Clinicopathological findings in pulmonary thromboembolism: a 24-year autopsy study*

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Background: Pulmonary thromboembolism (PTE) is still an enigmatic disorder in many epidemiological and clinical features, remaining one of the most commonly misdiagnosed disorders.

Objective: To describe the prevalence and pathological findings of PTE in a series of autopsies, to correlate these findings with underlying diseases, and to verify the frequency of PTE clinically suspected before death.

Method: The reports on 5261 consecutive autopsies performed from 1979 to 2002 in a Brazilian tertiary referral medical school were reviewed for a retrospective study. From the medical records and autopsy reports of the patients found with macroscopically and/or microscopically documented PTE, were gathered data on demographics, underlying diseases, antemortem suspicion of PTE, and probable PTE site of origin.

Results: The autopsy rate was 42.0% and PTE was found in 544 patients. In 225 cases, PTE was the main cause of death (fatal PTE). Infections (p=0.0003) were associated with nonfatal PTE and trauma (p=0.007) with fatal PTE. The rate of antemortem unsuspected PTE was 84.6% and 40.0% of these patients presented fatal PTE. Diseases of the circulatory system (p=0.0001), infections (p<0.0001), diseases of the digestive system (p=0.0001), neoplasia (p=0.024) and trauma (p=0.005) were associated with unsuspected PTE. The most frequent PTE site of origin was the lower limbs (48.9%). Probable PTE sites of origin such as right-sided cardiac chambers (p=0.012) and pelvic veins (p=0.015) were associated with fatal PTE.

Conclusion: A large number of cases do not have antemortem suspicion of PTE. Special attention should be paid to the possibility of PTE in patients with diseases of the circulatory system, infections, diseases of the digestive system, neoplasia, and trauma.

Key words: Autopsy. Epidemiology. Pulmonary Thromboembolism.

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INTRODUCTION

It is estimated that 10% of the cases of symptomatic pulmonary thromboembolism (PTE) will result in death within the first hour after the onset of symptoms. Patients who do not die during the acute phase usually present nonspecific symptoms and, therefore, diagnosis of PTE is frequently delayed or completely forgotten(1). Moreover, despite the present availability of sophisticated laboratory techniques, it is difficult to determine whether PTE was the main cause of death, only a contributing factor, or even a coincidental finding(1). Consequently, PTE remains one of the most commonly undiagnosed diseases.

Since most fatal episodes of PTE, whether occurring in hospitals or in the community, can only be identified through autopsy, it is difficult to obtain postmortem data on the disease. Therefore, PTE is still enigmatic in many of its epidemiological and clinical aspects(2,3).

With the intention of contributing to a better understanding of PTE, an objective of this study was to describe PTE prevalence and pathological findings in a series of 5261 autopsies carried out in a tertiary teaching hospital (in Botucatu, in the state of São Paulo, Brazil). In addition, we looked for correlations of these findings with underlying diseases and determined the frequency of clinical suspicion of PTE before death.

METHOD

The study was carried out at the Hospital das Clínicas da Faculdade de Medicina de Botucatu-Universidade Estadual de São Paulo (HCFMB-UNESP, Botucatu School of Medicine Hospital das Clinicas-State University of São Paulo). The HCFMB-UNESP is a tertiary reference hospital in the city of Botucatu, located in the west-central part of the state of São Paulo, and predominantly serves Sistema Único de Saúde (SUS, Unified Health Care System) patients. It is a well-equipped hospital and presently has 500 beds. Autopsies are performed routinely at the request of physicians, assuming that the family gives consent. Forensic autopsies are performed in another sector.

Design: All the reports for 5261 consecutive autopsies performed from 1979 to 2002 (a 24-year period) were reviewed. From the medical records and autopsy reports of the patients with macroscopically or microscopically documented PTE, the following data were gathered:

Demographic data: gender, age and race.

Clinical data: Underlying diseases and antemortem suspicion of PTE. Underlying diseases were considered those confirmed through clinical and laboratory testing, documented in the medical records and reported in the autopsy reports. Antemortem suspicion of PTE was defined as diagnostic hypothesis documented in the medical reports.

Location of thrombi (thrombi in the lungs and probable PTE site of origin): Thrombi caused by fat globules, sepsis or amniotic fluid were excluded from the study.

