Lymphangioleiomyomatosis: a case report and review of diagnosis and treatment

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Yi Liu*
Zhibin Guo*
Chenlong Zhao
Xin Li
Hongyu Liu
Jun Chen
Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin 300052, China

*These authors contributed equally to this work

Abstract: Lymphangioleiomyomatosis (LAM) is a rare disease that generally affects young women and involves the abnormal proliferation of smooth muscle-like cells (LAM cells) in the lungs (pulmonary LAM) and extrapulmonary sites (extrapulmonary LAM). This disease is rare in males. It is hard to distinguish between lung cancer and pulmonary LAM, especially during early stages. Herein, we present a case of a 66-year-old man with a small nodule in the right upper lobe that was first diagnosed as a lung malignancy using a chest CT scan. After a wedge dissection, a pathologist performed a histologic and immunohistochemical examination, and a diagnosis of pulmonary LAM was made. Further analysis of this case is discussed in this report.

Keywords: lymphangioleiomyomatosis, lung cancer, diagnosis and treatment

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease affecting almost exclusively women and involves many organs. It is characterized by cystic lung lesions and extra-pulmonary features consisting of renal angiomyolipomas and lymphatic involvement such as lymphangioleiomyomas and chylous effusions. There are two forms of LAM: one is a sporadic form that occurs in 3.3–7.7 million women and the other is an inherited form that occurs in 30%–80% of women with tuberous sclerosis complex (TSC). Although it has been reported in men, it is extremely rare. The causes of LAM remain unclear; therefore, currently, most patients with LAM around the world could not obtain an effective treatment. Herein, we report the case of a male patient with LAM and an analysis of a 518-gene panel using next-generation sequencing (NGS).

Case presentation

A 66-year-old man was admitted with the chief complaint of cough with bloodstained phlegm for approximately 3 days. No other complaint or remarkable past medical history was revealed. He had an approximate 15-year history of smoking. A family history of malignancy comprised only his mother who died of lung cancer. As shown in Figure 1, a chest CT scan revealed an isolated solid nodule with a vacuole and pleural traction signs in the right upper lobe, indicating a malignant nodule. The system review was noncontributory and normal, including peripheral blood count, baseline serum chemistry screening, and tumor biomarker tests (carcinoembryonic antigen, antigen 19-9, carbohydrate antigen 24-2, CYFRA21-1, and squamous cell carcinoma antigen). Upper abdominal CT scan and brain MRI were normal. Therefore, a clinical diagnosis of an upper right lung nodule, most possibly a malignant tumor, was given.

*These authors contributed equally to this work

Correspondence: Jun Chen
Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Anshan Road No 154, Heping District, Tianjin 300052, China
Email: huntercj2004@yahoo.com

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Then, a wedge resection was performed using video-assisted thoracoscopy. As shown in Figure 2, a histopathologic examination showed a piece of dense fibrous connective tissue with some differently shaped aqueducts. Immuno-histochemical staining was positive for CD34, SMA, and desmin, and negative for HMB-45. Therefore, a diagnosis of primary lung LAM was made by the pathologists. The patient recovered after the operation and was doing well during a 6-month follow-up.

As this was a rare case involving a male patient with primary lung LAM, we performed an analysis of the lesion tissues, using a 518 tumor-related gene panel, to explore possible molecular abnormalities using NGS (Zhongyuan Xiehe Gene Technology Co., Ltd., Tianjin, China; www.vcanbio.com); gene names are shown in Table S1. DNA in the patient’s blood was considered baseline to reduce the influence of leukocyte, but for the germline mutation-related genes, we reviewed the sequencing results from both sides of blood and tissues to avoid missing the important germline mutations. These genes are broadly divided into four categories: targeted drug-related genes (such as EGFR, ALK, Kras, BRAF, MET, ROSI, RET, HER2, NRAS, KIT, and PDGFR), chemotherapy efficacy and side effect-related genes, genetic susceptibility genes (including 78 related genes), and other genes, which were called Catalogue of Somatic Mutations in Cancer (COSMIC). In these detected genes, only three uncommon mutations were found that were from three genetic susceptibility genes named BARD1, BLM, and BRCA2. All these three mutations were germline mutations, since the mutations were found from both sides of blood and tissues sequencing analysis, as shown in Figure 3. The mutation in the BARD1 gene was in exon 6 with a mutation that has an unknown meaning at encoding sequence c.1518_1519CA; BLM and BRCA2 had missense mutations at encoding sequence c.2371C>T (p.R791C) and c.4136A>G (p.Q1379R) in exon 11, respectively. We also further checked the mutation of TSC1 and TSC2 genes from both sides of blood and tissues sequencing results and did not find the mutation for these two genes. These results indicated that the tumor mutation burden in this case of primary lung LAM was low and that no remarkable gene mutation was found.

