperitoneal zones if there was a lesion. necessary, bone structures were scanned.

Also, the content of one of the significant prognostic factors of Non-Hodgkin lymphomas in general and anaplastic large cell lymphoma in particular, the concentration of lactate dehydrogenase, was studied in blood patients [10, p. 455-470]. An increase in the concentration of lactate dehydrogenase above normal corresponds to 2-3 points and may refer the patient to a low or medium prognostic group in accordance with Ann Arbor classification [6, P. 50-55]. The content of lactate dehydrogenase in the blood was determined by the method of biochemical analysis using ready-made test systems HUMAN (Human GMBH, Germany) according to the instructions. Measurements were made on a Mindray BA88A semi-automatic biochemical analyzer.

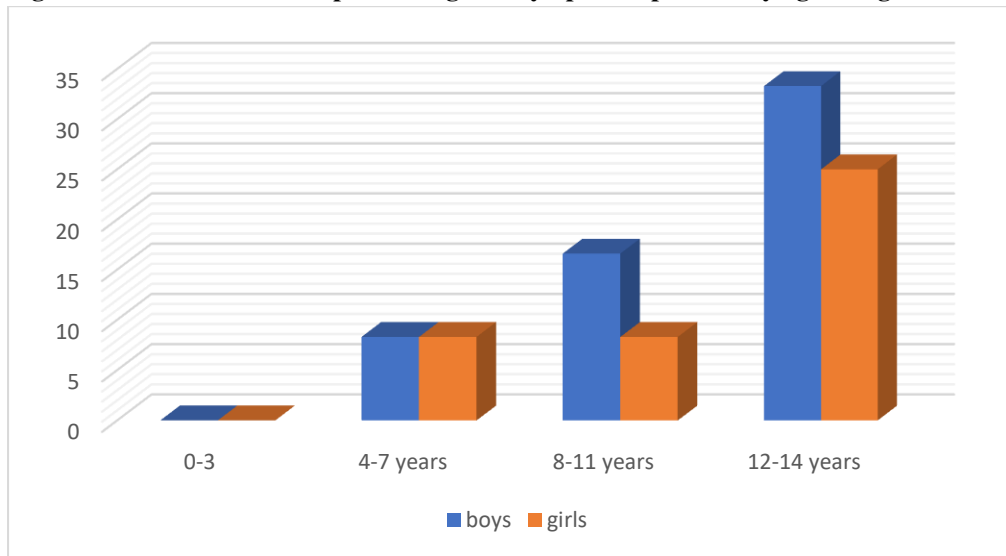
Statistical analysis was performed using Microsoft Office 2010. Evaluation of the parametric data was carried out by comparing the average values using the Student and Mann-Whitney test. Nonparametric data were compared by constructing the contingency tables of characters according to the Pearson chi-square ( $\chi^2$ ) criterion. The difference between the groups was considered statistically significant at  $p < 0.05$ .

## RESULTS AND DISCUSSION

Analysis of the data obtained retrospectively from case histories of 12 patients treated in the clinic of the RSPMSOR in the chemotherapy department with a diagnosis of anaplastic large cell lymphoma, the average age was 9.8 years (3-14 years), the ratio between boys was 7 (58.3%) ) and girls - 5 (41.6%) was 1.4: 1 (Fig. 1). At the same time, according to Levashov A.S. et al. (2016) anaplastic large cell lymphoma is more common among males, which is consistent with our data [5, p. 199-207].

As can be seen from Figure 1, the ratio of boys and girls was almost equal, with the greatest number of patients being aged 12-14 years old (OR = 6.042; 95% CI (CI): 2.264-16.123), of which mostly boys were 33, 3%, and girls - 25.0% (OR = 0.888; 95% CI (CI): 0.395-1994), no patients were observed between the ages of 0-3.

