

DOI: <https://doi.org/10.34921/amj.2024.4.029>**AĞCIYƏRİN NADİR RAST GƏLİNƏN TƏSNİF EDİLMƏMİŞ KARSİNOMASI:
DİAQNOSTİKA PROBLEMLƏRİ****B.N.Filenko¹, N.V.Royko¹, İ.İ.Starçenko¹, O.V.Starçenko²,
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Xülasə. Məqalədə sağ ikən klinik diaqnozu qoyulmayan, yalnız ölümündən sonrakı diferensial diaqnostika prosesində immunohistokimyəvi analiz vasitəsilə diaqnozu dəqiqləşdirilən ağciyərin psevdomezotetiometoz karsinoması xəstəsi haqqında məlumat verilmişdir. Bu xəstəlik diaqnostikasının çətinliyinə görə cərrah, onkoloq və patoloqanatomlardan xüsusi diqqət tələb edilir.

Psevdomezoteliometoz ağciyər karsinoması nadir rast gəlinən şiş xəstəliyidir. Buna görə plevranın zədələnməsi ilə və xüsusən də plevrada eksudat toplanması ilə müşayiət olunan xəstəliklər zamanı diferensial diaqnostika vasitəsilə xəstəyə diaqnoz qoyulduqda bu xəstəliyi də nəzərə almaq lazımdır. Bu xəstəliyin proqnozunun pis olmasına və effektiv müalicə metodunun olmamasına baxmayaraq, adı çəkilən şişin öyrənilməsi pasiyentlərin yaşama müddətinin artırmağa və diferensial diaqnostikanı yaxşılaşdırmağa imkan verə bilər. Nəzərə alınmalıdır ki, psevdomezotetiometoz karsinhomanın diaqnostikası əsasən şiş materialının immunohistokimyəvi analizindən asılıdır.

Açar sözlər: psevdomezotetiometoz karsinoma, multispiral kompüter-tomografiya, immunohistokimyəvi tədqiqat

Ключевые слова: псевдомезотелиоматозная карцинома, мультиспиральная компьютерная томография, иммуногистохимическое исследование

Key words: pseudomesotheliomatous carcinoma, multispiral computed tomography, immunohistochemical study

**A RARE CASE OF UNCLASSIFIED CARCINOMA OF THE LUNG:
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The article provides information about a case of pseudomesotheliomatous lung carcinoma, which was clinically undiagnosed but confirmed postmortem through immunohistochemical analysis during differential diagnosis. In the reported case, the diagnosis making was a challenge to physicians, and, therefore, this case deserves attention from surgeons, oncologists and pathologists.

Pseudomesotheliomatous carcinoma of the lung is a rare malignant lung tumor, but it should always be kept in mind until the final diagnosis is made in the differential diagnosis of pulmonary disease involving the pleura, especially in the presence of pleural effusion. Nonetheless the poor prognosis and lack of effective treatment approaches, the study of this tumor will further improve the survival of patients and improve the differential diagnosis, since the diagnosis depends mainly on its immunohistochemical verification.

Introduction. Pseudomesotheliomatous carcinoma of the lung (PMCL) is a rare variant of a malignant tumor characterized by diffuse subpleural growth beneath the visceral

pleura, which can mimic various diseases of the pleura. Epidemiological parameters of this tumor are unknown, since isolated cases have been found in the literature. In addition,

PMCL is difficult to diagnose because it clinically, radiologically, and macroscopically resembles malignant pleural mesothelioma. Also, difficulties in the diagnostic process occur in the presence of hemo-, hydro-, pneumothorax, which is rare in lung carcinomas [1, 2].

PMCL most commonly occurs in men aged 60-80 years, the vast majority of whom are smokers [3]. PMCL is divided into two main groups: primary lung tumors that diffuse into the pleura and metastatic tumors. Primary pseudomesotheliomatous tumors are histopathologically characterized by several subtypes: lung adenocarcinomas (more common), squamous cell lung cancer (rare), and other rarer variants [4]. The peculiarity of this tumor is its unusual behavior, characterized by diffuse growth into the pleura and, accordingly, the lack of effective treatment and poor prognosis [1].