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

**Discussion**

LAM is a devastating female-predominant pulmonary disease characterized by the accumulation of abnormal smooth muscle-like cells in the lung parenchyma and severe emphysema-like lung destruction that can lead to respiratory failure and death.4–7 LAM may be related to changes of female hormones in the body. LAM occurs both sporadically (sLAM) and in association with TSC (TSC-LAM). sLAM has a rare prevalence of 1:1,000,000, whereas TSC-LAM is more common, as approximately 30% of women with TSC have coexisting LAM.8,9 To a certain extent, the biological behavior of LAM is similar to that of low-grade neoplasms, and LAM can also metastasize.10

![Chest CT scan](https://www.dovepress.com/)

**Figure 1** Chest CT scan.

**Notes:** (A) Lung window; (B) mediastinal window; (C) coronal window. There was an isolated solid nodule with a vacuole and pleural traction in the right upper lobe, indicated by red arrows.
To diagnose LAM is difficult. In general, there are no specific symptoms at an early stage in patients with LAM, and many symptoms are similar to those of other lung conditions (such as asthma, chronic obstructive pulmonary disease, and bronchitis). Symptoms vary, but the two most frequent clinical presentations of LAM are recurrent pneumothoraces and dyspnea. Less frequently, the first manifestation of LAM is a chylous effusion, abdominal or pelvic tumor, hemoptysis, abdominal hemorrhage caused by a renal angiomyolipoma, or the incidental discovery of lung cysts.

**Figure 2** Histopathologic analysis.

**Note:** A diagnosis of lymphangioleiomyomatosis was made by pathologist with hematoxylin–eosin (H&E) staining and immunohistochemistry staining with different antibodies such as CD34, SMA, desmin, and HMB-45.
and/or abdominal tumors. To our knowledge, Ye et al reported in a study of 120 patients with LAM that there was dyspnea in 97.5%, cough in 48.3%, pneumothoraces in 42.5%, bloodstained phlegm in 40.8%, chylothorax in 28.3%, chest pain in 19.2%, and chyloperitoneum in 5.8%. Patients with LAM mostly experience an airflow obstruction and/or reduced lung-diffusing capacity. According to an article reported by Zhang et al, among 86 patients, the most

Figure 3 The next-generation sequencing maps for the mutations of three genes BARD1, BLM, and BRCA2.

Note: All these gene mutations can be found from both sides of blood and tissues sequencing results and indicate germline mutations of these three genes.
common form of pulmonary dysfunction was an obstructive ventilation dysfunction (65.1%, 56/86) and a diffusion dysfunction (38.4%, 33/86). In our case, the patient experienced a cough with bloodstained phlegm for 3 days. His pulmonary function test result was normal since the patient was at an early stage.

It is important to make a proper diagnosis. The European Respiratory Society guidelines state that we need to have a CT scan showing lung cysts, as well as another piece of evidence, for example, tuberous sclerosis, a kidney tumor, or a chyloous effusion. It is helpful to obtain a blood test showing a high level of a VEGF-D protein. In the presence of consistent clinical data and characteristic radiologic findings, serum levels of VEGF-D equal to or greater than 800 pg/mL are now accepted as being diagnostic of LAM because they are extremely rare in other cystic lung diseases. Unfortunately, we do not have an efficient method to test for VEGF-D. In rare cases in which a diagnosis cannot be made from a combination of the abovementioned symptoms, it is necessary to obtain a biopsy. Tissue samples are collected from the lungs and tested, wherein the tissue may show the histological features of LAM that include immunoreactivity of LAM cells with monoclonal antibody HMB-45. In addition, LAM cells exhibit positive immunoreactivity for ER and PR, β-catenin, E-cadherin, and EGFR. As indicated in Zhang et al’s report on 81 patients, the most common form of immunoreactivity was observed for HMB-45 (69.1%, 56/81) and SMA (46.9%, 38/81), followed by PR (43.2%, 35/81), ER (42.0%, 34/81), actin (34.6%, 28/81), desmin (29.6%, 34/81), CD34 (12.3%, 10/81), F-VIII (9.9%, 8/81), gp100 (6.2%, 5/81), and vimentin (4.9%, 4/81). Immunohistochemical staining of our patient was positive for CD34, D2-40, SMA, and desmin. In addition, the antipeptide antibody αPep13h reacting with a C-peptide terminal of the Pmel17 protein identifies over 82% of the LAM cells in lung nodules, but HMB-45 identifies only 25%. As LAM is such a rare condition, it is important to obtain a proper opinion from a specialist as early as possible and to discuss your individual case with an expert on the condition. Once LAM is diagnosed, effective treatment and management should be offered. Supportive treatment could be administered first for patients with an airflow obstruction and/or reduced lung-diffusing capacity that includes the use of inhalers to make breathing easier and oxygen to help the patients with breathlessness. For early pulmonary LAM with a nodule, a wedge/segmental dissection or lobectomy is the first choice. As the disease progresses, most patients will experience more than one pneumothorax (lung collapse) during their lives. Pleurodesis may be recommended to prevent this from reoccurring which can improve the quality of life for women with LAM. A total pleural covering with sheets composed of an oxidized regenerated cellulose mesh to wrap the entire visceral pleura can successfully prevent the recurrence of a pneumothorax in LAM; it is minimally invasive and rarely causes a restrictive ventilatory impairment. Lung transplant may be an option for some women with advanced LAM, for which no other treatment option exists. Many women with LAM have undergone a successful lung transplant and, as a result, experienced an improved quality of life.

