celecoxib and erlotinib therapy in a patient with RRP whose disease was refractory to antiviral (cidofovir) therapy. The effectiveness of this intervention in this patient supports the consideration of the regimen in clinical trials that assess this combination in patients with refractory disease.

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Utility of [¹⁸F]2-Fluoro-2-Deoxyglucose-PET in Sporadic and Tuberous Sclerosis-Associated Lymphangioliomyomatosis

Lisa R. Young, MD; David N. Franz, MD;
Preeti Nagarkatte, MD; Christopher D. M. Fletcher, MD;
Kathryn A. Wikenheiser-Brokamp, MD, PhD;
Matthew D. Galsky, MD; Thomas C. Corbridge, MD, FCCP;
Anna P. Lam, MD; Michael J. Gelfand, MD;
and Francis X. McCormack, MD, FCCP

Mutations in tuberous sclerosis complex (TSC) genes are associated with dysregulated mammalian target of rapamycin (mTOR)/Akt signaling and unusual neoplasms called perivascular epithelioid cell tumors (PEComas), including angiomyolipomas (AMLs) and lymphangioliomyomatosis (LAM). Tools that quantify metabolic activity and total body burden of AML and LAM cells would be valuable for the assessment of disease progression and the response to therapy in patients with TSC and LAM. Our hypothesis was that constitutive activation of mTOR in LAM and AML cells would result in increased glucose uptake of [¹⁸F]2-fluoro-2-deoxyglucose (FDG) on PET scanning, as has been suggested by a single prior case report. After institutional review board approval, FDG-PET scanning was performed in six LAM patients. Six additional LAM patients underwent FDG-PET scanning for clinical evaluation of suspected malignancy. Pleural uptake related to prior therapy was identified in four individuals with a remote history of talc pleurodesis. Focal increased uptake was observed in a supraclavicular lymph node in a patient with Hodgkin lymphoma and in a lung nodule in a patient with a biopsy-documented primary lung adenocarcinoma. In one TSC-LAM patient with a biopsy-documented malignant uterine PEComa, robust uptake was noted in metastatic nodules in the lung but not in the LAM-involved lung parenchyma or the patient's massive abdominal lymphangioliomyomas. No abnormal uptake was identified in the AMLs or LAM lesions in any patients. This pilot study suggests that FDG-PET scans are negative in patients with benign PEComas and therefore are not likely to be useful for estimating the burden of disease in patients with TSC or LAM, but that FDG-PET scans can be used to identify or exclude other neoplasms in these patients. (CHEST 2009; 136:926–933)

Abbreviations: AML = angiomyolipoma; FDG = [¹⁸F]2-fluoro-2-deoxyglucose; HMB-45 = human melanoma black-45; LAM = lymphangioliomyomatosis; LUL = left upper lobe; mTOR =

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Affiliations: From the Department of Pulmonary, Critical Care, and Sleep Medicine (Drs. Young and McCormack), University of Cincinnati College of Medicine, Cincinnati, OH; the Departments of Pulmonary Medicine (Dr. Young), Neurology (Dr. Franz), Pathology & Laboratory Medicine and Pulmonary Biology (Dr. Wikenheiser-Brokamp), and Radiology (Dr. Gelfand), Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Northeast Nephrology (Dr. Nagarkatte), Joliet, IL; the Department of Pathology (Dr. Fletcher), Brigham and Women's Hospital, Boston, MA; Comprehensive Cancer Centers of Nevada (Dr. Galsky), Las Vegas, NV; and the Department of Pulmonary and Critical Care (Drs. Corbridge and Lam), Northwestern University, Chicago, IL.

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Correspondence to: Francis X. McCormack, MD, Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati, 231 Albert Sabin Way, ML 0564, Cincinnati, OH 45267; e-mail: Frank.McCormack@uc.edu

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mammalian target of rapamycin; PEComa = perivascular epithelioid cell tumor; S-LAM = sporadic lymphangioleiomyomatosis; SUV = standardized uptake value; TSC = tuberous sclerosis complex

