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Lise Soares Barbosa Brosseron
Pulmonary thromboembolism and sudden unexpected death.

Medico-legal review.

Abril, 2011

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Mestrado Integrado em Medicina

Área: Medicina Legal

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Abstract

Background: Pulmonary thromboembolism (PTE) is one of the major causes of sudden unexpected death. PTE frequently presents with nonspecific manifestations which makes its clinical diagnosis difficult, resulting in a high fatality rate.

Objectives: The main objective of this study was to determine the prevalence of PTE in a series of forensic autopsies. Other aims were to describe the clinical characteristics, demographic data and risk factors present in PTE deaths.

Methods: This study was carried out retrospectively, and all the forensic expert reports of the 11 113 autopsies performed in a 5-year period (from 1st January 2005 to 31st December 2009), in Northern Portugal (Main Branch and Offices of the National Institute of Legal Medicine Porto, Portugal), were reviewed. Those who had findings of PTE were selected and the data collected was inserted into a database.

Results: PTE was found in 106 cases (1% of the total autopsies). The average age of the patients was $59,5 \pm 17$ years, ranging from 20 to 92 years. The female-male ratio was 1.5: 1. Regarding the time of death, 41% occurred between 6am-12am with a peak in Autumn (32,1%) and a minimum in Summer (18,9%). Emboli were found preferentially bilaterally (70,8%) with pulmonary infarct in 22% of cases. The most frequent associated conditions were cardiovascular diseases (51%), immobilization (43,4%), $BMI \geq 25$ (37%), systemic hypertension (34%), psychiatric disorder (33%), previous trauma (22,6%), pulmonary diseases (22,6%), diabetes mellitus (21%), infection (18%), previous surgery (16%) and chronic venous disease (16%). Antemortem suspicion of PTE was present in 5 cases. Symptoms prior to death were present in 66% with the most associated symptoms being nonspecific (50%), dyspnea (44,3%), alteration of mental status (40%) and thoracic pain (30,8%). After the appearance of symptoms, 65,7% died within 24 hours. Medical care was sought by 37,3% of patients in the previous two weeks.

Conclusions: PTE presented without antemortem suspicion in the majority of cases despite the frequent presence of prodromal symptoms and seek of medical care in the days prior to death. This highlights the importance of sensitizing physicians to the identification of PTE and to its prevention by applying appropriate prophylaxis in high-risk patients.

Keywords: Pulmonary thromboembolism; Pulmonary embolism; Sudden death

Introduction

Venous thromboembolic disease (VTE) is considered a major health problem and its clinical manifestations include among others deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). The importance of VTE is related to the high mortality resulting from PTE and the acute and long-term morbidity of DVT.

VTE is the result of a disruption of the normal hemostasis; thrombus formation results from venostasis, hypercoagulability and endothelial injury, known as the Virchow's triad.¹

PTE is one of the major causes of sudden unexpected death and usually results as a sequel of DVT in the lower limbs or pelvic venous system, frequently presenting with nonspecific manifestations.^{2, 3} This non specific manifestations makes its clinical diagnosis difficult, and despite the availability of sophisticated laboratory techniques, it is a cause of frequent misdiagnosis that leads to fatal outcome.³⁻⁵ Although it can have a recurrent course⁶, approximately half of the fatal cases die within one hour after their clinical onset⁷, and approximately 25% presents initially as sudden unexpected death.⁸ These sudden deaths can be associated with sudden cardiac chock induced by massive PTE, which leads to progressive pulmonary hypertension and right ventricular dysfunction.^{7, 9} In a high number of sudden unexpected deaths, only autopsy could prove their true diagnosis.^{7, 10} It's important to search for and recognize associated risk factors because the identification of high risk situations could prevent, by implementing appropriate prophylaxis, the associated high mortality rate. Therefore, it is useful to further assess the frequency and characteristics of PTE in autopsy with the intent of identifying specific situations in which an antemortem clinical diagnosis is often missed.