**Figure 1. Distribution of anaplastic large cell lymphoma patients by age and gender**



An analysis of clinical manifestations showed that in patients in the study group intoxication symptoms (weakness, lethargy, sweating, weight loss > 10%, fever) were observed in 9 (75.0%) patients. From the anamnesis it was found out that the first sign that parents paid attention to was an increase in l / y (58.3%), skin manifestations in the form of spots, plaques were detected in 4 (33.3%) children [18, p. 667–668; 27, p. 51-51], a pain symptom in the bones - did not occur frequently in 2 (16.6%) patients. An accidental finding during ultrasound and X-ray studies revealed tumor formations in 3 (25.0%) patients.

An analysis of the data showed that the prevailing lesion of peripheral lymph nodes (l / y) and

soft tissues is characteristic of the clinical picture of anaplastic large cell lymphoma - 58.3% [19, p. 173–177] and 50.0%, respectively, compared with rare cases of damage: spleen, lungs, skin - 33.3% [27, p. 51-51], bone tissue, l / y and abdominal cavity - 25.0%, mediastinum - 16.6% [21a, p. 18-23]. Isolated cases of damage were characteristic of the pancreas, stomach, liver, testicle [28, p. 165–166], central nervous system [6, p. 50-55] (table. 1). No bone marrow lesions were detected in any patient. With damage to the central nervous system (CNS), the clinic was characterized by changes in neurological symptoms for the brain [3, p. 1-44; 11, c. 60-68].

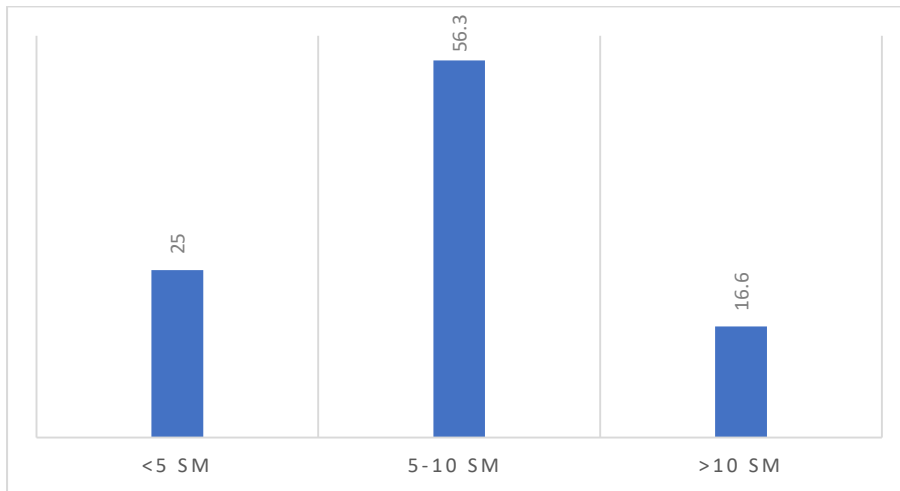
**Table 1. Localization of lesions of l / n and organs in anaplastic large cell lymphoma**

Lesion localization	Число больных, n=12	
	Abs.	%
Soft tissues	7	58,3
Peripheral L / N	6	50,0
Skin	4	33,3
L / n of retroperitoneal space	5	41,7
Bones	3	25,0
L / n of abdominal cavity	3	25,0
Mediastinum	2	16,7
Spleen	1	8,3
Lungs	1	8,3

