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Original Article

Clinical analysis of tumor and non-tumor patients complicated with pulmonary embolism

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Abstract: Objective: To analyze the differences of the clinical characteristics and risk factors between tumor and non-tumor patients complicated with pulmonary embolism. Methods: A retrospective analysis was conducted on 96 hospitalized patients complicated with pulmonary embolism admitted into 307 Hospital of PLA from January 2009 to December 2014. 96 cases were divided into tumor group (n=52) and non-tumor group (n=44) according to whether they were accompanied with malignant tumors. The relevant characteristics of tumor group, comparison of the risk factors and laboratory results between two groups were assessed. Results: Lung cancer was prone to pulmonary embolism in malignant tumors and adenocarcinoma was the commonest pathological type. 31 (59.6%) cases developed pulmonary embolism within 3 months after tumor was diagnosed. The level of serum D-dimer and leukemia in tumor group were higher than that in non-tumor group (3241.06±4514.16 μg/L *vs* 1238.49±1236.69 μg/L and 9.68±5.53×10^9/L *vs* 7.90±3.84×10^9/L), with a significant statistical difference (P=0.004 and 0.015). The level of serum platlet in tumor group were lower than that in non-tumor group (204.63±132.58×10^9/L *vs* 222.26±76.92×10^9/L), with a significant statistical difference (P=0.023). Coronary heart disease, chronic lung disease, diabetes, hyperlipemia and cerebral infarction were significantly different between two groups (P<0.01). Unexplained dyspnea (51/96, 53.1%) was the main symptom of pulmonary embolism, yet no significant difference was found between the two groups. 33 cases (34.4%) combined with deep venous thrombosis of lower limb, right lower limb more than the left. Right main pulmonary artery and its branches embolism were seen in 46 cases (47.9%) according to imaging examination, and no significant difference between two groups. After thrombolytic and anticoagulant therapy, only 9 cases died of Pulmonary embolism. Conclusion: There is no obvious and significant difference in clinical symptoms between tumor and non-tumor patients complicated with pulmonary embolism. Using of anticoagulant and thrombolytic therapy can obtain good curative effect upon diagnosis.

Keywords: Malignant tumor, pulmonary embolism, D-dimer

Introduction

Pulmonary embolism (pulmonary embolism, PE) is a general term of a disease in a variety of obstructive pulmonary embolism or clinical syndromes. PE, which is associated with potentially fatal outcomes, is common but frequently under-diagnosed [1, 2]. Annual morbidity was 1‰-3‰ in general population in western countries and morbidity of pulmonary embolism in tumor patients is 3-4 times that of the normal population [3-6]. In this study, we retrospectively analyzed the clinical data of our hospital patients with pulmonary embolism from 2009 January to 2014 December. All patients were divided into two groups, tumor and non-tumor group, and the clinical characteristics of tumor group were compared with that of non-tumor group.

Materials and methods

The 96 cases with pulmonary embolism were selected for data analysis, who were admitted into the PLA 307 hospital from January 1st 2009 to December 31th 2014.

Diagnosis of malignant tumors and PE

The cases were histopathologically confirmed malignancies. The diagnosis of PE was accord-

ing to the clinical symptoms, arterial blood gas test results, computerized tomographic pulmonary angiography (CTPA), and/or ventilation/perfusion (V/Q) scintigraphy.

Patient characteristics

The cases were divided into tumor and non-tumor group, according to whether malignant tumor was complicated with. Potential risk factors such as the gender, age, smoking and accompanied diseases were reviewed. The type of tumor was also analyzed to find out which type of tumor was prone to pulmonary embolism. The clinical symptoms and the sites of thrombosis were compared between the two groups. The result of anti-coagulation therapy and complications due to anticoagulation were also conducted.

Laboratory results

The level of hemoglobin (Hb), leukemia (WBC), platelet count (PLT), D-dimer and B type sodium acid titanium in the blood were determined. The arterial blood gas determination, arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), ultrasonography of veins of the lower extremities, CTPA, V/Q scintigraphy, and/or pulmonary angiography were also detected for the patients.

