CT of Pleural Abnormalities in Lymphangioleiomyomatosis and Comparison of Pleural Findings After Different Types of Pleurodesis

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OBJECTIVE. The objective of our article was to describe the spectrum and frequency of pleural abnormalities on CT in patients with lymphangioleiomyomatosis (LAM) and the pleural findings associated with different types of pleurodesis (talc, mechanical, and chemical) performed to treat the complications of pleural disease in these patients.

MATERIALS AND METHODS. Two hundred fifty-eight patients with LAM underwent CT of the chest. Pleural abnormalities assessed included pleural thickening, presence of a pleural mass, areas of high attenuation, effusion, and pneumothorax. In patients who had had pleurodesis, the CT findings were correlated with the type of procedure performed.

RESULTS. One hundred thirty-three (52%) of 258 patients had pleurodesis (unilateral, 68/133; bilateral, 65/133). Pleural abnormalities were more common in patients who had pleurodesis (101/133, 76%) than in those who had not (47/125, 38%) and were more prevalent on the operated side than on the unoperated side of those 68 patients who had unilateral pleurodesis. The frequencies of findings for the group without pleurodesis versus the group with pleurodesis were pleural thickening (26% vs 65%), effusion (10% vs 13%), loculated effusion (2.4% vs 11%), pneumothorax (1.6% vs 10%), areas of high attenuation (1.6% vs 23%), and mass (0.8% vs 14%), respectively. Areas of high attenuation in the pleura were present in all types of pleurodesis (mechanical, 8%; chemical, 13%; talc, 40%) and in two patients who had had repeated thoracentesis or pleurectomy. Pleural masses were present in patients who had had all types of pleurodesis (mechanical, 10%; chemical, 9%; talc, 24%) and in one patient who had had thoracentesis and thoracostomy; the masses commonly enhanced and did not change in size over time.

CONCLUSION. Pleural abnormalities are common in patients with LAM as complications of the disease itself and as sequelae of pleurodesis and other pleura manipulations. Pneumothorax and pleural effusion result from the underlying pathophysiology of LAM, whereas areas of high attenuation and masses develop after all types of pleurodesis and other manipulations of the pleura (i.e., thoracentesis, thoracostomy).

Keywords: CT, lung diseases, lymphangioleiomyomatosis, pleura, pleurodesis

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Lymphangioleiomyomatosis (LAM) is a rare idiopathic disease that most commonly affects women and results from the accumulation of abnormal smooth-muscle cells in the lymphatics. Common thoracic findings are lung cysts, pneumothorax, and chylous pleural effusion. Exertional dyspnea and pneumothorax are the major presenting complaints [1–3]. Recurrent pneumothorax and chylous pleural effusion may cause restrictive pulmonary dysfunction requiring pleurodesis in up to 54% of patients with LAM [1]. Because of the high frequency of pleurodesis in patients with LAM, an awareness of the pleural findings after pleurodesis is essential for the correct interpretation of pleural abnormalities in these patients.

Because the imaging literature on this topic is limited, we describe here the spectrum and prevalence of pleural findings on CT in 258 patients with LAM with and without pleurodesis. In the patients with pleurodesis, we analyze the relationship between the pleural findings and the type of pleurodesis performed.

Materials and Methods

The study protocol and consent documents were approved by the institutional review board of the National Heart, Lung, and Blood Institute. Our institution is a large referral center currently studying the natural history of LAM. Written informed consent was obtained from all study participants. This study includes 258 patients referred to our institution (all women; age range, 23–77 years; mean, 44 years) with pulmonary LAM evaluated at our institution between March 1996 and June 2003. The diagnosis of LAM was established by lung biopsy in 186 patients and biopsy of abdominopelvic masses in 11 patients. Sixty-one patients did not have tissue biopsy but had classic clinical findings (recurrent spontaneous pneumothorax, pleural effusions, or both) and pulmonary CT findings (diffusely scattered thin-walled lung cysts). We have previously reported some of the pleural findings (without correlation to type of pleurodesis) in 37 of these patients [4].

