outcome. Therefore, early recognition of sorafenib-induced lung injury is crucial for physicians and patients.

Keywords Sorafenib · Drug-induced lung injury · Interstitial lung disease · Drug-related adverse event · Japanese · Post-marketing surveillance

Introduction

Sorafenib is a small-molecule multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases and interacts with multiple intracellular (CRAF, BRAF, and mutant BRAF) and cell surface (KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β) kinases [1–3]. Sorafenib has been approved for renal cell and hepatocellular carcinoma [4, 5], and clinical studies are in progress for several other types of tumors. Sorafenib was approved in Japan for unresectable and/or metastatic renal cell carcinoma (RCC) in 2008 and for unresectable hepatocellular carcinoma (HCC) in 2009. The major drug-related adverse events (AE) of sorafenib include hand-foot skin reaction, diarrhea, hypertension, and increased pancreatic enzyme levels [4, 5]. Drug-induced lung injury (DLI) was added to the Japanese package insert of sorafenib, along with the issuance and distribution of "Safety information for acute lung injury/interstitial pneumonia" in December 2008 [6], and close monitoring of patients has been ongoing since then.

Chemotherapeutic drugs that most commonly cause DLI include paclitaxel, docetaxel, gemcitabine, and irinotecan [7, 8]. DLI in Japanese patients treated with molecular targeting agents has been the focus of many studies [9]. Among tyrosine kinase inhibitors, gefitinib and erlotinib are associated with an increase in the incidence of DLI in Japanese patients [10–12]. The precise incidence and clinical characteristics of DLI associated with sorafenib have not been reported although the cases of some individual patients have been reported [13]. Here, we investigated the clinical features of Japanese patients with sorafenib-associated lung injury in a post-marketing surveillance setting.

Patients and methods

Patients

The patient flow of the surveillance is shown in Fig. 1. Between April 2008 and March 2011, sorafenib was administered to approximately 13,600 patients (approximately 5,500 for RCC and 8,100 for HCC) within the frame of Special Drug Use Investigation (SDUI). SDUI is a post-marketing surveillance method specific to Japan, performed under the instruction of the Japanese Health Authority (Pharmaceuticals and Medical Device Agency [PMDA]) for investigating safety and efficacy of sorafenib in clinical practice. For sorafenib, an SDUI with all-patient investigation system was required. The institutions participating in the SDUI concluded a contract with Bayer Yakuhin, Ltd. Sixty-two patients with DLI were identified during the above period on the basis of either an AE reported by a physician or by an evaluation of image by a board of experts ("Safety Advisory Board for interstitial lung disease in Nexavar®"; hereafter, "the ILD Ad-board"). For the calculation of reporting frequency, the interim SDUI results of 2,407 patients with RCC and 647 patients with HCC were used [14, 15]. Reported terms were encoded to the Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA-PT).

Collection of clinical information

Clinical information was collected for the initial purpose of reporting AE from Bayer Yakuhin, Ltd. to the Japanese Health Authority.

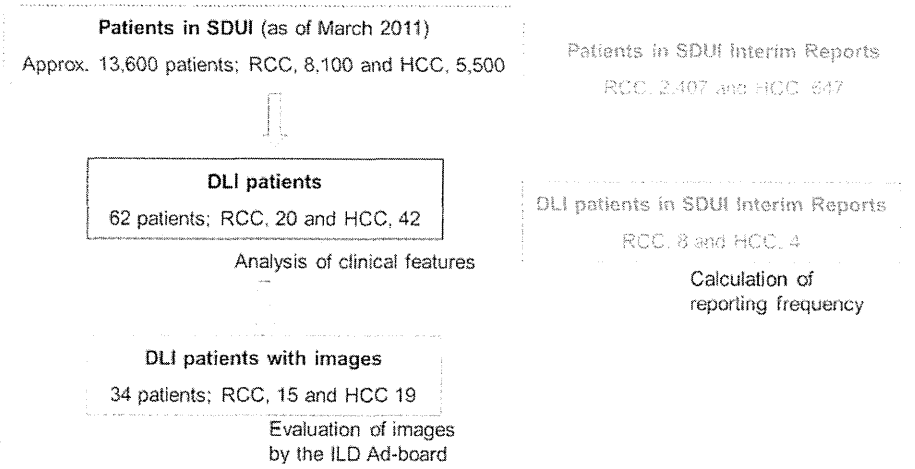

Fig. 1 Breakdown of patients according to SDUI and DLI. *DLI* drug-induced lung injury, *HCC* hepatocellular carcinoma, *ILD Ad-board* ILD Safety Advisory Board, *RCC* renal cell carcinoma, *SDUI* Special Drug Use Investigation

Table 1 Demographics of patients with DLI

	RCC $n = 20$	HCC $n = 42$	Total $n = 62$
Age (years)			
Median (range)	71.5 (50–83)	70 (51–84)	70 (50–84)
Gender			
Male/female	12/8	34/8	46/16
Performance status (ECOG-PS)			
0, 1/2 or over/unknown	16/0/4	37/2/3	53/2/7
Concomitant disease or past history of pulmonary disease			
Chronic type of interstitial pneumonia/pulmonary fibrosis	5	4	9
Other pulmonary disease	2	2	4

ECOG-PS Eastern Cooperative Oncology Group Performance Status

For all patients with DLI, reporting physicians were requested to respond to a special questionnaire. This questionnaire included detailed clinical course, laboratory data and reports of image evaluation, as well as basic information for AE reporting such as patient age, gender, past medical history, concomitant diseases, treatment duration of sorafenib, and concomitant medications. In addition, reporting physicians were requested to provide chest radiograph and/or chest computed tomography (CT) scan. "Fatal" cases included those patients in whom the outcome of DLI was reported as fatal by reporting physicians.

Image interpretation

Imaging data was provided by reporting physicians in the case of 34 patients. In 33 of these patients, conventional CT and/or high-resolution CT were used for evaluation at onset, and in 1 patient, only chest radiograph was used. These images were evaluated as digitized files in Digital Imaging and Communication in Medicine (DICOM) format with anonymization. The members of the ILD Ad-board were requested to independently evaluate these imaging data with DICOM viewer software by referring to clinical information according to a specific evaluation sheet, including preexisting pulmonary conditions, ILD scoring, and image pattern of DLI. ILD scoring indicates the compatibility with ILD in 5 levels, from the score 1 with the finding that ILD can be denied to the score 5 with the finding that ILD is definite. The image patterns were classified as being most consistent with 1 of 2 patterns: diffuse alveolar damage (DAD) or non-DAD [16, 17]. Image patterns demonstrating extensive bilateral ground-glass opacities with or without consolidation and/or architectural distortion, or features suggestive of fibrosis in a predominantly depending distribution were considered as DAD [18, 19]. Case review and final decision of image interpretation were made periodically in a panel discussion including all members of the ILD Ad-board. The conclusions of the ILD Ad-board were conveyed to each reporting physician and to the Japanese Health Authority.

Results

Patient demographics

Patient demographics are listed in Table 1. Among 62 patients with DLI, 20 had RCC and 42 had HCC as underlying disease. Concomitant disease and medical history included chronic type of interstitial pneumonia/pulmonary fibrosis in 9 patients. Other pulmonary diseases included bronchial asthma, emphysema, pleuritis, and history of surgical intervention to the lung.

Reporting frequency

The reporting frequency of DLI was 0.33 % (8/2,407, 4 out of 8 patients had fatal outcome of DLI) for RCC and 0.62 % (4/647, 2 out of 4 patients had fatal outcome of DLI) for HCC according to respective interim reports of SDUI on the basis of clarification of precise number of patients treated with sorafenib. The 8 patients with RCC and 4 patients with HCC are included in the 62 DLI patients among approximately 13,600 sorafenib-treated patients. The reporting frequency described above from interim results of SDUI is considered to be equivalent to the overall accumulation status of DLI patients as of March 2011: 20 among approximately 5,500 patients with RCC, and 42 among approximately 8,100 patients with HCC.

Time to onset

Time to onset, the interval between the start of administration and the onset of DLI, is shown in Fig. 2. Overall,

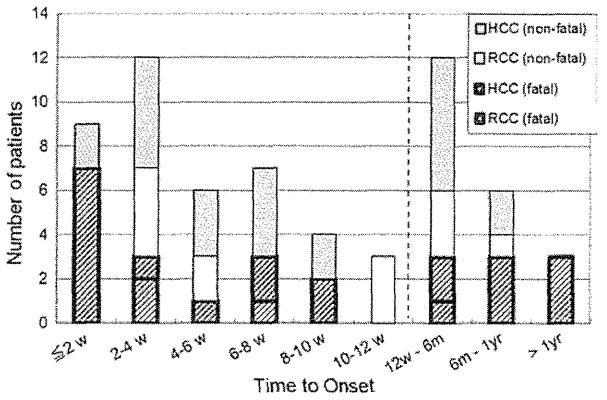

Fig. 2 Time to onset for DLI. *White bars* indicate patients with renal cell carcinoma. *Gray bars* indicate patients with hepatocellular carcinoma. *White shadow* or *gray shadow bars* indicate patients with renal cell carcinoma or hepatocellular carcinoma with a fatal outcome, respectively

Table 2 Treatment for DLI

Treatment for DLI	Number of patients (fatal)		
	RCC $n = 20$	HCC $n = 42$	Total $n = 62$
Steroid pulse therapy	8 (3)	18 (10)	26 (13)
Start on the day or the next day of onset	4 (1)	15 (10)	19 (11)
Start subsequently	4 (2)	1 (0)	5 (2)
No information about the timing of initiation	0 (0)	2 (0)	2 (0)
Other steroid (except pulse therapy)	2 (1)	7 (3)	9 (4)
Other medication (except steroid)	0 (0)	4 (3)	4 (3)
No medication	5 (1)	3 (1)	8 (2)
No information about treatment for DLI	5 (2)	10 (1)	15 (3)
Total	20 (7)	42 (18)	62 (25)

the peak time to onset in all patients was during 2–4 weeks after the start of administration; however, in some patients, DLI occurred more than 6 months after the start of administration. The 9 patients with time to onset within 2 weeks were all HCC patients. Furthermore, a tendency of earlier onset was observed in HCC patients (median 50 days, range 2–289 days) than in RCC patients (median 74 days, range 16–420 days).