Pancreas, stomach, liver, small intestine, testicle, central nervous system	Isolated cases
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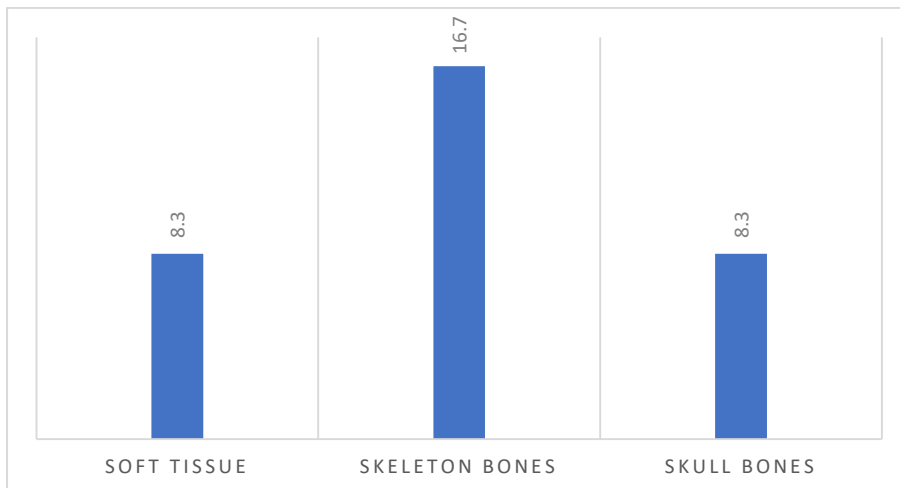
The data in Figure 2 suggest that anaplastic large cell lymphoma is not characterized by the formation of large tumor conglomerates, since in most patients (56.3%) the tumor size was 5-10 cm.

**Figure 2. Distribution of patients depending on the size of tumor conglomerates**



According to localization, it can be noted that primary extranodal lesions with anaplastic large cell lymphoma were found in 33.3%, without particular gender differences (Fig. 3).

**Figure 3. Extranodal lesions in children with anaplastic large cell lymphoma**



In the group of studied patients, the lesion of two or more anatomical areas was most often observed in 9 (75.1%) patients, who were mostly extranodal and met with the same frequency in both boys and girls, which is consistent with data from other authors [17, p. 1-4]. According to literature in clinical practice, in most children, lymph nodes are found to be affected. Extranodal localization is represented by a predominant lesion of the skin, soft tissues, bone tissue, lungs, liver and spleen [5, p. 199-207]. So according to L.G. Gorenkova et al. (2012) a characteristic feature of

anaplastic large cell lymphoma is a frequent lesion of extranodal areas and a higher incidence in childhood [2, p. 43-43; 7, c. 57-62]. In general, the results obtained for the detection of skin lesions do not contradict the literature. As you know, the primary skin form is described in isolated cases [16, p. 119-128].

According to ultrasound and CT, most often the tumors had sizes from 5 to 10 cm — 56.3%, more than 10 cm — at 16.6%, up to 5 cm — at 25.0% (Fig. 3).

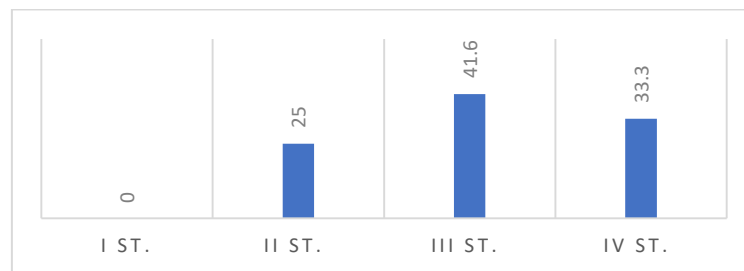
Lesions of skeleton bones were presented in the form of specific infiltrates of bone tissue, lower leg, shoulder, hip and ribs [21, p. 599-605]. In one patient, there was a lesion of the bones of the skull, which was characterized by a turbulent, aggressive and rapid process with damage to the brain, i.e. with skeletal bone damage, there is a rapid spread of the process to surrounding tissues and internal organs [22, p. 176-176]. The results obtained are consistent with the data of Kounami, S., Yoshikawa, N. (2012) [23, p. 597-598].

