Delays in Diagnosis of Acute Pulmonary Thromboembolism: Clinical Outcomes and Risk Factors

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ABSTRACT

Acute pulmonary thromboembolism is a common and potentially lethal disease. There is limited information about clinical importance of the delay in pulmonary embolism diagnosis. Between January 2009 and December 2010, consecutive 189 patients with PTE were enrolled to this retrospective study. Varriables including age, sex, educational level, smoking, Wells scores, symptoms, embolism types, clinical and radiological findings were analyzed for delay in diagnosis. Study group consisted of 104 (55%) female and 85 (45%) male patients. The mean age of the group was 57,95 (range 19-88) years. The mean time to presantation or patient delay was 7.9± 15.2 (median 3 days; range, 1-120) days. Diagnostic delay caused by initial misdiagnosis of the health care providers was 0.5± 3,9 (median 0; range 0-45) days. Seventy (37,04%) patients had a delay in diagnosis longer than seven days after onset of symptoms of pulmonary embolism. Current smokers, patients with low Wells scores(≤4) and having non spesific CT pulmonary angiographic findings for PTE at the first admission associated with delay in diagnosis in the present study (p<0.05). Massive type of embolism was associated with mortality (p=0,020). Delay in diagnosis in PTE may increase mortality and massive embolism should be monitored carefully.

Key words: *Pumonary thromboembolism, CT pulmonary angiography, late diagnosis, massive embolism*

Akut Akciğer Tromboemboli Tanısında Gecikme: Klinik Sonuçlar ve Risk Faktörleri

ÖZET

Akut pulmoner tromboemboli sık görülen ve ölümcül bir hastalıktır. Pulmoner emboli tanısında gecikmenin klinik önemiyle ilgili araştırmaya ihtiyaç duyulmaktadır. Ocak 2009 ile Aralık 2010 arasında kliniğimizde pulmoner tromboemboli tanısı konulan ardışık 189 hasta çalışmaya alınmıştır. Tanısal gecikmenin nedenleri ve süresi konusunda hastaların yaş, cinsiyet, eğitim düzeyi, sigara içme durumu, Wells skorları, semptomları, embolinin tipi, radyolojik ve klinik bulguları ayrıca ilk başvurulan sağlık kurumundan sevk gecikmesi gibi değişkenler retrospektif olarak araştırılmıştır. Çalışmaya alınan hastaların 104(%55)'ü kadın ve 85(%45)'i erkekti. Yaş ortalaması 57,95 (19-88 aralığında), ortalama tanısal gecikme süresi 7.9± 15.2 (ortanca değer 3 gün ve 1-120 aralığında), sağlık kurumundan sevk gecikme süresi ise ortalama 0.5± 3.9 gün (ortanca değer 0 gün ve 0-15 aralığında) bulundu. 70 (%37,04) hastada semptom başlangıcından sonra 7 günden daha uzun süreli tanısal gecikme olduğu saptandı. Sigara içenler, başvuru sırasında Wells skoru 4 ve daha düşük olanlar ile BT anjiyografide masif emboli bulgusu olmayanlar tanısal gecikme ile ilişkiliydi (p<0.05) ayrıca embolinin masif oluşu mortalite ile ilişkili bulundu (p=0,020). Pulmoner tromboemboli tanısında gecikme mortaliteyi arttırabilir. Masif tromboemboli hastaları yakından izlenmelidir.

