



## Case report

# Difficult diagnosis and rare morphology of lymphangioleiomyomatosis with giant cysts

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## ABSTRACT

We report on a 32-year-old woman with a second manifestation of a tension pneumothorax two weeks after drainage therapy. The chest CT-scan revealed multiple large bilateral pulmonary cysts. She underwent minimally invasive wedge resection and pleurectomy for treatment. The extensive histologic evaluation revealed the diagnosis of a lymphangioleiomyomatosis (LAM) with an uncommon pattern of lung cysts. Initial staining for HMB-45 was negative. Repeated evaluation of other sections and reference pathology examination detected minimal expression of HMB-45.

This case illustrates that immunohistochemistry for HMB-45 may be negative, although LAM is present and repeated immunohistochemistry may be necessary to establish the correct diagnosis.

## 1. Introduction

Diffuse cystic lung disease has many differential diagnoses which can be challenging to establish in some cases. Especially non-characteristic clinical presentation, unusual computed scan morphology and rare histologic findings needs the collaboration of different specialists to identify the underlying disease. (see [Table 1](#))

## 2. Case report

We report on a 32-year-old woman without relevant pulmonary symptoms in the past. She was transferred into our hospital with a second manifestation of a tension pneumothorax two weeks after external drainage therapy ([Fig. 1](#)). After immediate chest tube insertion the computed tomogram (CT) of the chest revealed multiple bilateral pulmonary cysts with thin walls ([Fig. 2](#)). The CT examination showed large cystic lesions with small walls with a maximum diameter up to 10 cm distributed all over both lungs. No fluid collections or nodules were present. Between those lesions normal lung parenchyma was present. The patient is a never-smoker and Alpha-1- antitrypsin was within normal ranges. A minimally invasive wedge resection from the right upper lobe followed by a spared talcum poudrage was performed. The postoperative course was prolonged by air leak but finally resolved

after one week. Elaborate histologic evaluation showed lung tissue with large cystic spaces partially with smooth muscle structures in the walls including interlobular septa ([Figs. 3 and 4](#)). Furthermore some walls were covered by a CD31 and sporadic D2-40 positive layer of endothelial cells. CD34 was negative, but rare HMB-45 positive perivascular epitheloid cells (PEC) were found by a reference pathologist. Parts of the cystic walls were fibrosed, and some cysts seem to have lymphatic origin. The final pathologic consensus diagnosis was a lymphangioleiomyomatosis. Differential diagnoses like langerhans cell histiocytosis, and Birt Hogg Dube syndrome were excluded by histology and radiomorphology. Congenital pulmonary adenomatoid malformation did not match with the case concerning distribution of the cysts. The patient was informed about the diagnosis and moved back into her home country.

## 3. Discussion

The differential diagnoses of diffuse cystic lung diseases include congenital malformations, neoplastic, inflammatory, infectious diseases and emphysema changes from smoking [1]. Large cysts in non-smoking adults are suspicious for congenital pulmonary adenomatoid malformations (CPAM). The latter ones are usually thin walled multiple cystic masses unilateral in one lobe and the cysts are lined by epithelial

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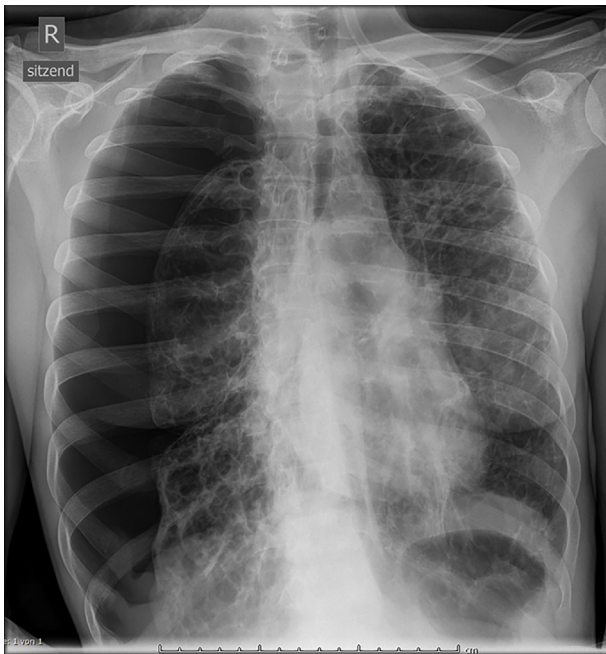
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**Table 1**  
Characteristics of cystic lung disease.

