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## Conflict of interest

The authors declare no conflict of interest.

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## Transbronchial cryobiopsy in the diagnosis of desquamative interstitial pneumonia



Desquamative interstitial pneumonia (DIP) is a rare interstitial pneumonia usually associated with cigarette smoke.<sup>1,2</sup> It is characterized by the accumulation of intra-alveolar macrophages, sometimes associated with giant cells.<sup>1,3</sup> The diagnosis may be suggested by patchy ground-glass opacification with a predilection for the mid and lower lung lobes on high-resolution computed tomography (HRCT); subpleural involvement is also typical. Irregular lines, traction bronchiectasis, cysts, emphysema, and nodules are other possible findings of DIP.<sup>4</sup> Bronchoalveolar lavage fluid nearly always contains an increased number of alveolar macrophages.<sup>2,4</sup> Histologically, DIP is characterized by the accumulation of macrophages in the alveolar spaces associated with interstitial inflammation and/or fibrosis. The macrophages usually contain light brown pigment. Lymphoid nodules and a sparse but distinct eosinophilic infiltrate are common.<sup>3</sup> Surgical lung biopsy is still required to make a definitive diagnosis.<sup>1–3</sup>

Transbronchial lung cryobiopsy (TBLC) is a new endoscopic technique that has recently shown superior diagnostic yield to conventional transbronchial biopsy (TBB).<sup>5–7</sup> The advantage of the cryoprobe, compared with conventional TBB or TBB using jumbo forceps is that larger pieces of tissue, without crush artifacts, can be extracted during the freeze-thaw cycle, allowing the identification of complex pathologic patterns. The technique permits visualization of

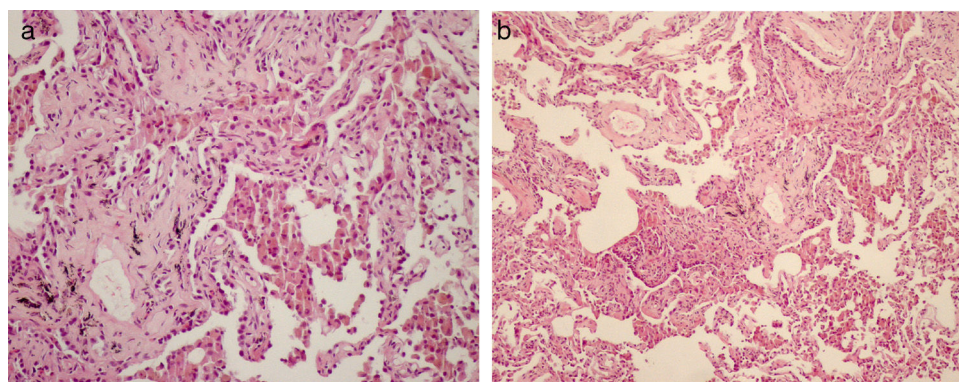
peripheral structures of the secondary pulmonary lobule and facilitates immunohistochemical staining. In addition, TBLC can be performed on an outpatient basis and is both an easier and safer procedure for patients with comorbidities, as it reduces the complications and mortality associated with surgical lung biopsy.<sup>6</sup>

Most of the data available to date is on TBLC overall diagnostic yield and complication rates.<sup>5</sup> However, it is also important for clinicians to know the diagnostic accuracy of TBLC in particular diffuse lung diseases, especially in cases in which histologic evaluation is an essential component of multidisciplinary diagnostic approach, as is the case with DIP.

Our aim was to investigate the diagnostic accuracy of TBLC in patients with clinical and radiological findings



**Figure 1** HRCT scan showing ground-glass pattern in the lower pulmonary lobes.



**Figure 2** Lung parenchyma with preserved architecture, with aggregates of macrophages within alveolar spaces and small bronchioles. The cytoplasm contains coarsely granular golden brown pigment.

compatible with DIP who underwent a multidisciplinary diagnostic evaluation.

Between September 2014 and September 2015, 48 patients underwent TBLC as part of an interstitial lung disease diagnostic approach at the pulmonology department at Centro Hospitalar São João in Porto, Portugal. The patients were anesthetized and intubated with a rigid bronchoscope under jet ventilation. Endoscopic exploration of the bronchial tree was performed through the endotracheal tube using a video bronchoscope, and a Fogarty balloon was introduced into the selected lobe. Subsequently, under fluoroscopic guidance, the transbronchial biopsy was performed using a flexible cryoprobe (2.4 mm in diameter and 900 mm in length). The cryoprobe was introduced through the flexible bronchoscope work channel, which was connected to a cryosurgical system (Erbokryo CA, Erbe, Germany). The tissue was frozen following the Joule-Thomson principle, using gas decompression (carbon dioxide) at the tip of the probe.