Key words: *Akciğer tromboembolizm, BT akciğer anjiografisi, geç tanı, masif emboli*

INTRODUCTION

Clinically significant venous thromboembolism (VTE) is a common cardiopulmonary and vascular illness affecting 1 to 2 of every 1000 adults per year (1,2). The mortality rate of acute pulmonary embolism (PE) is 17% during the first year after diagnosis (3). In terms of pathologic diagnosis, an embolus is acute if it is situated centrally within the vascular lumen or if it occludes and causes distention of the involved vessel. Immobilization, surgical interventions, trauma and cancer frequently trigger

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venous thrombosis. Delays between onset of symptoms and diagnosis are common in PTE. Earlier diagnoses of deep vein thrombosis (DVT) and PE may reduce the morbidity and mortality associated with VTE (4). Some studies about PE reported a correlation between disease severity and early presentation (5,6). Despite diagnostic advances, delays in PE diagnosis remain problematic (7). In this study, we investigated the effects of risk factors on diagnostic delays and also the relationship between diagnostic delays and the mortality in PE.

MATERIALS AND METHODS

Study design and patients

This retrospective study based on the medical records of all hospitalized patients with PE diagnosis between January 2009 and December 2010. The multidisciplinary investigation was conducted at Department of Chest Disease of Ondokuz Mayıs University Hospital, which is a referral center for PE patients. The study was approved by the local ethical committee. All of consecutive patients with PE were enrolled to study and assessed in terms of demography, clinical evaluation, laboratory finding, risk factors for PE, diagnostic tests and diagnotic delay representing the date between onset of symptoms and diagnosis. In case of coexisting illnesses, the day on which the symptoms of sudden dyspnea, chest pain or syncope attributed to PE were accepted as the date of symptom onset retrospectively. The time from the onset of symptoms to diagnosis was defined as "time to diagnosis". Diagnostic delay was defined as diagnosis of PE more than 7 days after symptom onset. In the analysis of outcomes, we evaluated patients dead (mortality) during the hospitalization, after their discharge and survivors that had completed at least12 months of surveillance. A pulmonary embolus is characterized as massive when it involves both pulmonary arteries or when it results in hemodynamic compromise and presenting with a systolic arterial pressure less than 90 mmHg (8).

Statistical analysis

Results are given as mean ± SD, odds ratio and 95% confidence interval. P values less than 0.05 were considered statistically significant. The Mann-Whitney U and ki-square tests were used for the statistical analysis of the correlations between delays, mortality, and clinical data. Possible risk factors for diagnostic delays were analyzed using multivariate logistic regression. Collected data were analyzed using SPSS.15 statistical software.

RESULTS

Demographic and general data

One hundred and eighty nine patients constituted the complete group of study with the mean age of 57.95 (range 19-88) years, 104 (55%) of them were female and 85 (45%) of them were male. Fifty (26.45%) of patients were illiterate and one hundred and thirty four (73.54%) had primary or high school education. Fifty-eight (30.68%) of them were current smokers during admission.

Symptoms and signs

Major symptoms and signs were showed in table-2. Most obvious symptoms among the patients were listed as sudden onset of dyspnea in 90 (47.6%), chest pain in 56 (29.6%), hemoptysis in 16 (8.5%), leg swelling and pain in 16 (8.5%) and syncope in 10 (5.3%) of the patients respectively. Tachycardia (heart rate >100 bpm) in 48 (25.3%) patients, hypoxemia (PO2 <60mmHg) in arterial blood of 74 (39.1%) patients, hypotension (systolic blood pressure <90 mmHg) in 25 (13.2%) patients were the other significant results during first definite diagnosis. Interventricular septal shift was determined in 45 (23.80%) patients and diastolic dysfunction of the right ventricule was found in 54 (28.57%) patients with echocardiography. The mean pressure of pulmonary arteries was 44.36±20.84 (range 20-150) mmHg. Clinical types of PTE were classified as massive (25.9%), submassive (33.9%) and non-massive (40.2%) with the aim of echocardiography and CT angiography findings.

Concomittant diseases and risk factors

Several patients had previous pathological conditions: heart failure and hypertension was present in 32(16.9%) patients and chronic respiratory disease in 15(8%) patients. A history of previous venous thromboembolism was reported in 16 (8.5%) patients (deep venous thrombosis in 7 patients, pulmonary embolism in 9 patients). History of immobilazation with or without operation in last three months was noted as the most common risk factor among the study group with a number of 68(36%) patients. Three of the patients had Behçet disease, six had cancer and three were pregnant as a risk cofactor.

