Utility of transbronchial biopsy in the diagnosis of lymphangioleiomyomatosis

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Abstract Pulmonary lymphangioleiomyomatosis (LAM) is a rare cystic lung disease that targets women during their reproductive years. A confident diagnosis can often be based on clinical grounds, but diagnostic certainty requires pathological analysis. Although surgical lung biopsy is considered the gold standard for obtaining tissue in patients with diffuse lung disease, it is also associated with higher morbidity and mortality than alternative, less invasive techniques. The objective of our study was to examine the utility of transbronchial biopsy in the diagnosis of LAM. We conducted two online surveys of over 1 000 LAM patients registered with the LAM Foundation who were accessible by email. Transbronchial biopsy specimens were subsequently collected and reviewed by an expert pathologist to validate the diagnosis. We found that transbronchial biopsy has a yield of approximately 60% in patients with LAM. We conclude that transbronchial biopsy may be a safe and effective method for establishing the diagnosis of LAM, obviating the need for surgical lung biopsy in more than half of LAM patients.

Keywords lymphangioleiomyomatosis; lymphangiomyomatosis; multicystic lung disease; diffuse cystic lung disease; transbronchial biopsy; perivascular epithelioid cell tumor (PEComa); HMB-45

Introduction

Lymphangioleiomyomatosis (LAM) is a cystic lung disease caused by smooth muscle cell proliferation, infiltration and tissue remodeling [1]. LAM occurs in up to 40% of women with tuberous sclerosis complex (TSC-LAM) and in a non-heritable sporadic form (S-LAM) that affects about 5 women per million. Although LAM is widely considered to be an interstitial lung disease (ILD) by clinicians, the pathology community has classified LAM as a low-grade malignant neoplasm since 2004 [2,3]. Genetic techniques have demonstrated that cells which comprise recurrent LAM lesions in the allograft of transplanted LAM patients arise from the recipient, consistent with a metastatic mechanism for the disease [4,5].

Because the disease is rare and the signs and symptoms can be non-specific, the diagnosis of LAM is often elusive and delayed, and many patients are treated for several years for asthma or chronic bronchitis before LAM is considered [6]. Even when the disease presents in a prototypical fashion with spontaneous pneumothorax, the diagnosis is typically delayed until after the first recurrence [7,8].

A clinically confident diagnosis of LAM can be made in patients who present with a characteristic high-resolution CT scan (HRCT) pattern of lung cysts and either TSC, chylous pleural effusion, chylous ascites, angiomyolipoma, lymphangioleiomyoma or lymph nodes involved by LAM [9] or a serum VEGF-D level of greater than 800 pg/ml [10]. The diagnosis can also be made on cytological grounds, based on transcutaneous needle biopsy of axial lymph nodes or lymphangioleiomyomas or the finding of LAM cells or LAM cell clusters in chylous fluid collections [11]. Approximately one third of patients present without the criteria for the clinical, serological, cytological and radiological based diagnoses mentioned above, however [10]. In those cases, if the patient and physician wish to achieve diagnostic certainty, lung biopsy is required.

Through the first half of the last century, all lung biopsies were obtained surgically by performing thoracotomy. Endoscopic procedures were subsequently developed that have
become highly effective diagnostic tools. In 1965, Andersen and colleagues at the Mayo Clinic described the technique of transbronchial biopsy in 13 patients using the rigid bronchoscope [12]. In the late 1960s, the flexible fiberoptic bronchoscope (FB) was introduced and over time transbronchial biopsy through a channel in the FB became a widely-employed diagnostic technique for lung cancer and selected diffuse lung disorders including granulomatous lung diseases [13]. In many of the interstitial lung diseases, however, accurate diagnosis requires tissue specimens that are large enough to characterize pathological patterns or capture lesions in more patchy processes. Video-assisted thoracoscopic biopsy was first described in the 1980–1990s [14], and is now the procedure of choice for surgical lung biopsy when diagnostic certainty is required and less invasive techniques are not feasible or not likely to be successful.