Nonetheless the poor prognosis and lack of effective treatment approaches, the study of this tumor will further improve the survival of patients and improve the differential diagnosis, since the diagnosis depends mainly on its immunohistochemical verification.

We report a lethal case of clinically nondiagnosed pseudomesotheliomatous carcinoma of the lung that was subsequently verified postmortem.

Case report. The 58-year-old male patient K. developed chest pain on the left, shortness of breath during physical activity, intermittent cough, general weakness, and fever up to 38°C two months prior his death. From the past medical history it is known that the man worked abroad at a factory for the production of canned fish, the influence of harmful factors of production was denied. He sought medical help from a family doctor who prescribed antibacterial and anti-inflammatory therapy. However, the patient's condition did not improve significantly, and he was hospitalized in the surgical department of the hospital at the place of residence. Chest X-ray revealed the level of fluid in the left pleural cavity, therefore the patient underwent Bülow drainage of the left pleural cavity and conservative treatment was provided. Cytological examination of pleural effusion was not performed. Due to the lack of positive dyna-

mics for further examination and treatment, he was referred to the thoracic department of the Regional Clinical Hospital with a diagnosis of left hydropneumothorax, bronchopleural fistula, drainage of the left pleural cavity.

In the hospital he was examined clinically and instrumentally, evaluated by a thoracic surgeon and other specialists, and repeatedly examined by the team of the physicians.

Blood test revealed: HGB – 108g/L; RBC – $4,0 \times 10^{12}$ /L; WBC – $24,5 \times 10^9$ /L without significant changes in the leukocyte formula; total plasma protein – 55.7 g/L; fibrinogen – 4.22 g/L. Other blood indicators were unremarkable.

Chest radiography revealed left polysegmental destructive pneumonia, the presence of fluid in the left pleural cavity. Multispiral computed tomography (**Fig. 1**) revealed signs of left pneumohydrothorax, pleural empyema, condition after drainage of the left pleural cavity, infiltrative changes of the left lung with the phenomena of lower lobe destruction, mediastinal lymphadenopathy, hydropericardium.

The findings of the laboratory and instrumental studies showed no other significant changes. The patient was diagnosed with community-acquired left polysegmental destructive pneumonia, parapneumonic empyema of the left pleural cavity (pyopneumothorax).

On the 14th day of inpatient antibiotic therapy, the patient experienced a sudden sharp violation of cardiopulmonary activity, resuscitation measures were unsuccessful and biological death was stated.

At the autopsy, it was found that the left pleural cavity, which is partially obliterated, contains a large amount of fibrous density of bundles, which makes it impossible to isolate the left lung in its entirety (**Fig. 2 a**), mainly in the area of the apex. The visceral pleura of the left lung is diffusely sharply thickened to 15 mm (**Fig. 2 b**), hilly, fibrous density with areas of fibrin layering. The lungs are not enlarged, doughy to the touch in all lobes, without the presence of focal seals. Lung tissue is grayish-red on the incision, moderate amount of bloody-foamy fluid flows from the incision surface.

