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Dyspnea in a 43-Year-Old Woman With Polycystic Kidney Disease

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A 43-year-old Vietnamese-American woman was referred for evaluation of dyspnea. Six months prior to presentation, left-sided chest pain radiating to her shoulder had developed, and she also noted nonproductive cough and decreased exercise tolerance. These symptoms resolved spontaneously after 10 days, and she returned to her usual state of good health. Within a few weeks began the insidious onset of progressive exertion-related dyspnea. She denied fevers, night sweats, weight loss, cough, sputum production, hemoptysis, wheezing, or recurrent chest pain. She was seen by her primary care physician who started her on loratadine, 10 mg/d, and albuterol by metered-dose inhaler. When her symptoms failed to improve, she was referred to our institution.

Her medical history was significant for hypertension, hyperlipidemia, and polycystic kidney disease. Her medications at the time of presentation to our center included hydrochlorothiazide, simvastatin, lansoprazole, and loratadine. She was a lifetime nonsmoker, denied recent travel, and had no risk factors for tuberculosis. There was no known family history of polycystic kidney or parenchymal lung disease.

On physical examination, vital signs were normal and pulse-derived oxygen saturation was 98% on room air. Lung auscultation revealed diminished breath sounds bilaterally, but without crackles, wheeze, or rhonchi. She was not clubbed, nor did she have peripheral edema, rash, or skin lesions. Neurologic examination was unremarkable.

Results for CBC count, chemistry panel, liver tests, and coagulation studies were normal. Room air, resting blood gas showed pH 7.45, PaCO₂ of 33 mm Hg, and PaO₂ of 71 mm Hg. Urinalysis was normal. Spot urine protein/creatinine ratio was 0.1. Spirometry showed the following: FVC, 3.67 L (86% of predicted); FEV₁, 2.92 L (85% of predicted); and FEV₁/FVC, 0.80. Lung volumes measured by body plethysmograph revealed total gas volume of 4.01 L (123% of predicted), residual volume of 3.25 L (171% of predicted), and total lung capacity of 6.82 L (118% of predicted). Diffusion capacity of the lung for carbon monoxide unadjusted for hemoglobin was 90% of predicted. High-resolution CT of the chest and unenhanced CT scans of the abdomen and pelvis were performed (Fig 1, 2).

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What is the diagnosis?

Diagnosis: TSC2-PKD1 contiguous gene syndrome

The patient presented with a 6-month history of progressive dyspnea, a diffusely abnormal chest examination, and normal laboratory data. Pulmonary function tests showed evidence of hyperinflation without evidence of airflow limitation or diffusion defect. Radiographic imaging revealed multiple cysts in both the lungs and kidneys.

Cystic lung disease can be subclassified into two types: (1) discrete, focal, or multifocal cysts; and (2) diffuse cysts with a panlobular distribution. The differential diagnosis of focal or multifocal cystic lung disease includes several congenital and acquired diseases (Table 1). Bronchogenic cysts, pulmonary sequestration, and congenital cystic adenomatoid malformations (CCAM) are congenital disorders that present clinically in early childhood or young adulthood. Bronchogenic cysts typically appear as either mediastinal or intraparenchymal homogeneous masses but may also manifest as thin-walled cystic cavities, with or without air-fluid levels, pneumothoraces, or recurrent pneumonia. In bronchopulmonary sequestration, a portion of lung develops with its own systemic arterial blood supply isolated from the main body of the lung. Most sequestrations are diagnosed in childhood or in young adults presenting with a history of recurrent pneumonia. CCAM refer to a group of pulmonary anomalies believed to represent localized arrested development of the fetal bronchial tree. Disease will be usually diagnosed within 1 month of birth, and patients will present with neonatal respiratory distress. In those who present after birth, pneumothorax or recurrent pneumonia are the typical manifestation.

Several infections may present with pneumatoceles, which are cysts that present acutely or subacutely and usually resolve when the underlying infection is treated. True infectious cysts that persist despite resolution of the primary infection may occur with *Pneumocystis jiroveci* pneumonia or echinococcosis (hydatid disease), occurring most commonly in the upper lobes. Although isolated cysts may occur in coccidioidomycosis, cavitary disease from a necrotizing infection remains the more common manifestation.

