

Cryobiopsy in the diagnosis of idiopathic pulmonary hemosiderosis: a case report

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Submitted Mar 23, 2019. Accepted for publication Jun 28, 2019.

doi: 10.21037/jtd.2019.07.17

View this article at: <http://dx.doi.org/10.21037/jtd.2019.07.17>

Introduction

Transbronchial lung cryobiopsy (TLCB) was first described in 2009 (1) and since then it has become a common diagnostic method in interventional pulmonology. Being a safe and cost-effective method, it has been used to diagnose interstitial lung diseases (ILDs) (2,3). It is estimated that its diagnostic yield varies from 75% to 91% (4-6) and it is superior to traditional transbronchial lung biopsy (TBLB) (6,7) in terms of effectiveness. Although not yet as effective as open lung biopsy, its efficacy and safety are unquestionable (8,9). Consequently, it becomes a good alternative to open lung biopsy (10) and is always the first recommended procedure (11). While several interstitial diseases have been diagnosed by histopathological analysis of cryobiopsy samples, there are no studies, which would refer to idiopathic pulmonary hemosiderosis (IPH) confirmed by this diagnostic method. Here, we present what we believe to be the first IPH case to be confirmed by TLCB.

Case presentation

A 54-year-old man was admitted to the pulmonary medicine department for diagnostics of ILD. He reported a reduced ability to exercise for the last 3 years. Since a few months he noted grade 2 dyspnea according to the modified Medical Research Council scale. He additionally complained of

coughing up sputum but denied hemoptysis. Five years earlier, the patient had an upper gastrointestinal tract bleeding due to a duodenal ulcer and gastritis resulting in anemia. He was further diagnosed with hiatal hernia with gastroesophageal reflux. He had not been smoking for 12 years but he had a 25 pack-year smoking history.

A year earlier, following abnormal chest X-ray findings (*Figure 1*), the patient had a high-resolution computed tomography (HRCT), which showed bilateral lung emphysema visible especially in upper lobes and coexisting interstitial fibrosis as well as broad interstitial opacities (*Figure 2*). He was then hospitalized at a regional pulmonology department where some preliminary tests were performed, including bronchoscopy, which did not show any abnormalities. In a 6-minute walk test (6-MWT) the patient walked 530 m with significant desaturation, but spirometry did not confirm any ventilation abnormalities.

On admission to the pulmonary clinic, the patient was in a good condition without significant abnormalities on physical examination. His arterial blood oxygen saturation was 97% at room air. Laboratory tests showed mild leukocytosis with an increased neutrophil level as well as mild normocytic anemia with high reticulocyte count. Following a hematological consultation, the patient was diagnosed with sideropenic anemia and chronic disease anemia due to low blood iron level with concurrent high iron-binding and absorption

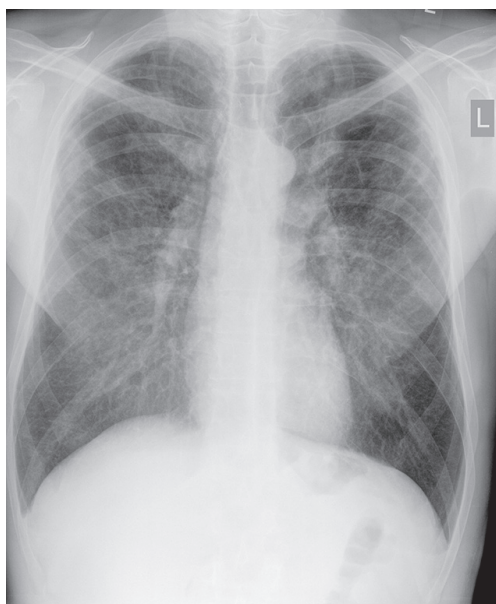


Figure 1 Chest X-ray in PA projection. Lung lobes with broad dense parenchymal opacification and numerous small nodules. PA, posteroanterior.

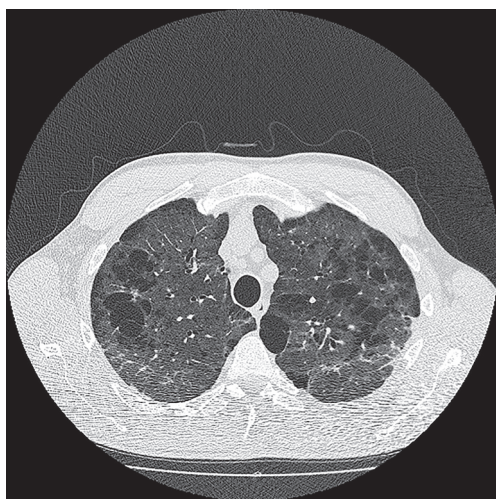


Figure 2 HRCT lung scan. Bilateral emphysema, especially visible in the upper zones of each lung lobe; concurrent interstitial fibrosis as well as broad ground glass opacities in lung parenchyma. HRCT, high-resolution computed tomography.

capability and high ferritin count.