***Table1**. Clinical estimating scores of Wells (Canadian) for PTE* (9)*

Symptoms and signs	*Score*
Presence of DVT symptoms and signs	*3.0*
Low possibility of alternative diagnosis	*3.0*
Tachycardia(>100/ minute)	*1.5*
History of immobilization or surgery in last 4 weeks	*1.5*
Previous DVT or PTE history	*1.5*
Hemoptysis	*1*
Cancer	*1*

**Total score: <2.0: Low clinical possibility, 2.0- 6.0: Medium clinical possibility, >6.0: High clinical possibility. * or ≤4: poor PE clinical possibility, >4: strong PE clinical possibility. DVT: deep vein thrombosis, PTE: pulmonary thromboembolism*

***Table 2**. Major symptoms and signs of the patients with PTE*

Symptoms	*Total (n=189)*
Dyspnea	*90(47,6%)*
Chest pain	*56(29,6%)*
Hemoptysis	*16(8,5%)*
Leg swelling and pain	*16(8,5%)*
Syncope	*10(5,3%)*
Signs	
Hypoxemia (PO_2<60mmHg)	*74(39,1%)*
Diastolic dysfunction	*54(28,5%)*
Tachycardia (>100/minute)	*48(25,3%)*
Hypotension (TA<90/60mmHg)	*25(13,2%)*

Diagnostic methods

Diagnosis was made by means of thoracic computerized tomographic (CT) angiography and ventilation-perfussion (V-P) scintigraphy. CT angiography clearly showed venous thrombosis in 81 (42.85%) patients. V-P scintigraphic results correlated with clinical and radiological findings were used in diagnosis of remaining 109 (57.15%) patients. Color doppler ultrasonography revealed the deep vein thrombosis of lower extremities in 86 (45.50%) patients.

Delay in diagnosis

Delays in the diagnosis of PE represented both delays between the onset of symptoms and the receipt of medical attention, and between the initial medical evaluation and confirmatory diagnostic testing. After onset of symptoms of pulmonary embolism, 70 (37.04%) patients had a delay longer than seven days. A total of 119 (62.96%) patients were diagnosed earlier; 29 (15,34%) patients in first twenty four hour and 90 (47.61%) patients in seven days. The mean time in patient delays occured by late presentation of the patients which was 7.9±15.2 (median 3; range 1-120) days. Diagnostic delay caused by initial misdiagnosis of the health care providers was 0.5± 3,9(median 0; range 0-45) days. Delay in diagnosis was found more frequent among the patients with low clinical risk scores according to Wells (Canadian) classification than the other group with high risk scores (p=0,002), (Table-1 and 3). Varriables including age, sex, educational level, smoking, Wells scores, symptoms, embolism types, clinical and radiological findings with the aspects of chest X-ray, CT angiography, ventilation-perfusion scintigraphy, echocardiography and Doppler ultrasonography were analyzed for delay in diagnosis. Current smokers (p=0,018), patients with low Wells scores (p=0,023) and having non spesific CT angiographic findings for PTE (p=0,009) associated with delay in diagnosis in the present study. (Table-4). As a survival analysis, 170 (89.9%) of the PTE cases recovered completely. Nineteen of the patients (10.1%) were died