The PTE was considered fatal when it was the main cause of death (i.e. no other cause of death was found), and when at least two lobar arteries (or multiple small-caliber arteries affecting an area corresponding to that affected by the obstruction of two lobar arteries) were obstructed. The PTE was considered nonfatal when the immediate cause of death was another disease, and the thrombotic obstruction affected an area smaller than that affected by the obstruction of two lobar arteries(2,3). Medical students gathered the data from medical records and autopsy reports under the supervision of two experienced pulmonologists.

The Committee for Ethics in Human Research of the Faculdade de Medicina de Botucatu approved the study protocol.

Autopsy routine: Professors and resident medical students of the Department of Pathology carried out the autopsies as a group. A well-established routine, consisting of sequential and systematic procedures, was followed. In this method, topography and in locus alterations to the organs are analyzed initially, followed by dissection and analysis of the organs in accordance with a detailed description given in a previous study(4).

Statistical analysis: We used the Student’s t-test for data related to age and these data are expressed as means ± standard deviation and variation. The chi-square test was used to compare proportions of fatal and nonfatal PTE to various variables (underlying diseases, antemortem clinical diagnosis and PTE site of origin). We used the statistical commercial software package SAS v.8.0 (licensed to UNESP) for statistical analysis. Values of p < 0.05 were considered statistically significant(5).

Abbreviations used in this paper:
PTE – Pulmonary thromboembolism
RESULTS

Prevalence and demographic data: During the period under study (1979-2002), 12,523 patients died at the HCFMB-UNESP, and autopsies were performed on 5261 (42.0%). Of these, confirmed cases of PTE were reported in 544 (10.3%). PTE was fatal in 225 (41.4%) of cases and nonfatal in 319 (58.6%). Considering the total number of autopsies performed within the period of the study, fatal PTE was identified in 4.3% and nonfatal PTE in 6.1%.

The PTE group comprised 323 males (59.0%) and 221 females (41.0%), with mean age of 54.7 ± 18.9 (range, 1-102); 445 patients (81.8%) were Caucasian, 95 (17.5%) were Black, and 4 (0.7%) were Asian.

The mean age of the males was 55.1 ± 18.4 (range, 1-99), and mean age of the females was 54.1 ± 19.5 (range, 1-102) (p = NS). The mean age of those with fatal PTE was 57.3 ± 17.7 (range, 1-102), and the mean age of those with nonfatal PTE was 52.8 ± 19.4 (range, 1-87) (p = 0.005).

Clinical data: In general, patients presented more than one underlying disease (average, 3; range, 1-7). Incidence of most common underlying diseases concomitant with PTE and the incidence of fatal and nonfatal PTE are shown in Table 1. Only two groups of underlying diseases correlated with dependent variables: infectious diseases (p = 0.0003) were correlated with nonfatal PTE, and trauma (p = 0.007) was correlated with fatal PTE. The most common infectious diseases were pneumonia (44.1%), and sepsis (17.8%), followed by other less frequently seen diseases such as Chagas disease (8.5%), urinary tract infection (8.3%), tuberculosis (7.2%), meningitis (4.4%), paracoccidioidomycosis (2.8%), tetanus (1.3%), schistosomiasis (0.8%), etc.

There was antemortem clinical suspicion of PTE in 84 patients (15.4%), although there was no correlation with the dependent variables. On the other hand, among the 460 patients in which there was no antemortem clinical suspicion of PTE, 184 (40.0%) died of fatal PTE, although suspected PTE did not correlate with

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TABLE 1

Incidence of the main underlying disease groups associated with pulmonary thromboembolism

