Rev Clin Esp. 2017;xxx(xx):xxx–xxx

Revista Clínica Española

www.elsevier.es/rce

FOR AND AGAINST

The case against performing pleural biopsies for the aetiological diagnosis of exudates☆

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Received 14 February 2017; accepted 18 February 2017

KEYWORDS
Pleural biopsy;
Pleural effusion;
Thoracoscopy;
Pleural tuberculosis;
Malignant pleural effusion

Abstract In most cases, the etiological diagnosis of pleural exudates does not require a pleural biopsy. However, when it is considered necessary, the biopsy should seldom be conducted using invasive methods such as thoracoscopy. Two paradigmatic examples are pleural tuberculosis and malignant effusions. In many centers, pleural fluid adenosine deaminase measurement has replaced closed pleural biopsies in the diagnosis of tuberculosis. Similarly, pathological and molecular studies on pleural fluid cell blocks or alternatively, image-guided pleural biopsies have drastically reduced the need for thoracoscopy.

PALABRAS CLAVE
Biopsia pleural;
Derrame pleural;
Toracoscopia;
Tuberculosis pleural;
Derrame pleural maligno

¿Se debe realizar una biopsia pleural para el diagnóstico etiológico de los exudados? No

Resumen En la mayoría de las ocasiones, el diagnóstico etiológico de un exudado pleural no requiere de una biopsia pleural y, si esta finalmente se considera imprescindible, excepcionalmente hay que recurrir a procedimientos invasivos como la toracoscopia. Dos ejemplos paradigmáticos son el derrame pleural tuberculoso y el maligno. En muchos centros, la medición de adenosina deaminasa en líquido pleural ha sustituido a la biopsia pleural cerrada para diagnosticar tuberculosis. Del mismo modo, el análisis anatomopatológico y molecular de los bloques celulares del líquido pleural o, en su defecto, de las biopsias pleurales dirigidas por técnicas de imagen ha reducido drásticamente la necesidad de una toracoscopia.

☆ Please cite this article as: Porcel J. ¿Se debe realizar una biopsia pleural para el diagnóstico etiológico de los exudados? No. Rev Clin Esp. 2017. http://dx.doi.org/10.1016/j.rce.2017.02.016
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Pleural exudates are a challenge to diagnose, given their numerous etiologies.[1] The most common causes of 2316 pleural effusions (PE) that met Light's criteria[1] for exudates were cancer (34.4%), pneumonia (23.4%) and tuberculosis (TB, 11.6%).[2] Parapneumonic PEs are relatively simple to identify. They appear during acute febrile processes and normally coincide with radiological pulmonary infiltrates. Neutrophils are predominant in the differential leukocyte count of pleural fluid (PF) in over 85% of cases.[3] Pleural biopsies (PB) have primarily been indicated when diagnosing TB and malignant PE.[1] The biopsies can be performed blindly (BPB), under radiological control (ultrasound or computed tomography [CT]) or by means of medical thoracoscopy or pleuroscopy.

