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ПАЦИЕНТКА С ДОБРОКАЧЕСТВЕННЫМ ЛЕЙОМИОМАТОЗОМ ЛЁГКИХ: ЕСТЬ ЛИ СЛОЖНОСТИ ДИАГНОСТИКИ И ВЕДЕНИЯ?

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A Patient with Benign Lung Leiomyomatosis: Are There Any Difficulties in Diagnosis and Management?

Резюме

Приводится клиническое наблюдение пациентки 48 лет, обратившейся в отделение пульмонологии в связи со случайно выявленными очаговыми образованиями в легких. Несмотря на неоднократные консультации специалистов узкого профиля и выполнение визуализирующих методов обследования диагноз был поставлен только спустя четыре года после трехкратного пересмотра гистологических блоков и исключения других причин очаговых легочных диссеминаций. Данный клинический случай демонстрирует редко встречаемую патологию и сложности дифференциальной диагностики, с которыми могут столкнуться врачи всех специальностей. Диагностика заболевания представляет трудность как для врачей широких специальностей, так и для узкопрофильных специалистов. Особенности заболевания и трудности дифференциальной диагностики определяют необходимость мультидисциплинарного подхода к ведению пациентов с данной патологией.

Ключевые слова: *лейомиоматоз легких, доброкачественная метастазирующая лейомиома матки, метастазы, редкие болезни, диагностика*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article presents a clinical observation of a 48-year-old patient who applied to the Department of pulmonology in connection with accidentally detected focal formations in the lungs during a preventive examination. In the presented clinical case, the patient's disease was asymptomatic for a long time, for the first time, focal formations in the lungs were identified in 2020 and only a year later non-specific symptoms joined. Despite multiple consultations with narrow-profile specialists and the implementation of visualization methods of examination, the diagnosis of «lung leiomyomatosis» was made only four years later after a three-fold revision of histological blocks and the exclusion of other causes of focal pulmonary dissemination. This clinical case demonstrates a rare pathology and the complexity of differential diagnosis that doctors of all specialties may encounter. The features of the disease and the complexity of differential diagnosis determine the necessity of a multidisciplinary approach to the treatment of patients with this pathology.

Key words: *leumiomatos pulmonary, leiomyomatosis of lungs and uterus, metastases, lung, rare diseases, diagnosis*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «A Patient with Benign Lung Leiomyomatosis: Are There Any Difficulties in Diagnosis and Management? » for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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SHI — State Healthcare Institution, BML — benign metastasizing leiomyoma, CO — chest organs, RCH — Regional Clinical Hospital, FEV_1 — forced expiratory capacity during the 1st second, CT – computed tomography, FVC — forced (expiratory) vital capacity of lungs

Introduction

The issue of differential diagnosis of focal pulmonary lesions is one of the most important objectives in modern medicine. Neoplastic dissemination has a specific place in the structure of pulmonary dissemination; the former one includes a benign metastatic leiomyoma (BML, ICD-O-3 8898/1) or, correctly speaking, "pulmonary leiomyomatosis", thus emphasizing the systemic and independent character of the disease [1]. For the first time this pathology was described in 1939 by the physician Paul Steiner in a 36-year-old female. In his study "Metastasizing fibroleiomyoma of the uterus: Report of a case and review of the literature", the author presented a thorough characteristics of the disease course, radiological signs, and results of histopathological examination in a patient with progressive uterine fibroleiomyoma and pulmonary metastases [2]. Starting from this period, less than 1,000 cases have been described in literature. According to the current concepts, pulmonary leiomyomatosis is a rare pathology which belongs to the group of "systemic leiomyomatoses". Based on the data of Russian and foreign authors, the incidence of this disease has been steadily increasing within the latest decade, while each five years the number of publications on this topic almost doubles, which may be related both to improved diagnosis and the true incidence growth [3-4].

