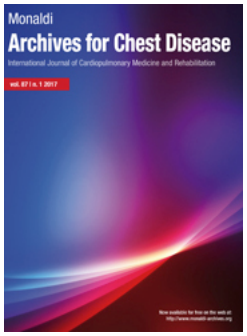

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Probe-based confocal laser endomicroscopy in diagnosis of diffuse cystic lung disease in Sjögren's syndrome

Igor Sergeevich Mamenko,[1] Igor V. Vasilev,[1] Roman V. Simonov,[1] Anna S. Zakharova,[1,2] Pavel V. Gavrilov,[1] Ivetta V. Dvorakovskaya,[1,2] Tatiana A. Novitskaya,[1,3] Petr K. Yablonskiy[1,3]

[1]Department of Interventional Pulmonology, St. Petersburg State Research Institute of Phthisiopulmonology, St. Petersburg
[2]Research Institute of Pulmonology, I.P. Pavlov First Saint Petersburg State Medical University, St. Petersburg
[3]Medical Faculty, St. Petersburg State University, Russia

*Corresponding Author: Igor Sergeevich Mamenko, Department of Interventional Pulmonology, St. Petersburg Scientific Research Institute of Phthisiopulmonology , Ligovskiy Ave. 2-4, St. Petersburg, 191036, Russia. Tel. +7.9217790109. E-mail: dr.mamenko.is@gmail.com

Abstract

Sjögren's syndrome is systemic autoimmune disease characterized by lymphocytic infiltration of various organs with wide frequency of pulmonary involvement. Diffuse cystic lung disease in Sjögren's syndrome is a rare condition and requires differential diagnosis with other cystic pathologies such as lymphangioleyomiomatosis or Langerhans cell histiocytosis. Probe-based confocal laser endomicroscopy (pCLE) is a method of *in vivo* investigation of airways and lung tissue on microscopic level during bronchoscopy. We used this method in diffuse cystic lung disease caused by Sjögren's syndrome. The pCLE image showed a large number of fluorescent cells presumably lymphocytes in bronchioles, dilated alveolar spaces with fluid and thin alveolar walls. We think that the presence of the bronchiolar cells pattern can be used to differentiate between the pulmonary manifestations of Sjögren's disease and other cystic lung diseases.

Keywords: confocal laser endomicroscopy; optical biopsy; diffuse cystic lung disease; Sjögren's syndrome; primary Sjögren; pulmonary manifestations of Sjögren's syndrome.

Introduction

Sjögren's syndrome is systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal glands and characterized by a triad of keratoconjuctivitis sicca, xerostomia, and a generalized connective tissue disorder [1,2]. It can occur in isolation (primary Sjögren) or be associated with other rheumatologic conditions, such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis (secondary Sjögren) [3]. Pulmonary involvement in patients with Sjögren syndrome has a wide frequency of 9% to 90% but it is clinically significant in 10%-20% [1,4]. The most common pulmonary manifestations are nonspecific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia, bronchiolitis, bronchiectasis, pulmonary amyloidosis, pulmonary lymphoma, cystic lung disease [1,5]. Cystic lung disease occurs in 7-46% of patients and usually associated with lymphocytic interstitial pneumonia, amyloidosis or lymphoproliferative disorders [4]. Cyst-only disease is less frequent (2.5-9%) and requires differential diagnosis with other cystic pathologies such as lymphangioleyomiomatosis or Langerhans cell histiocytosis [1,3,4].

Probe-based confocal laser endomicroscopy (pCLE) is a method of in vivo investigation of airways and lung tissue on microscopic level during bronchoscopy [6]. This tool is used in differential diagnosis of interstitial lung disease [7,8], but we did not find a description of the use of this method in Sjögren's disease in the scientific literature.

We report a case of using pCLE in diagnosis of diffuse cystic lung disease in Sjögren's syndrome.

