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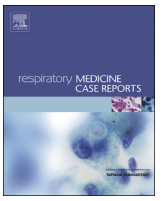

Case Report

Rare manifestation of pulmonary benign metastasizing leiomyoma: Respiratory failure

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ABSTRACT

We report a case of a 42-year-old woman diagnosed with pulmonary benign metastasizing leiomyomatosis with a random nodular pattern on image and with a rare clinical condition progressing with respiratory failure and severe hypoxemia. This study is relevant due to the rarity of the tomographic pattern and the patient's clinical presentation. There is no treatment guideline for this comorbidity, which further increases the importance of publishing case reports in the literature.

1. Introduction

Benign metastasizing leiomyoma (BML) is a rare lesion located in different regions of the body such as the abdominal cavity, lungs, retroperitoneum, lymph nodes, muscle tissue, or heart [1]. The lung is the most commonly affected site. BML can appear as nodules and/or lung masses of varying sizes, multiple or solitary [2]. It affects women of reproductive age, mainly between 35 and 40 years old, with a previous history of myomectomy or hysterectomy to treat uterine leiomyomas. About 167 cases have been published

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in the worldwide literature so far. This article aims to report a clinical case with atypical and serious manifestation of respiratory failure.

2. Case presentation

A 42-year-old woman was admitted to the Pulmonology Service after being referred from the Emergency Care Unit with a dry cough, progressive dyspnea, and weight loss of 15kg in 4 months. She presented dyspnea mMRC 4 on admission and history of hysterectomy due to uterine myomatosis 10 years ago. On physical examination: emaciated, lung auscultation with diffuse fine crackles, room air saturation 80 %, respiratory rate 32ipm. Chest tomography showed multiple and countless non-calcified solid nodules of hematogenous distribution, some confluent, diffusely affecting the lungs; the largest measured 3.9cm; with an absence of mediastinal lymph node enlargement (Fig. 1). Contrast examination showed enhancement in them; some with a cystic/necrotic appearance. The diagnostic hypothesis of secondary neoplastic implants was suggested. Complementary tests were performed to screen for a possible primary neoplastic site (colonoscopy, breast ultrasound, transvaginal ultrasound, thyroid ultrasound, mammography, and abdominal tomography with contrast, all without relevant findings). Serology and AFB smear sputum were negative. A surgical lung biopsy was performed. Macroscopically, the lung surface showed whitish, firm, and regular nodules (Fig. 2). The histology results showed multiple foci of spindle cell neoplasia without atypia, with low cellularity, absence of necrosis, and mitotic figures (Fig. 3). Immunohistochemistry revealed intense expression for actin, desmin, and estrogen receptors, confirming the diagnosis of metastasizing benign leiomyomatosis. The patient underwent bilateral oophorectomy for hormone blockade and was discharged with home O2. In an outpatient reassessment 2 months later, clinical and radiological worsening was evident, and raloxifene 60 mg/day was introduced. After 10 months of therapy, the patient deteriorated radiologically but remained clinically stable. Raloxifene was then suspended, and the oncologist recommended Anastrozole 1mg/day, and remains under outpatient follow-up to this date.