The World Health Organization considers pulmonary leiomyomatosis as a variant of benign mesenchymal smooth muscle tumors that are prone to metastases, with specific groups of leiomyomas, grown pattern variant, and smooth muscle tumors of uncertain malignant potential [5]. Besides pulmonary leiomyomatosis, benign uterine diseases metastasizing into lungs also include lymphangioleiomyomatosis and thoracic endometriosis, which modern primary diagnosis is less difficult than that of leiomyomatosis due to more precise diagnostic criteria [6]. As the location of benign tumor "metastases" may differ, the disease terminology varies from peritoneal leiomyomatosis (in abdominal leiomyomas) to intravascular or intravenous leiomyomatosis (if leiomyomas are located in cardiac chambers and blood vessels). Leiomyomatous nodules are most commonly detected in lungs, though they may be found in the retroperitoneal space, pelvic cavity, lymph nodes, central nervous system, and muscles of extremities [7, 8]. Several authors describe cases of cardiac involvement or very rare forms of intravenous leiomyomatosis which has some signs of malignancies (e.g., higher predisposition to atypia, increased mitotic activity) [9, 10].

Regarding clinical signs, patients with pulmonary leiomyomatosis predominantly present with the asymptomatic course — most commonly pulmonary nodules

resembling metastases are detected accidentally on routine chest X-ray. With that, the disease itself most often has a favorable course, without growth or with a very slow increase in the focal lesion diameter, usually without the increase in their number; however, several patients develop some typical complications with time, i.e. hemoptysis, signs of bronchial obstruction (if neoplastic nodules are located in bronchial walls), pneumothorax (with subpleural location of foci), obstructive emphysema, superficial and deep vein thrombosis. In specific patients the disease may have a quite unfavorable course — several authors describe clinical cases with multiple uterine leiomyoma "metastases". In such situations, besides pulmonary nodules, intravenous leiomyomatosis with aggressive growth (see above) is somewhat common — as a result of massive venous lesions, significant vascular symptoms are possible, while if neoplastic thrombi are located in cardiac chambers and the inferior vena cava, acute vascular accidents may emerge (even with sudden death) [7-10].

The nature and pathogenesis of systemic leiomyomatosis have not been sufficiently analyzed. The vast majority of authors believe that the mechanism of BML development is similar to that of endometriosis, paying specific attention to the implantation therapy and associating the emergence of leiomyomatosis nodules in various organs and tissues with the vascular embolism with smooth muscle cells occurring as a result of uterine surgeries. This theory is mainly based on statistical data, as leiomyoma "metastases" are most commonly detected in females who have a history surgical uterine myoma treatment (myomectomy or hysterectomy) [11]. The next theory explains the disease development from the position of asynchronous smooth muscle tissue proliferation in various organs, i.e. the uterus, lungs, or other muscles; in this case, BML is considered as a variant of a nodular dyshormonal hyperplasia. According to this point of view, leiomyomatosis is a pathological condition with impaired differentiation and increased smooth muscle tissue volume as a result of hormonal imbalance in the body (similar to, e.g., cystic mastopathy or hepatic adenomas). With that, genetic predisposition in specific persons is of special value, while such processes as hormonal disorders or uterine myomectomy are considered proliferation triggers [4]. The third theory presumes the development of BML as a result of hormonal overstimulation. It is considered that estrogen is a driving force of muscle tissue proliferation, provoking "metastasizing" and subsequent growth of the primary tumor "metastases". Based on the data of Russian authors, clinical, morphological, and immunophenotyping studies of neoplastic nodules in patients with BML foci in lungs confirm the high estrogen and progesterone receptor expression in leiomyoma "metastases". For example, specific clinical observations demonstrate the increased diameter of foci with the increased endogenous estrogen levels or estrogen effects as part of replacement therapy. The hormonal dependence of these tumors is also confirmed by the described cases of neoplastic nodule regression in patients during pregnancy or with the natural menopause, as well as when using gonadotropin- and releasing-hormone agonists, P-450 aromatase inhibitors, estrogen inhibitors, or after ovariectomy. However, despite the fact that estrogens play a significant role in the development and progression of leiomyomatosis, they should considered not as an etiological factor, but rather as one of the components of the systemic process pathogenesis [12, 13]. Some researchers still consider BML as a subtype of hamartomas, which in their turn are classified based on the predominance of a specific component into several histological types: lipomatous, chondromatous, and leiomyomatous hamartomas. It should be noted that according to the researchers' opinion, it is really important to differentiate these subtypes, as the management tactics depends on that. If for the first two forms scientists incline towards the theory of disembryogenesis (with exclusively surgical treatment), when speaking about leiomyomatous pulmonary hamartomas, one should note that their etiology, pathogenesis, hormonal dependence, and treatment prognosis are currently not well analyzed, and the attempts of their treatment in many cases should be started from the conservative strategy [13]. Due to the differences defined, the attempt to assign BML to hamartomas is rather conditional, and currently pulmonary leiomyomatosis is usually considered as an independent disease. All theories pay special attention to genetic predisposition to leiomyomatosis. Researches from all over the world search for the typical genetic aberrations, analyzing the expression of hormone receptors in females with uterine myoma. Several authors underline the high expression of a regulatory anti-apoptotic gene bcl-2 and a gene-suppressor of malignancies p53, with a low Ki67 (marker of the proliferative activity in tumor cells) [12, 14]. Despite a plenty of theories, currently the disease is considered multifactorial; due to this, the following pathogenetic events of BML should be considered for the correct establishment of diagnosis: prolonged hormonal stimulation (prolonged oral contraceptive use, pregnancy, menstrual disorders), possibility of lymphogenous and hematogenous dissemination or intraperitoneal implantation (as a result of uterine surgeries), family history, other signs of nodular hyperplasia.

