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CLINICAL AND MORPHOLOGICAL ANALYSIS OF A PULMONARY ALVEOLAR PROTEINOSIS CASE IN AN INFANT

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This paper presents a clinical case of undiagnosed pulmonary alveolar proteinosis in a 43-day-old child, verified pathomorphologically, including a detailed clinico-morphological analysis. Due to diverse etiopathogenetic mechanisms and non-specific clinical manifestations – specifically, progressive respiratory failure mimicking treatment-resistant interstitial pneumonia – pulmonary alveolar proteinosis remains a significant diagnostic challenge. Early detection is crucial for effective treatment and prognosis. The stages of differential diagnosis, based on the dynamics of clinico-laboratory and instrumental changes, are highlighted. Key diagnostic steps included radiographic detection of bilateral lung opacification without clear focal points and echocardiographic confirmation of severe pulmonary hypertension. A distinctive feature of this case was the paradoxical clinical presentation: the absence of fever and a negative SARS-CoV-2 antigen test despite the mother having moderate COVID-19 at 31–32 weeks of gestation, indicating profound immune reactivity. It was established that the cause of secondary PAP in this child was an immunodeficiency syndrome associated with thymus pathology. The immunodeficiency manifested as a deficiency of cells across all major lymphocyte subpopulations and reduced neutrophil phagocytic activity. Despite intensive therapy, the case was fatal on the 19th day of hospitalization. Pathomorphologically, the diagnosis was confirmed by the presence of PAS-positive eosinophilic material within the alveoli and grade V thymus atrophy.

Key words: immunodeficiency, etiology, differential diagnosis, pathomorphology, thymus atrophy, pulmonary alveolar proteinosis.

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КЛІНІКО-МОРФОЛОГІЧНИЙ АНАЛІЗ ВИПАДКУ ЛЕГЕНЕВОГО АЛЬВЕОЛЯРНОГО ПРОТЕЇНОЗУ У ДИТИНИ ГРУДНОГО ВІКУ

У даній роботі представлено клінічний випадок недіагностованого легеневого альвеолярного протеїнозу у дитини віком 43 дні, верифікований патоморфологічно, з проведенням детального клініко-морфологічного аналізу. Через різноманітність етіопатогенетичних механізмів та неспецифічність клінічних проявів – зокрема, прогресуючу дихальну недостатність, що імітує резистентну до лікування інтерстиціальну пневмонію – легеневий альвеолярний протеїноз залишається складним діагностичним завданням. Раннє виявлення є вирішальним для ефективного лікування та прогнозу. Висвітлено етапи диференціальної діагностики на основі динаміки клініко-лабораторних та інструментальних змін. Ключові діагностичні кроки включали рентгенологічне виявлення двобічного затінення легень без чітких вогнищ та ехокардіографічне підтвердження тяжкої легеневої гіпертензії. Відмінною рисою цього випадку була парадоксальна клінічна картина: відсутність лихоманки та негативний тест на антиген SARS-CoV-2 попри те, що мати перенесла COVID-19 середнього ступеня тяжкості на 31–32 тижні вагітності, що вказувало на глибоку імунну ареактивність. Встановлено, що причиною вторинного легеневого альвеолярного протеїнозу у цієї дитини став синдром імунодефіциту, пов'язаний із патологією тимуса. Імунодефіцит проявлявся дефіцитом клітин усіх основних субпопуляцій лімфоцитів та зниженням фагоцитарної активності нейтрофілів. Незважаючи на інтенсивну терапію, на 19-й день госпіталізації було зафіксовано летальний випадок. Патоморфологічно діагноз був підтверджений наявністю PAS-позитивного еозинофільного матеріалу в альвеолах та атрофією тимуса V ступеня.

Ключові слова: імунодефіцит, етіологія, диференціальна діагностика, патоморфологія, атрофія тимуса, легеневий альвеолярний протеїноз.

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Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by impaired surfactant clearance with the accumulation of protein-lipid PAS-positive material in the alveolar lumens, leading to impaired gas perfusion and progressive respiratory failure [7].

This rare disease occurs with an approximate frequency of 1–6 cases per 1 million population, predominantly in men aged 30–40 years. It is extremely rare in children and the elderly [6]. The development of this disease doesn't depend on ethnic origin, geographical region, or socioeconomic status, but it's observed more frequently among smokers [11].

PAP, as a syndrome of pathological surfactant homeostasis, depending on its etiology and pathogenesis, is divided into three types (Table 1) [7].

