Bilateral spontaneous persistent open pneumothorax with chylothorax

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Multiple pulmonary cystic lesions might occur owing to many causes, such as pulmonary Langerhans histiocytosis (*eosinophilic granuloma*), bullous emphysema, cystic fibrosis, idiopathic pulmonary fibrosis, and lymphangioleiomyomatosis (LAM).

Lymphangioleiomyomatosis is predominantly a disease that affects women of childbearing age. Rarely, however, sporadic LAM (S-LAM) has been reported in men, leading clinicians to now believe that the possibility of LAM should be seriously considered in men with diffuse cystic lung disease. We have reported one such case of possible S-LAM in an otherwise phenotypically normal 19-year-old man who initially presented to his family physician with bilateral, spontaneous, open pneumothoraces accompanied by a chylous effusion (*chylothorax*) on the left side.

Case

A 19-year-old Asian man presented to his family physician with complaints of acute breathlessness and generalized chest pain for the previous 3 hours. He was apparently all right before that, but following a bout of coughing, he became increasingly breathless and experienced generalized chest pain. He also complained of streaks of blood in his sputum, which he had never noticed before this episode. He had no history of trauma. There was no history of tuberculosis, nor was there any other relevant history. On examination, the patient was tachypneic. There were diminished chest wall movements bilaterally. There was a hyperresonant note on percussion in both the right and left upper and mid zones anteriorly. Air entry was absent bilaterally in the upper and mid zones and substantially reduced in both the lower zones anteriorly and posteriorly.

Tubular bronchial breath sounds were heard in the right mid zone in the interscapular region and in the left mid axillary line, suggestive of the possibility of multiple bronchopleural fistulas. The rest of the findings of the physical examination were unremarkable. The patient was advised by his family physician to undergo an urgent chest radiograph. The chest radiograph showed bilateral pneumothoraces (**Figure 1**). The patient was immediately hospitalized and intercostal drainage tubes were inserted on both sides. However, 2 weeks later it was found that there was only slight lung expansion on either side (**Figure 2**), indicative of the possibility of bilateral persistent air leaks (open pneumothoraces).

A high-resolution computed tomography (HRCT) scan of the chest (**Figures 3A** and **3B**) showed multiple, small, thin-walled, well-defined, rounded cysts that were evenly distributed throughout both lung fields. The intervening lung parenchyma appeared to be normal.

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EDITOR'S KEY POINTS

- Lymphangioleiomyomatosis (LAM) is predominantly a disease that occurs in women of childbearing age. Rare case reports of LAM in men exist, usually in combination with tuberous sclerosis complex (TSC). However, sporadic LAM has been reported in men, leading clinicians to believe this diagnosis should be seriously considered in men with diffuse cystic lung disease, even in the absence of clinical features of TSC.
- The presence on high-resolution computed tomography of the chest of multiple, small, well-defined, thin-walled cysts evenly distributed throughout both lungs with normal intervening lung parenchyma is characteristic of LAM when accompanied by other corroborative features such as pneumothorax, chylous effusion (*chylothorax*), and obstructive impairment on pulmonary function testing.
- Owing to the rarity of this condition in men, histologic and immunohistochemical confirmation from biopsy material along with karyotyping and confirmation of absence of genotypic evidence of TSC are needed for final confirmation of the diagnosis.

POINTS DE REPÈRE DU RÉDACTEUR

- La lymphangioléiomyomatose (LAM) est une maladie dont souffrent surtout les femmes en âge de procréer. De rares rapports de cas de LAM existent chez des hommes, habituellement en combinaison avec le complexe tubéro-sclérotique (TSC). Par ailleurs, des cas sporadiques de LAM ont été signalés chez des hommes, ce qui incite des cliniciens à croire que ce diagnostic devrait être sérieusement envisagé chez des hommes atteints de pneumopathie cystique diffuse, même en l'absence des caractéristiques cliniques de la LAM.
- La présence de multiples petits kystes bien définis à paroi mince, répartis également dans les 2 poumons, avec un parenchyme de poumon intervenant normal, sur une tomographie par ordinateur à haute résolution du thorax, est caractéristique de la LAM lorsqu'elle s'accompagne d'autres particularités corroborantes comme un pneumothorax, une effusion chyleuse (chylothorax) et une déficience obstructive observée dans un test de la fonction pulmonaire.
- Étant donné la rareté de ce problème chez l'homme, la confirmation histologique et immunohistochimique par analyse de spécimens de biopsie, ainsi qu'un caryotypage et l'absence confirmée d'un TSC génotypique sont nécessaires pour une confirmation définitive du diagnostic.