CT of the Chest

Two hundred forty-one patients underwent enhanced CT of the chest performed on a HiSpeed Advantage, CTi, or LightSpeed scanner (GE Healthcare). The images were obtained using 5- to 10-mm collimation at end inspiration after injection of 120 mL of IV contrast material (iopamidol 61% [Isovue 300, Bracco Diagnostics]) with the patient supine. Seventeen patients did not receive IV contrast material either because of a history of allergic reactions or because of poor renal function.

Image Analysis

An experienced board-certified radiologist, aware of the diagnosis of LAM, reviewed the CT images of the chest obtained in all 258 patients. Pleural abnormalities assessed included pneumothorax, effusion, pleural thickening (uniform increase in the width of pleura), calcification (areas of high attenuation [i.e., > 90 H]), mass (focal, round bulge of soft tissue attenuation [> 5 H] indenting the lung), and loculated effusion (focal bulge of water attenuation [0–5 H] indenting the lung) [5]. Rounded areas of parenchymal consolidation adjacent to abnormal pleura were recorded as round atelectasis.

In patients with pleural masses, we measured with electronic calipers the maximum diameter of the mass perpendicular to the pleural surface. In those patients with unenhanced and enhanced studies, we recorded the difference in attenuation of the mass (in Hounsfield units) between the enhanced and unenhanced images. A mass was categorized as enhancing if there was an increase in attenuation of 15 H or more between the enhanced and unenhanced images. We recorded the time interval between the date of the initial screening CT examination at our institution and the date of pleurodesis and the date of the most recent follow-up CT examination. We also recorded, when present, any change in the size of the pleural mass between the initial and the most recent follow-up CT examinations and described it as stable, decreased, or increased.

In patients with areas of high attenuation in the pleura, we measured with electronic calipers the thickness (maximum diameter perpendicular to the pleural surface) and the attenuation in Hounsfield units. The location of the area of high attenuation was correlated with the side of known pleurodesis, and the shape was categorized as focal plaque (punctate or coarse high-attenuation material) or continuous plaque (linear high-attenuation material that follows the outline of the pleural surface).

Medical History

The patients were interviewed for admission to the protocol, and their medical records were reviewed. We recorded any history of pleurodesis and the type of pleurodesis performed (talc, chemical, mechanical, or a combination of these).

Statistical Analysis

The prevalence of each of the pleural findings in the 133 patients who had had pleurodesis was compared with the prevalence in the 125 patients who had not had pleurodesis (chi-square test). Also, to control for potential confounding factors, we performed a matched analysis on the results from the 68 patients who had had unilateral pleurodesis; specifically, the prevalence of each pleural finding on the operated side was compared with the prevalence on the nonoperated side (McNemar test). The prevalences of pleural findings were compared for mechanical, chemical, and talc pleurodesis (chi-square test). The correlation between the degree of enhancement (enhanced attenuation [H]–unenhanced attenuation [H]) and the thickness of the pleural masses was assessed (Pearson's correlation coefficient [R]).

Results

One hundred forty-eight (57%) of the 258 patients had one or more pleural abnormalities on CT: pleural thickening in 117 (45%), pleural effusion in 28 (11%), loculated effusion in 17 (7%), pneumothorax in 15 (6%), areas of high attenuation in 32 (12%), and mass in 20 (8%) (Table 1 and Figs. 1–3).

One hundred thirty-three (52%) of 258 patients had had pleurodesis (unilateral, 68/133; bilateral, 65/133). The prevalences of the types of pleurodesis performed were as follows: mechanical in 40 patients (30%), talc in 25 (19%), chemical in 23 (17%), a combination of procedures in 38 (29%), and unknown or not recorded in seven (5%).