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Table 1

Etiopathogenetic Classification of Pulmonary Alveolar Proteinosis

Type of PAP	Etiology
Primary PAP – impaired GM-CSF*	1) Autoimmune PAP – formation of antibodies to GM-CSF. 2) Hereditary PAP – gene mutation of GM-CSF receptor (antibodies to GM-CSF absent)
Secondary PAP	1) Hematological diseases (myelodysplasia, leukemia, lymphomas). 2) Chronic infections (HIV, nocardiosis, pneumocystis). 3) Chronic inflammation. 4) Immunodeficiencies and immune dysregulation. 5) Drug effects (including chemotherapy).
Congenital PAP (impaired surfactant production)	Mutations in genes involved in various mechanisms of surfactant synthesis and transport (SFTPB, SFTPC, ABCA3, TTF1).

*GM-CSF – granulocyte-macrophage colony-stimulating factor.

There is a subgroup of PAP patients who don't meet the above criteria for any type, and the etiology of the disease is undefined; therefore, an unclassified type is distinguished separately [12].

PAP is a rare disease, the diagnosis of which is complex and requires a high level of knowledge. The causes of this disease, which are important for choosing a treatment method, differ in children and adults [4].

In children, the autoimmune form is very rare. Autoantibodies against GM-CSF, whose main function is the elimination of surfactant by alveolar macrophages, are the most common cause of PAP in adults [1]. In childhood, genetic factors are more prevalent, and cases of secondary PAP associated with congenital or acquired immunodeficiency are also encountered [8].

Therefore, PAP is not often encountered in medical practice, especially in pediatric practice, and causes significant diagnostic difficulties due to the absence of pathognomonic clinical manifestations.

The purpose of the study was to provide a clinico-morphological analysis of a case of undiagnosed pulmonary alveolar proteinosis in a child, pathomorphologically verified.

Materials and methods. This clinical case report was prepared in accordance with the CARE Guidelines (2013) and the ethical principles of the Declaration of Helsinki (2024 revision). Ethical approval was granted by the Bioethics Committee of Poltava State Medical University (Protocol No. 232, dated 21.11.2024).

A clinico-morphological analysis was conducted on a fatal case of a 43-day-old girl treated at the Poltava Regional Clinical Hospital from 12/2020 to 01/2021. Data were obtained from inpatient medical records, including laboratory tests performed on the HumaCount 80TS/Human GmbH analyzer and instrumental findings (X-ray, Ultrasound).

Post-mortem examination included a full autopsy and histological analysis. Tissue samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections (4–5 μm) were stained according to the standard technique with hematoxylin and eosin, and Periodic Acid-Schiff (PAS) staining was performed to identify the protein-lipid substrate. Bacteriological cultures were processed using VITEK 2 (bioMérieux, France). Written informed consent was obtained from the deceased's mother.

Results of the study and their discussion. A 43-day-old girl was hospitalized with food refusal and respiratory failure. The child was born from the II pregnancy, II delivery at 36 weeks of gestation (weight 2190 g, height 47 cm). The Apgar score was 6/7. Delivery was complicated by a prolonged anhydrous period according to the mother's history. The mother had moderate COVID-19 at 31–32 weeks of gestation. The infant's general condition at birth was satisfactory. Between discharge and the 43rd day of life, the child exhibited poor weight gain and lethargy.

Upon admission, the child's general condition was severe. Objectively: skin was pale, acrocyanosis; auscultation revealed weakened breathing on both sides, 85 respiratory movements per minute, moderate intercostal retraction, SpO2–84 %. Heart rate – 167/min. Respiratory support was initiated using a Hamilton-C3/Hamilton Medical ventilator in CPAP mode. Preliminary diagnosis included community-acquired pneumonia and congenital heart defect.

Reaction to examination – loud crying. Neurological examination: reflexes were elicited, but quickly exhausted; muscle tone was reduced; facial asymmetry was noted; palpebral fissures D>S, smoothed nasolabial fold on the right, ptosis of the left eyelid. The preliminary diagnosis was: community-acquired pneumonia, atrial septal defect complicated by respiratory failure II degree, hypoxic-ischemic damage to the central nervous system with a syndrome of increased neuro-reflex excitability. Concomitant diseases – left-sided ptosis, facial nerve paresis.

In the department, the child underwent a complete examination and was consulted by a cardiologist, neuropathologist, and immunologist.

Complete blood count: Hb – 88 g/L, RBC – 2.66×10^{12}/L, ESR – 2 mm/h, WBC – 12×10^{9}/L, LYM – 36.5 %, MID – 6.4 %, GRA – 57.1 %, PLT – 218×10^{9}/L. Urinalysis showed no pathological changes. The IgM test for SARS-CoV-2 was negative. Immunogram results revealed an absolute total decrease in all lymphocyte subpopulations defined by clusters of differentiation (CD) and reduced phagocytic activity of neutrophils.