Anti-coagulation and urokinase thrombolytic therapy

Patients with normal blood pressure were treated with anti-coagulations. Patients were injected with nadroparin calcium (Fraxiparine® 9,500 IU anti Xa/mL) injections of 0.4 mL once every 12 hours or enoxaparin at the dosage of 100 u/kg once every 12 hours subcutaneously as the initial therapy. After a heparin therapy for a minimum of 4 or 5 days, a personalized dosage of warfarin was administered orally to maintain a stable therapeutic effect of anticoagulation, i.e. an international normalized ratio (INR) of 2 to 3. Patients with massive embolism were treated with thrombolytic drugs.

Statistical analysis

SPSS13.0 statistical software was used. With measurement data and standard deviations (±s), the student t test was used. With count data expressed as the number of cases (%), the single factor analysis of the χ^2 test was used. $P<0.05$ mean that the difference was statistically significant.

Results

Lung cancer was prone to pulmonary embolism in malignant tumors and adenocarcinoma was the most common histological type. There are 52 cases in tumor group (male/female: 30/22) and 44 cases of non-tumor group (male/female: 22/22). The median age in tumor group was 59 year old (range from 12 to 84), and that in non-tumor group is 64 year old (range from 26 to 84). Among 52 cases, lung cancer 24 cases (46.2%), followed by the 12 cases (23.1%) of blood system tumors, 8 cases of digestive system tumor (15.4%), 3 cases (5.7%) of breast and gynecologic tumor respectively, 2 cases (3.8%) of nervous system tumor. Detailed results were shown in **Table 1**.

In 3 cases, tumor was diagnosed 1 to 3 months after the occurrence of PE. In 7 cases, tumor was diagnosed the same time as concurrent PE. 42 cases of PE occurred in the course of tumor, the median time of which was 6 months after primary tumor diagnosed (21 cases diagnosed in 3 months, 5 cases in 3 to 6 months, 4 cases in 6 to 12 months, 12 cases over 12 months). Among 40 cases with solid tumors, 38 cases were in stage IV and 35 cases were in the chemoradiotherapy process.

The main presenting symptoms of patients with PE

Unexplained dyspnea was seen in 51 cases (53.10%), Cough and expectoration was seen in 9 cases (9.4%), chest pain seen only18 cases (18.8%), only 7 cases (7.3%) complained with the typical triad, 8 cases with syncope onset (8.3%), 10 cases asymptomatic (10.4%). There was no significant differences between the two groups about symptoms, see **Table 2**.

The laboratory results of two groups

The level of Hb, WBC, PLT, D-Dimer, BNP, PaO_2 and $PaCO_2$ were compared in the two groups. The results showed that there was no significant difference between the two groups in the level of Hb, BNP, PaO_2 and $PaCO_2$ and the WBC, D-dimer level was significantly higher in tumor group than that in non-tumor group, the level of

Table 1. Tumor types of the 52 hospitalized cases with malignancies complicated with pulmonary embolism

Tumor location	Tumor types	n	Ratio (%)
Respiratory system	Squamous cell carcinoma of lung	2	3.8
	Adenocarcinoma of lung	14	26.9
	Small cell lung cancer	6	11.5
	Large cell lung cancer	1	1.9
	Pulmonary neuroendocrine tumor	1	1.9
	Total	24	46.2
Digestive system	Gastric cancer	3	5.8
	Peritoneal carcinoma	1	1.9
	Pancreatic cancer	2	3.8
	gallbladder carcinoma	1	1.9
	Colon cancer	1	1.9
	Total	8	15.4
Central nervous system	Meningioma	1	1.9
	Glioblastoma	1	1.9
	Total	2	3.8
Breast cancer	Breast cancer	3	5.8
Gynecological tumor	Ovarian cancer	2	3.8
	Endometrial carcinoma	1	1.9
	Total	3	5.8
Blood system tumors	Leukemia	5	9.6
	Lymphoma	7	13.7
	Totaltototal	12	23.1

Table 2. Clinical presentations of cases with PE in two groups

Main symptoms	Tumor team	Non-tumor team
Dyspnea	28	23
Cough and expectoration	5	4
Chest pain	9	9
Syncope	4	4
No symptom	6	4

χ^2=0.337, P=0.987.

PLT was opposite with a statistical difference (P<0.05), Results were shown in **Table 3**.

Type of DVT and PE in two groups

The 96 cases with PE were examined by lower vascular ultrasound to diagnose deep venous thrombosis. There were 33 cases (34.4%) with limb vein thrombosis, in which 12 cases in the left lower limb, 14 cases in the right lower extremity, 6 cases in the double lower limbs and 1 case had left subclavian vein thrombosis.