As you know, the histological structure of the tumor is closely interconnected with its localization. According to Levashov et al. (2016) and Lamant L. et al. (2011) in childhood, as a rule, establish a classic version of anaplastic large cell lymphoma. At the same time, small-cell and lymphohistiocytic variants are established in 32% of cases, which are significantly more often - in 31% of cases ( $p < 0.001$ ) associated with skin damage and in 55% of cases ( $p = 0.04$ ) with mediastinal damage [5, p. 199-207; 24, 4669-4676].

Analysis of the obtained clinical data showed that the largest number of patients had a generalized III-IV stage of anaplastic large cell lymphoma, with III-st. there were 41.6% of patients, and with IV- Art. - 33.3%; patients in I-Art. It was not detected, with II-Art. found in 25.0% (Fig. 4). Given the aggressiveness of anaplastic large cell lymphoma, the clinical manifestations of the disease have a “lightning fast” form with the rapid spread and generalization of the process, which explains the large percentage of patients in stages III-IV.

When studying the level of lactate dehydrogenase in the blood serum in order to determine the biological activity of lymphoma, lactate dehydrogenase levels of more than 1000 U / L were observed in only 1 (8.3%) patient (Fig. 5). At the same time, according to G. Tumyan. (2015) high levels of lactate dehydrogenase are among the diagnostic criteria for non-Hodgkin lymphomas [10, p. 455-470].

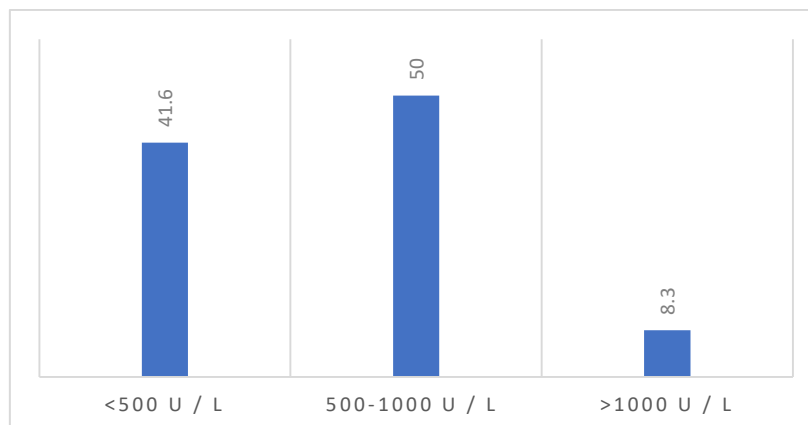
**Figure 4. Distribution of patients with anaplastic large cell lymphoma according to the stages of the process**



The largest percentage of patients had a lactate dehydrogenase level of 500-1000 U / L, which indicates the stability of this marker in patients with anaplastic large cell lymphoma, and the level of 500-1000 U / L corresponds to the reference value for this pathology.

According to the clinical characteristics of the disease, damage to the lung tissue, skin and bones is important for determining prognostic risk groups for anaplastic large cell lymphoma. Given the small number of these lesions among the patients included in our study, 66.6% had a 2 prognostic risk group (Fig. 5).

