

Sporadic Lymphangioloio-myomatosis and Tuberos Sclerosis Complex with Lymphangioloio-myomatosis: Comparison of CT Features¹

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Purpose:

To retrospectively compare the frequencies of computed tomographic (CT) findings in patients with lymphangioloio-myomatosis (LAM) and patients with tuberous sclerosis complex (TSC) and LAM.

Materials and Methods:

Institutional review board approval and informed consent were obtained for the HIPAA-compliant study. In 256 patients with LAM (mean age, 44 years) and 67 patients with TSC/LAM (mean age, 40 years), CT scans of the chest, abdomen, and pelvis were reviewed by a single radiologist. The fraction of lung involvement with cysts was estimated from high-spatial-resolution CT scans. Other findings assessed included noncalcified pulmonary nodules, pleural effusion, thoracic duct dilatation, hepatic and renal angiolipomas (AMLs), lymphangioloio-myoma (LALM), ascites, nephrectomy, and renal embolization. Confidence intervals and hypothesis tests of differences in frequencies, comparison of age quartiles, RIDIT analysis, analysis of variance, and correlation coefficients were used in the statistical analysis.

Results:

Patients with LAM had more extensive lung involvement (RIDIT score, 0.36) and higher frequency of LALM (29% vs 9%, $P < .001$), thoracic duct dilatation (4% vs 0, $P = .3$), pleural effusion (12% vs 6%, $P = .2$), or ascites (10% vs 6%, $P = .3$). Patients with TSC/LAM had higher frequency of noncalcified pulmonary nodules (12% vs 1%, $P < .01$), hepatic (33% vs 2%, $P < .001$) and renal (93% vs 32%, $P < .001$) AMLs, nephrectomy (25% vs 7%, $P < .001$), or renal artery embolization (9% vs 2%, $P < .05$).

Conclusion:

The extent of lung disease is greater in LAM than TSC/LAM. Hepatic and renal AMLs and noncalcified lung nodules are more common in TSC/LAM, while lymphatic involvement—thoracic duct dilatation, chylous pleural effusion, ascites, and LALM—is more common in LAM.

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Lymphangioliomyomatosis (LAM) is characterized by proliferation of abnormal appearing smooth muscle cells (LAM cells) in the lungs, the kidneys, and the lymphatic system. The diagnosis of pulmonary LAM is usually made with clinical history and computed tomographic (CT) demonstration of pulmonary cysts or lung biopsy (1–5). Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by hamartomas, seizures, and mental retardation. TSC is caused by mutation of two genes, *TSC1* or *TSC2*; its occurrence can be sporadic (approximately 60% of cases) or inherited (6). LAM has been considered a *forme fruste* of TSC (7). Findings of lung and kidney biopsies in both LAM and TSC demonstrate proliferation of LAM cells in the lymphatics and in renal angiomyolipoma (AML). These LAM cells exhibit loss of heterozygosity, as well as point mutations in the *TSC2* gene, which suggests that the findings in LAM are caused by the proliferation of LAM cells containing a *TSC2* mutation (8,9). Up to a third of women with TSC may exhibit lung cysts, the hallmark feature of LAM; these patients have been categorized as having TSC/LAM (10,11). Characterization of the spectrum and prevalence of findings in these overlap cases and comparison with features of sporadic LAM may assist in clarifying the phenotypes of sporadic LAM and TSC/LAM and their genetic basis.

Advances in Knowledge

- Lung cysts are present in all patients with sporadic lymphangioliomyomatosis (LAM) and in patients with tuberous sclerosis complex (TSC) and LAM but are more extensive in LAM.
- Lymphangioliomyomas are more common in sporadic LAM than in TSC/LAM.
- Noncalcified lung nodules are more common in TSC/LAM than in sporadic LAM.
- Renal and hepatic angiomyolipomas are more common in TSC/LAM than in sporadic LAM.

Thus, the purpose of our study was to retrospectively compare the frequencies of CT findings in patients with LAM and patients with TSC/LAM.