Lymphangioleiomyomatosis (LAM) is a progressive cystic lung disease that predominantly affects young women. The most common clinical features of LAM are dyspnea on exertion, recurrent pneumothoraces, and chylous effusions. LAM is characterized histologically by diffuse infiltration of the lung parenchyma with benign smooth muscle-like cells and the formation of cysts that vary in size from a few millimeters to several centimeters. Although LAM occurs sporadically in patients without evidence of systemic genetic disease (called *sporadic LAM* [S-LAM]), it also occurs in up to 40% of women with tuberous sclerosis complex (TSC).¹⁻³

TSC is an autosomal-dominant syndrome, arising from genetic mutations involving either the *TSC1* gene on chromosome 9⁴ or the *TSC2* gene on chromosome 16.⁵ Hamartomatous growths develop in patients with TSC in multiple organs, including the skin, eye, kidney, lung, and CNS. Somatic mutations in *TSC2* genes have recently been identified in smooth muscle-rich lesions involving the lung, lymphatics, and kidneys of patients with S-LAM. The respective protein products of *TSC1* and *TSC2*, hamartin and tuberlin, form a complex that functions to regulate cell growth and the PI3K/Akt/mTOR/S6K pathway, which controls multiple cellular processes, including Glut1 (glucose transporter) function and nutrient acquisition.⁶

Glucose uptake is regulated by a signaling cascade that is triggered by the binding of insulin to the insulin

Table 1—Characteristics of Study Subjects

Subject No.	FDG-PET Scan Indication	Age, yr	S-LAM or TSC-LAM	Prior Lung Biopsy	Prior Pleural Disease and Interventions	CT Scan Findings (in Addition to Lung Cysts)	FDG-PET Scan Findings
1	Research	46	S-LAM	Yes	None	Left renal AML, 3 cm	Normal study
2	Research	53	TSC-LAM	No	None	Bilateral renal AMLs, > 4 cm, tortuous	Normal study
3	Research	47	S-LAM	Yes	Pneumothorax	Pelvic lymphangioleiomyoma status post resection renal; AML	Normal study
4	Research	60	TSC-LAM	Yes	Pneumothorax; chylothorax talc pleurodesis	Liver AMLs, multiple, 1–2 cm	Peripheral pleural uptake bilaterally
5	Research	55	S-LAM	Yes	Pneumothorax; talc pleurodesis	Left renal AML, > 2 cm; Lymphangioleiomyoma	Uptake in pleura/chest wall
6	Research	63	S-LAM	Yes	Bilateral pneumothorax	Left renal AML	Possible rectosigmoid uptake; subsequent normal colonoscopy
7	Malignant uterine PEComa	36	TSC-LAM	No	Chylothorax; talc pleurodesis	Prior bilateral nephrectomy; Lymphangioleiomyoma; mesenteric and hilar LAD; multiple lung nodules	RUL nodule, SUV 7; RML nodule, SUV 3; multiple nodules without uptake; right hilar node, SUV 2.8; pleural uptake
8	Skin melanoma	40	TSC-LAM	No	Bilateral pneumothorax; talc pleurodesis	Bilateral renal AMLs, multiple, very large (> 8 cm)	Uptake in left pleural plaques
9	LUL mass: adenocarcinoma	50	S-LAM	Yes	Pneumothorax	LUL lung mass, 2 × 2.4 cm; Prevascular nodes > 1 cm; Liver AMLs	LUL mass, SUV 3.5; bilateral pleural nodular thickening with increased activity
10	RLL lung nodules	53	S-LAM	Yes	Chylothorax	Left renal AML, 1.2 cm; Mediastinal adenopathy; Multiple RLL nodules > 1 cm	8-mm focus in uterus, SUV 4.8; no other abnormal uptake
11	Hodgkin lymphoma	27	S-LAM	No	None	Cervical and mediastinal adenopathy; Retroperitoneal lymphangioleiomyoma	Avid FDG uptake in cervical and mediastinal lymph nodes; no uptake in abdominal lesions
12	Pelvic adenopathy	42	S-LAM	Yes	None	Retroperitoneal lymphadenopathy	No abnormal uptake

RLL = right lower lobe.

FIGURE 1. Negative FDG-PET scan findings in renal AMLs. Imaging of subject 2 reveals bilateral, large, amorphous, renal AMLs that expand the kidneys and distort the collecting system (A, arrows), but are negative on the FDG-PET scan (B, arrow [note that tracer is seen in renal collecting system only]). An MRI of subject 8 demonstrates bilateral large renal AMLs (C and D), which were negative on the FDG-PET scan (not shown).