Clinical symptoms

Data about clinical signs and symptoms were available in 47 of the 62 patients. Among these 47 patients, dyspnea, cough, and fever, were frequently reported symptoms

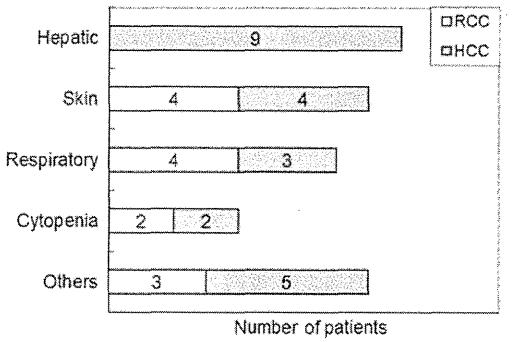

Fig. 3 Other serious drug-related adverse events of sorafenib in patients with DLI

Table 3 Image evaluation by the ILD Ad-board

Image pattern	Number of patients (fatal)		
	RCC $n = 20$	HCC $n = 42$	Total $n = 62$
DAD	8 (5)	10 (7)	18 (12)
Non-DAD	7 (1)	8 (2)	15 (3)
OP	3 (0)	1 (0)	4 (0)
Others	2 (1)	7 (2)	9 (3)
Pre-existing ILD	2 (0)	0 (0)	2 (0)
ILD excluded	0 (0)	1 (0)	1 (0)
Image not available	5 (1)	23 (9)	28 (10)
Total	20 (7)	42 (18)	62 (25)

Pre-existing ILD included asbestosis and chronic type of interstitial pneumonia

DAD diffuse alveolar damage, *ILD* interstitial lung disease, *OP* organizing pneumonia

(in 34, 20, and 15 patients, respectively). Hemoptysis was observed in 2 patients. Five patients were asymptomatic.

Treatment for DLI

Treatment for DLI is shown in Table 2. Among 47 patients for whom information about DLI treatment was provided, 35 received steroid administration, including steroid pulse therapy (intravenous high-dose steroid therapy) in 26 patients. Of the 26 patients receiving steroid pulse therapy, 19 were treated with pulse therapy on the day or the next day of the onset. Medications besides steroids included antibiotics and neutrophil elastase inhibitors.

Other serious drug-related AEs of sorafenib in patients with DLI

Sorafenib-related serious AEs reported in addition to DLI are shown in Fig. 3. Hepatic disorder was the most

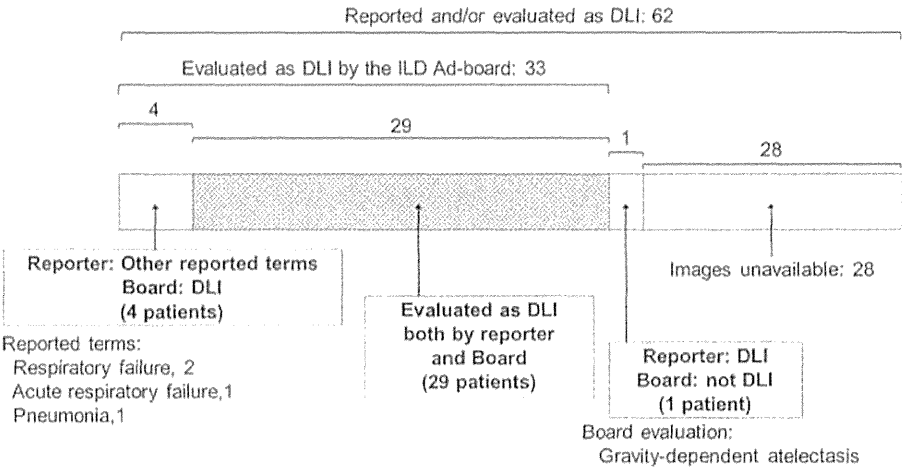

Fig. 4 Relation between the reported terms by reporting physicians and the result of image evaluation by the ILD Ad-board. *DLI* drug-induced lung injury, *ILD Ad-board* ILD Safety Advisory Board

frequently reported AE in 9 patients with HCC. Skin disorder and cytopenic events occurred in 8 and 4 patients, respectively. Respiratory disorders such as dyspnea or respiratory failure, which are the symptoms of DLI itself, were redundantly reported.

Imaging findings

The results of image evaluation are shown in Table 3. The images of 18 patients showed DAD pattern and 15 showed non-DAD pattern. Twelve out of 18 patients with DAD pattern had a fatal outcome. In contrast, 3 out of 15 patients with non-DAD pattern had a fatal outcome.

The relationship between the terms reported by reporting physicians and the result of image evaluation by the ILD Ad-board are shown in Fig. 4. In the cases of 29 patients, the terms reported by the reporting physicians and the result of the evaluation by the ILD Ad-board were consistent. The condition of 4 patients, ultimately diagnosed as DLI by the ILD Ad-board, had been reported initially by reporting physicians as respiratory failure (2 patients), acute respiratory failure (1 patient), and pneumonia (1 patient). The condition of 1 patient diagnosed as DLI by a reporting physician was excluded by the ILD Ad-board and was determined to be gravity-dependent atelectasis.

Discussion

Drug-induced lung injury, especially caused by novel anticancer drugs, has recently been the focus of many studies. Gefitinib-induced DLI is 3.5 % in a retrospective analysis [11] and 5.8 % in a prospective study [10] of Japanese patients with non-small cell lung cancer (NSCLC). In a cohort study, including gefitinib and chemotherapy in Japanese patients with NSCLC, the naive cumulative incidence rates at the end of 12-week follow-up were 4.0 % for gefitinib versus 2.1 % for conventional chemotherapy [20]. Another study in Japanese patients with NSCLC showed that the incidence of DLI within the first month of treatment was 1.0 % for erlotinib versus 2.4 % for gefitinib [12]. Although the reporting frequency of sorafenib-induced lung injury in RCC and HCC patients in the present analysis is not considered high, the difference in underlying malignancy between pulmonary and non-pulmonary origin should be taken into consideration.

Several reports indicate that Japanese patients are more likely to develop DLI. The worldwide prevalence of DLI in gefitinib-treated patients was approximately 1 %, and that in a US manufacturer expanded access program was 0.3 % [21]. One of the reasons for this difference is considered to be solicitation bias due to a difference in the system for collecting information about AE in the post-marketing setting. In Japan, active solicitation is required in the early phase of launch of new drugs under the Early Post-marketing Phase Vigilance (EPPV) requirement of the Japanese Health Authority, whereas worldwide reporting frequency is basically estimated from spontaneous reports or literature reports. In addition, the high incidence of DLI in Japan may be because of the greater awareness about DLI. Genetic susceptibility to DLI is also suggested; however, further research is required to address this issue [22].

The relation between underlying malignancy and DLI was that HCC patients tended to develop DLI earlier than RCC patients, and hepatic disorder was the most frequently reported AE other than DLI in HCC patients. The reason for this remains to be completely elucidated; however, several factors are postulated, such as impaired metabolism of sorafenib in patients with decreased hepatic function reserve and any patient background of susceptibility to DLI. Sorafenib is mainly metabolized in the liver, but

impaired metabolism of sorafenib because of decreased hepatic function reserve has not been proven according to the result that no clinically relevant difference was observed in pharmacokinetics between patients of Child–Pugh class A and class B in the Phase 1 study of sorafenib in Japanese patients with HCC [23].

Deteriorated performance status, pre-existing chronic fibrosing ILD, and smoking history were factors that contributed to DLI in NSCLC patients treated with gefitinib [9, 10, 20] and erlotinib [12]. Similarly, deteriorated systemic condition in advanced HCC patients may be attributed to decreased hepatic function reserve and/or multiple metastases. In addition, several reports suggest pathogenic role of chronic hepatitis C viral infection and its drug treatment in DLI, although the association between them remains controversial [24]. It is interesting that the difference in patient background because of underlying tumor types may be responsible for the occurrence of DLI.

In the present analysis, 18 out of 34 patients who had imaging data available showed DAD pattern. Furthermore, it is important to keep in mind that two-third of the patients with DAD pattern had a fatal outcome.

Diffuse alveolar damage is characterized histologically by the presence of alveolar airspace and interstitial oedema, hyaline membrane formation, and proliferation of type 2 pneumocytes [16, 19]. It manifests radiographically as bilateral hetero- or homogeneous opacities, usually in the mid and lower lungs, and on high-resolution CT scans as scattered or diffuse areas of ground-glass opacity, and architectural distortion can occur [18, 19]. The image findings from individual patients showed that several patients eventually presented the DAD pattern, although their image findings at onset were faint ground-glass opacity. The importance of early recognition, close observation, and initiation of treatment for DLI at an early stage should be emphasized to physicians. In addition, it is important to consult with specialists for pulmonary medicine at an early stage.

Currently, specific guidelines for the treatment of DLI are not available, and treatment tends to be administered on an empirical basis. High-dose methylprednisolone for several days followed by tapering of the dose is commonly used, in addition to withdrawal of the suspected drug [7, 25]. Overall, the treatment for DLI is considered appropriate in the present analysis. It should be noted, however, that the DLI of radiological DAD pattern often leads to poor prognosis despite early recognition and early initiation of treatment.