Materials and Methods

Patients

Our retrospective study included 256 women with sporadic LAM (age range, 23–75 years; mean, 44 years) and 67 women with TSC/LAM (age range, 19–68 years; mean, 40 years) evaluated between 1996 and 2005 as part of a natural history study of LAM and TSC/LAM. The study protocol and consent documents for the natural history study were approved by our institutional review board. Written informed consent was obtained from all study participants. The initial informed consent included consent for future retrospective analysis. Both the natural history study and our current retrospective study were compliant with the Health Insurance Portability and Accountability Act.

In the 256 women with LAM, the diagnosis was established with lung biopsy in 187 patients and biopsy of abdominal and pelvic masses in 11 patients. Fifty-eight patients did not undergo tissue biopsy but had classic clinical history (recurrent spontaneous pneumothorax and/or chyloous pleural effusion) and CT findings (diffusely scattered thin-walled lung cysts).

In the 67 patients with TSC/LAM, the diagnosis of TSC was made by means of established clinical and imaging criteria such as clinical history of seizures, mental retardation, characteristic dermatologic findings (adenoma sebaceum), and subcortical brain hamartomas or tubers on CT scans (12). The diagnosis of LAM was established with lung biopsy in 22 patients and lymph node biopsy in one patient. Forty-four patients did not undergo tissue biopsy but had classic clinical history (recurrent spontaneous pneumothorax and/or pleural effusion) and CT findings (diffusely scattered thin-walled lung cysts) of LAM.

Imaging

All patients underwent CT of the chest, abdomen, and pelvis. Most patients (306 of 323) underwent contrast material-enhanced CT (120 mL of iopamidol 61% [Isovue 300]; Bracco Diagnostics, Princeton, NJ); 17 patients did not receive intravenous contrast material because of either a history of allergic reactions or poor renal function. The studies were performed with a HiSpeed Advantage, CTi, or Lightspeed scanner (GE Medical Systems, Milwaukee, Wis). Images of the chest were obtained at end inspiration with patients in the supine position by using 5–10 mm collimation. High-spatial-resolution CT images of the chest were obtained with the patients in prone position by using 1 mm collimation every 3 cm.

Image Analysis

A board-certified radiologist (N.A.A.) with over 20 years experience in chest, abdominal, and pelvic CT reviewed all images in all patients during multiple separate sessions. The radiologist was blinded as to whether the patients had LAM or TSC/LAM.

Chest CT

The severity of cystic lung disease was graded from the high-spatial-resolution CT images. The grading process consisted of two steps. Patients that had few (one to 10) lung cysts were placed in the category of minimal disease

Published online before print
10.1148/radiol.2421051767

Radiology 2007; 242:277–285

Abbreviations:

AML = angiomyolipoma
LAM = lymphangioliomyomatosis
LALM = lymphangioliomyoma

Author contributions:

Guarantor of integrity of entire study, N.A.A.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, N.A.A., A.R., J.M.; clinical studies, N.A.A., A.R., J.M.; statistical analysis, N.A.A., A.J.D.; and manuscript editing, all authors

Authors stated no financial relationship to disclose.

(grade 0). If more than 10 cysts were identified, the lungs were divided into three zones—upper, middle, and lower—with corresponding equal subsets of images. The extent of cystic involvement in each of the three zones was graded individually and subjectively according to the lung volume replaced by the cysts, as follows: mild disease, less than one-third of the lungs involved with cysts (grade 1); moderate disease, cysts involved one- to two-thirds of the lungs (grade 2); severe disease, cysts involved more than two-thirds of the lungs (grade 3). A global score was obtained for each patient by averaging the grades from all three lung zones. This method of scoring was the same as previously reported except for the global category of minimal disease (grade 0), which was created to include patients with very few (one to 10) cysts since, in this study, all patients had to have lung cysts to fulfill the entrance criteria (13).

Other chest CT findings recorded included thoracic duct dilatation, pleural effusion, multiple (three or more) noncalcified pulmonary nodules, and evidence of lung transplant.

Abdominal and Pelvic CT

Findings recorded were hepatic and renal masses, lymphangiomyoma (LALM), and ascites. Hepatic and renal masses were considered to represent AMLs if they contained low-attenuation material (fat) that measured less than -10 HU. Renal masses were considered to be atypical AMLs if they enhanced homogeneously without low-attenuation foci typical of fatty attenuation. For renal AML, we recorded for each kidney (a) the number of masses (from zero to nine and 10—if 10 or more separate AMLs were seen) and (b) whether the patient underwent a nephrectomy or renal artery embolization. For each patient, the size of the largest renal AML was recorded.

