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Case Report

Effective treatment of inhaled corticosteroid and bronchodilator for "lymphocytic interstitial pneumonia" in primary Sjögren's syndrome

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ABSTRACT

We present a case of an 86-year-old woman who visited our hospital with a one-year history of exertional dyspnea (modified medical research council dyspnea scale; mMRC grade 2). Despite the absence of any smoking or dust exposure history, multiple cystic lesions were apparent in both lungs on her CT scan. We suspected Sjögren's syndrome-associated lymphocytic interstitial pneumonia (LIP) due to her additional symptoms of dry mouth and eyes. Her respiratory function test showed a restrictive disorder with a forced vital capacity (FVC) of 1.23 L (70.3 % predicted), forced expiratory volume in 1 s (FEV_1) of 0.88 L, and FEV_1/FVC of 71.5 %. The flow-volume curve showed a downward convex, suggesting peripheral airway obstruction. We initiated a daily inhalation treatment regimen comprising vilanterol 25 μg and fluticasone furoate 200 μg. One month later, at the follow-up visit, the clinical diagnosis of Sjögren's syndrome with LIP was made by positive SS-A and SS-B antibodies in the initial blood work, a Saxon test that confirmed decreased salivary secretion, and a confirmed diagnosis of dry eyes by her ophthalmologist. We noted improvement in FVC of 1.45 L (+17.8 %) and FEV_1 to 0.99 L (+12.5 %) in the subsequent respiratory function test, along with alleviation of her symptoms. The present case represents the first report of LIP treated exclusively with inhaled corticosteroids and bronchodilators, highlighting a potential therapeutic approach, particularly for elderly patients vulnerable to immunosuppressive therapies.

1. Introduction

Lymphocytic interstitial pneumonia (LIP) is a rare subset of interstitial lung diseases characterized by a diffuse pulmonary infiltrate dominated by lymphocytes, plasma cells, and other mononuclear cells within the interstitium [1]. An intriguing aspect of LIP is the presence of diffuse cystic lesions, observable in radiographic evaluations, contributing to its unique pathology. Its incidence remains very low, but its pathologic association with autoimmune diseases, notably Sjögren's Syndrome, brings it into unique focus within respirology [1]. The clinical manifestation of LIP is varied and often ambiguous, with symptoms ranging from asymptomatic

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radiographic findings to progressive dyspnea and coughing [1]. This wide spectrum of presentations, combined with its rarity, consistently poses challenges in diagnosing and treating LIP in medical practice.

Conventionally, systemic corticosteroids and immunosuppressive agents have been reported as the therapeutic mainstay for LIP associated with Sjögren's Syndrome [1,2]. These therapies, however, carry potentially harmful side effects, especially in elderly patients. A potential but understudied therapeutic alternative is inhaled corticosteroids and bronchodilators for LIP. Due to their localized action and lower systemic side effects, they could offer a beneficial treatment route, particularly for vulnerable populations. Therefore, this case report highlights the use of inhaled corticosteroids and bronchodilators for treating LIP in the context of primary Sjögren's Syndrome.

2. Case presentation

An 86-year-old female presented to our hospital with a chief complaint of dyspnea on exertion (mMRC grade 2) for a year prior to her visit. Despite her attempts at self-management, the symptom did not improve, prompting her visit to our institution. Her past medical history was notable for breast cancer surgery 6 years earlier, and she had no history of smoking or dust exposure.

On physical examination, the patient had a body temperature of 36.0 °C, a pulse rate of 107/min, and a room air oxygen saturation (SpO_2) of 98 %. The examination also revealed no jugular venous distention, clear breath sounds, no heart murmurs, and no lower leg edema. She exhibited signs of oral dryness and dry eyes. Laboratory findings showed a WBC count of 4710/μL (Neut 78.7 %, Lym 14.0 %, Mono 5.9 %, Eos 0.8 %, Baso 0.6 %), CRP 0.07 mg/dL, NT-pro BNP 177 pg/mL.

Chest X-ray revealed findings consistent with hyperinflation of the lung. Chest CT revealed multiple cystic lesions with a thin wall, varying their sizes in both lungs, with some calcified nodules within the cysts (Fig. 1). Pulmonary function tests demonstrated a forced vital capacity (FVC) of 1.23 L (70.3 % predicted), forced expiratory volume in 1 s (FEV_1) of 0.88 L (68.2 % predicted), FEV1/FVC of 71.5 %, and peak flow of 3.34 L (69.4 %) and a concave flow-volume curve, improving to FEV_1 0.95 L post-bronchodilator administration (Fig. 2).

