Syncope as the initial presentation of pulmonary embolism in a young adult with testicular tumor
A case report and literature review

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Abstract

Rationale: Venous thrombus embolism (VTE) includes deep-vein thrombosis (DVT) and pulmonary embolism (PE) which may be an initial symptom for patients with cancer. PE has diverse clinical manifestations and is a rare complication of testicular tumor (TT).

Patient concerns: Here, we report a 21-year-old man admitted to our hospital due to syncope.

Diagnoses: Clinical examinations upon admission demonstrated PE resulting in syncope. Further, a malignant TT, liver metastasis, and inferior vena cava (IVC) thrombosis were diagnosed.

Interventions: Low molecular heparin was administered immediately after PE was diagnosed.

Outcomes: The patient suffered from cardiac arrest on hospitalization.

Lessons: Physicians should consider the possibility of TT when a young male patient presents with syncope and is diagnosed with PE that cannot be explained by a common cause. Treatment for TT and PE should be performed as early as possible to improve the prognosis of patients combine with TT and PE.

Abbreviations: ACCP-10 = American College of Chest Physician guidelines-10, CT = computerized tomography, CTPA = computerized tomography pulmonary angiography, DVT = deep-vein thrombosis, ECG = electrocardiogram, IVC = inferior vena cava, LMWH = low molecular heparin, PaCO2 = arterial carbon dioxide tension, PaO2 = arterial oxygen tension, PE = pulmonary embolism, TT = testicular tumor, VTE = venous thrombus embolism.

Keywords: pulmonary embolism, syncope, testicular tumor

1. Introduction

Venous thrombus embolism (VTE) has high rates of recurrence and mortality,[1] and is now recognized to have a higher occurrence in oncological patients. Pulmonary embolism (PE) is the most serious complication of VTE. PE is also a rare complication of a testicular tumor (TT) and may be a presenting symptom for a TT.[2] The only or first symptom of PE can be syncope, which is a temporary loss of consciousness caused by a shortage of blood supply to the brain.[3] It is rare that cases eventually diagnosed as TT present with syncope as the initial PE symptom. In this article, we report one case of syncope resulting from PE that was later diagnosed with TT, and review previous case reports of PE in TT.

1.1. Case presentation

A 21-year-old man with a 2-year history of smoking presented with syncope. On admission, his bilateral lungs were clear, there were no rales on auscultation, cardiac rhythm was regular, and there was no heart murmur in each auscultatory valve. An arterial blood gas analysis showed that arterial oxygen tension (PaO2) was 58–45.0 mmHg (normal range, 80–100 mmHg). Electrocardiogram (ECG) readings showed sinus tachycardia and an incomplete right bundle branch block. Transthoracic echocardiography revealed a dilated right chamber in combination with mild pulmonary hypertension and mild tricuspid regurgitation. In view of these results, we strongly suspected PE. Therefore, we performed computerized tomography pulmonary angiography (CTPA) and the result showed multiple pulmonary artery embolisms (Fig. 1). Immediately after confirmation of PE diagnosis, low molecular heparin was administered. A lower limb venous compression ultrasonography revealed no abnormalities, so the cause of PE was unknown. We then considered the possibility of an underlying illness, such as cancer. Abdomen computerized tomography (CT) scanning found space occupying
lesions in front of the inferior vena cava (IVC) and a low-density lesion in the right lobe of the liver. A full abdominal enhanced CT revealed that the space occupying lesions in front of the inferior vena cava were malignant and also found an IVC thromboembolism; the low-density lesion in the right lobe of the liver indicated a metastatic tumor (Fig. 2) and a right TT (Fig. 3). Scrotal Doppler ultrasonography revealed an irregularly shaped 22 × 21 mm solid mass in the right testis, and a visible blood flow signal indicated the presence of a malignant tumor. Although there was no formal histological confirmation, the diagnoses of a metastatic TT, PE, and IVC thrombosis were strongly suggested by clinical findings, scrotal Doppler ultrasonography, and full abdominal enhanced CT. Immediately after we identified the cause of PE, the patient again experienced syncope and became pulseless, which required advanced cardiopulmonary life support. Cardiopulmonary resuscitation was sustained for approximately 20 minutes. Spontaneous circulation was not achieved and the patient died. Our case report was waived from the First Hospital of Jilin University Ethical Board, based upon their policy to review all intervention and observational study except for a case report. The patient’s family provided informed consent for the publication of his clinical data. The presented data are anonymized and risk of identification is minimal.

