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Characteristics of CD3 Marker Expression in Mesenteric Lymph Nodes in Necrotizing Enterocolitis in Infants

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Abstract This study analyzed histomorphological and immunohistochemical alterations in mesenteric lymph nodes using 200 biopsy specimens obtained from infants diagnosed with necrotizing enterocolitis (NEC) between 2015 and 2026. In the early neonatal period (0-7 days), mesenteric lymph nodes demonstrated structural immaturity and incomplete morphogenesis. A pronounced T-cell deficiency was identified, characterized by a significant reduction in CD3+ T lymphocytes, with low expression observed in 65.71% of cases. A compensatory activation of the B-cell compartment was noted in response to T-cell insufficiency. During age-related progression, by the late neonatal period (8-28 days), a marked maturation of functional zones within mesenteric lymph nodes was observed. CD3 expression increased approximately 3.33-fold compared with the early neonatal period, indicating partial restoration of T-cell-mediated immune activity. In NEC cases presenting as part of a systemic inflammatory response syndrome (SIRS), migration of activated lymphocytes toward inflammatory foci was observed. This process contributed to lymphoid depletion, structural collapse of lymphoid tissue, and the development of secondary immunodeficiency in mesenteric lymph nodes.

Keywords Neonates, Early and late neonatal period, Necrotizing enterocolitis, Mesenteric lymph nodes, Immunohistochemistry, CD3+ T lymphocytes, B lymphocytes, Systemic inflammatory response, Secondary immunodeficiency

1. Introduction

Necrotizing enterocolitis (NEC) is a severe inflammatory gastrointestinal disease that primarily affects premature and very low birth weight neonates and remains a major cause of neonatal morbidity and mortality worldwide [1,2]. Despite advances in neonatal intensive care, the clinical outcomes of NEC remain poor due to its rapid progression and multifactorial pathogenesis [1].

The development of NEC is associated with intestinal immaturity, ischemia-reperfusion injury, microbial dysbiosis, and dysregulated innate and adaptive immune responses [2,3]. These mechanisms collectively lead to epithelial barrier breakdown and excessive intestinal inflammation [3,4]. Recent studies indicate that immune dysregulation plays a central role in NEC pathogenesis, particularly involving Toll-like receptor 4 (TLR4)-mediated activation of the immature intestinal epithelium, which triggers inflammatory cascades and immune cell recruitment. This process results in exaggerated mucosal inflammation and tissue injury. Mesenteric lymph nodes (MLNs) are a critical component of intestinal immunity, functioning as the primary site for antigen presentation and lymphocyte activation in response to gut-derived microbial and inflammatory stimuli. In NEC, MLNs are actively involved in immune regulation and disease progression due to continuous antigenic stimulation [5,6,7].

Experimental and clinical studies have demonstrated that NEC is characterized by an imbalance in T-cell populations, including reduced regulatory T-cell activity and altered CD3+ T lymphocyte responses, contributing to impaired immune homeostasis [6,7]. This immune dysfunction is particularly pronounced in premature neonates due to incomplete maturation of adaptive immunity. During early neonatal life, mesenteric lymph nodes are structurally immature, with underdeveloped cortical and paracortical zones responsible for T-cell activation and immune coordination. This immaturity results in reduced CD3+ T-cell activity and weakened adaptive immune responses [7,8].

In response to T-cell deficiency, compensatory activation of B-cell compartments and germinal center formation may occur; however, this response is often insufficient to control inflammation in NEC [7,9]. In severe cases associated with systemic inflammatory response syndrome (SIRS), activated lymphocytes migrate toward inflamed intestinal tissue, leading to lymphoid depletion and secondary immunodeficiency [5,6].

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Age-dependent maturation of mesenteric lymph nodes has been observed during the late neonatal period, characterized by improved structural organization and increased CD3 expression, indicating partial restoration of T-cell–mediated immunity [8,12].

Purpose of the study

To investigate the pathomorphological and immunohistochemical changes associated with immune organ disintegration in necrotizing enterocolitis in infants under one year of age.

2. Materials and Methods

The study was based on archival materials obtained between 2015 and 2026 from the Andijan City Children's Multidisciplinary Clinical Hospital and the Fergana regional Pathoanatomical bureau. A total of 200 archival biopsy samples were analyzed.