***Table-3**. Characteristics of the patients with PE according to risk groups in the first clinical evaluation*

Characteristics	*Group-A (n:76)*	*Group-B (n:113)*	*Total (n:189)*	*p value*
Age (year)	*60.46 ±15.29*	*56.27±16.90*	*57.96±16.36*	*0.085*
Sex (female/male)	*37/39*	*67/46*	*104/ 85*	*0.150*
Spesific symptoms	*62/76 (81.6)*	*101/113 (89.4)*	*163*	*0.142*
Embolism in angiography	*32/76(42.1)*	*49/113(43.4)*	*81*	*0.864*
Defects in V-P scintigraphy	*24/76(31.6)*	*30/113(26.5)*	*54*	*0.457*
PPA>40mmHg	*37/76(51.3)*	*39/113(65.5)*	*76*	*0.051*
Massive embolism	*18/76(23.7)*	*31/113(27.4)*	*49*	*0.560*
Delayed more than 7days	*38/76(50.0)*	*32/113(28.3)*	*70*	*0.002**
Mortality	*7/76(9.2)*	*12/113(10.6)*	*19*	*0.749*

**Statistically significant, group-A included the patients with Wells risk scores <4, group-B included the patients with Wells risk scores >4 at first admission to emergency. PPA: pressure of pulmonary arteries, V-P: ventilation and perfusion.*

***Table-4**. Multivariate binary logistic regression analysis of delay in diagnosis (more than7 days) of pulmonary embolism and the varriables in all patients*

Variables	*p value*	*OR*	*95,0% CI*
Massive embolism	*0,684*	*1,926*	*0,082-45,131*
Sex	*0,112*	*2,069*	*0,845-5,068*
Age	*0,505*	*0,774*	*0,364-1,644*
Educational level	*0,818*	*1,103*	*0,479-2,541*
Smoking (current smokers)	*0,018**	*3,059*	*1,214-7,708*
Symptoms	*0,764*	*0,777*	*0,149-4,037*
Chest X-ray findings	*0,259*	*1,637*	*0,696-3,850*
Embolism in CT pulmonary angiography	*0,009**	*0,031*	*0,002-0,414*
Common defects in V-P scintigraphy	*0,641*	*0,743*	*0,213-2,588*
PPA >40mmHg	*0,270*	*0,574*	*0,215-1,538*
Septal shift in echocardiography	*0,715*	*1,355*	*0,265-6,913*
Ventriculer diastolic dysfunction	*0,678*	*0,706*	*0,136-3,665*
Localisation of deep vein thrombosis	*0,526*	*1,449*	*0,460-4,563*

**statistically significant, PPA: pressure of pulmonary arteries, V-P: ventilation and perfusion*

from the PTE and the mean delaying time in diagnosis was 13.21 (range 1-60) days in this group which was longer than the time of survived patients. Ten (52.63%) of the 19 patients who died from PTE had a delay in diagnosis longer than seven days. This was a higher rate than the patients who survived. Another result of the present study was a higher mortality in massive embolism than the submassive or nonmassive forms of PE (p=0.020).

DISCUSSION

Diagnosis and exclusion of pulmonary embolism remain problematic. Early diagnosis of VTE or PTE and thus immediate starting of antithrombotic therapy have the potential to reduce subsequental morbidity and mortality. Clinical signs and symptoms for pulmonary embolism are nonspecific; therefore, patients suspected of having pulmonary embolism must undergo diagnostic tests until the diagnosis is confirmed. The gold standard, pulmonary angiography, is invasive and expensive, with limited availability and serious potential effects (10). Ventilation–perfusion scanning provides a definitive diagnosis in fewer than 40% of cases (11). These limitations may explain why diagnosis often delay for in pulmonary embolism. PIOPED 'Prospective investigation of pulmonary embolism diagnosis' study reported the most common syptoms of PTE as dyspnea (73%), pleuritic chest pain (66%), cough (37%), leg swelling (26%) and hemoptysis(13%) respectively (11). Similarly, we have found dyspnea (46.5%) and chest pain (31%) as the most common symptoms. Swelling and pain in the leg should be accepted as an alarming symptom for DVT according to similar studies as well as the present study. This study documents probable reasons of delay in the diagnosis of acute PTE and relationship between these factors and prognosis. There are only a few studies about delays in diagnosis of PTE (5,6,12-16). Delayed diagnosis has not been clearly related to mortality rates in these previous investigations. It could be assumed that patients affected by massive pulmonary embolism feel sicker and they seek medical aid and treatment in a shorter time, delayed diagnosis or wrong diagnosis less frequent. Patients with an initial misdiagnosis had a longer delay in diagnosis of PTE (12). But we have found that delay in diagnosis is a risk factor for mortality. In a previous study investigating delay in PTE diagnosis, Martinez et al reported that half of their patients with PTE had a delay longer than 6 days, 25% a delay more than 14 days and even 10% had a delay more than 21 days (12). As a result they concluded that the more days of delay, the older the patients are. We determined in the present study, a high rate in diagnostic delay (37.04%) and we did not find a correlation between delay in diagnosis and the age of patients. The mean time in patient delays occured by late presentation of the patients which was 7,2±13.6 (median 3; range 0-89) days. Another expected finding of this study, diagnostic delay which was caused by initial misdiagnosis of the health care providers was 0.3±1.4 (median 0; range 0-15) days in primary health care providing centers lacking of many diagnostic tools for PTE. Delay in diagnosis was found more frequent among the patients with low clinical risk scores according to Wells (Canadian) classification than the ones with