In light of these clinical and imaging findings, the differential diagnosis was focused on Sjögren's Syndrome and associated LIP. Considering the results of the pulmonary function tests, it was hypothesized that peripheral airway obstruction caused by LIP could be the underlying cause of her symptoms. Owing to the patient's frailty, we refrained from using immunosuppressive agents or systemic corticosteroids to avoid severe adverse events. Treatment was initiated with an inhaler containing 25 μg of vilanterol and 200 μg of fluticasone furoate.

On a follow-up visit a month later, blood tests confirmed elevations of anti-SS-A antibodies (719 U/mL, reference <7.0 U/mL) and anti-SS-B antibodies (372 U/mL, reference <7.0 U/mL). Additionally, a Saxon test revealed a reduction (0.55 g/2 min, reference > 2.0 g/2 min) in salivary secretion. Her ophthalmologist confirmed her dry eyes. Although histopathological confirmation via biopsy had yet to be obtained, the clinical findings led to a diagnosis of Sjögren's syndrome and associated LIP. Compared to the initial visit, respiratory function tests on this follow-up visit showed improvement, with FVC of 1.45 L (+17.8 %), FEV_1 of 0.99 L (+12.5 %), and peak flow of 3.88 L (+16.1 %)(Fig. 2). After this treatment, the patient's respiratory symptoms were alleviated. However, four months

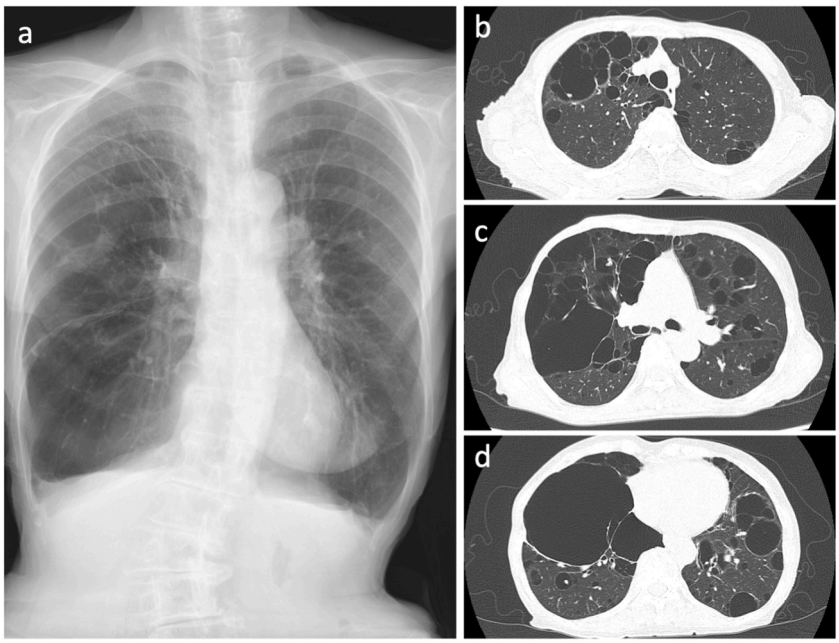

Fig. 1. Chest X-ray (a) and high-resolution CT images (b–d) of the patient.

