Pleural Effusions Associated with Pulmonary Thromboembolism: A Systematic Review

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ABSTRACT

Objective. To perform a review of the incidence, pathogenesis, clinical presentation, diagnosis and management of pleural effusions associated with pulmonary embolism (PE).

Methods. A search of the MEDLINE and EmBase databases from 1975 to 2007 was performed. A manual search was also performed of the references of each article.

Results. Pleural effusions occur in 19% to 61% of patients with PE. The incidence is higher if computed tomography (CT) of the chest is used for detection of pleural effusion (28.1% with chest radiograph and 43.3% with CT chest). The pleural fluid is almost always an exudate. Although usually unilateral, the pleural effusion can also be bilateral. The effusions are maximal by the third day, be larger in size, may develop loculations and can be associated with high leukocyte counts. The presence of pulmonary infarction may not be associated with large effusions.

Conclusions. Pleural effusions are a common occurrence in patients with PE. The possibility of PE should be entertained in any patient with undiagnosed exudative pleural effusion. The results of this review further suggest that many traditional concepts with PE, viz, unilateral small effusions, absence of loculations and transudative nature of the pleural fluid need reappraisal. [Indian J Chest Dis Allied Sci 2009;51:159-164]

Key words: Pleural effusion, Pulmonary embolism, Pulmonary thromboembolism, Venous thromboembolism, Hydrothorax.

INTRODUCTION

Pulmonary embolism (PE) is a common and a potentially life threatening condition associated with considerable morbidity and mortality. In fact, an estimated 10% of symptomatic PE cause death within one hour of onset.¹ The PE is also a disorder commonly overlooked in the work-up of a patient with pleural effusion and it is probable that PE may be responsible for a substantial fraction of undiagnosed pleural effusion.² In this paper, we systematically review the literature on the incidence, pathogenesis, clinical presentation, diagnosis and management of pleural effusions associated with PE.

SEARCH METHODS AND RESULTS

A search of the MEDLINE and EmBase databases from 1975 to 2007 was performed using two groups of search terms: (i) ‘pulmonary embolism and pleural effusions’, ‘pleural effusions and pulmonary thromboembolism’, ‘pleural effusions and venous thromboembolism’, ‘pleural effusions and deep venous thrombosis’, pleural effusions and deep vein thrombosis’, ‘computed tomography and pulmonary embolism and pleural effusion’; and (ii) ‘eosinophilic pleural effusions’, without any language limitations. A manual search was performed of the references of each article. Single patient case reports were excluded.

Our searches in the first group yielded 319 references (reasons for excluding other references: n=157, neither pleural effusion nor PE; n=37, PE but not pleural effusion; n=102, pleural effusion but not PE or single patient case reports) of which 25 references were related to pleural effusions in PE.³ In the second search, there were 206 references (reasons for excluding other references: n=36, not pleural effusion; n=102, pleural effusion but not PE or single patient case reports) of which 12 references were related to eosinophilic pleural effusions,²⁸⁻³⁹ which were excluded.

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INCIDENCE

The exact incidence of pleural effusion due to PE remains unknown because the exact occurrence of PE itself is unclear, although in one series, PE was the fourth leading cause of pleural effusion. An estimated 100 persons per 100,000 each year develop venous thromboembolism for the first time. The incidence rises exponentially from less than five cases per 100,000 persons in the second decade to approximately 500 cases (0.5%) per 100,000 persons at the eighth decade. The incidence is likely to be an under-estimation of the actual burden because many cases go unsuspected. In fact, in one series of 27 patients with undiagnosed pleural effusion, diagnosis could be achieved only in 16 patients, and two patients were diagnosed to have PE after autopsy. It is theoretically possible that many cases of undiagnosed pleural effusion may well be PE because the diagnosis is not suspected.

Pleural effusions have been reported to occur in 19% to 61% of patients with PE with approximately 48% in patients with no pre-existing cardiac or pulmonary disease. The detection rate is higher if computed tomography (CT) is used as a modality for the diagnosis of pleural effusion (85/3047 (28.1%) with chest radiograph, 142/328 (43.3%) with CT, p<0.0001; Table 1). In one study, CT detected 20 effusions which were missed by the chest radiograph. The incidence is also different in the post-operative setting depending on the surgical procedures with pleural effusion occurring more commonly in patients with PE following general surgical procedures than orthopedic surgeries. This probably reflects the incidence of common radiographic abnormalities after specific surgical procedures rather than the different chest radiographic abnormalities caused by PE.