Limitations of the present analysis include possible bias in patients with availability of detailed information, and lack of statistical analysis specifying prognostic factors or risk factors for sorafenib-associated lung injury. The observation period was not uniformly determined in the present analysis, because of an observational post-marketing surveillance setting. In addition, we did not perform in-depth analyses of the levels of serum markers, arterial blood gas, or the results of bronchoalveolar lavage/transbronchial lung biopsy. The information of pathological examination to confirm the image evaluation is also limited.

The present analysis will provide useful information about DLI to health care professionals involved in the treatment using sorafenib. An analysis to specify risk factors will be reported in the final result of SDUI. Further investigations are required to determine the difference in DLI according to causative drugs, cancer types, and ethnicity.

Acknowledgments We would like to express our deepest appreciation to the medical doctors participating in the Nexavar® SDUI in RCC and HCC in Japan as well as the reporting physicians for DLI patients for providing detailed information.

Conflict of interest Y. H-Y. is an employee of Bayer Yakuhin, Ltd. A.G. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript. H.T. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript. Y.I. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript. F.S. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript. T.J. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript, those from Chugai Seiyaku, Ltd., as a member of the ILD Ad-board, and conducted honorary lectures with support from Daiichi-Sankyo Seiyaku, Ltd., Kyorin Seiyaku, Ltd., and Eizai Ltd. K.F. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript. S.K. has received consulting fees from Bayer Yakuhin, Ltd. as a member of the ILD Ad-board in the subject of this manuscript.

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INTERNAL MEDICINE

□ CASE REPORT □

A Case of Combined Sarcoidosis and Usual Interstitial Pneumonia

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Abstract

Sarcoidosis is a systemic granulomatous disease of unknown etiology with characteristic pulmonary lesions, which are often distributed in the upper lung fields. We describe a unique case of sarcoidosis with lower lung field-dominant reticular shadows. Three years after the diagnosis of sarcoidosis based on histologic findings of the mediastinal lymph nodes and transbronchial lung biopsy specimens, the patient developed acute respiratory failure and died. The autopsy showed usual interstitial pneumonia (UIP), with honeycombing and superimposed diffuse alveolar damage of the lungs. The findings suggest that the patient had both sarcoidosis and UIP, and that the UIP later progressed to acute exacerbation.

Key words: sarcoidosis, usual interstitial pneumonia, acute exacerbation

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Its radiologic characteristics include reticular opacities that are distributed predominantly in the upper lung fields (1). The radiologic finding of lower zone-dominant reticular shadowing is encountered only rarely in sarcoidosis (2, 3); however, this pattern is one of the characteristics of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) (4). Some patients with IPF are known to experience an acute exacerbation following a period of chronic disease progression (5-8). We recently encountered a patient with both pulmonary sarcoidosis and UIP, who developed an acute exacerbation of the latter condition, leading to his death from acute respiratory failure. The patient's clinical course could not be explained solely by sarcoidosis, but mimicked IPF. Thus, this case may assist in understanding the potential for sarcoidosis and UIP comorbidity, as well as the pathogenesis of reticular opacities distributed predominantly in the lower lung fields in patients with sarcoidosis.

Case Report

A 62-year-old man, an ex-smoker, was admitted to the Kinki-Chuo Chest Medical Center for the assessment of abnormal chest X-ray and computed tomography (CT) findings in 2007. He had worked as a truck driver for 14 years (from the age of 23 until the age of 37 years) and as a building demolition worker for the subsequent 25 years (from the age of 37 years to 62 years). He reported a four-month history of dry cough and worsening of dyspnea on effort. His only other relevant medical history was fatty liver, and hyperuricemia, which was treated with allopurinol. He had used a down quilt on the bed since age 32. Physical examination on admission revealed no palpable surface lymph nodes, no finger clubbing, and no skin rash; however, fine crackles were heard on chest auscultation. Peripheral blood findings on admission were as follows: WBC count, 5,900/μL; lactate dehydrogenase (LDH), 255 IU/L; and C-reactive protein (CRP) 0.09 mg/dL. The levels of Krebs von den Lungen-6

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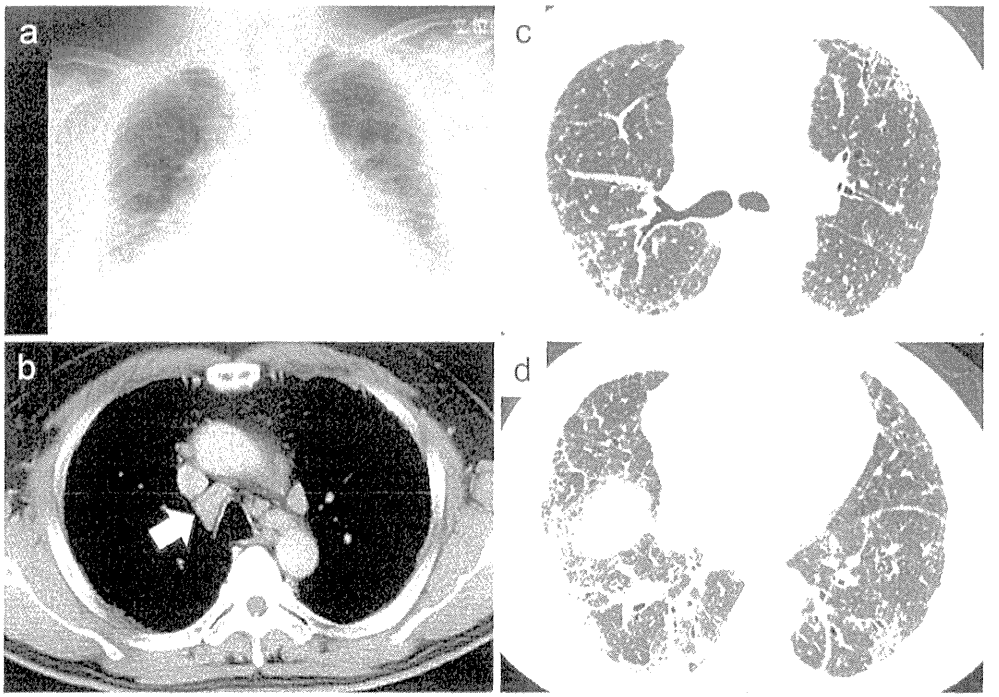

Figure 1. Chest radiograph (a) and CT scan (b-d) of the lung at the initial visit (2007), showing perilymphatic distributed small nodules, reticular opacities predominantly in the lower lung fields, and mediastinal lymphadenopathy (arrow).

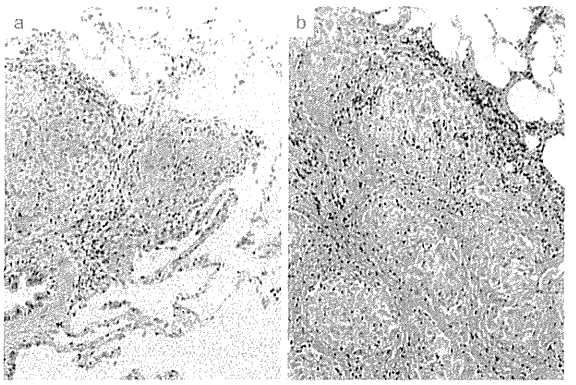

Figure 2. (a) The lung tissue of the right lower lobe (segment 8) was obtained by a transbronchoscopic biopsy in 2007. Epithelioid cell granulomas were formed in the wall of a respiratory bronchiole. Adjacent alveolar walls were relatively normal (Hematoxylin and Eosin staining, ×20). (b) The mediastinal lymph node was obtained by a mediastinoscopic biopsy in 2007. Numerous epithelioid cell granulomas were formed in the lymph node with perigranulomatous hyalinous fibrotic changes (Hematoxylin and Eosin staining, ×20). Based on the histologic evidence of the lung tissue and the mediastinal lymph node, the authors considered that the patient had sarcoidosis at the time of his initial visit in 2007.

(KL-6) and surfactant protein-D (SP-D) were increased (3,600 U/mL and 492 ng/mL, respectively), and an elevated activity of both angiotensin-converting enzyme (ACE) (25.1 U/lL; normal range: 8.3-21.4 U/L) and lysozyme (10.6 μg/mL; normal range: 5.0-10.2 μg/mL) was observed. The patient tested negative for antinuclear antibody and anti-double-stranded DNA. Tuberculin reaction was also negative.