<table>
<thead>
<tr>
<th>Disease group</th>
<th>PTE n (%)</th>
<th>Fatal n (%)</th>
<th>Non fatal n (%)</th>
<th>c2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the circulatory system</td>
<td>392 (72.0)</td>
<td>154 (28.3)</td>
<td>238 (43.7)</td>
<td>2.490</td>
<td>0.115</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>307 (71.1)</td>
<td>179 (32.9)</td>
<td>208 (38.2)</td>
<td>13.236</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>129 (23.7)</td>
<td>57 (10.5)</td>
<td>72 (13.2)</td>
<td>0.557</td>
<td>0.456</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>115 (21.1)</td>
<td>49 (9.0)</td>
<td>66 (12.1)</td>
<td>0.094</td>
<td>0.759</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>107 (19.7)</td>
<td>43 (7.9)</td>
<td>64 (11.8)</td>
<td>0.076</td>
<td>0.783</td>
</tr>
<tr>
<td>Postoperative diseases</td>
<td>85 (15.6)</td>
<td>42 (7.7)</td>
<td>43 (7.9)</td>
<td>2.692</td>
<td>0.101</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>60 (11.0)</td>
<td>21 (3.9)</td>
<td>39 (7.2)</td>
<td>1.125</td>
<td>0.289</td>
</tr>
<tr>
<td>Trauma</td>
<td>18 (3.3)</td>
<td>13 (2.4)</td>
<td>5 (0.9)</td>
<td>7.311</td>
<td>0.007</td>
</tr>
<tr>
<td>Prior deep vein thrombosis</td>
<td>14 (2.6)</td>
<td>3 (0.6)</td>
<td>11 (2.0)</td>
<td>2.354</td>
<td>0.125</td>
</tr>
<tr>
<td>Others</td>
<td>47 (8.6)</td>
<td>22 (4.0)</td>
<td>25 (4.6)</td>
<td>0.630</td>
<td>0.427</td>
</tr>
</tbody>
</table>

*Relative percentage in relation to the total number of patients with PTE (544)

Bold type indicates statistically significant correlations

PTE: pulmonary thromboembolism

TABLE 2

Incidence of patients with antemortem suspicion of pulmonary thromboembolism

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>PTE n (%)</th>
<th>Fatal n (%)</th>
<th>Nonfatal n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td>84 (15.4)</td>
<td>41 (48.8)</td>
<td>43 (51.2)</td>
</tr>
<tr>
<td>Unsuspected</td>
<td>460 (84.6)</td>
<td>184 (40.0)</td>
<td>276 (60.0)</td>
</tr>
</tbody>
</table>

p = NS

*Relative percentage (in relation to the total number of patients with PTE)

A relative percentage (in relation to the total number of patients clinically diagnosed with PTE)

PTE: pulmonary thromboembolism
either fatal or nonfatal PTE (Table 2). The incidence of antemortem suspected and unsuspected PTE in the various groups of underlying diseases is shown in Table 3. Diseases of the circulatory system, infectious diseases, diseases of the digestive system, neoplasia and trauma were associated with antemortem unsuspected PTE.

**DISCUSSION**

The most precise data on the prevalence, site of origin of thrombi, main causes of thrombosis, and clinical repercussions of PTE have been obtained from studies of randomly selected autopsies carried out in general hospitals, using rigid and systematic techniques. Therefore, we consider the data in this study to be adequate since they were taken from a relevant series of randomly selected autopsies carried out in a prominent teaching hospital that traditionally maintains the routine and technique of searching for thrombi during all autopsies performed. In addition, since the study was carried out in a teaching hospital in which patient charts are created and updated by medical students and resident physicians under the supervision of more experienced professors, the medical records can be considered trustworthy. Therefore, in the present study, we were able to determine comorbidities,
classify PTE as fatal or nonfatal according to pre-established criteria and, in 66.7% of cases, determine the probable site of origin of thrombi.

In our study, the autopsy rate was 42.0% and the prevalence of PTE was 10.3%. In the literature, PTE prevalence in autopsies varies because study results depend on diverse factors such as autopsy rate, number of cases, type of hospital, attentiveness and patience of the pathologists when looking for thrombi, and the preparation of the material to be examined. Despite this variation, PTE prevalence in autopsy studies seems to have been decreasing over the past few years. This phenomenon is probably more closely related to the improvement in prevention, the development of new diagnostic tools and therapeutic advances than to a reduction in autopsy rates, which has become a worldwide phenomenon. This phenomenon is probably more closely related to the improvement in prevention, the development of new diagnostic tools and therapeutic advances than to a reduction in autopsy rates, which has become a worldwide phenomenon. However, it is possible that, although the rate of PTE in autopsied patients has been decreasing, it may be increasing in the population of patients not submitted to autopsy due to adequate prevention and therapy. Consequently, in the long term, PTE prognosis may be limited only by underlying diseases.