The most frequent suggested PTE acquired risk factors are immobilization, increasing age, pregnancy, puerperium, oral contraceptives, long-haul air travels, trauma, surgery, obesity, heart diseases, malignancies and paraneoplastic states.^{1, 6, 11, 12} Hyperlipidemia, alcohol abuse/withdrawal, infection, environmental agents, vasculitis or dehydrated states are less recognized, and the exact factors that influence the development of acute episodes remain unclear.^{1, 6, 11, 12} Often, the precipitating event cannot be recognized, and it could be a multifactorial etiology or the result of a inherited thrombophilic disorder.^{1, 13}

In previous autopsy studies the global prevalence ranges from 1% to 4%.^{14, 15}

The main objective of this study is to evaluate the prevalence of pulmonary thromboembolism in the forensic autopsies performed in Northern Portugal (Main Branch and Offices of the National Institute of Legal Medicine Porto, Portugal), between 2005 and 2009.

Additionally, it has also the aim to determine the clinical characteristics, demographic data and risk factors of PTE sudden unexpected death.

Material and Methods

This study was carried out retrospectively, and all the forensic expert reports of the autopsies performed during a 5-year period (from 1st January 2005 to 31st December 2009), in Northern Portugal (Main Branch and Offices of the National Institute of Legal Medicine Porto [INML], Portugal), were reviewed. In order to select those who had findings of PTE as the major cause of death, the keyword “thromboembolism” was inserted in the informatics database MedLeg-Pat of the North Branch of INML. From a total of 11.113 reports, 106 cases were selected based on macroscopically and/or microscopically documented PTE.

The autopsy routine includes analysis of the topography and in loco alterations, followed by dissection as well as macroscopic and microscopic analyses of the organs. The extremities’ veins are not routinely dissected.

The forensic expert reports with the circumstances of death, autopsy findings, and clinical records were reviewed when available, in order to search for conditions or events that represented identifiable risk factors for the development of PTE. These findings were collected by an investigator and inserted into a computer database.

In this study the definition of sudden unexpected death used was according to commonly accepted criteria, as when an individual dies suddenly from natural causes within 24 hours since symptoms appear, in an individual who was apparently healthy or one whose disease was not severe enough in order to predict such an abrupt outcome.^{13, 16, 17}

Pulmonary embolism was considered the main cause of death when organized thrombi with gross features consistent with pre-mortem formation were observed to obstruct the majority of the pulmonary arterial tree, either in the pulmonary artery trunk or in the proximal right or left pulmonary arteries formed from the bifurcation of the main trunk, and other causes of death were definitely excluded. Emboli derived from the bone marrow, fat, tumor or amniotic fluid were excluded from this analysis.

The incidence of PTE found in the autopsies was calculated. Age, gender, place and time of death (between 0-6 am, 6am-12am, 12am-6pm and 6pm-12pm), and season of the year when the death occurred, were reviewed. Risk factors for thrombotic disease were also investigated: recent surgery or trauma (previous 8 weeks), immobilization, cardiovascular diseases (myocardial infarction, heart failure, stroke), systemic hypertension, diabetes

mellitus, neoplastic diseases, DVT, pulmonary diseases, presence of infection, pregnancy or puerperium, dislipidemia, digestive diseases, chronic venous disease, chronic alcoholism and personal or family history of thrombophilic disorders. Body mass index (BMI) was classified according to the World Health Organization criteria: obesity was defined as $BMI > 30 \text{ kg/m}^2$ and overweight between 25 and $29,9 \text{ kg/m}^2$. Psychiatric profiles (including chronic alcoholism and drug addiction according to DSM IV)¹⁸ as well as antipsychotic drug use, medications taken in the last two months (including anticoagulant therapy and oral contraception) were also investigated.

The need to visit an emergency department or to seek medical care in the previous two weeks; the identification of symptoms prior to death and the period of time elapsed between the beginning of symptoms and death; existence or clinical suspicion of the diagnosis of pulmonary embolism prior to death; presence of a typical clinical triad of prearrest clinical factors (overt dyspnea, alteration of mental status or syncope and shock) and death witnessed by a health professional were also analyzed.

Regarding post-mortem findings, we studied the localization and source of the emboli and the presence of pulmonary infarcts as well as histopathological and toxicological analysis, when performed. Genetic studies were not performed.

In order to guarantee the protection of the dead patients' identity, each case file was codified with numbers.

Statistical analysis was performed using SPSS (version 19). Statistical significance was set at p values less than 0.05. Mean values were compared by the Student t test or Mann-Whitney method appropriately. For the comparative study of proportions, the Chi-Squared test was utilized.