FIGURE 2. Absence of FDG uptake in a lymphangioliomyoma. CT imaging findings in subject 10 included a large left chylothous effusion (A, arrow), and numerous lung cysts, right lower lobe lung nodules, and a large fluid-filled lymphangioliomyoma (B, arrow). C: FDG-PET scan shows no uptake in the lymphangioliomyoma. Compressed lung exhibits low-level uptake superior to the pleural fluid (arrowhead). Normal activity is seen in the displaced right urinary tract and myocardium (dashed arrows). A presumed uterine fibroid tumor (8 mm; arrow) has a maximum SUV of 4.8 (hollow arrow), and clinical follow-up was recommended. No uptake was seen in the lung nodules, which had resolved on a follow-up chest CT scan (not shown).

FIGURE 3. FDG-PET is negative in the lung parenchyma of LAM patients, but abnormal FDG uptake can be seen in the pleura of patients who have undergone prior talc pleurodesis. A: PET-CT scan from subject 8 reveals typical cystic change in the lung and positive FDG uptake consistent with chronic pleural inflammatory reaction after talc pleurodesis (arrow). B and C: subject 5 underwent talc pleurodesis 13 years prior to this FDG-PET scan, which showed uptake in the right pleura and chest wall (arrows).

receptor, autophosphorylation of the tyrosine kinase domain of the receptor, and phosphorylation of members of the IRS family, Shc and Cbl. The phosphatidylinositol 3 kinase pathway is activated, including downstream effectors mTOR and S6K, as well as the PtdIns(3,4,5)P3-dependent protein kinases, ras, the mitogen-activated protein kinase (or MAPK) cascade, Cbl/CAP, and TC10. These pathways act in a concerted fashion to activate glucose metabolism, gene expression, protein synthesis, and the translocation of vesicles containing the glucose transport proteins (*eg*, Glut1 and Glut4) to the cell surface.⁷

Renal angiomyolipomas (AMLs), which are composed of abnormal blood vessels, smooth muscle, and fat cells, occur in 80% of patients with TSC and approximately 30 to 50% of patients with S-LAM.^{3,8} Although AMLs may form distinct isolated growths that can be solitary or multiple, they may also coalesce to form diffuse lesions throughout the kidney and may lead to renal failure. Additionally, AMLs contain tortuous, dysmorphic blood vessels that are prone to spontaneous hemorrhage.

LAM is known to be a low-grade neoplastic process, which despite innocent-appearing cytologic features, is

associated with spread through the lymphatics and tissue destruction. One theory of LAM pathogenesis, supported by genetic evidence for the recipient origin of cells comprising recurrent LAM lesions in lung transplantation patients,⁹ is that smooth muscle cells metastasize to the lung, where they proliferate and progressively replace the normal lung tissue. Through the elaboration of matrix-degrading enzymes or other mechanisms, progressive cystic degeneration and disruption of pulmonary parenchyma occur in the absence of significant inflammation. Shared phenotypic and genotypic characteristics of LAM cells isolated from the lung and renal AML cells, including staining with antibodies to melanocyte-derived antigens (human melanoma black-45 [HMB-45]) and to smooth muscle actin, have led to speculation that AMLs may be a source for metastases in some patients.¹⁰ Alternatively, LAM cells may disseminate from a source in the abdominal and pelvic viscera or axial lymphatics.

LAM and AMLs are members of the perivascular epithelioid cell tumor (PEComa) family of tumors, which are characterized by the coexpression of smooth muscle antigens (*eg*, smooth muscle actin and desmin) and melanocytic antigens (*eg*, HMB-45 and Melan-A).^{11,12} PEComas, including LAM, exhibit evidence of mTOR activation, including increased phosphorylation of S6.¹³ Given the neoplastic nature of the LAM lesion, and the evidence for constitutive activation of the mTOR pathway that controls glucose homeostasis, we postulated that the LAM lesion would exhibit increased metabolic uptake of [¹⁸F]2-fluoro-2-deoxyglucose (FDG) detected by PET scanning. Pandit and Yeung¹⁴ reported a single case with diffuse lung uptake in a LAM patient undergoing FDG-PET scanning for the evaluation of a lung nodule.

