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CONTENTS OF THE JOURNAL

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PATHOLOGOANATOMICAL FEATURES OF CHILDHOOD LEUKEMIAS: MORPHOLOGY OF ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract. *Acute lymphoblastic leukemia (ALL) in children is one of the most common malignant disorders of the hematopoietic system. This study investigates the pathologoanatomical and morphological features of ALL. Findings revealed diffuse infiltration of blast cells in the bone marrow, lymph nodes, spleen, liver, and thymus. Histological analysis demonstrated high proliferative activity of blasts and suppression of normal hematopoiesis. Immunohistochemical results confirmed the expression of CD10, CD19, and TdT markers in B-ALL, while CD3 was characteristic for T-ALL. The obtained data indicate the systemic nature of organ involvement in ALL and highlight the importance of morphological examination in early diagnosis.*

Keywords: *acute lymphoblastic leukemia; children; pathomorphology; bone marrow; blast cells; immunohistochemistry; thymus.*

Introduction.

Acute lymphoblastic leukemia (ALL) is a highly aggressive malignant disease of the hematopoietic system characterized by uncontrolled clonal proliferation of lymphoid precursor cells (lymphoblasts) resulting from genetic and epigenetic alterations. This pathology occupies a leading position in pediatric oncohematology, accounting for 25–30% of all oncological diseases diagnosed in children aged 0–14 years.

According to global epidemiological data, the annual incidence of ALL is 3–5 cases per 100,000 children, with the highest frequency observed between 2 and 5 years of age. Although the use of modern polychemotherapy protocols and risk stratification systems has increased the 5-year overall survival rate to 85–90%, the problem of relapse and resistant forms remains highly relevant. In this regard, an in-depth study of the pathoanatomical and morphological basis of the disease is essential for improving diagnostic accuracy, determining prognosis, and developing individualized therapeutic strategies.

The central mechanism in the pathogenesis of ALL involves disruption of proliferation, apoptosis, and differentiation processes in lymphoid precursor cells. This process is often associated with chromosomal translocations (e.g., t(12;21), t(9;22)), gene mutations, and activation of signaling pathways such as NOTCH1 and JAK-STAT. As a result, massive accumulation of blast cells occurs in the bone marrow, leading to suppression of normal hematopoiesis and infiltration into the peripheral blood and extramedullary organs.

Pathoanatomical examination is one of the key components in the diagnosis of ALL, as it enables identification of the morphological substrate of the disease at the organ and tissue level. This approach includes classical histological (H&E), cytological, immunohistochemical (CD markers), as well as molecular genetic methods. In particular, determining the phenotypic and genetic characteristics of blast cells plays a decisive role in the differential diagnosis of disease variants and in the formation of risk groups.

This article provides a systematic analysis of the pathoanatomical and morphological features of ALL in children based on modern international classifications (WHO 2022), and highlights in detail the multi-organ involvement of the disease as well as its key diagnostic markers.

Literature Review and Historical Background

Scientific understanding of leukemia first emerged in the mid-19th century. In 1845, Rudolf Virchow and John Hughes Bennett independently described the condition as "white blood disease." At that time, the disease was explained by a marked increase in leukocytes in the peripheral blood; however, its clonal and malignant nature was established later.

In the second half of the 20th century, advances in cytological and histological methods enabled the development of morphological classifications of leukemia. In 1976, the Franco-American-British (FAB) cooperative group proposed a classification that divided acute lymphoblastic leukemia into L1, L2, and L3 types. This classification was based on the morphological characteristics of blast cells and was widely used in clinical practice for many years. However, its main limitation was the lack of consideration of immunophenotypic and molecular genetic parameters.

Subsequently, the multiparametric classification proposed by the World Health Organization (WHO), with updates in 2001, 2008, 2016, and 2022, marked a significant breakthrough in leukemia evaluation. In particular, the 5th edition of the WHO classification (2022) ensures high diagnostic accuracy by integrating morphology, immunophenotype, cytogenetics, and molecular genetics. According to this system, B-lymphoblastic leukemia/lymphoma and T-lymphoblastic leukemia/lymphoma are defined as distinct nosological entities.

In modern scientific literature, the pathomorphological features of ALL have mainly been studied in relation to blast infiltration in the bone marrow and lymphoid organs. However, the mechanisms of extramedullary involvement (including the liver, spleen, thymus, and central nervous system) and their clinical and prognostic significance remain insufficiently elucidated.

