Benign pulmonary metastasizing leiomyomatosis: report of 3 cases and review of the literature

Leiomiomatose benigna metastatizante pulmonar: relato de 3 casos e revisão de literatura

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ABSTRACT
Benign pulmonary metastasizing leiomyomatosis (BPML) is a rare condition, most commonly found in premenopausal women in reproductive age with a history of hysterectomy for uterine leiomyoma or myomectomy. Most cases are asymptomatic and the diagnosis is usually incidental during routine examinations. Although the condition is benign, some patients may present with dyspnea and significant hypoxemia. The diagnosis is established through anatomopathological examination of the lung lesions. Treatment varies according to the clinical picture and the number and size of the lesions.

Keywords: leiomyoma, metastasis, lung.

RESUMO
A leiomiomatose benigna metastatizante pulmonar (LBMP) é uma condição rara, mais comumente encontrada em mulheres em idade reprodutiva, na pré-menopausa, com passado de histerectomia por leiomioma uterino ou miomectomia. A maioria dos casos são assintomáticos e geralmente o diagnóstico é incidental durante exames de rotina. Apesar de a condição ser benigna, alguns pacientes podem apresentar dispneia com hipoxemia importante. O diagnóstico é firmado através do exame anatomopatlógico das lesões pulmonares. O tratamento varia de acordo com quadro clínico, número e tamanho das lesões.

Palavras-chave: leiomioma, metástase, pulmão.

1 INTRODUCTION

PML is a rare disorder characterized by metastatic lesions formed by smooth muscle cells located in the extrauterine environment. The main sites of implants are lungs (80%), heart, bones, liver and lymph nodes (Tong et al. 2023). The confirmatory diagnosis is obtained from lesion biopsy with anatomopathological and immunohistochemical study. The aim of this study is to report three cases of PML and bring a literature review.

2 MATERIAL AND METHODS

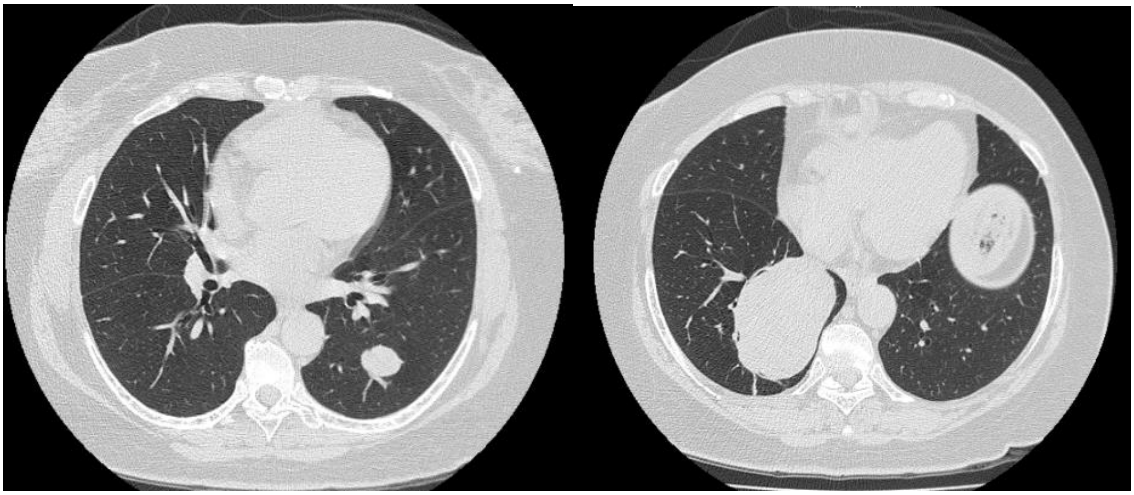
The present study aims to present three clinical cases diagnosed with benign metastatic pulmonary leiomyomatosis (PML) with distinct clinical courses and bring a literature review on the subject. Patients are aware of the study, and agreement is formalized through the signing of a Free and Informed Consent Term (ETC).