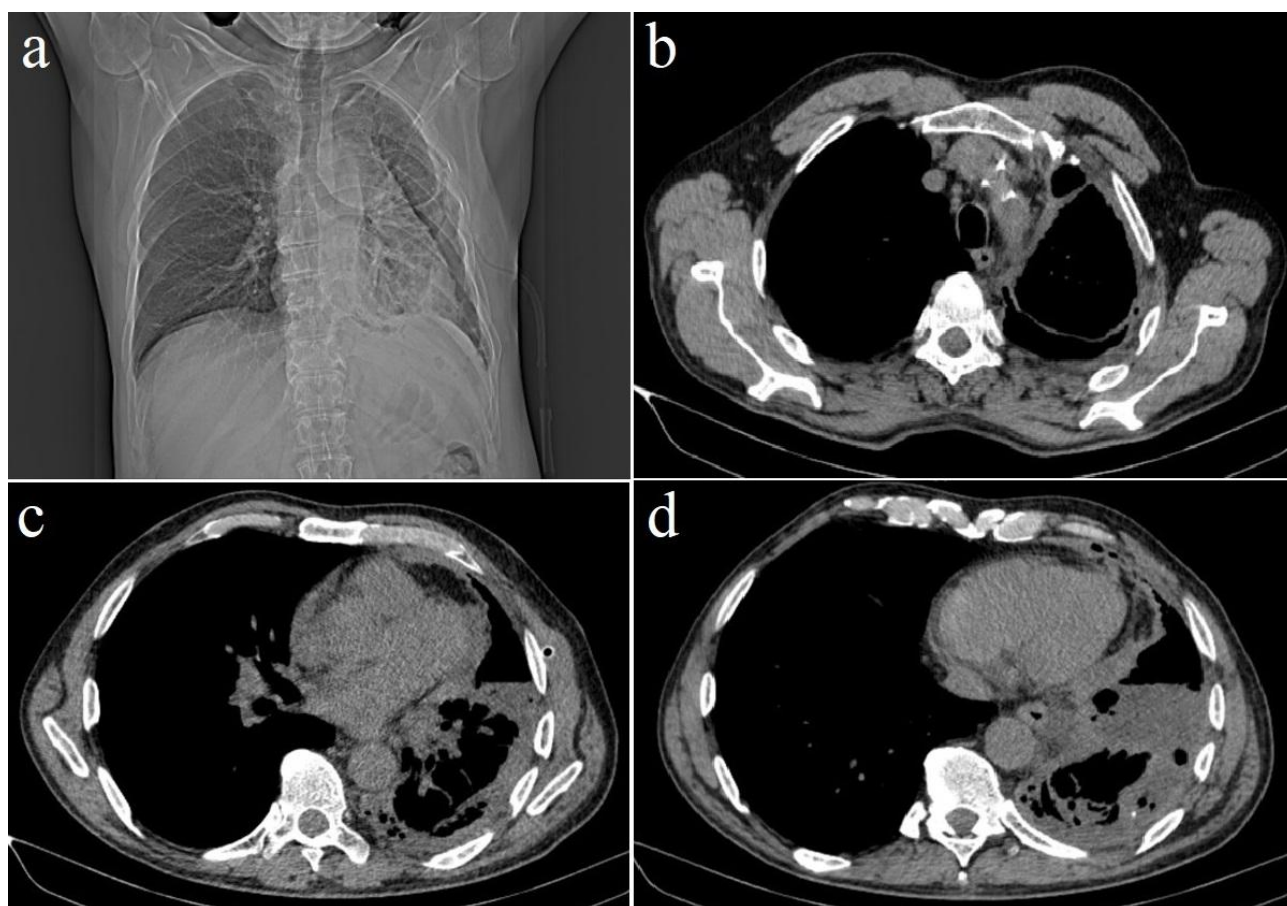


Fig. 1. Chest multispiral computed tomography of the patient K.: topogram (a); sections in the axial plane (b-d).