In both the patient-by-patient analysis and the matched analysis, pleural abnormalities were more common in the presence of a previous pleurodesis. The respective prevalences of pleural abnormalities for the 133 patients who had had pleurodesis and the 125 who had not and the levels of statistical significance of the differences were as follows: pleural thickening (65% vs 26%, $p < 0.001$), effusion (13% vs 10%, $p = 0.7$), loculated effusion (11% vs 2.4%, $p = 0.13$), areas of high attenuation (23% vs 1.6%, $p < 0.001$), and mass (14% vs 0.8%, $p < 0.001$) (Table 1). Every type of pleural abnormality (effusion, loculated effusion, pneumothorax, areas of high attenuation, and mass) was found with each type of pleurodesis (mechanical, chemical, talc) (Table 1).

TABLE 1: Prevalence of Pleural Abnormalities in Patients with Lymphangioleiomyomatosis With and Without Pleurodesis

Pleural Abnormality	Total No. (%) of All Patients (n = 258)	No Pleurodesis (n = 125)	Pleurodesis (n = 133)	Type of Pleurodesis (n = 133)				
				Mechanical (n = 40)	Talc (n = 25)	Chemical (n = 23)	Combination (n = 38)	Unknown (n = 7)
Thickening	117 (45)	33 (26)	86 (65)	20 (50)	18 (72)	17 (74)	29 (76)	2 (29)
Mass	20 (8)	1 (0.8)	19 (14)	4 (10)	6 (24)	2 (9)	7 (18)	1 (14)
Calcification	32 (12)	2 (1.6)	30 (23)	3 (8)	10 (40)	3 (13)	14 (37)	3 (43)
Effusion	28 (11)	13 (10)	17 (13)	3 (8)	5 (20)	3 (13)	6 (16)	0
Loculated effusion	17 (7)	3 (2.4)	14 (11)	7 (18)	4 (16)	2 (9)	1 (3)	1 (14)
Pneumothorax	15 (6)	2 (1.6)	13 (10)	3 (8)	3 (12)	3 (13)	5 (13)	0
None	110 (43)	78 (62)	32 (24)	10 (25)	6 (24)	8 (35)	8 (21)	0
Total	258	125 (48)	133 (52)	40 (30)	25 (19)	23 (17)	38 (29)	7 (5)

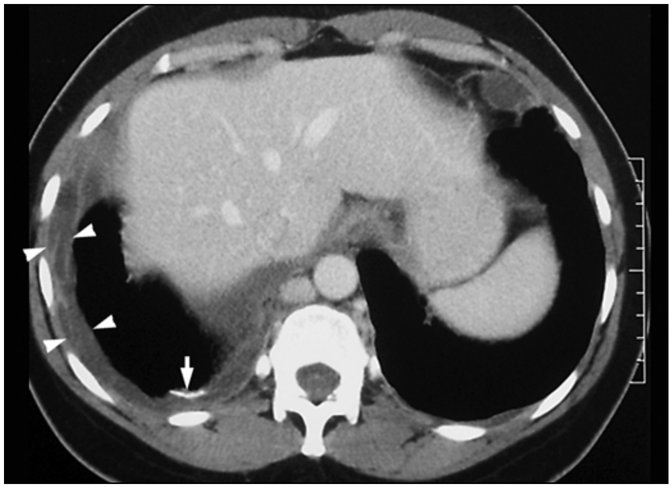

Fig. 1—39-year-old woman who had had right empyema, right thoracentesis, and right thoracoscopic biopsy (*arrow* on surgical clip) but no previous pleurodesis. Transverse contrast-enhanced CT image through lung bases shows extensive right pleural thickening (*arrowheads*).