Case Report

A 34-year-old nonsmoking female was admitted to St. Petersburg State Research Institute of Phtisiopulmonology with complaints of weakness and fatigue. In August, 2022 after having a COVID-19 infection patient underwent high-resolution CT, which revealed multiple thin-walled cysts 3-20 mm in diameter in intact lung tissue. Based on these findings presumptive diagnosis of lymphangioleiomyomatosis was made and she was sent to the St. Petersburg State Research Institute of Phthisiopulmonology to verify the diagnosis. From the anamnesis it is known that patient has chronic primary Sjögren syndrome with symptomatic keratoconjuctivitis sicca, xerostomia and connective tissue disorder and also pituitary microadenoma and hyperprolactinoma. High resolution chest computed tomography was repeated at the hospital. The presence of multiple cysts of varying sizes, some of which had internal septations and were associated with eccentric vessels, was noted (Figure 1). Laboratory test shows hemoglobin of 112 g/l, leukocyte count of 5.4 $*10^9$/L. Pulmonary function tests were normal. To clarify the diagnosis, it was decided to perform a bronchoscopy with pCLE and bronchoalveolar lavage. Bronchoscopy

was made under local anesthesia of 2% solution of lidocaine and showed mild endoscopic signs of bronchitis. pCLE was performed by the Cellvizio system and 1.4-mm semiflexible probe Alveoflex (Mauna Kea Technologies, Paris, France). Miniprobe was inserted through the instrumental channel of the endoscope and passed into the distal parts of the bronchial tree until a dynamic image of the alveoli was obtained. In alveolar areas with normal lung tissue by HRCT data (right segment 2,3) pCLE image showed normal round alveolar structures without pathological patterns (Figure 2A). When inserting the probe in subsegmental bronchi to most affected zones by HRCT data (right segment 4,5) before the appearance of alveoli al the level of bronchioles pCLE image showed a large number of small (average diameter 20 μm) highly fluorescent cells presumably lymphocytes (Figure 2B). After penetration of the bronchiole pCLE showed dilated alveolar spaces (corresponding to pulmonary cysts) with thin alveolar walls and vessels (Figure 3C,D). In lung tissue we did not find any highly fluorescent cells. Bronchoalveolar lavage was performed from right segment 5. Results of the analysis of bronchoalveolar lavage was not specific: 75% of macrophages and 11% of lymphocites, single erythrocytes. Due to the fact that the data obtained were nonspecific, and lymphangioleiomyomatosis could not be excluded, it was decided to perform a thoracoscopic lung biopsy. Histological examination of surgical biopsy sample showed thinning of the most intraalveolar septa, dilatation of individual bronchioles (the wall of some bronchioles is partially destroyed with focal and diffuse lymphoid infiltration, located peribronchially and subepithelially) and focal hypertrophy and hyperplasia of smooth muscle elements of bronchioles (Figure 3A). Also determined a large cyst, the wall of which is represented by the wall of the bronchiole, partly lined with a typical epithelium, partly the epithelium flattened or absent (Figure 3B). Immunohistochemical staining was negative for HBM-45, and D2-40, excluding the diagnosis of lymphangioleiomyomatosis. The patient was referred to a rheumatologist with a diagnosis of diffuse cystic lung disease in Sjögren's syndrome.

Discussion

Diffuse cystic lung disease is a rare pulmonary manifestation of Sjögren's syndrome and it requires differential diagnosis with lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis as most frequent in the clinical practice. For the diagnosis in that case, we used pCLE – method of *in vivo* investigation of airways and alveoli based on the phenomenon of autofluorescence, which is also called "alveoloscopy". This technology is used in a limited number of thoracic centers in the world. The role of pCLE in the diagnosis of lung disorders is not well understood, but it is expected that this method may provide additional information for the differential diagnosis of various interstitial lung diseases [7,8]. We used pCLE to investigate airways and lung tissue in patients with diffuse cystic lung disease and Sjögren's syndrome and