In these biopsy specimens, immunohistochemical expression of the CD3 marker, a protein associated with the surface co-receptor of T-lymphocytes, was evaluated in mesenteric lymph nodes.

3. Results and Discussion

The pathomorphological features of mesenteric lymph nodes in necrotizing enterocolitis (NEC) in neonates demonstrated a distinct pattern of development during the neonatal period, with clear differences between the early neonatal period (0–7 days) and the late neonatal period (8–28 days). These changes were closely associated with gestational maturity, including both term and preterm birth, and reflected the predominance of systemic vascular inflammatory responses in NEC.

During the early neonatal period, morphologically immature mesenteric lymph nodes exhibited structural underdevelopment, which was accompanied by functional insufficiency of the cortical and paracortical zones representing the main immunologically active areas.

In deceased neonates aged 0-7 days with NEC, a marked reduction of lymphocytes was observed in both the cortical and medullary regions of lymph nodes. This included a significant decrease in B-lymphocyte populations within lymphoid follicles, reduction in follicular size, and absence of germinal centers. In the paracortical zones, a decreased number of T-lymphocytes, particularly CD3 receptor–positive cells, was also identified.

The CD3 marker is a surface co-receptor protein of T-lymphocytes that plays a key role in antigen-presenting cell interaction and initiation of primary immune responses. It is characterized by a strong positive expression in response to infectious stimuli and is considered a key indicator of cellular immune activation. The observed findings confirm a deficiency of CD3+ T-lymphocytes in mucosa-associated lymphoid tissue (MALT) structures and mesenteric lymph nodes in NEC (see Figure 1).

In this study, CD3 marker expression was evaluated in 35 neonates who died within the first 7 days of life due to necrotizing enterocolitis (NEC). A low positive immunohistochemical reaction was observed in 23 cases (65.71%), a moderate positive reaction in 3 cases (8.57%), and a negative reaction in 9 cases (25.71%).

From a morphological perspective, these findings indicate a deficiency of CD3+ T lymphocytes in the paracortical regions of mesenteric lymph nodes and at the marginal zones of lymphoid follicles during the early neonatal period. This reflects either insufficient recruitment of CD3+ T cells or a loss of receptor-mediated signaling mechanisms necessary for immune cell activation and antigen recognition.

Clinically and morphologically, 89.1% of cases in this group were associated with preterm birth or exposure to maternal pathological conditions during pregnancy, indicating a strong correlation between NEC development, prematurity, and adverse intrauterine conditions (see Table 1).

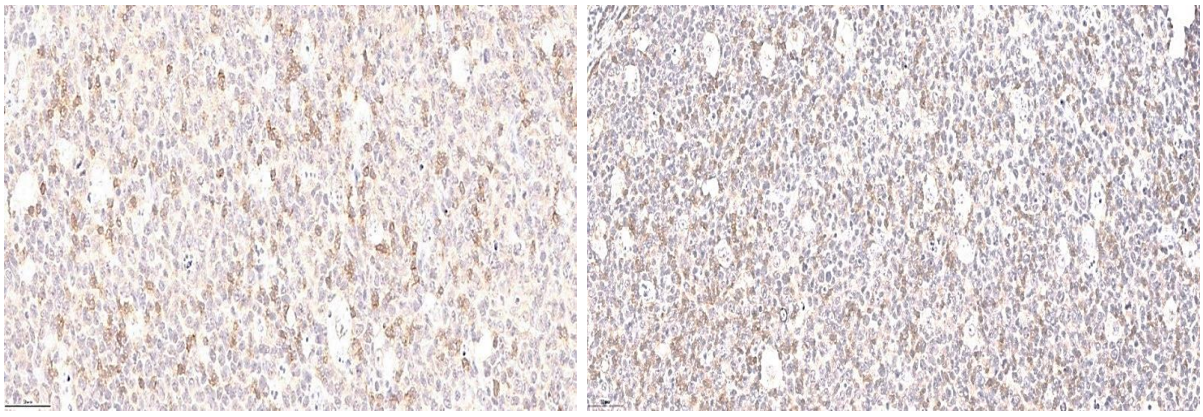

Figure 1. Early neonatal period. 6-day-old neonate. Low positive expression of the CD3 marker. In the paracortical region, the intensity of CD3 immunostaining on the lymphocyte membranes was very weak. Cystic spaces were also observed, likely associated with apoptotic processes. Staining method: DAB chromogen. Magnification: 10 ×10