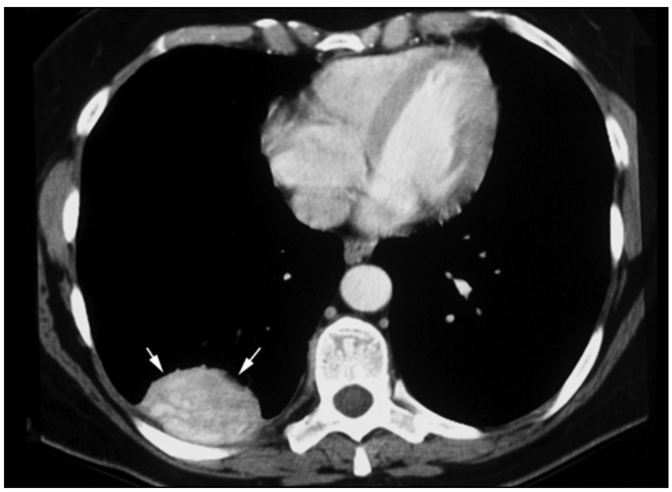

Fig. 2—49-year-old woman who had had right chemical pleurodesis. Transverse contrast-enhanced CT image through lung bases shows large enhancing right pleural mass (*arrows*).

Fig. 3—41-year-old woman who had had bilateral talc pleurodesis. Transverse contrast-enhanced CT image through lung bases shows extensive bilateral pleural thickening and bonelike calcification (360–680 H) (*arrows*) in right lung base.

Similarly, in the 68 patients who had had unilateral pleurodesis, the prevalences of pleural abnormalities were greater on the operated side than on the unoperated side: pleural thickening (53% vs 9%, $p < 0.001$), effusion (3% vs 1%, $p = 1.0$), loculated effusion (7% vs 3%, $p = 0.4$), pneumothorax (3% vs 0%, $p = 0.5$), areas of high attenuation (15% vs 1%, $p = 0.008$), and mass (9% vs 1%, $p = 0.125$) (Table 2).

Twenty patients had pleural masses (Table 3). These masses ranged in size from 0.8 to 3.7 cm in maximal thickness. The pleural masses enhanced in 13 (76%) of 17 patients that had had both unenhanced and enhanced studies. There was negligible correlation between the thickness of the masses and the degree of enhancement ($R^2 = 0.13$). Nineteen of the 20 patients with pleural masses had had pleurodesis; the other patient had had thoracentesis and thoracostomy for recurrent chylous pleural effusion (Fig. 4). The time interval between the date of the initial screening CT at our institution and the date of the pleurodesis in the 19 patients with pleural masses after pleurodesis was between 3 months and 12 years (mean, 2.7 years). Eighteen of the 19 patients with pleural masses after pleurodesis had follow-up studies. The length of follow-up after the date of the initial screening CT at our institution was 1–6 years (mean, 3.4 years). During follow-up, the masses remained stable in 15 (83%) of 18 patients, decreased in size in three (17%) of 18 patients, and increased in size in none (Table 3).

Thirty-two patients had areas of high attenuation in the pleura. These areas ranged in thickness from 0.3 to 2.2 cm and in attenuation from 90 to 3,070 H (Fig. 5). The shape was focal plaque (16/32, 50%), continuous plaque (9/32, 28%), or both (7/32, 22%). Thirty of the 32 patients had had pleurodesis. Areas of high attenuation in the pleura were seen with all three types of pleurodesis (talc, mechanical, and chemical); however, their prevalence was greater ($p = 0.01$) with talc (40%) than with chemical or mechanical pleurodesis (13% and 8%, respectively). Two patients had areas of high attenuation in the pleura without a history of pleurodesis; one of these had had several thoracentesis procedures, and the other had had pleurectomy complicated by empyema and bronchopleural fistula.

Three patients had rounded lung consolidations adjacent to abnormal pleura with associated peripheral bronchial structures consistent with round atelectasis (Fig. 6).