Chest X-ray: the right lung was unevenly opacified throughout its entire volume with greater intensity in the upper lobes; a clear strip paramediastinally on the right, and an area of increased transparency above the diaphragm. On the left, transparency was unevenly reduced up to the 5th rib. The position of the mediastinal shadow was normal, the shape and size of the heart shadow were normal. Large bronchi were visualized in both lungs. Conclusion: hyaline membranes, edema not excluded.

Echocardiography data – enlarged right heart chambers with myocardial hypertrophy. Reduced left heart chambers. Contractile function was satisfactory. Large atrial septal defect. Anomalous pulmonary venous drainage. High pulmonary hypertension. Thymus size was somewhat reduced.

Neurosonography – CSF pathways were not dilated. Small periventricular edema.

Ultrasound examination of the lungs and abdominal organs – pleural sinuses contained no fluid; against the background of interstitial syndrome, data indicated bilateral lower lobe pneumonia. Enlarged liver.

According to the diagnosis, the prescribed treatment included hemotransfusion, antibacterial therapy (Ampicillin 230 mg; amikacin 52 mg), immunoreplacement (human normal immunoglobulin 5% 14 ml), and hormonal therapy (hydrocortisone 7 mg). However, no clinical improvement was observed. On the 15th day, hemorrhagic syndrome with pulmonary hemorrhage developed, requiring rigid ventilation parameters, high oxygen dependence, and arterial hypotension. Despite rigid ventilation and dopamine support, the child died on the 19th day of treatment.

Pathomorphological Findings. During autopsy, the lungs were found to be gray with dark cherry areas, dense and poorly aerated. In a hydrostatic test, fragments of the lungs sank in water, indicating total loss of airiness due to alveolar filling.

Lung sizes: right – 9×4.5×4 cm, weight – 96 g; left – 9.3×4×3.5 cm, weight – 78 g. Heart sizes: 5.5×4.5×3 cm, weight – 34 g. A defect of 1 cm in diameter was found in the interatrial septum. The thickness of the right ventricular wall was 0.9 cm, the left – 0.8 cm. The width of the pulmonary artery at the valve level was 2.2 cm, the aorta – 2.0 cm. Spleen sizes: 7.5×4.5×1.3 cm, weight – 24 g; its pulp was dark cherry in color. Liver sizes: 13.5×7×6.5×4 cm, weight – 166 g; capsule was smooth, on section the parenchyma was dark brown, plethoric, homogeneous, and of dense-elastic consistency. Renal adipose capsule was weakly expressed. The surface of the kidneys was brown, embryonically lobulated. Kidney sizes: 5.5×2.5×2.5 cm, weight – 28 g each. On section, the layers were distinct, the thickness of the cortical layer was 0.3 cm, and the pyramids were dark red. Thymus size 4×3×0.4 cm, weight – 4 g, gray, mucinous. Pieces of internal organs were taken for histological examination. Pieces of liver and lung were taken for bacteriological examination.

Histological examination revealed alveoli filled with eosinophilic, PAS-positive masses containing small globules, desquamated alveolar cells, and blood elements. Interalveolar septa were thickened, fibrotic; vessels were plethoric, their walls thickened (Fig. 1). Hemorrhages were noted in numerous alveoli (Fig. 2).

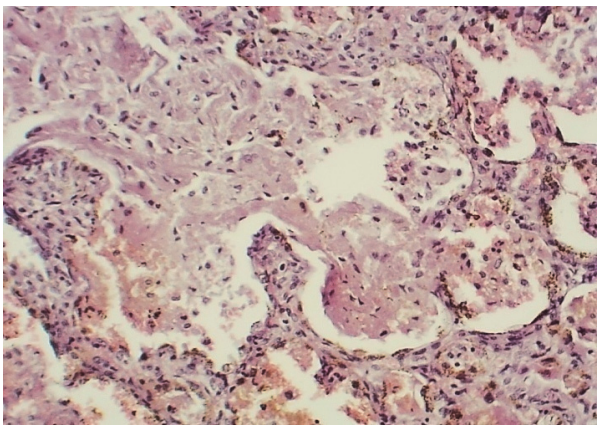

Fig. 1. Lung alveoli filled with homogeneous eosinophilic substance. Staining with hematoxylin and eosin. Magnification ×100.

