Pleural Fluid Analysis and Pleural Elastance as Predictors of Response to Pleurodesis in Patients With Malignant Pleural Effusion

Análisis del líquido y elastancia pleurales como predictores de respuesta a la pleuredesis en los derrames pleurales malignos

To the Editor,

The use of pleural manometry (PM) during therapeutic thoracentesis is controversial.\textsuperscript{1,2} A small study of malignant pleural effusions (MPE) conducted 20 years ago suggested that pleural elastance ($P_{\text{EL}}$), the ability of the lung to return to its natural position after the extraction of pleural fluid (PF),\textsuperscript{3} can predict the success of pleurodesis.\textsuperscript{4} This led to the recommendation that unexpansible lung (UEL)\textsuperscript{5} should be identified in order to guide management decisions.\textsuperscript{5} The objective of this study was to evaluate if the success of pleurodesis in MPE can be predicted by identifying various biochemical parameters in PF and determining $P_{\text{EL}}$.

We performed a retrospective study of all MPEs (cytology or pleural biopsy positive for malignancy) managed with therapeutic thoracentesis with PM and subsequent pleurodesis between January 2014 and October 2016. Exclusion criteria were previous chemotherapy/radiation therapy, life expectancy <1 month, or loculated PE. Patients signed an informed consent form before therapeutic thoracentesis with PM was performed. Our study was approved by the hospital ethics committee (registry 2016/518).

Pleural pressure was measured with a digital manometer (Compass; Mirador Biomedical),\textsuperscript{6} using a previously described technique.\textsuperscript{7} Thoracentesis was completed when no more fluid could be extracted, pleural pressure reached $-20\ \text{cmH}_2\text{O}$ or if chest pain developed.\textsuperscript{8} $P_{\text{EL}}$ was calculated based on the formula: [opening pressure–closing pressure (cmH$_2$O)/volume of fluid extracted (liter)]. A diagnosis of UEL was reached if incomplete pulmonary reexpansion was observed on the post-thoracocentesis chest X-ray.

Pleurodesis with a slow injection of suspension of 4 g talc in 50 cc 0.9% saline solution was administered after evacuating the PE via a chest tube (16F) and checking lung reexpansion on X-ray, irrespective of the amount of fluid drained on a daily basis.\textsuperscript{9} The tube was closed for 2–3 h, and then connected to mild progressive aspiration. The chest tube was removed after 24 h, regardless of the volume of fluid obtained, and without radiological monitoring.\textsuperscript{10} Pleurodesis was considered to have been successful if no reaccumulation or only partial accumulation of PE not requiring further thoracocentesis occurred until the time of death.\textsuperscript{11} It was considered to have failed if the effusion recurred or new procedures were needed for the relief of symptoms. The decision to perform pleurodesis was not based on the PF analyses or $P_{\text{EL}}$ results.

Fasting PF and blood specimens were obtained simultaneously. Biochemical parameters determined in PF were those included in the routine protocol of our hospital. Data are listed as mean ± standard deviation, or median and 25th–75th percentiles, depending on whether the distribution of the samples was normal or not. Pearson’s Chi-squared test was used for the comparison between groups if the variables were qualitative, and the non-parametric Mann–Whitney test was used if they were quantitative. ROC curves and the area under the curve were calculated to assess the discrimination capacity of the markers in the prognosis of pleurodesis (success/failure).

In total, 148 PMS were performed, of which 110 were cases of MPE. Pleurodesis was performed in 36 patients (20 women and 16 men [mean age: 65.2 ± 12.9 years; range: 18–89]). Seventy-four patients were excluded due to previous chemotherapy/radiation therapy (31), short life expectancy (28), loculated PE (8), and no signed informed consent (7). UEL was diagnosed in 8 patients (22.2%).

Pleurodesis was successful in 26 patients (72.2%), and failed in 10 (27.8%) (Table 1). Significant differences between the groups were only found for neuron-specific enolase in PF (NSE$_{\text{PF}}$) ($P$=0.046) and for $P_{\text{EL}}$ ($P$=0.000). The diagnostic yield of these 2 variables for predicting pleurodesis failure is shown in the same table [areas under the ROC curves for NSE$_{\text{PF}}$ and $P_{\text{EL}}$ of 0.717 (0.526–0.908) and 0.935 (0.842–1.027), respectively].

This study confirms that $P_{\text{EL}}$ is a useful parameter for predicting the response to pleurodesis in MPE, and that values $\geq 18\ \text{cmH}_2\text{O}/l$ suggest that the procedure will fail, due to poor apposition of the two pleural membranes\textsuperscript{12} and the inability of the lung to return to its natural position as the PF is extracted. Pleurodesis can also fail in patients with an expandable lung and $P_{\text{EL}}$ below this cut-off point (2/28; 7.1%). This seems to indicate that other factors may cause pleurodesis failure, such as insufficient inflammatory response to cause fibrosis and produce pleural symphysis, or time elapsed between diagnosis and starting drainage.\textsuperscript{13}

The only biochemical parameter that showed some discriminant value for predicting the failure of pleurodesis was NSE$_{\text{PF}}$, which was not significantly different from that of $P_{\text{EL}}$ ($P$=0.7564), probably because of the small size of the series and the width of the confidence intervals. Thus, the lower limit of the positive likelihood ratio of NSE$_{\text{PF}}$ (1.5) has little effect on the probability of diagnosing pleurodesis failure. The reason why NSE$_{\text{PF}}$ is high in these patients is still unknown. Perhaps, as in rheumatoid arthritis, a situation of hypoxia is generated that activates anaerobic glycolysis and causes this marker to rise.\textsuperscript{14,15} The main limitations of the study are its retrospective nature, the small number of cases in the study, and the fact that all patients were recruited in a single center.

