SUCCESSFUL DIAGNOSIS OF LYMPHANGIOLEIOMYOMATOSIS WITH TRANSBRONCHIAL LUNG CRYOBIOPSY

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ABSTRACT

A 47-year old female was evaluated in our clinic for an incidental discovery of diffuse cystic lung disease on high-resolution computed tomography (CT) scan of the chest. There was no personal or family history of tuberous sclerosis complex (TSC), sicca symptoms, pneumothorax, or skin or renal tumors. Review of her chest CT scan showed bilateral, round, uniform, thin-walled cysts present in a diffuse distribution characteristic of lymphangioleiomyomatosis (LAM). CT scan of the abdomen and pelvis did not reveal angiomyolipomas, lymphangioleiomyomas, abnormal lymphadenopathy, or chylous fluid collections. Serum vascular endothelial growth factor-D was non-diagnostic. In order to achieve diagnostic confirmation, the patient underwent transbronchial cryobiopsy of the lung, revealing changes consistent with LAM. Our case highlights the utility of transbronchial lung cryobiopsy in the evaluation of patients with suspected LAM and suggests that further investigation of this diagnostic technique is warranted in patients presenting with diffuse cystic lung disease.

Keywords: Lymphangioleiomyomatosis, LAM, bronchoscopy, biopsy, cryobiopsy

CASE REPORT

A 47-year-old non-smoking, Caucasian female presented to the University of Cincinnati lymphangioleiomyomatosis (LAM) clinic for further evaluation of cystic lung disease discovered incidentally on CT scan of her chest. There was no personal or family history of tuberous sclerosis complex (TSC), sicca symptoms, pneumothorax, or skin or renal tumors. The patient had undergone a complete hysterectomy 10 years prior for dysmenorrhea related to fibroids, and was not using any hormonal agents.

Physical examination was unremarkable with no signs of TSC. Pulmonary function tests (PFTs) showed a mild obstructive defect with her forced expiratory volume in 1-second (FEV_1) being 2.09 liters (81%). There was evidence of air trapping as evidenced by a residual volume of 178% of predicted. The diffusion capacity for carbon monoxide was normal. Review of her chest CT scan showed bilateral, round, uniform, thin-walled cysts present in a diffuse distribution characteristic of LAM (*Fig. 1*). CT scan of the abdomen and pelvis did not reveal angiomyolipomas or lymphangioleiomyomas. There was no evidence of chylous fluid collection in the thorax or abdomen, and
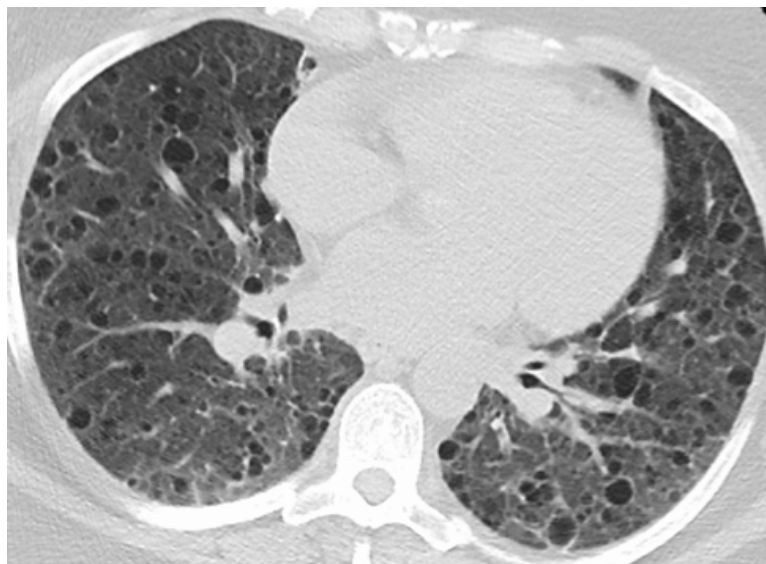
Fig. 1: Radiologic axial CT scan of the chest displays bilateral uniform, round, thin-walled cysts characteristic of LAM.

there was no lymphadenopathy in the mediastinal or abdomino-pelvic areas.

Serum vascular endothelial growth factor-D (VEGF-D) was obtained for non-invasive confirmation of LAM, and was non-diagnostic at a value of 419pg/ml. The histologic slides from her hysterectomy specimen were reviewed for the presence of characteristic LAM lesions. The grossly identified uterine lesions were histologically confirmed as leiomyomas, and there was no evidence of LAM in the uterus and cervix by routine histologic examination as well as immunohistochemical evaluation. Immuno-histochemistry was negative for HMB-45-positive LAM cells and lacked the slit-like spaces lined by D2-40-positive lymphatic endothelial cells characteristic of uterine involvement by LAM. Upon further discussion, the patient elected to undergo transbronchial lung cryobiopsy to obtain diagnostic tissue confirmation.