Statistical Analysis

In the analysis, the patients with LAM and those with TSC/LAM were handled separately. All calculations and graphs were generated by using software (Microsoft Excel Professional 2003; Mi-

crosoft Excel, Redmond, Wash). The frequencies of the CT abnormalities and conditional frequencies (ie, frequency of one finding given the presence of the other) among the abnormalities were calculated for patients with LAM and patients with TSC/LAM. Confidence intervals were calculated for the differences in the frequencies of the CT abnormalities observed in the two patient groups. Statistical significance was defined as $P \leq 0.05$.

RIDIT analysis was used to compare the distribution of the severity (grades) of lung disease between patients with LAM and those with TSC/LAM (14). The method has been given the acronym RIDIT since it determines the ranks of one set of measurements “relative to an identified distribution”; here, the scores for patients with TSC/LAM were ranked relative to the scores for patients with LAM.

The severity of renal disease in each patient was quantified in terms of the total renal score (total number of AMLs in both kidneys). A kidney with 10 or more AMLs was given a score of 10. Patients who underwent nephrectomy were presumed to have had at least one AML in the resected kidney.

The age distribution of the patients in the LAM and TSC/LAM groups was evaluated by comparing the cumulative probability plots; 25th, 50th, and 75th percentiles; means; and standard deviations. The Kolmogorov-Smirnov test was used to assess statistical significance between the cumulative distributions (15). The influence of patient age

on the findings was assessed by means of scatterplots of CT findings versus age and by stratifying the patients into age quartiles and comparing the frequencies or severity of the findings across the age quartiles.

Analysis of variance was used to assess the homogeneity of the lung scores among the quartiles. The relation between the severity of lung and renal disease in each patient group was assessed by comparing the distributions of renal scores for each grade of lung disease and by calculating the linear correlation coefficients.

Results

Chest CT Findings

On the basis of inclusion criteria, all patients in this study had well-circumscribed thin-walled cysts scattered diffusely in the lungs (Fig 1). Regarding the severity of lung cysts for patients with LAM and patients with TSC/LAM, RIDIT analysis demonstrated that patients with TSC/LAM have, on average, slightly less severe lung disease than patients with LAM (RIDIT score, 0.36; 95% confidence interval: 0.28, 0.44; $P < .001$). The meaning of the RIDIT score is similar to that of the area under the ROC curve; for example, a RIDIT score of 0.36 implies that the probability is 0.36 that a randomly selected patient with TSC/LAM will have a greater lung score than a randomly selected patient with LAM. The mean lung grades for patients with LAM were consistently

Figure 1



Figure 1: Transverse prone nonenhanced high-spatial-resolution 1-mm-thick CT section in a 56-year-old woman with LAM shows severe involvement of the lungs. Note almost complete replacement of lung tissue by cysts.

higher than the mean grades for patients with TSC/LAM across all four patient age quartiles (Fig 2).

The frequency of multiple noncalci-

Figure 2

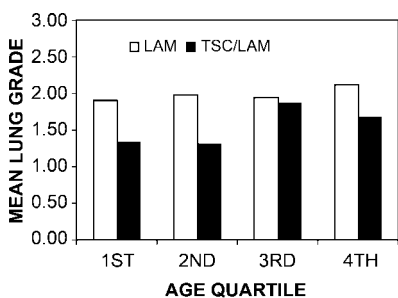


Figure 2: Graph shows that mean lung grades for patients with LAM are consistently greater than those for patients with TSC/LAM across all four age quartiles.

fied lung nodules was greater in TSC/LAM than in LAM ($P < .01$) (Fig 3). The observed frequency of thoracic duct dilatation, pleural effusion, and lung transplantation were higher in LAM than in TSC/LAM; however, the differences were not statistically significant at the $P = .05$ level (Table 1).

