Letter to the Editor

Pulmonary benign metastasizing leiomyoma with concurrent granulomatous inflammation: a diagnostic challenge

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Introduction

Pulmonary benign metastasizing leiomyoma (PBML), an exceptionally rare condition, represents a benign smooth muscle tumor characterized by a tendency to metastasize. First reported in 1939 (1), it primarily occurs in females with uterine leiomyomas, with its precise etiology remaining elusive. Clinical manifestations often lack clarity, though some patients may present with symptoms such as chest pain, hemoptysis, dyspnea, or pneumothorax (2). Generally, the prognosis of PBML is favorable. Radiographically, PBML commonly manifests as multiple bilateral miliary-like opacities or uneven small nodules in the lungs (3,4), posing a challenge for differential diagnosis from benign pulmonary proliferative lesions or pulmonary tuberculosis. This complexity is further exacerbated when coexisting pathologies are involved. In this study, we present a case of PBML concomitant with pulmonary granulomatous inflammation and conduct a comprehensive literature review, aiming to offer valuable insights for the intricate diagnosis of PBML cases.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 42-year-old female had experienced a persistent cough and sputum production for over 6 months, along with a weight loss of 3 kg. She had a history of allergic rhinitis for 20 years and irregular use of antiallergic medications. Over 20 years ago, she had worked at a printing press factory for 6 months and reported having been exposed to "carbon powder". Some 11 years prior, she underwent uterine fibroid resection, followed by a second resection 6 years ago. On physical examination, the bilateral lung breath sounded clear, and no enlarged lymph nodes were palpable in the submandibular, neck, supraclavicular, or axillary regions. Tumor markers were all within normal range. Chest enhanced computed tomography (CT) showed multiple diffuse solid nodules in both lungs with irregular distribution, smooth margins, and absence of lobulation (*Figure 1A*). No significantly enlarged mediastinal lymph nodes were observed, as depicted in the reconstructed 3-dimensional coronal view (*Figure 1B*). The initial diagnosis considered chronic proliferative lesions versus metastatic tumors. To rule out malignant tumor metastases,

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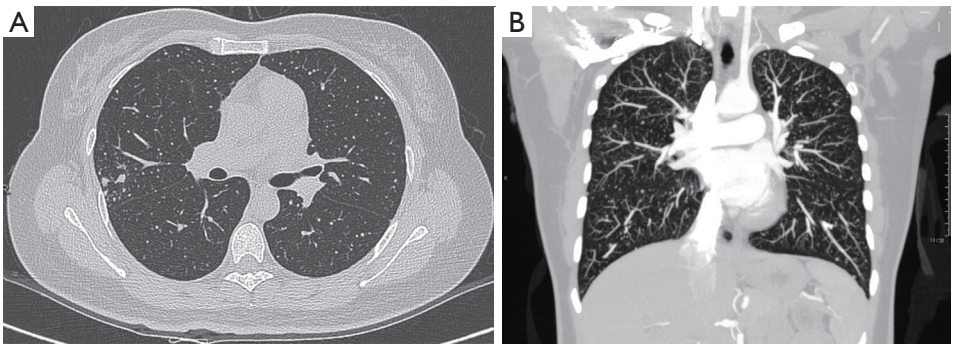

Figure 1 Non-contrast CT of the lungs. (A) Multiple solid nodules were present in both lungs, with larger nodules located in the lateral segment of the right lung middle lobe, there were multiple solid nodules in both lungs, and the larger nodule was located in the lateral segment of the middle lobe of the right lung, in which PET-CT showed mild uptake. Most of the remaining nodules were randomly distributed without obvious subpleural or centrilobular distribution patterns, and no obvious uptake was seen on PET-CT. (B) Coronal reconstruction of the lungs. Picture showed multiple diffuse small nodules in both lungs with clear edges. No significantly enlarged mediastinal lymph nodes were observed. CT, computed tomography; PET-CT, positron emission tomography/computed tomography.

