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STRUCTURAL CHANGES IN THE BRONCHUS AND LUNGS OF YOUNG CHILDREN WITH BRONCHOPULMONARY DYSPLASIA

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Abstract

Relevance. *Respiratory diseases in newborns remain one of the urgent problems of neonatology. In the structure of morbidity of newborns, respiratory disorders occupy the 2nd place -8.8% and most often develop in premature infants due to morphofunctional features of their respiratory system. There is no doubt that the mechanisms of the innate component of immunity play an important role in the primary response to infection. It is known that the morphofunctional state of the APUD system is closely related to the phases of inflammation developing in the organs. The literature provides data on structural changes of the lungs and bronchi in bronchopulmonary dysplasia in children, but there is no information about the relationship of immune-endocrine structures of the lungs in this pathology.*

The aim *of the study is to study the components of the immune system and regulatory systems of the bronchus and lungs in bronchopulmonary dysplasia in children.*

Material and methods of research. *The lungs of deceased newborns with bronchopulmonary dysplasia were the material for the study. All the children were born and died in maternity hospitals and children's intensive care units. Autopsy examination of the corpses of 27 deceased children was carried out in the pathology and anatomical department of the 1st clinic of SamSMU for the period from 2015 to 2022. To study the morphofunctional state of the lungs, the materials were stained with hematoxylin and eosin, according to Van Gieson, Weigert, Masson, impregnation was carried out using the Grimelius method, as well as immunohistochemical studies.*

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died in maternity hospitals and children's intensive care units.

The results of the study. *When studying the components of immunity and regulatory structures of the bronchus and lungs in bronchopulmonary dysplasia in children, it was found that pathognomonic changes occur sequentially as the disease progresses from bronchiolectasia, stellate atelectasis, rosette-like restructuring of bronchioles, mosaic and focal pneumosclerosis. Pneumosclerosis develops against the background of moire and fibromuscular atelectasis, small-cystic restructuring of bronchioles against the background of foci of pneumosclerosis and fibroatelectasis. In addition, the restructuring of small arteries and arterioles of the lungs is characterized by hypertrophy and hyperplasia of myocytes of the bronchioles muscle membrane, hyperelastosis, perivascular sclerosis and myoelastofibrosis. Thus, a constant sign of the manifestation of neonatal bronchopulmonary dysplasia are atelectases and fibroatelectases, the occurrence of which is associated with low activity of the anti-atelectatic factor. The level of its stability is affected by the gestational age of newborns and hyperoxygenation of lung tissue during artificial lung ventilation. The predominant localization of cells expressing Ki-67 protein topographically coincides with the location of generative zones in the bronchopulmonary system. A high level of expression of markers of proliferation, anti-apoptotic factor and apoptosis without significant differences in bronchopulmonary dysplasia indicates an increase in the rate of cellular renewal in the lungs in this disease and its progression during the entire follow-up period.*

Conclusions. *A high level of expression of proliferation markers and anti-apoptotic factor indicates increased rates of cellular renewal in the bronchus and lungs in bronchopulmonary dysplasia and disease progression. An increase in the number of apudocytes is observed mainly in the subsegmental and interlobular bronchi in bronchopulmonary dysplasia.*

Key words

bronchus, lungs, cellular and humoral immunity, apudocytes, IHC, bronchopulmonary dysplasia, children.