2. Literature review

Our literature search for related cases identified 24 young men with TT who also had PE in 21 articles\textsuperscript{[2-4,23]} from 1986 to 2018 in the PubMed database (Table 1). These patients were aged
between 17 and 49 years old (mean age: 33 years), and 62.5% of the cases occurred in the right testis, 20.8% in the left, and 16.7% of cases were not described in detail. Regarding the initial presenting symptoms of TT, PE was the first manifestation in 50% of cases, TT in 25%, TT metastasis in 0.83%, and the other 16.7% were not specified. Only 4.17% of TT patients did not receive tumor treatment and the remaining TT patients received surgery and/or chemotherapy. The first PE symptoms were dyspnea (54.2% of cases), chest pain (37.5%), collapse (12.5%), and other symptoms (12.5%). In 20.8% of cases, this information was not available. The embolus properties of PE included tumoral thrombi (37.5%) and thrombus (12.5%), although this information was not available in 50% of cases. Regarding the PE treatment, 58.3% patients received anticoagulation therapy, 20.8% received surgery, 8.3% received thrombolytic therapy. In 12.5% of cases, PE was not found until autopsy. Regarding outcomes, 70.8% patients had an improved prognosis, 20.8% patients died of PE, and the prognosis of 8.3% patients was not mentioned. Notably, 25% of PE occurred with cisplatin-based chemotherapy.

3. Discussion

TT is a rare disease, which accounts for approximately 1% of all male tumors,[24] however, TT incidence has increased in both the United States and Europe.[25-27] TT is very clinically significant because it affects young men aged 18 to 39 years.[28] Patients with cancer have a 4 to 7-fold higher risk of developing VTE, which includes deep-vein thrombosis (DVT), and PE.[29] Most PE occurs in patients with malignant tumors of the ovary, pancreas, brain, uterus, and multiple myeloma. PE is rarely found in patients with malignant TT (<1%).[30] TT normally appears as a
unilateral painless enlargement of the testicles, or the casual discovery of an intrascrotal mass.\[20\]

In our review, we found that the average age of TT patients is 33 years, and that 41.7% of the cases presented as a painless testicular mass, which is consistent with the reviewed literature. PE has a variety of symptoms and these lack specificity. The most frequent symptoms of PE were dyspnea and pleuritic chest pain, although syncope can be the only or initial symptom of PE. However, syncope as the initial presentation of PE in TT patients is particularly rare.

Syncope is a temporary loss of consciousness that is caused by a shortage of the brain’s blood supply, and is characterized by sudden attack and rapid recovery. The frequency of syncope in patients with high-risk PE is 29.9%.\[31\] There are 3 possible mechanisms for syncope in patients with PE.\[32\] The first is when thrombosis of more than half of the lung arterial system causes a significant decrease in cardiac output, resulting in arterial hypotension and reduced cerebral blood flow. The second possible mechanism is the activation of the vasovagal reflex. A third possible mechanism is an overload of the right ventricle that causes arrhythmias and conduction disturbances. The patient in our case report did not describe testicular discomfort, but was admitted to our department with syncope. On the basis of D-dimer measurements, a blood gas analysis, and CTPA, we clearly diagnosed PE. Thus, we investigated the cause of PE and found TT, hepatic metastases, and IVC thrombosis.

TT is more commonly right sided. In the case report, TT also occurred in the right testicle and involved IVC. TT can involve IVC through several mechanisms. The first is a hematogenous spread of the tumor that directly invades the right spermatic vein and then spreads into the IVC,\[21\] which explains why IVC invasion occurs more frequently in patients with right TT. The second explanation is a lymphatic spread and local invasion of retroperitoneal enlarged lymph nodes. Extrinsic obstruction of the IVC caused by lymphadenopathy may progressively erode the vessel wall and cause endothelial cell injury; consequently, this might promote thrombosis and IVC compression and lead to stasis and thrombosis, or even entrap tumor emboli that arise from the spermatic veins.\[4\] Thus, bulky retroperitoneal disease is a major risk factor for IVC thrombus, which may explain why 81.8% of TT patients with IVC metastases or thrombosis had bulky retroperitoneal masses in our review.