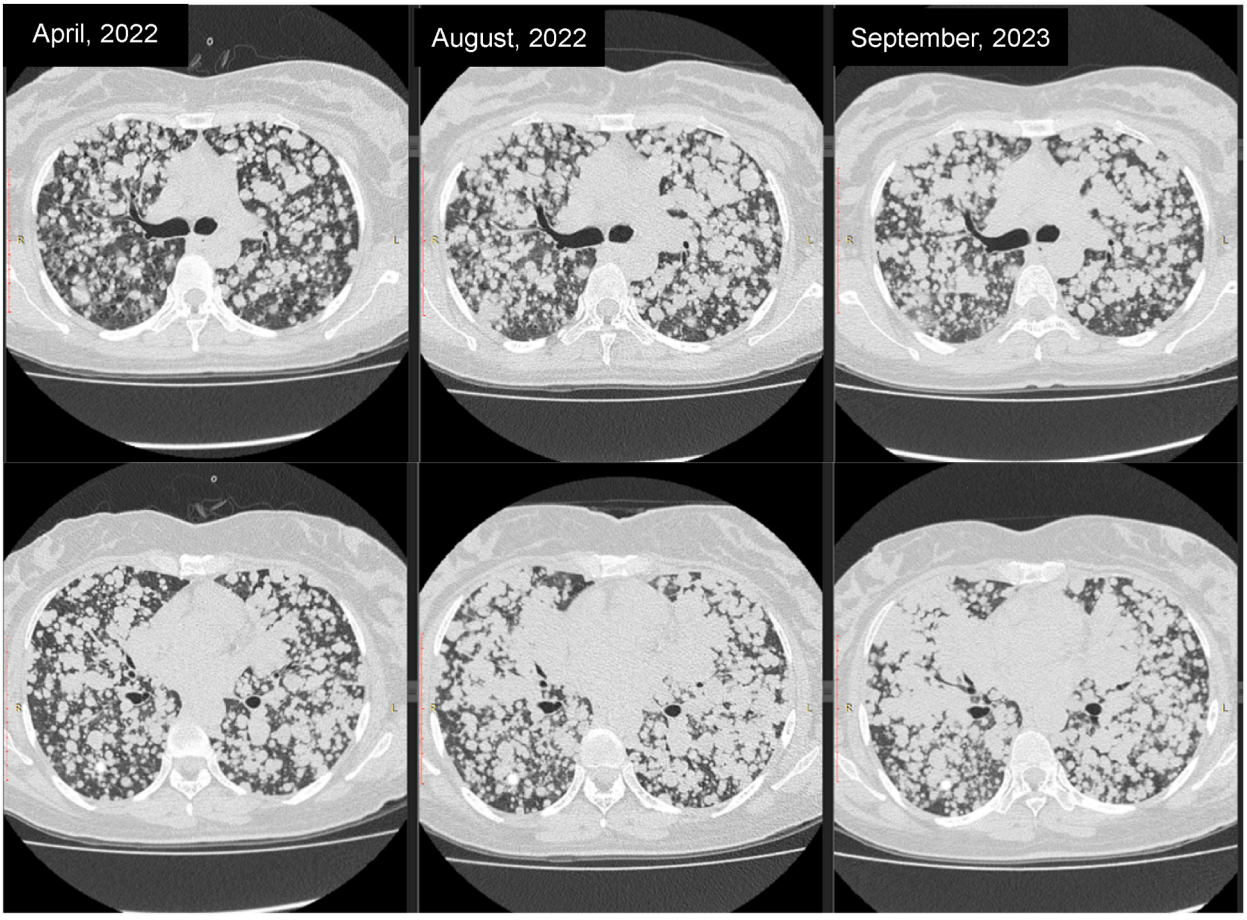

Fig. 1. Chest CT with multiple and countless nodules of random distribution. The first column corresponds to the first tomography performed, the second column to the examination four months after bilateral oophorectomy, and the third column corresponds to 10 months after the use of raloxifene.

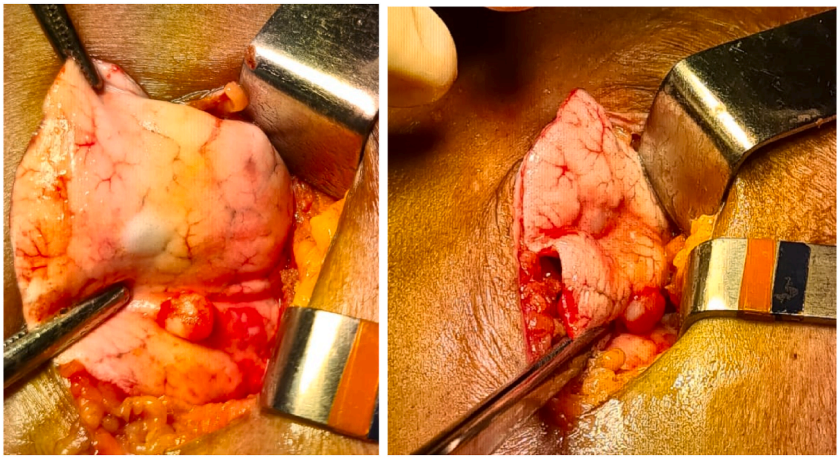

Fig. 2. Photo of the lung surface showing whitish, firm, smooth-surfaced nodules.