PTE morbidity and mortality increase exponentially with age, probably due to the concomitant increase in the number of risk factors. In our study, the mean age of patients with fatal PTE was significantly higher than that of patients with nonfatal PTE. No significant gender-based or race-based differences were found. It is notable that the proportion of Caucasian, Black and Asian patients reflects the demographics in the region served by the hospital.

The main groups of underlying diseases found in the patients were those that are well known, and reported in the literature, to be risk factors for PTE. In addition, we found a significant correlation between infectious diseases and nonfatal PTE, as well as between trauma and fatal PTE.

The most common infectious diseases were pneumonia and sepsis. The differential diagnosis between PTE and pneumonia, based solely upon clinical examination and chest X-rays, is not always easy since many patients with pneumonia frequently present nonspecific signs and symptoms, as well as the presence of infiltrate detected in X-rays. This can mimic, or even disguise, the existence of PTE. In fact, our results reinforce this idea. In most patients with infectious diseases, there was no antemortem suspicion of PTE. Although the exact relationship between infection and PTE has not been elucidated, venous thromboembolism is a frequent complication of septicemia, and PTE has been diagnosed in septicemic patients who were submitted to central venous catheterization or to surgery involving the abdomen or pelvis.

It is difficult to identify PTE in trauma patients because such patients are frequently unable to report their symptoms due to intubation or coma. In addition, few PTE screening tests are truly capable of confirming or ruling out the diagnosis. In the literature, PTE prevalence in trauma ranges from 0.3 to 2.3% and is usually related to fatal events, as reported in our study.

### TABLE 5

Incidence of the probable sites of PTE origin

<table>
<thead>
<tr>
<th>Site of origin</th>
<th>PTE n (%)</th>
<th>Fatal n (%)</th>
<th>Nonfatal n (%)</th>
<th>c2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limbs</td>
<td>266 (48.9)</td>
<td>123 (22.6)</td>
<td>143 (26.3)</td>
<td>5.117</td>
<td>0.024</td>
</tr>
<tr>
<td>Right heart chambers</td>
<td>54 (9.9)</td>
<td>31 (5.7)</td>
<td>23 (4.2)</td>
<td>6.365</td>
<td>0.012</td>
</tr>
<tr>
<td>Pelvic veins + limbs</td>
<td>23 (4.2)</td>
<td>13 (2.4)</td>
<td>10 (1.8)</td>
<td>2.726</td>
<td>0.131</td>
</tr>
<tr>
<td>Pelvic veins</td>
<td>19 (3.5)</td>
<td>13 (2.4)</td>
<td>6 (1.1)</td>
<td>5.944</td>
<td>0.015</td>
</tr>
<tr>
<td>Lower and upper limbs</td>
<td>6 (1.1)</td>
<td>4 (0.7)</td>
<td>2 (0.4)</td>
<td>1.602</td>
<td>0.206</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>5 (0.9)</td>
<td>2 (0.4)</td>
<td>3 (0.5)</td>
<td>0.004</td>
<td>0.500</td>
</tr>
<tr>
<td>Subclavian veins</td>
<td>19 (3.5)</td>
<td>8 (1.5)</td>
<td>11 (2.0)</td>
<td>0.004</td>
<td>0.946</td>
</tr>
<tr>
<td>Jugular veins</td>
<td>15 (2.7)</td>
<td>8 (1.5)</td>
<td>7 (1.2)</td>
<td>0.912</td>
<td>0.340</td>
</tr>
<tr>
<td>Other</td>
<td>16 (2.9)</td>
<td>4 (0.7)</td>
<td>12 (2.2)</td>
<td>1.819</td>
<td>0.177</td>
</tr>
<tr>
<td>Undetermined</td>
<td>181 (33.3)</td>
<td>51 (9.4)</td>
<td>130 (23.9)</td>
<td>19.438</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Relative percentage in relation to the total number of patients with PTE (544).