Abdominal and Pelvic CT Findings

The most common abdominal findings were renal AML, hepatic AML, and LALM (Table 2, Fig 4). Renal and hepatic AMLs were more common in patients with TSC/LAM than in patients with LAM; for renal AML, the frequencies were 93% versus 32%, a difference in frequency of 61% (95% confidence interval: 52%, 69%); for hepatic AML, the frequencies were 33% versus 2%, a

difference in frequency of 31% (95% confidence interval: 19%, 42%) (Fig 5). LALM was more common in patients with LAM than in patients with TSC/LAM: 29% versus 9%, a difference in frequency of 20% (95% confidence interval: 11%, 29%) (Fig 6).

Patients with LAM more commonly had a unilateral and single AML, while patients with TSC/LAM more commonly had bilateral and multiple (>10) AMLs (Table 3). Larger renal AMLs were found in TSC/LAM (range, 0.3–11.4 cm; mean, 3.5 cm) than in LAM (range, 0.2–9.8 cm; mean 2.7 cm). Patients with TSC/LAM were at higher risk of hemorrhage from their AMLs than were patients with LAM; this is reflected in the increased rates of nephrectomy and renal artery embolization in patients with TSC/LAM.

The frequency of renal AML and/or nephrectomy and the mean total renal score in patients with renal abnormalities were consistently much higher in the TSC/LAM patient group in each age quartile (Figs 7, 8). This was also reflected in the distribution of data points in the scatterplots for the mean total renal score versus age for each patient group (Fig 9).

For each grade of lung disease, both the probability of renal disease and the mean total renal score in patients with renal abnormalities were much higher in patients with TSC/LAM than in patients with LAM; however, in each group the probabilities and scores were relatively constant across the grades, clearly without evidence of a positive trend or correlation between lung and renal disease severity (Figs 10, 11). This lack of association was also reflected in a low correlation coefficient between total renal scores and lung grades ($R = -0.07$ for patients with LAM, $R = 0.04$ for patients with TSC/LAM).

Influence of Patient Age on CT Findings

Analysis of age data revealed only minor differences between the age distribution of the two patient groups and the relative independence between the severity of renal and lung abnormalities and age for each group. Comparison of the cumulative probability plots for the two

Figure 3



Figure 3: Transverse 5-mm-thick contrast-enhanced CT section through upper lungs in a 55-year-old woman with TSC/LAM. Multiple lung nodules (arrowheads) consistent with multifocal micronodular pneumocyte hyperplasia and few lung cysts (arrow) indicate minimal lung involvement with LAM.

Table 1

Comparison of Chest CT Findings

CT Finding	LAM (n = 256)	TSC/LAM (n = 67)
Extent of lung cysts		
Minimal	11 (4)	13 (19)
Mild	84 (33)	27 (40)
Moderate	58 (23)	10 (15)
Severe	103 (40)	17 (25)
Multiple noncalcified nodules*	3 (1)	8 (12)
Thoracic duct dilatation	9 (4)	0
Pleural effusion	30 (12)	4 (6)
Lung transplant	13 (5)	0

Note.—Data in parentheses are percentages.

* Three or more nodular opacities greater than 2 mm in diameter.

groups (Fig 12) demonstrated the age distributions to be similar in shape and/or spread but to differ slightly in “location”—our patients with LAM tended to be 4 years older on average than our patients with TSC/LAM. The mean and 25th, 50th, and 75th percentiles for the patients with LAM were all about 4 years greater than the corresponding statistics for the patients with TSC/LAM (ie, 44 vs 40 years, 37 vs 33 years, 43.5 vs 40 years, 50 vs 47 years). The standard deviations were 9 and 10, respectively, for LAM and TSC/LAM. The similarity in the shape and/or spread of the age distributions plots was confirmed by replotting the cumulative probability distributions after subtraction of 4 years from the age of each of the LAM patients; these age-shifted curves superimposed one another, save for slight differences that were far from statistically significant according to Kolmogorov-Smirnov analysis ($P < .4$).

