Bronchoscopic Journey of in vivo Real-Time Microscopic Imaging in ILD: A Case Series

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Abstract

\textbf{Background:} Patients with interstitial lung diseases (ILDs) frequently present with nondiagnostic high-resolution CT (HRCT) scan and bronchoalveolar lavage (BAL) results, resulting in the need for invasive surgical or cryo-lung biopsy that is associated with significant morbidity. Confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) are high-resolution laser and light-based techniques that provide real-time imaging of the alveolar compartment during bronchoscopy with a different depth and field of view.  

\textbf{Objectives:} The aim of the study was to correlate OCT and CLE imaging to HRCT imaging in ILD.  

\textbf{Methods:} This is a retrospective case series of 20 ILD patients who underwent alveolar CLE and OCT imaging during a standard bronchoscopy with BAL, followed by a lung biopsy when indicated. CLE and OCT imaging were compared to four main HRCT patterns and histology. The final diagnosis was based on the multidisciplinary discussion diagnosis.  

\textbf{Results:} Bronchoscopic CLE and OCT imaging were feasible and safe and provided additional high-detailed anatomical information compared to the HRCT. Bronchoscopic real-time CLE was capable of identification of “alveolar cells” (ground glass opacities) and lung fibrosis (increased alveolar elastin fibers). Bronchoscopic real-time OCT allowed for visualization of “patchy fibrotic disease”, “honeycombing” (microcysts), and mucosal granulomas in the airways.  

\textbf{Conclusions:} Bronchoscopic CLE and OCT of the alveolar compartment is feasible and safe and enables minimally invasive, high-resolution detection of specific ILD features with the potential to improve ILD diagnostics and monitoring and decrease the need for surgical or cryo-lung biopsies.

Introduction

High-resolution computed tomography (HRCT) scans are frequently nondiagnostic in patients with interstitial lung disease (ILD) \cite{1, 2} due to impairments in the resolution. HRCT imaging is, in these cases, often fol-
lowed by a bronchoscopy with bronchoalveolar lavage (BAL) and the results are discussed in a multidisciplinary discussion (MDD). In a significant number of patients, the MDD still lacks information to conclude a specific diagnosis, and following the guidelines, a surgical biopsy is indicated [3]. Recently, transbronchial cryobiopsy has been introduced as a promising and safer alternative to surgical lung biopsy (SLB) in the diagnostic approach to diffuse parenchymal lung diseases (DPLD) [4, 5]. However, both the SLB and TCBC are hampered by significant morbidity and risk of exacerbation [4, 6–10].

The standard workup of patients with ILD consists of a bronchoscopy with a (immune) BAL, where fluid is obtained in an attempt to diagnose a subtype of ILD based on the cellular composition, often extended by FACS-analysis of the fraction of mononuclear cells. Confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) are novel complementary microscopic laser and light-based imaging techniques that are minimally invasive and can be combined with bronchoscopy [11, 12]. The results in pulmonology so far have shown the techniques to be safe [13]. Studies in other fields have shown the potential of the two high-resolution techniques in visualizing tissue with resolutions resembling histology [14–16].

CLE and OCT provide high-resolution imaging of the airways and lung parenchyma [16]; however, they differ in their resolution. CLE enables real-time imaging on a cellular level, but it is limited in the field of view [17, 18]. While OCT has limitations in the visualization of individual cells, it has a wide field of view and improved imaging depth [13, 19].

CLE provides forward-looking imaging of a tissue plane with a resolution of 3.5 μm, which allows visualizations of the autofluorescent elastin fibers of the alveolar scaffold and autofluorescent cells including macrophages in the alveolar space [20]. Recently, pCLE features for a number of different ILD including idiopathic pulmonary fibrosis (IPF), asbestosis, sarcoidosis, desquamative interstitial pneumonia (DIP), amiodarone related pneumonia, and hypersensitivity pneumonitis were reported [17, 21]. However, the interpretation of lung confocal images in ILD remains challenging, as a comparison with pathology is in most cases not available. Therefore, this study aimed to compare the results of CLE and OCT with four main HRCT patterns (groundglass, fibrosis, granulomatous, and cysts).