We found that LAM and AMLs are FDG-PET scan silent, but that PET scanning can be useful for identifying other neoplasms, such as malignant PEComas, primary lung cancers, and lymphomas, on a background of diffuse infiltrative and cystic lung disease, thoracic and abdominal lymphadenopathy, and cystic lymphangiomyomas in patients with LAM.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board and Radiation Safety Board at Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine. Subjects were recruited from the LAM and TSC clinics at Cincinnati Children's Hospital Medical Center and The University of Cincinnati College of Medicine, and via referral through the Lymphangioleiomyomatosis (LAM) Foundation. Study inclusion criteria included the ability to give informed consent, a negative pregnancy test, and a clinically definite diagnosis of LAM, which was defined as the presence of characteristic cystic lung disease on a chest CT scan and (1) tuberous sclerosis, chylothorax, or radiographic/pathologic documentation of an AML, or (2) biopsy-documented LAM in the lung or lymph node.

FDG-PET scanning was performed in six LAM patients on a research basis. Subjects received an IV injection of 0.100 mCi/kg FDG. Subjects remained still in a quiet room for 45 min and then underwent imaging in the supine position, with tomographic images obtained from the base of the brain to the upper thighs. Images were obtained on a Siemens EXACT or ACCEL scanner (Siemens; Orlando, FL) for 5 min per bed position in the

FIGURE 4. FDG-PET scan identification of a primary lung carcinoma in a patient with LAM. A LAM patient with a primary lung cancer (subject 9) had positive uptake on the FDG-PET scan in the LUL tumor, but not in other LAM disease areas. A PET-CT scan was performed for staging after a needle biopsy revealed a well-differentiated adenocarcinoma in the LUL. The LUL tumor mass (A, white arrow) had an SUV of 3.5 (B and C, arrows). Additionally, there were extensive areas of increased activity throughout the right and left pleura corresponding to nodular pleural thickening (A and B, red arrows). The patient had a history of talc pleurodesis 7 years prior. Follow-up FDG-PET and chest CT scans showed no changes in the pleural abnormalities. The patient had known liver AMLs. No uptake was seen in the liver or in other locations.

three-dimensional mode with a 2-min attenuation collection of transmission data at each bed position for attenuation correction. PET scan images were analyzed visually and quantitatively by calculating the maximum standardized uptake value (SUV) at representative sites of abnormal FDG uptake. Two radiologists independently reviewed the research studies. Clinical FDG-PET scans and accompanying CT scans were also reviewed from an additional six LAM patients who underwent PET imaging for the evaluation of suspected malignancy. Clinical reports were from a nuclear medicine radiologist, and all positive PET scan findings were reviewed by a study radiologist.

RESULTS

Table 1 summarizes the clinical features and imaging findings of the study subjects. Eight of the 12 subjects had sporadic LAM, and four had LAM in the setting of TSC. Six subjects had renal AMLs, two subjects had hepatic AMLs, and four subjects had abdominal lymphangioleiomyomas. All subjects had cystic lung disease consistent with LAM. FDG uptake was not present in any of the renal or hepatic lesions, lymphangioleiomyomas, or in the lung parenchyma (Fig 1, 2). An incidental finding was the presence of pleural uptake (Fig 3, 4), which was observed in four subjects, all of who had a history of pneumothorax and talc pleurodesis.

In contrast to the lack of FDG uptake in benign PEComas, uptake of FDG occurred in malignant lesions

in several cases. Subject 9 had a PET scan performed to evaluate a lung nodule, which ultimately proved to be a lung adenocarcinoma. As shown in Figure 4, the FDG-PET scan revealed increased uptake in the left upper lobe (LUL) tumor but not in other regions of the lung affected by LAM. Another patient with TSC-LAM and polycystic kidney disease (subject 7), who was 7 years status post bilateral nephrectomy and renal transplant, had a malignant uterine PEComa (Fig 5E to G) and multiple spiculated pulmonary nodules discovered during evaluation for lung transplantation. A genotype analysis performed of the patient's peripheral blood revealed a very large gene deletion involving all *TSC2* exons. A FDG-PET scan performed after the hysterectomy showed uptake in some of her pulmonary masses, but no FDG uptake in her multiple abdominal lymph nodes, abdominal cystic lymphangioleiomyomas, or LAM-affected lung tissue (Fig 5, A–D). In this case, the FDG-PET scan revealed that the abdominal masses were most consistent with benign rather than malignant PEComas, a finding that had important prognostic implications for the patient. After modification of her renal immunosuppressive regimen to include sirolimus, there was significant reduction in the size of the patient's abdominal masses, and her pulmonary nodules remained stable in size and number over a 15-month follow-up period (not shown). Figure 6 displays