Introduction. Respiratory diseases in newborns remain a topical neonatology problem. In the morbidity structure of newborns, respiratory disorders occupy the 2nd place -8.8% and most often develop in premature children due to morphofunctional features of the respiratory system in them [1.4.6]. Respiratory diseases account for 56.7 per cent of neonatal and early childhood deaths [3.7.12]. A special place among neonatal respiratory diseases is occupied by bronchopulmonary dysplasia. This pathology of newborns is noninflammatory lung damage. There are age-specific lymphoid conditions in the airways. For example, newborn children lack diffuse associated lymphoid tissue in the trachea

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wall, and individual lymphocytes in the mucous membrane are extremely rare [8.11]. At this age, therefore, non-specific organ protection factors due to epithelial activity, glands and transcellular transport become the most important. The immune response may be induced in small lymph nodes located in the ventrics of the trachea, but such nodes are not yet typical because they lack lymphoid nodes. It is known that the morphofunctional state of the APUD system is closely related to the phases of inflammation developing in the organs. For example, in the phase of alternative necrotic changes, there is a relatively high level of serotonin in endocrine cells of the lungs, and in the proliferative phase, catecholamines [1,2,9]. Serotonin, according to many authors, has a pronounced inhibitory effect on cell division and tumor growth [10.12].

The phenomenon of adaptation and functional stress with increased production of regulatory peptides and biologically active substances as the disease progressed was replaced by a phase of depletion of neuroendocrine structures, culminating in dystrophy, necrobiosis and necrosis of endocrine cells and neuroepithelial cells in the respiratory tract [5.12].

The literature provides data on structural changes in the lungs and bronchial muscles in this pathology, but there is no information on the relationship of immune-endocrine structures of the bronchus and lungs in brochopulmonary dysplasia. We also evaluated the lung endocrine apparatus at various levels of disease. This article will present the results of the study of congenital and acquired immunity and regulatory structures of the lungs in bronchopulmonary dysplasia in children.

Material and methods of research. Material and methods of research. The following research methods were used to estimate the morphofunctional state of the bronchus and lungs: coloration of hematoxylin and eosin materials, coloration by Van Gison, Weigert and Masson methods, Grimelius impregnation. In addition, immunohistochemical studies were carried out. Two immunohistochemical markers were selected to determine cellular renewal: Ki67 and Bcl2. Immunohistochemical markers CD3 and CD20 were selected for lung lymphocytes.

Material for the study was the bronchus and lungs of deceased newborns who underwent artificial ventilation and contracted bronchopulmonary dysplasia. Autopsy examination of the corpses of deceased children was carried out in the pathological and anatomical department of the 1-clinic of SamSMU from 2015 to 2022. At the initial stage of the selection of the material, new-born children who died between 0 and 1.5 months of age were selected, for a total of 27 cases. During the further formation of the study groups, criteria for material selection were

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developed taking into account clinical and pathomorphological data. Based on inclusion criteria, 27 autopsy cases were selected for further study.

In turn, in order to systematize the clinical material, the core sample was divided into four groups of deceased ventilated children.

The first group includes very underweight newborns (less than 999g (9 cases - 42.9%), with an Apgar rating of 2± 0.8 points at birth, early use of artificial ventilation from birth and death at 11± 0.7 days. The second group included premature newborns - 6 cases (28.5%), with an average body weight of 1,982± 0.5, with an Apgar birth score of 4±0.6, who were on artificial ventilation for 20± 0.7 days and died at 22±0.8 days.

The third group were full-term newborns - 6 cases (28.5 per cent), their average body weight was 2,950±5 g, the Apgar rating was 4± 0.4, the duration of artificial ventilation 27.4 days, the age 33± 0.7 days.

The fourth group consisted of full-term newborns - 6 cases (28.5 per cent), their average body weight was 3,036± 0.5g, Apgar rating was 5 ±0.3, the duration of artificial ventilation 47± 0.8 days, 62± 0.6 days. During the post-mortem examination of the corpses of deceased children, material was collected from light histological examination. The autopsies were carried out between 2 hours and 1 day after the death of the children, in accordance with the provisions of orders of the Ministry of Health of Uzbekistan 574 of 04 November 1992 and Annexes 8. 9.10. Thus, according to our observations, the first group refers to the 1st and 2nd degree of bronchopulmonary dysplasia, the second group to the 3rd degree and the third observation group to the 4th degree of the disease.

