Case Report

LIMITATIONS IN AUTOPSY DIAGNOSIS OF FATAL PULMONARY THROMBOEMBOLISM IN INDIAN SETUP
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Abstract:

Pulmonary thromboembolism (PTE) caused due to deep vein thrombosis (DVT) is an important cause of sudden natural death; however it is a commonly missed diagnosis at autopsies in Indian setup. This is a well-recognized complication of recumbency following trauma, especially fractures and surgical operation or prolonged bed rest in medical cases. However in some cases, no apparent predisposing condition is identified. In such cases, occult hereditary thrombophilias may play a causal role.

In the present case, an apparently healthy young man became suddenly unconscious while kick starting his motorcycle. He was immediately rushed to the hospital where he died during treatment within 3 hours of admission. His autopsy showed presence of deep vein thrombosis with pulmonary emboli. Histopathological examination of lungs revealed presence of pulmonary infarction and dating of residual leg vein thrombus indicated a thrombus of not more than 3 days. He was apparently healthy, without any predisposition for deep vein thrombosis. Fatal pulmonary thromboembolism with pulmonary infarct in such a young, healthy person without any predisposition of common risk factors is an unusual occurrence. This case emphasizes the need for improved methodology including dating of residual thrombus in leg veins and postmortem testing for hereditary thrombophilias in death of young people due to PTE.

Key words: deep vein thrombosis, dating of thrombus, hereditary thrombophilia

Introduction:

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) are part of same spectrum of pulmonary thromboembolism (PTE). Homans first noted the relationship between DVT and PE. Symptomatology of this disorder ranges from asymptomatic patients to fatal massive embolism. It is one of the causes for sudden natural deaths. Thrombosis as per Virchow’s triad must have predisposing conditions like stasis of blood, injury to vessel wall and hypercoagulability. ‘Cause–effect’ relationship, that is, presence of predisposing factors like injury, surgical operation or immobility in bed, are often present in most of the cases, however about 20% of the cases are ambulant and are apparently healthy.

The overall annual incidence of PE increases as one ages, from 1 per 100,000 in childhood to 1 per 100 in old age. Incidence of fatal PTE is reported to be 10 to 12%. The incidence of PE at autopsy is strongly influenced by the nature of the population surveyed (age and nature of patients), by the type of cases included in postmortem study and by the care with which autopsies are carried out. Fineschi et al reported that 4.5% of pulmonary embolisms originated in the iliac veins, 20.7% in femoral veins, and, 74.8 % in deep crural veins.

The predisposition to form clots may be due to acquired or genetic risk factors. Acquired risk factors include immobilization, increasing age, surgery, malignancies, obesity, pregnancy, puerperium, oral contraceptives and long-haul air travels. Inherited conditions (hereditary thrombophilias) include factor V Leiden mutation to activated protein C resistance, prothrombin gene mutation, and deficiencies of antithrombin (I, II and III) and...
protein C or protein S. Often, however, the precipitating event may not be apparent. In such cases, the etiology may be multifactorial.

Occurrence of fatal PTE in the absence of any apparent predisposing conditions in a healthy young person makes the present case unusual and presence of pulmonary infarct makes it rare.

Case history:

A 24 year old healthy man, became suddenly unconscious while kick starting his motorcycle. He was immediately admitted to hospital and investigated.

At admission, his heart rate was 96 beats/min, blood pressure was 110/70 mm Hg, and respiratory rate was 34/min. The chest was clear on auscultation. Routine hematology testing revealed hemoglobin of 14.6 g/dL. Analysis of blood gas parameters showed pCO2 of 46.8 mmHg, pO2 of 163 mmHg, pH 7.12 and bicarbonate 14.6 mmol/L. International normalized ratio (INR) was 1.4. The oxygen saturation was 96%. X-ray chest was normal. CT scan of brain was normal. CT scan with contrast showed absence of contrast filling in pulmonary veins. ECG showed presence of S waves in lead I, and, Q and T waves in lead III (suggestive of pulmonary thromboembolism). He was diagnosed and treated as a case of pulmonary embolism. He died during the treatment, 3 hours after the admission.

At autopsy, on external examination, he was moderately built and nourished person. No injuries were present. On internal examination, both the lungs showed evidence of emboli in segmental and sub-segmental pulmonary arteries. Cut surface of thrombus was reddish brown in colour. Pulmonary infarction was noted in both the lungs with obliteration of air spaces with blood. Dissection of deep veins in the left leg showed thrombus in posterior tibial and popliteal veins, completely occluding the lumen. Other veins in both the legs did not contain any thrombus.

Fig. A. Histopathology of lung showing hemorrhagic infarction of lung parenchyma

Lungs and thrombus in-situ vessel wall were subjected for histopathological examination, which confirmed the presence of pulmonary infarction (Fig. A) and age of residual thrombus of not more than 3 days duration (Fig. B) respectively.

There was no history of trauma, immobility or injury to deep veins of leg by any other cause. There was no antecedent history of symptoms suggestive of deep vein thrombosis. Similarly there was no history of thrombotic events in first line surviving relatives of the deceased. Detection of genetic mutations which produce hypercoagulable state were not performed, because of unavailability of these investigations in this part of the country.
Fig. B. Histopathology of thrombus in the popliteal vessel wall

**Discussion:**

DVT occurs about three times more often than PE. About half of patients with pelvic vein thrombosis or proximal leg DVT develop PE, which is usually asymptomatic. Patients may present with symptoms like cardio respiratory shock as in the case discussed. Other symptoms that may be present are dyspnea, pleuritic pain, haemoptysis, tachycardia or anginal pain. Cardio respiratory shock is the presenting feature in 34.7% of patients of PTE. DVT and PTE should be suspected and actively searched during autopsy in natural deaths with above symptoms. Of all the venous thromboembolic deaths, 7% were diagnosed with PTE and treated, 34% were sudden fatal PE, and 59% were as undetected PE.