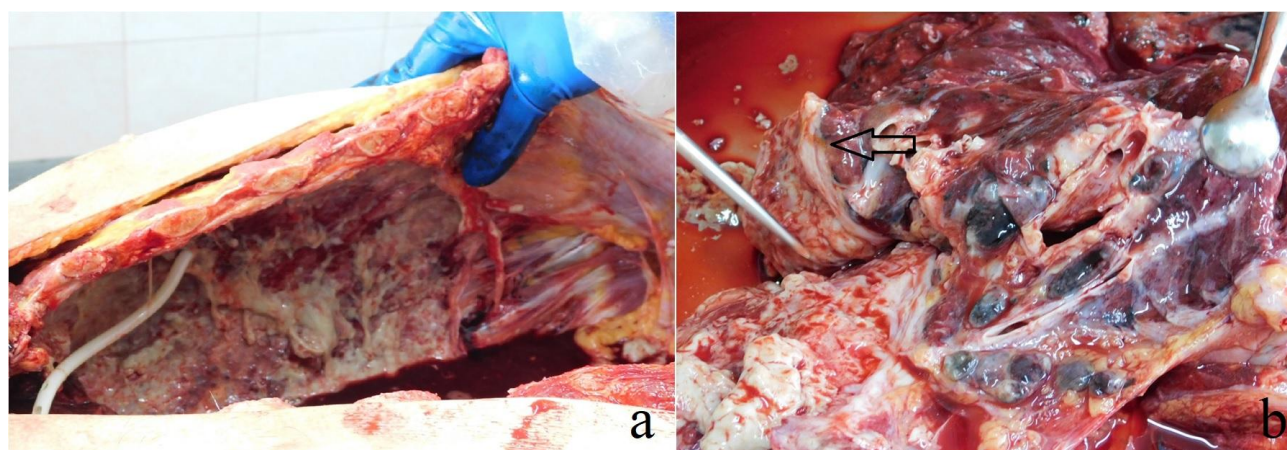


Fig. 2. Macroscopic appearance at the autopsy of a corpse:
a – parietal wall of the left pleural cavity with layers of fibrous bundles and tumor fragments after lung resection; b – visceral pleura of the left lung with diffuse thickening on the section (arrow).

The autopsy and the subsequent histological examination of the section material revealed that the patient suffered from a malignant neoplasm of the left lung pleura with proliferation to the subpleural parts of the left lung tissue, pericardium with metastases to parabronchial and paratracheal lymph nodes. Microscopically, the tumor was represented

by solid layers of large cancer cells with pronounced polymorphism (**Fig. 3a**), surrounded by the interlayers of loose connective tissue and glandular or ductal structures, lined with cuboidal or columnar cells surrounded by hyalinized stroma (**Fig. 3b**). Focal desquamation of cancer cells in layers was observed.

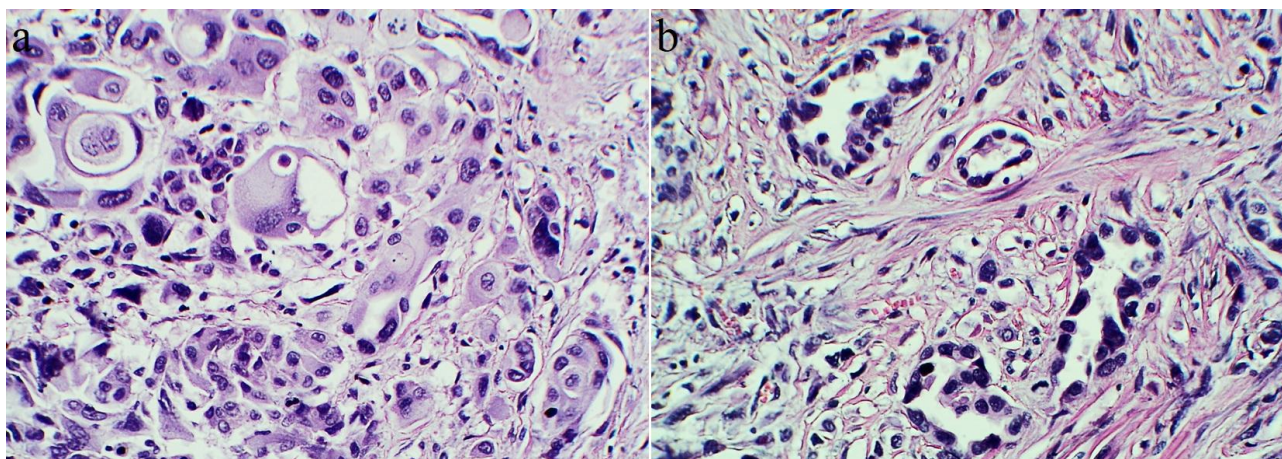


Fig. 3. Microscopic structure of the tumor: a – solid layers of polymorphic giant cells; b – duct-like structures lined with atypical cuboidal cells (H&E stain, $\times 100$ magnification).