Table 1. Incidence of pleural effusion in patients with pulmonary embolism

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Method of Diagnosis</th>
<th>Incidence n/N (%, 95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bynum and Wilson'7</td>
<td>Chest radiograph</td>
<td>79/155 (51.0, 47.2-57.7)</td>
</tr>
<tr>
<td>Stein et al'9</td>
<td>Chest radiograph</td>
<td>180/343 (52.5, 47.2-57.7)</td>
</tr>
<tr>
<td>Coche et al'15</td>
<td>Spiral computed tomography</td>
<td>13/26 (50.0, 32.1-67.9)</td>
</tr>
<tr>
<td>Johnson et al'17</td>
<td>Spiral computed tomography</td>
<td>14/61 (45.2, 29.2-62.2)</td>
</tr>
<tr>
<td>Shah et al'18</td>
<td>Spiral computed tomography</td>
<td>16/28 (57.1, 39.1-73.5)</td>
</tr>
<tr>
<td>Elliott et al'19</td>
<td>Chest radiograph</td>
<td>523/2319 (22.6, 20.9-24.3)</td>
</tr>
<tr>
<td>Enden and Klow'22</td>
<td>Spiral computed tomography</td>
<td>27/55 (49.1, 36.4-61.9)</td>
</tr>
<tr>
<td>Reissig et al'25</td>
<td>Spiral computed tomography</td>
<td>9/39 (23.1, 12.6-38.3)</td>
</tr>
<tr>
<td>Lobo et al'26</td>
<td>Chest radiograph</td>
<td>628/3391 (18.3, 17.2-19.9)</td>
</tr>
<tr>
<td>Porcel et al'27</td>
<td>Chest radiograph</td>
<td>73/230 (31.7, 26.1-38.0)</td>
</tr>
<tr>
<td>Porcel et al'27</td>
<td>Spiral computed tomography</td>
<td>63/119 (61.3, 52.4-69.6)</td>
</tr>
</tbody>
</table>

n=patients with pleural effusion; N=patients with pulmonary embolism

PATHOGENESIS OF PLEURAL EFFUSIONS IN PULMONARY EMBOLISM

The exact pathogenesis of pleural effusions associated with PE remain unknown. However, two mechanisms that can be hypothesised are increased capillary pressure in the parietal pleura and increased pulmonary vascular permeability. In the first mechanism, the thromboemboli increase the systemic venous pressure and capillary pressure in the parietal pleura. This leads to increased hydrostatic pressure in the capillaries with pleural fluid formation. As the systemic venous pressure increases, the lymphatic drainage from the pleura into the systemic veins also decreases with resultant pleural fluid accumulation. However, this mechanism does not seem to be predominating because patients with pulmonary hypertension and right heart failure rarely, if ever, develop pleural effusions.

The likely mechanism of pleural effusion in PE is increased permeability of pulmonary capillaries with the resultant interstitial fluid traversing the visceral pleura and causing accumulation of pleural fluid. In fact, it has been demonstrated that patients with pleural effusion secondary to PE have a large amount of protein entering and leaving the pleural space. The main cause of this increased capillary permeability is probably release of inflammatory mediators by the platelet-rich thrombi, and the levels of one inflammatory mediator, vascular endothelial growth factor (VEGF), have been demonstrated to be greatly increased in pleural fluid. It is likely that this mediator and other inflammatory mediators released from the pulmonary thrombi lead to increased capillary permeability and resultant pleural effusion. The pleural fluid formed by this mechanism will be an exudate.
The three major symptom complexes that occur in conjunction with PE are pulmonary infarction (pleuritic chest pain and/or haemoptysis), isolated dyspnoea and circulatory collapse.\textsuperscript{26,45}

In one study,\textsuperscript{26} pleural effusions occurred in 422 of 1709 patients (27\%) who had pleuritic chest pain-haemoptysis complexes, 119 of 1083 patients (12\%) who had isolated dyspnoea, and in 87 of the 599 (16\%) patients who had circulatory collapse. The clinical presentation also has a bearing on outcome with a reported mortality of 6.2\% and 6.5\% with isolated dyspnoea and circulatory collapse compared to 2.5\% for pulmonary infarction.\textsuperscript{26} In another study,\textsuperscript{10} pleuritic chest pain occurred in more than 75\% of patients with pleural effusion secondary to PE, and is generally on the side of the effusion if the effusion is unilateral.\textsuperscript{3} Thus, in any patient presenting with pleuritic chest pain and a pleural effusion, pulmonary embolism is a strong diagnostic possibility. In a study\textsuperscript{46} of 22 patients who presented to the emergency department with pleuritic chest pain and a pleural effusion, 12 (55\%) had PE.