Results

The North Branch of the National Institute of Legal Medicine includes the Main Branch in Porto and 9 Offices, with some of them located in more rural areas, and serves an estimated population of 3.637.889 inhabitants. Of the 11 113 autopsies performed during the 5-year study period, fatal PTE was found in 106 cases (1%). The annual percentage of fatal PTE was 1%.

The average age of the patients was $59,5 \pm 17$ years, ranging from 20 to 92 years (20 to 92 for women, 30 to 87 for men), with 90,6% of the cases ≥ 37 years. The average age of the

two sexes was similar ($p=0,730$). There were no deaths from PTE in patients under the age of 20 years. The distribution of cases according to age and sex is shown in Figure 1.

The female-male ratio was 1.5: 1, with fatal PTE being found in 63 women (59,4%) and 43 men (40,6%).

Regarding the time of death, 41% ($n=40$) occurred between 6am-12am; 26,5% (26 cases) and 24,5% ($n=24$) died between 12am- 6pm and 6pm- 12pm, respectively. Only 8,2% of deaths ($n=8$) occurred between 0-6am.

The seasonal variation of PTE found in the autopsies is shown in Figure 2. In relation to the different seasons, the summer had the lowest number of cases ($n=20$; 18,9%), while the autumn had the highest ($n=34$; 32,1%), with the spring and winter registering the same number of cases ($n=26$; 24,5%).

Regarding the place of death, 43 (41%) occurred at home, 7 (6.7%) in public places, 55 (52.4%) in the hospital (or during the transfer to a medical institution) of which 17 cases were hospitalized, 4 in a psychiatric unit.

Emboli were found preferentially bilaterally (70,8%); the main right pulmonary artery accounted for 15,1% ($n=16$) and the main left pulmonary artery and the arterial main trunk 6,6% ($n=7$) each. In one case the emboli were not detected in the main vessels. Pulmonary infarct was found in 15 cases (22%) of a total of 69 cases. The histopathological analysis was performed in 63 cases (60%), and of those, only 2 cases were not confirmed histologically. The source of the emboli was investigated in 22 cases (21%). 22,4% ($n=12$) of the emboli that occurred in the context of fatal PTE originated from the legs deep veins; 2 cases originated in the pelvic veins, 1 in the inferior vena cava and 1 in the cardiac chambers. The remaining six cases had unknown origin. Systematic microscopic evaluation of the thrombi and the leg's veins was not done.

Toxicological analysis was made in 76,4% of cases ($n=81$), with positive results in one third. The main substances found were antipsychotics ($n=13$), alcohol ($n=13$), benzodiazepines ($n=6$) and antidepressants ($n=5$). One case was positive to drugs of abuse.

Differences were found concerning the histopathological and toxicological analyses performed in the Main Branch and the Offices as well as relative to examining the source of the emboli. In the Main Branch the histopathological analysis was performed in 69.6 % of cases ($n=39$), comparatively to 52% in the Offices ($p=0,063$). As for toxicological analysis statistically significant differences were found, with the Main Branch performing it in 90,9% of cases versus 62% in the Offices ($p<0,001$). Statistically significant differences were also

found relative to the search of emboli's source: 30,4% in the Main Branch comparatively to 10% in the Offices ($p < 0,01$).

From the 106 cases, 97 were found to have an underlying identifiable predisposing risk factor. The most frequent associated conditions were cardiovascular diseases (51%), immobilization (43,4%), systemic hypertension (34%), previous trauma (22,6%), pulmonary diseases (22,6%), diabetes mellitus (21%), infection (18%), previous surgery (16%) and chronic venous disease (16%). Other associated conditions are described in table 1. In 9 of the cases there was no remarkable evidence of an underlying risk factor.

The majority of patients displayed more than one underlying condition. On average, they presented between 2 to 3 underlying conditions, with minimum of 0 to a maximum of 6. One case of metabolic lipid myopathy and one case of rheumatoid arthritis were found. Only 2 cases were known to be taking oral contraceptives and only one case was in the puerperium (15 days postpartum). None of the women was pregnant and neither long-haul travel nor pathological antecedents or family history of thrombophilic disorders were found.

Previous DVT was known in 3 cases while 7 cases were actually affected by DVT. Only 1 of those 7 was diagnosed, and no treatment was instituted.

The post-operative emboli occurred on the 10th day (median, range 1 to 60 days) after surgery and on the 15th day (median, range 1 to 60 days) after the trauma event.