On the basis of the resulting data the diagnosis was made: pleomorphic giant cell variation of pleural malignant mesothelioma. However, since no exposure of the patient to asbestos was declared and due to diverse histological picture of epithelioid mesotheliomas, they are difficult to distinguish from adenocarcinomas, affecting the serous membranes, under routine microscopy. Therefore, immunohistochemical study was performed to confirm the diagnosis based on the recommendations of the International Commission on Mesothelioma, which proposes a combination of two “positive” mesothelial and two “nega-

tive” markers of carcinoma. The choice of IH markers for inclusion into the panel varies depending on the localization, histological type and differential diagnosis, which is taken into account in each case [5].

We used monoclonal antibodies to Ber-EP4, Calretinin, CEA, CD15, S-100, TTF1, WT1. The reaction with Calretinin, WT1, TTF-1 and CD15 (**Fig. 4**) was negative in tumor tissue, though a pronounced expression of the CEA, CK 5/6, Ber-EP4 (**Fig. 4**) markers in cancer cells was noted, as well as the expression of the S-100 marker in both small cells and stromal tumor component.

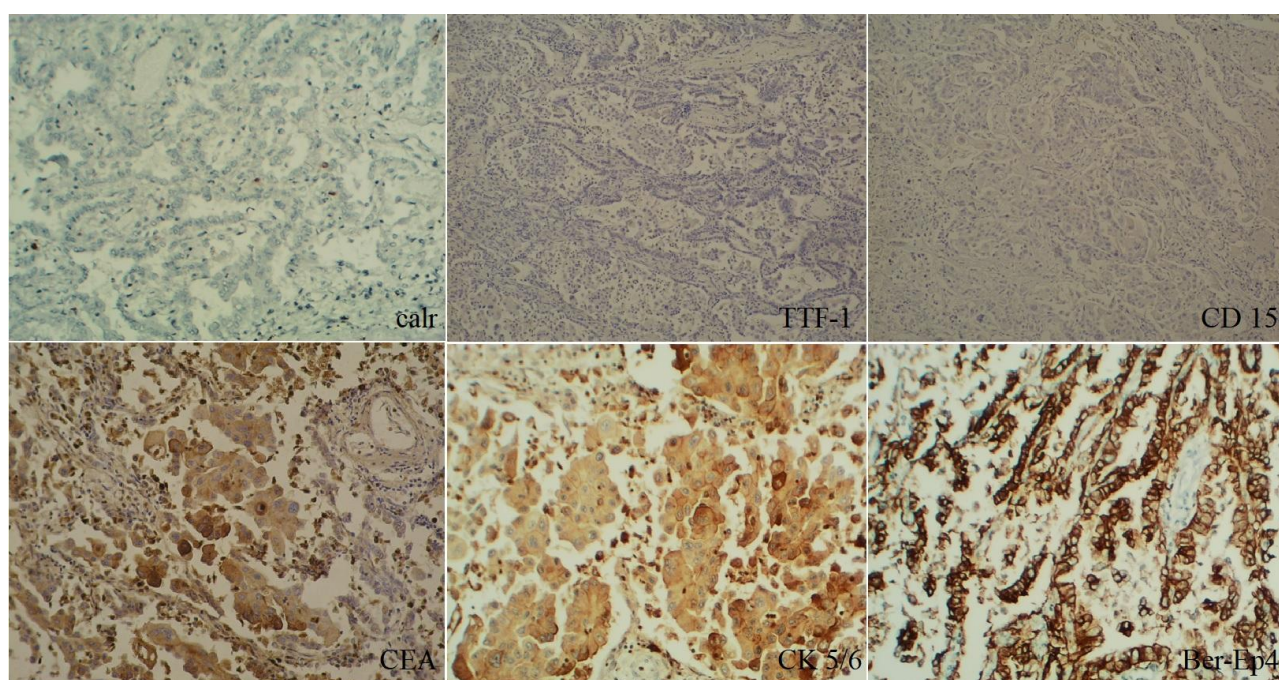


Fig. 4. Immunohistochemical study of the tumor: Calretinin ($\times 100$ magnification); TTF-1 ($\times 40$ magnification); CD15 ($\times 40$ magnification); CEA ($\times 200$ magnification); CK 5/6 ($\times 200$ magnification); Ber-Ep4 ($\times 100$ magnification).

