

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 examination of the abdomen was unremarkable. Laboratory findings showed that D-dimer levels were 40 times higher than normal. An arterial blood gas analysis showed that arterial carbon dioxide tension (PaCO₂) was 29.1 mmHg (normal range, 35.0–45.0 mmHg) and arterial oxygen tension (PaO₂) was 58 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

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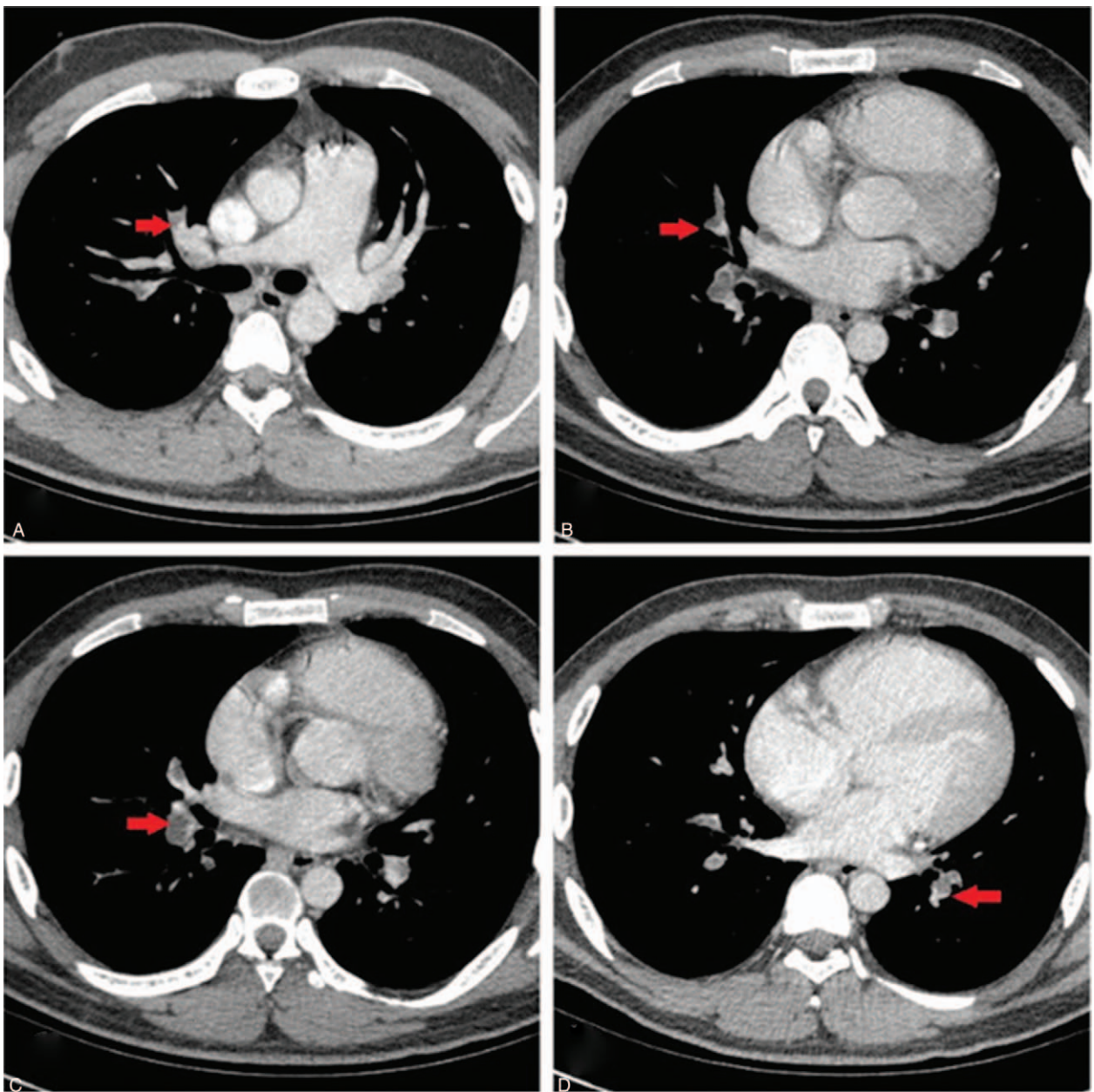


Figure 1. CTPA showed pulmonary embolism. PE in the upper lobe of the right lung (A); PE in the middle lobe of right lung (B); PE in the inferior lobe of right lung (C); PE in the inferior lobe of left lung (D). CTPA=computerized tomography pulmonary angiography; PE=pulmonary embolism.