**Figure 5. Changes in lactate dehydrogenase activity levels in patients with anaplastic large cell lymphoma**

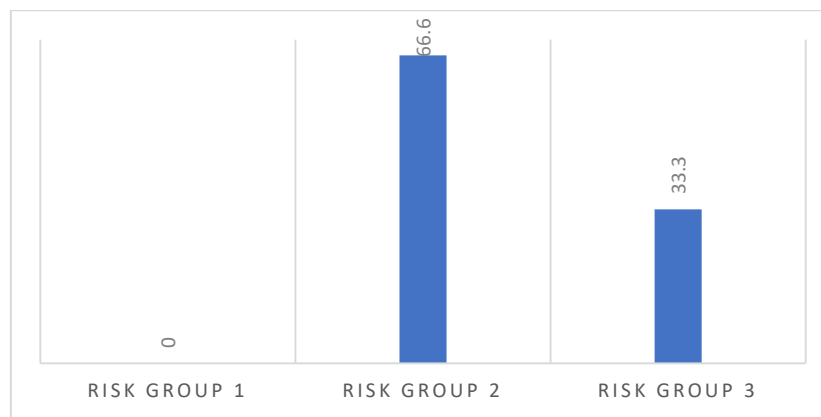


In this group of patients, the majority determined tumor conglomerates of more than 5 cm, which apparently explains the aggressive type of neoplasms, while in patients with T-LBL, tumors of more than 5 cm were 56.5%, and B-LBL was 50.0% . This is also confirmed by high (more than 500 U / L) indicators of serum lactate dehydrogenase, which reflect the biological activity and malignancy of the T-LBL tumor - 52.1%, and B-LBL - 44.4%.

The stages of the process with T-LBL show a predominance of stage III - 39.1%, and B-LBL - stage IV of the process is 50.0%.

To carry out the correct diagnosis of non-Hodgkin lymphomas and their types, a thorough analysis of clinical data is necessary to evaluate the damage to organs and systems (localization of various groups of lymph nodes, bone marrow, bone, and other organs), indicators of the biological activity of the tumor (serum lactate dehydrogenase levels) and process steps.

**Figure 6. Distribution of patients with anaplastic large cell lymphoma depending from prognostic risk groups**



Anaplastic large cell lymphoma has certain cytogenetic, immunological and clinical morphological features that are different from T and B lymphomas, the frequency of occurrence by sex is almost the same, most common in 12-14 years old, both among boys and girls. The close connection with the pathogenesis of Non-Hodgkin lymphomas in general and anaplastic large cell lymphomas in particular, and the close relationship with the immune system of lymphoid tissue largely determines both the clinic of the disease and its association with other diseases [26 p. 17-17; 27, c. 51-51; 29. c. 400-400].

In this variant of Non-Hodgkin’s lymphomas, according to clinical signs, soft tissue lesions (58.3%), peripheral l / y (50.0%), l / y retroperitoneal space (41.7%), primary-extranodal localization of bone lesions are most marked skeleton (16.7%), less often soft tissue and skull (8.3%). The largest number of patients is noted in the III-IV stages of the disease (41.6% and 33.3%, respectively), since this pathology is characterized by an aggressive and malignant course with a rapid spread of the process to nearby organs and tissues. Most often, tumor conglomerates up to 10 cm were found in patients (81.6%). In general, the data obtained are consistent with the data of researchers. So,

according to Valiev T.T. (2012) the clinical picture of anaplastic large cell lymphoma is characterized by heterogeneity and variability of clinical manifestations [1, p. 3-9]

To assess the biological activity of the tumor substrate, the activity of lactate dehydrogenase in blood serum was also studied, which was characterized by its content from 500 to 1000 U / L even with the prevalence of the process (50.0%), which indicates the absence of informational content of this tissue marker. Along with the stage of the disease, the presence / absence of damage to the lungs, skin, and bones was used to determine the prognostic risk group, which for anaplastic large cell lymphoma in the majority of patients at the time of diagnosis was second (66.6%). According to Fedorova A.S. et al. (2014) if the occurrence of the systemic form of anaplastic large cell lymphoma among children practically does not differ from the state of the immune system, then skin forms were more often detected in children with primary immunodeficiency [13, p. 23-33].

**CONCLUSION**

The most characteristic localization for anaplastic large cell lymphoma is damage to the soft

tissues (58.3%) and peripheral lymph nodes (50.0%). Also characteristic is the presence of tumor conglomerates and damage to the lung tissue, skin and bones, which can be considered a prognostic criterion.

Serum lactate dehydrogenase cannot be considered an informative diagnostic marker for the

differential diagnosis of non-Hodgkin lymphomas in general and for anaplastic large cell lymphoma in particular, and is an additional research method in the diagnosis of anaplastic large cell lymphoma.

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