Currently, no common treatment standards and protocols exist for systemic leiomyomatosis, including pulmonary leiomyomatosis. Recommendations based on Russian and foreign medical platforms include thorough patient follow-up, surgical resection of "metastatic" lesions, medication-induced or surgical termination of ovarian function using aromatase inhibitors, estrogen receptor antagonists, tyrosine kinase inhibitors, and gonadotropin-releasing hormone (GnRH) agonists. Determining the hormonal status of female patients is mandatory before starting the treatment. Several reports of efficient treatment with the immunosuppresant "sirolimus" have been observed in young females that wish to preserve the ovarian function; however, additional clinical trials are required for its active implementation into the treatment practice of this disease [1, 2, 12, 13].

Case study

The patient L. (born August 12, 1975) was hospitalized into the pulmonology department in December 2023. She complained of dry cough and sensation of incomplete inspiration. Life history revealed no data concerning bad habits, household or occupational hazards; the patient denied the coronavirus infection and corresponding vaccinations. The patient underwent hysterectomy due to a myoma (2010), suffered from breast fibroadenoma. Focal pulmonary lesions were detected in January 2020 during the scheduled chest X-ray; she was counseled by the tuberculosis specialist — no signs of tuberculosis were detected. In February 2020, she was referred to the pulmonology department: based on the results of the computed tomography of chest organs (CT CO), bilateral pulmonary lesions sized 4 to 22.6 mm were detected (Fig. 1 a, b). Pulmonary function tests revealed FVC 74 % of reference values, FEV_1 74 % of reference values, FEV_1/FVC 98 %, laboratory tests were normal.

The patient underwent additional examination to exclude the neoplastic process and tuberculosis — both diagnoses were refuted. Videothoracoscopy was arranged, according to the histological examination results, the pulmonary tissue contained areas of fibrosis, mild lymphocytic, perivascular, and peribronchial inflammatory infiltration. "Lymphocytic pneumonia" was established. CT of CO was conducted twice in 2020, without any changes detected. The patient took several cycles of acetylcysteine (ACC) within a year. During the hospitalization into the pulmonology department in June 2021, the diagnosis was changed to "sarcoidosis". Prednisolone was administered in the dose of 15 mg/day, though the patient stopped taking it spontaneously