The body mass index (BMI) ranged from 15,5 to 53,3 kg/m^2 . Of a total of 78 cases, half had a $\text{BMI} \geq 25 \text{ kg/m}^2$, with 6 being overweight and 33 obese, while 7 cases had a $\text{BMI} < 18,5 \text{ kg/m}^2$.

Concerning psychiatric disorders, we found 35 diagnosed cases (33%: 16 males; 19 females), 14 cases in the Offices and 21 cases in the Main Branch; 13 of them were medicated with antipsychotics (2 in the Offices and 11 in the Main Branch). Four were known to be under their effect with therapeutical concentrations at the moment of death. From the 13 cases, none had previous DVT and 3 had no additional risk factors. More details on table 2.

The percentage of patients taking medication in the previous 2 months was 95% (78 of 82).

Four patients were receiving anticoagulant prophylaxis and 3 were taking therapeutic anticoagulant doses by the time of death, 2 of whom due to clinical suspicion of PTE and the other for previous PTE. Antemortem suspicion or diagnose of PTE occurred in 5 of the patients which had PTE as cause of death. Previous PTE was known in 2 cases (6 months and 9 years earlier, respectively). Among the 4 cases who were taking anticoagulant prophylaxis,

3 had previous fracture of lower limbs, (2 of which underwent surgery), and 1 was in the 14th day after stroke.

Symptoms prior to death were found in 70 cases (66%), and from those, 47,1% (n=33) died within the first hour, 18,6% (n=13) in the first 24 hours and 34,3% (n=24) had symptoms in the previous days. The most frequent associated symptoms were dyspnea (44,3%), alteration of mental status (40%), thoracic pain (30,8%), legs pain (14,3%) and shock (11,4%). Nonspecific symptoms were seen in half of the patients. One case reported the occurrence of hemoptysis. No differences were found regarding the occurrence of prodromal symptoms in hospitalized patients (58,8%) and outpatients (68,2%) (p=0,454).

Regarding the presence of prearrest symptoms, only 20% were found to have more than one typical prearrest symptom (dyspnea, alteration of mental status and shock).

The death was witnessed by a health professional in about half of the cases.

Forty patients sought medical care (out-of-hospital and in-hospital) in the two weeks prior to death. Of them, 15 had typical clinical symptoms and history of PTE or DVT though those conditions were not suspected, and none had initiated appropriated therapy. Other conditions present were 3 cases with urinary tract infection, 2 with abdominal pain and 2 cases of psychotic crisis with psychomotor agitation. Some of those cases are described on table 3.

Discussion

The prevalence of PTE is mostly influenced by the studied population (general population versus hospitalized population), population characteristics (as age and underlying conditions) and also according to the techniques performed in the autopsy. Our study is settled in forensic autopsies, which might lead to distinct results when compared to autopsies performed in a hospital setting, the latter's showing higher prevalence, because hospitalized patients are more likely to have more risk factors than the general population surveyed in the forensic setting. In our findings PTE accounted for 1% of deaths, which is within the previous reported range in autopsies studies, such as 1,2% obtained by Lucena et al¹³ and 2,5% found by Hamanaka.⁹

The age distribution we are reporting show that, despite the presence of a relationship between advancing age and pulmonary embolism (with age being an independent risk factor, as stated in others studies), there is an important raise in the number of cases in the middle age, already seen in other series too.^{3, 5, 7, 14} The increase in PTE with advancing age is

probably associated with the increase in associated risk factors like cardiovascular diseases, and to the combination of reduced mobility and muscle tone with degenerative vascular changes that confer increased morbidity.¹⁹

Pulmonary embolism was more common in women, in agreement with the results found by other studies.^{5,9,20} Others show no sex difference or a male predominance.^{8,21}

PTE deaths in young, apparently healthy persons may reflect an underlying coagulation defect leading to hypercoagulability, which, if there is no identifiable cause, could represent an underlying thrombophilic disorder. These disorders can be of inherited or acquired nature, and its determination could be relevant to the decedent's family. Genetic tests were not performed in this study, and its application on routine autopsies is not recommended due to its expensive costs; however, in such cases, it could be important to search for a genetically determined coagulation defect.¹

We found that 41 % of the deaths occurred between 6 and 12 am, which suggest that the morning hours are more risky for the occurrence of PTE. This is probably related to the existence of a circadian pattern involving thrombus formation, with a morning peak in several pro-coagulation parameters.^{22, 23} Thrombus detachment is also more favorable in the first hours of morning until noon, due to a series of physiologic mechanisms.²³ The awareness of these circadian rhythms could be of interest concerning the best approach to prevention and treatment of PTE events.