Dyspnoea is a common accompaniment (82\% in one series\textsuperscript{19} of 2,454 patients) of patients with PE and is out of proportion to the chest radiographic findings including the size of the pleural effusion. Almost 50\% of the patients are febrile but temperature elevations above 38.5 °C and expectoration of purulent sputum occur in less than 10 percent.\textsuperscript{10,14} Cough is seen in 20\% to 45\% of the patients.\textsuperscript{10,14,19} In fact, if a patient has no dyspnoea, tachypnoea or pleuritic chest pain, PE is unlikely and overall only 3\% to 7\% patients with PE are asymptomatic at presentation.\textsuperscript{10,14,19}

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Small n/N(%)</th>
<th>Medium n/N(%)</th>
<th>Large n/N(%)</th>
<th>Blunting of Costophrenic Angles Only n/N(%)</th>
<th>Bilateral Effusions n/N(%)</th>
<th>Associated Pulmonary Opacities n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiographic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bynum and Wilson\textsuperscript{1} (1978)</td>
<td>62/62 (100)</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>4/62 (6.5)</td>
<td>38/62 (61.3)</td>
</tr>
<tr>
<td>Stein et al\textsuperscript{10} (1991)</td>
<td>56/56 (100)</td>
<td>-</td>
<td>-</td>
<td>48/56 (86)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Romero Candeira et al\textsuperscript{21} (2002)</td>
<td>48/60 (80)</td>
<td>12/60(20)</td>
<td>-</td>
<td>NA</td>
<td>8/60 (13)</td>
<td>8/60 (13)</td>
</tr>
<tr>
<td>Porcel et al\textsuperscript{27} (2007)</td>
<td>66/73 (90)</td>
<td>3/73 (4)</td>
<td>7/73(6)</td>
<td>NA</td>
<td>11/73 (15)*</td>
<td>-</td>
</tr>
<tr>
<td>Computed tomographic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Coche et al\textsuperscript{19} (1998)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
<td>6/26 (23)</td>
<td>NA</td>
</tr>
<tr>
<td>Johnson et al\textsuperscript{27} (1999)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
<td>NA</td>
<td>8/14 (60)</td>
</tr>
<tr>
<td>Shah et al\textsuperscript{19} (1999)</td>
<td>18/28 (64)</td>
<td>7/28 (25)</td>
<td>3/28 (11)</td>
<td>-</td>
<td>12/28 (43)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Small=less than 1/3rd of the haemithorax on chest radiograph or a maximum depth of 2-3cm on computed tomography (CT) of the chest
Medium=1/3rd to 1/2 of the haemithorax on chest radiograph or a maximum depth of 3cm-5cm on CT chest
Large=more than 1/2 of the haemithorax on chest radiograph or a maximum depth more than 5cm on CT chest

*+=16/63 (25\%) with CT
pleura adjoining the lung parenchyma with resultant fibrin strands and locule formation. In PE, hypercoagulable state which leads to the formation of intrapleural membranes is postulated to be the reason for locule formation. It is important to recognise loculations as a manifestation of PE, as in one study there was a delay of more than two weeks between the time the patient first became symptomatic and the diagnosis of PE. Interestingly, the multiple collections of loculated pleural fluid responded to systemic anticoagulation therapy.

Ultrasonography is probably the most sensitive technique for the assessment of pleural effusions and allows detection of extremely small volumes (5 mL) of pleural effusions. In a study, pleural effusions were found in 59% of patients by ultrasound examination as compared with only 23% with CT. However, ultrasonography of the chest is not routinely used for the diagnosis of PE and does not need to be performed in patients with suspected PE.

Ventilation-perfusion (V/Q) scans are characterised by matched V/Q defects corresponding to radiographically-evident pleural effusions and may be interpreted as low to intermediate probability for PE, and thus, may not be reliable for the diagnosis of PE in the presence of a pleural effusion. The pleural fluid be clear or haemorrhagic and the leukocyte counts can be as high as 45000/µL with neutrophil preponderance and occasionally low glucose levels (Table 3). This along with the presence of loculations can mimic pleural fluid infection and high suspicion should be maintained for a diagnosis of PE in any patient with exudative pleural effusion. The fluid can rarely also contain large numbers of eosinophils.

**PLEURAL FLUID FINDINGS IN PATIENTS WITH PULMONARY EMBOLISM**

Pleural fluid findings have been variedly reported in literature and analysis of pleural fluid, in isolation, is not generally helpful in establishing the diagnosis. The pleural effusion in PE is almost always an exudate. Four studies have reported pleural fluid biochemical findings and in all but one study the effusion was always an exudate (Table 3). Only one study reported that six of 26 (23%) pleural effusions in PE were transudates. However, in this study, the pleural fluid lactate dehydrogenase was not measured in all the patients, and a pleural fluid protein level more than 30 g/L was used to classify transudates and exudates. This can lead to misclassification of exudates.

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**DIAGNOSIS OF PULMONARY EMBOLISM**

The diagnosis of PE and pleural effusion can easily be made provided it is suspected, and is beyond the scope of this discussion, and the reader is referred to recent reviews for this purpose. The important point to highlight is that in patients with pleural effusion, V/Q scan is not generally indicated as it leads to a non-diagnostic scan.

