An unexpected finding on CT Pulmonary Angiogram

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CASE PRESENTATION

A 38-year old lady came to hospital after a fall while ice-skating with her two children. Initial X-ray in the emergency department showed communited tibial shaft and distal fibular fracture in the left lower limb. Although the alignment of fragmented fractures was deemed satisfactory, she was admitted under the orthopaedic team for conservative observation and casting due to risk of compartment syndrome.

This lady had a past medical history of Type 1 diabetes, hypercholesterolemia, fibromyalgia, Henoch-Schonlein purpura and what was known in 2014 to be bronchiectasis. Referred from primary care due to persistent chronic cough with minimal sputum, a high-resolution CT scan was reported to show upper zone bronchiectasis. There has been no known inherited respiratory disease within the family. She was investigated for cystic fibrosis (CF) and primary ciliary dyskinesia which returned negative.

During her first overnight stay in the orthopaedic ward, the patient developed continuous vomiting and epigastric pain. She became tachycardic and appeared unwell. Blood test results revealed CRP 369.4, WBC 19.4 and raised neutrophil count of 17.4. Ketones and amylase were normal as was CXR. Blood glucose was adequate at 9.8. The patient was kept nil by mouth and prescribed variable rate insulin (VRII). Poor urine output alongside distended bladder on CT scan confirmed the decision to insert a urinary catheter for suspected urosepsis. Mid-stream urine culture grew E.coli and the patient was started on IV amoxicillin + gentamicin after microbiology advice.

The patient deteriorated clinically the following afternoon complaining of breathlessness. She also mentioned new-onset central chest pain without radiation. Myocardial infarction was deemed unlikely with sinus tachycardia only observed on ECG. ABG (Table 1) indicated Type 1 respiratory failure (T1RF).

pH	7.40 (7.35-7.45)
PO_2	8.3 (10-13)
PCO_2	3.1 (4.7-6.0)
HCO_3^-	23.7 (22-26)
Lactate	0.8 (0.5-1.6)

Table 1

In light of her clinical progression and T1RF, there were some differential diagnoses (Table 2) to consider upon medical review. Because of urosepsis and recent fracture, the patient was in high risk of pulmonary embolism (PE). She was given therapeutic clexane 1.5mg/kg and a CT pulmonary angiogram (CTPA) was arranged in the same day.

Differential diagnosis for T1RF
Hospital-acquired pneumonia
Pulmonary oedema
Pulmonary embolism (PE)
Acute respiratory distress syndrome

Table 2

CTPA did not demonstrate any evidence of PE. However, it was reported to show multiple cystic areas within the lungs at the upper lobe segments, commented to be bronchiectasis few years ago (Figure 1). One of the right upper lobe cysts showed some small tissue density, possibly due to an inflammatory and infective cause (Figure 2). As per radiology advice, the patient was transferred to care under the respiratory team for further assessment and management of an infective exacerbation of cystic lung disease. Therapeutic clexane was stopped.

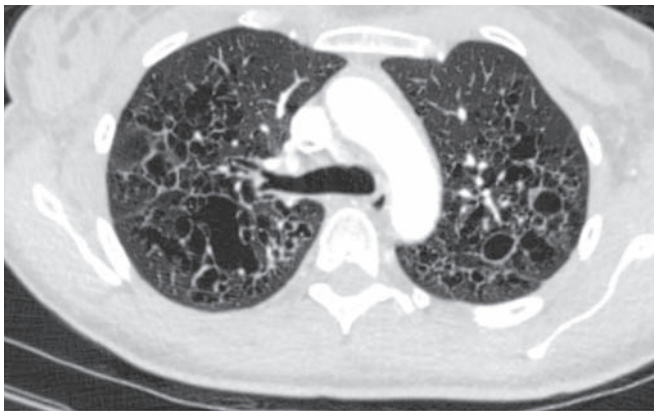

Figure 1: CTPA (lung view) showed multiple lung cysts bilaterally in the upper lung lobes

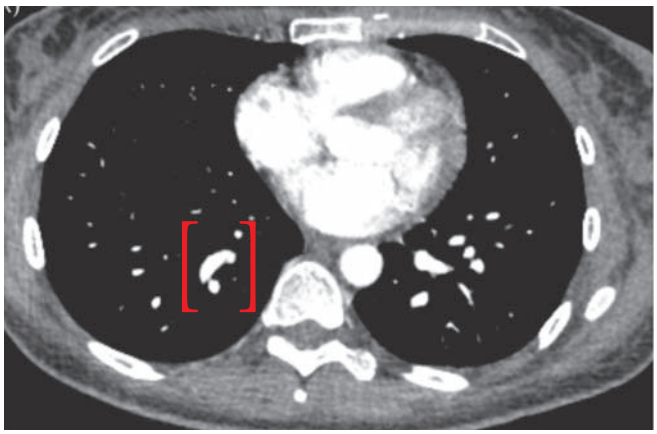

Figure 2: CTPA (soft tissue view) showing small tissue density in one of the right upper lobe cysts (bracketed red)