FIGURE 5. Discrimination of benign and malignant PEComas by FDG-PET scan. A TSC-LAM patient with a malignant uterine PEComa and lung nodules had uptake in pulmonary masses but not in abdominal masses or lung tissue on a FDG-PET scan. When this patient (subject 7) was found to have a malignant uterine mass, lung nodules (A, arrow), and large cystic abdominal masses (C, arrows), a widely metastatic uterine sarcoma was suspected. CT/FDG-PET scans performed for staging revealed intense uptake in some, but not all, pulmonary nodules (B and D, arrows) and no uptake in the lung tissue (B) or abdominal cystic lymphangioleiomyomas (C, arrow). Normal activity was present in the myocardium, bladder, and renal collecting system (dashed arrows). Pathology of the uterine lesion revealed marked cellular atypia and an increased number of mitotic figures consistent with a malignant PEComa (hematoxylin-eosin staining, E). Note the diffusely positive staining for desmin (F) and the focal positivity for HMB-45 (G) in a minority of cells. FDG-PET scanning revealed that the abdominal masses were most consistent with benign rather than malignant PEComas, which had important prognostic implications at the time.

a third case where FDG-PET scanning proved to be clinically useful in a patient with LAM. This individual (subject 11) had Hodgkin lymphoma (nodular sclerosing type), based on increased FDG uptake in the supraclavicular and mediastinal lymph nodes, and the biopsy findings for the supraclavicular lymph node. Initially, she was diagnosed and treated for stage IV Hodgkin disease, based on the presence of what were believed to be necrotic retroperitoneal lymph nodes on CT scan (Fig 6B). However, the abdominal masses were negative on staging FDG-PET scan, a chylous effusion developed, and a high-resolution CT scan of the chest revealed cystic changes that were typical for LAM. A percutaneous needle biopsy of the paraaortic retroperitoneal mass revealed a spindle cell neoplasm consistent with LAM, although HMB-45 staining was not demonstrated in the small sample obtained. Her abdominal lymphadenopathy, chylous effusion, and pulmonary cysts were attributed to LAM, and her staging was revised based on this information. Finally, a patient with biopsy-documented LAM (subject 12) was advised by her gynecologic consultant to have her enlarged retroperitoneal lymph nodes biopsied to rule out ovarian carcinoma or lymphoma (Fig 6C). The PET scan findings were negative except for focal uptake in

the ovary (not shown), possibly consistent with ovulation, and the biopsy was deferred.

DISCUSSION

This pilot study indicates that FDG-PET scanning is negative in patients with benign PEComas, including LAM and AMLs. Therefore, FDG-PET is not likely to be useful for the estimation of burden of disease in patients with TSC or LAM, or for following the response to therapy. It is important to note that prior talc pleurodesis may produce abnormal FDG uptake in the pleura in patients with LAM, presumably by inducing chronic pleural inflammation. The cases presented demonstrated that FDG-PET scanning can be clinically useful for the identification of malignancies on the complex background of cystic, nodular, and lymphangitic lesions that are common in patients with TSC and LAM and can lead to modifications in staging and therapeutic approach.

The uptake of FDG by cells is dependent on three key factors: tumor blood flow; glucose transport; and glycolytic rate. In LAM and TSC, the molecular defect is predicted to result in increased glucose transporter expression and utilization. Potential explanations for the lack of increased

FIGURE 6. Lack of FDG uptake suggests the association of abdominal lymphadenopathy with LAM rather than coincident neoplastic processes. Increased uptake in supraclavicular lymph nodes (A, arrows) was seen in this patient (subject 11) with biopsy-documented Hodgkin disease (nodular sclerosing type). She was presumed to have stage IV disease based on the presence of abdominal masses consistent with lymph nodes with hypodense centers on CT scan that displaced bowel and bladder (black arrow, B). However, these masses were negative on a FDG-PET scan, transcutaneous needle biopsy revealed a spindle cell neoplasm believed to be consistent with LAM, and a high-resolution CT scan of the chest revealed cystic changes that were typical for LAM (not shown). The diagnosis of LAM was made after the patient had completed her course of chemotherapy and radiation therapy. Her staging was revised based on this information. LAM was diagnosed in another subject (subject 12) by video-assisted thoracoscopic surgery lung biopsy after the subject presented with hemoptysis and cystic lung disease. Pelvic lymphadenopathy (C, arrow) was believed to be attributable to LAM, rather than another neoplasm, based on lack of uptake on FDG-PET scan (not shown).