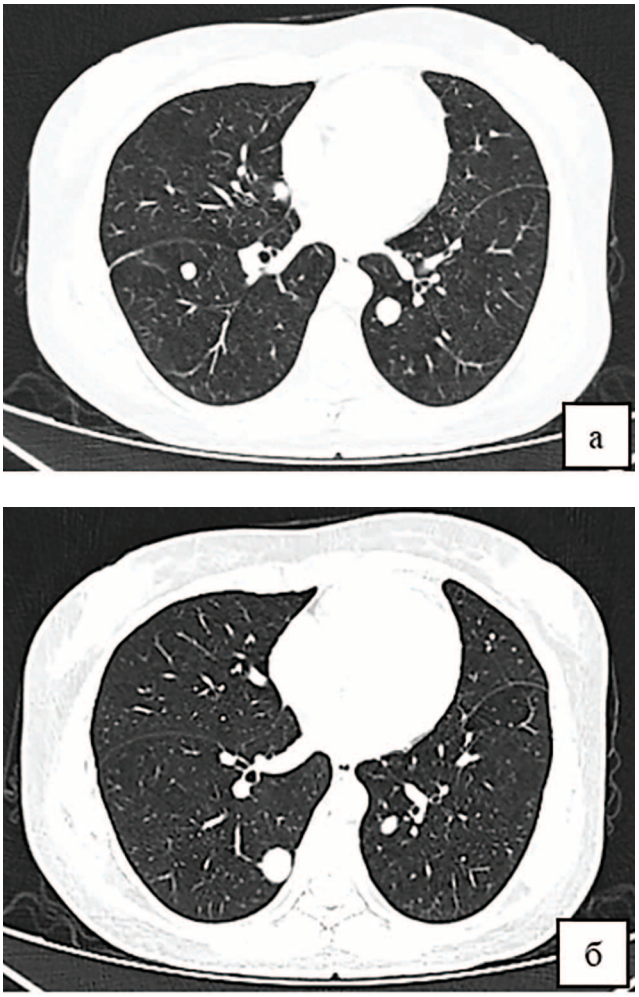

Figure 1. *CT scan of the chest (a, б)*
Note. Multiple rounded neoplasms of both lungs, with a diameter from 4 to 22.6 mm, the largest of them in the right lung (б)

several weeks later. In July 2021, she underwent another diagnostic surgery (atypical right lung resection) in the surgical department of SHI RCH, Samara, the histological examination revealed hamartomas. In January 2022, the follow-up CT demonstrated negative progression — lesions increased in size (Fig. 2 a, b).

Due to negative CT progression, it was decided to review histological blocks during the hospitalization in December 2023 in the Federal State Budget Institution Scientific-Research Pulmonology Institute, Federal Medical & Biological Agency of Russia (acknowledgements: M.V. Samsonova, A.L. Chernyaev). After review, the following description was obtained: presence of neoplastic tissue represented by multidirectional bands of spindle-like cells with multiple cavities lined with the single-layer cubical epithelium. Layers of the myxoid connective tissue were occasionally detected. The pulmonary tissue with thin interalveolar septa of the normal structure was found along the periphery of the tumor. The diagnosis of benign metastasizing leiomyoma was concluded.