Among 96 cases, 93 cases received CTPA imaging and 2 patients received pulmonary radionuclide V/Q imaging. 1 case received ultrasonic inspection. Central type pulmonary embolism was defined segmental or above vascular embolism, and the peripheral pulmonary embolism was defined branches of segmental vascular embolism. Data showed that 52 cases (54.2%) were central type pulmonary embolism and 44 cases (45.8%) were peripheral pulmonary embolism. There was no statistically difference between the tumor and non-tumor groups, see **Table 4**. Additionally, the right main pulmonary artery and its branches embolism was seen in 46 cases (47.9%), left pulmonary artery and its branches embolism in 12 cases (12.5%) and both were involved in 38 cases (39.6%).

Treatment and prognosis

PE is divided into massive pulmonary embolism and non-massive pulmonary embolism according to whether complicated with shock and hypotension. A part of patients in non-massive pulmonary embolism with right ventricular dysfunction performance called submassive pulmonary embolism. The 82 cases of non-massive pulmonary embolism (normal or abnormal of right ventricular function) were treated with low molecular weight heparin and warfarin as anticoagulant therapy, of which 2 cases received anticoagulation therapy after inferior vena cava filter implantation. 9 cases of massive pulmonary embolism received urokinase thrombolytic therapy, of which 4 cases were treated by pulmonary artery angiography: one of these patients was a male 52 year old one with the left lower poorly differentiated pulmonary adenocarcinoma (**Figure 1A-C**), brain metastases, and chronic atrial fibrillation history for 30 years. He received the exploratory thoracotomy, GP regimen chemotherapy and head gamma knife sequentially. On the sixth

Table 3. Comparison of laboratory markers of patients with PE in two groups

Items	Tumor team	Non-tumor team	χ^2	P
Hb (g/L)	114.07±23.76	131.63±24.52	0.09	0.770
WBC (10^9/L)	9.68±5.53	7.90±3.84	6.20	0.015
PLT (10^9/L)	204.63±132.58	222.26±76.92	5.36	0.023
D-Dimer (μg/L)	3241.06±4514.16	1238.49±1236.69	8.86	0.004
BNP (pg/mL)	2048.87±3079.68	3409.20±6943.27	2.66	0.110
PaO_2 (mmHg)	64.59±16.45	58.96±13.49	0.113	0.738
$PaCO_2$ (mmHg)	34.06±5.83	38.94±8.68	2.91	0.090

Table 4. Types of PE according to imaging examination

Item	Tumor group	Non-tumor group
Central type	28	17
Peripheral type	24	27

χ^2=2.214, P=0.100.

day of chemotherapy, shortness of breath occurred suddenly after the movement, oxygen treatment slightly alleviated symptom. 12 hours later, symptoms aggravated, pulmonary embolism considered in clinically. Low molecular heparin and warfarin were given and chest CT scan showed right main pulmonary artery and distal branch embolization. 24 hours later, urokinase 70 wu was intravenous injected within 5 min, and 80 wu continuous infusion for 30 minutes, heparin intravenous after 4 hours, symptoms slightly relieved, but blood pressure continuous at the lower level than normal 80-101/52-61 mmHg. The thrombolytic therapy in pulmonary artery came into operation on July 2nd 2009. Pulmonary thrombolysis at right pulmonary artery opening were seen under DSA (**Figure 2A-C**), urokinase 30 wu injected by pulmonary artery, 40 minutes later, embolism refused under DSA. Warfarin was given to maintain anticoagulation therapy for 3 months. 5 cases were treated by intravenous thrombolysis. 4 cases receiving anti-coagulation treatment, 1 case of massive pulmonary embolism died without treatment.

Only 9 cases of death (11.5%) reported in this study within 1 month, including 1 sudden death within 2 hours after symptoms appearing without treatment. 3 patients died of embolism again after thrombolysis and 5 patients died of systemic failure and infection. There were 2 cases of bleeding during thrombolytic therapy in this group (22.2%), but no major bleeding was observed.