Transbronchial lung cryobiopsy was performed under general anesthesia using a 2.4 mm cryoprobe. Five specimens were obtained from the right lung, including two from the upper lobe, one from the middle lobe, and two from the lower lobe. The specimens ranged from 2 mm to 4 mm in maximum diameter. There were no procedure-related complications; specifically, there was no bleeding or pneumothorax. The biopsy slides were independently reviewed by two expert thoracic pathologists (KAWB and DSZ) with consensus diagnosis of LAM. Enlarged distal airspaces were seen in all five biopsies with distinct cystic changes present in two biopsies (*Fig. 2 A-D*). In one of the biopsies, characteristic LAM cells were identified around the periphery of the cyst by routine histologic stains (*Fig. 2 C-D*). The LAM cells formed small clusters and nests of oval and spindled cells, some with clear cytoplasm, arranged in haphazard bundles rather than the orderly arrangement of normal smooth muscle cells present in airways and blood vessels (*Fig. 2 D-E*). A subpopulation of LAM cells was positive for estrogen and progesterone receptor by immunohistochemical stains and scattered rare cells were immunopositive for HMB-45 (*Fig. 2F*) consistent with a LAM cell pheno-type. Hemosiderin-laden macrophages were present within alveolar air spaces as is
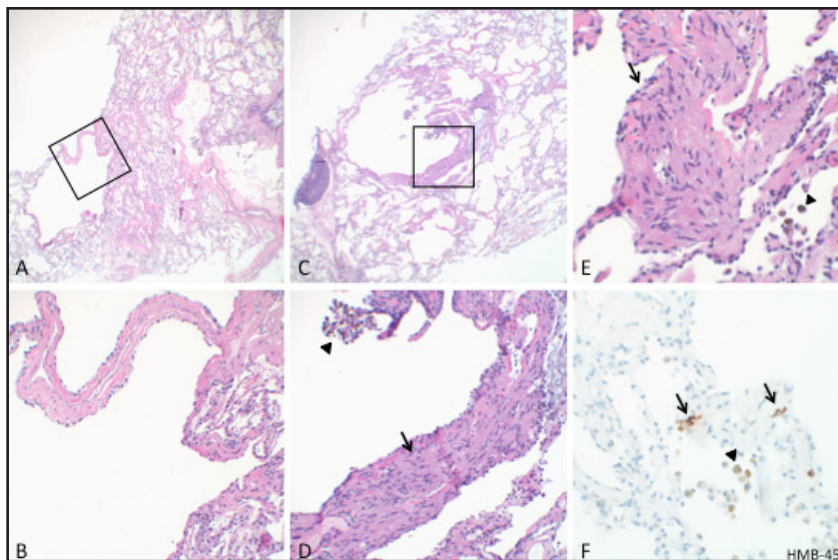
Fig. 2: Histopathology of the cryobiopsies depicting cystic spaces in two biopsies representing the right upper (A-B) and right middle lobes (C-D). Higher power images of the boxed areas show fibrovascular tissue (B) or nests of LAM cells (D, arrow) at the periphery of the cysts. The nests are comprised of round, oval and spindled LAM cells (E, arrow) with scattered LAM cells positive for HMB-45 by immunohistochemical stain (F, arrows) characteristic of LAM. Hemosiderin laden macrophages are present in airways adjacent to the LAM lesions (D-F, arrowheads). Original magnifications: 4x (A, C); 20x (B,D); 40X(E-F).

frequently seen in association with LAM lesions (*Fig. 2 D-F*). Taken together, the two key histologic features of LAM, cystic changes and LAM cell infiltrates, were present in the cryobiopsies, establishing the pathologic diagnosis of LAM.

DISCUSSION

In a substantial proportion of patients, the diagnosis of LAM can be established non-invasively if characteristic CT findings are accompanied by one of the following additional features: 1) Presence of TSC, 2) Angiomyolipomas, or lymphangioleio-myomas, 3) Chylous effusions, or 4) Elevated serum VEGF-D ≥ 800pg/ml (1-3). In the absence of one of these confirmatory features, tissue biopsy may be needed to establish the diagnosis of LAM with certainty. While video-assisted thoracoscopic surgery (VATS) guided surgical lung biopsy has been the gold standard for obtaining pathologic diagnosis

of LAM, small series have suggested that transbronchial lung biopsy can provide a diagnosis in 50-60% of cases with a reasonable safety profile (4,5).

Transbronchial lung cryobiopsy is a relatively new technique wherein tissue samples are obtained with a cryoprobe by freezing and subsequent retraction of the attached specimen using compressed gas. Multiple studies have assessed the diagnostic efficacy of transbronchial cryobiopsy in patients with diffuse parenchymal lung diseases and have reported a diagnostic yield of approximately 70-80% (6,7). However, there are concerns regarding the safety of this procedure, especially with regard to the higher risk of bleeding complications and pneumothorax (6,8). A recently conducted meta-analysis investigating the role of transbronchial cryobiopsies reported an overall diagnostic yield of 79% with a pneumothorax rate of 12% and moderate-severe bleeding in 39% of patients (9).

The safety and efficacy of transbronchial lung cryobiopsy in the evaluation of LAM is not known. To our knowledge, there have been two reported cases where the diagnosis of LAM was established based on transbronchial lung cryobiopsy (7,10). Our case highlights a few additional features. Only one out of the five biopsy specimens in our patient had definitive histologic LAM cells required for the diagnosis of LAM. The optimal number of biopsy specimens that provide a balance between optimizing diagnostic yield and minimizing complication risk is unknown and needs to be investigated. Our case also highlights the importance of critical review by expert pathologists who are familiar with the histopathological features of LAM.

In conclusion, we present a case of histopathologic diagnosis of LAM obtained by transbronchial lung cryobiopsy in a patient where CT and other non-invasive confirmatory features for LAM were non-diagnostic. The efficacy and safety of this technique with comparison to traditional transbronchial and surgical biopsy approaches to tissue diagnosis warrant further investigation in patients with suspected LAM.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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