Results. On the 4-10 and 11-30 days of bronchial dysplasia, the following morphological changes are observed in bronchial and lung. It is a rosette-expanded bronchiols with a serous fluid substance in its cavity. This indicates an impairment in the structure and function of bronchioli in bronchopulmonary dysplasia. The lungs become airless, dark purple and show emphysema. These changes indicate the breakdown of alveolar structures and the disruption of gas exchange. The presence of "outlet-shaped" bronchiols, which may be complete or incomplete, indicates the progression of broncholegic dysplasia. Hyalin membranes, which prevent the development of socket-shaped bronchiolis, are absent in most cases. There are changes in the structure and composition of bronchial and lung tissues, such as red on the epithelial surface, the presence of randomly arranged collagen and reticular fibers, fibrin filaments and lymphocytes. These changes indicate inflammatory and fibrous processes in the pulmonary tissue. Bronchial walls of different calibers contain granulation tissue, sclerotized connective tissue and

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infiltrates consisting of fibroblasts, fibroblasts, lymphocytes and mast cells. These changes indicate a progressive fibrosis response. Pneumosclerosis foci arise, which begin with the mosaic pneumosclerosis and progress to focal pneumosclerosis. Fetal pneumosclerosis is characterized by sclerotized scar tissue, optically empty intercellular slits and deformed bronchiols. A four-group study found that infants with bronchodilated dysplasia who died in their second month of life had the following macroscopic and microscopic changes. There were deformations in the bronchi, and there was mucosal exudate in their cavity. In the lungs there were atelectases (narrowing or collapse alveoli), which were extensive and combined with small areas of emphysema. The lungs were densely elastic and had a dark crimson color. Enlarged alveolar strokes were observed against the background of the sleeping alveoli. Microscopically, most of the bronchial mucosa was lined with prismatic epithelium. On the epithelial surface and in the cavity of the bronchi, destructed epitheliocytes, fibrin filaments and mucus were found. The small bronchi were thickened and hyperplazed, and there was hypersecretion and destruction of the glandular ducts. In the walls of bronchial and blood vessels of the lung were observed foci of infiltration of lymphocytes, neutrophilic leukocytes, fibroblasts and fibroblasts. Large pockets of fibrosis and sclerosis in the walls of blood vessels led to a decrease in the number of pulmonary arteriols and capillaries. The interalveolar partitions are thicker and swollen, and fibroblast elements proliferate. There's massive fibrosis in the lungs with the destruction of alveoli and air duct walls. In addition, children with bronchopulmonary dysplasia had "Moyar atelectases", characterized by branching ribbons made of connective tissue. When studying the height of the epithelium of bronchial and lung in 2 months of life, the following changes were observed in children with bronchial dysplasia - The thickness of the mucous membrane in large bronchials was 28.4 mm, in middle bronchus - 34.8 mm, in small bronchials - 24.8 mm, and in the respiratory department of the lungs - 18.5 mm. The height of the epithelial cover exceeded its own plate in large bronchi by 1.50 times, in medium bronchi - by 2.06 times, in small bronchi - by 1.88 times, and in respiratory department of lungs - by 1.98 times.

In comparison with the control group, the thickness of large bronchials in children with bronchopulmonary dysplasia increased by 0.21 times, medium bronchial - by 0.014 times, small bronchial - by 0.26 times, and in the respiratory department of the lung - by 0.28 times. This data indicates hyperplasia and hypertrophy of the bronchial epithelium and lung in children with bronchopulmonary dysplasia for two months.