Lymphoid interstitial pneumonia usually manifests radiologically as a combination of peribronchovascular cysts and a combination of ground-glass and reticular opacities with or without nodules. Lymphoid interstitial pneumonia is classified as an idiopathic interstitial pneumonia but is most often seen in association with an underlying condition, such as Sjögren syndrome or an immune deficiency. Desquamative interstitial pneumonia is another idiopathic interstitial pneumonia and, in most cases, is smoking related. Cysts occur in desquamative interstitial pneumonia, but they are typically small and clustered either peripherally in honeycombed areas or in a peribronchovascular distribution.

Other causes of cystic lungs include asbestosis, idiopathic pulmonary fibrosis, collagen vascular disease, hypersensitivity pneumonitis, and sarcoidosis. However, these diseases typically manifest radiographically with honeycombing and honeycomb cysts, which are often associated with traction bronchiectasis. Cystic lung disease has also been described in Down syndrome and Birt-Hogg-Dube syndrome. Finally, trauma, hydrocarbon ingestion and positive pressure ventilation can also lead to formation of pneumatoceles.

The diffuse nature of the cysts and lack of corroborating clinical features exclude all of the aforementioned possibilities. Diffuse cystic lung disease is most often caused by two uncommon disorders: pulmonary Langerhans-cell histiocytosis (PLCH) and lymphangioleiomyomatosis (LAM). PLCH is one of the Langerhans-cell histiocytoses characterized by uncontrolled proliferation and infiltration of various organs by Langerhans cells. Organ systems involved by Langerhans-cell histiocytoses may include skin, bone,

pituitary gland, lymph nodes, and lungs. PLCH afflicts predominantly white subjects and is uncommon in individuals of African or Asian descent.² The disease occurs primarily in young adults between the ages of 20 and 40 years, although sometimes other age groups are affected. The principal epidemiologic factor associated with isolated PLCH (rather than multisystemic Langerhans-cell histiocytoses) is cigarette smoking, and > 90% of patients with PLCH are active smokers.³

Patients with PLCH commonly present with non-specific respiratory symptoms such as cough and exertional dyspnea. Spontaneous pneumothorax is the presenting symptom in approximately 10 to 15% of patients.³ Constitutional symptoms of varying severity occur in up to one third of patients. The physical examination is often normal, and digital clubbing is unusual. Approximately 75% of patients have some pulmonary function abnormality at the time of diagnosis, including obstructive, restrictive, or mixed patterns of impairment.³ Overall, the most consistent physiologic abnormality is a reduced diffusing capacity of the lung for carbon monoxide, reported to occur in 60 to 85% of patients.³

The chest radiograph appearance in PLCH demonstrates micronodular or reticulonodular infiltrates in a symmetric distribution with relative sparing of costophrenic angles.⁴ High-resolution CT of the chest typically shows nodules and bizarre-shaped cysts that involve predominantly upper lung zones with basilar sparing.⁵ The definitive diagnosis of PLCH requires histologic demonstration of bronchiolocentric granulomatous lesions containing Langerhans cells; this may be accomplished by either transbronchoscopic lung biopsy or surgical lung biopsy. An increase in BAL CD1a+ cells (Langerhans cells) > 5% occurs almost exclusively in PLCH,^{6,7} although this can also be seen in cigarette smokers and in patients with other diseases that lead to alveolar epithelial hyperplasia (including fibrotic interstitial lung diseases).

Although the patient described has diffuse cystic lung disease, the lack of a cigarette-smoking history renders the diagnosis of PLCH unlikely. Her chest CT demonstrates thin-walled cysts of variable size, diffusely distributed throughout all lung fields, instead of the bizarre-shaped cysts and nodules (with relative basilar sparing) that are characteristic of PLCH. And while Langerhans-cell histiocytoses can affect organ systems other than the lungs, the kidneys are typically unaffected.

This patient likely has a syndrome that results in both pulmonary and renal cysts. The possible conditions responsible include one of the following: (1) a singular disease with atypical disease-related renal manifestations: tuberous sclerosis complex (TSC); (2) two distinct diseases: sporadic LAM and unrelated polycystic kidney disease; or (3) the TSC2-PKD1 contiguous gene syndrome.

