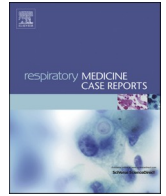


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Respiratory Medicine Case Reports

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Case report

Successful treatment of diffuse pulmonary lymphangiomatosis with sirolimus

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ARTICLE INFO

Keywords:

Diffuse pulmonary lymphangiomatosis
Lymphatic malformations
Rapamycin
Sirolimus

ABSTRACT

Diffuse pulmonary lymphangiomatosis (DPL) is a rare disease characterized by uncontrolled proliferation of anastomosing lymphatic channels in the lungs, pleura and mediastinum. Several palliative treatment options have been suggested for this condition, such as surgical interventions, radiotherapy and systemic medications. However, the existing treatment modalities yield inconsistent results, and their use is often limited by toxic side effects. The aim of this case report is to demonstrate the diagnostic challenges of a rare disease and improvement in the condition of a DPL patient treated with sirolimus. A 27-year-old man presented to the pulmonologist with exertional dyspnea, chronic cough and intermittent hemoptysis. Upon medical investigation, a chest computed tomography (CT) scan revealed soft tissue masses infiltrating the mediastinum and bilateral interlobular septal thickening. A surgical biopsy was performed, and pathological tissue analysis showed findings consistent with the diagnosis of DPL. Treatment with sirolimus was initiated, maintaining trough concentrations between 10 and 15 ng/ml. At 21 months of treatment, the patient reported reduced symptoms of cough and dyspnea. A CT scan showed decreased interstitial thickening and reduced infiltrations in the mediastinum. Moreover, pulmonary function tests revealed a significant increase in FEV1 and FVC. The authors believe this is the first article reporting pulmonary function improvement in an adult DPL patient treated with sirolimus. Therefore, sirolimus therapy should be considered for DPL patients as it may be effective in improving their condition and preventing disease progression.

1. Introduction

Diffuse pulmonary lymphangiomatosis (DPL) is a rare disease characterized by progressive proliferation of lymphatic vessels in the lungs, pleura and mediastinum. The prevalence of this extremely rare disease is unknown whereas the most reported cases are sporadic and the etiology is not completely understood [1]. DPL is generally considered to be congenital, resulting from developmental errors of the lymphatic system before the 20th week of gestation [2,3]. It most commonly manifests in children and young adults with an equal sex distribution [1,4]. The symptoms can vary greatly in severity from one individual to another

and are nonspecific, e.g. chronic cough, hemoptysis, dyspnea and chest pain [5]. Thus, an extensive work-up that includes radiological imaging, pathological tissue analysis and pulmonary function tests (PFTs) is required to diagnose DPL [1]. There is currently no standardized treatment, although several different options have been suggested in literature with inconsistent results [6]. In this paper, we report a case of DPL in a 27-year-old man treated with sirolimus, which reduced the patient's symptoms and improved pulmonary function.

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Received 7 January 2020; Received in revised form 28 January 2020; Accepted 31 January 2020

Available online 1 February 2020

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2. Case presentation

A 27-year-old male was referred to the pulmonologist with symptoms of exertional dyspnea, cough and intermittent hemoptysis for nine months. According to medical history, 8 years prior to the referral the patient was hospitalized at the department of Internal Diseases with high blood pressure and vestibular syndrome. Upon medical investigation at that time, the patient's radiological images showed features suggestive of interstitial lung disease: in chest radiographs, increased interstitial markings and Kerley lines were observed, and a chest computed tomography (CT) scan revealed bilateral pulmonary interstitial thickening and patchy ground glass opacities in the right upper lobe (Fig. 1). Bronchoscopy was also performed, which showed edema and hyperemia of the bronchial mucosa, leading to the diagnosis of acute bronchitis. During the hospitalization, a rare disease was not suspected as the patient's radiological images were misinterpreted and he was not referred to a pulmonologist for further evaluation. The patient's past medical history was also notable for approximately 10 pack-years of smoking.