For both the LAM and TSC/LAM groups, the probabilities of a renal abnormality (mass or nephrectomy) and the mean renal score were both relatively constant across all four age quartiles, without evidence of an age-related trend. This relative independence of the severity of renal disease across the adult age range of our patients is also indicated in the low correlation coefficients ($R = -0.03$ for LAM, $R = -0.15$ for TSC/LAM) and scatterplots of age versus renal score (Fig 9). Similarly, no trend was found relating the severity of lung disease to age. Although Figure 2 demonstrates a slight increase in mean lung grades in the upper two quartiles relative to the lower two quartiles for patients with TSC/LAM, for neither group is the variation of mean scores among the age quartiles statistically significant (analysis of variance; $P = .5$ for LAM, $P = .6$ for TSC/LAM), and the correlation coefficients between age and lung grade are small ($R = 0.085$ for LAM, $R = 0.14$ for TSC/LAM).

Discussion

The hallmark feature of LAM is well-circumscribed thin-walled lung cysts that replace normal lung parenchyma

Table 2

CT Finding	LAM (<i>n</i> = 256)	TSC/LAM (<i>n</i> = 67)
Hepatic AML	6 (2)	22 (33)
Renal AML	83 (32)	62 (93)
LALM	74 (29)	6 (9)
Ascites	26 (10)	4 (6)

Note.—Data in parentheses are percentages.

Figure 4

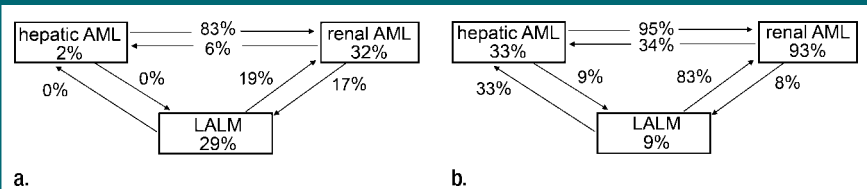


Figure 4: Schematics show overall and conditional probabilities of renal AML, hepatic AML, and LALM in patients with (a) LAM and (b) TSC/LAM. Numbers in boxes are overall probabilities of findings in each group. Number associated with each arrow is conditional probability of the finding to which the arrow points, given presence of the finding from which the arrow originates. For example, in patients with LAM, 32% had a renal abnormality, and of those 17% had LALM; 29% had LALM, and of those 19% had a renal abnormality. Renal and hepatic AMLs were more common in patients with TSC/LAM than in patients with LAM. LALM was more common in patients with LAM.

Figure 5



Figure 5: Transverse 5-mm-thick contrast-enhanced CT section through midabdomen in a 46-year-old woman with TSC/LAM. Note fatty hepatic lesion (arrowhead) and too-numerous-to-count bilateral renal fatty lesions.

and, if severe, may cause respiratory failure and require lung transplantation (3,5). In our study, all patients had lung cysts, but the extent of lung involvement was less severe in TSC/LAM than in LAM. More patients with TSC/LAM had minimal or mild lung involvement than did patients with sporadic LAM (60% vs 37%); also, 5% of patients with LAM had had a lung transplant versus none with TSC/LAM.

In our series, the frequency of multiple noncalcified pulmonary nodules was higher in TSC/LAM (12%) than in LAM (1%). Although none were examined with biopsy in our series, they likely represent a multifocal micronodular pneumocyte hyperplasia, which was initially described in patients with TSC but more recently has also been reported in patients with TSC/LAM (16,17). These benign noncalcified pul-

monary nodules range in size from 2 mm to 1 cm and are distributed randomly in the lungs; they are composed of thickened fibrotic alveolar septa lined by pleomorphic type II pneumocytes. The absence of immunohistochemical staining for HMB45 (stains smooth muscle cells, or "LAM cells," diagnostic for LAM) suggests a histogenesis separate from the lesions in LAM (16–18).

Renal AMLs have been reported in up to 80% of patients with TSC and in up to 54% of patients with LAM (19–22). Although they are benign masses, renal AMLs can grow large, can distort renal architecture, and may compromise renal function; renal failure is the leading cause of death in adults with TSC (22,23). Renal AMLs may hemorrhage, resulting in severe abdominal

pain and ureteral obstruction. Awareness of this complication is important lest a hemorrhagic AML be mistaken for malignancy and total nephrectomy rather than kidney-sparing intervention be performed. Since the risk for hemorrhage has been shown to increase with size, the recommended management of renal AML is based on tumor size and symptoms (24). Patients with asymptomatic lesions (<4 cm in diameter) should be followed up with yearly sonography or CT. Patients with larger lesions (>4 cm in diameter) should be followed up with semiannual sonography or CT. In patients who are symptomatic, angiography and selective embolization, enucleation, or partial nephrectomy, rather than total nephrectomy, are recommended (24).