TABLE 2: Comparison of Pleural Abnormalities in the Operated Versus the Unoperated Side of the Thorax in 68 Patients with Unilateral Pleurodesis

Pleural Abnormality	No. (%) of Patients	
	Operated Side of Thorax (Pleurodesis)	Unoperated Side of Thorax (No Pleurodesis)
None (normal)	19 (28)	47 (69)
Thickening	36 (53)	6 (9)
Calcification	10 (15)	1 (1)
Effusion	2 (3)	1 (1)
Loculated effusion	5 (7)	2 (3)
Mass	6 (9)	1 (1)
Pneumothorax	2 (3)	0

Discussion

LAM is caused by atypical smooth-muscle cell (LAM cell) proliferation in the lymphatics. Hyperplasia of LAM cells in the bronchial wall lymphatics causes obstruction and air trapping distal to the small airways resulting in the development of lung cysts [6]. The classic triad of radiographic findings in LAM includes interstitial lung disease, recurrent pneumothorax, and chylous pleural effusion. The interstitial changes described on chest radiographs actually result from superimposition of parenchymal cysts, which are a hallmark of this disease and which are best shown with CT [2].

Spontaneous pneumothorax results from rupture of lung cysts causing air to escape into the pleural space. It occurs in about 40% of patients with LAM over the course of the disease and is usually managed after the second episode with open thoracotomy and pleurodesis [1]. The prevalence of pneumothorax in our study was much lower (6%) than previously reported; this discrepancy is because we assessed prevalence at the time of initial presentation to our institution—rather than the cumulative incidence over the course of the disease—and because more than half of the patients in our study group had had pleurodesis to prevent pneumothorax.

Pleural effusions usually result from leakage of chyle from abnormal lymphatics. Although patients may be asymptomatic, many develop dyspnea, cough, and chest pain [7, 8]. Treatments include thoracentesis, pleurodesis, pleural stripping, and placement of a pleuroperitoneal shunt [7–12].

It is important for the radiologist to be aware of the sequelae of pleurodesis given the common use of this procedure not only in patients with LAM but also in patients with other disease processes (i.e., patients with recurrent neoplastic pleural effusions) [13].

TABLE 3: Pleural Mass Size, Enhancement, Time Interval Between Pleurodesis and Initial CT, Length of Follow-Up, and Change in Appearance at Follow-Up

Patient No.	Size of Mass (cm)	Type of Pleurodesis	Attenuation of Mass (H)		Enhance	Interval Between Surgery and CT (yr)	Length of Follow-Up (yr)	Appearance at Follow-Up
			Before Contrast Administration	After Contrast Administration				
1	2.4	Talc	15	20		1	5	Stable
2	3.7	Chemical	81	130	Yes	2	6	Stable
3	2.9	Mechanical	18	23		9	4	Stable
4	1.4	Mechanical	32	96	Yes	0.25	5	Decrease
5	2.7	Combination	82	111	Yes	3	3	Decrease
6	2.8	Mechanical	NA	17		1	4	Stable
7	1.5	Talc	50	97	Yes	4	5	Stable
8	2.5	Talc	35	42		3	3	Stable
9	1.5	Talc	30	140	Yes	1	0	
10	1.1	Chemical	22	87	Yes	3	3	Stable
11	1.4	Combination	NA	94		2	3	Stable
12	1.4	Combination	47	105	Yes	1	3	Stable
13	2.5	None	49	78	Yes	0	3	Stable
14	1.0	Unknown	NA	78		1	0	
15	1.9	Talc	52	67	Yes	2	3	Stable
16	2.5	Mechanical	30	31		0.25	2	Stable
17	2.4	Combination	30	47	Yes	4	2	Stable
18	1.4	Combination	60	90	Yes	0.5	3	Stable
19	1.4	Talc	55	87	Yes	2	1	Stable
20	0.8	Combination	68	95	Yes	12	2	Decrease

Note—NA = not available.

