Case Report

Bronchoscopic lung cryobiopsy for the diagnosis of pulmonary alveolar proteinosis in a hypoxemic patient

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by the intra-alveolar accumulation of surfactant due to macrophage dysfunction or the production of abnormal surfactant. Diagnosis is usually confirmed by lung biopsy either bronchoscopically or by video-assisted thoracoscopic surgery. Bronchoscopic lung cryobiopsy (BLC) is increasingly being utilized for the histopathological diagnosis of diffuse parenchymal lung diseases; however, it has rarely been reported for PAP. We report a case of 59-year-old male who presented to our center with gradually worsening breathlessness and cough of 1-year duration. Chest radiograph revealed bilateral extensive pulmonary infiltrates and high-resolution computerized tomography scan revealed extensive bilateral ground-glass opacities with areas of sparing. BAL and transbronchial lung biopsy failed to confirm the diagnosis; hence, BLC was done which revealed pathologic findings suggesting PAP. BLC appears to be a promising diagnostic tool for the diagnosis of PAP and offers several diagnostic advantages compared to conventional techniques.

KEY WORDS: Bronchoscopic cryobiopsy, pulmonary alveolar proteinosis, whole lung lavage

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the alveolar accumulation of surfactant material with reduced lung function and resulting hypoxemia.¹ Clinical presentation is nonspecific, usually with dyspnea on exertion. A chest X-ray shows bilateral alveolar opacities with a perihilar distribution.²,³ Computed tomography (CT) scan shows ground-glass opacities with thickened intralobular and interlobular septae, forming a “crazy-paving pattern.”⁴ Typical high-resolution chest tomography (HRCT) and BAL findings in combination with positive serologic tests for anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies provide a confident diagnosis of autoimmune PAP. However, in India, anti-GM-CSF serology is not available; hence, a biopsy is usually required for a definite diagnosis. Tissue for histopathological confirmation is obtained either by conventional transbronchial lung biopsy (TBLB) or by video-assisted thoracoscopic surgery (VATS). The diagnostic yield of bronchoscopic lung cryobiopsy (BLC) (86.3, 95% confidence interval [CI] 80.2–90.8) is significantly higher than that of flexible forceps biopsy (56.5%, 95% CI 27.5–83.2) as BLC provides larger artifact-free tissue.⁵ Hence, BLC is nowadays increasingly being utilized for histopathological diagnosis of diffuse parenchymal

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lungs (DPLD); however, its use has rarely been reported for PAP. We report a case of 59-year-old male who presented to our center with gradually worsening breathlessness and chronic cough in respiratory failure. BAL and trans-bronchial lung biopsy done previously were inconclusive; hence, BLC was done which demonstrated pathologic findings suggesting PAP. BLC appears to be a promising diagnostic modality and should be utilized if conventional techniques fail to confirm the diagnosis of PAP.

CASE REPORT

A 59-year-old male initially presented to another hospital with progressive shortness of breath and cough with mucoid expectoration of 1 year duration. He was an ex-smoker with the smoking index of 600. The chest X-ray demonstrated bilateral diffuse opacities in all lung fields. Chest CT revealed extensive bilateral patchy ground-glass opacities. He was treated by a physician with multiple courses of antibiotics, but his dyspnea progressed. Fiberoptic bronchoscopy at that hospital was normal, and microbiological workup of bronchoalveolar lavage (BAL) was negative; BAL cytology was negative for malignant cells and TBLB suggested chronic inflammation. He was then commenced on oral steroids, but the symptoms persisted. He then reported to our hospital for further evaluation. He denied fever, rash, joint pain, dry eyes or mouth, muscle weakness, or swelling of ankles. On examination, he had tachypnea, tachycardia with oxygen saturation of 86% on room air. Chest examination demonstrated fine crackles over bilateral infrascapular regions.

Investigations revealed a normal white blood cell count; autoimmune markers, including rheumatoid factor, antinuclear antibody, and anti-cyclic citrullinated peptide were all negative. Serum lactate dehydrogenase was raised (625 U/L), but the rest of the biochemical and metabolic parameters were normal. The chest X-ray showed diffuse opacities bilaterally [Figure 1]. Sputum was negative for acid-fast bacilli and Pneumocystis jirovecii. ABG demonstrated hypoxemia with a raised alveolo–arterial gradient (PaO₂ 58 mm Hg, AaDO₂ 45). HRCT disclosed extensive patchy ground-glass opacities superimposed with interlobular septal thickening bilaterally, demonstrating a “crazy-paving” pattern [Figure 2]. Ultrasound of the abdomen was normal. He was unable to perform spirometry, but he had a significant desaturation on 6-min walk test.