Surgical lung biopsy has higher diagnostic yield compared to transbronchial lung biopsy but is also associated with higher morbidity and mortality. Complications of surgical lung biopsy include postoperative respiratory failure, prolonged air-leak, infection, chronic pain and death [15–17]. Surgical lung biopsy for the diagnosis of interstitial lung disease has a postoperative mortality rate of 2% to 4.5% [12]. Transbronchial biopsy, in contrast, has a much more favorable risk profile in most cases. Pneumothorax, hemorrhage and infection all occur in less than 5% of patients [13,18,19–25], and death occurs in less than 0.12% – 0.24% of patients [20,21]. Although transbronchial lung biopsy in experienced hands is considered a safe and well-tolerated procedure, caution is advised in patients with bleeding diatheses, respiratory failure, need for positive pressure ventilation and pulmonary hypertension. One must also consider the projected diagnostic yield before exposing patients to transbronchial biopsy, since unsuccessful procedures invariably lead to subsequent procedures with the associated cumulative risk. Little is known about the risk of complications from transbronchial biopsy in patients with LAM.

The yield of transbronchial biopsy in diagnosing LAM is generally considered to be low [26]. We report here that LAM can be diagnosed in up to 60% of patients using tissue specimens obtained transbronchially, and thus transbronchial biology is a plausible diagnostic approach in selected patients being evaluated for LAM.

Materials and methods

All patients 18 years of age or older who were registered with the LAM Foundation, a patient advocacy organization in the United States, were invited to perform two online surveys (Fig. 1). The first survey was sent to all patients with email access and was followed by phone interviews. A second online survey, refined based on the responses to the first questionnaire, was conducted using an online survey instrument (SurveyMonkey. Com, LLC, Palo Alto, CA, USA) to identify more patients who had undergone transbronchial biopsy and for the purpose of obtaining additional slides from the identified procedures for our review. The LAM patients who reported they had undergone transbronchial biopsy in the first survey were excluded from the second survey.

Institutional review board (IRB) approval was obtained from University of Cincinnati (IRB #:10-10-26-01). Written consents were obtained and a copy of the consent was mailed to the patients for their records. Attempts were made to collect both stained and unstained slides of the lung tissue obtained transbronchially for blinded histological review by the study pathologist.

Results

The schema that describes the study is depicted in Fig. 1. The first survey was electronically delivered to 847 LAM Foundation registered patients. Of the 217 patients who responded to the survey, 52 reported a history of transbronchial biopsy and 14% reported complications, including pneumothorax (6%), bleeding (4%), chest pain (2%), and pneumonia (2%). Phone interviews were then conducted for the 52 positive respondents. After excluding 8 patients who could not be contacted, 3 patients who withdrew consent and 15 patients who through phone discourse were found not to have had transbronchial biopsy for the express purpose of making a diagnosis of LAM, it was determined that only 26 of the initial 52 affirmative responders had undergone transbronchial biopsy for bona fide diagnostic purposes. Of those 26 patients, 15 reported that the procedure was diagnostic for LAM, indicating a yield of 58%.

Through time, additional patients registered with the LAM Foundation. A second online survey with questions modified to remove identified ambiguities was sent to 1 082 LAM Foundation registered patients, excluding the 52 patients who reported having had transbronchial biopsies in the first survey, but otherwise overlapping extensively with the original cohort. Of the 380 patients who responded, 37 patients reported they had undergone transbronchial biopsy for diagnostic purposes and 20 (54%) were self-reported to be positive for LAM. Because the primary purpose of the second survey was to obtain additional biopsy specimens for blinded pathological review, and because the questions had been refined to reduce ambiguity, phone interviews were not conducted.

Collectively, 35 of 63 patients identified through these two surveys had self-reported, diagnostic transbronchial biopsies indicating a diagnostic yield of 56%.

A vigorous attempt was made to collect transbronchial biopsies from both of these survey participant groups. Thirty two hospital pathology departments were contacted to inquire about the availability of transbronchial biopsy specimens, and tissue release forms were faxed to 29 hospitals in the United