high risk scores in this study. This finding is reasonable, because the patients with low Well scores may have mild to moderate clinical table at presantation. In another study Jimenez Castro et al found diagnostic delay more than seven days in 18%, and more than 25 days in 6% of PTE (14). Bulbul et al reported that patients with PTE presented to hospital after 8.4±11.4 days (mean 4 days, range0-75) from the onset of symptoms and 30.4% of the patients diagnosed after 7 days of the symptoms (5). Our results showed concordance with these studies. Previous studies showed a higher mortality rate when right ventricular dysfunction was present while the others had not associated mortality with echocardiographic right ventricular dysfunction in PTE (17-19). In a retrospective study, echocardiographic RV/LV ratio greater than 0,9 was shown to be an independent predictive factor for hospital mortality in patients with acute pulmonary embolism (18). We analyzed high pressure of pulmonary arteries (>40mmHg), presence of septal shift and ventriculer diastolic dysfunction as echocardiographic varriables in diagnostic delays and mortality but our analytic results were not significant statistically. Eliot et al performed a generalizable investigation in 2005, and they enrolled a large number of consecutive patients with PE at 70 medical centers throughout North America to the study (11). They have found that fifty-nine of 344 patients (17%) with acute PE had more than7 days elapsed and 17 (5%) patients had more than 25 days elapsed between symptom onset and the diagnosis. But they did not provide outcome data to link delays in diagnosis to clinically important outcomes such as death, recurrent PE, or post-phlebitic syndrome. The widespread inclusion of CT pulmonary angiography as a diagnostic method in medical approaches of emergency and inpatients was recommended to reduce the time to diagnosis of acute PE in suspected cases (11). In this study, we put PTE diagnosis apparently by CT pulmonary angiography in 81 (42.85%) patients and by combination of CT pulmonary angiography, V-P scintigraphic results and clinical findings in 109 (57.15%) patients. The mortality rate of published registries was 3.3% vs 22.5% in Management Strategies and Prognosis in Patients With Pulmonary Embolism (MAPPET) registry and 15,3% in the International Cooperative Pulmonary Embolism Registry (ICOPER) (17,20). This study has limitations: its retrospective design and restricted number of patients obviously, but also its lack of power for survival rates since the hospital mortality was low (n:19 and 10,1%).

In conclusion, delay in diagnosis is frequent in acute PTE however, it is not an independent risk factor for mortality. Syncope, the sudden onset of dyspnea and chest pain are the main clinical manifestations of PTE and determination of embolism with CT angiography cause a shorter time up to diagnosis. On the otherhand current smokers, patients with a low Wells scores and non-diagnostic CT angiography results at first admissions show an increased time up to diagnosis.

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