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^[2,4-23] from 1986 to 2018 in the PubMed database (Table 1). These patients were aged

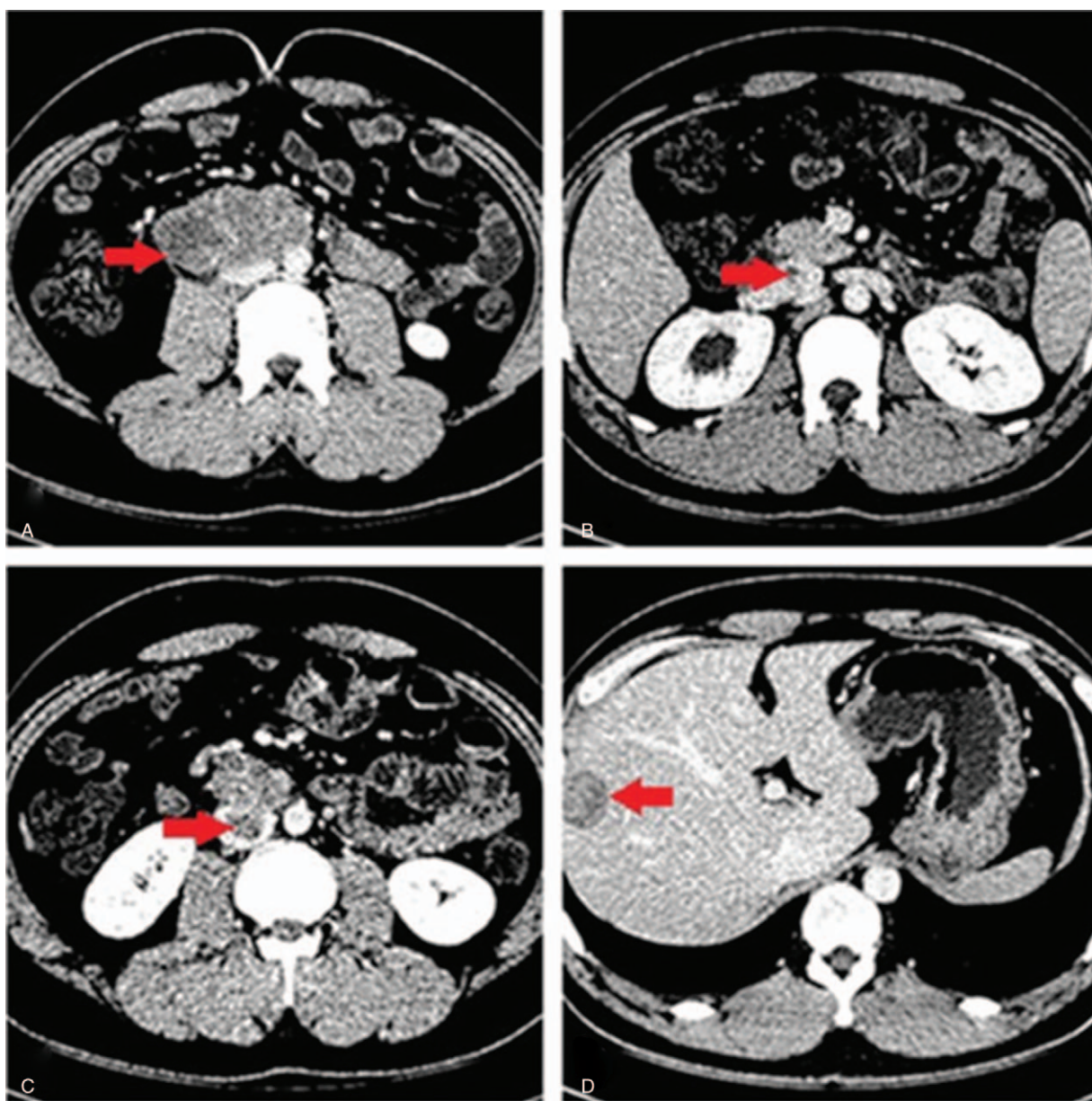


Figure 2. Abdominal enhanced CT results. Abdominal lymph node metastasis IVC (A); IVC beginning thrombosis (B); IVC termination thrombosis (C); hepatic metastasis (D). CT=computerized tomography; IVC=inferior vena cava.

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

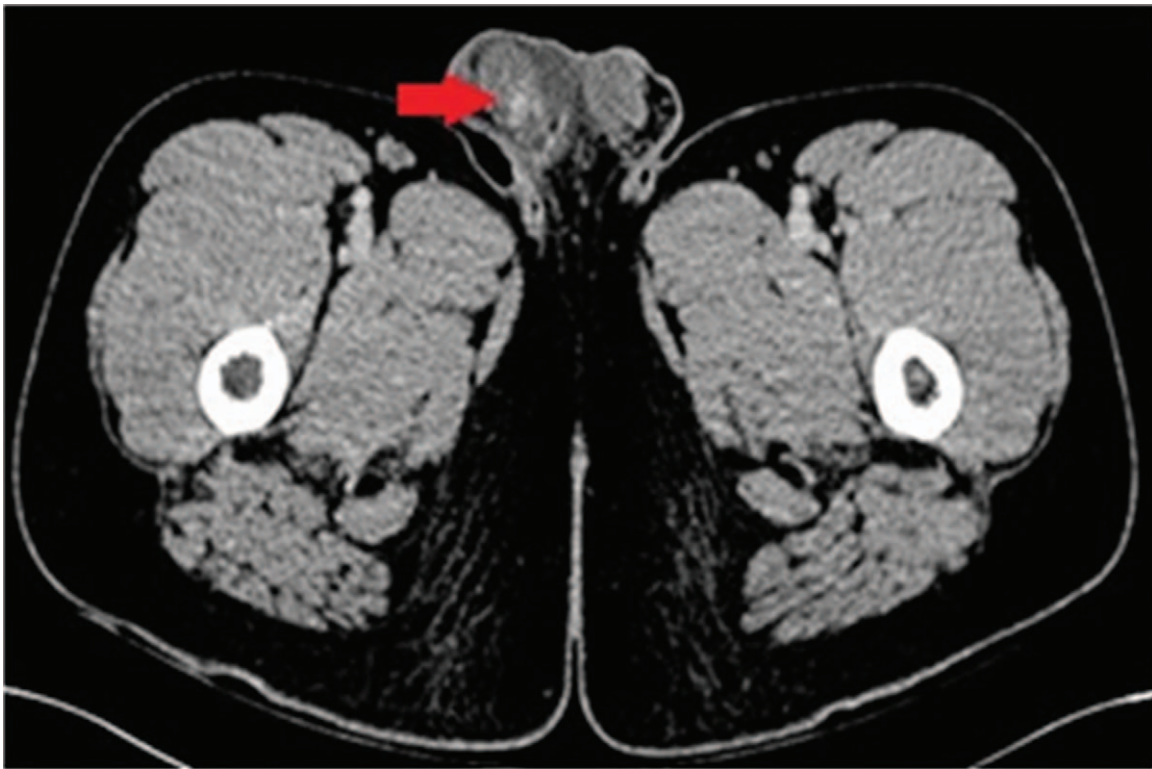


Figure 3. Abdominal enhanced CT showed right TT. TT=testicular tumor.