The results of ANA, ANCA, anti-glomerular basement membrane antibodies tests as well as alpha-1 antitrypsin level and test showed no abnormalities. Chest HRCT showed clearly visible interstitial fibrosis. Lung function

Table 1 Results of bronchoalveolar lavage evaluation

Test type	Result
Total cell number	3,209
Cell concentration/mL	53,483
Macrophages (%)	74
Lymphocytes (%)	3
Neutrophils (%)	22
Eosinophils (%)	1
Epithelial cells (glandular and squamous)	Insignificant number
Birefringent bodies	Negative
CD1a	Negative
S100	Negative

tests presented lowered CO diffusion capacity single breath transfer factor for carbon monoxide (DLCO SB) was 47.6%) while spirometry and body plethysmography values were normal. In the 6-MWT the patient walked 589 m with significant desaturation. Echocardiography did not show any significant valvular defects and Doppler-measured systolic pulmonary artery pressure was 44 mmHg. Due to the abnormalities in HRCT imaging, the patient was suspected of having pulmonary Langerhans cell histiocytosis but bronchoalveolar lavage (BAL) immunohistochemical analysis of Langerhans cells was negative for S-100 protein and anti-CD1a antibodies. Unexpectedly, BAL showed the presence of hemosiderin-laden macrophages (74%) (*Table 1*). The patient was admitted for TLCB to an interventional bronchoscopy unit. A radial EBUS mini-probe was used to select the optimal site for biopsy and thus there was no fluoroscopy. Cryobiopsy samples were obtained from two segments of the middle lobe with a 1.9 mm probe (freezing time of 5–8 seconds). In total, there were 5 samples taken. Histopathological examination revealed numerous hemosiderophages (i.e., hemosiderin-laden macrophages) and erythrocytes within alveolar spaces, interalveolar septal thickening and fibrosis as well as alveolar pneumocyte hyperplasia. A delicate incrustation of some vascular walls by iron deposits was noted (*Figure 3*). There were no features of concurrent vasculitis. Thus an intra-alveolar hemorrhage was diagnosed.

The additional diagnostic tests shown in *Table 2* were performed. Considering the result of the microscopic examination of the lung tissue and the broad panel of tests employed which did not show the origin of the intra-

