Frequency of Undiagnosed Cystic Lung Disease in Patients With Sporadic Renal Angiomyolipomas

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Objective: The aim of this study was to assess the frequency of undiagnosed cystic lung lesions suggestive of pulmonary lymphangioleiomyomatosis (LAM) in patients who received a diagnosis of sporadic renal angiomyolipomas (AMLs).

Methods: We conducted a retrospective review of CT scans of the chest or abdomen for cystic lung lesions on 176 adult patients who received a diagnosis of sporadic renal AML during a 10-year period, 1997 to 2006, and comparison with chest CT scans of 176 control subjects without renal AML but matched for age, sex, and smoking history. Patients presenting with suspected or known pulmonary LAM and those with underlying tuberous sclerosis were excluded.

Results: Sporadic renal AML was diagnosed in 176 patients with a median age of 58 years (range, 20-91 years), the majority of whom were women (81.8%). Renal tumor was an incidental finding on imaging studies for most patients (90.3%). Nineteen patients (10.8%) had one or more cystic lung lesions and included nine patients (5.1%) with four or more cysts, all of whom were women. In comparison, eight control subjects (4.6%) had one to three cystic lung lesions and none of them exhibited four or more cysts. None of the patients with renal AML and cystic lung lesions, including six women with 10 or more cysts, had undergone an evaluation of their cystic lung disease.

Conclusions: We conclude that a significant portion of women with sporadic renal AMLs exhibit cystic lung lesions suggestive of pulmonary LAM but may remain undiagnosed. Coexistence of pulmonary LAM should be considered in women incidentally found to have sporadic renal AMLs.

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Abbreviations: AML = angiomyolipoma; LAM = lymphangioleiomyomatosis; TSC = tuberous sclerosis complex

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease characterized by infiltration and proliferation of atypical smooth muscle-like cells ("LAM cells") in the lung and affects almost exclusively women.¹⁻³ It is associated with progressive cystic lung disease that can lead to respiratory failure and death. Pneumothorax and chylothorax are well-recognized complications.

Pulmonary LAM may be seen in a sporadic form or as lung involvement in tuberous sclerosis complex (TSC), an inheritable disorder characterized by multisystem hamartomas.¹⁻⁵ Sporadic LAM and TSC-related LAM share some features, including an association with extrapulmonary lymphangiomyomas and renal angiomyolipomas (AMLs). Renal AMLs are identified in approximately 50% of patients with

sporadic LAM and up to 80% of those with TSC-related LAM.^{6,7} However, TSC stigmata, such as CNS, retinal, and skin lesions, are not seen in patients with sporadic LAM.

The association of LAM with renal AML has been of interest. Renal AMLs are benign tumors consisting of adipose tissue, smooth muscle-like cells (LAM cells), and dysplastic vascular elements in varying proportions.⁶ Although LAM is rare, renal AMLs are relatively common, occurring in 0.1% to 0.3% of the general population.⁸⁻¹⁰ Most renal AMLs encountered in clinical practice are of sporadic form, and only 10% of patients with renal AML have underlying TSC.⁶ In both sporadic and TSC-related LAM, LAM cells in the lung and renal AML have been shown to be genetically related and appear to

arise from a common progenitor cell.^{4,11} Hence, it has been proposed that pulmonary LAM represents benign metastasis of LAM cells from renal AML or some other extrapulmonary source.⁴

In recent years it has become apparent that many patients with LAM have mild asymptomatic disease that may be difficult to detect.³ In this study, we sought to assess the frequency of undiagnosed cystic lung disease suggestive of pulmonary LAM in patients diagnosed to have sporadic renal AML. We hypothesized that some patients with renal AMLs may have mild or subclinical pulmonary LAM that may go undiagnosed.

MATERIALS AND METHODS

A computer-assisted search of medical records was conducted to identify patients aged 18 years or older diagnosed to have sporadic renal AML (without underlying TSC) at Mayo Clinic, Rochester, Minnesota, over a 10-year-period between January 1, 1997, and December 31, 2006. The patients' confidentiality was maintained by limiting access to patient-identifiable information to two of the authors (J. H. R., T. E. H.) gathering data from the medical records and imaging studies with the data stored in a secure database. Approval was obtained from the Mayo Foundation institutional review board prior to beginning the study, approval number 10-007459. At the end of the study the institutional review board was consulted regarding the results. The clinicians who conducted the evaluation of patients identified to have cystic lung disease were notified by the lead author (J. H. R.) in a written communication.