In our series, the frequency of renal

AML was higher in TSC/LAM than in LAM (93% vs 32%). The number and size of renal AML was higher in TSC/LAM than in LAM. Not surprisingly, the frequency of hemorrhage from renal AML, reflected by prior nephrectomy or renal artery embolization, was higher in TSC/LAM (25% and 9%) than in LAM (7% and 2%). There is an increased risk of renal carcinoma in patients with TSC (25). Thus, a renal mass in a patient with TSC/LAM, although much more likely due to AML or complications of AML, could also represent a renal cell cancer.

In LAM, abnormal smooth muscle cells proliferate in the lymphatics and result in various lymphatic abnormalities: (a) thoracic duct dilatation results from deposition of LAM cells in the walls of the thoracic duct, causing narrowing of the duct, which blocks and dilates the lymphatics proximal to the obstruction; (b) chylous pleural effusion and abdominal and pelvic ascites result from leakage of lymph from the involved lymphatics; and (c) LALMs are benign complex lymphatic masses that result from the proliferation of LAM cells in the lymphatics, causing mural thickening, obstruction, dilatation, and formation of cystic collections of chylous material (20). In our series, all findings related to abnormalities of the lymphatics were less common in TSC/LAM than in LAM: dilated thoracic duct (0% vs 4%), pleural effusion (6% vs 12%), ab-

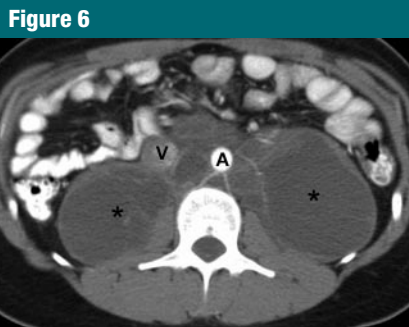


Figure 6: Transverse 5-mm-thick contrast-enhanced CT section through lower abdomen in a 25-year-old woman with LAM and large multiseptated complex retroperitoneal mass consistent with LALM. Note anterior displacement of aorta (A) and IVC (V) by the mass (*).

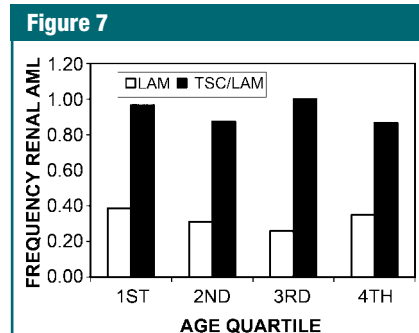


Figure 7: Graph shows that frequencies of renal AML and/or nephrectomy were consistently much higher in TSC/LAM group than in LAM group across all age quartiles.

Table 3
Frequency and Distribution of Renal AML, Nephrectomy, and Renal Artery Embolization

CT Finding	LAM	TSC/LAM
No renal AML	173/256 (68)	5/67 (7)
Renal AML	83/256 (32)	62/67 (93)
Unilateral AML	67/83 (81)	5/62 (8)
Bilateral AML	16/83 (19)	57/62 (92)
Single AML	38/83 (46)	0/62 (0)
Multiple (>10) AML	5/83 (6)	37/62 (60)
Nephrectomy	19/256 (7)	17/67 (25)
Embolization	4/256 (2)	6/67 (9)

Note.—Data in parentheses are percentages.

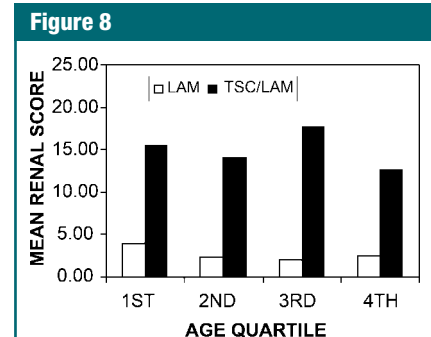


Figure 8: Graph shows that mean total renal score (total number of AMLs and nephrectomies in both kidneys) in patients with renal abnormalities was consistently much higher in TSC/LAM group than in LAM group across all age quartiles.