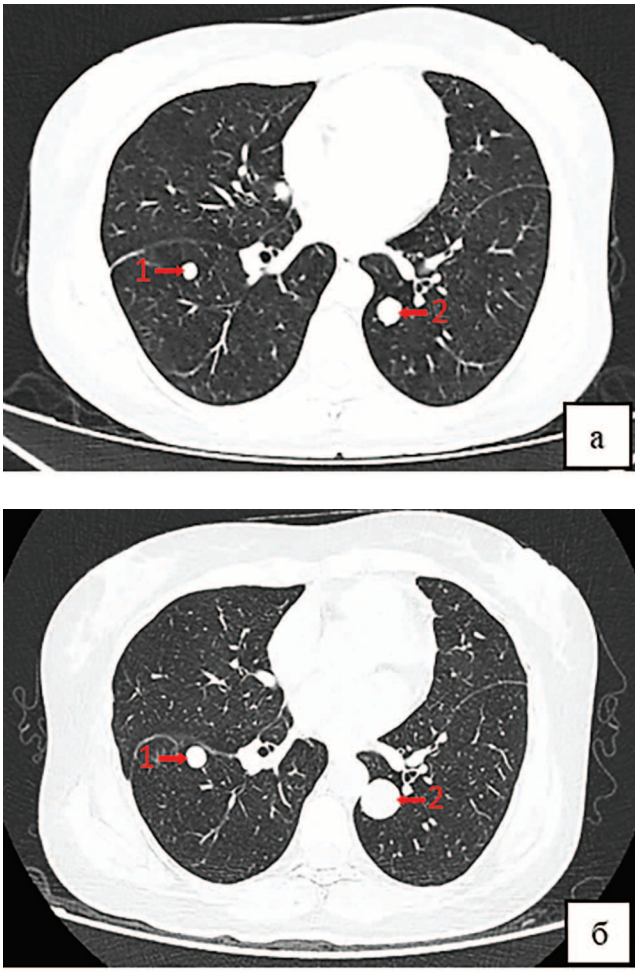

Figure 2. *CT of the chest*
Note. а — multiple rounded soft-tissue neoplasms, number 1 — diameter 9.41 mm, number 2 — diameter 14.86 mm, (02.13.2020);
б — negative dynamics, diameter of neoplasm number 1 — 12.44 mm, diameter of neoplasm number 2 — 23.85 mm, (01.24.2022)

The patient was counseled in the Federal State Budget Institution National Medical Research Radiology Center, where the histological material was reviewed again, and adenoleiomyomatous hamartomas were confirmed in lungs. According to the consilium results, daily anti-estrogen therapy (tamoxifen 40 mg) was administered, and the hormonal profile assessment was recommended — if the hormone levels corresponded to functioning ovaries, termination of the ovarian function (using the surgical or medication-induced method) would be recommended with subsequent letrozole treatment and further follow-up. The patient underwent ovariectomy, and letrozole was administered.

Discussion

In the case study presented, the disease in the patient was asymptomatic for a long time: focal pulmonary lesions were detected for the first time in 2020 during the prophylactic examination, while non-specific symptoms emerged only a year later. Despite several episodes of counseling by specializing physicians and imaging methods, the diagnosis was established only four years later after a three-fold review of histological blocks and exclusion of other causes of focal pulmonary disseminations.

Another problem presumed patient triaging after the conclusion of a benign metastasizing leiomyoma. Who should manage this patient? Unfortunately, city gynecologists and oncologists were not ready to decide upon the patient's fate and her treatment. Only after the remote (and subsequently offline) counseling one could receive recommendations about the further tactics of her management. However, the issue of further patient follow-up is considered not solved.

Conclusion

The differential diagnosis of pulmonary leiomyomatosis requires complex approach and high qualification of physicians. This case study demonstrates a rare pathology and complexity of differential diagnosis, which can be tackled by physicians of all specialties. The disease diagnosis is difficult both for general practitioners and specializing physicians. The low incidence of the pathology, lack of physician experience with the category of patients with this disease, insufficient awareness of the aforementioned risk factors, small number of publications in Russian journals concerning the diagnosis and treatment of systemic leiomyomatosis and its manifestations lead to the absence of timely diagnosis and adequate treatment of diseases, which in turn results in complications and subsequent massive surgeries. It is almost impossible to establish such diagnosis alone without morphological verification and follow-up. However, even morphology does not demonstrate the final result from the start; in such cases, the attending physician should be tolerant and provide a personalized approach, arrange counseling with other specialists, and send the histological material for review (if possible). The disease features and difficulties in the differential diagnosis determine the necessity of a multidisciplinary approach to the management of patients with this pathology.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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