Role of blind closed pleural biopsy in the management of pleural exudates

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INTRODUCTION: The performance of blind closed pleural biopsy (BCPB) in the study of pleural exudates is controversial.

OBJECTIVE: To assess the diagnostic yield of BCPB in clinical practice and its role in the study of pleural exudates.

METHODS: Data were retrospectively collected on all patients who underwent BCPB performed between January 1999 and December 2011.

RESULTS: A total of 658 BCPBs were performed on 575 patients. Pleural tissue was obtained in 592 (89.7%) of the biopsies. A malignant pleural effusion was found in 35% of patients. The cytology and the BCPB were positive in 69.2% and 59.2% of the patients, respectively. Of the patients with negative cytology, 21 had a positive BCPB (diagnostic improvement, 15%), which would have avoided one pleuroscopy for every seven BCPBs that were performed. Of the 113 patients with a tuberculous effusion, granulomas were observed in 87 and the Lowenstein culture was positive in an additional 17 (sensitivity 92%). The overall sensitivity was 33.9%, with a specificity and positive predictive value of 100%, and a negative predictive value of 71%. Complications were recorded in 14.4% of patients (pneumothorax 9.4%; chest pain 5.6%; vasovagal reaction, 4.1%; biopsy of another organ 0.5%).

CONCLUSIONS: BCPB still has a significant role in the study of a pleural exudate. If an image-guided technique is unavailable, it seems reasonable to perform BCPB before resorting to a pleuroscopy. These results support BCPB as a relatively safe technique.

Key Words: Blind closed pleural biopsy; Malignant pleural effusion; Pleural exudates; Pleuroscopy; Tuberculous pleural effusion

The aim of the present study was to determine the diagnostic yield of BCPB in clinical practice in our region, and to assess whether this technique still has a relevant role in the study of pleural exudates.

METHODS

Data were collected from all patients who underwent BCPB performed in the period between January 1, 1999 (the date when the histopathology department database was computerized) and December 31, 2011. The study was performed in a university general hospital in Galicia, located in the northwest of Spain, where the incidence of tuberculosis in 1996 (first year of available reliable data) was 72.3 per 100,000 inhabitants (21) and 28 per 100,000 (22) inhabitants in 2010, with an incidence of tuberculosis pleural effusion (TBPE) in 2009 of 4.8 per 100,000 inhabitants (23). The protocol was evaluated and approved by the Clinical Research Ethics Committee of Galicia (registry 2012/076) before commencement of the study.

The diagnostic algorithm used was that recommended by the Spanish Society of Chest Diseases and Thoracic Surgery (Sociedad Española de Neumología y Cirugía Torácica [SEPAR]) (2) with the difference that, depending on the clinical suspicion, the BCPB was occasionally performed at the same time as thoracocentesis, if pretest clinical
Role of BCPB in the management of pleural exudates

Table 1

<table>
<thead>
<tr>
<th>Effusion</th>
<th>Age, years</th>
<th>Sex, M/F (% M)</th>
<th>Side of effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>Mean ± SD</td>
<td>Range</td>
<td>120/81 (59.7)</td>
</tr>
<tr>
<td>Paramalignant</td>
<td>70±11.2</td>
<td>37–90</td>
<td>50/26 (65.8)</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>48±22.1</td>
<td>15–93</td>
<td>64/49 (56.6)</td>
</tr>
<tr>
<td>Acute inflammatory pleuritis</td>
<td>70±15.6</td>
<td>22–95</td>
<td>60/21 (74.1)</td>
</tr>
<tr>
<td>Nonspecific chronic pleuritis/pleural fibrosis</td>
<td>68±15.6</td>
<td>24–93</td>
<td>33/14 (70.2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0±2</td>
<td></td>
<td>24/18/5 (51/38.3/10.7)</td>
</tr>
<tr>
<td>No disease demonstrated</td>
<td>69±16.8</td>
<td>28–91</td>
<td>43/12 (78.2)</td>
</tr>
<tr>
<td>Total</td>
<td>65±18</td>
<td>15–95</td>
<td>370/205 (64.3/35.7)</td>
</tr>
</tbody>
</table>

M Male; F Female

The overall sensitivity of the BCPB was 33.9% if all the biopsies performed are taken into account. The specificity and positive predictive value for the diagnostic yield of MPE and TBPE was 100%. The probability of a case being neither tuberculosis nor pleural neoplasia (negative predictive value) when the pleural biopsy specimen was nonspecific (taking into account the total of the procedures performed [n=658]) was 71%, although a negative result does not exclude these diagnoses.

There was no change in the diagnosis throughout the follow-up period. In the specific case of paramalignant effusions, 90 pleural fluid cytologies were performed in the follow-up year and none were positive.