The seasonal variation in PTE deaths has been studied for a while; however, those attempts haven't reached definite conclusions yet. Some studies found that it was more frequent in the winter, maybe related to the cold weather, while others found peaks in autumn and spring.^{11, 23, 24} The shape of our graph showing the seasonal variation is similar to what Green and Edwards found, with a peak in autumn and a reduction in summer cases.^{11, 20} The reason for this finding is not clear, while there is still some indication that the weather could be implicated in regions where the climatic seasons are well defined.^{24, 25}

The microscopic examination of the thrombi and veins was not performed, and on the literature there are only a few forensic studies on thrombus age estimation; despite that, forensic pathologists should always search the emboli's source and estimate how old the thrombi are.^{2, 26} Searching for the source is important, and a detailed examination including the crural veins could help to highlight the conditions and risk factors for PTE.⁷ It could be an important medico-legal issue to know if a pulmonary embolus arose prior to, or subsequent to some traumatic event, and the best method is to examine and to date the residual thrombus.⁴ However, in this sample, the search of the emboli's source was performed only in 22 cases

(21%). Most PTE arise from DVT that occur in the deep leg veins, proximal to and including the popliteal veins.^{4, 10, 20} Despite the impossibility to sometimes find the source of the emboli, the absence of thrombi in the deep leg veins does not exclude them, as the thrombi can be dislodged, be involuted by organization or be submitted to therapeutic or postmortem thrombolysis, leaving no residual disease.^{4, 6, 20, 27} Cardiac thrombi are related to fatal PTE, mainly in patients with cardiac right chambers dysfunction, as well as large pelvic veins thrombi, more frequent following pelvic surgery and trauma.²⁷

The microscopic examination of the emboli is a way to minimize the risk of misclassification of the PTE as the main cause of death, and was only performed in 60% of the cases. Pulmonary infarction was only seen in 22% of the cases, remaining an infrequent finding. This could be related to the dual perfusion by the pulmonary artery and the bronchial artery or to the short period from onset to death.^{7, 13}

The most frequent underlying conditions found were in agreement with those established in previous studies.^{4, 8} The disease most associated with PTE was cardiovascular disease (51%), similarly to the findings of the majority of studies.²⁵ Acute infectious illness was found in 18% of the cases, with respiratory infection being one of the most often associated infectious conditions, together with urinary tract infections, which have recently been associated with a transient risk.^{14, 27, 28} The pathophysiology of VTD in the presence of acute infection remains to be fully defined, but recent evidence suggest the involvement of respiratory viruses capable of infecting endothelial cells and causing a shift from anti-coagulant to procoagulant activity that is associated with induction of tissue factor expression.²⁹

PTE should also be of concern in trauma patient, especially in those who present thoracic discomfort, representing 22,6% in our findings.²⁷ Regarding surgical procedures, we found 16%, with the emboli occurring mainly in the 10th day after surgery, close to the 13th day reported by Lindblad et al.^{10, 30} Associated with those two conditions, immobilization is present in 43,4% of cases. The thrombus formation can happen due to immobilization even for a short time, like car driving, with crural type DVT often associated with bilateral venous stasis.^{2, 7} Other factors increasing thrombotic predisposition combine synergistically with immobilization for thrombi formation.⁷

The association between malignancy and PTE is well known, because of the state of induced hypercoagulability, however we found cancer in only 9 cases.^{7, 12, 14} Obesity was an important risk factor found, with 50% of the cases being overweight or obese, which supports

the findings of previous studies; nevertheless its specific relation to PTE as an independent risk factor is still being studied.¹³

We found 33% of the cases having a psychiatric disorder diagnosis, which is in agreement with other recent studies.^{7, 9, 31, 32} These studies suggest that antipsychotics drugs confer a higher risk for PTE; indeed, in Western countries, PTE has been reported among patients treated with antipsychotics.^{9, 33} However some authors state that there is no strait relationship between antipsychotics and VTD.^{34, 35} We found some differences according to the geographical area: from a total of 13 cases taking antipsychotics, 11 (from 56 PTE cases found in the Main Branch) were located in an urban area and only 2 (from 50 from the Offices) in more rural regions. This could be related to a more difficult access to medical care according to the reality of our rural zones, with fewer patients diagnosed and consequently fewer cases medicated.