Pleural biopsies in tuberculosis

Pleural TB has been considered a paucibacillary disease from which microbiological confirmation is only obtained in a minority of cases. Therefore, mycobacteria identification (Ziehl–Neelsen or auramine) and cultures in PF solid media (Lowenstein–Jensen) were positive in only 6% and 36%, respectively, of 548 patients with tuberculous PE.[4] In sputum, these respective percentages were 8% and 41% in another set of 1835 patients with pleural TB.[5] The low yield of cultures and the delayed availability of results (4–6 weeks) mean that PBs are the preferred option, in the BPB modality (given the unclear involvement of pleura in TB), as a standard diagnostic method. In one study, BPBs demonstrated caseating granulomas in 401 (78%) out of 517 patients with pleural TB, whereas microscopic examination of the biopsy found tuberculous bacilli in 24% of cases, and the culture was positive in 53% of cases.[4] In any event, BPBs are still invasive procedures and there is a risk of complications: 7% of cases have pneumothorax (19% of which required thoracic drainage), 5% have chest pain and 3.5% have vagal reactions, by adding 2 sets with a total of 1072 BPBs.[6,7] Furthermore, in at least 10% of cases, rather than pleural tissue, chest fat and muscle are obtained.[6,7] Therefore, the way in which tuberculosis PE is diagnosed has drastically changed since the discovery of adenosine deaminase (ADA) as an effective, economical and easy-to-measure biomarker.[8] Various meta-analyses have shown that the ADA of PE (in concentrations of >35–40 U/L) has an mean sensitivity of 92% and specificity of 90% in identifying tuberculous PE.[8] Levels of this enzyme are often increased in complicated parapneumonic PEs (where neutrophils are predominant in PF, which is observed in only 10% of TB cases), empyemas (purulent appearance) and lymphomas.[9] The use of ADA has been prominent in areas with a medium prevalence (e.g., Spain) or high prevalence of TB, where it has generally replaced BPB as the first diagnostic procedure. However, even in regions with a low prevalence of infection, the negative predictive value of ADA is almost 100% (i.e., the probability of PF being TB with ADA <35 U/L is minimal).[9] On the other hand, the increasing use of liquid culture media for mycobacteria has markedly improved microbiological isolates (e.g., 63% positive cultures in PF, 48% in sputum and 79% in a combination of the two, in a set of 382 pleural TB patients)[10] and reduced the waiting time for results to 2 weeks. Therefore, a BPB would only be indicated when TB is suspected and any of the following circumstances are met: 1) inability to measure ADA, 2) pleural ADA <35 U/L in an area with moderate or high TB prevalence, 3) pleural ADA >35 U/L in an area with very low TB prevalence and 4) possibility of multi-resistant TB (prevalence in Catalonia: 1.4% in 2015),[11] if the cultures in PF liquid media or sputum were negative.

Pleural biopsies in malignant effusion

Malignant PEs are another etiology in which a PB might be necessary. PF cytological examination is the simplest method to diagnose malignancy. This includes smears (Papanicolaou) and cell blocks (hematoxylin-eosin) obtained after PF centrifugation.[12] With the analysis of 2 smears and PF cell blocks, malignancy is diagnosed in about 60% of cases.[12] This leaves 40% of false-negative cytologies, a percentage that is much higher (70–75%) in squamous carcinomas of the lung and mesotheliomas.[2] In this group of patients, a diagnostic pleuroscopy has been historically indicated, which would also allow a therapeutic procedure to be conducted simultaneously, such as pleurodesis with talc. Are there arguments for reconsidering this classical approach?

First, not all patients with a likely malignant PE, no cytological confirmation and a PB demonstrating a pleural tumor invasion will be offered an active cancer treatment (due, for example, to a low quality of life or an Eastern Cooperative Oncology Group [ECOG] score $\geq$3) or a different treatment from that already planned (e.g., due to the presence of metastases in other locations). Therefore, the need for confirmatory PBs must be decided on a case-by-case basis, without precluding palliative pleural procedures in symptomatic patients (e.g., insertion of a tunneled pleural catheter or PleurX®). Where a PB is considered necessary, the next issue requiring consideration is the type of PB. BPBs are not the best option because of the inconsistent disposition of tumor implants in the pleura and the fact that they are mostly located in inaccessible areas, such as the diaphragmatic or medial pleura. The addition of 4 sets with a total of 797 patients with malignant PEs showed that the sensitivity of PF cytology was 63.5% and that of BPB was 48%.[6,7,13,14] Twenty-three percent of malignant PEs with negative cytology had positive BPBs. Overall, BPBs increased the yield of cytology by 8.5%, with a combined (insufficient) percentage of diagnoses of 72% with both procedures.[6,7,13,14]

Thoracoscopy has 93–95% sensitivity when confirming the malignancy of a PE[15,16] but has a single contraindication: the absence of pleural space. This situation can occur in the context of intense pleural adhesions or in patients who have undergone pleurodesis in the past. The technique is relatively safe, with a mortality rate of 0.3%, major complications in 1.8% and minor complications in 7.3% of cases.[15,16] Pulmonologists or thoracic surgeons can perform the technique, but certain infrastructure is required (for example, if performed by a pulmonologist in an endoscopy room, a thoracic surgery department is required for complications), and physicians should perform approximately 20 procedures annually in order to maintain competence.[17] As a result, more attention has been paid in recent years to a variety of less invasive and more accessible PBs (e.g., image-guided PBs), which are easily performed by pulmonologists and interventional radiologists.