Figure 9

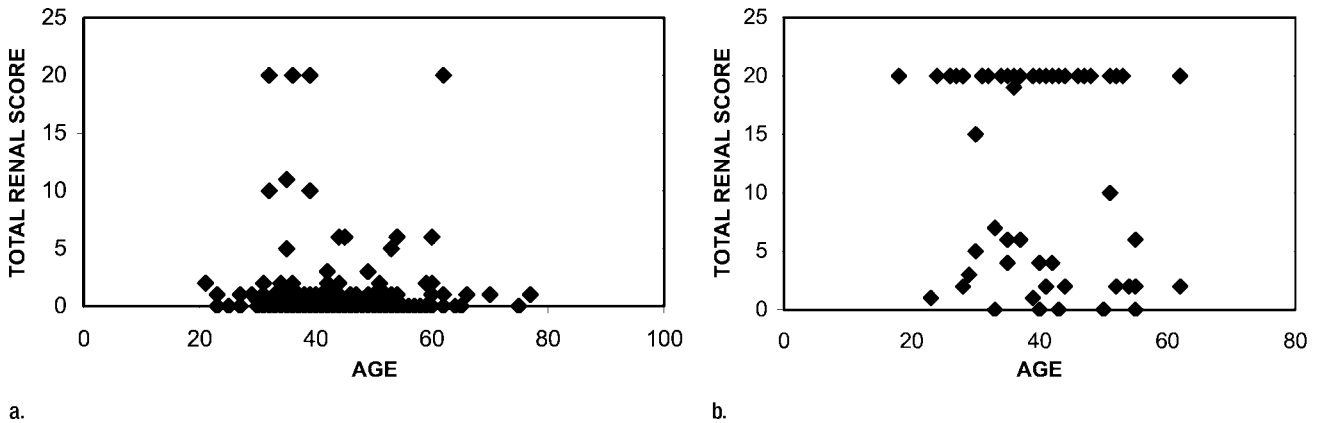


Figure 9: Scatterplots of age versus total renal score for patients with (a) LAM and (b) TSC/LAM. Comparison of distribution of data points demonstrates tendency of total renal scores of patients with LAM to be lower than those of patients with TSC/LAM across age range of patients examined.

dominal and pelvic ascites (6% vs 10%), and LALM (9% vs 29%).

Hepatic AMLs are rare benign fatty tumors that have been reported in 13%–45% of patients with TSC. The identification of multiple hepatic AMLs should prompt a search for further evidence of TSC. Their identification per se in a patient with known TSC does not appear to be a cause for concern or biopsy (26–29). However, because of the reported risk of rupture and hemorrhage, it has been recommended that hepatic lesions larger than 4 cm in diameter be monitored for growth, as is recommended for renal AML (30). In our study, hepatic AMLs were more common in TSC/LAM than in LAM (33% vs 2%). In a study of patients with TSC, hepatic AMLs were found only in association with bilateral renal AMLs (29). In our patients with TSC/LAM, we found a similarly high frequency of a renal AML in patients who had a hepatic AML; of 21 patients with a hepatic AML, 20 had a renal AML, one had a unilateral AML, and 19 had bilateral AMLs. However, in our patient population, the high likelihood of renal AML being present when hepatic AML is present is not the result of a strong correlation between hepatic and renal AML. Rather, it reflects, in large measure, the high frequency of renal AML in the TSC/LAM patients. The conditional probability of renal AML, given the probability of hepatic

Figure 10

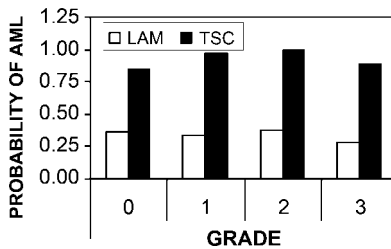


Figure 10: Graph shows that for each grade (extent of lung disease), probability of renal disease is much higher in patients with TSC/LAM than in patients with LAM and is relatively constant across grades, without evidence of positive trend or correlation between extent of lung cysts and probability of renal disease.