A complication following BCPB was recorded in 95 (14.4%) of the procedures. A pneumothorax was documented in 62 (9.4%) and 12 (1.8%) required a chest drain. Intense chest pain following BCPB occurred in 17 (2.6%) cases; in two cases, samples of lung were obtained and of the liver in another. No cases of hemorrhage, sepsis or death were reported.


discussion

When pleural fluid cytology is negative in a suspected case of MPE, there are several options for further investigations, including BCPB. However, in the past few years, several studies have shown that image-guided pleural biopsy and pleuroscopy have a higher yield in the diagnosis of MPE (10,12). The relatively low yield of BCPB is due to scarce, patchy and irregular distribution of the tumour invasion of
TABLE 2
Final diagnoses established in all patients (n=575) and diagnostic yield of pleural biopsies (n=658)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Biopsies, n</th>
<th>Patients, n</th>
<th>Diagnosed, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>225</td>
<td>201</td>
<td>119 (52.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>114</td>
<td>105</td>
<td>64 (56.1)</td>
</tr>
<tr>
<td>Non-small cell</td>
<td>105</td>
<td>98</td>
<td>61 (58.1)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>79</td>
<td>79</td>
<td>48 (60.8)</td>
</tr>
<tr>
<td>Epidermoid</td>
<td>18</td>
<td>14</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Large cell</td>
<td>8</td>
<td>5</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Small cell</td>
<td>9</td>
<td>7</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Breast</td>
<td>43</td>
<td>40</td>
<td>21 (48.8)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>18</td>
<td>18</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Stomach</td>
<td>9</td>
<td>8</td>
<td>5 (55.5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>7</td>
<td>5</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6</td>
<td>4</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>6</td>
<td>4</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
<td>12</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>8</td>
<td>5</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Paramalignant</td>
<td>90</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>113</td>
<td>113</td>
<td>104 (92)</td>
</tr>
<tr>
<td>Acute inflammatory pleuritis</td>
<td>86</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Nonspecific chronic pleuritis/pleural fibrosis</td>
<td>67</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td>75</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

BCPB Blind closed pleural biopsy

The diagnostic yield obtained in MPEs (59.2%) was in the range reported by other authors (Table 3). Mungall et al (31) obtained a sensitivity of 47% in MPEs (which would have reached 72% if the cases with a suggestive diagnosis were considered). Edmondstone et al (32) and McLean et al (33) reported slightly lower diagnostic sensitivities of 60% and 62%, respectively. On the other hand, in another four series, the sensitivity varied between 43.8% and 48.5% (3,10,34,35). These data are important as they demonstrate the improvement in the diagnostic sensitivity of the cytology that BCPB provides, which was 15% in our series, and would have avoided one pleuroscopy for every seven pleuroscopies that were performed – figures slightly lower than those obtained in a review on this topic (an improvement of 19.4%, and the need for 5.2 BCPB to avoid one pleuroscopy) (36). This improvement varies between 7% and 27% in the literature (37,38) for a similar cytology yield (71% and 72.6%, respectively). Lung cancer was the most common origin of MPE in our series (the majority [75%] being adenocarcinomas), followed by breast cancer and lymphoma, with a slightly higher diagnostic yield of BCPB in the former (61% versus 52.5% and 50%, respectively). Few mesotheliomas are diagnosed in our region (6) (four cases in the present series), likely due to the limited settlement of industry associated with asbestos in our area. The BCPB was diagnostic in 33.3% (six biopsies were needed to diagnose two cases), much lower than the 71.4% of Beauchamp et al (39) and higher than the 20.7% reported by Boutin et al (40).

The diagnostic sensitivity of BCPB in TBPE (92%) was similar to that reported in previous studies by our group (7) and by other authors (5). The remaining cases were diagnosed based on the observation of patients <40 years of age, with an ADA level >45 U/L and lymphocyte count >80% (19 cases) (15). Our usual practice is to attempt to confirm the diagnosis by performing a pleural biopsy because ADA level and the percentage of lymphocytes are markers that are not provided in the culture or yield information on whether resistance is present. In areas with a high incidence of tuberculosis and a low level of resistance, an elevated ADA level, along with a lymphocytic exudate, could establish the diagnosis. If there is also a high level of resistance, it is very risky to have confidence in the diagnosis and treatment based only on these markers. In these cases, it is recommended to perform a biopsy and culture, and determine drug susceptibility (41). The practical consequence of this elevated diagnostic sensitivity is that pleuroscopy will only be needed on few occasions to diagnose this pleuritis. In a review of nine series, mainly performed in Europe and the United States, the sensitivity of BCPB in TBPE was 54% (48 of 89), and was 7.6% of the total cases studied (89 of 1167) (3,10,31-35,37,38). It may be that tuberculosis was not a problem in the geographical areas where these studies were conducted, but this is not the situation in emerging and developing countries where tuberculosis is a major public health problem and the resources that they have to combat it are limited.

The overall sensitivity of BCPB in our series was 33.9%. However, it does appear that this is the best indicator to assess the diagnostic yield of this technique because the results will depend on, among other factors, the case mix of each series (better yield when more TBPE are included) or on the number of cases included with diagnoses other than MPE or TBPE. Thus, in our series, the fact of having performed a BCPB simultaneously in 81 patients who were subsequently diagnosed with acute inflammatory pleuritis has led to the overall yield of BCPB being lower. This is because it is sometimes difficult to differentiate these cases from TBPE. Thus, it seems more useful to assess its diagnostic sensitivity in accordance with the yield obtained in the diagnosis of
a particular condition. No false-positive results with BCPB have been reported in any of the series, including ours, which shows that it is a highly specific technique.