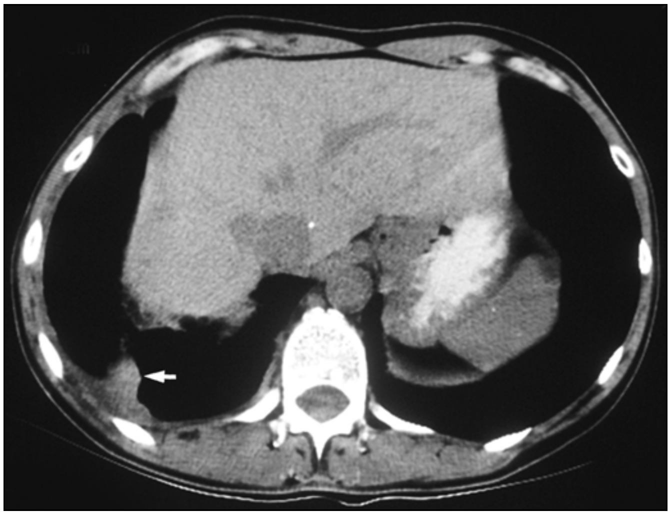

Fig. 4—44-year-old woman with no history of pleurodesis but had had thoracentesis and thoracostomy for recurrent chylous pleural effusions. Transverse unenhanced CT image through lung bases shows right pleural mass (*arrow*).

Fig. 5—35-year-old woman who had had bilateral chemical pleurodesis and left talc pleurodesis. Transverse contrast-enhanced CT image through lung bases shows left pleural thickening and areas of increased-attenuation material (90–167 H) (*arrows*) in pleura that are less dense than expected for bone.

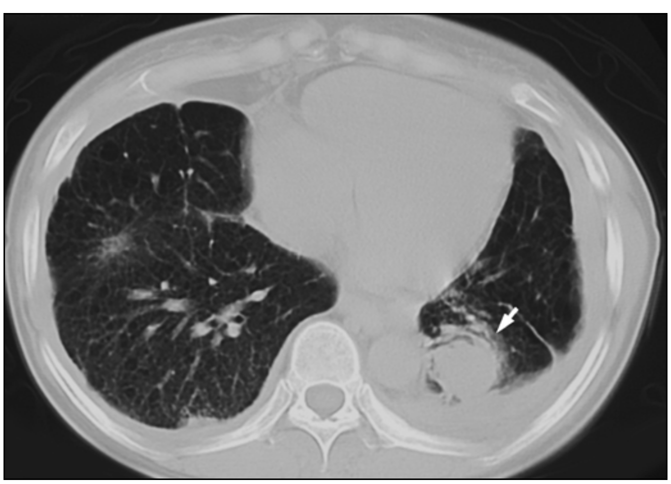

Fig. 6—40-year-old woman who had had right mechanical and left chemical pleurodesis. Transverse contrast-enhanced CT image through lung bases shows round parenchymal consolidation (*arrow*) in left lung base adjacent to abnormal pleura consistent with rounded atelectasis and bilateral pleural thickening.

During pleurodesis, the parietal and visceral pleura are adhered to one another, thereby obliterating the pleural space and preventing the accumulation of air or fluid within it. Pleurodesis may be performed by installation of talc or other sclerosing agent into the pleural cavity (chemical pleurodesis) or by surgical abrasion of the pleura with a dry gauze sponge (mechanical pleurodesis) [14]. The effectiveness of pleurodesis derives from the pleuritis produced by chemical irritation or mechanical abrasion. This inflammatory reaction results ultimately in pleural fibrosis [15]. The distribution and pattern of the pleural fibrosis are variable. In most patients, uniform pleural thickening develops, whereas in some patients focal masses develop. Pleural fibrosis also accounts for the increased frequency of loculated pleural effusion observed in patients after pleurodesis.