Discussion

PTE is a kind of disease with high morbidity and mortality. The clinical under-diagnosed and misdiagnosis of PTE is very serious, which aroused the attention of domestic and foreign researchers [1, 7, 8]. According to reports in the literature in recent years, the incidence has an increasing trend [9-11], for the doctors paid more attention about PTE. In this study, patients diagnosed with PE in 2014 were 2.57 times that in 2009. The rate of malignant tumor thrombosis was 4-7 times that of normal people. In this group of 96 patients with PE, malignant tumor was most common risk factor with a rate of 54.2%, which was higher than that reported by Bajaj N with 27%. The reason might be that about 60% patients were diagnosed with tumor in our hospital.

Malignant tumors are the risk factors of pulmonary embolism, associated with hypercoagulable state in blood in advanced cancer patients after operation [12-15]. In addition, multi cycle chemotherapy and radiotherapy are secondary factors associated to pulmonary embolism in patients with malignant tumor [16]. Geerts reported that consistent systemic chemotherapy could increase the risk of thrombosis in patients with tumor [17]. The possible mechanism for this might be the direct damage to endothelial cells causing by chemotherapy and operation or inducing the coagulation pathway or activating the coagulation system in vivo by the release of tissue factor and so on. Antitumor biotherapy during treatment with erythropoietin hormone or granulocyte colony-stimulating factor could also cause a hypercoagulable state [18]. Tumor metastasis aggravates high blood coagulation state, which is a major cause of the increasing rate of pulmonary embolism in patients with advanced cancer [19, 20]. In the solid tumor group, 38 cases (95%) were at state IV, 35 patients (67.3%) were in the chemoradiotherapy process in the diagnosis of pulmonary embolism.

Though lung cancer was the most common malignancy diagnosed in patients with PE [21,

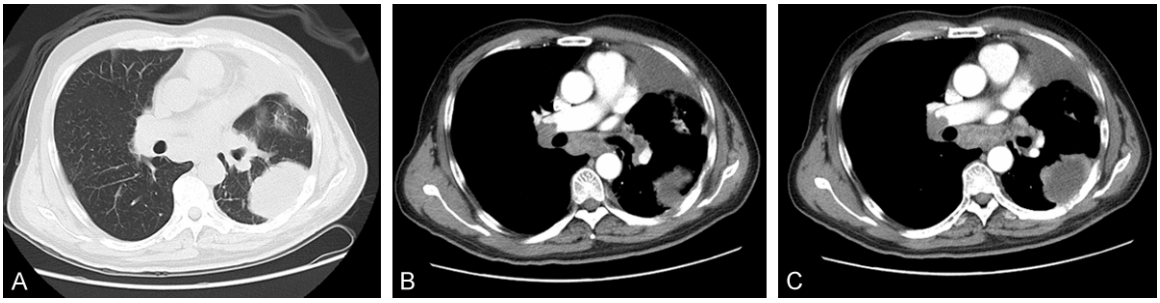

Figure 1. A. Lung window shows left lung lesion; B and C. Mediastinal window shows left lung lesion and right main pulmonary artery thrombosis.

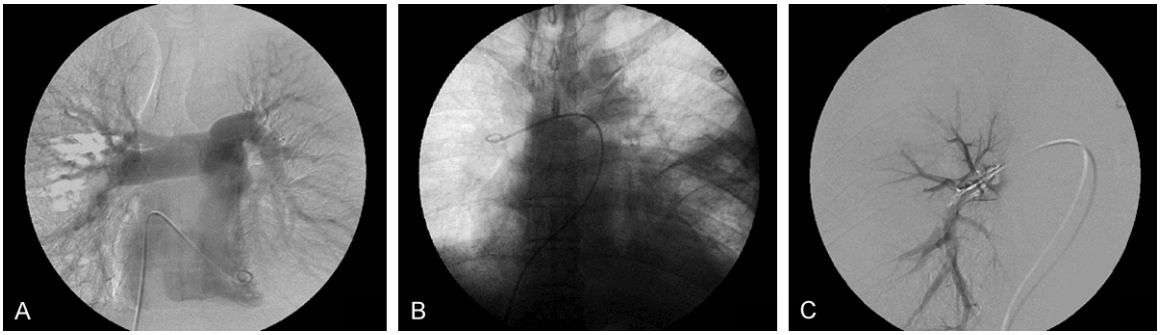

Figure 2. A. Right ventricular angiography showed obvious thickening of right inferior pulmonary artery, the lower part in the branch had a lot of white thrombus; B. Catheter into the right pulmonary artery and catheter thrombolytic (urokinase injection 30 wu); C. After 20 mins right pulmonary artery angiography showed artery branch white thrombus disappeared.