3 CASE REPORTS

3.1 CASE REPORT 1

A woman, 66 years old, with hypertension, a history of hysterectomy and oophorectomy on her left for 32 years due to myomatosis, denies previous pneumopathies and smoking. 10 years ago, he started a persistent dry cough, with no other symptoms associated with it. Reviewed by a doctor in the Basic Health Unit who requested a chest x-ray and according to the patient the doctor commented on a lung injury, but the investigation did not continue. Only after nine years, in the face of the persistence of the symptom of a dry cough, did he again seek medical assistance. He performed a chest tomography (CT) that showed solid mass, with regular outlines measuring 1.7 x 1.6 x 2.1 cm located in the posterior basal segment of the lower lobe of the left lung and another solid mass, located in the upper segment of the lower lobe of the right lung, measuring 7.2 x 8.1 x 6.1 cm (figure 1). In spirometry, he had a mild restrictive ventilatory disorder. He had bronchoscopy with transbronchial biopsy that was inconclusive. She was then referred to a reference service in pneumology and at this time persisted with a dry cough and denied hemoptysis, dyspnea, wheezing, fever and weight loss. The physical examination showed no changes. Contrast-enhanced chest CT showed homogeneous contrast-enhancing lesions with characteristics and sizes similar to prior CT. It underwent right inferior lobectomy, with anatomopathological evidence of low-grade fusocellular proliferation, rare figures of mitosis and absence of necrosis. Immunohistochemistry was positive for desmin and AML, Ki-67 was 1%, and there was no expression of CD177, S100 and CD34, and the diagnosis of PML was confirmed. The patient is followed in ambulatory, asymptomatic and with control CT 6 months after lobectomy presenting the same lump in the lower lobe of the left lung with unchanged characteristics.

Figure 1: Non-contrast chest CT showing lung mass in LID measuring 7.2 x 8.1 x 6.1 cm and solid nodule in LID measuring 1.7 x 1.6 x 2.1 cm.