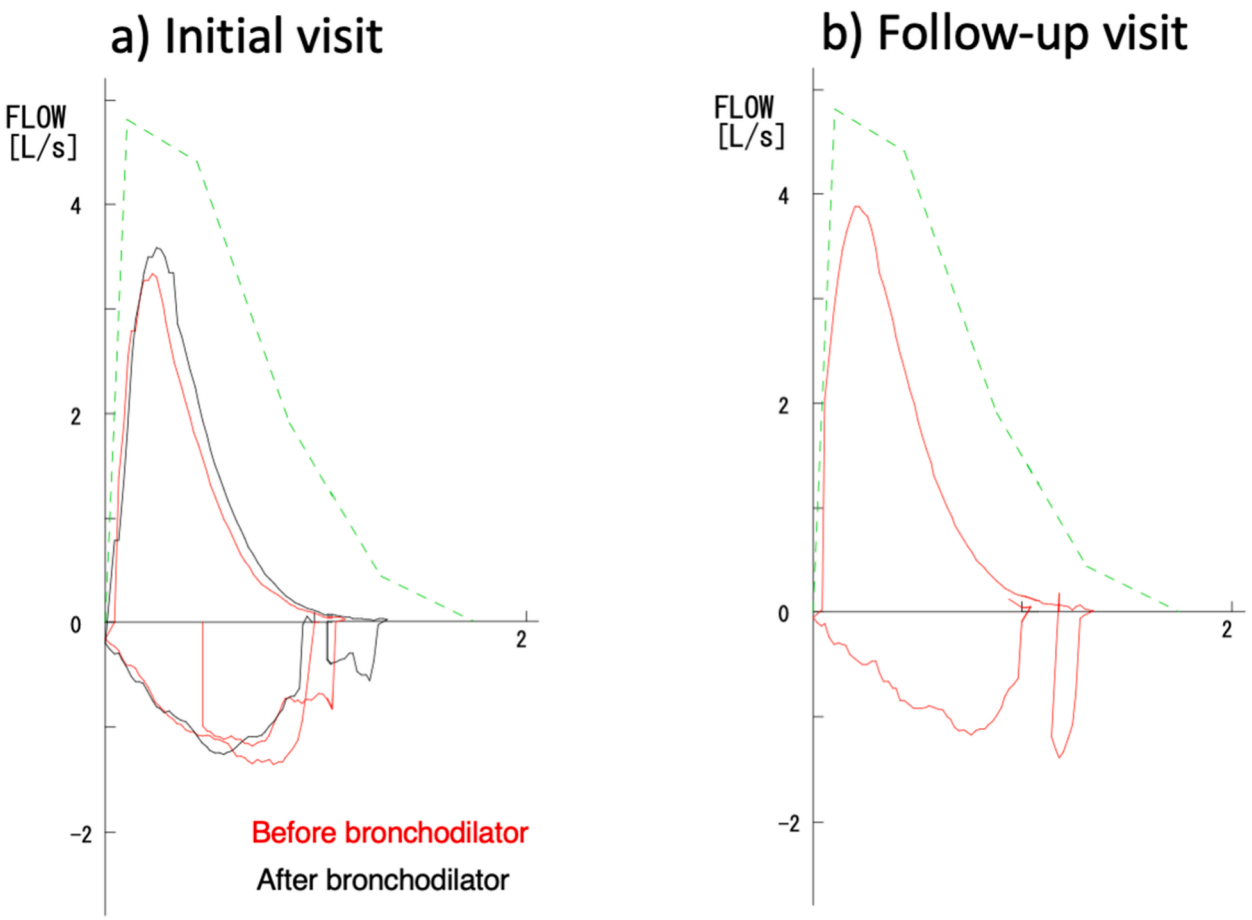

Fig. 2. Pulmonary function test (a) before and (b) one month after initiating inhaled vilanterol 25 μg and fluticasone furoate 200 μg.

following the initial visit to our hospital, the patient was diagnosed with recurrent breast cancer at another hospital and decided to opt for hospice care.

3. Discussion

This case report illuminates the effective treatment of a patient clinically diagnosed with LIP secondary to Sjögren's syndrome through inhaled corticosteroids and bronchodilators. A review of the literature reveals 27 reported instances of LIP secondary to Sjögren's syndrome from 1996 to 2023 [2]. In these cases, clinical symptoms were not captured in 11 of the 27, yet, the majority reported exertional dyspnea (9/16) and dry cough (6/16). Other respiratory manifestations encompassed chest pain, hemoptysis, and acute respiratory failure necessitating mechanical ventilation.

Treatment regimens for the 16 patients, as documented in their medical records, varied significantly. Most patients, except one, were treated with corticosteroids and/or immunosuppressants. Corticosteroid dosage typically ranged between 0.5 and 1 mg/kg/day [3–5]. A combination therapy of methylprednisolone pulse and hydroxychloroquine was administered to three patients [6,7]. Immunosuppressive medications, such as cyclophosphamide pulse, azathioprine, rituximab, and abatacept, were respectively prescribed to six patients [2,8–12]. Documentation shows either improvement or stabilization of pulmonary status post-therapeutic intervention in 13 out of the 16 patients, indicating systemic corticosteroids and immunosuppressive agents as therapeutic mainstays for LIP associated with Sjögren's syndrome.

However, conventional treatment could potentially be deleterious, especially for elderly patients prone to adverse effects. Considering that cystic airspaces could arise from partial airway obstruction due to peribronchiolar lymphoid cell infiltration [13], inhaled corticosteroids could alleviate peribronchiolitis. Bronchodilators may lessen check-valves, contributing to beneficial outcomes. Indeed, inhaled corticosteroids and bronchodilators improved the patient's symptoms and pulmonary function data, suggesting their potential as an alternative treatment for patients with diffuse cystic lesions of LIP.

Patients with LIP typically exhibit a restrictive ventilatory defect, while an obstructive ventilatory defect is considered atypical. Our patient presented with a restrictive pattern, evidenced by an %FVC of 70.3 %, aligning with the characteristic presentation of LIP. Notably, the FEV_1/FVC ratio was 71.5 %, slightly exceeding the standard threshold delineating obstructive defects (FEV_1/FVC $<$70 %). Furthermore, the flow-volume curve's downward convex pattern suggests the possibility of peripheral airway obstruction.

