

Pathomorphological Changes in the Thymus in Neonatal Necrotizing Enterocolitis in Newborn Infants

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Abstract The present study investigated the pathomorphological and morphometric features of immune organ disintegration in the thymus of newborn infants with necrotizing enterocolitis during the neonatal period, and developed a diagnostic algorithm. It was established that, in the early neonatal period, the thymus—being an incompletely developed gland—was unable to fully perform its functional activity. This was characterized by a marked decrease in various lymphocyte populations, induced apoptosis, and a compensatory proliferation of different mesenchymal cells. In addition, a reduction of the cortical layer and the loss of clear corticomedullary boundaries were observed. The thymic lobules were reduced in size compared to normal, with a significant decrease in the number of thymocytes or small lymphocytes within the cortical region of the parenchyma. Proliferative active foci were absent, while reticuloepithelial cells exhibited shortened and thickened processes, and multiple accumulations of reticulocytes were identified along the periphery. A pronounced deficiency and depletion of immune cells in the cortical layer were also noted. Between days 8 and 28, signs of thymic maturation were observed. In response to various infectious conditions, massive hyperplastic foci of small lymphocytes appeared in the cortical region. Enlarged nurse cells and dendritic epithelial cells of varying localization were detected, along with an increased number of lymphocytes surrounding their processes.

Keywords Newborn, Neonatal period, Necrotizing enterocolitis, Pathomorphological changes

1. Introduction

Necrotizing enterocolitis [NEC] is one of the most severe and life-threatening conditions among newborn infants, particularly in preterm neonates. Its pathogenesis involves ischemic injury of the intestinal wall, dysbiosis of the microbiota, and immaturity of the immune system. Therefore, NEC remains one of the most pressing challenges in modern neonatology [1,2].

During the neonatal period, the thymus, as a central organ of the immune system, plays a crucial role in determining the newborn's immune response to infections. Structural and functional alterations in the thymus, particularly disturbances in T-lymphocyte differentiation and proliferation, lead to impaired immune responses and an increased risk of infectious complications [3,4].

Recent studies have demonstrated that, in addition to local intestinal damage, systemic immune dysfunction plays a significant role in the development of NEC. In particular, atrophic and degenerative changes in the thymus, lymphocyte depletion, and enhanced apoptosis contribute to the severity

of the disease [5,6].

Furthermore, morphometric assessment of pathomorphological changes in the thymus provides an opportunity to evaluate the degree of immune deficiency during the neonatal period and to predict disease outcomes. This approach is of great importance for early diagnosis and the development of individualized therapeutic strategies [7,8].

Currently, thymic structural and functional alterations in NEC remain insufficiently studied, and there is a limited number of pathomorphological and morphometric investigations in this field. In particular, the assessment of dynamic changes in the thymus across different stages of the neonatal period remains a highly relevant issue [9,10].

Therefore, comprehensive investigation of pathomorphological changes in the thymus in newborns with necrotizing enterocolitis, determination of their relationship with the immune system status, and development of a diagnostic algorithm represent important tasks of contemporary medical science [11,14].

Purpose of the study

To investigate the pathomorphological and morphometric features of immune organ disintegration in the thymus in newborn infants aged 0-28 days with necrotizing enterocolitis, and to develop a diagnostic algorithm.

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2. Materials and Methods

The study materials were obtained from archival records of Andijan Regional Multidisciplinary Pediatric Clinical Hospital and Fergana Regional Pathological Bureau for the period of 2015-2026. The analyzed data included patients' medical histories, autopsy reports, and biopsy materials.

A total of 386 patient cases were included in the study, of which 186 were medical histories and 200 consisted of autopsy and biopsy materials. Pathomorphological changes in the intestinal wall and thymus were examined.

Pathomorphological investigations were carried out using standard histological methods. Morphometric analysis was performed to assess structural changes in the thymus and intestinal tissues. The obtained results were comparatively analyzed and correlated with clinical data.

3. Results and Discussion

In the early neonatal period, the thymus performing its functional responsibilities is highly sensitive to various stress factors, including glucocorticoid-associated immunosuppression. Microscopically, the thymus was surrounded by a fibrous capsule of uniform thickness, its sparse-fibered structures remained unchanged, and vascular integrity was preserved. Thymic lobules were reduced in size compared to normal. Within the parenchyma, there was a quantitative reduction of thymocytes and small lymphocytes in the cortical layer, absence of active proliferative foci, and reticuloepithelial cell processes appeared shortened and thickened, with multiple accumulations of reticulocytes observed along the periphery. A marked deficiency or depletion of immune cells in the cortical layer was identified.