Renal AML was diagnosed by the characteristic appearance on CT scan or ultrasonography.^{9,12} We excluded patients presenting primarily for evaluation of suspected or known LAM who were subsequently found to have associated renal AMLs. For the purposes of this study, we limited the study cohort to those who underwent a CT scan of the chest or CT scan of the abdomen on which the lung parenchyma could be adequately evaluated with views of the lung extending above the dome of the diaphragm. Of 176 patients identified, CT scan of the chest was available in 62 patients (35.2%) and CT scan of the abdomen in 174 patients (98.9%).

The CT scans were reviewed by two of the authors (J. H. R., T. E. H.) independently and without knowledge of the clinical context (smoking history, clinical presentation, pulmonary symptoms or diseases) to identify cystic lesions (defined as round lucency with a definable thin wall) in the lung. The number and sizes of the cysts

in the lung were noted. Differences in interpretation were settled by consensus. Medical records of these patients were separately reviewed to extract data regarding age, sex, smoking history, clinical presentation, imaging studies, biopsy procedures, and diagnoses.

For comparison, we also identified a group of control subjects without renal AML who underwent a CT scan of the chest over the same 10-year interval and matched for age (within 2 years), sex, and smoking history (current, previous, never). These control subjects were selected from a list of those undergoing a chest CT scan for evaluation of dyspnea, cough, or chest pain in the absence of identifiable lung disease on clinical evaluation and chest radiography. These CT scans were reviewed using the same method described here.

Statistical Analysis

Comparisons across groups were made using the two-sample rank sum test or χ^2 (exact) test as appropriate. Logistic regression was used to investigate the association of select variables with one or more lung cyst vs no cysts. Variables included number of renal AMLs, unilateral vs bilateral AML, and size of AML (largest size for those with multiple AMLs). This analysis was performed for all subjects and separately for the AML and control cohorts. The analysis for all subjects included AML vs control as a covariate. This analysis was also repeated in the AML cohort with four or more lung cysts vs fewer than four cysts as the outcome. In all cases, *P* values < .05 were considered statistically significant.

RESULTS

Among 176 subjects with sporadic renal AMLs, 144 were women (81.8%) (Table 1). For most patients (90.3%), renal AML was an incidental finding on ultrasonography or CT scan of the abdomen or chest (with views of the kidneys) performed for evaluation of unrelated issues (Table 2). In 17 patients (9.7%), imaging had been performed for evaluation of pain that was caused by the renal AML, either bleeding or large size.

The majority of patients (79.5%) had a single tumor. Among those with multiple renal AMLs or bilateral kidney involvement there were no features suspicious for TSC. One patient with bilateral renal AMLs had undergone genetic testing for TSC, which was negative. The median size of renal AML was 2 cm; 39 patients (22.2%) had renal AMLs measuring ≥ 4 cm. Fifty-six patients (31.8%) underwent surgical resection of the renal tumor, which included 39 partial nephrectomies and 17 total nephrectomies. Eight patients were treated nonsurgically: embolization therapy for six, alcohol ablation for one, and radiofrequency ablation for one patient. No treatment was pursued in the remaining 112 patients (63.6%).

Among 176 patients with renal AMLs, 19 (10.8%) subjects were noted to have one or more cysts in the lungs and included 10 (5.7%) with one to three cysts, three (1.7%) with four to nine cysts, and six (3.4%) with 10 or more cysts (Table 3). Eight of 62 patients (12.9%) with CT scan of the chest were

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Table 1—Demographic and Clinical Characteristics of Subjects With Renal AMLs

Characteristic	Patients With AML (n = 176)	Control Subjects (n = 176)
Age, mean $\pm$ SD, y	57.3 $\pm$ 14.1	57.4 $\pm$ 14.1
Female sex, No. (%)	144 (81.8)	144 (81.8)
Smoking status, No. (%)		
Never	104 (59.1)	104 (59.1)
Previous	59 (33.5)	59 (33.5)
Current	13 (7.4)	13 (7.4)
No. of renal AMLs, No. (%)		
1	140 (79.5)	NA
2	23 (13.1)	NA
≥ 3	13 (7.4)	NA
Size of largest renal AML, cm, median (range)	2.0 (0.4-19)	NA
Bilateral renal involvement, No. (%)	20 (11.4)	NA