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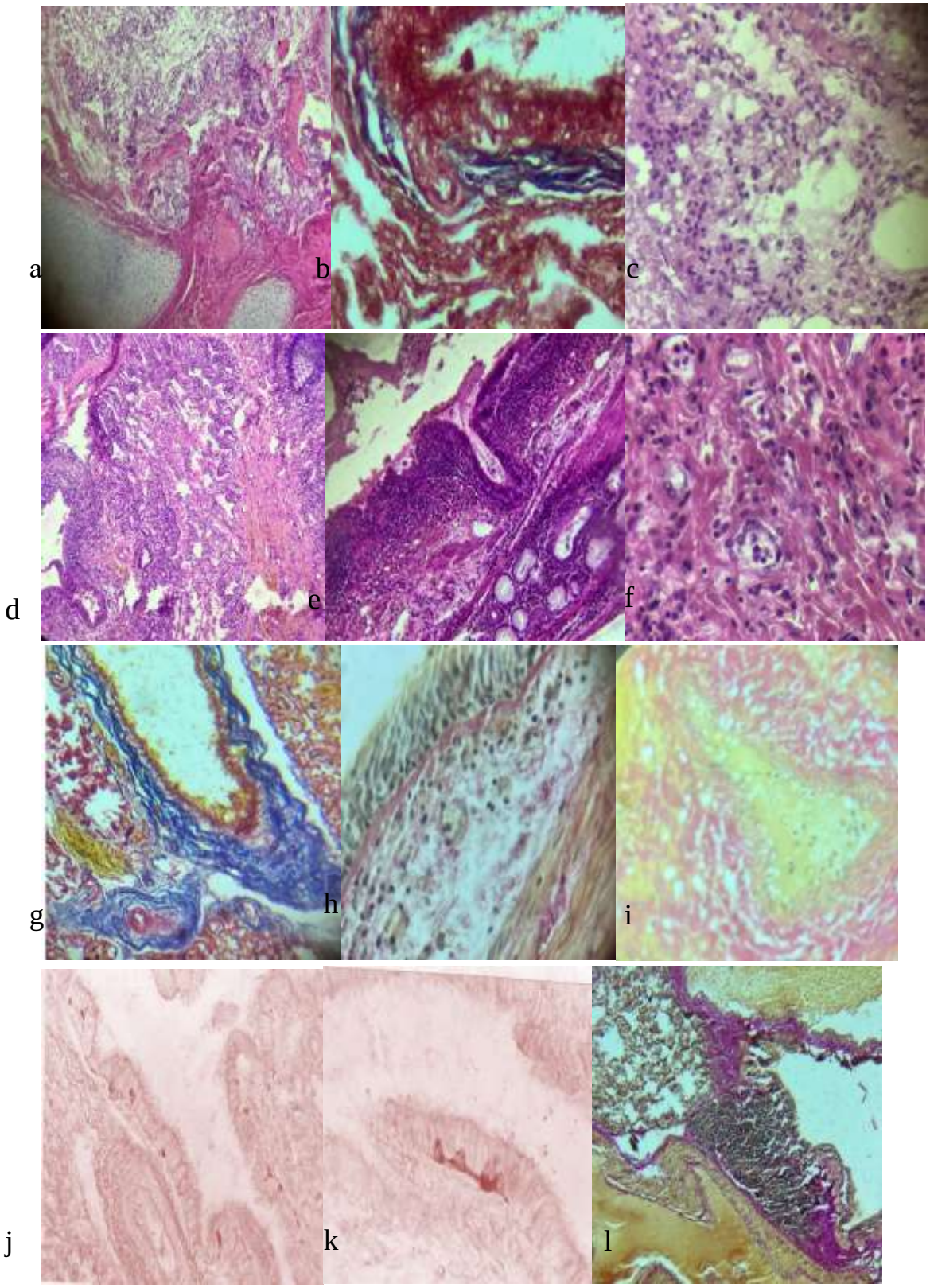
Fig.3. Pathomorphological changes of lungs in bronchopulmonary dysplasia in 3 and 4 observation groups. About 40, approx. 10.