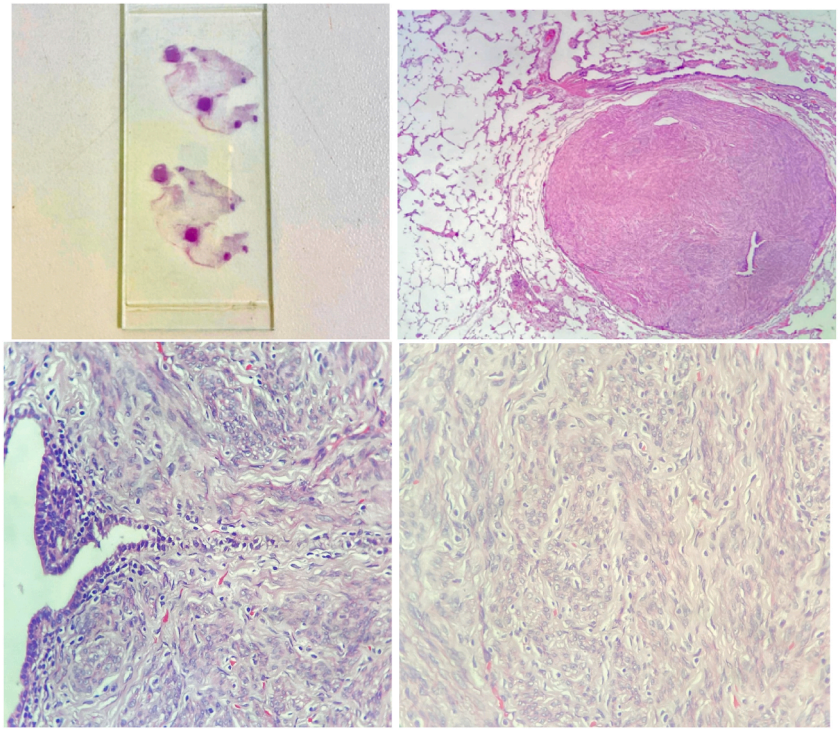

Fig. 3. Microscopy of the lesion showing low cellular neoplasia, without atypia, without pleomorphism, absence of necrosis or mitosis, and transition with well-delimited lung parenchyma.

3. Discussion

The term benign metastasizing leiomyomatosis (BML) was initially reported by Steiner in 1939 and is currently used to describe the presence of tumors composed of smooth muscle cells, without atypia and with a low mitotic index in extrauterine locations [3]. The most frequent sites of metastasis are the lungs, and BML can also be found in lymph nodes, mediastinum, retroperitoneum, vessels, bones, heart, skeletal muscle, and soft tissues [4]. BML a rare condition that mainly affects women of late reproductive age, in the pre-menopausal period, and with a previous history of surgical treatment for leiomyomas. According to a recent systematic review of the literature, most of affected women have a history of myomectomy or hysterectomy with a mean age of 38.5 years [5]. Despite the strong association with previous surgical manipulation, in the global literature, there are around 10 case reports of patients with no prior history of surgical treatment for uterine leiomyomas [6]. According to Taftaf et al., the average time between hysterectomy or myomectomy and diagnosis ranged from 3 to 20 years, with an average of 10 years [7,8]. In this study, the reported case had a history of hysterectomy due to uterine myomatosis 10 years ago.