OCT imaging is performed with a rotating near-infrared light source and provides imaging over an area of 5.4 cm of the alveolar space and airways, with a depth of approximately 2–3 mm and a resolution of 10–15 μm [22, 23]. Recently, it has been demonstrated that OCT accurately distinguishes usual interstitial pneumonia (UIP) from fibrotic nonspecific interstitial pneumonia (fNSIP) and airway-centered fibrosis by visualizing specific fibrotic features [24] and by correlating the OCT findings to the histology of lung biopsies. OCT imaging in fNSIP showed homogeneous fibrotic thickening of the interstitial alveolar walls, while in UIP, microscopic honeycombing cysts and dense, destructive subpleural fibrosis were found on OCT imaging. OCT studies in other types of (nonfibrotic) ILD are, to the best of our knowledge, currently lacking.

Radiologists describe four basic patterns of radiological lung disease on HRCT: (1) increased attenuation (referred to as “ground glass opacity” and “consolidation”); (2) reticulation with parenchymal distortion (fibrosis); (3) nodules (large or small, singular or multiple); and (4) mosaic patterns and cysts [25]. Since ILD is a heterogeneous disease, there is a wide variety of characteristics which play a role in diagnosing ILD. The aim of this study was to correlate CLE and OCT with HRCT scan imaging in ILD patients.

Secondary objectives were to compare the CLE and OCT imaging to the BAL and pathology results of lung biopsies and evaluate the feasibility and safety of CLE and OCT during bronchoscopy in ILD patients. The data are presented in descriptive visual correlations. The reference standard was the final diagnosis made by multidisciplinary discussion based on patient history, laboratory blood results, high-resolution CT scan, BAL, and histology from the lung biopsies when available.

Methods

Enrollment Criteria

ILD patients referred for bronchoscopy with BAL and optional transbronchial cryobiopsy or SLB were consented for this study (Clin.Trials.gov nr: NCT02689102) between October 2015 and April 2017. Patients could be included when >18 years of age. Excluded were pregnant or lactating patients. Patients who smoked in the last 3 months could not participate in the study in order to avoid disturbance of the CLE imaging by foamy macrophages.

OCT and CLE Measurements

After the introduction of the bronchoscope, a BAL was performed in the contralateral lung. This was followed by fluoroscopy-guided CLE and OCT measurements in previously determined segments based on the abnormalities on the HRCT scan. Subsequently, either fluoroscopy-guided TCBC or video-assisted thoracic surgery-assisted SLB was taken. The final diagnosis was established based on patient history, laboratory blood results,
HRCT scan, BAL, and, when available, the histology from the lung biopsies.

The in vivo CLE measurements were performed by inserting the thin (1.4 mm) CLE probe into the working channel of the bronchoscope. From the conducting airways, the CLE probe was slowly advanced into the alveolar compartment until the pleura was reached. In a single patient, several lung segments were assessed and multiple sequences recorded. CLE imaging was performed with the Alveo-flex miniprobe (Mauna Kea Technologies, Paris, France) with a 488 nm wavelength and the following properties: resolution 3.5 μm, depth 0–50 μm, and field of view 600 μm. CLE imaging was analyzed using Cellvizio-viewer software and the automatic mosaic function was used to knit images together for a wider overview. This method is described in more detail in a previous publication [26].

The in vivo OCT imaging was performed by use of a C7-XR St. Jude Medical Inc. system by inserting a guide sheet containing the C7 Dragonfly catheter (Ø 0.9 mm diameter) (St. Jude Medical Inc., St. Paul, MN, USA) into the working channel of the bronchoscope. From the conducting airways, the OCT-probe was slowly advanced into the alveolar compartment. When alveolar structures were visualized on the OCT imaging, the guidance sheet was retracted and the probe was left behind in the alveolar space. A small amount of saline (0.5 mL NaCl 0.9%) was flushed into the alveoli via the OCT-catheter, in order to open the alveolar spaces. The flushing of saline was immediately followed by an automated pull-back imaging collection over 5.4 cm, of which the alveolar part was used for analysis. ImageJ’s FIJI software for Windows (National Institutes of Health, Bethesda, MD, USA) was used to create a 3D reconstructions.