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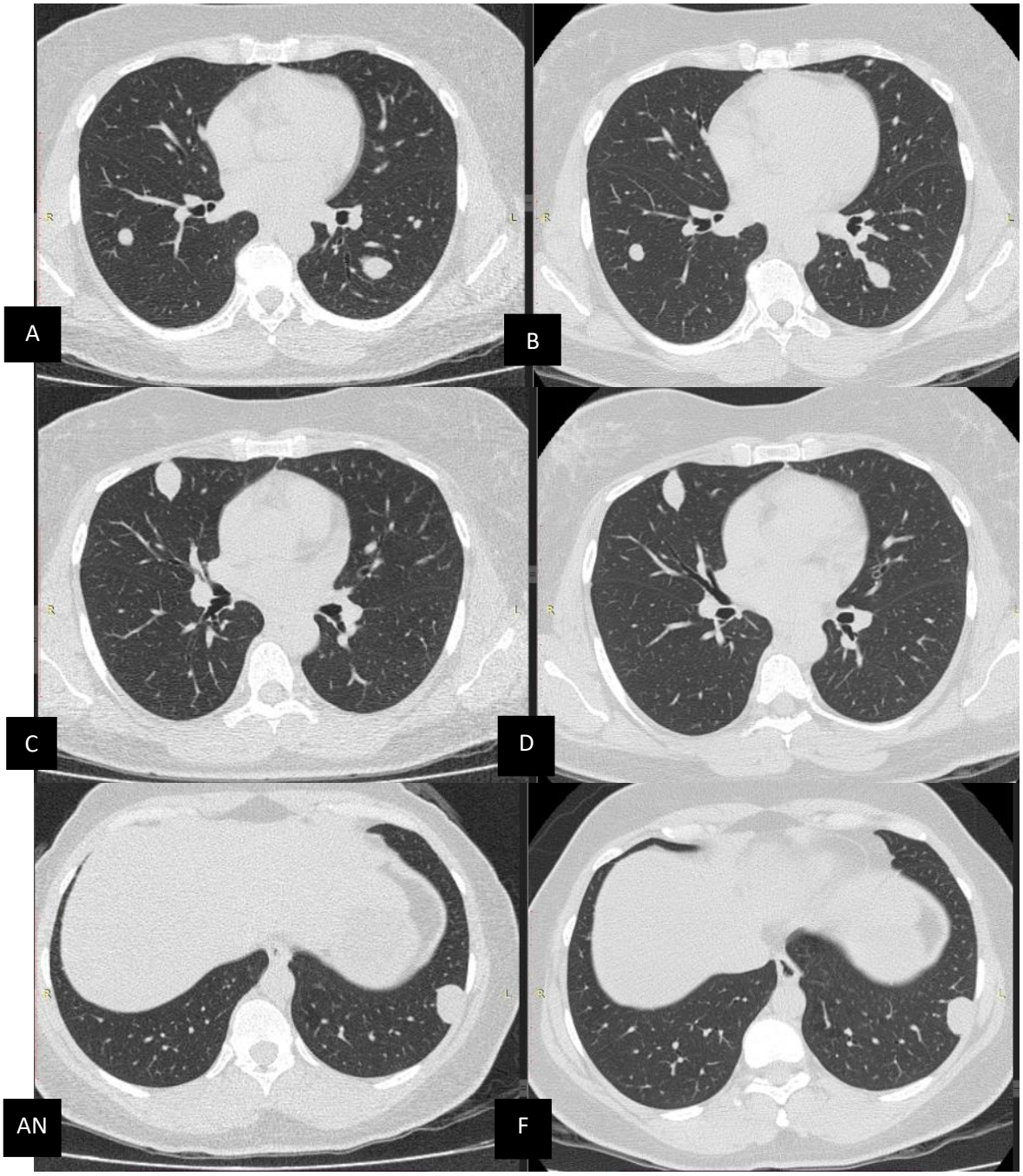
3.2 CASE REPORT 2

A woman, 45 years old, denies previous comorbidities, submitted to hysterectomy and right oophorectomy 15 years ago by uterine myomatosis, previously hygiid and without respiratory symptoms. He did a pre-admitted routine chest x-ray of the job, showing multiple pulmonary nodules. She was referred to a reference service in Pneumology for diagnostic evaluation. He denied hemoptysis, dyspnea, wheezing, fever, and weight loss. He showed no changes in physical examination. Chest CT revealed multiple pulmonary nodules in all lobes, with soft tissue density, the largest lobulates and elongates, the smallest rounded and smooth, some subpleural and perifissural, highlighting the largest in left lateral basal segment measuring 2.2 x 1.5 cm, in upper left inferior lobe segment measuring 2.0 x 1.4 cm, and in medial segment of the middle lobe, subpleural, measuring 2.6 x 1.6 cm (figure 2). Chosen to perform pulmonary biopsy by videothoracoscopy with pathological anatomy showing mesenchymal neoplasia of smooth, well differentiated muscle cells, arranged in intertwined beams forming nodular arrangement, sometimes permeating alveolar septa and absence of figures of mitosis and necrosis. Immunohistochemistry showed Ki-67 of 2%, Desmina, AML and estrogen receptor positive. The S100, GP100 and Melan were expressionless. The patient is followed up in an outpatient follow-up with the team of Pneumology, Gynecology and Oncology. Laboratory criteria for postmenopause have been closed and the patient remains asymptomatic. Subsequent chest scans showed reduction of some nodules and stability of others.