After admission into the respiratory ward, she was investigated for immunoglobulin deficiency, aspergillus

disease, HIV and alpha 1-antitrypsin deficiency in which all tests returned negative. A further cystic fibrosis genetic screen including atypical variants was negative. The patient improved with IV antibiotic treatment and serum inflammatory markers gradually returned to normal levels after 6 days. Her antibiotic regime was stepped down to oral ciprofloxacin for 7 days and she was discharged.

Prior to discharge, this case was discussed in the thoracic-radiology MDT meeting. Considering the patient's past medical history and demographic profile, there was general consensus that possibility of lymphangioleiomyomatosis (LAM) could not be excluded and tuberous sclerosis genetic test should be completed prior to her leaving the hospital. Advice on further management from the Manchester and Nottingham genetic respiratory disease units would be sought. The patient was arranged for an outpatient clinic review in 4-6 weeks' time. It was decided she may need lung biopsy if aetiology remained uncertain or if there was progression of disease.

CAUSES AND CHARACTERISATION OF DIFFUSE CYSTIC LUNG DISEASE (DCLD)

Diffuse cystic lung disease is typically characterised with cross sectional imaging, appearing as multiple parenchymal lucencies that have a well-defined interface with normal lung. These are defined by a thin wall (<4mm) and are usually filled with air, though they can contain solid or fluid material.[1] It is unusual to see lung cysts in healthy patients under the age of 50. Several conditions result in radiographic changes that may mimic cystic lung disease (Table 3). It is therefore important to review changes seen on cross sectional imaging as a MDT.

Determining the cause of true diffuse cystic lung disease (Figure 3) relies on considering a multitude of factors including patient demographics, smoking history, symptom course and existence of extra-pulmonary features. These combined with reviewing all of the HRCT (high resolution computed tomography) features can result in an accurate diagnosis. True lung cysts may develop acutely in the context of inflammation or infection. Patients with ***pneumocystis jiroveci pneumonia*** can develop cysts, typically in the apical regions. This should therefore be considered in immunosuppressed patients with new cystic lung disease; usually associated with ground-glass changes on HRCT. Likewise, connective tissue diseases can predispose to ***lymphocytic interstial pneumonia***, a benign lymphoproliferative disorder. This condition typically affects middle-age women and is particularly associated with Sjogrens Syndrome. The cysts tend to follow lymphatic channels, appearing in alveolar septa and peribronchovascular regions. In young smokers with cystic lung disease, ***pulmonary langerhans cell histiocytosis (PLCH)*** should be strongly considered. This would be further supported if the cysts were diffuse and irregularly shaped with sparing of the costophrenic angle. ***Lymphangioleiomyomatosis (LAM)*** typically affects females of child-bearing age. The cysts tend to be uniform in shape and spherical. This differs from ***Birt-Hogg-Dube Syndrome (BHD)*** in which the cysts may be more irregular and large bullae can be seen. A family history and thorough examination will also help establish this diagnosis, as the condition is autosomal dominant and associated with skin fibrofolliculomas. It is also important to note that not all cases of cystic lung disease can be characterised and the aetiology remains uncertain.

LYMPHANGIOLEIOMYOMATOSIS (LAM)

LAM is a rare disorder with an incidence of one in 1.1 million people characterised by abnormal proliferation of smooth muscle cells. The condition is hormone dependent so almost exclusively affects women of child bearing age. There is an association with the autosomal dominant condition, tuberous sclerosis (TSC-LAM); with 40% of women with this condition developing cysts identical to those seen in patients with LAM. TSC-LAM is thought to be 5-10 times more common than LAM.[2]