22], the PE associated to lung cancer was often under diagnosed. The frequency of the pulmonary embolism (PE) in lung cancer was 2.58% as reported, followed by blood system tumors. In addition, venous thrombosis is likely to be a symptom of occult malignancy, pulmonary embolism is often the first manifestation of tumor patients [23]. In the group of patients with tumor, 50% patients with pulmonary embolism occurred at a frequency of 50% in the 3 months before or after the diagnosis of tumor. In this study, factors such as age, gender, smoking history and hypertension were not significantly different between tumor and non-tumor groups, but factors such as coronary heart disease, the hyperlipidemia, chronic obstructive pulmonary disease and diabetes were significantly different between the two groups, especially in patients with chronic lung, COPD, which was the main basis disease in non-tumor patients with pulmonary embolism.

There were no significant differences about the main clinical manifestations of pulmonary embolism between the two groups. Only 7 cases (7.3%) were characterized by pulmonary embolism triple typical syndrome manifestations, which include dyspnea, chest pain and hemoptysis. 8 cases with syncope onset (8.3%), which were massive pulmonary embolism. 51 cases complained with dyspnea without obvious causes (53.1%), which might mean that unexplained dyspnea should be a high degree of vigilance of pulmonary embolism [24]. In this study, there were 10 cases without symptom, which should attract doctors' attention.

According to pulmonary embolism guideline, D-dimer level below 500 μg/L is a pulmonary embolism exclusion criteria. D-dimer level was elevated in 90.9% of the PE patients as Bai CM reported [13]. Among 17 patients with plasma D-dimer levels lower than 500 μg/L, 4 cases had pulmonary embolism history, 7 cases with venous thrombosis of the lower limbs. They were classified to non massive pulmonary embolism and all receiving low molecular weight heparin and warfarin anticoagulation therapy. These patients had relativity good prognosis [25-28]. The level of D-dimer in

patients with tumor was significantly higher than that of non-tumor group, considering that D-dimer was a degradation product of fibrin, many factors such as anti-coagulant and thrombosis therapy and tumor secreted factors could affect the level of D-dimer. The patients with D-dimer lower than 500 μg/L in blood had relatively good prognosis and this should attract the doctor's attention. Pulmonary embolism could induce right ventricular system changing and BNP could reflect the heart function, so elevating BNP levels might be used as an indirect sign of pulmonary embolism.

Signs of DVT reported by Bajaj N [6] were present in 29% patients with PE. In this study, we found that 33 patients (34.4%) had deep vein thrombosis. It meant that we should recognize the possibility of pulmonary embolism for patients with lower extremity venous thrombosis. Types of imaging diagnosis of PE in the right pulmonary artery trunk or branch embolization were more than that of left considering the right pulmonary artery relatively long [29, 30].

Only 3 cases of death related to therapy in this study receiving anticoagulation and thrombolytic therapy, the rest of the patients were cured or alleviated. For the patient with risk factor, especially with many risk factors at the same time [31-33], the prevention and timely diagnosis was very important. Once pulmonary embolism was diagnosed, thrombolytic or anticoagulant treatment according to the illness might improve the prognosis of the patients [34, 35]. From 2013, ASCO guidelines recommended low molecular weight heparin, the initial onset of 5-10 day priority selection for patients with lower extremity deep vein thrombosis or pulmonary embolism induced by tumor, except for serum creatinine clearance rate higher than that of CrCl. 30 mL/min, low molecular weight heparin is better than warfarin or other new oral anticoagulants, unless the low molecular weight heparins intolerance, treatment should continue for at least 6 months. For a time, there were multiple metastasis and patients receiving chemotherapy may prolong the time [36-40].

In sum, PE in recent years is not a rare disease, and its morbidity is increasing. The incidence rate of pulmonary embolism in patients with malignant tumor is high. Adequate manners for prevention and treatment of thrombosis are very important [23, 31, 33]. Significant risk factors were determined in this study. Patients with tumor should be periodically assessed for PE risk and oncology doctors should provide patients with the information on the signs and symptoms of PE.

Disclosure of conflict of interest

None.

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