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a- Lung of newborn dead for 11 days of life. Epithelium cells, mucus and fibrin filaments are found in the large bronchial cavity. MRE is hyperplazed and desqualized in places. Coloration with hematoxylin and eosin.

b- The average bronchial baby of the deceased at 1.5 months of life. Pronounced edema of reticular and collagen fibers in the wall. Coloration by Masson.

c- the Lung of a newborn dead for 30 days of life. In the cavity, the alveol is a penile fluid, in the IT of the lung infiltration by lymphocytes, plasmacytes, fibroblasts and fibroblasts. Coloration with hematoxylin and eosin.

d- Lung of the newborn dead for 1.5 months of life. The cavity of terminal bronchiol is overflowing with mucous-hemorrhagic exudate. Most alveoli are atelectasized. See the growth of connective tissue fibers in the lungs. Coloration of hematoxylin and eosin.

e- the lung of the newborn deceased in 2 months of life. MEP is metaplazed in IEE. On the epithelium surface of the mucous-fibrinous exudate. Hypertrophy and hyperplasia of muscle tissue, as well as cystic enlarged KZŁ. Coloration of hematoxylin and eosin.

f- Lung of newborn dead in 2 months of life. Neoangiogenesis and growth of connective tissue fibers in lung interstitial. Coloration with hematoxylin and eosin.

g -The lung of a child who died within 1.5 months of life. Hyperplasia of reticular and collagen fibers in the wall of a large and small vessel of the lung. The Masson method of painting.

h -Light child of the deceased on 1.5 months of life. Picrinophilia of collagen fibers in the joint under the OCE of the lung. Coloration on Van Gizon. About 40, approx.10.

i - Lung of infant deceased at 2 months of life. Metaplasia of IRES in IEE. Severe edema and swelling of collagen fibers SP. Painting on Van Gizon.

j - Lung of the infant of the deceased at 2 months of life. Picrinophilia of collagen fibers of the middle wall of the large blood vessel of the lung. Painting on Van Gizon.

k - Lung of the infant of the deceased in 2 months of life. Sclerosis and pronounced disengagement of the middle wall of the large blood vessel of the lung. Painting on Van Gizon.

l - Apudocytes in the epithelium of the intercolular bronchus. Large number of apudocytes on the longitudinal section of the bronchus. Impregnation on Grimelius.

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m - Binding of apudocytes with basal processes. Light fruit 28 weeks. Impregnation by Grimelius.

n -Medium bronchial baby of the deceased for 38 weeks of ontogeny. Centers of growth of fuxinophilic collagen fibers in IT lung. Painting in Van Gizon.

The percentage of lymphocytes in bronchi of newborn children with bronchial dysplasia in 2 and 3 is 5.68%, and in respiratory department - 10.80%. Its own lymphocyte content is 2.75%.

Compared with epithelium to its own plate, the percentage of lymphocytes in the epithelium to the respiratory tract increases by 2.88. Compared to the control group, the percentage of lymphocytes in the respiratory tract is reduced by 0.77 times. In the case of 4 groups of broncholegic dysplasia, the percentage of lymphocytes in bronchial cells is 5.85%, in respiratory department - 9.40%, and in own record - 2.98%. Compared with epithelium to its own plate, the percentage of lymphocytes in the epithelium to the respiratory tract increases by 2.87 times. Compared to the control group, the percentage of lymphocytes in the respiratory tract decreases by 0.89 times.

In Stage 2 and Stage 3, the number of Ki67-expressing cells in the stroma of the respiratory departments did not decrease. They were mainly concentrated primarily perivascular, sometimes peribronchiolar, and even in the course of long-orbital partitions. In the monitoring group, only single Ki67-positive cells were detected in both the bronchial lining and the alveolar tissue. When analyzing the expression of marker BC1-2, which is one of the main inhibitors of apoptosis, it is found to be most manifest in cells of bronchial and alveolar epithelium, smooth-headed sheaves, alveolocytes and cells of the stroma of the lung. Significant differences have been found in the expression of BC1-2 marker between the third and fourth stages of broncholecular dysplasia. The localization of the Bcl-2 protein largely coincides with the localization of Ki67, but in muscle cells that undergo significant alteration, the expression of Bcl-2 protein predominates over the expression of Ki67. In the control group, no expression of Bc1-2 protein was found in lung cells. Thus, the synthesis of these proteins in the lungs in bronholegic dysplasia increases significantly without significant differences between the second and third stages of the disease, indicating the activation of both genes in the disease. In the 2 and 3 groups of bronchopulmonary pulmonary dysplasia, there is a decrease in the number of apudocytes and net in all bronchi. In the first group, the number of apudocytes was 4.5, but for 4-10 days it fell sharply to 1.8. Similar declines in the number of apudocytes and NETs were observed in other bronchus,