**TREATMENT OF PULMONARY EMBOLISM**

The treatment of pleural effusion associated with PE is identical as that for any other patient with PE, and depends on the clinical status of the patient. Anticoagulation is a critical component in the management of all patients with PE. The treatment is initiated with heparin and followed by three to six months of oral anticoagulants. Thrombolysis is usually indicated in patients with massive PE (PE with haemodynamic instability) or in occasional patients with submassive PE (PE with normotension but echocardiography demonstrating right ventricular hypokinesia).

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### Table 3. Pleural fluid characteristics in patients with pulmonary embolism

<table>
<thead>
<tr>
<th>Pleural Fluid Characteristics</th>
<th>Porcel et al&lt;sup&gt;27&lt;/sup&gt; (n=26)</th>
<th>Erkan et al&lt;sup&gt;24&lt;/sup&gt; (n=5)</th>
<th>Romero Candeira et al&lt;sup&gt;21&lt;/sup&gt; (n=60)</th>
<th>Bynum and Wilson&lt;sup&gt;3&lt;/sup&gt; (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross bloody appearance, No. (%)</td>
<td>NA</td>
<td>4 (80)</td>
<td>34 (57)</td>
<td>16 (65)</td>
</tr>
<tr>
<td>RBC (cells/µL)</td>
<td>198000 (16000-578000)</td>
<td>12000 (3000-20000)</td>
<td>26600 (20-115000)</td>
<td>15688 (6000-39400)</td>
</tr>
<tr>
<td>Leukocytes (cells/µL)</td>
<td>2340 ± 2430</td>
<td>3300 (2500-5500)</td>
<td>3200 (190-45000)</td>
<td>9600 (2200-16750)</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>46±30</td>
<td>NA</td>
<td>NA</td>
<td>55±29.9</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>42±9</td>
<td>48±5</td>
<td>44±7.1</td>
<td>40.2±17</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>788±473</td>
<td>873±919</td>
<td>449.5 (228-2783)</td>
<td>172.5 (65-324.5) [n=12]</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>109.8±27</td>
<td>NA</td>
<td>106 (11-364)</td>
<td>NA</td>
</tr>
<tr>
<td>Light’s criteria for exudate, No. (%)</td>
<td>26 (100)</td>
<td>5 (100)</td>
<td>60 (100)</td>
<td>NA</td>
</tr>
</tbody>
</table>

The values are expressed as mean±SD or median ([quartiles]) in Porcel et al<sup>27</sup> and Bynum and Wilson<sup>3</sup> or (range) in Romero Candeira<sup>21</sup> and Erkan et al<sup>24</sup> unless otherwise indicated.

The number in square brackets indicates the number of patients in whom the test was carried out if not done in all patients.

RBC=red blood cell; NA=not available; LDH=lactate dehydrogenase
The presence of haemorrhagic fluid is not a contraindication to thrombolysis or anticoagulation, and in fact, with the treatment pleural effusions gradually resolve. The resolution is, however, delayed in patients who have associated pulmonary infarction. An increase in size of the pleural effusion or development of contralateral effusion indicates recurrent thromboemboli, infection of the pleural fluid or haemothorax. In the series of Bynum et al, two patients had effusions that enlarged after three days of admission; one patient was documented to have fresh thromboemboli and the other developed pleural empyema. In the same series, two patients developed contralateral effusions, and were documented to have recurrent PE. Haemothorax usually develops within the first week of anticoagulation and in many patients the clotting studies are within an acceptable range.

If patient develops increasing pleural effusion or a contralateral effusion, recurrent PE should be excluded, and a pleural fluid analysis be performed to rule out pleural infection and haemothorax. If the patient develops haemothorax, anticoagulants should be stopped, a tube thoracostomy should be performed and the patient should be considered for insertion of inferior vena cava filter.

**CONCLUSIONS**

Pleural effusions are commonly encountered in patients with pulmonary thromboembolism with a higher incidence if CT of the chest is used for its detection. The possibility of PE should be entertained in any patient with undiagnosed exudative pleural effusion. Although generally unilateral, the pleural effusion can also be bilateral. The effusions are maximal by the third day, are generally mild to moderate but can occasionally be larger in size. The effusion may develop loculations and can be associated with high leukocyte counts. The pleural fluid is almost always an exudate. In patients having pleural effusion with suspected PE, ventilation-perfusion scan is not generally indicated as it leads to a non-diagnostic scan. The presence of haemorrhagic fluid is not a contraindication to thrombolysis or anticoagulation, and in fact, with treatment the pleural effusions gradually resolve. Finally, many current concepts with PE such as unilateral small effusions, absence of loculations, and transudate nature of the pleural fluid need reappraisal.

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