Figure 11

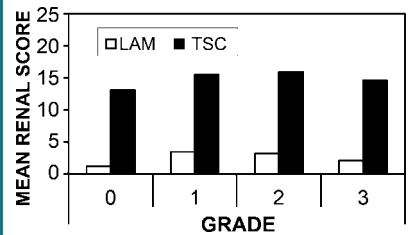


Figure 11: Graph shows that for each grade (extent of lung disease), mean total renal score in patients with renal abnormalities is much higher in patients with TSC/LAM than in patients with LAM, without evidence of positive trend or correlation between lung and renal disease severity.

Figure 12

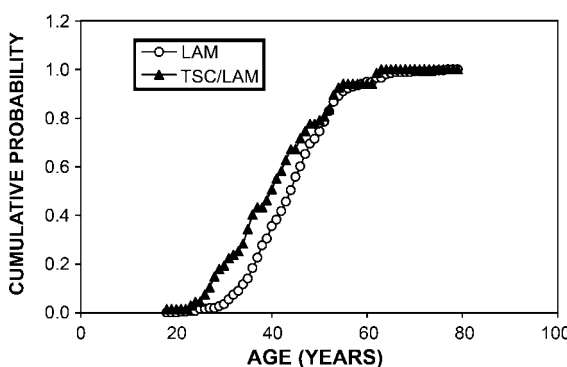


Figure 12: Cumulative probability distribution of patients' ages. Curves are shifted about 4 years relative to one another but are similar in shape, indicating that LAM patients were, on average, about 4 years older than TSC/LAM patients. Age distribution plots of patients in the two groups were of similar shape and/or spread.

AML (95%), is only slightly greater than the probability of renal AML alone (93%); this is also reflected in a low correlation coefficient between the total renal score and the number of hepatic AMLs ($R = 0.11$). On the other hand, for patients with LAM, the marked differences between the conditional probability associated with hepatic AML and the prevalence of LALM and renal AML should not be construed as conclusive demonstration of correlations between hepatic AML, renal AML, and LALM; the small number of hepatic AMLs precludes precise statistical analysis.

Our results demonstrated no association for the frequency and severity of findings with age. This is somewhat surprising given the acquired nature of abnormalities in LAM and TSC/LAM. Moreover, this finding differs from previous reports about an increase in the frequency and severity of findings with age in young patients with TSC (29). Several possible explanations should be considered. First is the adult age range of our patients: 23–75 years (mean, 44 years) for LAM and 19–68 years (mean, 40 years) for TSC/LAM patients. For most cases, the time course of the findings may consist of an initial period of appearance and development followed by a period of quiescence or slow progression, which was the case for most of our patients. Second is the cross-sectional nature of our data. In our study, the data consist of patients' findings at their initial evaluation at our institution—a single time point in the course of each patient's disease. The dynamics of each disease are inferred by analyzing these single "snapshots" collectively and assessing the associations of their findings with patient age. This differs from a longitudinal study in which the patients are evaluated at multiple times and the disease dynamics are assessed by analyzing changes in the findings of each patient over time. A longitudinal study has the advantages of being based on matched serial data, which allows a more direct and sensitive assessment of changes over time. Ideally, the results suggested by this study should be evaluated in a longitudinal study.

Our study had limitations in addition to those described earlier related to its cross-sectional nature and lack of longitudinal data. These include the selection biases inherent in our institution being a referral center—biases toward cases of diseases of longer duration. Another limitation was that not all findings had pathologic correlation.

In conclusion, the same set of findings (lung cysts, renal and hepatic AMLs, and LALM) comprises the CT features of both sporadic LAM and TSC/LAM; however, the frequency and severity with which they occur differ between the two groups. Hepatic and renal AMLs and lung nodules are more common in TSC/LAM, while lymphatic involvement—thoracic duct dilatation, chylous pleural effusion, ascites, and LALM—is more common in LAM. These results appear to be relatively independent of age in adult patients. Assessment of the relation between these phenotypic differences and patients' genetic data may provide insight into the genetic basis of LAM and TSC/LAM.

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