During days 0–7 of the early neonatal period, newborns who developed necrotizing enterocolitis, often in combination with pneumonia, sepsis, or septic shock, exhibited multi-organ dysfunction. Classical patterns of accidental thymic transformation were not consistently observed. Microscopically, the main morphological features included a reduction in thymocyte numbers, apoptosis of nurse (epithelial) cells, and an increase in reticulocytes within the processes of reticuloepithelial cells. Consequently, the ratio of stromal to mesenchymal tissue in the thymus was altered, mainly manifested as an increase in sparse-fibered connective tissue within the cortical layer.

Small-caliber vessels demonstrated complete filling, erythrocytes exhibited sludging phenomena, and perivascular areas showed edema and plasmatic condensation within the stroma. These changes led to disruption of thymic histoarchitecture, marked depletion of young or small thymocytes around nurse cells, a quantitative reduction of lymphocytes in subcapsular regions and around reticuloepithelial cells, and an increase in dendritic cells, fibroblasts, and histiocytes. As a result, massive parenchymal depletion or stromal collapse in the cortical region of the thymus was observed.

At the corticomedullary boundary, homogeneous, rounded Hassall's bodies composed of epithelial whorls were identified. Normally, Hassall's bodies are absent in corticomedullary areas (see Figure 1 and 2).

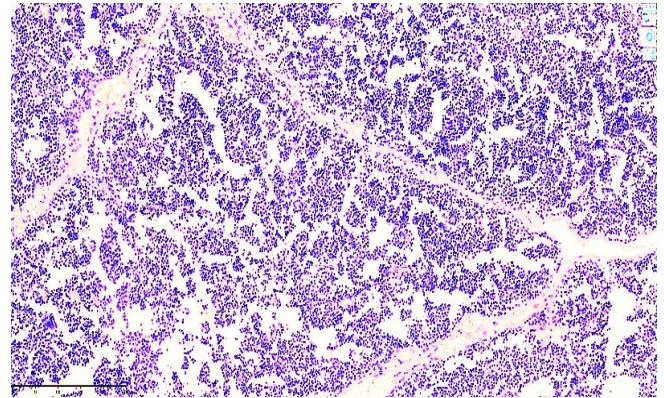


Figure 1. Thymic tissue in the early neonatal period. Thymic tissue of a deceased patient, R., on day 3. The boundaries between the cortical and medullary regions are almost indistinguishable. Numerous spaces are observed. The stroma shows fibrillar structures at various stages of maturation. Most of the blood vessels appear fully filled. Staining: H&E. Magnification: 4×10

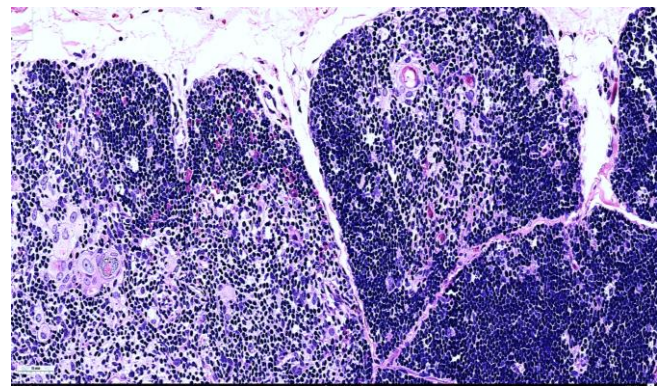


Figure 2. Thymic tissue in the early neonatal period. Thymic tissue of a deceased patient, Y., on day 7. Focal hypercellularity is observed in the cortical region, and the postcapillary venules are fully filled. Large and elongated reticuloepithelial and nurse epithelial cells are visible. In the corticomedullary and medullary regions, Hassall's bodies of varying sizes and degrees of maturation are identified. Most lymphoblasts and histiocytes are clearly seen, and in areas of sparse stroma, phagocytically active macrophages are present. Staining: H&E. Magnification: 10×10

In the medullary region, there was a quantitative reduction of mature lymphocytes. The stroma predominantly exhibited plasmatic condensation, with trabecular structures resembling fibrillar formations. Surrounding these structures, small elongated reticulocytes, lymphoblasts, histiocytes, and macrophages were observed. Postcapillary venules in the medullary layer had transformed into simple capillaries, and the number of large mature lymphocytes that had undergone antigen-independent differentiation was sharply reduced, most of them localized in perivascular regions. In areas with decreased lymphocytes, macrophages, lymphoblasts, histiocytes, and epithelial cells of various sizes were present, while sparse-fibered connective tissue and fibrillar protein structures increased, indicating thymic atrophy associated with accidental transformation.

During the early neonatal period, the thymus still an incompletely developed gland—was unable to fully perform its functional activity. This was accompanied by a pronounced decrease in various lymphocyte populations, induced apoptosis, proliferation of mesenchymal cells, reduction of the cortical layer, and loss of clear corticomedullary boundaries.