Some cysts were located in the subpleural region. A moderate-sized pleural effusion was also noted on the left side that, on aspiration, proved to be chylous (**Figure 4**). Clinically, the patient was re-examined for any signs of hypopigmented maculae, angiofibromas, subungual fibromas, and "confetti" lesions suggestive of tuberous sclerosis complex (TSC). However, none of these were present. In view of the various differential diagnoses being considered, it was also believed to be necessary to confirm the sex of this patient by

Figure 1. Chest radiograph showing bilateral pneumothoraces

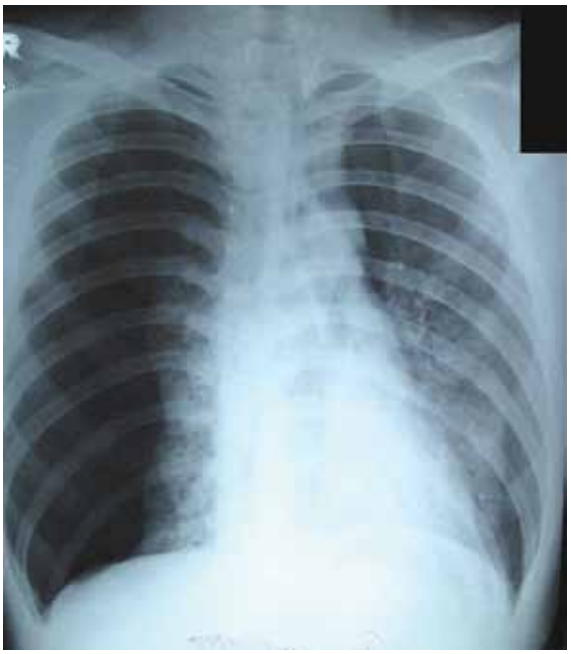


Figure 2. Chest radiograph taken 2 weeks after the first radiograph showing persistent bilateral pneumothoraces

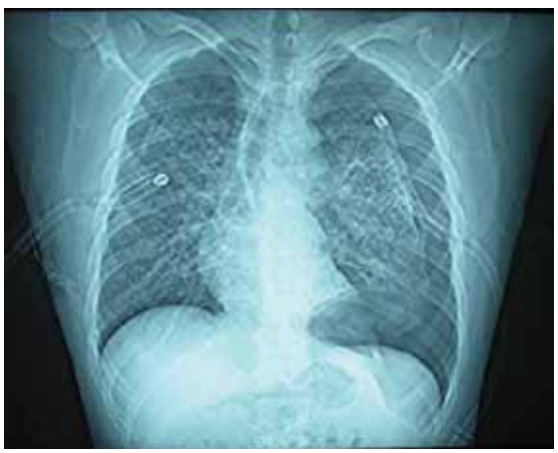
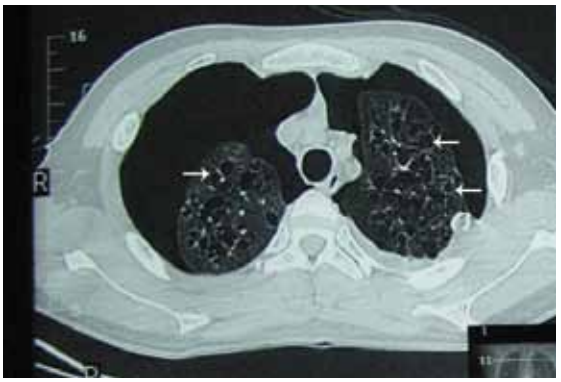


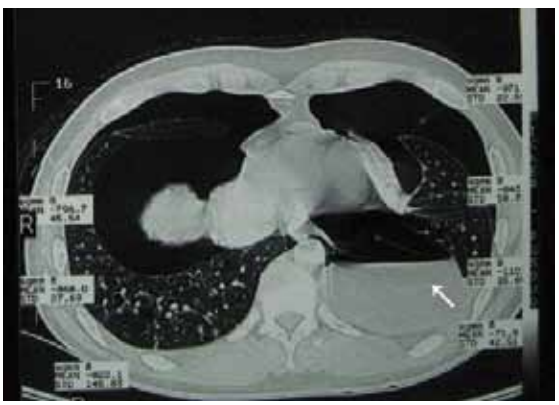
Figure 3. High-resolution computed tomography chest scans showing bilateral pneumothoraces with numerous, well-defined, thin-walled cysts evenly distributed throughout both lung fields (white arrows); no nodular infiltrates can be seen