Figure 2. Cuts of 2 CT scans showing temporal evolution of nodules. Cuts A, C, and E are before surgical biopsy and Cs B, D, and F are 8 months after



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3.3 CASE REPORTING 3

A 42-year-old woman with a dry cough, progressive dyspnea with minimal exertion and weight loss of 15 kg in 4 months. Past history of uterine myomatosis hysterectomy 10 years ago. On physical examination, she was slimmed, with pulmonary auscultation with diffuse thin crackles, saturation in ambient air 80%, respiratory rate of 32 ipm. Chest CT showed multiple and uncountable uncalcified solid nodules of hematogenous distribution, some confluents,

affecting the lungs diffusely. The largest measuring 3.9 cm; absence of mediastinal lymph node enlargement (figure 3). Diagnostic hypothesis of secondary neoplastic implants has been suggested. However, all complementary imaging studies at other sites did not indicate metastatic or primary neoplasm changes. A surgical lung biopsy was performed. The histopathology result showed multiple foci of fusocellular neoplasia without atypia, low cellularity, absence of necrosis and mitosis figures (Figure 4). Immunohistochemistry revealed intense expression for actin, desmin and estrogen receptor. The diagnosis of PML was then confirmed. The patient underwent bilateral oophorectomy and was discharged with home oxygen therapy at 2 L/min. In outpatient reassessment after two months, clinical and tomographic deterioration was evidenced. Raloxifene 60mg orally was introduced daily. After 10 months of use, the patient continues with radiological deterioration, but with clinical stability and maintaining the need for oxygen therapy. Raloxifene was then stopped and anastrazole 1mg was started orally each day by the oncologist and the patient is followed up on an outpatient basis, awaiting further response assessment.

Figure 3: Chest CT with multiple, uncountable nodes of random distribution. The first column corresponds to the first tomography performed, the second column to the examination 4 months after bilateral oophorectomy and the third column, with 10 months of ralofixene use.