AML = angiomyolipoma; NA = not applicable.

noted to have at least one lung cyst, whereas 11 of 114 patients (9.6%) with only CT scan of the abdomen available had one or more cysts identified ($P = .55$). All 19 subjects noted to have lung cysts associated with renal AMLs were women (13.2% of women), whereas none of the men with renal AMLs exhibited such lesions ($P = .047$). Nine of these women (6.3% of women) had four or more cysts identified.

Table 2—Type of Imaging Study and Indications Leading to Initial Detection of Renal AML

Type of Study	No. (%)
Ultrasonography of abdomen	55 (31.3)
Abdominal pain, cause not identified	14 (8.0)
Chronic kidney disease	12 (6.8)
Renovascular evaluation for hypertension	10 (5.7)
Recurrent urinary tract infections, stone or hematuria	5 (2.8)
Suspected liver disease	5 (2.8)
Screening for abdominal aortic aneurysm	4 (2.3)
Abdominal pain of GI origin	3 (1.7)
Pregnancy	1 (0.6)
Pain related to renal AML/bleeding	1 (0.6)
CT scan abdomen	105 (59.7)
Abdominal pain, cause not identified	24 (13.6)
Pain related to renal AML/bleeding	16 (9.1)
Recurrent urinary tract infections, stone or hematuria	16 (9.1)
Abdominal pain of GI origin	15 (8.5)
Reassessment for prior or current cancer	12 (6.8)
Weight loss or persistent nausea	6 (3.4)
Suspected liver disease	5 (2.8)
Screening for abdominal aortic aneurysm or colon cancer	4 (2.3)
Renovascular evaluation for hypertension	3 (1.7)
Pelvic pain	2 (1.1)
Kidney donor	2 (1.1)
CT scan chest	10 (5.7)
Lung nodule or infiltrate	9 (5.1)
Persistent cough	1 (0.6)
Excretory urogram (for stones)	4 (2.3)
MRI spine (for back pain)	2 (1.1)

N = 176. See Table 1 legend for expansion of abbreviation.

In comparison, eight of 176 control subjects (4.6%) had one or more cystic lesions identified on review of their chest CT scans. Six of these patients had one cyst and the remaining two patients had two and three cysts, respectively. Three of these eight patients were nonsmokers and two were men. In this control group, there was no difference between men and women in the percentage of respective sex found to have cysts (6.3% and 4.2%, respectively; $P = .64$).

Compared with control subjects, patients with AML were more likely to have cysts (OR = 2.54 [95% CI, 1.1-6.0], $P = .032$). In an analysis limited to the AML cohort, bilateral involvement (OR = 3.4 [95% CI, 1.1-10.7], $P = .038$) and size (OR = 1.2 [95% CI, 1.0-1.3], $P = .010$) were associated with the presence of cysts.

Clinical characteristics of nine study patients with four or more lung cysts are outlined in Table 4. These cysts were identified on limited views of the lung parenchyma visible on abdominal CT scan of seven patients. None of these patients had a prior history of pneumothorax or any other lung disease. Three of nine patients (33%) with cystic lung disease compared with 14 of 167 patients (8.4%) without cystic lung disease had presented for evaluation of abdominal pain that was determined to be due to the renal AML ($P = .044$). In seven of these nine patients, the presence of lung cysts had been acknowledged on the radiology report as “emphysematous changes,” “blebs,” “bullae,” or “cysts,” without mention of possible pulmonary LAM. In the remaining two patients, the presence of cysts was not mentioned. No clinical evaluation had been performed to clarify the underlying nature of the cystic lung disease in any patient, including six women with 10 or more cysts (Fig 1). Only one of these women (54-year-old nonsmoker) underwent pulmonary function testing, which revealed mild airflow obstruction and a reduced diffusing capacity. There were no other LAM-related lesions (eg, lymphangiomyomas) seen on the CT scans. Follow-up data on this group of patients were limited; four patients had CT scan of the abdomen (three patients) or chest (one patient) available for review over an interval of 12 to 40 months. No evidence of radiologic progression was seen. None of the patients was noted to have experienced pneumothorax, to have other symptoms referable to the cystic lung disease, or to have pulmonary LAM diagnosed.