On current physical examination, vesicular breathing pattern with bilateral crackles was noted while auscultating. PFTs showed a restrictive ventilatory defect and a moderate degree of gas diffusion disorder (Table 1). A CT scan demonstrated heterogeneous low-density masses infiltrating the mediastinum and extending along the main, lobar and segmental bronchi, as well as interlobular septal, peribronchovascular and pleural thickening (Fig. 2a and b). Subsequently, fibrobronchoscopy was performed, which revealed multiple bronchial hemorrhages and mucosal inflammation (Fig. 3). Bronchoalveolar lavage fluid (BALF) was analyzed, in which an elevated total cell count was found ($0.53 \times 10^9/L$), with an increased percentage of lymphocytes and neutrophils (32% and 27%, respectively), and a decreased percentage of macrophages (36%). Erythrocytes and several foreign-body-type giant cells were also observed during BALF cytological examination. Microbiological analysis of the BALF was negative for *Mycobacterium tuberculosis*, acid-fast bacilli, *Pneumocystis jirovecii* and *Aspergillus* galactomannan antigen. Given the indeterminate masses seen in the CT scan, suspicion of malignancy was raised, and the patient underwent video-assisted thoracoscopic biopsy of

Table 1

Pulmonary function test parameters before and during treatment.

Spirometry	Pre-treatment	12 mos treatment	21 mos treatment
FEV1 (L)	1.69 (39% ^a)	2.14 (49%)	2.25 (51%)
FVC (L)	2.38 (46%)	3.12 (60%)	3.05 (59%)
FEV1/FVC	71	69	74
TLC (L)	4.55 (64%)	5.14 (72%)	4.95 (68%)
DLCO Adj (mmol/kPa·min)	6.7 (56%)	7.5 (63%)	7.2 (60%)

^a Percent of predicted value.

the mediastinal masses and marginal resection of the left lung.

Macroscopically, a fragment of firm lung tissue, measuring $3 \times 1.6 \times 1.2$ cm, and small fragments of brownish tissue, measuring $1.2 \times 0.6 \times 0.2$ cm, were received for pathological examination. Histologically, the subpleural and interstitial lung tissue contained marked proliferation of endothelialized thin-walled vessels with formation of small nodules or lobule-like structures (Fig. 4a). The adjacent pulmonary parenchyma contained fibrous septation and proliferating fibroblasts, focal emphysema or alveolar collapse, lymphoid follicles, intra-alveolar edema or hemorrhages with macrophages. Separate fragments of thick fibrous tissue with mesothelial lining contained analogous changes with an increased number of thin-walled vessels. Immunohistochemically, the endothelial cells in proliferations were diffusely positive for D2-40 and CD31 (Fig. 4b and c) and negative for HHV-8. Only a small part of vessels was positive for CD34 (Fig. 4d). Ki67 proliferation index was low (up to 5%). Stromal cells and myocytes in the walls of vessels were positive for Desmin and Asm Actin. HMB45 positive elements were not found. These findings were consistent with spreading of lymphangiomatosis in the lung and pleura. In order to exclude any possible extrathoracic lesions, magnetic resonance imaging (MRI) of the brain and a full-body CT scan were performed. No pathological findings were observed in the MRI scan, and the only notable extrathoracic findings in the CT scan were hepatomegaly along with periportal and periaortic lymphadenopathy. Since the disease appeared to be limited to the thorax, the patient was diagnosed with DPL.



Fig. 1. Thoracic CT scan images 8 years prior to diagnosing DPL. (a) Contrast enhanced CT imaging with lung window showing interlobular septal thickening (white arrow), peribronchovascular interstitial thickening (black arrow) and (b) patchy ground glass opacities (black arrow). (c) CT image with soft-tissue window showing infiltration of the mediastinum (white arrow).