In Uzbekistan, significant research has also been conducted on pediatric leukemia. In particular, the Tashkent Pediatric Medical Institute and the Republican Specialized Oncology and Hematology Centers have studied the clinical and morphological features of ALL. Nevertheless, comprehensive analyses based on a pathoanatomical approach (combining morphology, immunohistochemistry, and molecular methods) remain relatively limited, highlighting the relevance of further in-depth research in this field.

Aim of the Study.

The aim of this study is to comprehensively investigate the pathoanatomical and morphological features of acute lymphoblastic leukemia (ALL) in children, to determine the degree of blast cell infiltration in the bone marrow and extramedullary organs, and to evaluate the immunophenotypic variants of the disease based on immunohistochemical markers (TdT, CD10, CD19, CD3, CD7, Ki-67).

In addition, an important objective of the study is to improve the diagnostic criteria of ALL based on the obtained morphological and immunophenotypic findings, as well as to assess their clinical and prognostic significance.

Materials and Methods.

This study was retrospective and analytical in design, including clinical, laboratory, and pathoanatomical data from 148 patients aged 0–15 years diagnosed with acute lymphoblastic leukemia (ALL) between 2018 and 2023 in specialized pediatric oncology and hematology institutions of the Republic of Uzbekistan.

To establish the pathoanatomical diagnosis, a комплекс of morphological examinations was performed. Histological analysis was conducted using hematoxylin–eosin (H&E) staining, allowing assessment of the degree of blast cell infiltration and the extent of disruption of tissue architecture in the bone marrow and other tissues. Cytological examination was carried out using bone marrow aspirates, where the percentage of blast cells was determined; a threshold of >25% blasts was considered a diagnostic criterion.

In addition, immunohistochemical analysis was used to determine the immunophenotype of the cells. The TdT marker was applied to confirm lymphoid precursor cells; CD10 and CD19 were used to identify B-cell acute lymphoblastic leukemia, while CD3 and CD7 markers were used to identify the T-cell variant. The proliferative activity was assessed using the Ki-67 index, which reflects the degree of blast cell division and biological aggressiveness.

Statistical analysis was performed using SPSS version 26.0. Quantitative data were expressed as mean ± standard error (M ± m). Categorical variables were analyzed using the chi-square (χ^2) test to assess differences between groups. In cases of small sample sizes ($n < 5$), Fisher's exact test was applied. Comparisons of quantitative variables were performed using Student's t-test under conditions of normal distribution. When the data did not follow a normal distribution, the Mann–Whitney U test was used.

A p-value of < 0.05 was considered statistically significant.

Results and Discussion.

During the study, the clinical-demographic, morphological, and immunophenotypic characteristics of 148 patients aged 0–15 years diagnosed with acute lymphoblastic leukemia (ALL) were comprehensively analyzed. The obtained results made it possible to identify sex- and age-related features of the disease in children, as well as its morphological substrate.

According to the demographic analysis, ALL was found to occur more frequently in males, suggesting that genetic and hormonal factors may play an important role in the development of the disease. Analysis of age distribution revealed that the highest incidence was observed in children aged 2–5 years, which can be explained by the period of active proliferation of lymphoid tissues.

Morphological examination revealed massive infiltration of blast cells in the bone marrow, accompanied by marked suppression of normal hematopoietic elements. Blast cells were characterized by a high nuclear-to-cytoplasmic ratio, fine chromatin structure, and the presence of multiple nucleoli. These changes represent the principal pathomorphological features of the disease and lead to the development of cytopenias in the peripheral blood