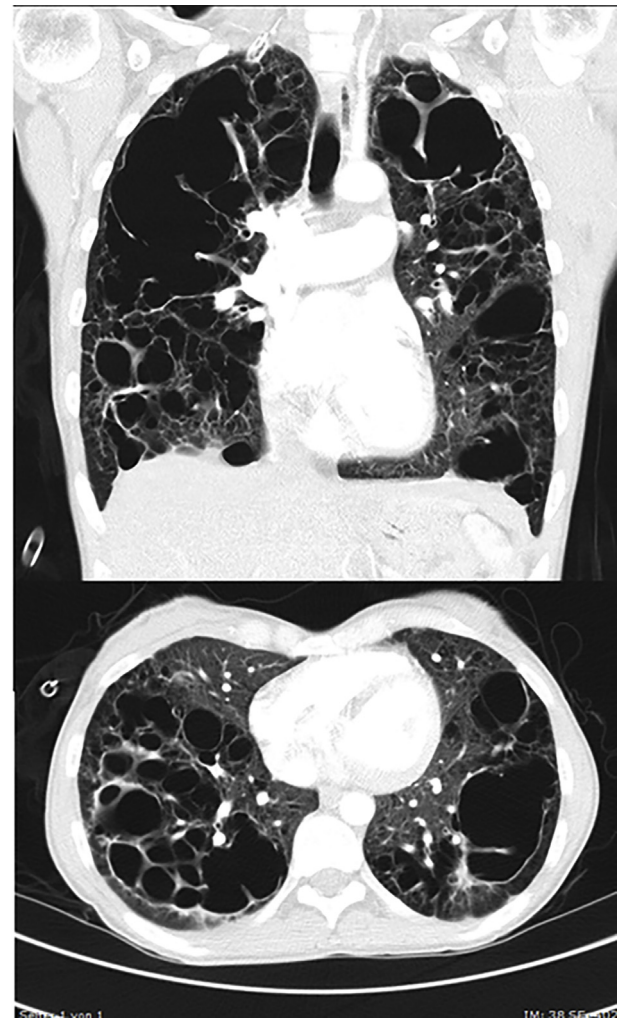
Diagnosis	Pathology
congenital pulmonary adenomatoid malformations (CPAM)	thin walled multiple cystic masses unilateral in one lobe and the cysts are lined by epithelial cells often able to produce mucus obstruction
Lymphangiomatosis	Congenital disease with cystic collections of chylus, chylothorax or dilated fluid filled lymph vessels
Diffuse pulmonary lymphangiomatosis	Abnormally dilated lymphatic spaces in the lung and other organs or diffuse infiltration of lymphangiomas
Lymphangioliomyomatosis	Congenital progressive disease caused by proliferating smooth muscle-like cells with multiple bilateral thin walled pulmonary cysts
Pulmonary Langerhans cell histiocytosis	Langerhans cell infiltrations causing centrilobular or peribronchiolar nodules of 1–10 mm combined with cystic lesions



**Fig. 1.** Chest X-ray at the day of admission with a tension pneumothorax on the right side. Emphysematous changes, cysts and fibrous strands are homogeneously distributed over both lungs.

cells often able to produce mucus [2,3]. This definition of CPAM does not fit with our case. Because in this case the morphology was unusual for any type of congenital cystic pulmonary malformation (CCPAM) and immunohistochemistry demonstrated a lymphatic origin of the cysts stained by CD31 and D2-40, the preliminary pathologic diagnosis was lymphangiomatosis. Lymphangiomatosis usually comes along with collections of chylus, chylothorax or dilated fluid filled lymph vessels [4]. Diffuse pulmonary lymphangiomatosis is characterized by abnormally dilated or reduplicated lymphatic spaces in the lung and extra thoracic organs [4]. Other authors described lymphangiomatosis is a rare disease characterized by diffuse infiltration of lymphangiomas in the lung, bone, kidney and other organs [5]. Again, none of these conditions were found in this patient.