In the lungs, BML usually appears as nodules of varying sizes that are often confused with malignant metastases [2]. The random nodular pattern is rare and can lead to respiratory failure depending on the number of nodules, as evidenced in this case, which raises the diagnostic hypothesis of a metastatic malignant disease.

The etiology of benign metastasizing leiomyomatosis is not yet well defined. Some theories try to explain the occurrence of this condition. One theory says that they are primary lesions of the lungs. In 2019, Ofori et al. [9] described a case report that identified MED12 mutation in both uterine leiomyomas and pulmonary nodules. MED12 resides on the long arm of the X chromosome (Xq12.1) and is a component of the Mediator complex, which regulates the initiation of RNA polymerase II transcription. This mutation is present in 37 %–85.5 % of uterine leiomyomas, and concomitant detection in pulmonary nodules is consistent with the origin of the lesions from the same clone. Another theory, the transport theory, says that smooth muscle cells are possibly transported through lymphatic and blood vessels during surgical manipulation, such as after hysterectomy or myomectomy [10]. Although most patients have a history of gynecological surgical approach, this theory is becoming less likely due to the records of cases in which there was no history of hysterectomy or myomectomy [9]. Furthermore, Fan et al. [11] published in 2020 a series of 23 cases of BML, and 2 of them had no history of uterine fibroids. A third theory says that these lesions would actually be metastases from a low-grade uterine leiomyosarcoma, but histology and molecular studies make this unlikely. The majority of patients are incidentally diagnosed due to the absence of symptoms. Around 30 % may present some non-specific symptoms such as cough, dyspnea, and chest pain [8]. Severe respiratory failure can also be found mainly in cases where there are multiple lesions of miliary distribution. In 2019, Ofori et al. [9] described a case report with a miliary pattern that progressed to respiratory failure and death within a period of 3 months after diagnosis. Findings on imaging tests are also nonspecific and are indistinguishable from other conditions such as malignant metastatic lesions.

In most cases, the absence of symptoms leads to an incidental diagnosis. Nonspecific symptoms are found in 30 % of patients, such as cough, dyspnea, and chest pain [8,10]. Severe respiratory failure can also be found mainly in cases where there are multiple lesions of random distribution, as in the case in question.

Chest tomography usually shows multiple bilateral solid nodules, with well-defined margins, non-calcified, with variable sizes. Unilateral or solitary nodules may also be found. There are still some possible, but rare, patterns, such as the miliary pattern, cystic lesions, and cavitated lesions [4]. There is usually no associated pleural effusion or mediastinal lymphadenopathy. The lesions can be lobulated, contrast-enhancing, and generally have low FDG-PET uptake, which can help differentiate them from leiomyosarcomas and malignant metastases [10,11].

Diagnosis can be confirmed through biopsy, which can be performed guided by imaging examination in more peripheral lesions, open surgical biopsy, bronchoscopy, and video-assisted thoracoscopy. Histologically, highly differentiated spindle cells are found, with a low mitotic index, absence of atypia, and coagulative necrosis [3].

The immunohistochemical profile of MBL is positive for desmin and smooth muscle actin and has low expression of Ki-67 (<5 %) in addition to positive receptors for estrogen and progesterone. High levels of tumor suppressor gene p53 were also found [12].

As it is a rare condition and most of the published works are case reports, there is still no established treatment guideline. As most patients are asymptomatic and the diagnosis is incidental, the wait-and-see strategy can be applied in some cases by carrying out radiological monitoring to observe whether the lesions are stable, as seen in post-menopause. However, the preferred option is the primary excision of lesions subject to surgical resection to avoid complications such as rapid progression of lesions, emergence of symptoms, and loss of lung function [13]. Resection of single and limited lesions can cure in some cases in addition to avoiding the side effects and complications of chemical or surgical castration [11].

Bilateral oophorectomy as a form of surgical castration is performed in cases that resection of the lesions is not possible. Despite the radiological stabilization that most publications evidence, a growing number of reports indicate that despite this therapy, some lesions continue to grow [3,11], as seen in the case of this study. Therefore, hormone therapy seems to be a fundamental pillar to complement the treatment.