TBLC confirmed the diagnosis of DIP in all five patients (four women) in whom this condition was suspected. Their mean age was  $45.2 \pm 8.5$  years and they were all active smokers. Three of the patients reported dyspnea on exertion, one reported dry cough, and one had no relevant respiratory symptoms. One of the women had systemic sclerosis. Three patients had a moderate restrictive ventilatory pattern (FVC  $64.9\% \pm 8.2\%$ ), and all five patients had mild diffusion capacity impairment (DLCO  $57.5\% \pm 8.4\%$ ). All the patients had a ground-glass pattern with a lower-lung predilection on the thoracic HRCT scan (Fig. 1). Two patients had eosinophilic alveolitis in the bronchoalveolar lavage fluid, while the other three had a higher total cell count with a normal differential.

TBLC was performed in different segments of the same lobe in four patients (right lower lobe in three cases and left lower lobe in one) and in two lobes (right superior and lower lobes) in one patient. Three patients underwent four biopsies, one underwent three biopsies, and one underwent two. The mean size of the samples was 5 mm (range, 3–8 mm). The histologic features were compatible with DIP (Fig. 2). One patient had a pneumothorax, which required chest tube insertion; none of the patients had significant hemorrhage.

All the patients had a definitive diagnosis of DIP after the final multidisciplinary diagnostic evaluation. The results from this series support previous findings showing that TBLC seems to be a reliable, effective, and safe diagnostic tool for collecting a representative lung sample. TBLC may have a major role in the multidisciplinary work-up of DIP, an entity that has traditionally required surgical lung biopsy for an accurate diagnosis.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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## Pleural effusion cytology due to malignancy. A combined cytomorphological–immunocytochemical study of 500 cases



Dear Editor,

The first step in the evaluation of patients with pleural effusion is to determine whether the effusion is a transudate or an exudate. An exudative effusion is diagnosed if the patient meets Light's criteria, although new formulas have been proposed.<sup>1</sup>

The serum to pleural fluid protein or albumin gradients may help improve categorization of the occasional transudate misidentified as an exudate by these criteria. If the patient has a transudative effusion, therapy should be directed toward the underlying cause like heart failure or cirrhosis. If the patient has an exudative effusion, attempts should be made to define the etiology. Pneumonia, cancer, tuberculosis, and pulmonary embolism account for most exudative effusions.

Cytomorphology is the hallmark for the diagnosis of malignancy.

The specificity of cytomorphology is very good and ranges from 91% to 100% with an average of 97%. Sensitivity ranges from 22% to 81% with an average of 58.2%.<sup>2</sup>

Morphologic distinction between reactive mesothelial cells and malignant cells can be difficult. Immunocytochemistry is a common adjunct method that serves to improve the sensitivity and specificity of cytology diagnosis.<sup>3</sup> We used Ber-EP4 and calretinin in all malignant effusions. Ber-EP4 (epithelial cell adhesion molecule) is the most common marker expressed in all epithelial cells but not in mesothelial and hematopoietic cells.<sup>4</sup> Calretinin is expressed in benign and malignant mesothelial cells but not in epithelial cells.

Five hundred malignant pleural effusion samples received for cytopathological examination from 500 patients hospitalized at the University Hospital of Heraklion Crete over a 5-year period were analyzed retrospectively.

Table 1 shows distribution of malignancies in 500 neoplastic pleural effusions.

Table 2 shows immunocytochemical markers expressed in studied malignancies.

Cytological examination of pleural fluids is often the first line of investigation to detect and type the neoplastic cells based on their subtle morphological features.<sup>5</sup>

Pleural metastases are more common in the visceral pleura and tend to be focal in the parietal pleura which is why pleural fluid cytology is a more sensitive diagnostic test than closed percutaneous pleural biopsy.<sup>6</sup>

The most common type of tumor to produce metastasis is the broad group of adenocarcinomas, most of them from lung, breast, ovary and GIT. In the present study the most frequent cause of malignant pleural effusion was lung. The neoplastic cells showed classical features of

**Table 1** Distribution of malignancies in 500 pleural effusion specimens.

No of neoplastic pleural effusions 500	(%)
350	Adenocarcinoma (lung, breast, ovary and GIT)
50	Hodgkin and NHL (B and T) lymphoma
40	Squamous carcinoma (lung, head and neck, larynx, genital track)
30	Neuroendocrine tumors (SCLC)
25	Malignant Melanoma
5	Mesothelioma

**Table 2** Markers expressed in studied malignancies.

Malignancy	Markers
Metastatic lung adenocarcinoma	CK7, TTF-1
Metastatic breast carcinoma	CK19, Her2 neu, PR, ER receptors
Non-Hodgkin's lymphomas	PAX5 (PEL, B-cell type), CD4 (T-cell type)
Hodgkin's lymphomas	CD15, CD30
Metastatic squamous carcinoma	Involucrin, CK5/6
Metastatic neuroendocrine tumors	Chromogranin, Synaptophysin, NSE, CD56
Malignant melanoma	HMB45, Melan-A
Malignant mesotheliomas	Calretinin, WT-1