Author's response to reviews

Title: Solitary Pulmonary Nodule of Benign Metastasizing Leiomyoma associated with Primary Lung Cancer: a case report

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Author's response to reviews: see over
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Dear Sir Editor,

Thanks very much for your letter providing us the results of the review process on the above-mentioned manuscript. Herewith, we are sending you the revised form of the paper, which was corrected following the suggestions of the reviewers. The answers to reviewers are described below.

Thanks very much for your kindness and interest in our work and we look forward receiving a positive response from you.

Best regards

Answer to Reviewer 1
Comment 1
The authors should add some data about the association, in the literature, between lung cancer and leiomyoma.
Answer
Thanks very much for your suggestions. Tsunoda et al reported the only one case of benign metastasizing leiomyoma of the lung complicated with primary lung cancer. (Japanese Journal of Lung Cancer, 2009). There are not other description in the literature about the association between lung cancer and leiomyoma other than this report. Therefore, we believe that BML in association with primary lung cancer is a very rare case. The explanation about it was described in the “Discussion” section of the revised manuscript.

Answer to Reviewer 2,
We greatly appreciate the Reviewer’s comments, insights and constructive suggestions for improving the manuscript. Below we have answered the questions raised by the Reviewer and described the corrections described in the revised from of the manuscript.

First of all, we must inform you that we have modified the number of paragraph of the “Discussion” section adding one new paragraph).

Comment 1
Case presentation, paragraph 3: The clinical rationale for resection is very unclear to me, as is the 6 month delay between initially finding the lesions and the resection. Was there interval growth on imaging that led to surgery? Why wasn’t biopsy, at least of the 1.3cm GGO, considered first? This appeared a rather invasive approach, especially if the lesion hadn’t grown, but perhaps there are further details that explain this decisionmaking process.

Answer

We believe this comment about interval between the first finding of GGO and the resection of GGO is a very important point. We apologized for insufficient explanation. From the beginning, we have suspected lung carcinoma, but we could not get the patient’s consent for doing bronchoscopic examination and surgical resection. In CT follow-up after 6 months, the GGO size slightly increased and the size of the small nodule did not change. We have also suspected that GGO was lung carcinoma, but it was difficult to judge whether the small nodule was lung metastasis. If the small nodule was not lung metastasis, the lung carcinoma could have been considered as being in early stage. Therefore, we considered that pathological examination by surgical resection would be more appropriate and because it may also allow the decision on whether to indicate treatment against lung carcinoma. The explanation was also added to the “Case presentation” section.

Comment 2

Case presentation, paragraph 3: Please clarify whether TTF-1 stained positive or negative and explain how this helped clarify the diagnosis. Most readers in the general audience might think of TTF-1 in isolation as a confirmatory marker for NSCLC rather than this unusual entity of BML.

Answer

As the reviewer pointed out, TTF-1 is a confirmatory marker for NSCLC(specially adenocarcinoma). But the aim of immunohistochemical staining of TTF-1 in our case was to decide whether the low cuboidal metaplastic bronchiolar epithelium observed in the pathological sample derives from a pre-existing bronchiolar epithelium because it is known that TTF-1 is only expressed by normal epithelium of the lungs and thyroids. We think that the diagnosis of BML is not dependent on TTF-1. This explanation was also detailed in the section “Discussion” section.

Comment 3

Case presentation, paragraph 1, sentence one: Replace “has” with “had”. And paragraph
3: Please standardize all verbs to past tense, especially in sentence 5 and 6.
Answer
A suggested by the reviewer, we have made the corrections in the text. And I have also standardized them in the text.

Comment 4
Case presentation, paragraph 4: Consider replacing “Up to date” with the actual length of follow-up so far (and correct the type BLM to BML).
Answer
We have made the corrections as suggested by the reviewer.

Comment 5
Discussion, paragraph 1: Replace “lung” with “lungs” as you cite cases of multifocal disease.
Answer
As suggested we have made the necessary corrections in the text.

Comment 6
Discussion, paragraph 2, last sentence: “a very rare clinical presentation”? To make your case more strong, you might say “it has not yet been reported at all in the literature!”
Answer
Thanks very much for these comments. Actually, Tsunoda et al reported only one case of benign metastasizing leiomyoma of the lung complicated with primary lung cancer (Japanese Journal of Lung Cancer, 2009). But, there are not papers about the association between lung cancer and BML other than this report. And thus we believe that BML associated with primary lung cancer is a very rare case. This explanation was also described in the section “Discussion”.

Comment 7
Discussion, paragraph 3: Is there other evidence about the means of metastasis?
Consider mentioning the work of Patton KT (Modern Pathology, 2006)
Answer
As suggested, we cited the work of Patton KT about the means of metastasis in the “Discussion” section.
Comment 8  
Discussion, paragraph 4: First 2 sentences are essentially the same, would advise condensing one.  
Answer  
As suggested we have condensed the sentences in the text.