During treatment, LAM arises from mutations in the TSC genes (TSC1 and TSC2) that normally do not get activated, and the TSC genes encode the proteins, hamartin and tuberin, which combine to form a complex (TSC1–TSC2 complex). Through the mTORC1 pathway, the complex can regulate the mTOR protein that is a necessary factor to regulate cell proliferation and lymphangiogenesis. In LAM, the absence of the TSC1–TSC2 complex leads to the uncontrolled activation of mTOR. As pharmacologic inhibitors of mTOR, such as everolimus and sirolimus, can directly inhibit T-lymphocyte proliferation, there is ample evidence that mTOR inhibitors are effective for the treatment of pulmonary and renal LAM. Li et al reported that IGFBP2 could bind insulin, IGF1, and IGF2 in the circulation to modulate cell survival, migration, and invasion of neoplasms. Targeting IGFBP2 may serve as a potential therapeutic strategy for women with LAM and other female gender-specific neoplasms. Another study demonstrated that Syk inhibition is a potential therapy for patients with LAM. Recent research involving cells derived from patients with LAM showed that estrogen increased cell resistance to anoikis in vitro that was accompanied by a decreased accumulation of the proapoptotic protein, Bim, an activator of anoikis. Therefore, targeting Bim may be a plausible future treatment strategy for patients with LAM.

There were few reports so far on the role of the germline mutations of BARD1, BLM, and BRCA2 in LAM. BARD1 is a kind of tumor suppressor gene. BARD1 can combine with BRCA1 protein to form a heterodimer, which can repair the DNA damage and maintain stable cytogenetics. Mutations in any part of the heterodimer result in decreasing tumor suppressor activity, leading to tumorigenesis. As reported, mutations of the heterodimer can regulate the expression of aromatase to participate in the development of breast cancer. BRCA2 is also a kind of tumor suppressor gene. Predominantly presenting in mammary gland cells, BRCA2 gene mutation can lead to the failure of gene repair and the tumorigenesis of breast cancer. Aromatase is an important enzyme in the synthesis of estrogen in vivo. As reported
above, estrogen is related to LAM. In the case of our patient, the gene mutations may have been caused by the abnormal level of aromatase, leading to the synthesis of estrogen, and finally the development of LAM. BLM gene is one of the members of the RecQ DNA helicase family. The RecQ DNA helicase family plays an important role in inhibiting human tumorigenesis.\(^{41,42}\) Bloom syndrome is related to the mutation of BLM gene, but the interaction between BLM and various proteins in the DNA metabolism pathway is not yet clear.

Moreover, LAM is a rare female-predominant pulmonary disease with nonspecific symptoms. The diagnosis of LAM must combine a CT scan showing lung cysts, evidence of tuberous sclerosis or a kidney tumor, a chylous effusion, and a serum examination, such as serum levels of VEGF-D. Treatment depends on the stage of the disease, and new targeted drugs are anticipated.

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**Author contributions**

Yi Liu, Zhibin Guo, and Jun Chen wrote this manuscript and analyzed all data. Yi Liu, Zhibin Guo, Chenlong Zhao, and Xin Li provided medical care for the patients and collected the data. Hongyu Liu and Jun Chen revised the article. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


### Table S1 List of the detected 518 genes

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