The findings of immunohistochemical study were the reason for the change of the final pathological diagnosis: Pseudomesotheliomatous adenocarcinoma of the lung with proliferation in the pericardium and with metastases to parabronchial and paratracheal lymph nodes.

Discussion. The reported case is interesting because it was clinically neglected and not diagnosed during the patient's life, but was detected morphologically in the process of differential diagnosis.

According to some data, pseudomesotheliomatous carcinoma of the lung occurs in 6% of cases that mimic malignant pleural mesothelioma, which in 70% of cases is represented by lung adenocarcinoma and rarely by other highly malignant variants of lung cancer or metastatic tumors. Adequate diagnosis of these tumors has medical and legal significance [6]. Therefore, the diagnosis of pulmonary and pleural diseases, faced by surgeons and pathologists, requires improvement of instrumental and morphological diagnostic criteria.

During the lifetime, the patient was diagnosed with the community-onset left-sided multisegmental destructive pneumonia, parapneumonic empyema of the left pleural cavity (pyopneumothorax), therefore, the first thing to do was to differentially diagnose pleural empyema with other causes of pleural effusion. Its the most common causes are known to be congestive heart failure, cancer, pneumonia, and pulmonary embolism, but multifactorial pleural

effusion can occur, which can pose a significant challenge in diagnosis and treatment [7, 8]. A detailed differential diagnosis of pleural effusion is presented in the work of Jany B. and Welte T. [9], based on the diligent literature analysis and personal observations.

Radiological methods reveal nonuniform diffuse thickening of the pleura and the presence of transudate in the pleural cavity, which does not exclude reactive changes in the pleura or malignant or inflammatory lesions of the lungs, such as mesothelioma, lymphoma, tuberculosis, tumor metastases to the pleura, and others [10]. Pleural thickening of more than 1 cm, the presence of nodules, and mediastinal pleural involvement are unreliable CT signs of malignancy. Thoracoscopy can provide additional information. However, the radiologic or thoracoscopic picture of pseudomesotheliomatous carcinoma resembles pleural mesothelioma, that is why the key method to make a clear diagnosis is morphological examination [11]. For the differential diagnosis of pleural effusion, ultrasound is a useful examination method, especially in the presence of pleural septa. When the cause of the effusion is unclear, diagnostic puncture of the pleural effusion under ultrasound guidance is indicated to obtain a small amount of fluid. The removed fluid during the puncture is divided into aliquots for microbiological (5 ml), biochemical (2-5 ml) and cytological (20-40 ml) analysis. Differential diagnostic indicators of pleural effusion are shown in Table.

Table. Differential diagnostic indicators of pleural empyema and pleural effusion of tumor genesis

Indicator	Empyema of the pleura	Tumors of the lungs and pleura
Localization	Two-sided or one-sided	More often one-sided
Appearance of the liquid	Manure (clear supernatant is available after centrifugation)	bloody discharge
Lactate dehydrogenase	above 200 U/ml	
Cholesterol	above 55 mg/dL	
pH	less than 7.2	acidosis
Glucose	Low concentration	Low concentration
Blood cells	Increase in the concentration of neutrophils	lymphocyte pattern
Microbiological examination	Not very informative for Gram staining and acid-fast bacteria	
Cytological examination	-	is confirmed in 50-60% of cases

If pleural effusion is suspected to be caused by a malignant tumor, additional diagnostic tests should be performed. If the results of imaging and fluid analysis of the pleural effusion are inconclusive, a pleural biopsy with subsequent histologic examination might be necessary.

Patients with diffuse pleural lesions must undergo cytological analysis of the pleural contents or a biopsy followed by microscopic and immunohistochemical studies, which was not done in the reported case [9, 12, 13].