Chest radiography revealed diffuse reticular opacities in the outer and lower zones of the lungs along with elevation of the diaphragm (Fig. 1a). A high-resolution CT scan of the chest demonstrated reticular shadows in the subpleural area, traction bronchiectasis, small nodules in perilymphatic and random distribution, and enlargement of the mediastinal lymph nodes (lower paratracheal lymph nodes) (Fig. 1b-d). Bronchoscopy revealed normal bronchial mucosa. Bronchoalveolar lavage (BAL) was performed in the right B^4b. The recovery rate of the bronchoalveolar lavage fluid (BALF) was 47%, and the total cell count in the fluid was 3.12×10^5/mL, with a breakdown of 45.8% macrophages, 16.3% lymphocytes, 11.7% neutrophils, and 26.2% eosinophils. The lymphocyte CD4/CD8 ratio was 7.41. No pathogen was detected in the BALF. Transbronchial biopsies of the right lung revealed noncaseating epithelioid cell granulomas in both S^3 and S^8 (Fig. 2a and data not shown). A mediastinoscopic biopsy of the mediastinal lymph nodes revealed numerous noncaseating epithelioid granulomas surrounded by hyalinous fibrotic changes (Fig. 2b). Based on these findings, a diagnosis of sarcoidosis involving the lungs and mediastinal lymph nodes was made. No sarcoidosis lesions were observed in other tissues including the heart, eyes and skin. At this time, the findings on chest X-ray and

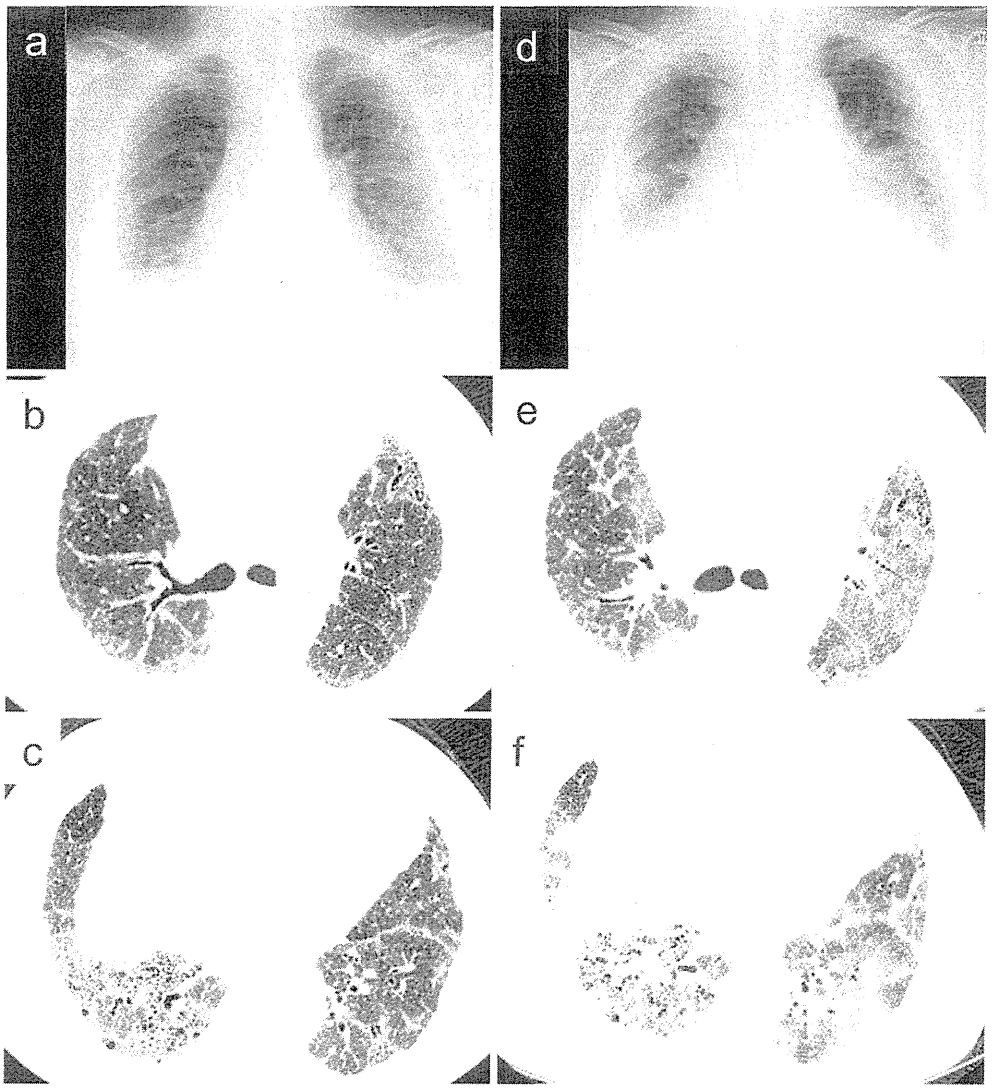

Figure 3. Chest radiograph (a) and CT scan (b, c) of the lung, 3 years after the initial visit (2007), showing progressed reticulation and volume loss. Chest radiograph (d) and CT scan (e, f) of the lung at the time of acute respiratory failure, showing diffuse ground glass opacities superimposed on reticular opacities.

on CT of the bilateral fibrotic lung lesions, predominantly in the lower lung zones, were considered to be due to the fibrotic lesions of sarcoidosis itself.

As treatment, 35 mg per day of oral prednisolone was started and then tapered. The patient's cough and dyspnea on exertion improved in two weeks, and an increase in vital capacity (VC) and diffusing capacity of the lung for carbon monoxide (DLco) were observed after a month, along with a slight improvement of small nodules in the lung detected on high-resolution CT and a decrease in the level of serum ACE. However, 20 months later, the patient experienced increasing shortness of breath, and chest imaging showed worsening of fibrotic shadows. Red-brown papules also appeared on the patient's lower legs, and these were diagnosed as cutaneous sarcoidosis by a dermatologist. These findings were presumed to indicate progression of the patient's sarcoidosis, and he was therefore treated with 35 mg per day of oral prednisolone, combined with 100 mg per day of azathioprine for the first seven months, switched to 100 mg of cyclosporine for the latter four months of this period, and 50 mg per week of etanercept for the final three months. However, this treatment was unsuccessful in preventing progression of the disease (Fig. 3a-c). Three years and two months after the initial diagnosis of sarcoidosis, a mass shadow in the right lung (S^6) was noted on chest CT. A CT-guided needle biopsy revealed adenocarcinoma with thyroid transcription factor-1 (TTF-1)-positivity, suggestive of primary lung cancer.

One and a half months later, just before staging of the lung cancer, the patient presented with sudden onset of dyspnea and hemosputum. Chest X-ray and CT showed diffuse ground glass opacities (Fig. 3d-f) in both lungs. The

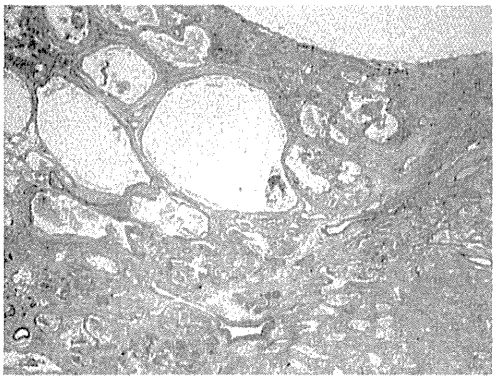

Figure 4. The lung tissue was obtained from the left lower lobe (segment 8) by an autopsy in 2010. The subpleural region (upper and left) showed cystic changes measuring 0.7-4 mm in diameter surrounded with fibrotic lesions (honeycombing). The inner lung parenchyma (lower and left) showed diffuse interstitial fibrotic thickening with temporal homogeneity. The authors considered the lung tissue as showing usual interstitial pneumonia (UIP) superimposed with fibrotic stage of diffuse alveolar damage (DAD). No granulomas were found (Hematoxylin and Eosin staining, ×1).

level of serum ACE remained normal. Treatment with high-dose corticosteroids, cyclophosphamide, antibiotics, and invasive positive-pressure ventilation was ineffective, and the patient died from respiratory failure 40 months after the initial diagnosis of sarcoidosis (nine days after the commencement of high-dose corticosteroid treatment).

An autopsy was performed, focusing on the thoracic and abdominal organs, which revealed multiple bilateral parietal pleural plaques (right: 50×50 mm, 20×20 mm; left: 45×20 mm, 40×12 mm, 30×15 mm, 40×12 mm). Eighty-three paraffin blocks were prepared for histopathologic diagnosis, including 14 from the right lung, 13 from the left lung, 4 from the mediastinal lymph nodes, and 2 each from the right and left parietal pleural plaque regions. We diagnosed the lung tissues as showing an UIP pattern, with honeycombing and superimposed diffuse alveolar damage (DAD) (Fig. 4). Asbestos bodies were not detected histologically, even after Prussian blue iron staining of the lung specimens. Therefore, bilateral lung tissues from the upper and lower lobes (right S^{2}, right S^{10}, left S^{1+2}, and left S^{10}) were measured for asbestos bodies. A total of 328 asbestos bodies per gram of dry weight of lung tissue were detected in the left lower lobe (S^{10}). The Helsinki Criteria for significant or occupational asbestos exposure is >1,000 asbestos bodies per gram of dry weight of lung tissue (9). Poorly differentiated adenocarcinoma (20×19×15 mm in size) was observed in the right lung (S^{6}), and metastatic carcinoma was noted in the right pleura, liver, and the pulmonary hilar and mediastinal lymph nodes. However, no granulomas were found in the examined tissues.

Based on these findings, we concluded that the patient suffered from sarcoidosis and UIP during the observation period, and subsequently succumbed to an acute exacerbation 3 years later. Taken together, we propose that our findings more likely indicate that the UIP and bilateral parietal pleural plaques had been present concurrently with the sarcoidosis at the time of diagnosis of the latter, rather than a scenario where the sarcoid granulomas underwent progressive pulmonary fibrosis.

Discussion

We have described a patient with evidence of both sarcoidosis and UIP characterized by lower lung field-predominant pulmonary fibrosis, who developed an acute exacerbation 3 years after the initial diagnosis of sarcoidosis.

The patient died from acute respiratory failure. It is possible that this was acute respiratory failure due to sarcoidosis (10-13), in which severe alveolitis with inflammatory or organized exudates in some alveolar spaces and noncaseating epithelioid granulomas are observed (14). However, this is unlikely in the present case for a number of reasons: (i) the autopsy revealed no granulomas in the lungs and lymph nodes, but rather showed diffuse alveolar damage superimposed on UIP; (ii) the level of serum ACE remained in the normal range; and, (iii) in cases of acute respiratory failure due to sarcoidosis, granulomas are usually observed in the lung despite having been treated with corticosteroids (14). As a result, we consider it more likely that this case was an acute exacerbation that developed during the course of UIP rather than acute respiratory failure due to sarcoidosis.