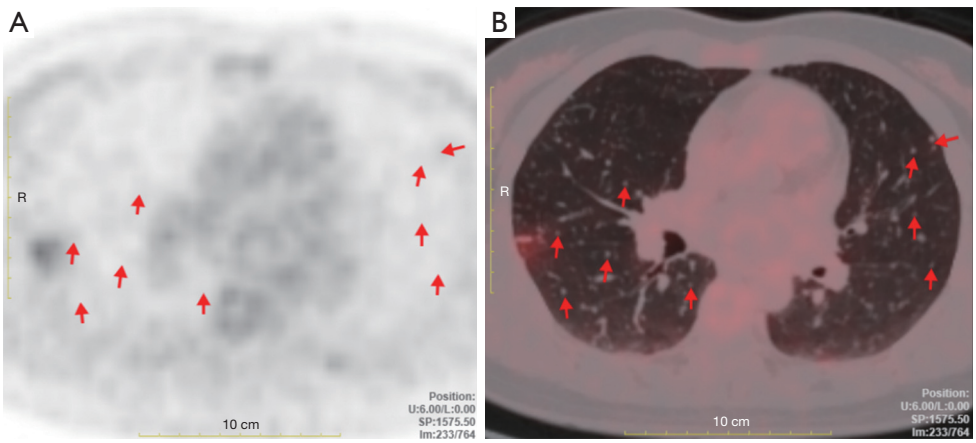

Figure 2 PET-CT examination images of pulmonary. Diffuse small nodules in both lungs with no significant increase in metabolism (red arrows), often considered as chronic proliferative nodules. PET-CT, positron emission tomography-computed tomography.

a subsequent positron emission tomography-CT (PET-CT) examination was performed. The results indicated diffuse 2–4 mm nodules in both lungs without detectable radiotracer uptake (*Figure 2*), and no significant abnormal radioactivity uptake was observed throughout the rest of the body. Taking into account the patient's medical history, an initial clinical diagnosis of benign proliferative nodules within the lungs was made, with a consideration of potential correlation with dust exposure history, yet concomitant pulmonary tuberculosis was not excluded. Subsequently, fiberoptic bronchoscopy lavage and cryobiopsy of the right lung (B4) were performed. Acid-fast bacilli staining indicated negativity. Pathogenic microbial cultures revealed the presence of bacteria resembling rod-shaped bacilli. Pathological examination under the microscope showed spindle cell proliferation arranged in a fascicular pattern, with elongated nuclei, abundant cytoplasm that stained red, rare nuclear division, and no necrosis (*Figure 3A*). The results of immunohistochemical analysis were as follows: (I) SMA (++), Ki67 (<1%+), CD117 (–), SOX10 (–), Galdesmon (++), estrogen receptor (ER) (+++), progesterone receptor (PR) (+++), P16 (–), P53 (20% weak+), CD34 (vascular+), desmin (++), and HMB45 (–); special staining results: periodic acid-Schiff (PAS) (–), PM (–), and acid-fast (–). (II)

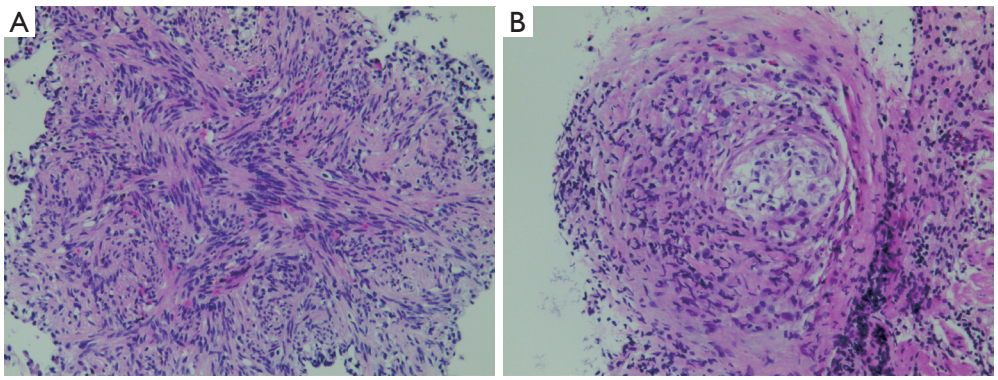

Figure 3 Pathological results of right lung cryobiopsy (hematoxylin eosin staining, ×100). (A) Spindle shaped cell proliferation can be seen in the bronchial mucosa, arranged in bundles; the nucleus is rod-shaped, with abundant cytoplasm and red staining. Nuclear division is rare, and no necrosis is observed. (B) After continuous sectioning of the tissue, granulomatous nodules can be seen with necrosis in the center.