Comment 9  
Discussion, paragraph 5: You might suggest what frequency of CT follow-up you plan for this patient, if any; just the same frequency as you’d follow up resected NSCLC? Also, do the recent studies suggest using the hormonal treatments in the setting of multifocal, unresectable disease? Worth fleshing out for the reader’s sake.  
Answer  
Thank you for the reviewer’s suggestion. In this case, although the pathological staging of lung carcinoma was stage I A, we considered that CT follow-up was necessary at intervals of 3 to 6 months including follow-up of BML recurrence. In a recent study, Patton KT suggested the hormonal treatments for BML with positive immunoreactivity for estrogen receptor(ER) and progesterone receptor (PgR). This explanation is also added to the “Discussion” section.
Solitary Pulmonary Nodule of Benign Metastasizing Leiomyoma associated with Primary Lung Cancer: a case report

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Abstract

Introduction: Benign metastasizing leiomyoma in the lung is a very rare disease characterized by the growth of uterine leiomyoma tissue. In most cases there is a previous history of hysterectomy for uterine leiomyoma.

Case presentation: A 50-year-old Asian woman underwent total abdominal hysterectomy for uterine leiomyoma at the age of 37 years old. She was referred to our hospital because of sudden anterior chest pain. Chest CT scan revealed a ground-glass opacity (GGO) in the left bronchial segment S10, and a solitary small nodule in the left S4. We performed a left lower lobectomy and an upper lung partial resection in order to make a definitive diagnosis and for further therapeutic strategy plan. The GGO in the left S10 was a primary lung adenocarcinoma, while the small nodule in the left S4 was diagnosed as a benign metastasizing leiomyoma (BML). No additional therapy was done and, the patient was followed up by chest CT scan. Up to date, repetitive evaluation by chest CT scan showed no sign of BML or lung cancer recurrence.

Conclusion: This is a very rare case of benign metastasizing leiomyoma of the lung associated with primary lung cancer. This comorbid association should be considered in the differential diagnosis when a lung solitary nodule is detected in a patient with a history of uterine leiomyoma.
Introduction

Benign metastasizing leiomyoma (BML) is a very rare disease characterized by the growth of uterine leiomyoma tissue in the lung (1). In most cases there is a previous history of hysterectomy for uterine leiomyoma; however, the pathogenesis of the disease has not been as yet elucidated. The comorbid association of primary lung cancer and BML is even more uncommon. Here, we report a case of BML associated with primary lung cancer.

Case Presentation

The patient was a 50-year-old Asian woman that had undergone total abdominal hysterectomy for uterine leiomyoma at the age of 37 years old. She was non-smoker and her alcohol intake was only social.

She was referred to our hospital because of sudden anterior chest pain. Hematology, biochemistry and blood gas analysis were normal. Chest CT scan revealed a ground-glass opacity (GGO) in the left S10 lung segment (Figure 1A) with 1.3 cm in size, and a solitary small nodule of 5 mm in diameter localized in the left S4 segment (Figure 1B).

From the beginning, we suspected lung carcinoma, but we could not get the patient’s consent for performing bronchoscopic examination and surgical resection. Follow-up with CT showed that the GGO size slightly increased and that small nodule size had not changed. We suspected that GGO was lung carcinoma, but it was difficult to rule out whether the small nodule was lung metastasis. If this small nodule was not lung metastasis, the lung carcinoma could have been considered as being in early stage. We considered that pathological examination by surgical resection was appropriate because it was also an approach for treating the lung carcinoma. We performed a left lower lobectomy and an upper lung partial resection in order to make a definitive diagnosis and to decide further therapeutic strategies. The pathological diagnosis of the GGO in the left S10 was primary lung adenocarcinoma (localized bronchioloalveolar carcinoma)(Figure 2). On the other hand, pathological examination of the small nodule in the left S4 showed spindle-shaped smooth muscle cells and low cuboidal metaplastic bronchiolar epithelia surrounded by fascicles of smooth muscle cells without mitosis and nuclear atypia (Figure 3A). Immunohistochemical staining of thyroid transcription factor-1 (TTF-1) and surfactant apoprotein A (SP-A) showed epithelial structures composed of alveoli or bronchioli (Figure 3B, 3C), suggesting that the low cuboidal metaplastic bronchiolar epithelium derived from the pre-existing bronchiolar epithelium. There was positive immunohistochemical staining for α-smooth muscle
actin (α-SMA) and spindle-shaped cells (Figure 3D), suggesting that spindle-shaped cells were smooth muscle cells. Positive immunoreactivity for estrogen receptor (ER) and progesterone receptor (PgR), suggests that the spindle-shaped cells were uterine smooth muscle cells (Figure 3E, 3F). Unfortunately, histological sample of the uterine leiomyoma was not available for comparison. The small nodule was diagnosed BML based on the results of immunohistochemical staining and the past history of uterine leiomyoma.

No additional therapy was done and follow-up of the patient by chest CT scan was continued. During four years of follow-up, no recurrence of either BML or lung cancer could be detected.