Pleural tissue was not obtained in 68 of the 658 BCPBs (10.3%). This result is consistent with those obtained by other authors in which the ranges varied between 9% by Koegelenberg et al (11) and 29% in the series by Walsh et al (42) (performed by nonrespiratory teams). Other series obtained pleural tissue in 79% (3) and 90% (43) of cases.

The complications recorded were limited to pneumothorax (62 [9.4%] patients, of whom 12 [1.8%] required a chest drain), chest pain (34 [5.2%] patients who had pneumothorax and an additional three in whom nerve fascicles were obtained in the biopsy), a vasovagal reaction (27 patients [4.1%]) and obtaining a specimen of other organs (two from the lung and one from the liver). The complications reported after BCPB in other series are, in general, also low, and are limited to a pneumothorax (with the need of a chest drain in 1% of cases), pain or bruising at the puncture site, vasovagal reaction, biopsy of other organs and hemorhorax (1,3,5,13,32,43), although in one series, two deaths were reported after experiencing a hemorhorax (37).

The most important limitation of our study was its retrospective nature. The phase of the disease at the time of diagnosis was also not taken into account, which could have influenced the diagnostic yield of BCPB. This should be higher in advanced phases because it is more likely that the outer pleura are also affected, in addition to the visceral pleura. Many different chest physicians (staff members or residents) performed the BCPB throughout the study, and their experience with the procedure, which could influence the results, as well as complications, were not taken into account. It could also be argued that some of the effusions labelled as malignant were, in fact, an authentic MPE in which the diagnostic tests may have been negative. This appears to be highly unlikely because, at the time of diagnosis, all of them had mediastinal lymph nodes in the computed tomography scan that would lead to a blockage of lymphatic drainage and the subsequent pleural effusion. Besides, no malignancy was found in the 90 pleural fluid cytologies that were performed during the year of follow-up.

That the diagnostic yield of image-guided pleural biopsy is superior to BCPB is unquestionable, due to the information that it provides (size of effusion, presence of loculations, pleural nodes, etc), which helps in selecting the ideal puncture site and avoids potential complications. Although the present study was not designed to assess economic aspects, the costs of image-guided pleural biopsy and pleuroscopy (training of doctors, hospital stay, etc) are considerable and, for these reasons, have a significant impact in financial terms. We should consider whether all radiologists are trained to obtain image-guided pleural biopsies and if they would be available when needed. The sensitivity of BCPB in the diagnosis of MPE and TBPE in our series was sufficiently high to take these factors into account. This is of particular importance in areas with limited resources and difficulties with access to pleuroscopy or to imaging tests needed to guide the biopsy. On the other hand, it is likely that BCPB would be better tolerated than pleuroscopy because patients with an MPE are generally in a poorer state of health and, therefore, the risk associated with any type of surgery is also avoided. Furthermore, if pneumologists abandon BCPB, new generations would not be familiar with this technique and those working in hospitals with limited resources will not be able to perform pleural biopsies and must transfer patients to tertiary hospitals to obtain a small pleural tissue sample.

SUMMARY
Our results suggest that BCPB still has an important role in the study of pleural exudates, particularly when malignancy or tuberculosis is suspected. In the diagnosis of an MPE, if an image-guided technique is not available, it seems reasonable, given its sensitivity, to perform a BCPB before resorting to a pleuroscopy because it helps to improve the diagnostic accuracy of cytology and avoids one pleuroscopy for every seven BCPB that are performed. Similarly, the high sensitivity obtained in the diagnosis of TBPE, a widely prevalent disease in developing countries, suggests that resorting to pleuroscopy would only be required in a few cases. The number of complications documented, and the low severity of these, supports it as a relatively safe technique. In the suspicion of an MPE, further studies will be needed to predict which patient phenotype is more likely to benefit from this examination.

FUNDING: This work was performed without funding.

DISCLOSURES: All authors have signed a conflict of interest form. There are no financial disclosures or conflicts of interest to declare.

AUTHOR CONTRIBUTIONS: Marco F Pereyra: Approval of the submitted and final versions, acquisition of data, drafting the manuscript. Esther San-José: Approval of the submitted and final versions, research design, analysis or interpretation of data, drafting and critical revision of the manuscript. Lucía Ferreiro: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. Antonio Golpe: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. José Antúnez: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. Francisco-Javier González-Barcala: Approval of the submitted and final versions, research design, analysis or interpretation of data, drafting the manuscript, critical revision of the manuscript. Ihab Abdulkader: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. José M Álvarez-Dobaño: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. Nuria Rodríguez-Núñez: Approval of the submitted and final versions, acquisition of data, critical revision of the manuscript. Luis Valdés: Approval of the submitted and final versions, research design, analysis or interpretation of data, drafting the manuscript, critical revision of the manuscript.

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