To reduce the incidence of PTE, persons at risk must be identified and recent studies, such as ours, show a high number of medical conditions like cardiovascular and acute infection diseases associated with fatal events. This goes against the old idea that the most affected patients were surgical.^{8, 13, 14} This could be related to a higher knowledge of the need to prevent VTD in patients submitted to surgery and consequently, to its targeted prevention with appropriate prophylaxis. Despite the availability of effective prophylaxis and treatment, high rates of VTD are still common in hospitalized patients, with untreated acute proximal DVT causing clinical PTE in 33-50% of the patients.^{4, 14, 36} It's urgent to emphasize that high-risk patients hospitalized for medical conditions should also be provided with prophylaxis, as recommended by different guidelines, with an impact in potentially preventable deaths.^{8, 14}

Clinical symptoms as a method for diagnosis of thromboemboli have low sensitivity.³ From the 66% of patients that presented with symptoms, the most frequent was dyspnea 44,3%, in agreement with previous studies.¹³ Ro et al reports the existence of pre-existing symptoms in 65% of cases.³⁷ Vague and nonspecific symptoms were present in half of the cases and this is an important question because patients without underlying cardiopulmonary disease may appear anxious but otherwise well compensated despite an anatomically large PTE.^{10, 12} We found one case of hemoptysis which could indicate an early smaller peripherally located PTE.¹²

About 65,7% of patients died within 24 hours after the first symptoms, similar to the one third of patients that died within 24 hours of admission as reported by Karwinsky and Svendsen.⁵ This suggests that PTE must be rapidly recognized and treatment shortly instituted.

The PTE prearrest symptom triad could be recognizable compared with other causes of death, and this could offer an opportunity to treat the patient acutely. According to Courtney and Kline¹⁵, the sequence of prodromal effects is prolonged enough (period of minutes to hours) to allow its identification in many cases, with one third of the cases with all 3 symptoms present, and about a half with 2. However, in our study, a low percentage (20%) presented more than 1 symptom of the triad (dyspnea, alteration of mental status and shock). It is also important to determine if most of the deaths are witnessed by a health professional, because if so, we could intervene rapidly to prevent PTE deaths.^{15, 38} Our results showed that half of the cases were witnessed, which corroborates the percentage (57%) found by the study mentioned above.¹⁵

It is suggested that most of the cases of fatal PTE might have a subclinical history of nonfatal PTE, and that an increasing rate of consulting doctors and proper diagnosis of PTE at an early stage might prevent fatal PTE.⁷ In a previous study, PTE patients were five times more likely to have been seen by a physician within two weeks of arrest compared to patients who died suddenly from other causes; indeed, other authors found that about half of the cases with pre-existing symptoms had consulted a doctor^{7, 15} and in our study 40 cases (37,3%) sought medical care in the previous two weeks. Other issue of concern is that in our series, almost 24 from those 40 cases (60%) presented symptoms that could raise the suspicion of PTE or the need to preventing thrombotic events by applying appropriate prophylaxis, but none had been medicated. Previous studies found one third of patients under the conditions mentioned above and others that only 25% of the patients had been suspected of PTE.^{7, 15}

PTE continues to challenge the physicians with great number of cases without antemortem diagnosis²⁷ and autopsy is still regarded as the diagnostic gold standard.⁴ The accuracy of antemortem diagnosis of DVT and PTE is within the range of just 10-30%,²⁰ representing one of the most frequently missed diagnosis in sudden unexpected death.^{4, 15} In our series, 95% had absence of clinical antemortem suspicion, in agreement with the 84% missed diagnosis reported by Karwinsky and Svendsen⁵ and close to the range of 67% to 91% described in the literature.²⁷ So, despite the availability of complementary diagnostic means there is a general difficulty in diagnosing PTE and this high rate of underdiagnosed PTE is probably responsible for the high mortality that results when this condition is forgotten.²⁷

One limitation of our study is that it was done retrospectively, and in different centers, so the protocol of autopsy, despite the general rules followed by all, was not completely uniform, as we were able to see, with statistically significant differences in the use of toxicological analysis and search for the emboli's source. Other limitation found was the

frequent lack of information regarding previous clinical features, like medication taken and pathological antecedents.