DISCUSSION

To our knowledge, the risk of pulmonary LAM in patients presenting with sporadic renal AML has not previously been assessed. In this study we found a significant portion of women (6.3%) diagnosed to

Table 3—Frequency of Cystic Lung Lesions Seen on CT Scan

No. Cysts	Patients With Renal AML, No. (%)	Control Group, No. (%)	P Value
None	157 (89.2)	168 (95.5)	.028
≥ 1 cyst	19 (10.8)	8 (4.6)	...
1 to 3	10 (5.7)	8 (4.6)	...
4 to 9	3 (1.7)	0	...
≥ 10	6 (3.4)	0	...

N = 176 for each group. See Table 1 legend for expansion of abbreviation.

have sporadic renal AMLs to display cystic lung disease (four or more cysts) suspicious for pulmonary LAM. Based on the known prevalence of renal AMLs in the general population, we calculate that approximately 7,000 to 22,000 women in the United States may have undiagnosed LAM associated with their sporadic renal AMLs.^{6,8-10} For some of the patients in this study the number of cysts was relatively modest, which, in part, can be attributed to their assessment being limited to lung views available on abdominal CT scans. Thus, our results probably underestimate the frequency of cystic lung disease associated with sporadic AMLs. It is not surprising that two-thirds of our study cohort did not undergo a CT scan of the chest, since potential significance of these cysts seen on CT scan of the abdomen was not appreciated during their clinical evaluation for nonpulmonary issues. Possible presence of LAM was not addressed in any of these patients. It is notable that all nine patients identified to have cystic lung disease in this study were women, since pulmonary LAM is a disorder that afflicts almost exclusively women.

Renal AMLs are relatively common, particularly in comparison with pulmonary LAM.⁸ In the current

era, these benign renal tumors are usually discovered as an incidental finding on imaging studies.^{9,12} Although 90% of renal AMLs are sporadic, they are also a well-recognized manifestation of TSC and occur in 60% to 80% of patients with TSC in whom renal AMLs are usually multiple and present at a younger age compared with the sporadic form.^{4,6,7,13-15} Renal AMLs are also encountered in patients with sporadic LAM, with approximately 30% to 50% exhibiting renal AML, usually as a solitary lesion.¹⁶⁻¹⁹

The association of renal AML and LAM has been of interest because LAM cells, characterized by mutations in the *TSC1* or *TSC2* genes, are found in both lesions.^{1,20,21} Identical *TSC2* gene mutations have been detected in LAM cells in the lung and renal AMLs of patients with TSC-related LAM.¹¹ In addition, LAM cells have been isolated from body fluids, including blood, urine, and chylous fluids.^{22,23} These observations support the current hypothesis of “benign metastasis” as the mechanism underlying multifocal presence of LAM cells. Pulmonary LAM is believed to result from migration of LAM cells from renal AMLs or some other origin.^{1,21,24,25}

More than 80% of the patients with renal AMLs were women, which is consistent with previous observations regarding female predilection for both sporadic and TSC-related renal AMLs.^{6,7,26,27} In addition, renal AMLs have shown a greater propensity for growth in women.^{6,7,14,15} Similarly, sporadic and TSC-related LAM are seen almost exclusively in women.¹⁻³ This sex predisposition may partly be explained by recent experimental data suggesting estrogen to promote metastasis and survival of LAM cells.^{24,28,29}

We excluded patients with known TSC from our study cohort, and none of them had a family history