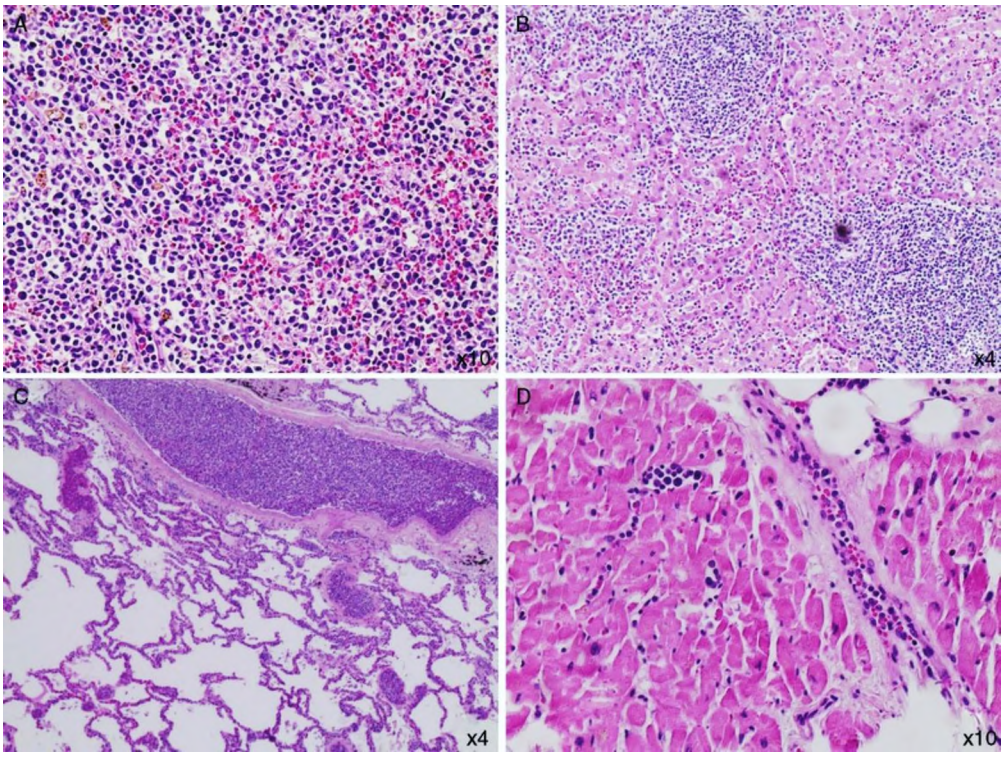

Figure 1. A–D. Infiltration of Blast Cells in Various Organs in Acute Lymphoblastic Leukemia (ALL) (H&E Staining)

A (×10): Diffuse blast infiltration is observed in the bone marrow tissue. Normal hematopoietic elements are almost completely replaced. Blast cells are characterized by a high nuclear-to-cytoplasmic ratio, fine chromatin, and distinct nucleoli, indicating malignant proliferation.

B (×4): Diffuse infiltration of blast cells is detected in the liver parenchyma along the portal tracts and sinusoids. Hepatocytes appear compressed, with focal dystrophic changes observed in some areas. These findings reflect the extramedullary spread of ALL.

C (×4): Accumulation of blast cells is observed in the interstitial and perivascular regions of the lung tissue. Although the alveolar architecture is partially preserved, interstitial infiltration may impair gas exchange.

D (×10): In the myocardial tissue, perivascular and interstitial blast infiltration is observed. The presence of leukemic cells between cardiomyocytes may lead to functional impairment of the myocardium.

Significant morphological changes were also observed in extramedullary organs. In lymph nodes, complete disruption of normal architecture and diffuse blast infiltration were identified, indicating impairment of immune system function. In the spleen, infiltration of the red pulp and a reduction in white pulp elements were noted, while in the liver, accumulation of blast cells was observed within portal tracts and sinusoids.

Notably, in the T-ALL variant, marked enlargement of the thymus and disruption of corticomedullary differentiation were observed, confirming the central role of the thymus in the pathogenesis of the disease.