Lymphangioliomyomatosis is characterized as a low-grade, destructive, metastasizing neoplasm, and manifests as the proliferation of abnormal smooth muscle-like cells in the lung stroma, which can often be identified with routine H&E staining. The gold-standard immunohistochemical diagnostic for LAM is immunopositive reaction with HMB-45 antibody, but the specificity and sensitivity of these markers has not been defined. LAM cells are positive for HMB45 in only 17%–67% and represent the more epitheloid fraction of the immature smooth muscle cells. They may be found at unusual structural positions within the lung but not all over [6]. Besides HMB-45, the most commonly used markers in the immunohistochemical diagnosis of LAM are  $\alpha$ -smooth muscle actin ( $\alpha$ SMA), estrogen receptor (ER), and



**Fig. 2.** Chest CT-scan after insertion of a chest tube demonstrating large bilateral central cysts with thin walls surrounded by unchanged and slightly emphysematous lung tissue.

progesterone receptor (PR) [6–8]. It was demonstrated that LAM tissue with a high mitotic index has no or only few HMB45 positive cells but higher levels of proliferating-cell nuclear antigen (PCNA) [9]. PCNA was not examined in our patient but could explain the large cysts being a consequence of lung destruction from proliferating, HMB45 negative LAM-cells.

#### 4. Conclusion

This case illustrates that immunohistochemistry for HMB-45 may be negative, although LAM is present. If clinical suspicion for LAM is high, repeated HMB-45-immunohistochemistry of additional histological

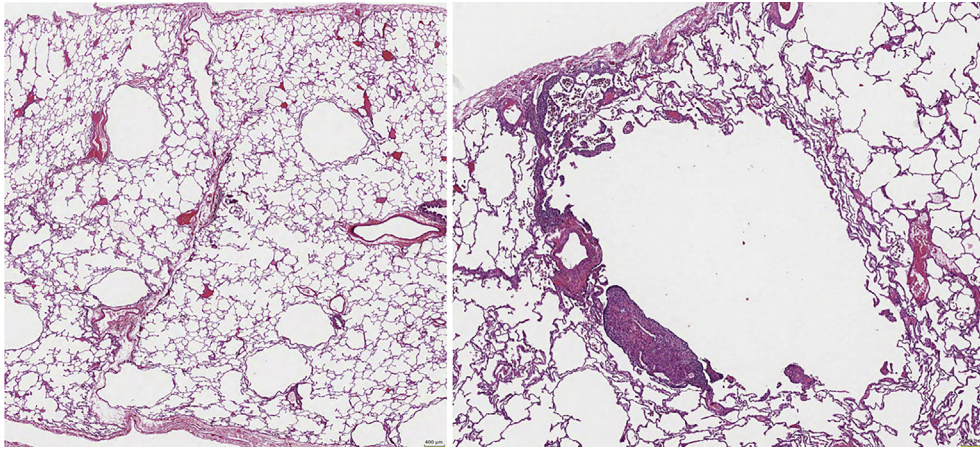


Fig. 3. H&E stained section. Left, overview of cystic lesions. Bar 400μm. Right, cystic lesion with pronounced muscular proliferation. Bar 200μm.

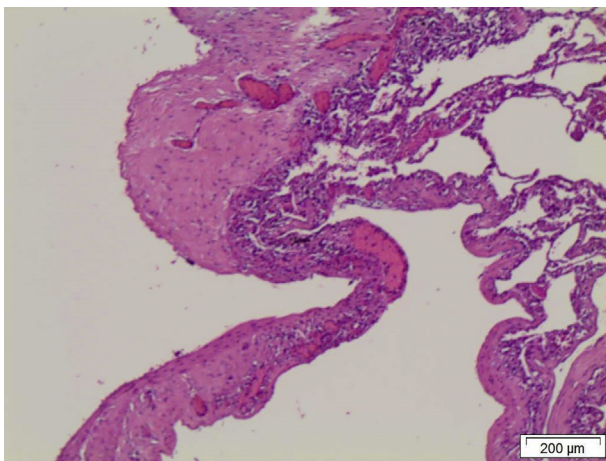


Fig. 4. H&E stained section demonstrating large cysts and interstitial fibrosis.

sections should be forwarded, because sometimes there may be only scarce HMB-45 positivity. The establishment of a definite LAM-diagnosis has relevant therapeutic implications, especially regarding mTOR-inhibitor-therapy.

#### Conflicts of interest

There are no conflicts of interest to state.

- This case report is not funded.
- This report was approved by our institutional review board.
- Consent: Orally consent was given by the patient. Written consent was not available as the patient is an analphabet. She moved to her

home country and was lost to follow-up.

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