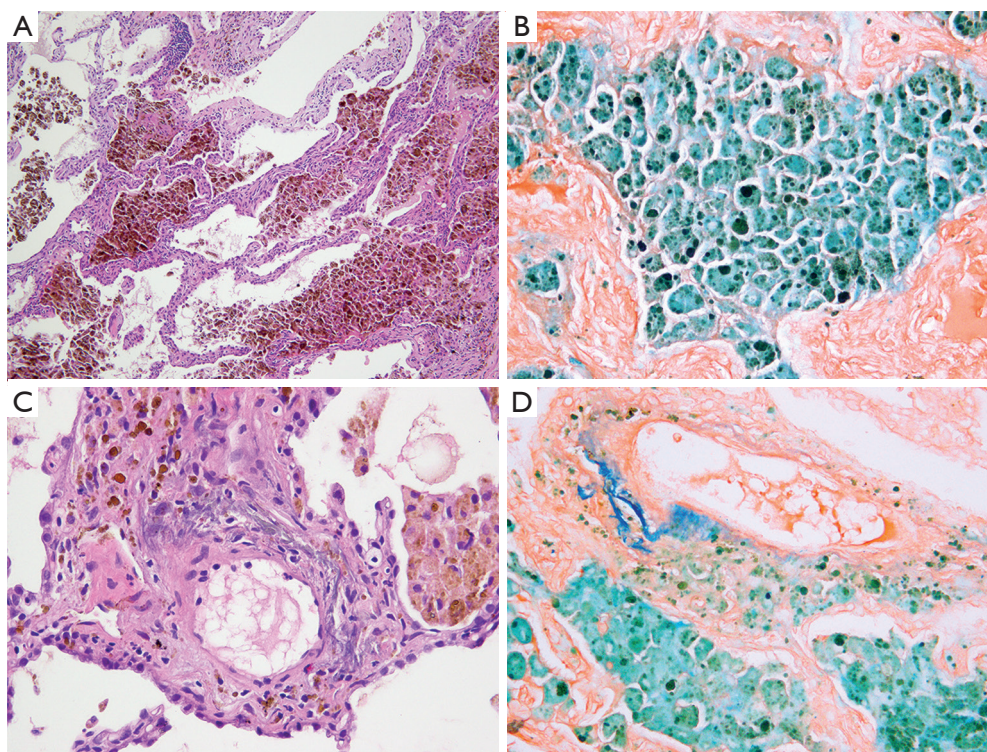


Figure 3 Microscopic images of pulmonary hemosiderosis. (A) Hemosiderin laden macrophages (cells with golden-brown pigment) filling alveolar spaces. Mild interstitial fibrosis with hyperplasia of type II pneumocytes lining the interalveolar septa; (B) hemosiderin globules stain intensively with Prussian blue; (C) iron encrustation of the elastic laminae of blood vessels can be observed as grey mineralized fibers in vessel walls; (D) the same fibers show intensively blue color in Prussian blue reaction (A: HE staining, magnification $\times 100$; B and D: Prussian blue staining, magnification $\times 400$; C: HE staining, magnification $\times 400$).

Table 2 Tests performed to diagnose the origin of intra-alveolar bleeding

Test type	Result
ANA	Negative
ANCA	Negative
Rheumatoid factor	Negative
Lupus anticoagulant	Negative
Endomysial antibodies IgA	Negative
Glomerular basement membrane GBM	Negative
IgA and IgG (tTG) antibodies	Negative
Anti-CCP antibodies	Negative
IgG anti-cardiolipin antibodies	Negative
IgM anti-cardiolipin antibodies	Negative
Beta 2 glycoprotein 1 antibodies IgG	Negative
Negative migrating immunological complexes (Caq-CIC)	Negative

alveolar bleeding, the final diagnosis of primary IPH was established.

Following the diagnosis, the patient was subsequently readmitted to the pulmonary clinic for treatment. On admission he was not in a good condition with no rest dyspnea but peripheral oxygen saturation was 90% at room air. Arterial blood gases showed mild hypoxemic respiratory failure ($\text{PaO}_2 = 51$ mmHg, $\text{PaCO}_2 = 34$ mmHg and $\text{pH} = 7.43$). Initially, 32 mg/day methylprednisolone *per os* was introduced. On the third day of treatment, the patient became febrile and had moderate hemoptysis. Chest X-rays showed new lung infiltrates. The C-reactive protein (CRP) level was 210 mg/L. Flexible bronchoscopy revealed fresh bleeding into the bronchial tree. *Klebsiella pneumoniae* was cultivated at 10^6 CFU/mL. The patient was diagnosed with hospital acquired pneumonia and diffuse alveolar hemorrhage. Broad-spectrum antibiotic therapy was introduced along with oxygen therapy and 150 mg/day methylprednisolone administered intravenously. As the

patient's condition stabilized after a few days of treatment, azathioprine 150 mg/d was introduced. Methylprednisolone doses were then gradually reduced. After the patient's condition improved and inflammation regressed, control lung function tests were performed: TLCO SB was at a low but stable level (39%) and in the 6-MWT the patient walked 627 m without significant desaturation.

Azathioprine 150 mg/d was continued and methylprednisolone was gradually reduced (20 mg/day at present). After discharge he was referred for a transplant consultation but was disqualified due to the high risk of relapse observed in IPH patients (12). In the first three months of treatment, the patient reported a significant clinical improvement and he felt even better in the following months. Presently, the patient's peripheral oxygen saturation at air room is 93% and he does not require long-term oxygen therapy.

In order to broaden the discussion of this case we invited 3 experts from different fields of medicine to participate in the case discussion and answer our questions.

Discussion

Question 1: What is the main advantage of cryobiopsy over the conventional forceps one?

Expert 1 (Antonio Bugalho, expert in interventional pulmonology)

Transbronchial lung cryobiopsy (TBLC) can improve the diagnostic yield in diffuse parenchymal lung diseases especially when clinical and radiological data is insufficient to establish a definitive diagnosis, as in the present case. Current evidence shows that performing two transbronchial lung cryobiopsies from two different segments within the same lobe increases diagnostic yield in diffuse parenchymal lung diseases, nevertheless most centers usually perform 3 to 5 biopsies.