Lung Biopsy
Fluoroscopy-guided TBCB and video-assisted thoracic surgery-assisted SLB were obtained in the same segment as the in vivo CLE and OCT imaging. The cryobiopsy procedure was performed under deep propofol sedation in a day-clinic setting, with a flexible uncuffed endotracheal tube (Rush; Teleflex Medical, Westmeath, Ireland) for airway management and a prophylactically placed 6Fr Fogarty balloon in the assessed airway to control bleeding. Lung biopsies were fixed in 10% buffered formalin and embedded in paraffin, after which 4-μm thick sections were cut and stained with standard H&E plus staining for the elastin fibers (Elastica von Gieson [EvG]), in a routinely fashion. The slides were digitalized for analysis by Philips software (Eindhoven, The Netherlands). The histology images of the lung biopsies were assessed by an experienced pulmonary pathologist (JR) and discussed in an ILD MDD. Lung biopsy histology was compared to CLE and OCT imaging.

HRCT scan imaging was performed with 64 slice scanners (CT Philips Brilliance [Philips Medical Systems, Best, The Netherlands] and CT Siemens Sensation [Siemens Healthineers, Erlangen, Germany]). HRCT scan imaging was reviewed in a standard fashion by radiologists specialized in DPLD and discussed in a multidisciplinary ILD meeting.

For study purposes, four main internationally adopted radiological patterns for DPLD were used in order to make a descriptive visual overview of subgroups of ILD patients: (1) increased attenuation (“ground glass opacity” and “consolidation”); (2) reticulation with parenchymal distortion (fibrosis); (3) nodules; and (4) mosaic patterns and cysts [25]. The presence of one of these dominant radiological patterns was concluded by a radiologist specialized in DPLD (I.A.H.B.).

Results
In 20 ILD patients, HRCT, CLE, and OCT imaging and histology of lung biopsy were performed, except for a single patient not having OCT imaging. Patient characteristics and final diagnosis are presented in Table 1. CLE and OCT imaging were feasible in the assessed patients, and no adverse events related to the study measurements oc-
Normal Lung Parenchyma

Normal lung parenchyma is characterized by thin alveolar fibers shaping the alveolar openings on the CLE imaging (Fig. 1d), which correlates to the histology of a normal lung biopsy (Fig. 1e). OCT imaging of normal lung parenchyma visualizes a network structure with homogenously distributed and sized alveolar dark airspaces bordered by thin bright alveolar septa (Fig. 1c).

Increased Attenuation

The radiological pattern of “increased attenuation” is referred to on the HRCT as “ground glass opacity” and “consolidation.” A total of 12 patients had a dominant pattern of ground glass or consolidations (final diagnosis desquamative interstitial pneumonia (DIP) (n = 1), lymphocytic interstitial pneumonia (LIP) (n = 1), cellular and fNSIP (n = 5), sarcoidosis (n = 2), chronic hypersensitivity pneumonitis (cHP) (n = 1), alveolar proteinosis (n = 1), and unknown diagnosis (n = 1)) (Table 1). Cellular filling of the alveolar space with motile cellular structures on CLE imaging was found in patients with DIP, LIP, and cellular NSIP with corresponding cellular infiltrates in the alveolar space in the histopathology of the lung biopsy. An example of CLE imaging in a patient diagnosed with desquamative interstitial pneumonia (DIP) is demonstrated (Fig. 2c). OCT was capable of identification of consolidations with loss of air-filled alveolar spaces (Fig. 2b).

Fig. 1. Overview of examples of normal imaging of the lung parenchyma with different imaging techniques and pathology. a HRCT scan of normal lung parenchyma. b White light image of the airways during bronchoscopy where the CLE-catheter is visualized in the right lung. c OCT image of normal alveoli with thin alveolar septa (p: OCT-probe). d CLE image of normal alveoli visualizing the autofluorescent elastin fibers. e Histology of a lung biopsy in ILD patient of lung parenchyma without any abnormalities at pathological evaluation.