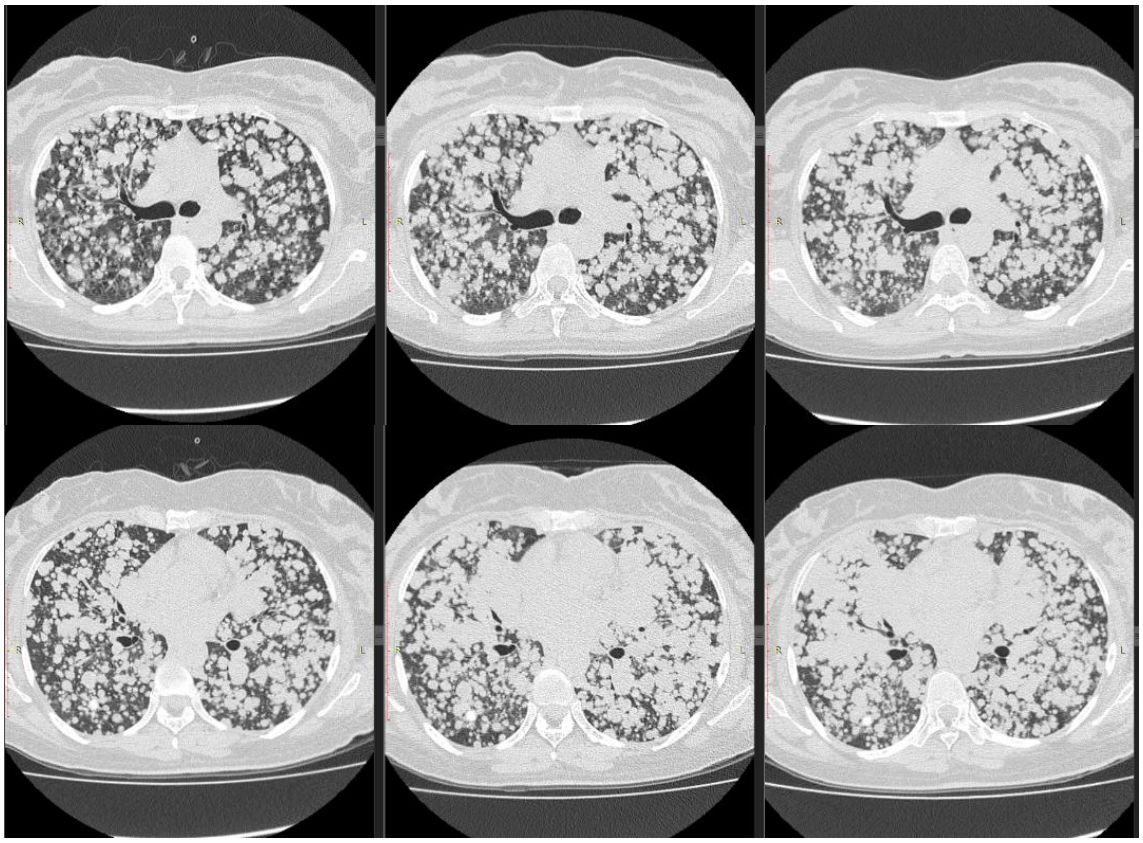

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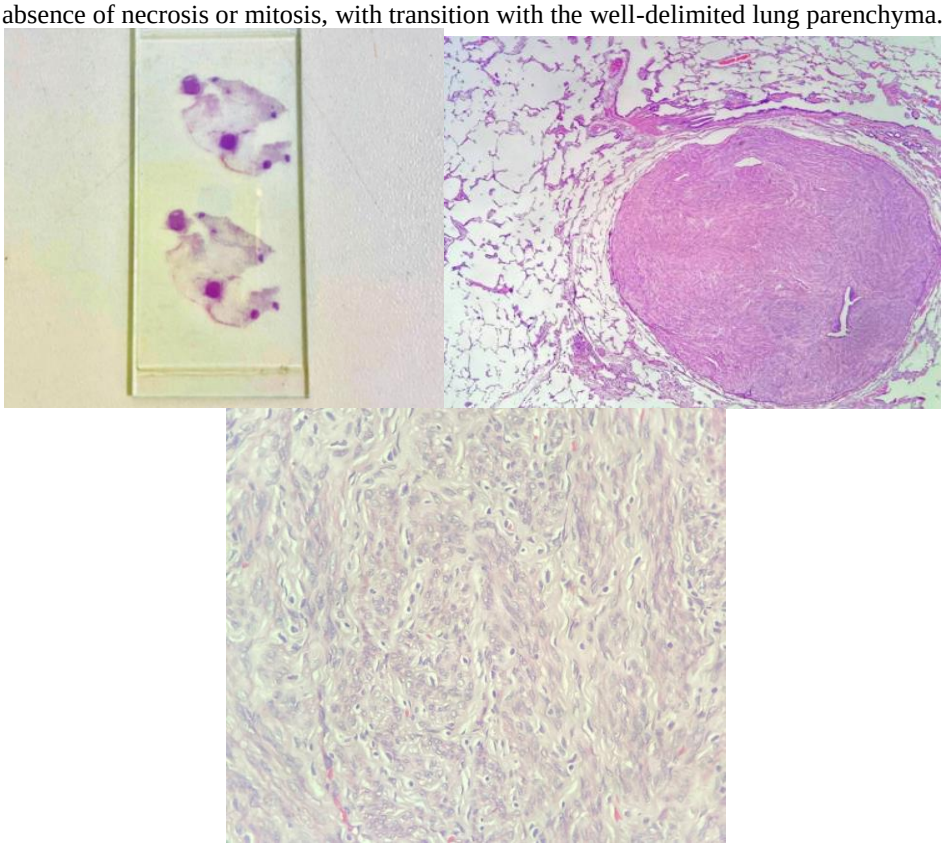
Figure 4: Microscopy of the lesion showing low cellular neoplasm, without atypies, without pleomorphism, absence of necrosis or mitosis, with transition with the well-delimited lung parenchyma.



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4 DISCUSSION

In the literature there are only 67 published reports of PML, a fact that highlights the relevance of our sample.