A



B

Figure 4. High-resolution computed tomography chest scan showing bilateral pneumothoraces with numerous, well-defined, thin-walled cysts evenly distributed throughout both lung fields; a moderate-sized pleural effusion is also seen on the left side (white arrow)



closely examining the external sexual characteristics. On examination, the patient was confirmed to be phenotypically male with normal male external genitalia, 2 normally descended testes, normal hair distribution over the face, chest, and pubic area, no breast development, and a normal male voice. Bronchoscopic biopsy of lung tissue was advised but could not be undertaken, as the patient refused the procedure.

Discussion

Our patient presented with symptoms of acute breathlessness, cough, generalized chest pain, and streaking hemoptysis, and was found to have bilateral, spontaneous, persistent open pneumothoraces. The HRCT chest scan showed numerous, small, well-defined, thin-walled, rounded cysts (some subpleural) evenly distributed throughout both lungs with normal intervening lung parenchyma. There were no nodular opacities seen. A left-sided pleural effusion was also noted. The aspirated pleural fluid had a creamy appearance, with grossly elevated triglyceride levels (4.633 mmol/L) and presence of chylomicrons, indicative of chylothorax. Pulmonary function testing revealed moderate obstructive impairment, with forced expiratory volume in the first second of expiration (FEV_1) and FEV_1–forced vital capacity levels at 53% and 55% of their predicted values, respectively. Findings of abdominal ultrasonography were normal. There was no evidence of kidney cysts or angiomyolipomas.

Differential diagnosis. Initially, the possibility of pulmonary Langerhans histiocytosis was strongly considered. However, the chest radiographs and HRCT scans in such patients classically demonstrate bilateral, ill-defined nodular opacities, thick-walled cysts, and interstitial infiltrates in the middle and upper lung fields with relative sparing of the lung bases. Moreover, pleural effusion is very uncommon in these patients. Hence, the possibility of pulmonary Langerhans histiocytosis appeared unlikely.

Other potential causes were also considered, namely bullous emphysema, idiopathic pulmonary fibrosis, metastatic leiomyosarcoma, metastatic melanoma, cystic fibrosis, and LAM. Bullous emphysema presents as emphysematous areas with complete destruction of the intervening lung parenchyma, producing air spaces of more than 1 cm in diameter. A bulla can be clearly distinguished from a lung cyst, as most of its outer surface is made of visceral pleura while the inner layer consists of fibrous tissue formed by the destroyed adjacent lung. Moreover, α_1-antitrypsin levels in our patient were normal (55.2 µmol/L). Hence, bullous emphysema was a highly unlikely possibility in this case.

Idiopathic pulmonary fibrosis was also ruled out because of the age of the patient, his clinical history (no gradually increasing symptoms of dry cough, breathlessness, and chest pain), lung function findings (which showed no restrictive impairment), and HRCT chest scan findings (which showed no interstitial infiltrates, reticulonodular shadowing, or honeycombing).

Metastatic leiomyosarcoma was ruled out as a possibility as it does not form lung cysts but rather large nodular lesions. Moreover, there was no evidence of any primary soft-tissue lesion in the patient. Metastatic melanoma was also excluded as a possibility, as it does not form lung cysts, and there was no evidence of primary skin lesions.

Cystic fibrosis was ruled out, as the patient was not white and did not have the multisystem involvement characteristic of this condition. There was no history of failure to thrive, increased frequency of stools, pancreatic insufficiency, cholecystitis, or gallstones. Sweat chloride levels measured using the quantitative pilocarpine iontophoresis test were 32 mmol/L (normal <40 mmol/L). In patients with cystic fibrosis, sweat chloride levels are greater than 60 mmol/L.

Clinical course and types of LAM. Lymphangioleiomyomatosis is a rare disease that was first described by von Stossel in 1937.[1] The disease is characterized by an increased proliferation of smooth muscle cells in a disorderly manner throughout the bronchioles, interalveolar septa, perivascular spaces, and the surrounding lymph vessels. This results in a blockage of the small airways and surrounding lymph vessels, leading to cystic changes in the lung and chylothorax. Obstruction of venules results in hemosiderosis and hemoptysis. Excessive proteolytic activity due to an imbalance in the elastase–α_1-antitrypsin system and metalloproteinases and their inhibitors is also believed to lead to lung destruction and formation of cystlike lesions. Clinically, these patients usually present with cough, breathlessness, and chest pain. On examination, there are signs suggestive of pneumothorax, chylothorax, or pericardial effusion. The clinical course of patients with LAM varies considerably. It is usually slowly progressive, eventually leading to respiratory failure and death. The 10-year survival rate from the start of symptoms ranges from 49% to 79%. Differences in survival rates might be owing to improvement in the diagnostic process, particularly the contribution of the HRCT scan, and do not imply that the progression of the disease has changed substantially. It is believed that the diagnosis of mild asymptomatic forms might also contribute to longer survival rates.[2]