Bold type indicates statistically significant correlations.
We also found a significant correlation between trauma and unsuspected PTE \((p = 0.005)\). In patients with trauma who are diagnosed with PTE, the ratio of arterial oxygen tension to fraction of inspired oxygen seems to be an important predictor of mortality\(^{(10)}\). Therefore, PTE must always be considered a possible diagnosis in trauma patients who present signs of pulmonary distress.

In our study, the rate of antemortem unsuspected PTE was 84.6\%, which, although high, is within the 67\% to 91\% range reported in the literature\(^{(2,17-20)}\). Therefore, despite the plethora of tests currently available, the difficulty in diagnosing PTE is seen worldwide. This high rate at which PTE is underdiagnosed is probably a marked reflection of the high mortality rate when a diagnosis of PTE is not considered. In the present study, of the 460 patients in which PTE was not suspected antemortem, 40\% presented fatal PTE. Although there was no significant correlation between antemortem suspected PTE and fatal or nonfatal PTE, we can infer that an expressive number of patients died without receiving any kind of treatment for PTE. In our study, unsuspected PTE was markedly associated with various diseases that can make the diagnosis of PTE more difficult, such as diseases of the circulatory system, infections, neoplasia and trauma.

The prevalence of fatal and nonfatal PTE in our study was 4.3\% and 6.1\%, respectively. Regarding the prevalence of fatal and nonfatal PTE, there are conflicting data in the literature\(^{(21-24)}\). These discrepancies are mainly attributable to the varying definitions of fatal and nonfatal PTE used in each study. However, a bias in our study, and in other similar studies, is that small fatal embolisms may occur in patients with impaired cardiopulmonary function\(^{(24)}\).

We found no significant correlation between the probable site of thrombi origin and the frequency of any of the underlying disease groups. However, our data suggest that the size and location of the thrombus, more than the existence of underlying diseases, are crucial in the determining the fatal nature of PTE. Thrombi in the segmental or subsegmental arteries were prevalent in nonfatal PTE, whereas thrombi in the main pulmonary arteries, as well as in arteries in the trunk or higher, were prevalent in fatal PTE, which demonstrates the habitually fatal nature of larger thrombi. The presence of isolated hemorrhagic pulmonary infarctions without macroscopic thrombi was interpreted as a sign that PTE had undergone endogenous lysis or that it was caused by thrombolytic therapy\(^{(23)}\). There was no correlation between isolated infarctions and fatal or nonfatal PTE. Similarly, the fact that the cause of PTE could not be determined in 33.3\% of cases might be at least partially attributed to the total detachment of the thrombus from its site of origin or to physiological disintegration of the thrombus – or even to thrombolytic therapy or postmortem lysis\(^{(23)}\). This hypothesis is corroborated by the significantly higher incidence of nonfatal PTE cases \((p < 0.001)\).

Among the probable sites of thrombi origin, right heart chambers \((p = 0.012)\) and pelvic veins \((p = 0.015)\) were associated with fatal PTE. Coronary thrombi have been associated with fatal events because they are usually large and mobile, are frequently found in patients presenting abnormalities of the right atrium or ventricle, or can come from peripheral veins and adhere to cardiac walls in a transitory or permanent way. It is known that 42\% of patients who present coronary thrombosis involving the left wall only are likely to have PTE. Therefore, any cardiac mural thrombus might indicate severe heart disease, in which marked hemodynamic alterations would predispose these patients to more frequent formation of thrombi in the lower limbs, and PTE would subsequently originate from this site\(^{(10,26-28)}\). Free thrombi in right heart chambers are rare and are usually revealed when patients with suspected or confirmed PTE are submitted to echocardiography. These thrombi may serve to identify patients at risk for dying from recurring venous thromboembolism\(^{(28,29)}\).

As previously discussed, thrombi in pelvic veins are one of the main causes of fatal PTE due to their large size. In addition to trauma and pelvic surgeries, these thrombi may be caused by prolonged periods with untreated distal deep venous thrombosis\(^{(30-32)}\).

In summation, old age, trauma, and probable PTE sites of origin such as right heart chambers and pelvic veins were associated with fatal PTE. This disease is still challenging for physicians since there is no antemortem suspicion of PTE in a large number of cases. Special attention should be given to the possibility of PTE in patients with diseases of the circulatory system, infections, diseases of the digestive system, neoplasia or trauma.
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