Several mechanisms contributing to PE in patients with TT have been identified. DVT in a lower extremity is a common cause of PE, but no DVT was found in our case and 83.3% of reviewed cases had no DVT of the lower limbs. Postmortem examination of patients with a tumor combined with PE showed that the embolus contained tumor tissue. Unfortunately, the properties of embolus in our case report were not clear because the patient’s family did not consent to an autopsy. Half of the PE patients were autopsied, and up to 75% of the PE was tumoral thrombi in these patients. Therefore, tumor embolism may be the main mechanism for PE in TT patients. The mechanism could be explained as tumor cells activating the coagulation system by producing pro-coagulant factors, inflammatory cytokines, and other factors, or as direct interaction between tumor cells and the host’s vascular and blood cells.\[33\] Our review also found that up to 87.5% of the cases had a tumor metastasis in one or more sites. This finding indicates that distant metastases significantly increase the risk of PE in TT patients, which could be due to the tumor metastasis aggravating the hypercoagulative state of the blood and increasing the risk of PE. IVC thrombosis also increased the risk of PE, as mentioned above. Notably, 25% of TT patients developed PE after cisplatin treatment, suggesting that TT patients treated with cisplatin may increase PE risk. Cisplatin-based drugs increase the risk of thrombotic events.
### Table 1

Reported cases of young men with TT had PE.

| Case | Author/Year | Age | Position of TT | TT initial symptom | TT treatment | First symptom of PE | Histopathologic examination of PE | PE treatment | Prognosis | Note |
|------|-------------|-----|----------------|-------------------|--------------|---------------------|-----------------------------------|--------------|-----------|------|
| 1    | O'Brien WM/1986 | 22  | Right TT metastasis | Surgery + chemotherapy | Dyspnea | Tumoral thrombi | Intavenous heparin, and | Improve |
| 2    | Lederman GS/1987 | 30  | NA | Surgery + chemotherapy | Cardiovascular collapse | Thrombi-embolism | PE found at autopsy | Died of PE | PE occurred after cisplatin based chemotherapy |
| 3    | Lederman GS/1987 | 31  | NA | Chemotherapy | Pleuritic chest pain, severe shortness of breath and hemoptysis | NA | Anticoagulation therapy | Improve |
| 4    | Stockler M/1991 | 17  | Right | Surgery + chemotherapy | Collapsed | Tumoral emboli | PE found at autopsy | Died of PE | PE occurred after cisplatin based chemotherapy |
| 5    | Stockler M/1991 | 44  | Right TT metastasis | Surgery | Collapsed | Thrombi | Thoracic + emboli removing, heparin then warfarin | Improve |
| 6    | Stockler M/1991 | 30  | Right | Surgery + chemotherapy | Collapsed | Tumoral emboli | PE found at autopsy | Died of PE | PE occurred after cisplatin based chemotherapy |
| 7    | Kwek CK/1993 | 40  | Right PE | Surgery + chemotherapy | Dyspnea, chest tightness and thoracic back pain | NA | Anticoagulation therapy | Improve |
| 8    | Dada MA/1993 | 37  | Right PE | None | Back pain | Partial malignant cells | PE found at autopsy | Sudden death of PE |
| 9    | Karla Cohen D/1999 | 35  | Right PE | Surgery + chemotherapy | Acute dyspnea | Choriocarcinoma and a fibrinous thrombus | Thrombolysis then heparin | Improve |
| 10   | Haibel F/1999 | 35  | NA | Surgery + chemotherapy | None | NA | Surgical thrombectomy | Improve |
| 11   | Leslie JA/2003 | 30  | Right PE | Surgery + chemotherapy | Shortness of breath | NA | Anticoagulation therapy | Improve |
| 12   | Aikamatsu S/2004 | 21  | Right TT | Surgery + chemotherapy | Sudden dyspnea | NA | Thrombolysis | Improve |
| 13   | Huwer H/2004 | 39  | Right PE | Surgery + chemotherapy | Right ventricular pain and dyspnea | Thrombi | Urgent surgery of thrombi removing | Improve |
| 14   | Barton SJ/2005 | 21  | Right PE | Chemotherapy + surgery | Chest pain and shortness of breath | NA | Low molecular weight heparin | Improve |
| 15   | Hoshiba A/2006 | 40  | NA | Surgery + chemotherapy | Dyspnea | Thrombi-embolism | Thrombolysis | Died of PE |
| 16   | May M/2006 | 42  | Left TT | Surgery + chemotherapy | Left-sided thoracic pain | Tumoral thrombi | Anticoagulation therapy | Improve |
| 17   | Ramesh Bathra/2009 | 36  | Left NA | Surgery + chemotherapy | NA | NA | Warfarin | Improve |
| 18   | Talha S/2009 | 49  | Right PE | Surgery + chemotherapy | Shortness of breath | Tumoral thrombi | None | Improve |
| 19   | Mikovska V/2010 | 49  | Right NA | Surgery + chemotherapy | Right hemithorax pain and dyspnea | NA | Low molecular weight heparin | Improve |
| 20   | Singh R/2013 | 20  | Right PE | Chemotherapy + surgery | Chest pain, cough | NA | Low molecular weight heparin | Improve |
| 21   | Ihani Berber/2013 | 25  | Left PE | Surgery | Right chest pain and dyspnea | NA | Enoxaparin and warfarin then warfarin | NA |
| 22   | Marie Dusaud/2015 | 45  | Left TT | Surgery + chemotherapy | NA | NA | Anticoagulation therapy | Improve |
| 23   | de Nascimento FR/2016 | 31  | Left TT | Surgery | NA | Tumoral thrombi | None | Died of PE |
| 24   | Rosenfeldt K/2016 | 29  | Right PE | Surgery + chemotherapy | Dyspnea and right chest pain | Tumoral thrombi | None | Improve |