There are 2 types of LAM: S-LAM and LAM associated with TSC (TSC-LAM). There is as yet no known cause for S-LAM. However, TSC-LAM is known to be genetically inherited and is associated with mutations in the TSC genes, *TSC1* and *TSC2*. Patients who have TSC-LAM usually have other clinical signs such as kidney cysts or

angiomyolipomas, or brain tumours such as astrocytomas. Clinically, patients with TSC-LAM often present with insidious onset of dyspnea and are less likely to experience chylothorax.[3]

In comparison, patients with S-LAM present with acute breathlessness (usually secondary to pneumothorax),[4] cough, and hemoptysis. An HRCT chest scan in these patients shows thin-walled, small, well-defined, cystic lesions spread diffusely throughout both lung fields.[5] The cysts near or on the surface of the lung usually rupture, causing air to escape into the pleural cavity and the underlying lung to collapse, leading to the formation of pneumothorax. The excessive smooth muscle proliferation also causes a blockage of blood vessels in the lungs leading to their distention and eventual rupture, causing the patient to cough up blood in the sputum (hemoptysis). Similarly, blockage of lymph vessels by the proliferating smooth muscles also leads to formation of fluid in the pleural cavity, usually chyle.[6]

It is now an accepted fact that the presence on HRCT chest scan of multiple, small, well-defined, thin-walled cysts evenly distributed throughout both lungs with normal intervening lung parenchyma is characteristic of LAM[5] when accompanied by other corroborative features such as pneumothorax,[4] chylothorax,[6] and obstructive impairment on pulmonary function testing.[7] In such cases, a tissue biopsy is no longer considered essential to arriving at a diagnosis.[8-10] Thus, because our patient had typical HRCT chest scan findings of multiple, small, well-defined, thin-walled cysts evenly distributed throughout both lungs with normal intervening lung parenchyma, presence of chylothorax, bilateral spontaneous persistent open pneumothoraces, obstructive impairment on pulmonary function testing, and normal abdominal ultrasonography with no evidence of kidney cysts or angiomyolipomas, a highly probable diagnosis of S-LAM was made, with a tentative differential diagnosis of pulmonary Langerhans histiocytosis. The patient is now awaiting bilateral lung transplantation. During surgery, tissue biopsy will be undertaken for histologic and immunohistochemical confirmation of the diagnosis. Meanwhile, he has been fitted with a chest drain valve on the right side owing to the presence of persistent open pneumothorax.

Conclusion

Cystic lung disease is commonly encountered by family physicians during the course of their busy medical practices. This makes it necessary for them to remember that multiple pulmonary cystic lesions can occur owing to a variety of conditions. These include pulmonary Langerhans histiocytosis, bullous emphysema, cystic fibrosis, idiopathic pulmonary fibrosis, and LAM.

Although LAM is predominantly a disease that occurs in women of childbearing age, rare case reports of LAM in men exist, usually in the context of TSC.[11] Rarely, S-LAM has been reported in men, leading clinicians to now believe that the possibility of LAM should be seriously considered in men with diffuse cystic lung disease, even in the absence of clinical features of TSC. Schiavina and colleagues[12] described a case of pulmonary LAM in a 37-year-old karyotypically and phenotypically normal man without TSC. The patient in this case presented with left-sided pneumothorax and massive pulmonary collapse. On an HRCT scan, widespread thin-walled cysts were seen throughout both lungs. A histologic diagnosis of LAM was made after biopsy and was immunohistochemically confirmed with the HMB-45 monoclonal antibody test.

Sporadic LAM should be seriously considered in men with diffuse cystic lung disease who present with pneumothorax and chylothorax accompanied by typical HRCT chest scan findings in the absence of clinical signs of TSC. However, owing to the rarity of this condition in men, histologic and immunohistochemical confirmation of the diagnosis from biopsy material along with karyotyping and confirmation of the absence of genotypic evidence of TSC are needed for final confirmation of the diagnosis.

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Competing interests
None declared

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