Fig. 2. a HRCT scan imaging with ground glass as the dominant pattern, which is suspected for an adenocarcinoma in situ. b OCT images show the loss of alveolar spaces by infiltrates. CLE visualizes filling of the alveolar space with autofluorescent cells (c), without signs of fibrosis (no additional fibers), which is comparable to the histology of the biopsy (d). This patient is diagnosed with a desquamative interstitial pneumonia (DIP) in the multidisciplinary ILD meeting.
able for the identification of characteristics of lung fibrosis. CLE enabled visualization of increased and distorted elastin fibers in pulmonary fibrosis, which matched with the structure of the elastin fibers in the histology of the lung biopsies (Fig. 3c). OCT visualized thickened alveolar walls and a loss of “network” structure in fibrosis (Fig. 3b). CLE and OCT were both capable of identification of patchy fibrosis in a patient with cHP by visualizing areas with normal lung parenchyma with adjacent areas with lung parenchyma with signs of fibrosis (Fig. 4).

Nodular Pattern
In patients with a nodular dominant pattern \((n = 2)\), granulomas were not sufficiently autofluorescent to be easily visualized on the CLE imaging (Fig. 5d) and these results were comparable to the entire subgroup of patients diagnosed with sarcoidosis \((n = 4)\) and silicosis \((n = 1)\). Similarly, OCT did not identify single parenchymal granulomas but did visualize parenchymal changes (Fig. 5c) and detect macroscopic airway abnormalities in a sarcoidosis patient with mucosal granulomas (Fig. 5b). Histology of a peripheral lung biopsy was available in 1 patient with silicosis; the other patients were diagnosed by a multidisciplinary board based on the HRCT scan and cytology from endoscopic needle biopsies (e.g., endobronchial/esophageal ultrasound with transbronchial/ fine needle aspirations (EBUS-TBNA/EUS-FNA) from mediastinal lymph nodes and/or mucosal biopsies from the airway).

Pulmonary Cysts
In patients with cysts as the dominant radiological pattern \((n = 3)\), OCT imaging detected solitary pulmonary cysts and microscopic honeycombing, demonstrating

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Fig. 3. a Inconclusive HRCT scan with reticulation as the dominant pattern. b OCT imaging visualized characteristics for homogeneous lung fibrosis with a loss of the alveolar airspaces. c Mosaiced CLE imaging of a lung area, visualizing an increased number of elastin fibers. d Histology image of the corresponding lung biopsy with homogeneously distributed fibrosis in a patient with the final diagnosis fibrotic nonspecific idiopathic pneumonia.

Fig. 4. a Inconclusive HRCT scan with reticulation as the dominant pattern. b OCT imaging visualized characteristics for patchy lung fibrosis (*) with adjacent preserved but distorted and thickened alveolar structures on the right side of the image probe (#). c Mosaiced CLE imaging of a lung area, similarly visualizing an area suspected for fibrosis (*) (increased elastin fibers with loss of alveolar architecture) alternated by an area with preserved alveolar structure (#). d Histology image of the corresponding lung biopsy with patchy fibrosis in a patient with the final diagnosis cHP.
dark, round-shaped entities that did not originate from the airway lumen (Fig. 6). We show examples of in vivo OCT and CLE imaging of cysts in Langerhans cell histiocytosis (LCH) and cHP (Fig. 6, 7). With OCT, clear visualization of large and microscopic cystic structures was realized (Fig. 6b). With CLE, an increased diameter of the alveolar opening was found in cysts (Fig. 7c) and the presence of a large amount of large autofluorescent cells (hampering a clear visualization of the alveolar structures) The BAL of the corresponding segments of the lung revealed the presence of macrophages and few CD1a+ positive cells.

**Overview Results OCT**

OCT was capable of recognizing abnormalities in all four dominant radiological patterns. OCT provided additional information compared to HRCT imaging in patients with dominant radiological patterns of (1) “reticulation” by identification of a homogeneous distribution versus a patchy distribution of fibrosis (Fig. 3, 4), (2) “cysts” by visualizing microscopic honeycombing (Fig. 7), and (3) “nodular pattern” by detection of mucosal irregularities caused by granulomas in the airway (Fig. 5).