Radiographic and histologic findings suggest that the patient had both sarcoidosis and UIP. There are two possibilities: that the sarcoidosis and UIP existed concurrently; or that the fibrotic lesions developed as a fibrotic stage of sarcoidosis. For instance, Nobata et al. have reported a case of pulmonary sarcoidosis with UIP distributed predominantly in the lower lung fields. They noted the possibility of a fibrotic stage of pulmonary sarcoidosis (3) because the fibrosis was distributed along the bronchovascular bundles, which is a feature of the fibrotic stage of pulmonary sarcoidosis (15). In the present case, however, it is thought that the acute exacerbation developed during the chronic course of UIP as mentioned above. This theory is supported by the fact that the autopsy revealed no concentric fibrosis or concentric lamellar calcifications (Schumann bodies), which are characteristic of the fibrotic stage of sarcoidosis (16). Moreover, fibrotic lesions caused by sarcoidosis are predominantly distributed in the upper lung fields; 68% of sarcoidosis cases had fibrotic lesions predominantly in the upper lung fields, with no more than 4.5% of cases in the lower lung fields (2). As noted, in the present case, the UIP lesions were predominantly distributed in the lower lung fields. Taken together, these findings lead us to suggest that the present patient was concurrently suffering from both sarcoidosis and UIP.

During the course of observation, the patient had been

suspected of having chronic hypersensitivity pneumonia because of his history of using a down quilt on the bed. However, cessation of the use of down quilt neither improved the patient's condition nor stopped the disease progression. In addition, numerous well-developed granulomas were observed in the mediastinal lymph nodes (Fig. 2b). These findings therefore did not support the likelihood of chronic hypersensitivity pneumonia.

The autopsy showed parietal pleural plaques bilaterally, suggesting asbestos exposure. In general, asbestosis (a kind of lung fibrosis) is associated with a high level of exposure to asbestos (9). Unlike the present case, patients with asbestosis generally have a significant asbestos fiber burden and more extensive pleural plaques, which may be detected on chest CT (9). We believe that this patient probably had UIP and associated bilateral parietal pleural plaques as a result of his long duration of low-dose exposure to asbestos fibers, although progression of asbestosis is generally slow, the ten-year survival rate being around 70% (17, 18). This raises the possibility that the low-dose asbestos exposure might have caused sarcoid-like reaction as reported in cases of high-dose asbestos exposure (19, 20).

In summary, we have presented here a case of combined sarcoidosis and UIP with an acute exacerbation. This case is important in highlighting the possibility that sarcoidosis may develop after long-standing pulmonary fibrosis. Additional cases of lower lung field-predominant sarcoidosis should be studied in the future in order to further develop our understanding of this condition.

The authors state that they have no Conflict of Interest (COI).

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CHEST

Original Research

DIFFUSE LUNG DISEASE

St. George's Respiratory Questionnaire Has Longitudinal Construct Validity in Lymphangioleiomyomatosis

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Background: **Lymphangioleiomyomatosis (LAM) is an uncommon, progressive, cystic lung disease that causes shortness of breath, hypoxemia, and impaired health-related quality of life (HRQL). Whether St. George's Respiratory Questionnaire (SGRQ), a respiratory-specific HRQL instrument, captures longitudinal changes in HRQL in patients with LAM is unknown.**

Methods: **Using data from the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus trial, we performed analyses to examine associations between SGRQ scores and values for four external measures (anchors). Anchors included (1) FEV_1, (2) diffusing capacity of the lung for carbon monoxide, (3) distance walked during the 6-min walk test, and (4) serum vascular endothelial growth factor-D.**

Results: **SGRQ scores correlated with the majority of anchor values at baseline, 6 months, and 12 months. Results from longitudinal analyses demonstrated that SGRQ change scores tracked changes over time in values for each of the four anchors. At 12 months, subjects with the greatest improvement from baseline in FEV_1 experienced the greatest improvement in SGRQ scores (Symptoms domain, -13.4 ± 14.6 points; Activity domain, -6.46 ± 8.20 points; Impacts domain, -6.25 ± 12.8 points; SGRQ total, -7.53 ± 10.0 points). Plots of cumulative distribution functions further supported the longitudinal validity of the SGRQ in LAM.**

Conclusions: **In LAM, SGRQ scores are associated with variables used to assess LAM severity. The SGRQ is sensitive to change in LAM severity, particularly when change is defined by FEV_1, perhaps the most clinically relevant and prognostically important variable in LAM. The constellation of results here supports the validity of the SGRQ as capable of assessing longitudinal change in HRQL in LAM.**

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Abbreviations: 6MWD = distance walked during 6-min walk test; CDF = cumulative distribution function; DLCO = diffusing capacity of the lung for carbon monoxide; LAM = lymphangioleiomyomatosis; SGRQ = St. George's Respiratory Questionnaire; VEGF-D = serum vascular endothelial growth factor D level

Lymphangioleiomyomatosis (LAM) is an uncommon, progressive lung disease that affects women and occurs either sporadically or in association with tuberous sclerosis complex.[1-3] In LAM, hallmark cystic destruction of the pulmonary parenchyma impairs lung function and induces debilitating dyspnea.[4,5] In most patients, hypoxemia develops within a decade of symptom onset.[6] Given the breathlessness, functional limitation, and need for supplemental oxygen that ultimately develop, it is not surprising that patients with LAM experience impaired health-related quality of life (HRQL), particularly in domains that reflect respiratory symptoms or physical health and activities.[7]

St. George's Respiratory Questionnaire (SGRQ) is a respiratory-specific instrument that was designed to assess HRQL in patients with asthma or COPD.[8] Despite the developer's initial intent—to develop a questionnaire for patients with either of those two conditions—the SGRQ has been used to assess HRQL in patients with other lung diseases, including women with LAM.[9] In fact, investigators have observed that baseline scores from the SGRQ correlate with certain

baseline measures of pulmonary physiology, oxygenation, and functional capacity.[7,9] The SGRQ has been shown to be sensitive to change when used in patients with various respiratory diseases,[10-12] but whether in patients with LAM it can track changes in HRQL that might occur as a result of disease progression or in response to a clinically beneficial (or harmful) medication has never been assessed. An HRQL instrument must possess this attribute to be considered useful as an outcome measure in longitudinal research. We conducted this study to examine the ability of the SGRQ to assess HRQL over time in patients with LAM (ie, to determine its longitudinal construct validity in this disease).

Materials and Methods

We used data collected at baseline, 6 months, and 12 months in the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial.[13] The MILES trial was a two-stage trial—a 12-month randomized, double-blinded comparison of sirolimus vs placebo followed by a 12-month observation period—involving 89 patients with LAM who had a $FEV_1 < 70\%$ predicted. The primary end point was the difference between the groups in the rate of change in FEV_1. There were a number of secondary end points, including HRQL as assessed by the SGRQ. We assessed the association between SGRQ scores and certain variables hypothesized to be clinically meaningful measures of LAM severity; henceforth, we refer to those variables as anchors. We hypothesized that changes in the anchors (ie, disease status or severity) would be associated with changes in HRQL and, thus, changes in SGRQ scores.

Saint George's Respiratory Questionnaire

The SGRQ is a self-administered, respiratory-specific questionnaire with three domains (Symptoms, Activity, and Impacts) and a total score designed to assess HRQL.[8] The Symptoms domain, as its name implies, focuses on respiratory symptoms, including breathlessness, cough, and wheeze. The Activity domain probes for physical activities that either cause or are limited by dyspnea. The Impacts domain covers the effects of respiratory disease on several factors, including employment, social interactions, emotional well-being, and the sense of being in control. Scoring weights for the response options for each of the 50 items were derived using data from patients with asthma or COPD.[14] Each domain score and the total score range from 0 to 100, and higher scores connote greater impairment.

Anchors

The four anchors we selected were: (1) FEV_1, (2) diffusing capacity of the lung for carbon monoxide (DLCO), (3) distance walked during the 6-min walk test (6MWD), and (4) serum vascular endothelial growth factor D level (VEGF-D). We chose FEV_1 and DLCO because each has been shown to be impaired in patients with LAM, and as such, they—particularly FEV_1—are measures used universally to characterize LAM severity.[7] Both the FEV_1 and DLCO have been shown in prior cross-sectional studies to correlate with SGRQ scores.[7,9] The 6-min walk test, and 6MWD in particular, is commonly used as a functional assessment in patients with respiratory diseases.[15] We hypothesized that changes in 6MWD would reflect changes in overall physical functionality and that changes in physical functionality would lead to changes in subjects' perceptions of their HRQL. Serum VEGF-D level distinguishes LAM from other diseases, and here, changes in VEGF-D levels were hypothesized to track changes in LAM severity (eg, increases in VEGF-D would be associated with increased LAM severity) and, by association, HRQL.[16]

Statistical Analysis

We performed analyses to examine the association between SGRQ scores and anchor values cross-sectionally, as well as longitudinally, using the data collected at three different time points: baseline, 6 months, and 12 months. To enhance interpretability of results, serum VEGF-D values were log-transformed. In the first set of analyses, Spearman rank correlation was used to assess the relationship among variables cross-sectionally and longitudinally. Linear mixed-effects models were used to further examine these cross-sectional and longitudinal associations simultaneously. For each anchor, we generated four separate mixed-effects models (one model for each of the three SGRQ domains and one for the SGRQ total score). In each model, SGRQ score was the response variable and the anchor was a covariate. Each model included age at enrollment as a time-constant variable, the baseline anchor value (to allow examination of the cross-sectional association between SGRQ score and anchor), and the anchor change from baseline (to allow examination of the longitudinal association). For each model, to account for the within-subject correlation among the repeated measures in SGRQ score, anchor intercept and slope were incorporated as random effects with unstructured covariance. Next, we used general linear models to examine the association between SGRQ changes and quartiles of anchor change (defined as percent change from baseline at 6 or 12 months) after adjusting for the corresponding baseline SGRQ score. Finally, as a visual representation of the relationship between SGRQ change

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scores and anchor change scores (again, defined as percent change from baseline), we generated cumulative distribution function (CDF) plots for each SGRQ score using data from subjects in the two extreme quartiles of anchor changes (greatest decline vs greatest improvement). Institutional review board approval was not needed for this study of deidentified, previously collected data. All statistical analyses were performed using SAS, Version 9.2 (SAS Institute Inc.), and $P < .05$ was considered to represent statistical significance for each analysis. Because our analyses were hypothesis driven, we did not adjust for multiple comparisons.