Studies like ours stress the importance of the performance of a complete autopsy with the use of classical complementary techniques, like histological analysis, in order to achieve a detailed characterization of the population affected by PTE, identifying the specific situations that could constitute risk factors.¹⁶ For that, autopsy diagnosis of PTE sudden unexpected death depends on the use of a rigorous protocol in order to not forget any step and its application in a uniform manner is essential.

Final Remarks

It is important to bear in mind that PTE is an important life-threatening condition in our societies and that acute responses are needed after the onset. This implies rapid recognition along with identification of the high risk population in order to initiate appropriate prophylaxis that has been proven in series of clinical trials to be effective.

Our study showed a high number of associated medical conditions, and its presence should alert physicians to the risk of PTE, because the rate of PTE antemortem suspicion was unacceptably low, regarding the presence of prodromal symptoms and seek of medical care.

As stated before, the initial manifestation of PTE in 25% of the patients is sudden death.¹⁵ Recent studies, as ours, showing that fatal PTE can be found in relative healthy ambulatory patients in the fourth or fifth decade of life, should lead to more active research into the rapid recognition of PTE and its effective prevention.^{15, 21}

In order to reach some conclusions regarding the possible association of the use of antipsychotics drugs and PTE, concern should raise regarding the identification of those specific drugs. The importance of collecting previous clinical information in clinical records or with the family should be stressed.

Autopsies are essential to study PTE associated risk factors, but to be even more effective, we recommend that they should be performed following a strict protocol in PTE cases, emphasizing the importance of searching for the emboli's source.

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Conflict of interest

Nothing to declare.

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Ethical approval

This study has been carried out in accordance with ethical rules and it has not been submitted to Ethical Approval because it is a retrospective case review in which no invasive studies were carried out nor identification of the individuals were given.

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Table 1: Characteristics of patients taking antipsychotics drugs

Age	Sex	Diagnosis	Antipsychotics	Place of Death
31	F	Unknown	Olanzapine, haloperidol, chlorpromazine	Hospital
38	F	Schizophrenia	Levomepromazine, clozapine	Hospital
39	M	Psychosis not specified	Levomepromazine, chlorpromazine	Hospital
44	M	Bipolar disorder, chronic alcoholism	Levomepromazine	Home
50	F	Bipolar disorder	Unknown	Hospital
58	F	Unknown	Haloperidol, cyamemazine	Hospital
62	M	Unknown	Cyamemazine	Home
64	F	Schizophrenia, dementia	Olanzapine, haloperidol	Hospital
66	M	Unknown	Risperidone	Hospital
78	M	Vascular and Alzheimer's dementia	Quetiapine	Hospital
86	F	Unknown	Cyamemazine	Hospital
87	M	Unknown	Melperone	Home
92	F	Unknown	Melperone	Hospital

Table 2: Underlying conditions associated with PTE cases.

Underlying conditions	Cases (N / %)	Details
Cardiovascular diseases	54 (51%)	
Immobilization	46 (43%)	
BMI \geq 25 kg/m ²	39 (37%)	
Systemic hypertension	36 (34%)	
Psychiatric disease	35 (33%)	
Pulmonary diseases	24 (23%)	
Previous trauma	24 (23%)	18 fractures of lower limbs;1 burn injury;1 abdominal blunt trauma
Diabetes mellitus	22 (21%)	
Infection	19 (18%)	8 respiratory; 4 urinary tract
Previous surgery	17 (16%)	9 orthopedic
Chronic venous disease	17 (16%)	3 previous DVT
Digestive diseases	14 (13%)	
Dislipidemia	11 (10%)	
Neoplasia	9 (8,5%)	2 melanomas; 2 gastric cancers
Chronic Alcoholism	6 (5,7%)	

Table 3: Characteristics of patients who sought medical care in the last 2 weeks before PTE.