**Overview Results CLE**

CLE was capable of recognizing abnormalities in three out of four dominant radiological patterns. CLE provided additional information compared to HRCT imaging in patients with dominant radiological patterns of (1) “increased attenuation” by identification of individual cells and cellular infiltrates and the lack of signs of fibrosis (Fig. 2) and (2) “reticulation” by visualizing areas with a homogeneous distribution versus a patchy distribution of fibrosis.
Discussion

Bronchoscopic CLE and OCT were able to identify important anatomical ILD features not visible on HRCT scan imaging, such as microscopic cysts, cellular infiltrates, patchy fibrosis, and airway granulomas. This is a unique overview of the comparison between HRCT, histopathology, and the combination of OCT and CLE. OCT and CLE are complementary techniques, with OCT visualizing lung parenchyma and airway over a stretch of 5.4 cm with a depth of 1–2 mm and CLE imaging a small area with very high resolutions. Since ILD patients frequently need to undergo lung biopsy procedures when their HRCT scan is inconclusive, which coincides with complication risk, minimal invasive bronchoscopic imaging techniques have the potential to guide lung biopsies and narrow the differential diagnoses that are associated with different dominant radiological patterns. Hereby, CLE and OCT in the future may contribute to a decrease in the number of required lung biopsies.

OCT was capable of imaging fibrosis and distinguishing “patchy” from homogenous fibrosis and the identification of airway granulomas. Furthermore, OCT visualized macroscopic and microscopic cysts with different underlying ILD, in line with the microscopic cysts that were previously published by Hariri et al. [12] of OCT in patients with IPF [24]. Indeed, we showed that these cysts are detectable in a patient with chronic HP and LCH and that homogenous fibrosis was visualized in patients with NSIP.

In the presented study population, OCT imaging was not suitable for detecting individual cells and granulomas that are located in the alveolar space caused by limitations in the resolution (>10 μm). However, irregularities in the mucosa of the airways were imaged with OCT and corresponded to the localization of granulomas. In summary, we found that OCT provided additional valuable information in patients with dominant radiological patterns of fibrosis (reticulation), nodular pattern, and cysts. OCT was less informative in patients with ground glass based on cellular alveolar infiltrates.

CLE could provide additional information regarding the underlying cause for groundglass opacities. CLE detected the presence of cells in DIP and LIP. The cellular abnormalities with a preservation of the normal elastin scaffold of the alveolar compartment were clearly distinguished from the patients with a radiological dominant pattern of ground glass with on CLE imaging a noncellular fibrotic pattern with an increase in the number of elastin fibers. In a recent publication, we demonstrated that CLE seems to be an adequate technique to identify areas with mild and severe lung fibrosis during cryobiopsy procedures [26].

For this study, we did not use an autofluorescent dye. Based on autofluorescence, we could not detect granulomas with CLE. If granulomas would be detectable when using an autofluorescent dye needs further investigation. Therefore, we argue that CLE based on autofluorescence is especially suitable for patients with dominant radiological patterns of ground glass and reticulation and less suitable for patients with the patterns of nodules and cysts.

This study is limited by the small number of patients (n = 20). Due to the fact that ILD is a heterogeneous dis-
ease, we have included a wide array of ILD subsets. However, this also causes a substantial number of ILD subsets to be represented by only a single patient. Therefore, future studies with larger cohorts are desirable. Another limitation of this study is the limited number of patients with UIP/IPF in our study (n = 1). IPF patients represent an important group since antifibrotic medication is approved by the guidelines for this specific type of ILD and because the differentiation between IPF and a cHP or fN-SIP is often difficult. Fortunately, there is an OCT study that correlates the imaging results to pathology of SLBs, which was performed in 27 fibrotic ILD patients (12 UIP and 15 non-UIP-other fibrotic ILDs) [24] and the authors conclude that their study provides evidence supporting the utility of OCT, particularly for the diagnosis of histopathologic UIP and clinical IPF and supports OCT as a potential future part of ILD diagnostic workup and alternative to SLB. The current study reports the findings of OCT in nonfibrotic ILD, which to the best of our knowledge, has not been presented before.

In conclusion, we demonstrate that minimal invasive bronchoscopic CLE and OCT provided real-time imaging of ILD features in fibrotic and nonfibrotic ILDs, with higher resolutions compared to HRCT scan. These results imply that there is potential for CLE and OCT to narrow the differential diagnosis of ILD for patients with inconclusive HRCT, omitting the risk of lung biopsy procedures. Future studies are needed to further explore whether the application of CLE and OCT will lead to an actual decrease in necessary lung biopsies in ILD.

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