**Discussion**

Benign metastasizing leiomyoma (BML) is a disease in which a tissue from benign uterine leiomyoma is detected as a solitary nodule or as multiple nodules in the lungs of patients with a previous history of hysterectomy for uterine leiomyoma. In 1939, Steiner et al (1) reported for the first time BML as metastasizing fibroleiomyoma of the uterus, and since then there have been several similar reports.

Abramson et al (2) reported that the average age of patients with BML is forty-eight, that the period from hysterectomy to nodule discovery is variable from three months to twenty-six years and that the first symptom of BML is almost nothing or sometimes cough or chest pain. Horstmann et al (3) reported that the radiological presentation of BML can be as multiple nodules in 87% of cases (bilateral nodules, 70% and unilateral nodule, 17%) or as a solitary nodule in 13%. The main metastatic site of BML is the lung but other sites including lymph nodes, soft tissue of the pelvis, bone, bone marrow, greater omentum, peritoneum, and heart have been also reported (4). Tsunoda et al (5) reported only one case of benign metastasizing leiomyoma of the lung complicated with primary lung cancer. There is no case in the literature about the association between lung cancer and BML other than this report. Thus, we believe that this is a very rare case of BML associated with primary lung cancer.

Recent studies have shown that BML is caused by lung metastasis of uterine leiomyoma, which is histologically a benign tumor with very low grade of malignancy: this latter has been reported to depend on sex hormones (1,6,7,8). On the other hand, Patton KT et al have previously reported that BML results from the monoclonal, hematogenous spread of an apparently benign uterine leiomyoma (9). However, these conclusions are still controversial.

Pathological examination of BML showed spindle-shaped cells without mitotic activity or nuclear atypia surrounded by cuboidal bronchiolar epithelial cells; additional
immunohistochemical stainings showed that the spindle-shaped cells derived from smooth muscle cells of the uterus, and that the low cuboidal metaplastic cells derive from pre-existing bronchial cells (4). The presence of TTF-1 is usually assessed to confirm the diagnosis of primary non-small cell lung carcinoma (specially adenocarcinoma) (10); but the purpose of TTF-1 staining in our particular case was to decide whether the low cuboidal metaplastic bronchiolar epithelium observed in the pathological specimens derived from the pre-existing bronchiolar epithelium because it is known that TTF-1 is only expressed on the normal epithelium of lung and thyroid (10). We believe that the diagnosis of BML is not dependent on the expression of TTF-1. Pathological comparison between the solitary pulmonary nodule and the original uterine tumor should provide confirmatory evidence but the sample was not available. However, the small lung nodule was diagnosed as BML based on the results of the immunohistochemical staining and the past history of hysterectomy for uterine leiomyoma.

There is no standard therapy for BML. Recently, Patton KT et al (9) suggested the possibility of hormonal treatment for BML with positive immunoreactivity for ER and PgR. Other studies have shown improvement of BML after ovariectomy, administration of progesterone or Gn-RH agonist and menopause (11). The prognosis of the disease is also unclear. In the present reported case, although the pathological stage of lung carcinoma was stage IA, we considered that CT follow-up was necessary at intervals of 3 to 6 months including follow-up of BML recurrence. No additional therapy was done and the follow-up by chest CT scan showed no recurrence of BML or lung cancer.

**Conclusion**

We reported a very rare case of BML associated with primary lung cancer. This comorbid association should be considered in the differential diagnosis when a lung solitary nodule is detected in a patient with a history of uterine leiomyoma.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

NT wrote the manuscript. TK was responsible for the manuscript concept and final corrections to the manuscript. ECG, YT, MY and OT supervised this patient care and manuscript. KF, MO, AF, TT and HK were participated in patient care as a team. All
authors have read and approved the final manuscript.

References
**Figure Legends**

**Figure 1. Computed tomography (CT) scan of the chest on admission to our hospital.**

(A) Chest CT scan shows ground-glass opacity (arrow) in the left S10 lung segment (GGO) of 1.3 cm in size. (B) Chest CT scan shows a solitary small nodule (arrow) of 5 mm in diameter in the left S4 segment.

**Figure 2. Histopathology of the lung tumor in the left S10.**

Pathological examination of the GGO in the left S10 depicts a localized bronchioloalveolar carcinoma (H&E staining, x400).

**Figure 3. Histopathology of the lung tumor in the left S4.**

(A) Pathological examination of the lung small nodule in the left S4 segment reveals that the tumor is composed of spindle-shaped smooth muscle cells and a low cuboidal metaplastic bronchiolar epithelium surrounded by fascicles of smooth muscle cells without mitosis or nuclear atypia (H&E staining, x400).

(B) Immunohistochemical staining of TTF-1 shows positive immunoreactivity in epithelial structures including alveoli or bronchioli (x400).

(C) Immunohistochemical staining of SP-A shows positive immunoreactivity for epithelial structures including alveoli or bronchioli (x800).

(D) Immunohistochemical staining of α-SMA is positive in spindle-shaped cells (x400).

(E) Immunohistochemical staining of ER is positive in spindle-shaped cells (x400).

(F) Immunohistochemical staining of PgR is positive in spindle-shaped cells (x400).