Our study suggests that NSE$_{\text{PF}}$ and $P_{\text{EL}}$ measurements can predict response to pleurodesis in MPE. In patients with raised $P_{\text{EL}}$ ($\geq 18\ \text{cmH}_2\text{O}/l$), the probability of pleurodesis failure is very high and, therefore, other therapeutic alternatives that may offer a chance of success should be considered for the prompt control of the patient’s symptoms.

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Table 1  
Characteristics of the Total Number of Patients by Pleurodesis Response and Diagnostic Yield of the Variables with Significant Differences Between the Pleurodesis Response Groups to Predict Failure [Percentages (95% CI)].

<table>
<thead>
<tr>
<th>Pleurodesis Success</th>
<th>Pleurodesis Failure</th>
<th>P</th>
<th>CO</th>
<th>Sen (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>PLR</th>
<th>NLR</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>26 (72.2)</td>
<td>10 (27.8)</td>
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<tr>
<td>Age</td>
<td>65.7 ± 13.9</td>
<td>64 ± 10.9</td>
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<tr>
<td>Men/women</td>
<td>11/15</td>
<td>5/5</td>
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<tr>
<td>Time (days)</td>
<td>20 (8–40)</td>
<td>37.5 (27.5–60)</td>
<td></td>
<td>.677</td>
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<tr>
<td>Pleurodesis response</td>
<td>9/10/7</td>
<td>6/3/1</td>
<td></td>
<td></td>
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<tr>
<td>PF (&lt;1/3&gt;/1/3–&lt;2/3&gt;/2/3)</td>
<td>3/16/7</td>
<td>0/3/7</td>
<td></td>
<td></td>
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<tr>
<td>Chest pain (yes/no)</td>
<td>12/14</td>
<td>2/8</td>
<td></td>
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<tr>
<td>PF appearance</td>
<td>14/9/2/1</td>
<td>3/5/0/0</td>
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Red blood cells  
Leukocytes  
Segmented (%)  
Lymphocytes (%)  
PF pH  
PF glucose (mg/dl)  
PF cholesterol (mg/dl)  
PF amylase (U/l)  
PF total protein (g/dl)  
PF albumin (g/dl)  
PF LDH (IU/l)  
PF CA 15–3 (U/ml)  
PF CA 19–9 (U/ml)  
PF CYF 21–1 (ng/ml)  
PF NSE (ng/ml)  
Pc (cm H₂O/l)  

[Median (25th–75th percentiles)].

CA 125, cancer antigen 125; CA 15–3, carbohydrate antigen 15–3; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CO, cut-off point; CYF 21–1, cytokeratin fragment 21–1; LDH, lactate dehydrogenase; NA, not applicable; NPV, negative predictive value; NSE, neuron-specific enolase; Pc, pleural elastance; PF, pleural fluid; PPV, positive predictive value; PVR, positive likelihood ratio; RVN, negative likelihood ratio; Sen, sensitivity; Spec, specificity.

a Evaluated until time of death.

b Time between onset of symptoms and performing therapeutic thoracentesis.
Congenital Pulmonary Malformations Diagnosed Over a Period of 10 Years

Malformaciones congénitas pulmonares diagnostcadas en un periodo de 10 años

To the Editor,

Congenital lung malformations (CLM) are a group of entities caused by alterations in the embryogenesis of the lung and airways. Both the site within the tracheobronchial tree and the gestational age at the time of the embryological insult correlate with lesion type and histopathology.1

Clinical, radiological and histopathological criteria have been established for the classification of most CLM. Diseases currently considered CLM are congenital pulmonary airway malformations (CPAM), pulmonary sequestration, bronchogenic cyst, congenital lobar emphysema, and bronchial atresia. Stocker2 classifies CPAM, formerly known as congenital cystic adenomatoid malformation, into 5 subtypes based on the number and size of the cysts and their anatomical origin: Type 0: lung consisting of small cysts (0.5 cm), incompatible with life; Type 1: single or multiple cysts (0.5–2 cm) arising from the bronchi or bronchioles; Type 2: multiple cysts (0.5–2 cm) in the bronchioles; Type 3: solid lesion with cysts (<0.5 cm) in the bronchioles and alveolar tract; and Type 4: cysts up to 7 cm, originating in the distal acinar region.

Pulmonary sequestration refers to a non-functioning sector of the lung that is irrigated by the systemic circulation, and is classified as intralobar or extralobar, depending on whether it is contained within the visceral pleura of lung or it has its own pleural lining, respectively.1

CLMs are rare, accounting for between 7.5% and 18.7% of all organ malformation, and their clinical presentation and severity vary widely, especially in terms of the degree of pulmonary involvement. Manifestations can occur at any age, but typically develop in infancy and childhood. The risk of recurrent respiratory infections or malignant transformation has been described in the course of some CLM, particularly CPAM.3,4

CLM may be diagnosed at birth due to the onset of clinical symptoms, incidentally during radiological studies, or without symptoms, or in ultrasonography tests performed in the prenatal period.1,3,5

The management of these lesions depends on the type of malformation and the development of symptoms, so management must be individualized for each case and type of malformation; most authors recommend resection of the lesion, but there is currently no consensus on the surgical approach, especially in asymptomatic patients.1,3,7

The aim of this review is to describe the clinical, radiological, pathological findings, progress, and follow-up of 20 children diagnosed with CLM in the University Hospital Parc Taulí between 2006 and 2016.

We reviewed the medical records of 20 children with CLM: 12 boys (60%) and 8 girls (40%). Twelve children (60%) were diagnosed during the prenatal period. Congenital lung malformations were identified as: pulmonary sequestration: 9 cases, (45%), 7 extralobar (77.7%), 2 intralobar (22.2%); CPAM: 5 cases (25%),

References