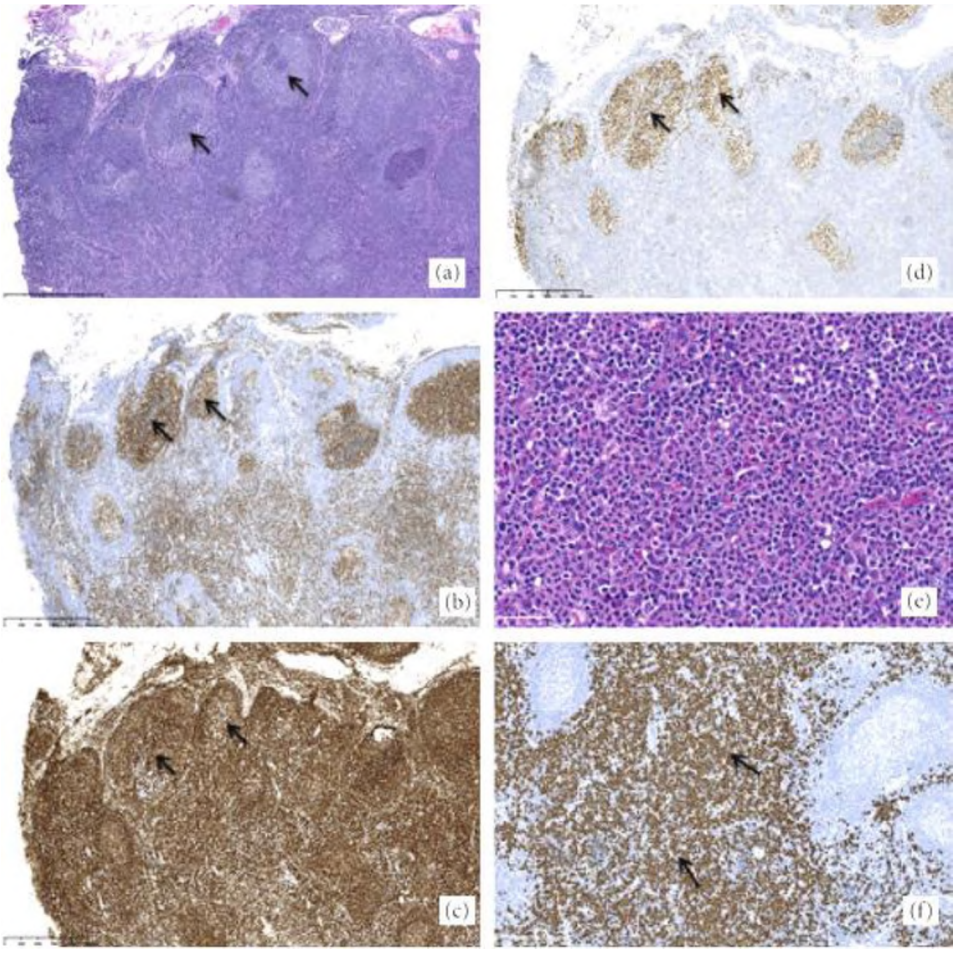

Figure 2. (a–f). Morphological and Immunohistochemical Features of Lymphoid Tissue in Acute Lymphoblastic Leukemia (ALL)

(a) (H&E): The overall architecture of the lymph node is disrupted, with loss of distinction between cortical and medullary zones. Due to diffuse blast infiltration, normal lymphoid follicles are compressed or completely absent (indicated by arrows). This reflects malignant transformation of lymphoid tissue.

(b) (IHC, CD20/CD10): Focal expression of B-cell markers is detected in certain areas of the lymphoid infiltrate (indicated by arrows). This indicates B-lineage differentiation of the blast cells.

(c) (IHC, TdT): Diffuse and intense nuclear staining is observed throughout the lymphoid tissue, confirming a high presence of lymphoid precursor cells. The widespread expression of TdT is a key diagnostic criterion for ALL.

(d) (IHC, Ki-67): The proliferation index is elevated, with a significant proportion of lymphoid cells showing Ki-67 positivity. This reflects high mitotic activity and the aggressive biological behavior of the disease.

(e) (H&E, high magnification): Blast cell morphology is clearly visible: a high nuclear-to-cytoplasmic ratio, fine chromatin, and prominent nucleoli. The cytoplasm is scant and basophilic, features typical of lymphoblasts.

(f) (IHC, CD3/CD7): Expression of T-cell markers is detected in certain areas (indicated by arrows), suggesting a T-cell variant of ALL or the possibility of a mixed immunophenotype.

Note: These histological images clearly demonstrate the main pathomorphological hallmark of ALL in lymphoid tissue—diffuse blast infiltration and loss of normal architecture. Immunohistochemical findings confirm the precursor nature of blast cells (TdT+), their high proliferative activity (Ki-67↑), and immunophenotypic variability (B- and T-cell markers).

The widespread expression of TdT confirms the origin of the disease from undifferentiated lymphoid precursor cells, while the elevated Ki-67 index reflects its aggressive biological behavior. Identification of immunophenotype using CD markers is crucial for distinguishing between B-ALL and T-ALL, which plays a decisive role in determining prognosis and treatment strategy.

Immunohistochemical analysis showed that the majority of patients belonged to the B-cell variant (CD10+, CD19+), consistent with global literature data. The T-cell variant (CD3+, CD7+) was less frequent but was associated with a more aggressive clinical course. Universal positivity for TdT in all patients confirmed the presence of lymphoid precursor cells and reinforced its diagnostic value. The high Ki-67 proliferation index reflects intensive blast cell division and indicates the biological aggressiveness of the disease, with higher levels correlating with more rapidly progressing forms of ALL.

Table 1.

Clinical, demographic, and immunophenotypic characteristics of children with acute lymphoblastic leukemia (ALL) (n = 148)

Indicators	Groups	n	%
Gender	Male	86	58,1
	Female	62	41,9
Age groups	0–2 age	28	18,9
	2–5 age	64	43,2
	6–10 age	36	24,3
	11–15 age	20	13,6
Immunophenotype	B-ALL (CD10+, CD19+)	112	75,7
	T-ALL (CD3+, CD7+)	36	24,3
TdT ekpression	Positive	148	100
	Negative	0	0
Ki-67 index	≥70%	109	73,6
	<70%	39	26,4

Note: Among children with acute lymphoblastic leukemia, a predominance of male patients is observed, with the highest incidence occurring in the 2–5-year age group. Immunophenotypic analysis showed that the majority of patients belong to the B-cell variant, while the T-cell form is relatively rare. Universal positive expression of the TdT marker in all cases confirms that it is a characteristic feature of lymphoid precursor cells. The high level of the Ki-67 proliferation index indicates intensive proliferation of blast cells and high biological activity of the disease. These findings confirm that ALL is characterized by an aggressive course and multisystem involvement, and they also highlight the high diagnostic value of immunohistochemical markers.