TSC is an autosomal dominant genetic disorder that affects cellular differentiation, proliferation, and migration in early development.⁸ These alterations lead to a variety of hamartomatous lesions that can affect virtually all organ systems. Two genes are known to cause TSC: *TSC1*, located on chromosome 9q34 encodes hamartin; and *TSC2*, located on chromosome 16p13 encodes tuberin. The typical diagnostic triad for TSC consists of seizures, mental retardation, and facial angiofibromas, but fewer than one third of affected persons demonstrate the triad. Comprehensive diagnostic criteria have been established in an National Institutes of Health consensus conference,⁹ and are shown in Table 2. Neurologic and dermatologic abnormalities are the most common physical findings, with brain or skin pathology occurring in 90 to 95% of affected individuals. Patients with TSC can also have LAM; in one study,¹⁰ 39% of asymptomatic women with TSC were found to have chest CT evidence of LAM. These women are usually discovered when they are > 40 years of age; interestingly, the complete clinical triad of TSC is uncommon when LAM is present.¹¹ In

the kidney, the principal manifestations of TSC are cysts and angiomyolipomas; these lesions often coexist.¹² Renal cysts are frequent in patients with TSC, and one series estimated a prevalence of 32%.¹³ Less common lesions in the kidney include intraglomerular microlesions and LAM of the renal sinus. Renal epithelial neoplasms have also been described, but these are rare.

This patient demonstrates one major (LAM) and one minor (multiple renal cysts) feature of TSC, and could therefore be classified as “probable TSC.” However, polycystic kidney disease occurs in only 3% of persons with TSC¹⁴ and usually presents early in life with hypertension, hematuria, or renal failure.¹³ Moreover, the lack of other skin or CNS manifestations and the lack of any first-degree relatives affected by TSC make it less likely.

An alternative possibility is that this case represents two separate conditions: sporadic LAM and adult dominant polycystic kidney disease (ADPKD). Sporadic LAM occurs almost exclusively in young women, with an average age of onset of 30 years.¹⁵ These women lack neurologic, dermatologic, and retinal signs and symptoms of TSC. LAM is characterized histologically by nonneoplastic proliferation of atypical smooth-muscle cells (*ie*, LAM cells) within the lung parenchyma and elsewhere. Abdominal tumors are often seen in patients with LAM, especially renal angiomyolipomas. The interesting demographics of sporadic LAM and the fact that LAM also occurs in TSC has led to numerous theories about its pathogenesis. One, invoking a loss of heterozygosity in the *TSC2* gene, is supported by the discovery of loss of heterozygosity in angiomyolipomas from patients with sporadic LAM.^{16,17}

ADPKD is the most common genetic renal disease and accounts for up to 10% of all cases of end-stage renal disease.¹⁸ ADPKD is characterized by enlargement of the kidneys and replacement of renal parenchyma by numerous fluid-filled cysts. Other lesions associated with ADPKD include hepatic cysts, pancreatic cysts, aortic and cerebral aneurysms, hepatic fibrosis, intestinal diverticula and heart valve defects. Pulmonary cysts, although reported, are very rare.¹⁹ Approximately 85 to 90% of ADPKD cases are linked to mutations in the *PKD1* gene, which is located on chromosome 16p13.¹⁴

The chest CT finding (Fig 1) is entirely consistent with a diagnosis of LAM. The symptoms of chest pain and reduced exercise tolerance 6 months prior to presentation were likely manifestations of a pneumothorax, a not-infrequent occurrence in patients with LAM. Her abdominal CT, however, does not show angiomyolipomas, the most common renal manifestation of LAM. Her renal lesions are cysts, not angiomyolipomas; as such, they are due to a condition other than LAM. Conversely, although her abdominal CT is consistent with a diagnosis of ADPKD, numerous pulmonary cysts have not previously been reported in isolated ADPKD and are not likely due to that condition. Lastly, she has no family history of ADPKD, so we believe there must be an alternative explanation for her renal cysts.