Table 4—Nine Patients With Renal AMLs and Four or More Cysts in the Lung

Age, y/Sex	Smoking History	Presentation	Renal AML, No. (Maximum Size, mm)	CT Scan Type	Lung Cysts, No. (Maximum Size, mm)	Treatment, Follow-up Data
71/Female	Never	Abdominal pain, cause not identified	1 (20)	Abdomen	> 10 (14)	No treatment
52/Female	Current	Abdominal pain due to large uterine fibroid	1 (17)	Abdomen	> 10 (9)	Partial nephrectomy
31/Female	Previous	Pain from renal AML bleed	1 (85)	Chest	10 (22)	Partial nephrectomy
54/Female	Never	US for evaluation of chronic kidney disease	1 (9)	Chest	7 (26)	No treatment
48/Female	Current	Abdominal pain due to irritable bowel syndrome	1 (7)	Abdomen	> 10 (8)	No treatment
57/Female	Never	Abdominal pain due to pancreatic cancer	1 (16)	Abdomen	> 10 (17)	No treatment
45/Female	Previous	Pain from renal AML bleed	3 (60), bilateral	Abdomen	8 (6)	Total nephrectomy elsewhere; embolization therapy
28/Female	Previous	US during pregnancy	5 (170), bilateral	Abdomen	5 (6)	Bilateral partial nephrectomies
33/Female	Current	Pain from large renal AML	1 (190)	Abdomen	> 10 (9)	Partial nephrectomy

US = ultrasonography. See Table 1 legend for expansion of other abbreviation.

FIGURE 1. CT scan of the abdomen on a 57-year-old woman, non-smoker. Multiple cysts of varying sizes are seen in both lungs. This patient had a 1.6-cm solitary renal angiomyolipoma that was biopsied.

suggestive of TSC. Review of their medical records, including the clinical examination, laboratory test results, and imaging studies, failed to reveal any findings suggestive of TSC stigmata. Nonetheless, we cannot completely exclude the possibility that some of these patients, particularly those with bilateral renal AMLs, may have undiagnosed TSC, given the variable expressivity of this disorder. Patients identified to have renal AMLs in this retrospective study had not undergone a methodical evaluation for possible TSC.

The clinical significance of cysts in the lungs of the study patients with renal AMLs could be questioned, particularly in those with a limited number of cysts. None of the patients underwent a lung biopsy to confirm the suspected diagnosis of LAM. Furthermore, the presence of blebs and bullae has been described in healthy subjects. For example, Amjadi and colleagues³⁰ identified blebs in 6% of 250 otherwise healthy subjects (mean age, 29 years) by bilateral thoracoscopic evaluation in the course of thoracoscopic sympathectomy for idiopathic hyperhidrosis. Lesur and colleagues³¹ described the presence of bullae on CT scanning in two of 20 control subjects (10%) with no history of lung disease. Similarly, we observed cystic lung lesions by CT chest scan in 4.6% of the control group of subjects. However, none of these control subjects had more than three cysts. None of the patients with renal AMLs and cystic lung disease had features (family history, extrapulmonary findings, underlying diseases, associated CT scan findings, laboratory results) to suggest any other cause for their cystic lung disease, such as pulmonary Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, light-chain deposition disease, and lymphocytic interstitial pneumonia.

There are limitations in our study related to the retrospective design. Chest CT scan was not available in more than one-half of our study cohort, although all of the control subjects had chest CT scans available. This imbalance likely led to an underestimation of the frequency of cystic lung lesions in patients with renal AMLs. We had previously used a similar design in examining the frequency of cystic lung lesions suggestive of LAM in women with TSC and obtained results that were similar to those found in subsequent prospective studies examining the same issue.³²⁻³⁴ Another limitation is inherent in the method of diagnosing renal AMLs that required characteristic imaging appearance of these tumors. Not all renal AMLs contain radiologically detectable amounts of fat, and, thus, some patients with renal AMLs without this feature were excluded in the absence of histologic diagnosis. However, such tumors account only for a small minority of renal AMLs.³⁵ Last, we realize that the possibility of underlying TSC cannot be completely excluded in these patients, particularly for those with multiple renal AMLs, since our analysis was limited to data available in the medical records.

We conclude that a significant portion of women with sporadic renal AMLs have cystic lung disease suspicious for LAM but may remain undiagnosed. Possible presence of LAM should be evaluated in women found to have sporadic renal AMLs. Further studies are needed to address the frequency of LAM in patients with sporadic renal AMLs.

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Dr Hartman: contributed to the study design; collection, analysis, and interpretation of data; drafting and critical review of the manuscript; and reading and approving the final version.

Dr Torres: contributed to the analysis and interpretation of data, drafting and critical review of the manuscript, and reading and approving the final version.

Mr Decker: contributed to analysis and interpretation of data, drafting and critical review of the manuscript, and reading and approving the final version.

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