Table 2.

Pathomorphological and Immunophenotypic Characteristics of Organs in Children with Acute Lymphoblastic Leukemia (ALL) (n=148)

Organ	(n)	%	Macroscopic changes	Microscopic changes	Immunohistochemical merkers	Diagnostic significance
Bone marrow	148	100	Hyper-cellularity	Blast infiltration (>25%), suppression of hemato-poiesis	TdT+ (148), CD10/CD19+ (112), CD3/CD7+ (36), Ki-67↑ (109)	Main diagnostic criterion
Spleen	102	68,9	Spleno-megaly	Red pulp infiltration, reduction of white pulp	TdT+, Ki-67↑	Extramedul-lary spread
Liver	96	64,9	Hepa-tomegaly	Portal and sinusoidal infiltration	TdT+, CD markers	Systemic involvement
Lymph nodes	118	79,7	Lympha-denopathy	Architectural disruption, diffuse infiltration	CD10/CD19+, CD3/CD7+, Ki-67↑	Immuno-phenotyping

Note: According to the obtained results, bone marrow involvement was detected in 100% of patients, confirming that it is the main diagnostic criterion for ALL. Lymph node involvement was recorded in 79.7% of cases, and it was found to be more frequent compared to the liver (64.9%) and spleen (68.9%). Immunophenotypic analysis showed that the B-ALL variant was identified in 75.7% (n=112) of cases, while T-ALL was detected in 24.3% (n=36), and this difference was statistically significant (χ^2, $p < 0.05$). A high Ki-67 proliferation index (73.6%; n=109) indicated intensive proliferative activity of blast cells. Extramedullary organ involvement exceeded 60% overall, confirming that ALL is a systemic disease. Differences in the frequency of organ involvement were considered important factors affecting clinical course and prognosis.

When compared with modern scientific literature, the main pathomorphological features of ALL were confirmed to include multisystem blast infiltration, suppression of hematopoiesis, and involvement of immune system organs [1–5]. In addition, immunophenotypic markers were shown to be important diagnostic tools for disease identification, differential diagnosis, and prognosis assessment.

In the context of Uzbekistan, several factors limit the full implementation of pathological and anatomical examination, including a shortage of immunohistochemical reagents, a lack of cytogenetic

laboratories, and a shortage of qualified specialists. Addressing these issues would significantly contribute to the development of pediatric oncohematology in the country [3].

In comparison with global practice, the remission rate of ALL in Uzbekistan is somewhat lower than global indicators, which may be associated with delayed diagnosis, limited access to biological diagnostic methods, non-adherence to treatment protocols, and the presence of comorbidities.

Overall, morphological changes and immunophenotypic characteristics in the pathogenesis of ALL are closely interconnected [3,5,7] and serve as key factors determining the clinical course and outcome of the disease. Therefore, a comprehensive pathoanatomical and immunohistochemical approach is essential for early diagnosis and the development of effective treatment strategies.

Conclusion

Acute lymphoblastic leukemia (ALL) is one of the most common hematological malignancies among children, in which the uncontrolled proliferation of lymphoid precursor cells plays a central role in its pathogenesis. The results of the conducted study demonstrated that the main pathomorphological changes in ALL are characterized by massive infiltration of blast cells in the bone marrow and suppression of normal hematopoiesis [6–8].

In addition, infiltration of blast cells was identified in the liver, spleen, and lymph nodes, confirming the systemic nature of the disease. Immunohistochemical analysis revealed the predominance of the B-cell variant (CD10+, CD19+) and a relatively lower occurrence of the T-cell form. The universal expression of the TdT marker confirmed the presence of lymphoid precursor cells, while the high Ki-67 index indicated a high proliferative activity of the disease [9–12].

The obtained results demonstrate that pathoanatomical and immunohistochemical examinations are of great importance in the diagnosis of ALL, and that these indicators play a crucial role in assessing the prognosis of the disease. Therefore, a comprehensive morphological approach is of significant scientific and practical importance for the early detection of ALL and the development of effective treatment strategies.

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