A unifying and, we believe, most likely explanation for the findings in this patient is the TSC2-PKD1 contiguous gene syndrome. The *TSC2* and *PKD1* genes are adjacent to each other on chromosome 16, being a few nucleotides apart in a tail-to-tail orientation.^{14,20} In 1994, the TSC2-PKD1 contiguous gene syndrome was reported in six children with TSC who presented during early childhood with markedly enlarged polycystic kidneys.²¹ Although the contiguous gene syndrome has historically been associated with severe juvenile polycystic kidney disease,^{22–24} more recent reports^{25,26} suggest that severe juvenile polycystic disease is not an obligatory feature. It has been proposed that polycystic kidneys develop later in life in some of these patients because of somatic mosaicism, or because the TSC2-PKD1 contiguous gene syndrome requires loss of heterozygosity for both *PKD1* and *TSC2*. Definitive diagnosis of TSC2-PKD1 contiguous gene syndrome requires pulsed-field

gel electrophoresis, fluorescence *in situ* hybridization, or polymerase chain reaction studies that demonstrate a deletion in both *TSC2* and *PKD1*.

The clinical data of the *TSC2*-*PKD1* contiguous gene syndromes so far reported are sparse, and treatments center around the various manifestations of the contiguous gene syndrome. Renal manifestations dominate, frequently with severe congenital or juvenile polycystic kidney disease leading to abdominal masses or distension and early onset of renal failure. These findings are combined with variable phenotypic expression of tuberous sclerosis. Pulmonary manifestations include development of LAM, and recurrent pneumothoraces have been described in patients with *TSC2*-*PKD1* contiguous gene syndrome. It remains unclear whether patients with *TSC2*-*PKD1* contiguous gene syndrome, such as patients with LAM, will have a progressive decline in lung function or whether they will benefit from therapy.

Clinical Follow-up

MRI/magnetic resonance angiography of the brain was performed to evaluate for cerebral aneurysm associated with polycystic kidney disease and to screen for other signs of TSC. The results showed mild generalized atrophy and nonspecific supratentorial white matter disease and normal flow-related enhancement within vertebral, basilar, and carotid circulations without evidence of aneurysm. The patient declined further evaluation, including *TSC2*-*PKD1* gene sequencing, and she was subsequently unavailable for follow-up.

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Figure 1.
Chest CT scan demonstrating innumerable thin-walled cysts of varying sizes randomly distributed throughout the parenchyma of both lungs.

Figure 2.
Abdominal CT scan showing massive kidneys with innumerable fluid-filled cysts.

Table 1**Etiology of Cystic Lung Disease***

Focal or multifocal cystic lung disease
Congenital
Bronchogenic cysts
Pulmonary sequestration
CCAM
Infectious
Pulmonary tuberculosis
Coccidioidomycosis
<i>P jiroveci</i> pneumonia
<i>Echinococcus granulosus</i> or <i>Echinococcus multilocularis</i>
Lymphoid interstitial pneumonia
Desquamative interstitial pneumonia
Diffuse cystic lung disease
PLCH
LAM
Honeycomb cystic lung disease
Asbestosis
Idiopathic pulmonary fibrosis
Collagen vascular disease
Hypersensitivity pneumonitis
Sarcoidosis
Miscellaneous
Cystic lung disease in Down syndrome
Birt-Hogg-Dube syndrome
Trauma

* Adapted with permission from Cosgrove et al.¹

Table 2**Revised Diagnostic Criteria for TSC^{*}**

Major features
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibromas
Hypomelanotic macules (> 3)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber
Subependymal nodule
Subependymal giant-cell astrocytoma
Cardiac rhabdomyoma, single or multiple
LAM [†]
Renal angiomyolipoma [‡]
Minor features
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter migration lines
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
“Confetti” skin lesions
Multiple renal cysts [‡]
Definite TSC: either two major features or one major feature with two minor features
Probable TSC: one major feature and one minor feature
Possible TSC: either one major feature or two or more minor features

^{*} Adapted from Hyman and Whittemore.⁹

[†] When both LAM and renal angiomyolipomas are present, other features of TSC should be present before a definitive diagnosis is assigned.

[‡] Histologic confirmation is suggested.