In this case, a 1.9 mm probe was used through the flexible bronchoscope working channel. Commonly, with this cryoprobe, a freezing time of 7 seconds is sufficient to get a good tissue sample but the duration should be adjusted according to the obtained sample size. A radial ultrasound probe was previously used to identify the aimed lung parenchyma and to exclude adjacent blood vessels.

The correct selection of patients is crucial in order to provide an effective diagnosis and diminish complications. This patient had no severe pulmonary hypertension (as defined by a pulmonary arterial pressure of >50 mmHg),

forced vital capacity (FVC) <50% or DLCO <35% which are considered relative contraindications for TBLC.

It is a very important point that cryobiopsies have been performed heterogeneously with different strategies regarding the procedure (intubation methods, sedation/anesthesia, probe sizes, freezing time), lung tissue sampling (number of samples, one or multiple lobes, distance to the pleura) and complications (rates, methods to control). Thus, systematization of knowledge in this respect as well as standardization are needed. The TBLB technique is definitely more systematized. However, considering the efficacy of TBLC in the diagnosis of interstitial lung diseases, it is advisable to use this method when TBLB proves insufficient or even as a primary method because it can provide pathologists with considerably better samples for microscope examination.

Expert 2 (Martina Vašáková, clinical expert)

For clinicians, the efficacy and safety of a diagnostic method are of key importance. Sharp's meta-analysis of 11 studies on TBLB, 11 on TBLC and 24 on surgical lung biopsy (SLB) revealed a diagnostic yield of 64.3%, 84.4% and 91.1% respectively (6). Furthermore, the recent meta-analysis by Iftikhar, comparing TBLC with SLB, showed that diagnostic accuracy of TBLC is comparable with SLB with an acceptable safety profile (9). While we should never forget about individual clinical context, we may agree that TBLC is often the optimal diagnostic method for interstitial lung diseases.

The case describes an ex-smoker with shortness of breath, anemia and dominant emphysema with some interstitial changes at HRCT. Initially, the diagnosis of pulmonary Langerhans cell histiocytosis (PLCH) was suspected, but since the BALF proved inconclusive further diagnostics had to be undertaken. Following the cryobiopsy, the patient was diagnosed with idiopathic pulmonary hemosiderosis (IPH). The CT scan resembles rather that of emphysema or inactive PLCH, since emphysema is not typical for IPH. If it was not for the cryobiopsy performed, the patient would have been misdiagnosed with PLCH.

Expert 3 (Anja C. Roden, specialist in pathomorphology)

The images of this case illustrate and support the advantages of cryobiopsies over conventional forceps biopsies that in general include larger specimen size and well expanded alveoli allowing for easier histologic interpretation.

The cryobiopsy samples show a large piece of lung

parenchyma with no crush artifact. I agree that the morphologic findings of large intra-alveolar clusters of hemosiderophages and iron-encrustation of elastic laminae of vessels suggestive of mineralizing pulmonary elastosis are typical for pulmonary hemorrhage. Reportedly, extensive clinical and serologic workup was essentially negative except for a suggestion of pulmonary hypertension given a pulmonary artery pressure of 44 mmHg. There are only a few causes of alveolar hemorrhage that might be recognized morphologically; these include necrotizing vasculitis, pulmonary veno-occlusive disease (PVOD), possibly aspiration, infection, or neoplasms such as angiosarcoma. No morphologic features in this cryobiopsy are suggestive of any of these potential causes. There is some mild interstitial thickening which appears to be due, at least in part, to a mild capillary proliferation, however, the typical morphological features of PVOD such as more pronounced patchy capillary proliferation together with intimal fibrosis of small veins and venules leading at least focally to their occlusion is not appreciated in this specimen. An elastic stain would be helpful to further exclude that possibility. However, many causes of pulmonary hemorrhage have no morphologic correlate and require clinico-radiologic correlation which is necessary before a diagnosis of idiopathic pulmonary hemorrhage can be rendered. It also remains unclear why this patient has pulmonary hypertension.

Question 2: How do you assess the efficacy of cryobiopsy in the diagnostics of IPH on the basis of this case?

Expert 1 (Antonio Bugalho)

I emphasize that TBLC should always be part of a multidisciplinary approach to diffuse lung diseases. When performed by trained professionals in an adequate setting, it may be able to provide good quality histological material that contributes to IPH diagnosis.