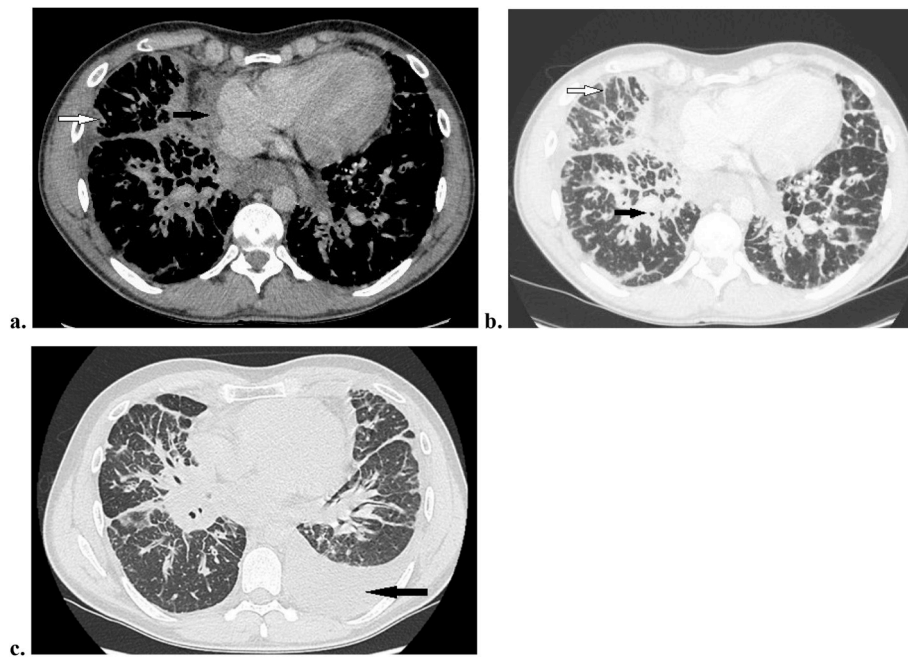


Fig. 2. Thoracic CT scan images at the time of diagnosing DPL. (a) Contrast enhanced CT image with soft-tissue window showing diffuse infiltration of the mediastinum (black arrow) and thickening of the pleura (white arrow). (b) Contrast enhanced CT image with lung window showing diffuse interlobular septal thickening (white arrow), peribronchovascular interstitial thickening (black arrow) and (c) pleural effusion (black arrow).

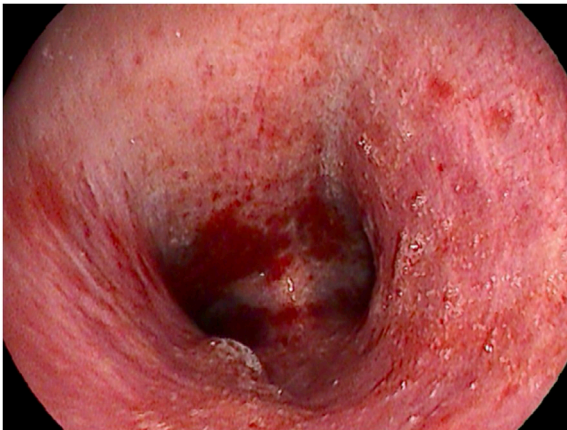


Fig. 3. Fibrobronchoscopic image at the time of diagnosing DPL. Multiple hemorrhages and inflammation of the bronchial mucosa can be seen.

The initial treatment plan was to start bevacizumab therapy. However, shortly after being diagnosed with DPL, the patient presented with increased dyspnea, orthopnea and discomfort in the left side of chest. The CT scan revealed left-sided pleural effusion (Fig. 2c), which was treated by aspirating 1500 ml of hemorrhagic fluid. Due to the hemorrhagic pleural effusion and hemoptysis, treatment with bevacizumab was contraindicated, and sirolimus was selected instead. The initial dose was 2mg/day, which was later adjusted to achieve sirolimus trough concentrations between 10 and 15 ng/ml. At 21 months of treatment, the mediastinal masses seen in the CT scan appeared slightly decreased in size (Fig. 5). PFTs demonstrated a 33.1% improvement of FEV1, a 28.2% increase in FVC, an 8.8% increase in TLC, and a 7.5% increase in DLCO since the initiation of sirolimus (Table 1). No recurrent pleural or pericardial effusions were observed. Currently, the patient reports reduced symptoms of cough and dyspnea. The only adverse reaction to the treatment was acne.

3. Discussion

As illustrated in this case, diagnosing DPL presents its challenges. Even though the symptoms experienced by our patient (chronic cough, dyspnea, and expectoration of blood) are common in DPL, they can be attributed to a wide variety of pulmonary disorders. Similarly to this case, PFTs typically reveal a restrictive ventilatory defect, although a mixed restrictive-obstructive pattern can sometimes be present [1]. In chest radiographs, diffuse pulmonary opacities and increased interstitial markings are usually observed [5]. The main findings in CT scans are diffuse infiltrations in the mediastinum, bilateral smooth interlobular septal thickening, patchy ground glass opacities and pleural effusions [7]. However, no radiological sign is pathognomonic, and definitive diagnosis can only be established by pathological tissue examination. In our patient's case, radiological signs suggestive of interstitial lung disease were already evident 8 years prior to the diagnosis of DPL. Unfortunately, the findings were not interpreted correctly at the time, thus resulting in a long diagnostic delay. Without treatment, the progressive growth of lymphatic vessels can lead to chylothorax and respiratory dysfunction [1]. To this day, our patient has experienced one episode of a clinically significant pleural effusion. Although chylothorax was suspected at first, which is associated with a poor prognosis, the effusion was later proved to be hemorrhagic and was successfully treated with a single aspiration procedure. In our case, thoracic CT helped to suspect the rare disease, but the definitive diagnosis became clear only after a surgical lung biopsy and pathologist's investigation.

