Tracheobronchial Amyloidosis and Confocal Endomicroscopy

Richard C. Newtona, b  Samuel V. Kempc  Guang-Zhong Yangb  Ara Darzia
Mary N. Sheppardd  Pallav L. Shahc

aDepartment of Surgery and Cancer and bThe Hamlyn Centre for Robotic Surgery, Imperial College London, and Departments of cRespiratory Medicine and dHistopathology, Royal Brompton Hospital, London, UK

Established Facts

- Tracheobronchial amyloidosis is a rare disease creating circumferential bronchial nodularity and narrowing; it requires typical endobronchial biopsy findings for diagnosis.
- Probe-based confocal endomicroscopy (pCLE) is a cellular resolution optical biopsy technique that may have a role in diagnosing endobronchial malignancy.

Novel Insights

- In vivo pCLE images of endobronchial amyloid have a 'cotton wool'-like appearance, supporting a potential role for pCLE in the investigation of benign endobronchial diseases such as amyloidosis.

Key Words
Endobronchial biopsy · Pulmonary amyloidosis · Confocal endomicroscopy

Abstract

Tracheobronchial amyloidosis is one of many causes of endobronchial stenosis and nodularity, the concrete diagnosis of which currently requires the finding of apple-green birefringence from endobronchial biopsies. Bronchoscopic probe-based confocal endomicroscopy (pCLE) is a novel optical biopsy technique which provides real-time images of the lattice structure of the bronchial basement membrane – a finding lost in malignancy. This case study outlines the imperfect, essentially palliative management of this rare disease, and shows for the first time the unusual dappled in vivo pCLE images of amyloid-affected endobronchium.

Introduction

Bronchoscopic probe-based confocal endomicroscopy (pCLE) is the product of the recent miniaturisation of the confocal microscope [1]. A 1.4-mm diameter probe is passed down the operating channel of a conventional
bronchoscope to fluoresce endogenous fluorophores, such as elastin, with a 488-nm laser light. The resulting autofluorescence provides 3.5-μm resolution in vivo optical biopsies, showing a reticular pattern of the basement membrane beneath the epithelium of the tracheobronchial tree, which is eliminated by dysplasia or neoplasia [2]. Courtesy of a rare case of primary laryngotracheobronchial amyloidosis, we describe how pCLE may also provide adjunctive images in the diagnosis of benign endobronchial disease.

**Case Report**

A 41-year-old black British stonemason developed increasing shortness of breath and dysphonia. He was a current smoker with a 15 pack-year smoking history, but had no previous medical problems. Fixed monophasic wheeze was heard throughout both lung fields, more prominent in the right middle and lower lobes. When a trial of inhaled salbutamol failed to improve his breathing, he was fully investigated. Lung spirometry showed a mixed restrictive and obstructive deficit, an erect chest radiograph showed no abnormalities, and high-resolution computed tomography showed circumferential irregular narrowing and nodularity of the laryngotracheobronchial wall (fig. 1a, b) with some opacity in the left lower and right middle lobes. Flexible bronchoscopy revealed nodular thickening and plaques over the vocal cords and throughout the visible tracheobronchial tree with some mucosal friability (fig. 1e, f). The pCLE probe (Cellvizio® Lung, Mauna Kea Technologies, France) acquired optical biopsies of the mucosa during the bronchoscopy, showing two distinctive patterns: 3 out of 4 macroscopically spared walls produced the fine reticular pattern observed in healthy subjects [2] (fig. 1d); however, 4 out of 5 images acquired from the nodular areas, as well as one macroscopically normal area, showed a fluorescent dappled effect representative of the excrescences caused by the amyloid (fig. 1g).

Endobronchial biopsies of the lesions were fixed and embedded in paraffin, with standard stains showing some squamous metaplasia of the mucosal epithelium overlying extensive amyloid fibrosis containing scattered foreign body-type giant cells. Congo red staining demonstrated extensive amorphous material displaying apple-green birefringence when viewed under high-intensity cross-polarised light [3]: the classical histochemical sign of amyloid (fig. 1h). Immunohistochemistry showed binding only of monoclonal antibodies to lambda immunoglobulin light chains. Fibreoptic laryngoscopy showed restriction of the right vocal cord from supraglottic laryngeal disease. Serum and urine electrophoresis along with bone marrow biopsy excluded systemic disease, and a serum amyloid P component scintigraph [4] confirmed amyloid confined to the larynx, trachea, bronchi and lungs.
The patient’s voice has strengthened with otorhinolaryngological CO₂ laser treatment of the vocal cord foci. There has also been some reduction in dyspnoea from endobronchial balloon dilatation, with subsequent debulking initially using cryotherapy and then an argon plasma laser.

**Discussion**

Amyloidosis represents a spectrum of diseases which feature abnormal deposition of randomly orientated insoluble extracellular fibrillar proteins. Whilst more commonly a systemic condition (primary or secondary), localised amyloidosis is restricted to a single organ such as the bladder, skin, heart or respiratory tract. Respiratory amyloidosis, first described in 1877 [5], is described as diffuse parenchymal (the worst prognosis), nodular parenchymal (often an incidental finding) [6] or, as in this patient, (laryngo)tracheobronchial amyloidosis [7]. Unlike in tracheobronchopathia osteochondroplastica, the lesions do not spare the posterior wall. Presumptive diagnoses of asthma or chronic bronchitis often precede definitive diagnosis from bronchoscopy and endobronchial biopsy. Screening for fibrillar-type and systemic disease should follow [8]. In terms of therapy, pharmacological prevention of deposition remains an aspiration [9], whereas symptomatic treatment includes debulking using the methods in this case, along with stenting and external beam radiation [10].

The amyloid material appears to be fluorescent with 488-nm pCLE. A previous paper demonstrated innate fluorescence of the macroscopically abnormal amyloid plaques during autofluorescence bronchoscopy with blue light [11]. The pCLE images have a patchy ‘cotton wool’-like appearance due to the accumulation of the autofluorescent amyloid material in the mucosa and submucosa. The normal reticular pattern from the elastin component of the lamina densa and lamina reticularis [2] is disrupted. As this appearance was also observed in a macroscopically normal region, confocal endomicroscopy may have a role in identifying early-stage tracheobronchial amyloidosis, as well as affected areas that are macroscopically normal under white light imaging.

**References**