NA = not available; PE = pulmonary embolism; Ref. = reference; TT = testicular tumor.
because they can damage vascular endothelial cells, increase levels of Von Willebrand factor antigen, induce platelet activation, and stimulate fibroblast proliferation.\[^{16}\]

Sudden death from TT due to PE is rare. Bredael et al.\[^{34}\] reported that 9% of TT patients died of PE in autopsy cases. In our case, the patient’s death may have been due to acute right ventricular failure caused by a massive thrombus entering the pulmonary artery. Right ventricular failure is the leading cause of death for PE; thus, the findings of right ventricular dysfunction and dilatation observed in this patient are prognostically important. Surgery and/or chemotherapy are the main treatments for TT. Although the patient in our case suffered sudden death before TT treatment, our review showed that 95.83% of TT patients received surgery and/or chemotherapy and 83.3% of PE patients received anticoagulation or surgery or thrombolysis. Overall, 70.8% of patients had a good prognosis, indicating that early treatment of TT and PE may improve long-term prognosis and reduce mortality.

There are different mechanisms involved in the different treatments for PE in TT. Anticoagulant therapy is the foundation treatment for all patients with PE. According to the recommendations in the American College of Chest Physician guidelines-10 (ACCP-10), low molecular heparin (LMWH) is indefinitely administered as an anticoagulation therapy to prevent recurrent VTE in patients with cancer.\[^{35}\] For patients who refuse or have compelling reasons to avoid LMWH, apixaban or rivaroxaban are acceptable alternatives for managing VTE.\[^{36}\] However, PE occurred in our case, despite anticoagulation treatment. A temporary IVC filter is a safe and useful method to lower the risk of PE. For patients with IVC thrombosis that extends into the cardiac chambers, appropriate treatment includes chemotherapy and surgery.\[^{21}\]

In conclusion, we report a case of PE presented with syncope that finally recognized as TT and review previous case reports of PE in TT. We should be alert to TT in young men when syncope is the initial presentation of PE. We should also note that sudden death occurs easily in cancer patients when PE is combined with IVC thrombosis or right ventricular dysfunction and/or dilatation. Treatment for TT and PE should be performed as early as possible to improve the prognosis of patients of PE in TT.

Acknowledgments

We thank all participants for their supports and participation.

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