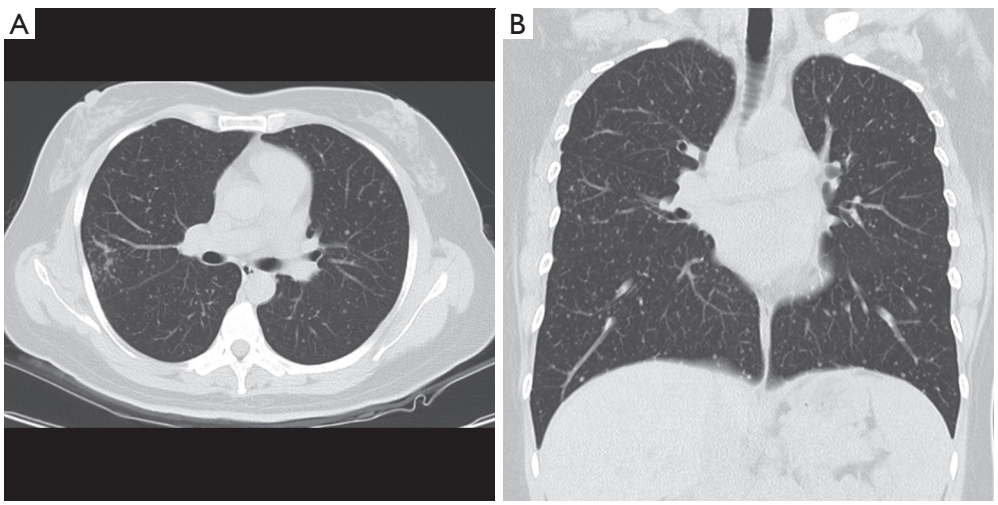

Figure 4 The 3-month follow-up CT Follow-up showed that the nodules in the lateral segment of the right lung middle lobe were partially reduced, and the diffuse distribution of pulmonary nodules was not significantly altered. CT, computed tomography.

After continuous sectioning of the tissue, granulomatous nodules could be seen with necrosis in the center (*Figure 3B*). Based on the patient's history of uterine fibroids and clinical indicators, a final diagnosis was made: PBML concomitant with granulomatous inflammation. Subsequently, the patient was treated with norfloxacin antimicrobial therapy and symptomatic treatment for 2 weeks, resulting in significant symptom relief and a successful discharge. A 3-month follow-up CT showed that the nodules in the lateral segment of the right lung middle lobe were partially reduced, and the diffuse distribution of pulmonary nodules was not significantly altered (*Figure 4A*,*4B*).

Discussion

PBML is an exceptionally rare condition characterized by a unique interplay between benign pathological features and the propensity for malignant tumor-like metastasis (5). This uncommon amalgamation of traits renders PBML diagnostically perplexing. It frequently manifests in premenopausal and perimenopausal women who also have uterine fibroids. Metastases of PBML can occur within the cardiovascular, lymphatic, skeletal systems, or other locations, with reports of metastases to the heart's atrium-right atrium junction and the lungs being most

prevalent (2,6).

The etiology of PBML remains unclear and controversial, with 3 prevailing hypotheses: (I) transport theory. The majority of researchers posit that smooth muscle cells disseminate through blood vessels and lymphatics following uterine fibroid resection or hysterectomy, eventually colonizing and proliferating in the lungs and other sites. The lungs and the atrium-right atrium junction are the most frequently reported sites of benign leiomyoma metastases (2), lending support to this theory. However, the challenge arises from cases where PBML occurs in non-surgical patients, presenting a theoretical paradox (7). (II) Multifocal origin: PBML is proposed as a manifestation of multiple smooth muscle hamartomas rather than true metastases. Some PBML cases have been observed prior to uterine fibroids (4), implying a primary pulmonary origin rather than a derivation solely from uterine fibroid cells. (III) A third hypothesis suggests that PBML metastases to other organs and systems represent a low-grade, malignantly transforming, well-differentiated smooth muscle sarcoma. However, in clinical practice, pathological evidence of malignant tumor cells is often elusive under microscopic examination (8). We believe that genomics and proteomics will provide additional evidence in the near future.

Clinical symptoms are often absent in PBML patients. Approximately one-third of patients may experience respiratory difficulties, cough, and chest pain as pulmonary manifestations (4,9). Additionally, PBML patients might develop pneumothorax and cysts, with a tendency for recurrence, necessitating differentiation from lymphangioleiomyomatosis (LAM). Rare complications include progressive pneumothorax leading to respiratory failure in PBML patients (9). Uterine leiomyomas themselves may cause gynecological symptoms such as abnormal uterine bleeding and pelvic pressure or pain. However, the appearance of skeletal (10) or cardiovascular metastases can lead to limb pain, clinical manifestations related to vascular narrowing causing obstructive flow, and impaired cardiac function.