Reports of regression of lesions after menopause and pregnancy, and progression of lesions in patients undergoing hormone replacement therapy and using oral contraceptives strongly suggest hormonal influence.

In 1980, Cramer et al. were the first to show that benign metastatic leiomyomas had high levels of estrogen receptors. Historically analyzing the cases that were published from 1986 to 2012, 93.2 % of the 74 cases that tested for estrogen receptors were positive, and 89.7 % of the 68 cases that tested for progesterone receptors were positive [14]. This study found positivity only for estrogen receptor.

The first attempt to block estrogen receptors was made with tamoxifen, a selective modulator, but despite showing clinical improvement in some patients, its use was associated with the progression and growth of the lesions. What can justify it is its estrogen agonism in the myometrium, which can cause the growth of extrauterine leiomyomas [15].

Raloxifene, another selective estrogen receptor modulator that has an antiestrogenic effect on the breast and uterus, has shown success in cases of BML. However, studies indicate that despite the effect of inducing apoptosis and inhibiting cell proliferation in postmenopausal women, this medication still has mixed and uncertain effects in premenopausal women [14]. In the case this article presents, the patient started using raloxifene, and her symptoms became stable after 6 months. However, her pulmonary nodules considerably grew.

GnRH analogues have shown effective results with significant regression of lesions after 3 months of use. They act by suppressing ovarian steroidogenesis and can also inhibit the expression of aromatase P450, an enzyme that catalyzes androgens into estrogens. GnRH analogues can also be used in association with aromatase inhibitors, which have been used after surgical castration and demonstrated regression of the disease in most cases [14]. A study of 5 cases and a literature review regarding hormonal treatment that was made by Lewis et al. [14] in 2013 showed that patients who are treated with GnRH analogues and/or aromatase inhibitors showed a

control of tumor burden and disease stability. Therefore, this suggests that synergistic combinations of hormonal therapies can be used to amplify the response. In the present case, the patient started using anastrozole 1mg/day after stopping raloxifene due to disease progression.

4. Conclusion

This is a rare condition that needs more studies to comprehend it in addition to the creation of guidelines for the therapeutic approach. Although most cases are asymptomatic, the patient may present a clinical condition with hypoxemia and risk of death, mainly related to the tomographic pattern of multiple nodules with random distribution, as in the case in question. Diagnosis is confirmed with the anatomopathological study, and treatment varies according to the clinical condition, number, and extension of lesions. Pulmonary benign metastasizing leiomyomatosis must be include as a differential diagnosis in cases of women of reproductive age with diffuse pulmonary nodules and a history of previous gynecological surgeries for treatment of uterin leiomyoma.

5. Informed consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

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The authors received no financial or other material support for this study.

CRediT authorship contribution statement

Naiana Mota Araujo: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Isabella Maria da Silva Cardoso:** Formal analysis. **Thaysa Karlla de Albuquerque da Silva Jatobá:** Conceptualization, Data curation. **Luana Porto Mencato Sabey:** Formal analysis, Funding acquisition. **Alina Karime Austregesilo de Athayde Ferreira Teixeira:** Methodology, Project administration. **Anaelze Siqueira Tavares Tojal:** Conceptualization, Investigation. **Francisco José Nascimento Lima:** Validation, Writing – original draft. **Edson Franco Filho:** Methodology, Supervision. **José Barreto Neto:** Supervision, Visualization, Writing – original draft, Writing – review & editing. **Thalyta Porto Fraga:** Conceptualization. **Grasielle Santos Bezerra:** Validation, Visualization. **Marcell Coutinho Silva:** Investigation, Project administration. **George Andre Almeida de Araújo:** Formal analysis. **William Giovanni Panfiglio Soares:** Conceptualization, Data curation. **Maria Luiza Dória Almeida:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

I declare on behalf of my co-authors and myself that we do not have any conflict of interest to declare.

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