Cyst Mimic	Radiology Appearances	Associated Conditions
Cavity	Gas filled space within consolidation or mass. Characterised by thicker walls and irregular shape (>4mm)	Infections – Tuberculosis/ non-Tuberculosis mycobacteria Malignancy
Bullae	Sharply demarcated spherical areas of lung destruction that are >1cm. Thin walls (<1mm). Reduced vascularity	Chronic Obstructive Pulmonary Disease Alpha 1-antitrypsin deficiency
Centrilobular emphysema	Usually upper zones, up to 1cm, lack distinct walls	Chronic Obstructive Pulmonary Disease Alpha 1-antitrypsin deficiency
Honeycombing	Irregular thick-walled air-spaces, lower lobe predominance	Hallmark of Usual Interstitial Pneumonia (UIP) seen in Idiopathic Pulmonary Fibrosis, Sarcoidosis and Rheumatoid Arthritis

Table 3

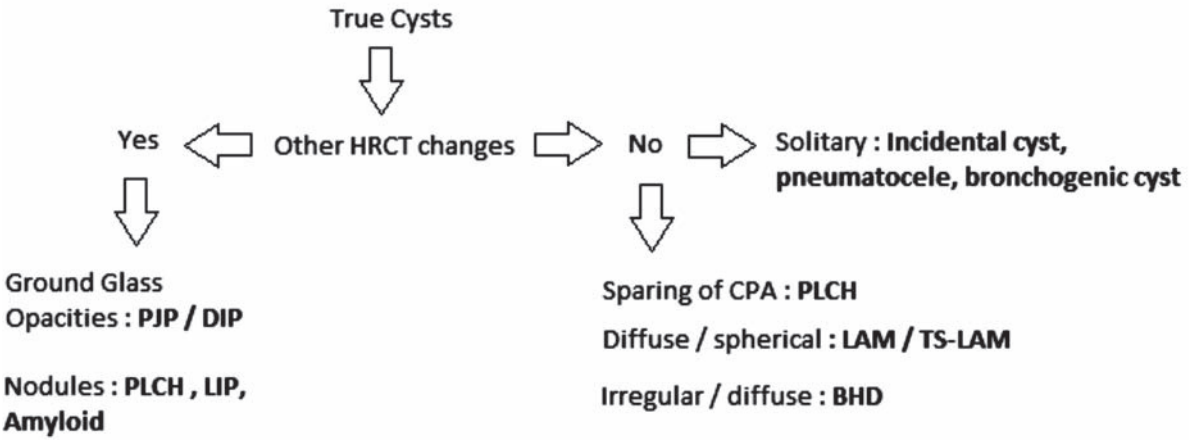

Figure 3: Flowchart of differentials for cystic lung disease

LAM is sometimes picked up incidentally in asymptomatic individuals but usually presents with slowly progressive respiratory symptoms. These symptoms include dyspnoea, cough, haemoptysis and chest pain.[3-4] There is also a considerable risk of secondary pneumothorax; 40-50% of initial presentation and a lifetime risk of up to 80%.[5]

Diagnosis is based on typical HRCT appearances of multiple diffusely distributed cysts with normal intervening lung. These are variable in size; from 2mm to 30mm without any lobar predominance.[6-7] In some cases, changes may be visible on chest x-ray, most commonly hyperinflation, reticular shadowing and septal lines. Pulmonary function tests may be normal or show an obstructive pattern. There is an association between LAM and renal angiomyolipoma (occurring in up to 50% of patients) and therefore screening for this as diagnosis with a CT abdomen is necessary. Lymphadenopathy due to lymphatic obstruction also occurs and can be seen on thoracic and abdominal CT imaging.

Management should occur in specialist centres (Queen's Hospital at Nottingham is the national LAM centre). Bronchodilators may help with airflow obstruction and smoking cessation should be strongly advised. Oestrogen therapy, either in the form of contraception or hormonal replacement therapy, should be avoided. TSC mutations lead to the activation of mammalian target of rapamycin kinase (mTOR) and inhibitors of this such as sirolimus can reduce the decline in lung function.[8] Patients with progressive disease should also be considered for lung transplantation.

CASE OUTCOME

Tuberous sclerosis genetic testing returned from the Department of Clinical Genetics, St. Mary's Hospital, Manchester showing normal findings. The patient has since been referred to Nottingham for further assessment to rule out possible non-TSC LAM disease. Considering normal lung function on spirometry (Table 4) 6 weeks post-discharge and the patient asymptomatic, it has been agreed by the teams involved to employ a wait-and-see approach over the next 12 months without active management before clinic review. Further treatment will be determined by her clinical course and results from surveillance pulmonary function tests and/or CT imaging.

FEV1	2.36 L (72%)
FVC	2.86 L (74%)
FEV1/FVC ratio	82%
TLCO	44%
KCO	71%
TLC	64%
RV/TLC ratio	93%

Table 4

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