In histopathology, PBML may present as extramural proliferation of smooth muscle cells, characterized by spindle-shaped cells and a low mitotic index (3). Consequently, PBML nodules exhibit slow growth, with long-term follow-up often revealing no morphological changes. Cells display minimal nuclear atypia and absence of necrosis, and they do not invade surrounding tissues. Smooth muscle cells express positive ER and PR, further affirming the uterine origin of PBML. This observation holds true for the present case of PBML, where typical muscle cell markers smooth muscle actin (SMA) and desmin are both positive, reinforcing the diagnosis (2). Furthermore, continuous sections of the tissue in this case reveal granulomatous nodules with central necrosis, confirming the coexistence of granulomatous inflammatory lesions. There are various types of granulomatous lung diseases, broadly categorized into infectious and non-infectious conditions. Common infectious pathogens comprise bacteria and fungi, whereas parasitic infections are relatively infrequent. Non-infectious causes include conditions such as sarcoidosis and hypersensitivity pneumonitis. In the case of sarcoidosis, the lesions often exhibit a distribution along the lymphatic vessels, presenting as nodular and patchy formations in the interlobar pleura or septa. Metastases, tuberculosis lesions, and fungal infections also have characteristic manifestations of pleural nodules, but the CT findings are mostly irregular and randomly distributed. The distribution of nodules in bacterial pneumonia, bronchoalveolar carcinoma, and Langerhans cell pleocytosis is mostly centrilobular. In this case, the plain chest CT scan revealed that the majority of pulmonary nodules were scattered and distributed randomly. However, a small number of nodules were also located in the pleura or nocturnal clefts, with a few displaying the distinctive 'tree bud' sign. The halo sign around the nodule was even observed in the lateral segment of the right middle lobe, presenting as a mixture of solid and ground-glass nodules. Considering the alterations in lesions within the middle lobe of the right lung post short-term anti-inflammatory therapy and the minimal changes in most nodules across the remaining lungs, we hypothesized that the multiple nodules in the lungs constituted a combination of PBML lesions and granulomatous lesions, with the possibility of bacterial pneumonia not entirely ruled out, despite the absence of definite evidence of infection in the biochemical results. In addition to morphological identification, PET-CT can also provide certain evidence to distinguish lesion types. However, when the diameter of multiple nodules is <5 mm, the incidence of false negatives affects its clinical application. Although the above diseases can generally be differentially diagnosed when they show typical imaging features, when multiple infections and different types of diseases are combined, the imaging signs become confusing and difficult to distinguish. The final diagnosis still relies on pathological evidence. Due to the long and complex course of the disease in this patient, we speculated that there may be multiple granulomatous nodules in the lungs, resulting

in complex and atypical imaging findings, thus posing a diagnostic challenge.

PBML on CT imaging can manifest in various patterns (3), including solitary or diffuse distribution, presenting as isolated small nodules or masses, and very rarely as diffuse miliary nodules (11). In this case, the nodules in both lungs exhibited a miliary-like random distribution, measuring approximately 2–4 mm in diameter. Due to the patient's history of exposure to "carbon powder", a misdiagnosis of granulomatous lesions was initially considered. However, the patient's short duration of "carbon powder" exposure and the absence of symptoms such as low-grade fever and night sweats make tuberculosis less likely, requiring differentiation from silicosis and hematogenous disseminated pulmonary tuberculosis. In a study conducted by Sawai *et al.* (4), PBML was assessed on ^{18}F-FDG-PET-CT scans, categorized into no (minimal) uptake, low (moderate) uptake, and high (positive) uptake. Most PBML lung nodules exhibited low or no metabolic uptake (12), consistent with the present case, possibly correlating with nodule size and benign-malignant characteristics. However, a small subset of nodules showed high uptake, warranting differentiation from smooth muscle sarcoma.

In conclusion, PBML is a rare benign tumor with metastatic potential, characterized by gradual progression and atypical clinical symptoms. Diagnosis becomes exceptionally challenging when concurrent pulmonary tuberculosis, intrapulmonary granulomatous nodules, or other lesions are present. A comprehensive approach combining clinical history, imaging, and pathology is crucial to ensure accurate diagnosis, avoiding misdiagnosis and potentially irreversible medical consequences for the patient.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1201/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee (s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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