Between days 8 and 28, signs of thymic maturation were observed. In response to various infectious diseases, massive hyperplastic foci of small lymphocytes appeared in the cortical region, while nurse cells and dendritic epithelial cells of various sizes and locations were enlarged. Lymphocyte numbers around these cells were increased.

In the mature, morphofunctionally developed thymus, immune-competent cells exhibited tolerance to strong stress factors through hypersecretion and enhanced lymphocyte apoptosis. In newborns aged 8-28 days, adrenal cortex activity under normal conditions reached 500 nmol/L on day 1, whereas in NEC it increased to 1500-1800 nmol/L. This corresponded to an elevated apoptotic index in the thymus (see Table 1).

The described clinical and morphological changes, as well as the evaluation of the thymic apoptotic index, are highly significant, providing an opportunity to differentiate the late neonatal thymus from accidental transformation. Microscopically, in the cortical region, gaps formed as a result of thymocyte apoptosis and sparse focal areas were identified. This allowed for the observation of interstitial spaces among densely packed cortical lymphocytes, enlarged nurse cells within proliferative foci, small lymphocytes surrounding them, and an increased number of reticuloepithelial cells, reflecting the appearance of a mature thymus (see Figures 3

and 4).

In the morphologically mature thymus of the first group, involutional changes were mainly represented by the preservation of proliferative lymphocyte centers in the cortical region, while surrounding incompletely matured small lymphocytes exhibited increased apoptosis. The nuclei of these cells were preserved, with only clastolytic changes observed. Dendritic and reticuloepithelial cells were surrounded by lymphocytes, blood vessels were fully filled, and the stroma showed plasmatic condensation and increased macrophages, predominantly in the late neonatal period. This pattern indicates that the thymus maintains adaptive and reparative-regenerative properties for approximately 2-3 days.

Between days 12 and 28 of the late neonatal period, catastrophic changes were observed: cortical gaps became more prominent, various epithelial cells underwent necrobiosis, and Hassall's bodies transformed into initial substrates. The corticomedullary boundary remained preserved. In the medullary layer, cell density exceeded that of the cortical layer, and large lymphocytes showed increased tolerance to apoptosis with a decrease in programmed cell death.

The cortical region exhibited the highest apoptotic index, with a pronounced decrease in thymocyte numbers and extensive apoptosis. This peak was observed between days 3-7 following the onset of necrotizing enterocolitis. Microscopically, lymphocyte persistence in the thymus during the late neonatal period, approximately between days 12-18, led to medullary depletion, resulting in an appearance reminiscent of the early neonatal thymic landscape. These changes were largely uniform, characterized by a massive reduction of lymphocytes, including NK lymphocytes (see Figures 3 and 4).

Table 1. Age-related comparative algorithm of pathomorphological changes in the thymus

Indicators [IHC & histology]	Early neonatal period [0–7 days]	Late neonatal period [8–28 days]
Involution stage [t.e. ivanovskaya]	I-II stage [2 points]	III stage [3 points]
Lymphocyte Depletion [CD1a/CD3]	Mild / Migratory [2 points]	Moderate / Scattered [3 points]
Apoptotic activity [Caspase-3]	Single cells [1 point]	Extensive foci [4 points]
Hassall's body status	Formation stage [1 point]	Hypertrophy / Detritus [3 points]
Proliferation [Ki-67]	High / Preserved [1 point]	Decreased [3 points]
Stroma status [Edema/Fibrosis]	Mild edema [2 points]	Congestion [4 points]
Overall average score	1.5-2.0 points	3.0-3.5 points
Final assessment	Mild / Adaptive	Moderate–severe / Decompensation

Table 2. Morphometric parameters of thymic tissue in necrotizing enterocolitis (nec)

Morphometric parameters	Control [Normal]	0-7 Days	8-28 Days	P [ANOVA]
Thymus relative weight [g/kg]	4.2 ± 0.4	3.5 ± 0.3	1.2 ± 0.2	≤0.001***
Cortical layer thickness [µm]	320 ± 15	210 ± 12	65 ± 8	≤0.001***
Medullary area [%]	35.4 ± 2.1	42.6 ± 2.8	68.2 ± 3.4	≤0.01**
Lymphocyte density [per 1 mm]	1850 ± 110	1100 ± 95	320 ± 45	≤0.001***
Hassall's body diameter [µm]	28.4 ± 2.2	45.6 ± 3.4	72.8 ± 5.2	≤0.01**

*Note: **– P < 0.01; *** – P < 0.001 [level of statistical significance].