Since 1935, talc ($3MgO–4SiO_2–H_2O$) has been instilled into the pleural space to treat recurrent pneumothoraces and effusions. Talc remains the most common sclerosing agent for pleurodesis and can be administered as a slurry by chest tube or by poudrage at the time of thoracoscopy [16]. Complications attributed to talc pleurodesis include increased risk of mesothelioma and adult respiratory distress syndrome [17, 18]. The development of mesothelioma has been attributed to the asbestos in unpurified talc [17]. The talc now used for pleurodesis is purified and free of asbestos [19]. The risk of development of adult respiratory distress syndrome has been found to be dependent on the dose of talc administered [18]. Adult respiratory distress syndrome is almost completely eliminated by using a dose of 2 g or less of talc [18, 20].

A number of other sclerosing agents have been used for chemical pleurodesis. These include tetracycline, doxycycline, and bleomycin. Tetracycline is a safe and effective (77% response rate) agent; however, the IV form of this drug used for sclerotherapy is no longer manufactured in the United States [10, 20]. Doxycycline, a tetracycline analogue, has a similar success rate but may require repeated doses to achieve response in as many as 72% of patients [21, 22]. Bleomycin, an antineoplastic agent, has a 54% response rate, but adverse effects such as nausea, vomiting, bone marrow suppression, rash, and diarrhea and high cost have limited its use [8, 9].

Previous reports have described areas of focal high attenuation in the pleura after talc pleurodesis; some have stated that they are specific for talc [23–27]. Our results expand on this knowledge. In our series, focal areas of high attenuation in the pleura follow all types of pleurodesis; are more prevalent after talc pleurodesis (40%) than after other types of pleurodesis that do not use talc (13% and 8% with chemical and mechanical pleurodesis, respectively); and are also seen in some patients who have not had pleurodesis but have had other pleural manipulations. Thus, these areas of high attenuation in the pleura cannot be attributed solely to deposition of talc; rather, they may in addition be caused by dystrophic calcification of the inflamed pleura after installation of talc and other sclerosing agents and pleural manipulation.

Pleural masses after talc pleurodesis have been reported in two prior case reports [28, 29]. Williams et al. [28] reported an apical pleural mass that developed after talc pleurodesis and had CT attenuation characteristics of a cyst with a calcified capsule. Ahmed and Shrager [29] reported a calcified anterior mediastinal mass that proved to represent a giant talc granuloma after resection. We observed in our series solid pleural masses in 19 (14%) of 133 patients developing after all types of pleurodesis (chemical, mechanical, and talc pleurodesis). We also observed a pleural mass in a patient who did not have pleurodesis but had thoracentesis for treatment of recurrent pleural effusion and chest tube placement for treatment of pneumothorax.

In this series, contrast enhancement was useful in distinguishing solid pleural masses from loculated effusions. A majority (76%) of the pleural masses in this series enhanced; this finding is important because an enhancing pleural mass may be misdiagnosed as mesothelioma or pleural metastasis and may prompt biopsy. We propose that pleural masses that result from pleurodesis and other pleural manipulations result from the accumulation of fibrotic tissue secondary to the postsurgical inflammatory reaction during the process of healing. This fibrotic tissue may enhance depending on the amount of vascular granulation tissue in it. All pleural masses in this series remained stable or decreased in size in the 1- to 6-year follow-up period. Thus, enhancing pleural masses—even when associated with pleural calcification—that develop after pleurodesis in patients with LAM do not require follow-up because their cause is most likely benign. However, in patients with cancer who have had pleurodesis as a palliative procedure for malignant pleural effusion, the development of pleural masses may represent metastasis.

Pleural abnormalities are common in patients with LAM as complications of the disease itself and as sequelae of pleurodesis and other pleural manipulations. Pneumothorax and pleural effusion result from the underlying pathophysiology of LAM, whereas areas of high attenuation in the pleura and masses develop after all types of pleurodesis and other pleural manipulations (thoracentesis, thoracostomy). Solid pleural masses commonly enhance on CT but do not change in size over time. An awareness of this is important to prevent unnecessary biopsy to exclude pleural malignancy such as mesothelioma or pleural metastasis.

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