Results

Baseline characteristics of the subjects are displayed in Table 1. On average, airflow limitation was moderately severe. At baseline, 6 months, and 12 months, there were significant correlations—most moderately strong—between various anchor values and SGRQ scores (Table 2). For each anchor, at each time point, the strongest correlations were with Activity domain scores (Table 2). Simple correlations between SGRQ change scores and anchor change scores are presented in Table 3.

The results from the mixed-effects models extend the results from the correlation analyses by yielding estimates for the cross-sectional relationship between SGRQ scores and anchors at baseline (Table 4, "Cross-sectional") as well as how SGRQ scores were predicted to change in relation to changes over time in the anchors (Table 4, "Longitudinal"). At any time point (ie, 6 or 12 months), improvements from baseline in any of the four anchors were predicted to generate improved (lower) SGRQ scores. For example, at 6 or 12 months, every 1% increase in FEV_1% was predicted to yield about a 0.5-point decrease (improved HRQL) in any SGRQ score (domain or total), and a 100-m increase in 6MWD was predicted to yield a 4-point decrease (improved HRQL) in the Symptoms, Activity, or SGRQ total score and a 5-point decrease in Impacts score.

Table 5 displays mean SGRQ change scores for subgroups stratified on quartiles of change in each anchor. After adjusting for baseline SGRQ score, there were significant differences between various SGRQ scores across quartiles of change in FEV_1, 6MWD, and log(VEGF-D). Although not all relationships were statistically significant, on balance, we observed that greater impairments (ie, decline in FEV_1, decline in DLCO, decline in 6MWD, or increase in VEGF-D) in the anchors were associated with greater impairments (increase) in SGRQ scores, and greater improvement in the anchors were associated with greater improvements (decrease) in SGRQ scores.

The CDF plots (Fig 1) provide a graphical representation of SGRQ change scores for subgroups in the extreme quartiles of change for each anchor. Consider an arbitrarily chosen improvement of at least 10 points in the Symptoms domain (ie, −10 or more extreme on the x-axis in Fig 1A): only 33% of subjects in the first quartile of change in FEV_1 (Q1: subjects with decline in raw FEV_1 of > 11.1% from baseline) compared with 61% of subjects in the fourth quartile of change in FEV_1 (Q4: subjects with an improvement in FEV_1 of > 4.4%) had improvement of at least 10 points in the Symptoms domain from baseline to 12 months. For the Activity domain, 17% in Q1 vs 42% in Q4 had improvement of at least 10 points; for the Impacts domain, 17% in Q1 vs 32% in Q4 had improvement of at least 10 points; and for the SGRQ total, 17% in Q1 vs 28% in Q4 had improvement of at least 10 points.

Table 1—*Characteristics of Study Sample*

Variable	Baseline (n = 89)	6 mo (n = 83)	12 mo (n = 74)
Age, y	45.4 ± 10.6	...	...
Race, No. (%)			
White	59 (66)	...	...
Asian	27 (30)	...	...
Other	3 (3)	...	...
Oxygen therapy, No. (%)			
Intermittent use	52 (58)	...	...
Continuous use	28 (31)	...	...
FEV_1			
L	1.37 ± 0.42	1.35 ± 0.42	1.33 ± 0.40
% Predicted	48.5 ± 13.8	48.5 ± 15.0	48.1 ± 14.1
DLCO			
mL/min/mm Hg	10.23 ± 4.61	9.95 ± 4.00	9.62 ± 3.95
% Predicted	43.4 ± 19.0	42.3 ± 16.3	41.2 ± 16.8
6MWD, m	403 ± 105	415 ± 119	425 ± 104
log(VEGF-D), pg/mL	7.22 ± 0.85	7.00 ± 0.82	6.90 ± 0.84
SGRQ scores			
Symptom domain	52.1 ± 18.4	49.8 ± 18.3	48.5 ± 19.2
Activity domain	65.5 ± 17.7	65.2 ± 16.3	64.5 ± 17.6
Impact domain	33.4 ± 17.4	34.5 ± 17.9	31.3 ± 15.0
Total	46.4 ± 15.2	46.6 ± 15.6	44.6 ± 13.7

Data are presented as mean ± SD unless otherwise noted. 6MWD = distance walked during 6-min walk test; DLCO = diffusing capacity of the lung for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire; VEGF-D = serum vascular endothelial growth factor D level.

Discussion

Using data from the MILES trial, we performed several analyses whose results support the SGRQ as an instrument capable of assessing and responding to change over time in HRQL in patients with LAM. When investigators aim to generate data to support the validity of something (for an intended purpose), ideally, there is a gold standard against which it can be measured. Unfortunately, in the realm of HRQL, there is no gold standard. Thus, investigators must choose other variables, hypothesized—or known—to be related to HRQL to serve as anchors. In patients with LAM, pulmonary function tests (FEV_1 in particular)

Table 2—*Spearman Correlation Coefficients Between SGRQ Scores and Anchors at Baseline, 6 Months, and 12 Months*

Domain	Symptom	Activity	Impact	Total
FEV_1%				
Baseline	−0.33 (.002)	−0.35 (.0007)	−0.26 (.01)	−0.33 (.001)
6 mo	−0.41 (.0001)	−0.48 (<.0001)	−0.42 (<.0001)	−0.49 (<.0001)
12 mo	−0.35 (.002)	−0.46 (<.0001)	−0.29 (.01)	−0.40 (.0005)
DLCO%				
Baseline	−0.21 (.048)	−0.43 (<.0001)	−0.20 (.06)	−0.33 (.002)
6 mo	−0.30 (.006)	−0.49 (<.0001)	−0.34 (.002)	−0.45 (<.0001)
12 mo	−0.17 (.14)	−0.54 (<.0001)	−0.33 (.005)	−0.41 (.0004)
6MWD				
Baseline	−0.14 (.19)	−0.36 (.0005)	−0.13 (.23)	−0.23 (.03)
6 mo	−0.28 (.01)	−0.45 (<.0001)	−0.37 (.0006)	−0.46 (<.0001)
12 mo	−0.20 (.08)	−0.49 (<.0001)	−0.37 (.001)	−0.41 (.0003)
Log(VEGF-D)				
Baseline	0.09 (.42)	0.23 (.03)	0.18 (.10)	0.23 (.03)
6 mo	0.21 (.07)	0.27 (.02)	0.10 (.37)	0.19 (.09)
12 mo	0.19 (.12)	0.23 (.06)	0.15 (.20)	0.21 (.08)

Values are Spearman correlation coefficients (*P* value). See Table 1 legend for expansion of abbreviations.

yield important prognostic information and are commonly used to assess disease status. And by extension, they yield some information about patients' well-being or HRQL. Thus, we hypothesized FEV_1 and DLCO as well as 6MWD (as a measure of functional status) would be related to HRQL in patients with LAM and, as such, in the absence of a gold standard for HRQL, would be useful as external anchors for our analyses. Serum VEGF-D has emerged as a diagnostic biomarker for LAM[16]; like FEV_1, DLCO, and 6MWD, we hypothesized VEGF-D levels would change in response to changes in clinically defined disease severity and might, therefore, be associated with HRQL.

The MILES trial revealed that targeting the mTOR (mammalian Target of Rapamycin) pathway is an effective approach to treating LAM, and MILES very likely paved the way for future trials of other mTOR signaling antagonists for LAM. The hope for such a trial is that any physiologic benefit of a drug would translate into improvements in survival and—arguably, perhaps even more importantly—patient symptoms, functional capacity, and sense of well-being. Survival is easy to assess; symptoms and the more abstract constructs (eg, HRQL) are more challenging, but they can be measured, too. The key to doing so is using reliable, valid instruments that are sensitive to underlying change in the construct of interest. Results from the current study support the SGRQ as such an instrument. We identified a number of significant correlations between SGRQ scores and anchors at each of the study time points. The moderately strong correlations we observed (common to analyses like this), rather than being disappointing, are in fact reassuring. They show that the SGRQ performed as hypothesized, but, most importantly, they reveal that the SGRQ captures information about patients with LAM that FEV_1, DLCO, 6MWD, and serum VEGF-D levels do not.

Even more important for the process of building longitudinal validity than identifying significant

Table 3—*Spearman Correlation Coefficients Between SGRQ Change Scores and Anchor Change Scores From Baseline to 6 and 12 Months*

Domain	Symptom	Activity	Impact	Total
FEV_1%				
6 mo	−0.18 (.09)	−0.34 (.0016)	−0.37 (.0005)	−0.42 (<.0001)
12 mo	−0.16 (.18)	−0.16 (.1621)	−0.24 (.0378)	−0.27 (.0204)
DLCO%				
6 mo	−0.02 (.83)	0.07 (.51)	−0.08 (.46)	−0.05 (.65)
12 mo	−0.04 (.76)	−0.11 (.32)	−0.05 (.66)	−0.08 (.52)
6MWD				
6 mo	−0.07 (.51)	−0.17 (.1181)	−0.15 (.18)	−0.18 (.1128)
12 mo	−0.22 (.06)	−0.30 (.0086)	−0.22 (.06)	−0.35 (.0023)
Log(VEGF-D)				
6 mo	0.06 (.63)	0.09 (.45)	0.19 (.09)	0.20 (.09)
12 mo	0.10 (.39)	0.15 (.23)	0.09 (.46)	0.15 (.23)

Values are Spearman correlation coefficients (*P* value). See Table 1 legend for expansion of abbreviations.