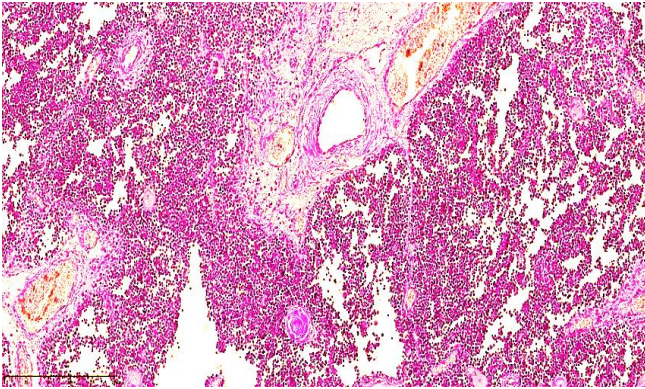


Figure 3. Thymic Tissue in the Late Neonatal Period (Day 12). Thymic tissue at 12 days of the late neonatal period. Development of dense fibrous connective tissue is observed between the cortical and medullary layers. In the cortex, gaps are formed in areas where small lymphocytes undergo pronounced apoptosis. Hassall's bodies at various stages of maturation are present in the central region. Staining: H&E. Magnification: 4×10

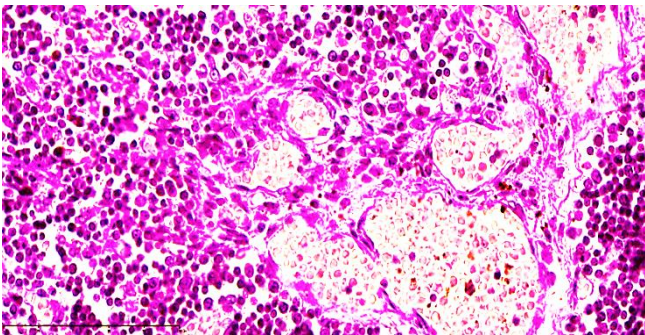


Figure 4. Thymic Tissue in the Late Neonatal Period (Day 18). Thymic tissue at 18 days of the late neonatal period. In the medullary layer, mature lymphocytes are localized in perivascular regions. The vessel walls are massively dilated, and vascular permeability is disrupted. Large mature lymphocytes with foci of apoptosis are observed. Staining: H&E. Magnification: 40×10

The prolonged accumulation of mature lymphocytes in the perivascular regions of the medullary layer (average 3-5 days) confirms an enhanced process of induced apoptosis in lymphocytes and the development of cellular immunodeficiency (see Table 2).

During the period following confirmation of necrotizing enterocolitis (NEC), within an average of 24-72 hours, the intestinal mucosal layer develops erosive-ulcerative and necrotic changes. These changes lead to collapse of the regional immune system and massive release of degraded and necrotic cells into the bloodstream, accompanied by the secretion of leukotrienes and cytokines. Specifically, following tissue necrosis and immune cell death, the excessive cytokine release into plasma triggers a “cytokine storm,” resulting in systemic vascular responses, including widespread vasodilation and leakage of plasma into perivascular spaces.

Similar alterations occur in the thymus, where postcapillary venules impede the egress of mature lymphocytes into peripheral blood. This leads to the formation of erythrocyte sludging within thymic vessels. Concurrently, metabolic disturbances in thymic tissue and plasmatic congestion in the stroma are observed, promoting a disintegrative state that

disrupts interconnections with other peripheral immune organs. Consequently, these changes contribute to accidental thymic transformation and involution.

4. Conclusions

The study demonstrates distinct patterns of accidental thymic transformation during both early and late neonatal periods in newborns with necrotizing enterocolitis (NEC). In the early neonatal period (0-7 days), the thymus is still morphologically immature, particularly in the cortical region, where there is a pronounced depletion of thymocytes. This depletion occurs simultaneously across both cortical and medullary layers, resulting in the near absence of mature thymocytes. These observations indicate that the thymus during this stage is highly vulnerable to stress and immune challenges, and its structural and functional capacity to support T-cell differentiation is significantly limited.

In the late neonatal period (8-28 days), although the thymus shows more advanced maturation, functional disruptions are evident. Mature thymocytes form proliferatively active foci; however, these areas are interspersed with apoptotic gaps, reflecting ongoing cell death. In the medullary layer, mature lymphocytes accumulate around postcapillary venules, suggesting impaired lymphocyte egress into the peripheral circulation. These phenomena indicate that even in a structurally more mature thymus, NEC induces localized immunological stress, triggering apoptotic processes and stromal alterations that compromise the organ's integrity.

Overall, these findings highlight the critical impact of NEC on thymic structure and function across the neonatal period. The differential patterns of thymocyte depletion, apoptotic gap formation, and perivascular lymphocyte accumulation provide a morphofunctional basis for understanding the development of immunodeficiency in affected neonates. The results underscore the importance of early detection and monitoring of thymic changes, as these alterations may significantly influence systemic immune competence and the risk of secondary infections.

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