found a large number of fluorescent cells corresponding in size to lymphocytes in bronchioles, dilated alveolar spaces with fluid and thin alveolar walls corresponding to pulmonary cysts. These findings correlated with the changes revealed in the histological examination. Thus, the presence of autofluorescent bronchiolar cells in pCLE is the main feature of diffuse cystic transformation in Sjögren's disease. Some scientific reports proved that in primary Sjögren's syndrome small airways is the main target for lymphocytic infiltration [2,9]. Also suggested that lymphocytic cells infiltration of the bronchiolar wall, leading to airway narrowing, postobstructive bronchiolar ectasia and distal air-trapping (check-valve mechanism), is the main cause of cyst formation in Sjögren's syndrome [10]. Salaün *et al*. earlier performed pCLE in patients with connective tissue disease-associated interstitial lung diseases and noted a high frequency (up to 29.5%) of bronchiolar fluorescent cells. At the same time, no changes in the level of bronchioles have been described in patients with lymphangioleyomyomatosis [11]. To best of our knowledge it is the first case of pCLE investigation of a patient with cyst-only lung disease in Sjögren's syndrome. We think that pCLE finding of fluorescent bronchiolar cells with specific HRCT signs (such as eccentric vessels and internal septations) may confirm cystic lung disease as pulmonary manifestations of Sjögren's syndrome in the corresponding group of patients and avoid thoracoscopic lung biopsy in further cases.

Conclusions

Probe-based confocal laser endomicroscopy is useful in diagnosis of diffuse cystic lung disease in Sjögren's syndrome. The presence of the bronchiolar cells pattern can be used to differentiate between the pulmonary manifestations of Sjögren's disease and other cystic lung diseases.

Statement of Ethics

The use of pCLE was approved by the local Ethical Committee and patient gave inform consent to participate.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Mamenko I.S. and Vasilev I.V. conceived of the presented idea. Mamenko I.S., Vasilev I.V. and Simonov R.V. carried out the experiment. Mamenko I.S. took the lead in writing the manuscript. Mamenko I.S., Vasilev I.V., Simonov R.V., Zakharova A.S. and Gavrilov P.V. contributed to the interpretation of the results. Dvorakovskaya I.V., Novitskaya T.A. contributed to sample preparation. Simonov R.V., Zakharova A.S. and Gavrilov P.V contributed to the design and

implementation of the research, to the analysis of the results and to the writing of the manuscript. Yablonskiy P.K. supervised the project. All authors discussed the results and contributed to the final manuscript.

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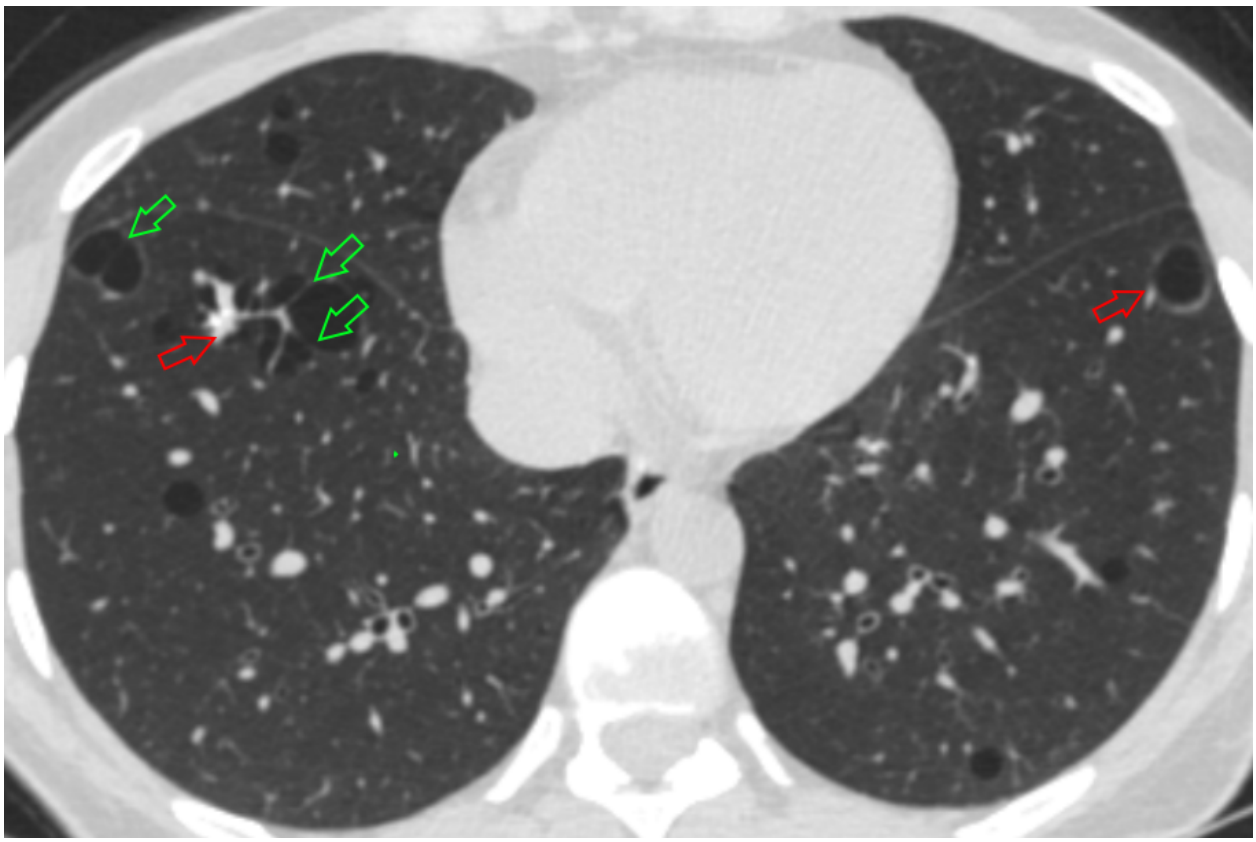