Table 1. CD3 marker expression in mesenteric lymph nodes (%)

Period	Negative reaction	Low positive expression	Moderate positive expression	High positive expression
CD3 (0–7-day-old neonates, n = 35)	9 (25.71%)	23 (65.71%)	3 (8.57%)	-

Note: The positive reaction index was evaluated using the saturation (intensity) scale according to the Remmele and Stegner scoring system. The level of expression was assessed based on immunoreactivity grading

Table 2. CD3 marker expression in mesenteric lymph nodes (%)

Period	Negative reaction	Low positive expression	Moderate positive expression	High positive expression
CD3 (8–28-day-old neonates, n = 35)	4 (11.43%)	19 (54.28%)	11 (31.42%)	-

Note: The positive reaction index was evaluated according to the Remmele and Stegner immunoreactive score (IRS) system, based on the degree of immunohistochemical expression intensity.

Table 3. CD3 marker expression in mesenteric lymph nodes (%)

Period	Negative reaction	Low positive expression	Moderate positive expression	High positive expression
CD3 (3-month-old infants, n = 35)	1 (2.86%)	13 (37.14%)	16 (45.71%)	5 (14.28%)

Note: The positive reaction index was evaluated using the Remmele and Stegner immunoreactivity (IRS) scoring system, based on the intensity of immunohistochemical expression.

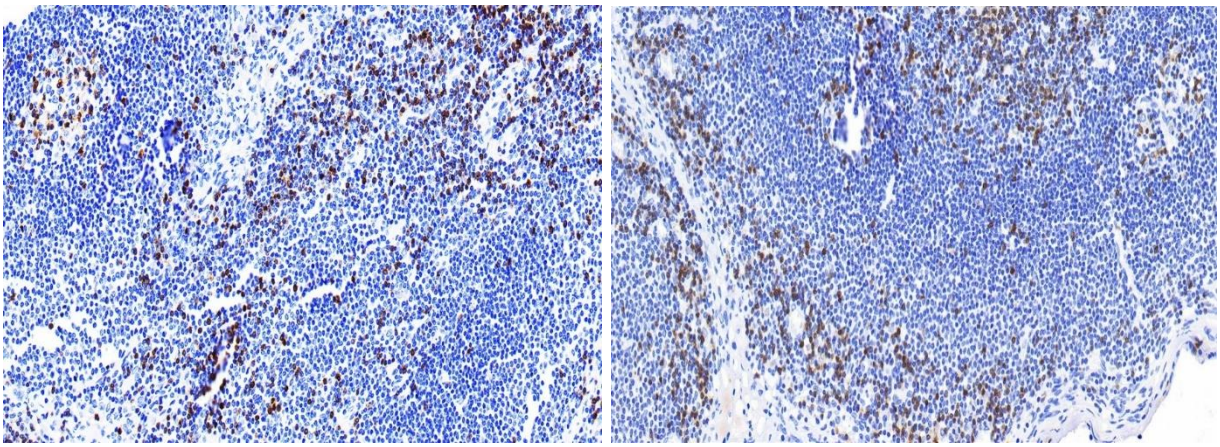

Figure 2. Late neonatal period (18–25 days). Low positive expression of the CD3 marker. A small number of T lymphocytes were detected around lymphoid follicles. Staining method: DAB chromogen. Magnification: 4 × 10

In neonates aged 0–7 days, CD3 marker expression was predominantly characterized by low and moderate positive reactions, with most cases detected in 6–7-day-old infants. This pattern indicates a time-dependent maturation of mesenteric lymph node immune function during the early neonatal period. Morphologically, mesenteric lymph nodes exhibited structural immaturity, and weak CD3-positive lymphocytes were mainly localized in the paracortical regions, which represent the T-cell–dependent functional zone of the lymph node. These CD3-positive cells were predominantly arranged around postcapillary venules and were embedded within a sparse reticular fiber network, with interspersed macrophages observed in the interfollicular areas. Such a microenvironment reflects incomplete organization of the immune architecture and reduced antigen-driven T-cell activation during early postnatal adaptation. Overall, these findings suggest delayed maturation of T-cell–mediated immune responses in mesenteric lymph nodes during the early neonatal period.