This is a compelling observation, indicating that obstructive features may manifest in LIP, albeit infrequently discussed in current literature. A study in the *European Respiratory Journal* [1], reported mean %FVC (65.0 ± 15.0 %), %FEV_1 (67.3 ± 18.4 %), and FEV_1/FVC (80.3 ± 5.0) in LIP patients, with increased residual volume (%RV) (120.53 ± 6.3), suggesting air-trapping indicative of small airway disease. Such findings support the notion that LIP may encompass a broader spectrum of pulmonary function abnormalities, including peripheral airway obstruction. This case thus highlights the potential complexity within the pulmonary function phenotype of LIP and posits peribronchiolitis as a potential underlying pathogenic factor.

One of the limitations in the present case is the lack of histological examination of the lung due to the patient's advanced age. Therefore, a clinical diagnosis was made by multidisciplinary team discussion (MDD) as discussed below. The differential diagnosis of diffuse cystic lung diseases with visible thin walls includes Birt-Hogg-Dube syndrome (BHD), Langerhans cell histiocytosis, lymphangioleiomyomatosis (LAM), amyloidosis, and LIP [14]. Among these diseases, cysts in LAM are round and smooth, with normal lung parenchyma in a diffuse distribution. Cysts in BHD are lentiform, abutting pleura vessels in a basilar predominant distribution. Cysts in LCH are bizarre, along with nodules and cavities in an upper zone predominant distribution. Cysts in LIP and amyloidosis are round of varying size and may have associated ground-glass attenuation, septal thickening, and nodules in diffuse distribution. In this patient, varying cyst sizes led to considering LIP or amyloidosis. With the presence of Sjögren's Syndrome, the diffuse cystic disease was clinically diagnosed as LIP. However, the possibility of amyloidosis cannot be completely dismissed. Genetic testing for *FLCN* gene, fat pad biopsy, serum/urine electrophoresis, serum free light chain could be tested to assess BHD and amyloidosis. A notable proportion of prior LIP studies also lack histological assessment information.

Another limitation was the inability to definitively exclude the coexistence of bronchial asthma in the patient. Ideally, a fractional exhaled nitric oxide (FeNO) examination, a methacholine challenge test, or peak flow variability monitoring should have been performed prior to corticosteroid treatment initiation to assess the potential confounding effects of bronchial asthma. A measurement of the functional residual volume would have provided a better understanding of the check-valve effect before and after inhaled treatment. Ho et al. revealed that bronchitis is common in connective tissue disease-related interstitial lung diseases [15]. They reported that sputum-guided management of airway eosinophilia was associated with FEV_1 improvement. In this context, sputum cell count could be instrumental in identifying infiltrated immune cells that may contribute to airflow obstruction.

Lastly, the concept of LIP as a distinct disease entity has been a subject of debate. A comprehensive study published in 2023 examining 201 cases suggests a reconsideration of LIP's classification [16]. The overlap between pathologic and radiologic criteria is scant, underscoring the challenge in distinguishing LIP from other benign lymphoid proliferations. Further, the rarity of idiopathic LIP cases and the broad clinical overlap with other conditions question the validity of LIP as a standalone diagnosis. While we have followed contemporary classifications to formulate a provisional diagnosis, recent evidence [16] advises caution in employing LIP as a definitive diagnostic term pending a more refined definition. It is important to clarify that our focus is on therapeutic outcomes rather than the nomenclature of the disease.

In conclusion, this case underlines the potential effectiveness of inhaled corticosteroids and bronchodilators as an alternative treatment strategy for LIP with an obstructive defect secondary to Sjögren's Syndrome, particularly for elderly patients. These findings pave the way for further validation through subsequent investigations. Our case report could potentially impact the future course of treatment strategies for LIP.

Patient consent for publication

Written, informed consent was obtained from the patient.

CRediT authorship contribution statement

Yuki Moriuchi: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Toyoshi Yanagihara:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Hiroaki Ogata:** Formal analysis, Investigation, Writing – review & editing. **Mitsuo Amemiya:** Formal analysis, Investigation, Writing – review & editing. **Aimi Ogawa:** Formal analysis, Investigation, Writing – review & editing. **Akiko Ishimatsu:** Formal analysis, Investigation, Supervision, Writing – review & editing. **Junji Otsuka:** Investigation, Supervision, Writing – original draft. **Kazuhito Taguchi:** Investigation, Supervision, Writing – review & editing. **Masako Kadowaki:** Investigation, Supervision, Writing – review & editing. **Hiromasa Maemura:** Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Atsushi Moriwaki:** Investigation, Supervision, Writing – review & editing. **Makoto Yoshida:** Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

All authors of this manuscript declare that they have no conflicts of interest.

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