Expert 2 (Martina Vašáková)

The case discussed here proves how important cryobiopsy can be for IPH diagnosis. However, cryobiopsy alone should not be considered sufficient because it must be admitted that diagnosis of IPH is *per exclusionem* and thus it needs to exclude other causes of hemorrhage, mainly vasculitis, antiphospholipid syndrome and anti-basement membrane disease.

Expert 3 (Anja C. Roden)

Histopathological images are not sufficient to diagnose IPH but the information obtained by a pathologist thanks to

TBLC can be extremely useful in the differential diagnosis of intra-alveolar hemorrhages and in the final clinical diagnosis.

Conclusions

Idiopathic pulmonary hemosiderosis is a rare disease, which is a result of an alveolar capillary bleeding and it is characterized by a high mortality rate (13,14). The disease is extremely rare in adults (15-18). The clinical course usually suggests intra-alveolar bleeding with characteristic hemoptysis (19) observed in about 80% of patients (15,17,18). In cases similar to the present one, i.e., where there are lung interstitial alterations with a concurrent anemia, IPH should always be considered in the differential diagnosis even though hemoptysis might not be reported by the patient (14,17,19-22). The disease is usually found in children and young adults and thus lung interstitial alterations appear amid a healthy lung tissue. However in adults, comorbidities are more frequently present, also in the case of the respiratory system. Our patient, a former smoker, had pulmonary emphysema further aggravated by concurrent IPH. Consequently, his lung HRCT imaging was equivocal. Flexible bronchoscopy with BAL can also be helpful in diagnostics (15). Apart from newly found bleeding, proof of chronic intra-alveolar bleeding in the form of hemosiderin-laden macrophages is necessary for establishing the diagnosis and this feature has also been found in our patient.

It is known that the progression of idiopathic pulmonary hemosiderosis can be gradual but in some cases the disease can relapse resulting in sudden intra-alveolar bleeding. The risk factors for relapses are not known as such relapses are often spontaneous. However, it seems that in the case of our patient respiratory tract infection could be an important risk factor (16). This is a life-threatening condition and should be treated immediately. Although the use of steroids in such a situation has been questioned (23), the benefits of this therapy cannot be ignored (24). Steroids were applied in the present case and led to clinical improvement of the patient's condition. Since general practice in severe exacerbations of ILDs is to use steroids with other immunosuppressants, the same has been applied in the present case. Azathioprine allowed to reduce gradually the doses of methylprednisolone. Mesenchymal stem cells (25) can also be used as an additional therapy option. As we had no experience in applying this method, we did not offer it to the patient.

To our best knowledge, there are no case studies on primary IPH diagnosed with TLCB but we observe a growing number of publications describing the usefulness of TLCB based on samples obtained in cryobiopsies (26). This method can be used in cases of interstitial lung diseases, e.g., idiopathic pulmonary fibrosis, to secure diagnostic material for microscopic examination of ILDs when traditional TBLB is usually inadequate, like in IPF (27). The clinical usefulness of TLCB in other ILDs which have been diagnosed previously with open lung biopsy has also already been described in other studies (5). We may thus further confirm the hypothesis that TLCB can be considered an effective method for obtaining a sample suitable for histopathological examination of other rare diseases such as IPH.

In the present case TLCB was uncomplicated and hence, when IPH is suspected, it could be considered as the method of choice before an open lung biopsy. When determining whether to perform TLCB from one or two lung segments, it should be remembered that the latter is more effective (28). Bearing that in mind, we also decided for cryobiopsy from two segments of the middle lobe.

TBLB is a very valuable method for the diagnosis of IPH and, according to the experts bronchoscopy specialist, its use should be recommended because it is safe and effective. It also provides sufficient samples for the pathologist and finally allows the clinical specialist to make a correct diagnosis. Although prognoses are uncertain for IPH, immunosuppressive treatment is a good chance to achieve a stable patient's condition.

Acknowledgments

None.

Footnote

Conflicts of Interest: M. Szołkowska declares paid lectures for Roche Polska. The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. The signed form is available from the corresponding author upon reasonable request.

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Cite this article as: Kania A, Misiaszek M, Vařáková M, Szlubowski A, Bugalho A, Pankowski J, Szólkowska M, Roden AC, Celejewska-Wójcik N, Nastałek P, Gnass M, Śladek K. Cryobiopsy in the diagnosis of idiopathic pulmonary hemosiderosis: a case report. *J Thorac Dis* 2019;11(7):3195-3201. doi: 10.21037/jtd.2019.07.17