Several palliative DPL treatment modalities have been suggested in clinical case reports, all aimed at alleviating symptoms, reducing the frequency and amount of chylothorax or chylopericardium, and managing the proliferation of lymphatic tissues [1]. Treatment options include surgical interventions, radiation therapy and systemic medications. Surgical resection may be indicated for some patients with localized lesions, although there is a high risk of disease recurrence [1, 8]. In our case, surgery was not a viable option due to the large volume and diffuse spreading of the lymphatic malformations. Some authors have reported successful use of radiotherapy for managing pleural effusions and eliminating pulmonary infiltrations [9,10]. Systemic

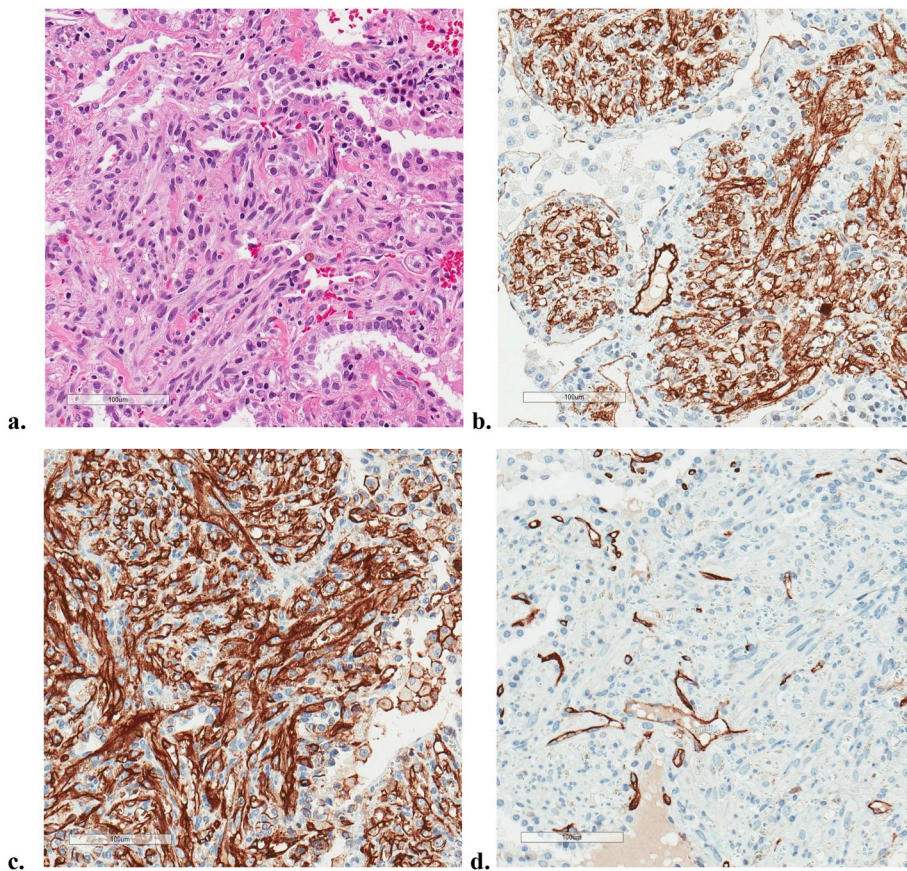


Fig. 4. Biopsy from the lung and pleura. (a) Hematoxylin and eosin, magnification x200, dense proliferations of numerous thin-walled vessels and spindle cells. (b) D2-40, magnification x200, moderate immunohistochemical membranous reaction in the proliferations of lymphatic vessels. (c) CD31, magnification x200, strong membranous reaction in endothelial cells of anastomosing vessels. (d) CD34, magnification x200, positive reaction in surrounding capillaries and mostly negative reaction in the proliferation.

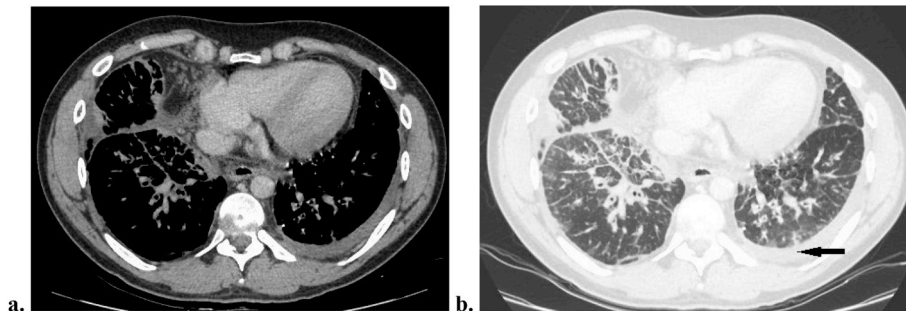


Fig. 5. Thoracic CT scan images at 21 months of treatment. (a) CT image with soft-tissue window showing decreased infiltration of the mediastinum and thickening of the pleura. (b) CT image with lung window showing decreased interlobular septal thickening and peribronchovascular interstitial thickening, and a small amount of pleural effusion (black arrow).