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including subsegmental and terminal bronchus, where they were 0.8. As a result, the total number of endocrine structures also decreased. The localization of apudocytes within the lungs varied slightly.

In four patients with bronchopulmonary dysplasia, there was an increase in the number of apudocytes in the APUD system in the lungs in sub-segmental bronchus (mean 3.7) and intercolculus bronchials (mean 2.1) over the observed period. On transverse sections of the lungs, the number of apudocytes reached 2-3 in bronchi of different diameters, and there were 0.1-1.3 apudocytes per unit area of terminal bronchiol. In intralobular bronchial (0.6) and terminal bronchial (0.4) the number of apudocytes decreased compared to previous observations. In the 2 and 3 groups of bronchopulmonary pulmonary dysplasia, there is a decrease in the number of apudocytes and net in all bronchi. In the first group, the number of apudocytes was 4.5, but for 4-10 days it fell sharply to 1.8. Similar declines in the number of apudocytes and NETs were observed in other bronchus, including subsegmental and terminal bronchus, where they were 0.8. As a result, the total number of endocrine structures also decreased. The localization of apudocytes within the lungs varied slightly.

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Discussion of results. Thus, pathognomonical changes occur sequentially as the disease progresses from bronchioloectasis, stellate atelectasis, bronchiolis, mosaic and focal pneumosclerosis. Pneumosclerosis develop against the backdrop of mumps and fibrous-muscular atectases, small-cystic remodeling of bronchioli against the background of pneumosclerosis and fibrotheliectases. In addition, the restructuring of small arteries and lung arteriol is characterized by hypertrophy and myocyte hyperplasia of bronchioli, hyperelastosis, perivascular sclerosis and myoelastofibrosis. Thus, a permanent sign of neonatal broncholegic dysplasia are atelectases and fibrotelectases, the appearance of which is associated with low activity of the antiatelectic factor. Its stability is influenced by the gestational age of newborns and the hyperoxygenation of pulmonary tissue during artificial ventilation. The predominant localization of cells expressing Ki-67-protein is topographically consistent with the location of generative zones in the

bronchopulmonary system. The high level of expression of markers of proliferation, antiapoptotic factor 3 and 4 stages of bronchopulmonary dysplasia indicates an increase in the rate of cellular renewal in the lungs of this disease and its progression during the entire observation period. Thus, the highest number of apudocytes is found in sub-segmental bronchii.

Conclusions.

1. In the progression of the disease from bronchioloectasis to the mosaic and center pneumonic sclerosis, pathognomonical changes appear successively, including stellate atectases, rosette reconstruction of bronchiol and mosaic pneumosclerosis.

2. In the reconstruction of small arteries and lung arteriol, hypertrophy and muscle hyperplasia of bronchiol, hyperelastosis, perivascular sclerosis and myoelastofibrosis.

3. The cells expressing Ki-67-protein in the bronchial system are located primarily in generative zones.

4. The high level of expression of markers of proliferation and antiapoptotic factor indicates an increased rate of cellular renewal in the lungs during bronchopulmonary dysplasia and disease progression.

5. The increase in the number of apudocytes is mainly observed in sub-segment and interregional bronchial cells in bronchopulmonary dysplasia.

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