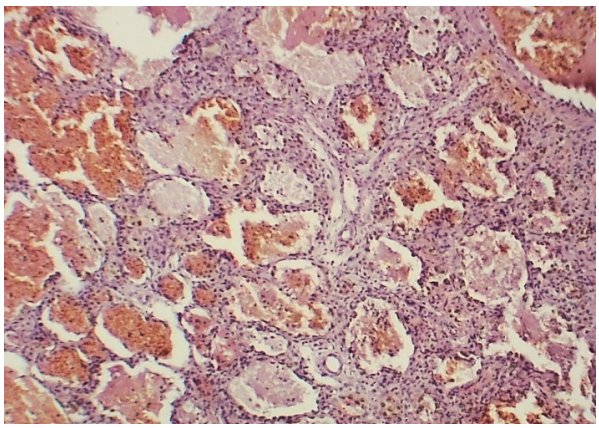

Fig. 2. Hemorrhages in the alveolar lumens. Staining with hematoxylin and eosin. Magnification ×40.

In the thymus, a sharp collapse of lobules was noted; the interlobular septa were wide, edematous, the lobules consisted of reticulocytes and lymphocytes, and thymic corpuscles were scarce, consistent with grade V atrophy. In other organs, microscopic examination revealed dystrophic changes and edema.

Bacteriological examination of lung and liver samples yielded no bacteria.

Based on the changes found and the analysis of laboratory data, a pathological diagnosis was formulated.

Main Combined Disease:

1. Pulmonary alveolar proteinosis.

2. Congenital heart defect – atrial septal defect, anomalous pulmonary venous drainage.

Background Disease: Thymus atrophy Grade V. Secondary immunodeficiency (clinical).

Complications of the Main Disease: Hypertrophy of the walls of the right and left ventricles of the heart; cerebral edema; dystrophy and hyperemia of internal organs.

Respiratory diseases are difficult to diagnose, especially if they are rare or combined with other pathologies that alter the clinical picture [3]. This case is no exception.

Differential diagnosis of PAP is challenging because this disease is rare and characterized by non-specific symptoms. Often, PAP is mistakenly diagnosed as pneumonia, but the ineffectiveness of antibiotic therapy should prompt clinicians to reconsider the diagnosis. Diagnosis of PAP is based on a combination of symptoms, radiological imaging, computed tomography, and bronchoscopy with PAS staining of bronchial contents. In addition, testing for autoantibodies against GM-CSF is part of the diagnostic process [12]. Radiographically, PAP manifests as diffuse symmetrical bilateral opacification, which can progress to confluent infiltrates of the “ground-glass” type [2]. However, the COVID-19 pandemic has introduced its own adjustments to the diagnostic process, as a combination of fever and ground-glass opacities on radiographs is characteristic of SARS-CoV-2 induced pneumonia at any age [10].

Differential diagnosis of PAP is challenging due to non-specific symptoms. In this case, the “clinical mask’ of pneumonia was deceptive; however, the lack of fever and negative COVID-19 tests during the pandemic suggested a state of deep immune areactivity.

In the presented case, the child didn't have an elevated body temperature and had a negative test for the SARS-CoV-2 nucleocapsid antigen, which ruled out COVID-19. The negative dynamics during antibiotic therapy should also have alerted doctors regarding pneumonia.

Congenital PAP accounts for 1.5 % among all types and predominantly occurs in newborns [5]. In infants homozygous for recessive SFTPB mutations, respiratory failure with a fatal outcome develops [11]. In children heterozygous for recessive SFTPB alleles, lung function is not impaired. With autosomal dominant SFTPC mutations, interstitial lung disease can develop regardless of the age group. Homozygous infants with recessive ABCA3 mutations suffer from surfactant deficiency. Other ABCA3 mutations lead to surfactant insufficiency, which contributes to the development of chronic respiratory diseases in older children and adults. TTF1 deficiency can lead to combined manifestations in newborns, including hypothyroidism, brain abnormalities, and acute and chronic lung diseases [12].

In some children with PAP, especially with GM-CSF receptor mutations, the disease may manifest with symptoms of acute respiratory infection, accompanied by fever or chest pain [1].

Genetic testing wasn't performed on the child, but the symptom complex, the results of laboratory methods, and the post-mortem examination indicate the development of secondary PAP caused by immunodeficiency in the deceased child. In this case, immunodeficiency was manifested by a decrease in all CD classes and phagocytic activity of neutrophils, and pathomorphologically, grade V thymus atrophy was found. This is supported by some reports [9] that the most common immunodeficiency syndromes that may be associated with secondary PAP include thymic lymphoplasia (lymphocyte deficiency in the thymus), immunoglobulin A deficiency, immunosuppression after organ transplantation, and AIDS, and survival in such children is extremely rare.