corticosteroids, cyclophosphamide, interferon- α -2b and tamoxifen have also been reported to be rather effective in symptom reduction. Nevertheless, the use of both radiotherapy and systemic therapy is limited by toxic side-effects [11]. Recently, it has been shown that bevacizumab, a recombinant monoclonal antibody, can lead to lymphatic tumor regression and respiratory function improvement [12,13]. This drug acts by inhibiting vascular endothelial growth factor (VEGF), which is responsible for inducing angiogenesis and lymphangiogenesis [14]. Unfortunately, bevacizumab was contraindicated in our patient due to hemoptysis and a recent episode of hemorrhagic pleural effusion. Given the drawbacks of the other therapy options, it was decided to initiate treatment with sirolimus, a mammalian target of rapamycin (mTOR) inhibitor.

Sirolimus is an immunosuppressive agent generally used for preventing rejection of renal transplants and treating patients with sporadic lymphangioleiomyomatosis. However, several small studies have shown

sirolimus to be effective in treating other lymphatic abnormalities, e.g. generalized lymphatic anomaly and Gorham-Stout disease [15]. For instance, Ozeki et al. performed a prospective study of 25 patients with various lymphatic anomalies, in which they concluded that sirolimus helps reduce the lymphatic tissue volume and leads to improvement of clinical symptoms [15]. Triana et al. reached the same conclusion in a retrospective analysis of 41 patients, noting that the clinical and radiological improvements occurred at a median time of 10 weeks [16]. Experimental evidence suggests that sirolimus suppresses the growth of lymphatic endothelial cells by inhibiting VEGF-A and VEGF-C driven proliferation and migration, thus impeding lymphangiogenesis [17,18]. Theoretically, the newer sirolimus analogs, such as everolimus and zotarolimus, should also be effective in downregulating VEGF expression and reducing lymphangiogenic activity [18]. However, there is a lack of clinical research proving their effectiveness in treating pulmonary lymphatic anomalies, including DPL. Everolimus is currently used

as an antineoplastic chemotherapy drug and an immunosuppressant for solid organ transplantation, while the indications of zotarolimus are limited to coating drug-eluting stents [19]. Therefore, due to the absence of evidence and much higher price, sirolimus analogs were not considered for treatment in our patient's case.

On the other hand, information regarding the effectiveness of sirolimus for treating DPL is scarce, as well. To our knowledge, this is only the second case report in the English literature describing an adult DPL patient treated with sirolimus. Previously, *Ernotte* et al. reported a 20-year-old DPL patient who remained in a good clinical condition for 4 years after initiating the treatment. However, the authors did not provide details of the patient's follow-up PFTs and CT scan results [6]. In our case, sirolimus has been effective in preventing disease progression as well as reducing the volume of the lymphatic masses, as seen in recent chest CT scans. We also observed a significant increase in FEV1 and FVC at 12 and 21 months of treatment.

Sirolimus is usually well-tolerated and most of the adverse reactions are mild, e.g. dyslipidemia, rash, anemia, thrombocytopenia, edemas, and diarrhea [20]. There is also an increased risk of infections due to the drug's immunosuppressive effects. In the study by *Ozeki* et al., 80% of patients treated with sirolimus experienced side effects, the most significant ones being pneumonia and cellulitis [15]. Fortunately, our patient has tolerated the treatment well and has not experienced any severe adverse reactions, even though sirolimus dosage was adjusted to achieve relatively high trough concentrations (10–15 ng/ml).

4. Conclusions

Due to its rarity, DPL poses certain diagnostic and therapeutic difficulties. Clinical and radiological signs are nonspecific, which is why a surgical lung biopsy is necessary for establishing an accurate diagnosis. To this day, no specific treatment for DPL has been approved. In this article we demonstrated that systemic treatment with sirolimus may be effective in preventing DPL progression and improving pulmonary function.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent for publication

Written consent was obtained from the patient for publication of this case report and for the use of accompanying images.

Declarations of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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