Diffuse malignant pleural mesothelioma is characterized by the presence of various pathologic types and subtypes, and histologically may have an acinar pattern similar to lung adenocarcinoma. Histologic recognition of the tumor is very important for treatment and prognosis [12, 14-16]. The International Mesothelioma Interest Group recommended the following immunohistochemical markers for the differential diagnosis of tumors: Calretinin, D2-40 (podoplanin), WT1 for mesothelioma; CEA, TTF-1, Napsin-A for lung adenocarcinoma and p63, p40, MOC-31 for squamous cell lung cancer [17, 18]. Other markers such as Intelectin-1, DAB2 and MUC4 [19], Ber-EP4 [18] are also proposed to be used, which may be useful in unusual cases.

A panel of immunohistochemical markers mentioned above was selected for morphological verification of the diagnosis. Prominent immunoreactivity of Ber-EP4, CEA and S-100 protein were indicators of lung adenocarcinoma, and S-100 protein is associated with its unfavorable prognosis [20, 21]. Negative WT1 and Calretinin expression were the markers of the non-mesothelial origin of this tumor, which are the most specific and sensitive features for mesothelioma of any localization [5, 22, 23], especially in combination with Ber-EP4 [21]. However, negative expression of TTF-1 and CD15 markers was questioned. Although TTF-1 is a differential marker of squamous cell carcinoma and adenocarcinoma, its expression

has recently been reported to be absent in 21% of patients with adenocarcinoma, which correlates with low patient survival [24]. However, Vuković J. et al. have reported that expression of this marker was detected in only 30% of cells of pseudomesotheliomatous carcinoma of the lung, and CD15 in approximately 15% [1]. Therefore, in our opinion, these markers cannot be reliable diagnostic criteria, especially in poorly differentiated tumors.

In the reported case, the diagnosis making was a challenge to physicians, and, therefore, this case deserves attention from surgeons, oncologists and pathologists. Based on the studies conducted in this case, it can be concluded that for the differential diagnosis of pseudomesothelioma of the lung and pleural mesothelioma, it is necessary to take into account the histological characteristics of the tumor, as well as use an expanded panel of immunohistochemical markers. This will allow not only to establish the histologic type of the tumor but also to determine its prognosis.

Further study of the etiology and biological markers, as well as their importance in the morpho- and histogenesis of malignant lung tumors will improve its diagnosis, course, prognosis, and future treatment [25], especially of the rare variants of tumors about which very little is known.

Conclusions. Notwithstanding that pseudomesotheliomatous carcinoma of the lung is a rare malignant lung tumor, it should always be kept in mind until the final diagnosis is made in the differential diagnosis of pulmonary disease involving the pleura, especially in the presence of pleural effusion. Every effort should be made to cytological study of the contents of the pleural cavity and biopsy, which will facilitate an accurate diagnosis, and in the future, with the expansion of knowledge about this tumor, its treatment. Consequently, it is necessary to continue the search for the novel diagnostic signs and improve the existing criteria for the diagnosis of malignant tumors of the pleura and lung.

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РЕДКИЙ СЛУЧАЙ НЕКЛАССИФИЦИРОВАННОЙ КАРЦИНОМЫ ЛЕГКОГО: ПРОБЛЕМЫ ДИАГНОСТИКИ

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Резюме. В статье сообщается о летальном случае клинически недиагностированной псевдомезотелиоматозной карциномы легкого, которая впоследствии была верифицирована посмертно в процессе дифференциальной диагностики с помощью иммуногистохимического анализа. В данном случае постановка диагноза представляла собой сложную задачу для врачей, поэтому этот случай заслуживает внимания хирургов, онкологов и патологоанатомов.

Псевдомезотелиоматозная карцинома легкого является редкой злокачественной опухолью легкого, ее всегда следует иметь в виду до постановки окончательного диагноза при дифференциальной диагностике легочных заболеваний с поражением плевры, особенно при наличии плеврального выпота. Несмотря на плохой прогноз и отсутствие эффективных методов лечения, изучение этой опухоли позволит еще больше повысить выживаемость пациентов и улучшить дифференциальную диагностику, поскольку диагноз зависит в основном от ее иммуногистохимической верификации.

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