Table 4—*Mixed-Effects Model-Generated Parameter Estimates for SGRQ Change Scores Resulting From Change in Anchor Scores*

Associations	Domain	Symptoms	Activity	Impact	Total
Cross-sectional	FEV_1, mL	−0.014 ± 0.004 (.002)	−0.016 ± 0.004 (< .0001)	−0.015 ± 0.004 (.0009)	−0.015 ± 0.004 (.0001)
	FEV_1%	−0.46 ± 0.13 (.0009)	−0.48 ± 0.11 (< .0001)	−0.39 ± 0.13 (.003)	−0.42 ± 0.11 (.0002)
	DLCO, mL/min/mm Hg	−1.11 ± 0.45 (.02)	−1.72 ± 0.40 (< .0001)	−0.84 ± 0.58 (.21)	−1.15 ± 0.38 (.005)
	DLCO %	−0.30 ± 0.11 (.01)	−0.42 ± 0.10 (< .0001)	−0.20 ± 0.11 (.08)	−0.29 ± 0.09 (.004)
	6MWD, m	−0.03 ± 0.02 (.12)	−0.07 ± 0.02 (.0002)	−0.04 ± 0.02 (.03)	−0.05 ± 0.02 (.004)
	Log(VEGF-D)	4.14 ± 2.16 (.06)	5.95 ± 2.22 (.009)	3.45 ± 2.17 (.12)	4.34 ± 1.95 (.03)
Longitudinal	FEV_1, mL	−0.018 ± 0.007 (.02)	−0.020 ± 0.005 (< .0001)	−0.021 ± 0.006 (.0007)	−0.020 ± 0.005 (< .0001)
		0.583	0.744	0.714	0.750
	FEV_1%	−0.49 ± 0.22 (.03)	−0.56 ± 0.14 (< .0001)	−0.61 ± 0.18 (.001)	−0.57 ± 0.14 (.0003)
		0.531	0.759	0.744	0.776
	DLCO, mL/min/mm Hg	−0.23 ± 0.75 (.76)	−0.42 ± 0.56 (.47)	−0.03 ± 0.82 (.97)	−0.28 ± 0.53 (.60)
		0.580	0.788	0.784	0.797
	DLCO %	−0.06 ± 0.18 (.73)	−0.10 ± 0.14 (.49)	−0.05 ± 0.15 (.76)	−0.09 ± 0.12 (.47)
		0.580	0.798	0.783	0.803
	6MWD, m	−0.05 ± 0.02 (.01)	−0.02 ± 0.02 (.15)	−0.05 ± 0.02 (.008)	−0.04 ± 0.01 (.003)
		0.612	0.789	0.716	0.776
	Log(VEGF-D)	4.85 ± 2.51 (.06)	1.63 ± 1.70 (.34)	3.86 ± 1.89 (.04)	3.27 ± 1.51 (.03)
		0.636	0.825	0.763	0.815

Values are mixed-effects model parameter estimate ± SE (*P* value). In the Longitudinal section of the table, the value below the *P* value is the lowest of the estimated within-patient correlations from the model. See Table 1 for expansion of abbreviations.

correlations between static anchor values and SGRQ scores, we found that SGRQ scores tracked changes in each of the four anchors over time. For example, from the mixed-effects analyses, a 200-mL increase in FEV_1, or an 8% increase in FEV_1%, was predicted to result in a 4-point decline in SGRQ total score (connoting an improvement in HRQL). Likewise, a 5% increase in DLCO% was predicted to result in a >5-point decline in SGRQ Activity score. These analyses also revealed that change in VEGF-D was significantly associated with change in SGRQ scores, but this was for very large (one log) changes in serum VEGF-D levels. Given what is known about serum VEGF-D, this was not too surprising to us: VEGF-D is a diagnostic marker, but its value as a biomarker of pulmonary disease activity (i.e., whether longitudinal changes in VEGF-D correlate with lung disease progression in LAM) is, at present, uncertain. Perhaps

Table 5—*SGRQ Change Scores for Subjects Stratified Into Quartiles Based on Change From Baseline to 12 Months in Anchor Values*

Anchor	Symptoms	*P* Value	Activity	*P* Value	Impacts	*P* Value	Total	*P* Value
FEV_1		**.01**		**.006**		**.16**		**.01**
≤ −11.2% (Q1)	−0.12 ± 14.6	.017	−1.71 ± 8.76	.06	0.95 ± 12.1	.025	−0.13 ± 7.98	.006
−11.2% to −3.4% (Q2)	1.45 ± 13.1	.015	1.31 ± 9.84	.004	−0.34 ± 9.96	.17	0.34 ± 8.16	.01
−3.4% to 4.4% (Q3)	4.57 ± 21.4	.002	3.26 ± 8.43	.001	−2.30 ± 13.1	.24	0.66 ± 10.0	.007
>4.4% (Q4)	−13.4 ± 14.6	Ref	−6.46 ± 8.20	Ref	−6.25 ± 12.8	Ref	−7.53 ± 10.0	Ref
DLCO		**.6**		**.5**		**.6**		**.6**
≤ −9.9% (Q1)	−3.74 ± 15.2	.736	0.65 ± 8.57	.418	−1.83 ± 13.1	.363	−1.29 ± 8.42	.388
−9.9% to −4.7% (Q2)	2.27 ± 18.5	.193	0.06 ± 8.28	.559	−2.06 ± 10.1	.582	−0.82 ± 8.58	.402
−4.7% to 4.7% (Q3)	−1.02 ± 15.9	.438	−3.14 ± 9.75	.522	−3.15 ± 11.7	.687	−2.92 ± 9.98	.789
>4.7% (Q4)	−4.60 ± 20.1	Ref	−1.04 ± 11.1	Ref	−2.20 ± 13.9	Ref	−2.07 ± 11.8	Ref
6MWD		**.7**		**.02**		**.17**		**.04**
≤ −2.3% (Q1)	−1.03 ± 17.9	.400	2.87 ± 7.73	.05	1.81 ± 11.9	.233	2.02 ± 9.18	.06
−2.3% to 4.5% (Q2)	2.54 ± 22.7	.241	0.97 ± 6.53	.37	−0.75 ± 9.35	.662	0.34 ± 7.99	.36
4.5% to 17.1% (Q3)	−3.32 ± 14.5	.449	−5.41 ± 10.8	.26	−6.56 ± 14.8	.301	−5.88 ± 10.2	.33
> 17.1% (Q4)	−5.53 ± 11.9	Ref	−2.22 ± 10.7	Ref	−2.60 ± 11.4	Ref	−2.88 ± 9.41	Ref
Log(VEGF-D)		**.04**		**.8**		**.5**		**.16**
≤ −9.0% (Q1)	−7.54 ± 15.3	.7	−2.22 ± 8.43	.602	−5.97 ± 16.1	.452	−5.17 ± 11.6	.437
−9.0% to −3.7% (Q2)	−2.70 ± 18.4	.4	−2.48 ± 9.75	.859	−0.78 ± 11.6	.628	−1.51 ± 10.1	.440
−3.7% to 0.8% (Q3)	6.29 ± 17.9	.02	1.43 ± 9.65	.625	2.76 ± 11.5	.505	2.95 ± 9.03	.158
>0.8% (Q4)	−4.88 ± 12.8	Ref	0.14 ± 10.8	Ref	−3.27 ± 8.49	Ref	−2.44 ± 5.86	Ref

Values are mean ± SD. Boldface numbers are *P* values for comparison across SGRQ means within anchor; other *P* values correspond to pairwise comparisons of SGRQ means with anchor using Q4 as the reference. See Table 1 legend for expansion of abbreviations.