Most affected women have a history of myomectomy or hysterectomy and the average age of diagnosis is 47.3 years, with median time between hysterectomy or myomectomy and diagnosis of 8.8 years. Total hysterectomy is the surgery most associated with subsequent diagnosis of PML (Barnás et al., 2017). Although most of the time the diagnosis is incidental due to the absence of symptoms, about 30% of patients may experience complaints such as cough, chest pain and dyspnea (K. Ofori et al., 2019). Severe respiratory insufficiency can also be found mainly in cases where there are multiple lesions of hematogenous distribution. Ofori et al. described in 2019 a case report with a miliary pattern that had respiratory failure and death within 3 months of diagnosis. Of the 3 cases presented in this study, the first presented symptoms of dry cough, the second case was diagnosed incidentally during a pre-admission examination. However, the third had a respiratory failure picture.

The aetiology of PML is not well explained and there are some theories that attempt to explain such a disorder. The main and most accepted one is the ‘theory of transport’ in which

smooth muscle cells spread through blood and lymphatic vessels to the lungs and other locations (Dai HY et al., 2020).

PML is usually a challenging diagnosis because imaging findings are nonspecific and commonly indistinguishable from malignant metastases, and this hypothesis should be ruled out first. Therefore, additional tests are needed to rule out the presence of lesions in other organs (Wojtys et al., 2022).

There are no established diagnostic criteria for PML and 3 aspects should be considered: clinical history (history of prior gynecologicsurgery for uterine leiomyoma); imaging findings and histopathological findings (DaiHY).

In imaging studies, lesions are usually solid; they vary in size; they may be solitary or multiple; they have well-bounded edges; usually no calcification; and they have contrast enhancement. Some rarer forms show cavitated, lobulated, or miliary or random lesions (Dai HY et al., 2020) (Awonuga et al., 2010). Two of the three reported cases presented multiple nodules or masses, of varied sizes, bilaterally; with precise boundaries and regular edges. The third case exemplifies one of the rare tomographic presentations that is the nodular pattern with distribution.

The definitive diagnosis is made by performing the lesion biopsy, which can be performed by bronchoscopy, guided by tomography, video thoracoscopy or open thoracotomy (Su et al., 2023). Histology usually presents proliferation of smooth, well-differentiated muscle cells, without atypias with absence of necrosis (Pacheco-Rodriguez et al., 2016). The immunohistochemical study is positive for smooth muscle actin and desmin and has low Ki-67 (<5%) expression; they generally have hormone receptors positive for estrogen and progesterone and elevated levels of the tumor suppressor gene p53 (Tong et al., 2023).

All the cases in this study showed a low mitotic index with Ki-67 of 1% in the first case and 2% in the second case, which was also positive for estrogen receptor, as well as the third case.

In relation to treatment, due to the rarity of the entity, there is no established therapeutic protocol yet. The management will vary according to the clinical picture, number and extent of lesions (Ofori et al., 2019).

Considering that estrogen receptors are usually positive, antiestrogen therapy has been used as first line in the treatment of PML (Su et al., 2023). Some examples of commonly used classes of antiestrogens are selective estrogen receptor modulators and aromatase inhibitors.

A study conducted in 2020 showed that curative surgical resection is possible in cases of single and well-defined nodules, showing good results (Fan et al.,2020).

Oophorectomy as a form of surgical castration and use of GnRH analogs are the most commonly used treatments today. These therapies have shown a more promising effect on disease control. However, estrogen deficiency diminishes patients' quality of life, bringing morbidity to treatment. (Su et al., 2023).

Regarding prognosis, patients with PML generally have favorable clinical evolution (Taftaf et al., 2014).

5 CONCLUSION

The present study exemplifies the possibility of different clinical presentations in patients with PML, the majority being indolent, but with the possibility of aggressive courses. It is a condition still without clear etiopathogeny and without diagnostic and therapeutic guidelines. Diagnosis should be considered in cases of lung nodules or masses in women of reproductive age with a history of uterine myoma hysterectomy or myomectomy.

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