Figure 1. HRCT images showing multiple thin-walled and variable-sized cysts in lung tissue often bordered by an eccentric vessel (red arrows), some of cyst contains internal septations (green arrows).

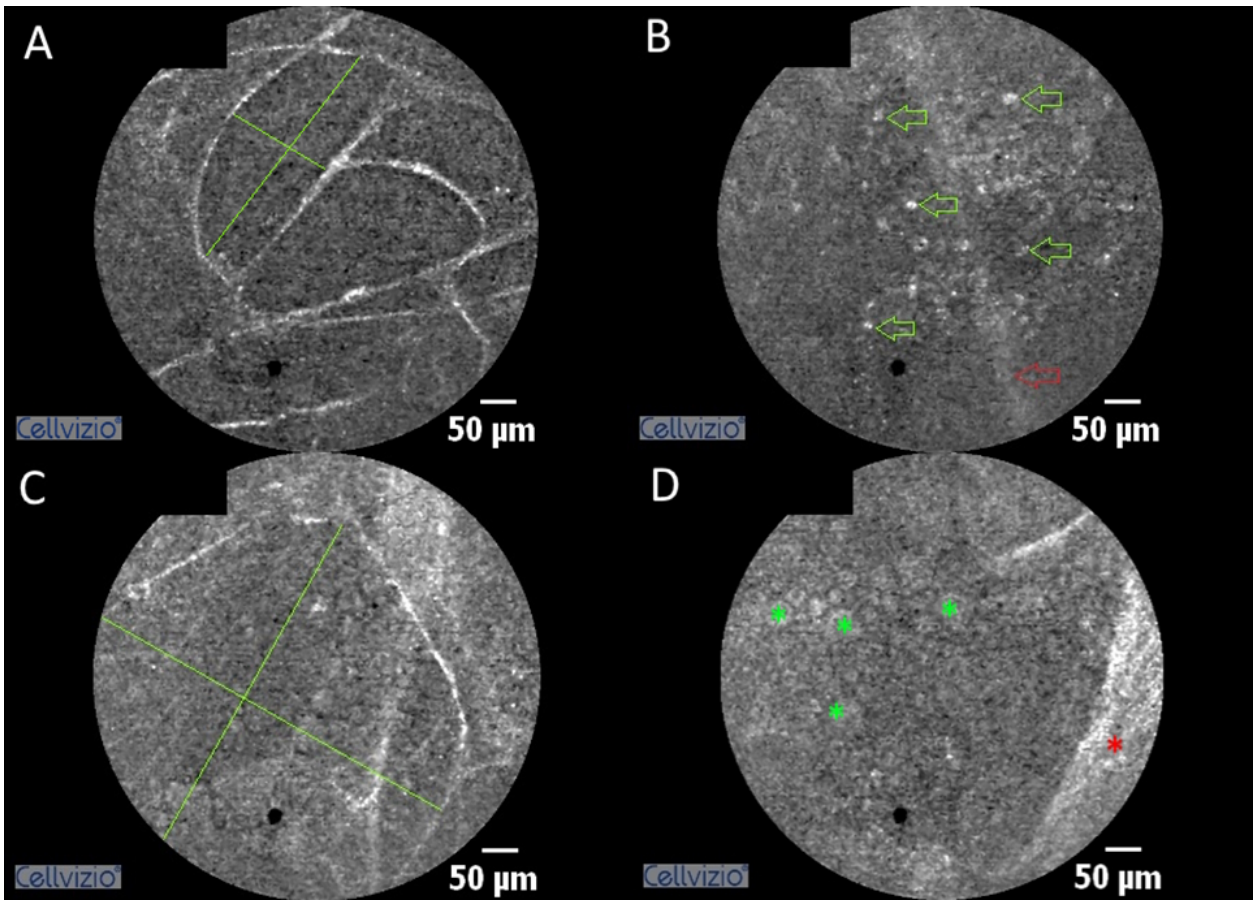

Figure 2. pCLE examination of airways and alveoli. A) Normal alveolar structures. B) Highly fluorescent cells (green arrow) in bronchiolar area (bronchiolar wall – red arrow). C) Dilated alveoli and thinned alveolar walls. D) Dilated alveolar space filled with secretion (green *) and adjacent microvessel (red *).

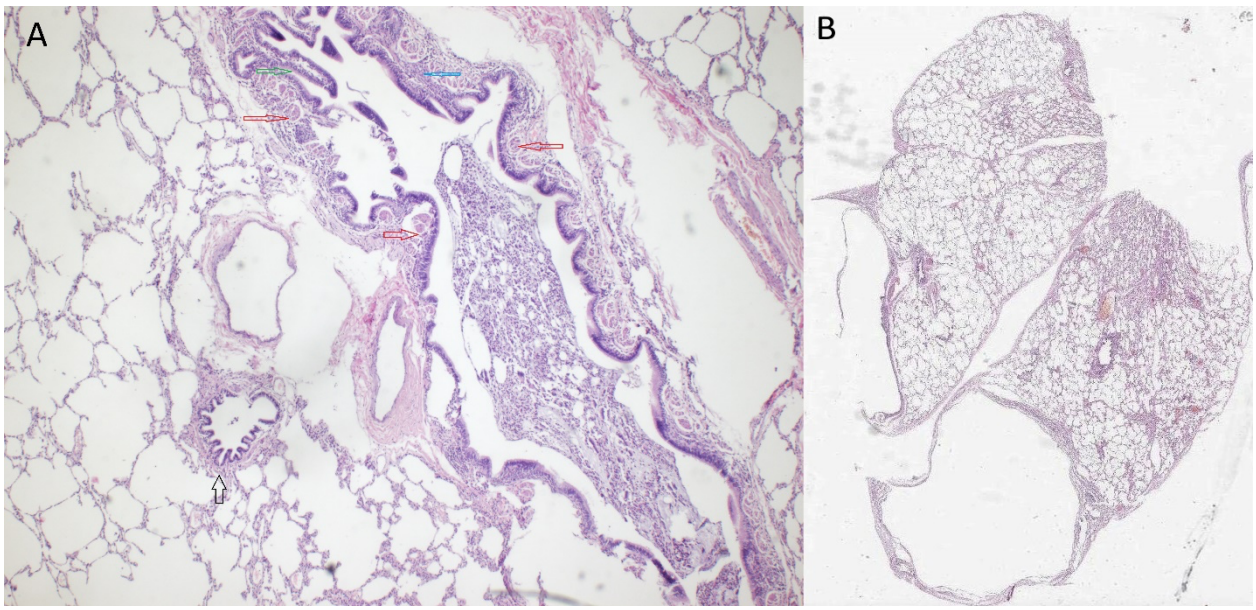

Figure 3. Histological examination of lung tissue. A) The lumen of the bronchiole is dilated, the respiratory epithelium is preserved (green arrow), there is focal hypertrophy of smooth muscles in the wall of the bronchiole (red arrows), and a mild lymphoid infiltration is detected subepithelially (blue arrow); in the lumen of the bronchioles there is mucus, desquamated cells of the bronchial epithelium, lymphocytes and leukocytes. Normal bronchiole (black arrow) (H&E staining, x 100). B) Lung tissue with areas of acinar emphysema and thin-walled cyst (H&E staining, x 40).