Age	Sex	Symptoms	Diagnosis	Treatment
23	F	Left leg pain and swelling	Spinal column pathology	NSAID*, analgesics
33	F	Left leg pain	Thrombophlebitis	Antibiotics, NSAID*
33	F	Palpitations, thoracic discomfort, dyspnea, fatigue	Sinus tachycardia	Benzodiazepines, beta-blocker
35	F	Convulsive crises (3)	Depression	Fluid therapy, antidepressants
36	F	Leg pain and swelling	Muscular pain	None
51	M	Thoracic pain	Congestive heart failure	Antiarrhythmic, antihypertensives, carvedilol, diuretics
53	M	Dyspnea, hemoptysis	Respiratory infection, heart failure	Aspirin, antihypertensives, diuretics, antibiotics, analgesics
68	M	Left thoracic pain	Unknown (no cardiac pathology found)	Heart catheterization
75	F	Dyspnea, fatigue	Respiratory infection, anemia	Antibiotics

* Non steroidal anti-inflammatory drugs

Figure captions

Figure 1: Age and sex distribution of PTE cases.

Figure 2: Seasonal variation in autopsies with PTE.

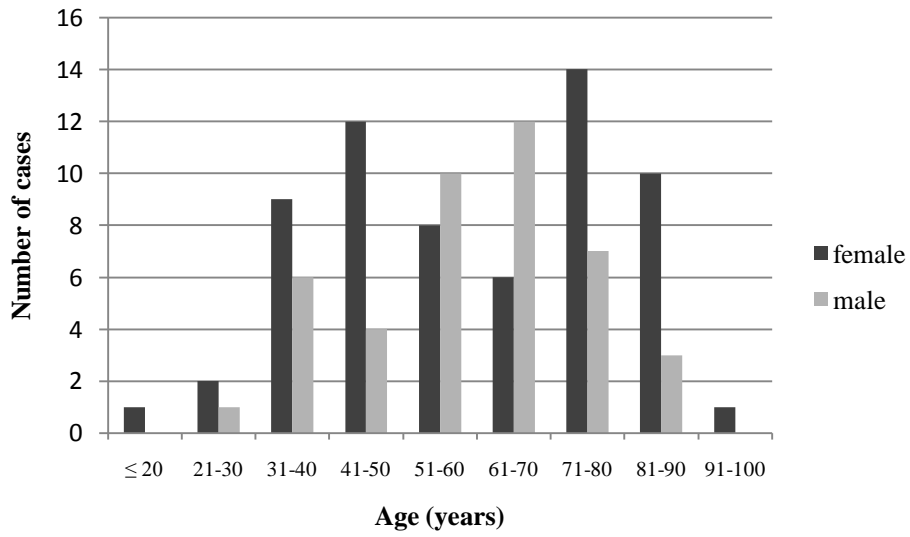


Figure 1

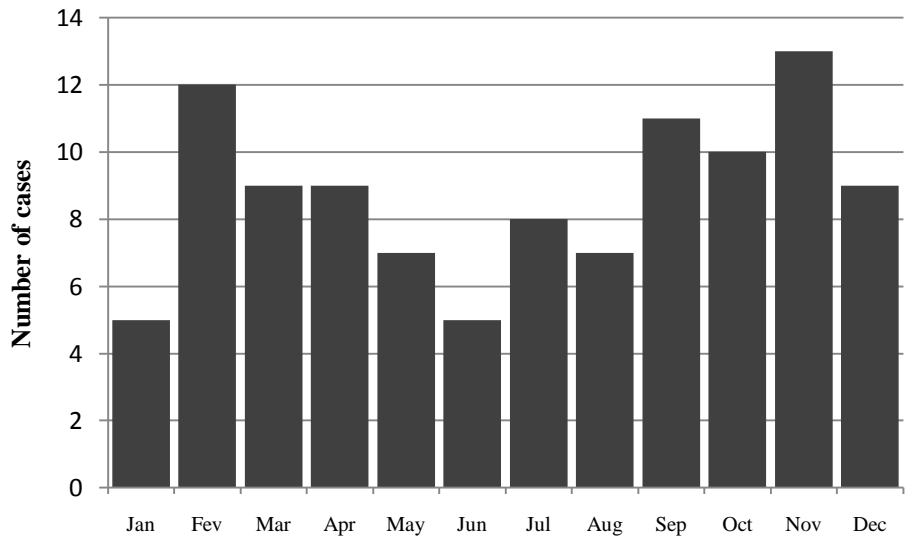


Figure 2

Attachment: Guide for Authors



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AUTHOR INFORMATION PACK

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