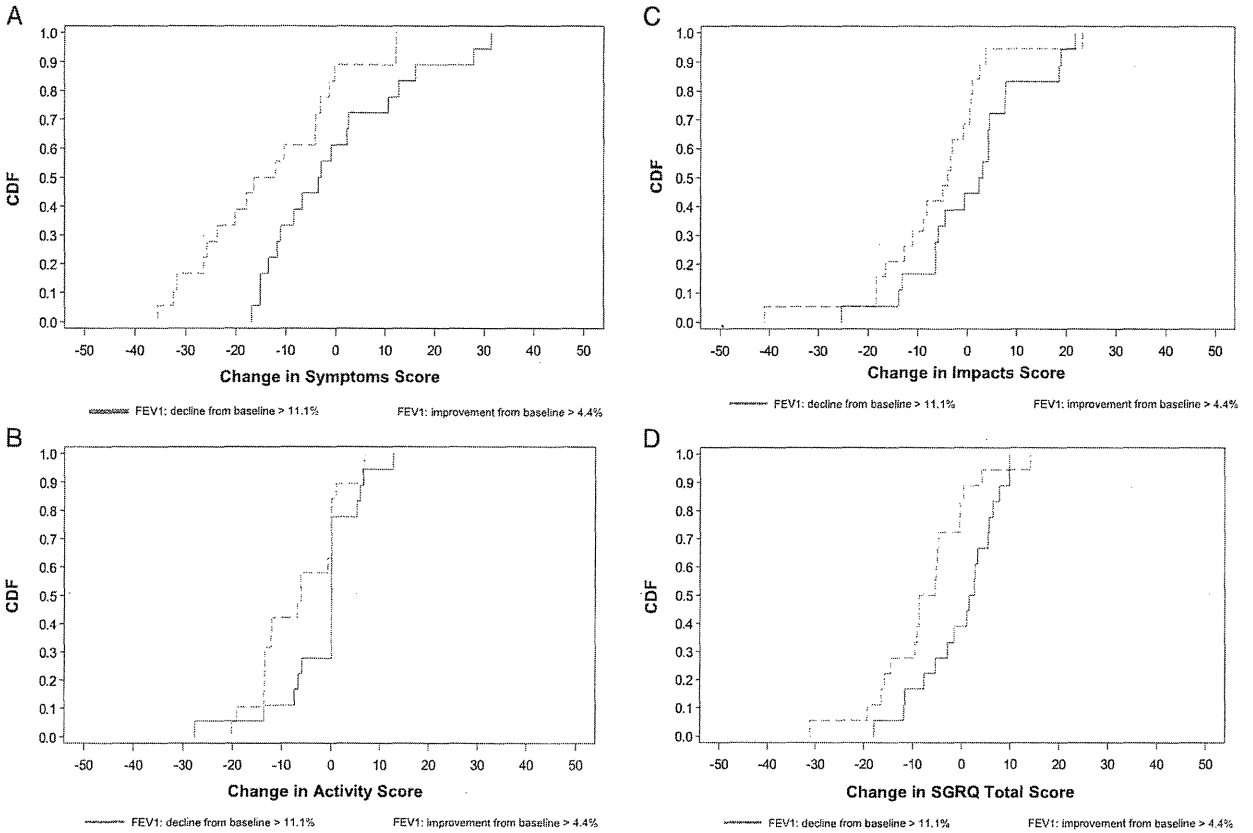

FIGURE 1. A, Plot of CDF for the two extreme quartiles of change from baseline in FEV_1 for SGRQ Symptoms domain. B, Plot of CDF for the two extreme quartiles of change from baseline in FEV_1 for SGRQ Activity domain. C, Plot of CDF for the two extreme quartiles of change from baseline in FEV_1 for SGRQ Impacts domain. D, Plot of CDF for the two extreme quartiles of change from baseline in FEV_1 for SGRQ total score. CDF = cumulative distribution function; SGRQ = St. George's Respiratory Questionnaire.

VEGF-D levels are exquisitely sensitive to LAM activity (at least lymphatic involvement) at the molecular level, but our clinical metrics (eg, FEV_1, DLCO, and 6MWD) are not: only extensive and prolonged lymphatic involvement (that drives up VEGF-D) translates into clinical worsening able to be captured by FEV_1, DLCO, or 6MWD. Clearly, more research into the role of VEGF-D as a biomarker of disease activity in patients with established LAM is warranted.

An effect of being sensitive to longitudinal changes in HRQL within a population is the ability to distinguish change over time between subgroups in that population. When we grouped subjects according to change over time in FEV_1, on balance, the SGRQ performed as hypothesized: subjects with the greatest improvement in FEV_1 experienced the greatest improvement in HRQL. For that particular set of analyses, as has been noted previously in similar analyses for another respiratory disease,[12] DLCO presents challenges as an anchor. First, DLCO changed very little (average change < 1 mL/mm Hg/min among all subjects) over the duration of MILES. Second, DLCO is a statistically noisy variable, and changes in DLCO may fluctuate for reasons unrelated to changes in LAM severity. For example, DLCO is affected by changes in hemoglobin; DLCO was not adjusted for hemoglobin in MILES. Also, DLCO results are often affected by maldistribution of the inspired test gas mixture. This can occur when residual volume is elevated; in MILES, average residual volume was 141% of the predicted value. Finally, for DLCO and the other anchors, the loss of power induced by categorizing variables (as we did in this set of analyses) likely contributed to the inability to identify statistically significant differences between subgroups.

The SGRQ is just one of many instruments designed to assess HRQL and one of several respiratory-specific tools developed for this purpose. A mistake that has been perpetuated in the medical literature is that one cross-sectional correlation study—if statistically significant results emerge—"validates" an instrument for use in a longitudinal trial.[17] In a handful of studies, investigators have generated data to support this so-called "concurrent validity" for the SGRQ (and other instruments) in LAM,[7,9] but, to our knowledge, ours is the first to assess whether the SGRQ can be used confidently in LAM to assess change in longitudinal studies (eg, drug trials).[18-20] The results of our

analyses are not surprising; however, these analyses must be done to confirm the SGRQ performs as hypothesized in LAM. This is the essence of building validity. The FDA has formalized recommendations for how instruments like the SGRQ might qualify as a valid, reliable outcome measure whose scores have "interpretable meaning" in a target population.[21] To our knowledge, there have been no HRQL questionnaires submitted to the FDA for LAM, but data from this study could be useful in such a submission.

This study has limitations: the first is that subjects in the MILES trial may not be representative of the general LAM population. Given how uncommon LAM is, we doubt this is the case. However, subjects in MILES had moderately severe airflow limitation—more severe than the cohort enrolled in a nationwide registry[7]—so whether the SGRQ would perform equally well in a trial that included only subjects with milder LAM is uncertain. The results of our study cannot be extended to other HRQL questionnaires. It is possible that other HRQL questionnaires would perform similarly (or even better than the SGRQ) in LAM under the same circumstances. Until their longitudinal construct validity is assessed, those instruments cannot be used confidently in longitudinal LAM research. On the face of it, the SGRQ contains many items—those that ask about wheeze, cough, dyspnea, and physical activities—relevant to LAM patients.[7] However, the SGRQ was not developed specifically for patients with LAM. Whether an instrument developed by specifically incorporating perspectives from patients with LAM would perform better than the SGRQ is unknown. Although not necessarily relevant to this study, in certain studies of patients with COPD, women's scores are higher (greater impairment in HRQL) than men's for the SGRQ.[22] Some readers may not be familiar with mixed-effects models, but they are believed by most experts to be the models of choice when analyzing longitudinal data (including HRQL data from therapeutic trials).[23] These models parameterize the within-subject correlation that results from repeatedly measuring an outcome over time in the same individual, and they accommodate both incomplete data and time-varying covariates. In contrast, when simple correlation (or even linear regression) is used to assess the relationship between two variables, if data for either variable are missing for a subject, by necessity the subject is deleted from the analysis. Thus, mixed-effects models provide the most statistically efficient method for analyzing longitudinal data. Finally, certain analyses did not yield statistically significant results, but this was largely due to a loss of power resulting from categorization of continuous variables (eg, those in which the anchors were stratified into quartiles). The majority of our analyses support the longitudinal validity of the SGRQ in LAM.

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Dr Swigris: contributed to study conceptualization and planning, generating intellectual content for the manuscript, and critiquing and approving final content.
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Dr Inoue: generating intellectual content for the manuscript and critiquing and approving final content.
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Differentiation between Birt–Hogg–Dubé syndrome and lymphangioleiomyomatosis: Quantitative analysis of pulmonary cysts on computed tomography of the chest in 66 females

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ABSTRACT

Backgrounds: Since Birt–Hogg–Dubé syndrome (BHDS) and lymphangioleiomyomatosis (LAM) share some clinical manifestations (multiple pulmonary cysts with pneumothorax, renal tumors, and sometimes skin lesions), the differential diagnosis of the two diseases becomes problem especially in female patients. This study aims to quantify pulmonary cysts in computed tomography (CT) of females with BHDS and those with LAM and also to identify the independent parameters for differentiating the two diseases.
Methods: Fourteen patients with BHDS and 52 with LAM were studied. In CT scans, lung fields were defined as areas with fewer than −200 Hounsfield units (HU) and pulmonary cysts as areas consisting of 10 or more consecutive pixels with fewer than −960 HU. The extent, number, size and circularity of cysts were calculated by using hand-made software and compared between the two diseases. Moreover, the lung fields were divided into six zones and analyzed for the distribution of cysts. Finally, a stepwise discriminant analysis employing quantitative measurements of cysts and clinical features was performed.
Results: The two diseases were significantly different in all quantitative measurements of cysts. Stepwise discriminant analysis accepted the following four variables: the family history of pneumothorax within the second degree relatives, lower-medial zone predominance of cysts, diffusing capacity and mean size of cysts in this order.
Conclusion: The quantitative characteristics of pulmonary cysts are significantly different between BHDS and LAM. The independent parameters for differentiating the two diseases are the family history of pneumothorax, zonal predominance of cysts, diffusing capacity and size of cysts.

1. Introduction

Birt–Hogg–Dubé syndrome (BHDS) is an autosomal dominant inherited genodermatosis stemming from a defect in the *folliculin* (*FLCN*) gene [1,2]. Clinical manifestations of BHDS include fibrofolliculomas of the skin, renal tumors and multiple pulmonary cysts with recurrent pneumothoraces [3]. The most important disease to be differentiated from BHDS is lymphangioleiomyomatosis (LAM) especially in female patients [4], because the two diseases share some clinical manifestations (lung, skin and kidney lesions). However, the prognosis and management of these diseases are quite different. Although LAM usually progresses to respiratory insufficiency, BHDS does not. Consequently, the definitive diagnosis of BHDS relies on genetic testing, whereas that of LAM derives from pathological examination, both usually available only in specialized institutions. Taking advantage of its non-invasiveness and recent progress in image data processing, chest computed tomography (CT) appears to play an important role in this setting. The visual features of chest CTs in each of BHDS and LAM have been characterized [10–14]; however, no study has been reported that quantitatively analyzes the characteristics of pulmonary cysts and tests whether those have a role in the differentiation among cystic lung diseases.

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