The primary limitation of the study is the absence of genetic testing for SFTPB or ABCA3 mutations. While autopsy findings (Grade V thymus atrophy) confirm a secondary type of PAP due to immunodeficiency, a potential genetic defect cannot be entirely ruled out.

Conclusions

1. The analyzed clinical case confirms that pulmonary alveolar proteinosis (PAP) remains extremely difficult to diagnose during life in pediatric practice. This is due to the rarity of the pathology and its ability to mimic severe, treatment-resistant pneumonia, congenital heart defects, or acute respiratory distress syndrome (ARDS).

2. It was established that the secondary form of PAP in this infant was caused by a profound immunodeficiency state, the morphological substrate of which was Grade V thymus atrophy. This resulted

in a global lymphocyte deficiency and impaired macrophage phagocytic function, both of which are critical for the clearance of spent surfactant from the alveoli.

3. The absence of fever and negative SARS-CoV-2 test results, amidst progressive respiratory failure and "ground-glass" opacities on radiographs, should be interpreted as signs of immune areactivity. Such a clinical picture necessitates an immediate expansion of diagnostic efforts, including an immunogram and, if feasible, bronchoalveolar lavage.

4. Pathomorphological verification remains the "gold standard" for diagnosis. The detection of eosinophilic masses within the alveolar lumens allows for the differentiation of PAP from other interstitial lung diseases. Early recognition of this specific substrate is crucial for initiating pathogenesis-based therapy and improving the prognosis for survival in children with underlying immunodeficiency syndromes.

Prospects for further research include substantiating the differential diagnosis of various types of pulmonary alveolar proteinosis based on clinico-morphological data.

References

1. Bush A, Pabary R. Pulmonary alveolar proteinosis in children. Breathe. 2020; 16:200001. doi: https://doi.org/10.1183/20734735.0001-2020.

2. Carrington JM, Hershberger DM. Pulmonary Alveolar Proteinosis; Stat Pearls: St. Petersburg, FL, USA, 2023.

3. Filenko BM, Roiko NV, Starchenko II, Proskurnya SA, Nikolenko DY. Clinical and morphological analysis of pulmonary aspergillosis coinfection in COVID-19. Azerbaijan Medical Journal. 2022;2:145–150. doi: https://doi.org/10.34921/amj.2022.2.023.

4. Griese M, Panagiotou P, Manali ED, Stahl M, Schwerk N, Costa V, et al. Autoimmune pulmonary alveolar proteinosis in children. ERJ Open Res 2022;8:00701-2021. doi: https://doi.org/10.1183/23120541.00701-2021.

5. Iftikhar H, Nair GB, Kumar A. Update on Diagnosis and Treatment of Adult Pulmonary Alveolar Proteinosis. Ther. Clin. Risk Manag. 2021;17:701-710. doi: https://doi.org/10.2147/TCRM.S193884.

6. Jayaram IN, Kumar RRBK. Pulmonary alveolar proteinosis in children: An unusual presentation with significant clinical impact. IJPM. 2018; 61(3): 418-20. doi: https://doi.org/10.4103/IJPM.IJPM_17_17.

7. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary Alveolar Proteinosis in Adults: Pathophysiology and Clinical Approach. Lancet Respir. Med. 2018;6:554–565. doi: https://doi.org/10.1016/S2213-2600(18)30043-2.

8. McCarthy C, Bonella F, O'Callaghan M, Dupin C, Alfaro T, Fally M, Borie R, et al. European Respiratory Society guidelines for the diagnosis and management of pulmonary alveolar proteinosis. Eur Respir J. 2024;64(5):2400725. doi: https://doi.org/10.1183/13993003.00725-2024.

9. Salvaterra E, Campo I. Pulmonary alveolar proteinosis: from classification to therapy. Breathe. 2020;16(2):200018 doi: https://doi.org/10.1183/20734735.0018-2020.

10. Sisman M, Karapolat S, Topaloglu O, Akdogan A, Turkyilmaz A. A case of pulmonary alveolar proteinosis misdiagnosed as COVID-19 pneumonia. Cirugía y cirujanos. 2022;90(3):402-405. doi: https://doi.org/10.24875/ciru.21000746.

11. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers. 2019;5(1):16. doi: https://doi.org/10.1038/s41572-019-0066-3.

12. Wołoszczak J, Wrześniewska M, Hrapkowicz A, Janowska K, Szydziak J, Gomułka K. A Comprehensive Outlook on Pulmonary Alveolar Proteinosis – A Review. International Journal of Molecular Sciences. 2024; 25(13):7092. doi: https://doi.org/10.3390/ijms25137092.

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