Since he had shown poor response to steroids, and his previous TBLB was inconclusive, we discussed the options of repeating TBLB or performing BLC with the patient. We explained the possible risks of pneumothorax, bleeding, and prolonged mechanical ventilation with BLC to the patient. The patient opted for BLC in view of higher diagnostic yield as compared to repeating conventional TBLB. We obtained informed high-risk consent in view of resting hypoxemia. As pneumothorax would have been catastrophic in a patient with baseline hypoxemia and diffuse lung disease, chest drain was kept ready in the operating room to manage such a complication. The patient was thereafter intubated with an 8.5-mm endotracheal tube under general anesthesia, and 6.0-mm diameter flexible video-bronchoscope (2.8 mm channel, Olympus BF-1T150, Olympus Corporation, Japan) was then introduced into the tube. Balloon occlusion catheter (Fogarty; Edwards Lifesciences, Irvine, CA, USA) was then introduced alongside the bronchoscope into the right lower lobe bronchus and balloon was checked by inflation with saline. We then performed three transbronchial cryobiopsies with 1.9-mm cryoprobes (nitrous oxide cryogen) from different segments of the right lower lobe with the freezing time of 3–4 s. The balloon was inflated in the right lower lobe bronchus after each cryobiopsy to prevent flooding of the airway by blood. An endobronchial blocker (Arndt; Cook Medical, Bloomington, IN, USA) was also kept ready in the operating room to exclude bleeding during the biopsy. A screening ultrasound of the thorax was performed immediately following the procedure to exclude pneumothorax. We also obtained a chest radiograph 2 h after the BLC as pneumothorax/pneumomediastinum can occur as delayed complications and can be catastrophic in a hypoxic patient. The procedure was uneventful, but the patient was kept hospitalized in view of oxygen requirements.

Cryobiopsy showed periodic acid–Schiff positive eosinophilic amorphous, granular proteinaceous material within the alveoli and mixed inflammatory infiltrates in the interalveolar septae with numerous alveolar macrophages.

Figure 1: Chest radiograph of the patient showing bilateral diffuse acinar opacities and significant clearance 4 weeks post whole lung lavage

Figure 2: High-resolution chest tomography of the chest demonstrating bilateral diffuse ground-glass opacities with geographic pattern and interlobular septal thickening-characteristic “crazy-paving” appearance.
PAP is a rare disease characterized by the accumulation of surfactant, which is comprised lipoproteinaceous material within the alveoli. PAP occurs due to disorders of surfactant production or surfactant clearance. PAP is further divided into three types: auto-immune (primary) PAP, secondary PAP, or congenital PAP. Congenital PAP is usually seen in children, caused by an autosomal dominant, autosomal recessive, or X-linked recessive pattern of gene mutation with the radioclinical presentation dependent on the mutated gene. Secondary PAP is usually due to the reduced number or function of alveolar macrophages secondary to chronic infections, chronic inflammatory or immunodeficiency syndromes, dust exposure, or hematological disorders.

Adult forms of PAP constitute majorly of auto-immune (primary) PAP. Autoimmune PAP has a high concentration of neutralizing anti-GM-CSF IgG antibodies. These bind to the GM-CSF preventing their function of surfactant clearance. Secondary PAP is treated by the management of the underlying cause, whereas WLL is the standard of care for autoimmune PAP.

Chest HRCT findings of “crazy-paving” pattern are suggestive of PAP, but the gold standard of the diagnosis of PAP is pathological evaluation of lung biopsy specimen. The diagnostic yield of traditional forceps biopsy alone was 73.1% in a meta-analysis. Rarely, VATS is required to obtain biopsy specimens. While VATS carries a sensitivity of 90% in diagnosing PAP, it inevitably prolongs inhospital stay increases cost and has a significantly higher incidence of pneumothorax and severe bleeding as compared to other modalities. In our case, the risk of adverse outcomes with VATS was even higher as the patient had hypoxemic respiratory failure.

BLC is being utilized increasingly to aid the diagnosis of DPLD. Cryobiopsy has the advantage of acquiring larger specimen as well as keeping the tissue architecture intact compared to forceps biopsy. In our case, we performed cryobiopsy as transbronchial forceps lung biopsy done previously was inconclusive. The higher yield compared to conventional TBLB can be explained since the size of the cryobiopsy tissue specimen is much larger and also because cryoprobe allows the sampling of lung tissue in the lateral direction.

The diagnosis of PAP through BLC has rarely been reported in literature previously. Only one of the patients was diagnosed with PAP in a case series by Poletti et al. that included 176 patients with DPLD who received BLC. Ussavarungsi et al. retrospectively analyzed 74 cases with DPLD by cryobiopsy, and only one patient from their study was diagnosed with PAP. Shen et al. also reported a case of PAP that was diagnosed by BLC when conventional forceps biopsy was nondiagnostic. While a small number of cases have been reported, BLC appears to be an excellent tool, with increasing potential for diagnosing PAP. The value is even more in resource-constrained settings like ours, where VATS is not easily available.

BLC should not be attempted upfront in hypoxemic patients and should only be done after carefully weighing the risks and benefits. The complications reported with BLC are pneumothorax, endobronchial bleeding, postprocedure hypoxemia, prolonged mechanical ventilation, and death. Pneumomediastinum and extensive subcutaneous emphysema after BLC have also been reported from India. An artificial airway, either endotracheal tube or rigid bronchoscope is recommended during the procedure as it allows isolation and ventilation of the contralateral lung in the event of significant bleeding. Severe hypoxemia (PaO₂ <50 mmHg on room air) is an absolute contraindication of the procedure. Even though our patient had higher PaO₂, we were very cautious and used balloon occlusion catheter after every biopsy to prevent flooding of the bronchial tree and also did ultrasonography in the operating room to screen for pneumothorax. Noninvasive ventilation-assisted TBLB has safely been performed in a series of 27 cases from India and can be considered as an alternative in hypoxemic patients with diffuse pulmonary infiltrates. We had discussed this option, but the patient opted for BLC in view of higher diagnostic yield of the latter.
WLL is indicated in PAP for patients who have progressive symptoms and those with AaDO$_2$ > 40;[5] our patient met the criteria and was hence offered WLL to which he had a favorable clinicoradiological and functional response. BLC is a promising modality which enabled definite histopathological diagnosis, leading to successful management of the case by therapeutic WLL.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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