In necrotizing enterocolitis (NEC), CD3 marker expression in mesenteric lymph nodes during the late neonatal period was characterized by a more advanced degree of morphological maturation. The paracortical regions demonstrated the presence of lymphoblasts and lymphocytes predominantly around postcapillary venules, which corresponded mainly to moderate positive CD3 expression.

In the study group, among neonates who died at 8-28 days of age (n = 35), moderate positive CD3 expression was detected in 11 cases (31.42%), low positive expression in 19 cases (54.28%), and negative reactions in 4 cases (11.43%) (see Table 2).

In the late neonatal period (18–25 days), CD3 marker expression was predominantly characterized by low positive immunoreactivity. A reduced number of T lymphocytes was observed in the regions surrounding lymphoid follicles, indicating decreased cellular immune activity in mesenteric lymph nodes during this developmental stage (see Figure 2).

Morphologically, these findings indicate a relative maturation of T-lymphocyte development and a predominance of cellular immune responses in mesenteric lymph nodes during this period.

From a clinicomorphological perspective, among neonates aged 8–28 days, 67.16% were born at term, while 32.84% were term-born infants with a history of maternal pathological conditions and/or nosocomial infection. The overall lethality rate in neonates with necrotizing enterocolitis (NEC) within this age group averaged 31.13%.

CD3 marker expression during the 8-28-day period demonstrated a 3.33-fold increase in moderate positive immunoreactivity compared to the 0-7-day neonatal group, indicating a higher degree of morphological maturation and a more developed cellular immune response.

In the 3-month age group, CD3 expression was characterized by a further increase in morphological and functional immune maturity, with a predominance of moderate positive expression. This was associated with enhanced immune reactivity and the presence of lymphocytes predominantly localized around postcapillary venules in the paracortical regions of mesenteric lymph nodes.

In this group, histological analysis revealed that in most deceased infants, secondary lymphoid follicles were well-formed, and germinal centers contained numerous macrophages, indicating a highly active immune response. Macrophages were also identified within areas of B-lymphocyte proliferation, suggesting ongoing antigen-driven immune activation.

Immunohistochemical evaluation showed that in this group (n = 35), moderate positive CD3 expression was observed in 5 cases (14.28%), while 16 cases (45.71%) demonstrated intermediate/moderate expression, 19 cases (54.28%) showed low positive expression, and 4 cases (11.43%) exhibited negative reactions (see Table 3).

Morphologically, these findings indicate a higher degree of maturation compared with the early neonatal period, as well as a more developed cellular immune response. In addition, they reflect a greater level of T-lymphocyte maturation, suggesting a predominance of cell-mediated immune activity.

From a clinicomorphological perspective, in comparison with both the early and late neonatal periods, the prolonged process of morphological development of mesenteric lymph nodes indicates an age-related increase in structural and functional maturation. In this context, a high level of CD3 expression was observed in 14.28% of cases. Clinically and morphologically, in 3-month-old infants, the mortality rate associated with necrotizing enterocolitis (NEC) decreased to 13.3–25.2%, which further supports the notion of enhanced T-lymphocyte maturation and a more effective immune response during this developmental stage.

4. Conclusions

In the early neonatal period (0–7 days), mesenteric lymph nodes (MLNs) were morphologically immature and incompletely developed. This structural and functional immaturity was identified as a key factor contributing to immune deficiency in the course of necrotizing enterocolitis (NEC).

A pronounced T-lymphocyte deficiency was observed in 0–7-day-old neonates, characterized by a marked reduction in CD3+ T lymphocytes, with low expression detected in 65.71% of cases. This finding reflects a weakened specific immune response to antigenic stimulation.

In age-related dynamics, by the late neonatal period (8–28 days), functional zones of mesenteric lymph nodes showed significant maturation, and CD3 marker expression increased approximately 3.33-fold compared with the early neonatal period. This indicates a gradual restoration and improvement of T-cell–mediated immune activity during postnatal development.

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