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 hypercoagulable 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 ^[4]	22	Right	TT metastasis	Surgery + chemotherapy	Dyspnea	Tumoral thrombi	Intravenous heparin, and a surgical embolectomy	Improve	
2	Lederman GS/1987 ^[5]	30	NA	NA	Surgery + chemotherapy	Cardiovascular collapse	Thrombi-embolism	PE found at autopsy	Died of PE	PE occurred after cisplatin based chemotherapy
3	Lederman GS/1987 ^[5]	31	NA	NA	Chemotherapy	Pleuritic chest pain, severe shortness of breath and hemoptysis	NA	Anticoagulation therapy	Improve	PE occurred after cisplatin based chemotherapy
4	Stockler M/1991 ^[6]	17	Right	TT	Surgery + chemotherapy	NA	NA	Heparin then warfarin	Improve	PE occurred after cisplatin based chemotherapy
5	Stockler M/1991 ^[6]	44	right	TT metastasis	Surgery	Collapsed	Tumoral emboli	PE found at autopsy	Died of PE	
6	Stockler M/1991 ^[6]	30	Right	Collapse	Chemotherapy + surgery	Collapsed	Thrombi	Thoracotomy + emboli removing, heparin then warfarin	Improve	
7	Kwok CK/1993 ^[2]	40	Right	PE	Surgery + Chemotherapy	Dyspnea, chest tightness and thoracic back pain	NA	Anticoagulation therapy	Improve	
8	Dada MA/1995 ^[7]	37	Right	PE	None	Back pain	Partial malignant cells	PE found at autopsy	Sudden death of PE	
9	Karila-Cohen D/1995 ^[8]	35	Right	PE	Surgery + chemotherapy	Acute dyspnea	Choriocarcinoma and a fibrinous thrombus	Thrombolysis then heparine	Improve	
10	HaabF/1996 ^[9]	35	NA	PE	Surgery + chemotherapy	NA	NA	Surgical thrombectomy	Improve	
11	Leslie JA/2003 ^[10]	30	Right	PE	Surgery + chemotherapy	Shortness of breath	NA	Anticoagulation therapy	Improve	
12	Akamatsu S/2004 ^[11]	21	Right	TT	Surgery + chemotherapy	Sudden dyspnoea	NA	Thrombolysis	Improve	PE occurred after cisplatin based chemotherapy
13	Huwer H/2004 ^[12]	39	Right	PE	Surgery + chemotherapy	Retrosternal pain and dyspnea	Thrombi	Urgent surgery of thrombi removing	Improve	
14	Barton SJ/2005 ^[13]	21	Right	PE	Chemotherapy + surgery	Chest pain and shortness of breath	NA	Low molecular weight heparin	Improve	
15	Hoshino A/2006 ^[14]	40	NA	TT	Surgery + chemotherapy	Dyspnoea	Thrombi-embolism	Thrombolysis	Died of PE	
16	May M/2006 ^[15]	42	Left	TT	Surgery + chemotherapy	Left-sided thoracic pain	Tumoral thrombi	Anticoagulation therapy	Improve	
17	Ramesh Batra/2009 ^[16]	36	Left	NA	Surgery + chemotherapy	NA	NA	Warfarin	Improve	PE occur after cisplatin based chemotherapy
18	Talra S/2009 ^[17]	49	Right	PE	Chemotherapy + surgery	Shortness of breath	Tumoral thrombi	NA	NA	
19	Miskovska V/2010 ^[18]	49	Right	NA	Surgery + chemotherapy	Right hemithorax pain and dyspnoea	NA	Low molecular weight heparin	Improve	PE occurred after cisplatin based chemotherapy
20	Singh RK/2013 ^[19]	20	Right	PE	Chemotherapy + surgery	Chest pain, cough	NA	Low molecular weight heparin	Improve	
21	Ilhami Berber/2013 ^[20]	25	Left	PE	Surgery	Right chest pain and dyspnoea	NA	Enoxaparin and warfarin then warfarin	NA	
22	Marie Dusaud/2015 ^[21]	45	left	TT	Surgery + chemotherapy	NA	NA	Anticoagulation therapy	Improve	
23	do Nascimento FB/2016 ^[22]	31	Left	TT	Surgery + Chemotherapy	NA	Tumoral thrombi	NA	died of PE	
24	Rosenfield K/2016 ^[23]	29	Right	PE	Surgery + chemotherapy	Dyspnoea and right chest pain	Tumoral thrombi	Heparin	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.

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