The incidence of PTE is approximately equal in men and women. 2.8% of sudden natural deaths in men are attributed to PTE. Young age is not known to be a risk factor for PTE. However, PTE in a person below 45 years of age is suggested as a criterion for screening for hereditary thrombophilia. Dickens et al noted only one case each of fatal pulmonary embolism in age group of 20-29 years in 97 and 60 cases of PTE deaths at Hongkong and Wales respectively. However, we found no epidemiological data of PTE as a cause of sudden natural death and percentage of PTE detection in overall autopsy cases in Indian population. This may be due to the fact the many autopsies in Indian setup are conducted by Medical officers placed at peripheral health centers, who may have apathy towards detailed autopsy due to lack of adequate training or ignorance to add to malady.

Thorough autopsy in deaths due to PTE requires knowledge of the general and specific pathology of PTE. Once the thrombus dislodges and travels to the lung, depending on its size and coexisting cardiovascular diseases, it interferes with patient’s haemodynamics. Because of the dual blood supply of the lungs (bronchial and pulmonary) and the rapidity of death, histological changes of infarction may not be evident in case of these sudden deaths. Pulmonary infarction is reported to be in about 6% to 10% cases of PTE. In present case, pulmonary infarction in a death occurring in short duration makes it more peculiar.

The clinical diagnosis of pulmonary thromboembolism is notoriously inaccurate, with many cases either wrongly diagnosed (overdiagnosed) or missed (underdiagnosed), and autopsy is still regarded as the diagnostic gold standard. Detection rate can be improved by complete methodological approach, integrating clinical data by means of autopsy findings and histological study. Search for residual thrombus and age estimation of thrombus must be a routine workup in cases of PTE with DVT, as, these may be of concern at a later date. Bilateral dissection of the deep veins of the pelvis and legs in PTE deaths can provide valuable information regarding the proximate cause and manner of death. The detection of
thrombi in both legs can be seen with risk factors like stasis and decreased mobility as opposed to a direct injury of one leg which show presence of thrombus in injured vessel. Thrombus along with surrounding vessel wall must be examined histopathologically for dating. It must always be remembered that other veins or other segments of same veins may have thrombi of different dates. In the presented case, deceased was young and was not having any of the common acquired risk factors for PTE. Histological age of residual thrombus was not more than 3 days, as determined by histopathological grading reported by Irninger (1963), and, Fineschi et al (2009) as shown in Table 1. Autopsy in a case of PTE is never complete unless underlying predisposing factors are screened for.

Table 1: Histological age determination of thrombus at Phase I.

<table>
<thead>
<tr>
<th>2nd day (1st–3rd day) (after Irninger)</th>
<th>No reactions between endothelium and thrombus. White blood cells, fibrinous ribbons with blood platelets unchanged. Erythrocytes mainly densely packed in the center (agglomerated), peripherally looser.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-7th day</td>
<td>Flowing blood on an eroded endothelium, eliciting a platelet plug and fibrin deposition with a layered growth (Zahn’s lines). No reaction between endothelium and thrombus is visible. Erythrocytes are preserved and agglomerated. Initial white blood cells pyknosis. Monocytes cells with enlarged nuclei.</td>
</tr>
</tbody>
</table>

Common acquired risk factors of PTE can be screened for by taking proper clinical history of the patient. However, uncommon risk factors like inherited thrombophilias also contribute to the likelihood of PTE and hence should be screened for. The two most common autosomal dominant genetic mutations are the factor V Leiden (FVL) and the prothrombin (PT) gene mutations. It is proposed that some of those persons who are immobilized, obese, postoperative, pregnant, taking OCP’s, aged, leukemic, and/or have cancer and die as a result of a PTE because they also carry a heterozygous mutation of hereditary thrombophilias. The benefits of screening for these defects and the parameters of patient selection continue to be debated, and prophylactic treatment is controversial. We agree with conclusions of previous studies, that testing is not indicated for all individuals presenting with PTE, but rather should be reserved for those presenting at a young age (below 45 years of age) or with a compelling positive family history of thrombosis. In current case, tests for thrombophilia were not done due to absence of family history of thrombosis, and, lack of testing facilities and budgetary constraints.

Sparse data is available in Indian literature regarding epidemiology and causative factors of fatal PTE. This is mainly because, large amount of medicolegal autopsies are being conducted at rural primary health centres by medical officers who are not well trained. Unavailability of ancillary investigations makes the situation grimmer. This has lead to erratic reporting of ‘cause of death’ in sudden natural deaths, especially pulmonary thromboembolism being commonly missed one. Similarly at the other end, dating of residual thrombus and screening of precipitating factors (particularly hereditary thrombophilias) are less commonly looked for by many of the Forensic pathologists in India. Apart from medicolegal implications, detection and complete investigation of death due to PTE is necessary as it also has a potentially life-saving importance to surviving family members having compelling positive history of thrombosis.

Conclusion:
With the background of the above discussion, we emphasize the following measures for the investigation of sudden natural deaths:

1. High index of suspicion of PTE is necessary in sudden natural deaths, particularly in young asymptomatic persons.
2. Increased training of medical officers and provision of basic infrastructure for detection, collection, preservation, processing, and transport of necessary samples for further investigations.
3. Detection and dating of residual thrombus in fatal PTE cases.
4. Use of ancillary investigations like those for detection of hereditary thrombophilias at the higher medical centres, to facilitate further identification of similar disorder in blood relatives.
5. Further studies in Indian populations are needed to assess the role of hereditary thrombophilias in fatal PTE.

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