uptake of FDG during PET scanning in LAM patients include the limitations of sensitivity of imaging detection because of the diminutive size of LAM lesions or the dilution of the signal in the lung due to the sparse and diffuse nature of LAM cell infiltration throughout the interstitium. Another possible explanation for the lack of increased uptake of FDG was provided in a recent study by Jiang et al,⁶ which reported that mTOR activity is insufficient for the induction of increased glycolysis in tumors and that constitutive mTOR activity paradoxically down-regulates glucose transporter trafficking. They found that FDG uptake was not increased in the AMLs of three patients with TSC, which is consistent with our findings. The current study further demonstrates FDG-PET scan negativity in LAM patients, and the utility of FDG-PET scanning for the identification of other neoplasms in patients with TSC and LAM.

Patients with LAM and TSC often have lymphadenopathy, nodular lesions, and abdominal masses that can raise the specter of superimposed malignancy. In addition, coincidental neoplasms that are unrelated to TSC genetic mutations can develop in TSC and LAM patients. In this

context, knowledge that LAM is PET scan silent can be clinically useful. In case 11, for example, the presence of abdominal masses and lymphadenopathy in a patient with lymphoma was used to determine the staging of her disease and her treatment. She was subsequently discovered to have LAM, and the absence of FDG uptake in her abdominal lesions combined with a needle biopsy that was negative for lymphoma (and cytologically consistent with LAM) proved that her subdiaphragmatic lesions were not associated with her hematologic malignancy and altered her staging. In case 9, FDG uptake in a nodular lesion on the complex background of LAM-involved lung correctly identified the presence of primary lung cancer. In case 12, the lack of FDG uptake in the retroperitoneal lymph nodes of a patient with lung biopsy-documented LAM modified the treatment plan such that transcutaneous needle biopsy of the masses was cancelled. Perhaps the most interesting example is case 7, in which a patient with TSC-LAM and polycystic kidney disease (a contiguous gene deletion syndrome) and a known malignant PEComa of the uterus was found to have increased FDG uptake in metastatic pulmonary nodules more than a year after the

primary tumor was resected. These data suggest that the development of a malignant LAM phenotype is associated with reversal of the negative regulation of glucose transporter trafficking described by Jiang et al.⁶ This patient was told by her oncologist that she had a uterine sarcoma with extensive abdominal spread. The absence of PET scan positivity in her abdomen was more consistent with LAM, as was the marked reduction in the size of these tumors after therapy with sirolimus. The patient was ineligible for lung transplantation based on her metastatic pulmonary disease, but she remained active while receiving oxygen therapy for 15 months, until FDG-PET scan-positive lesions in the liver and abdominal cavity developed.

Recognition that talc pleurodesis can produce abnormal uptake of FDG during PET scanning is important in patients with LAM because approximately 45% of patients with LAM undergo pleurodesis at some point in the course of their disease.¹⁵ Intense and prolonged abnormal FDG uptake has been reported previously^{16–19} after pleurodesis in patients with other forms of chronic lung disease but not in those with LAM. This phenomenon appears to be restricted to talc pleurodesis; we were unable to find reports of FDG-PET scan positivity in patients with a remote history of doxycycline pleurodesis, mechanical abrasion, or pleurectomy. The mechanism of enhanced pleural FDG uptake after talc pleurodesis is not clear, but in one LAM patient with a history of pneumothorax and talc pleurodesis who underwent pleural biopsy to exclude late metastasis of an osteosarcoma, an exuberant foreign-body giant cell reaction with focal necrosis, hyaline fibrosis, and polarizable foreign material was found.²⁰ The FDG-PET scan positivity present in talcomas is likely attributable to the chronic, smoldering inflammatory process associated with these lesions. These data suggest that an FDG-PET scan is useful for the identification, staging, and/or exclusion of more aggressive neoplasms in patients with LAM and TSC.

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