Case Report: iMDT Corner

# Chordoma combined with Trousseau syndrome: a case report and literature review

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**Background:** Trousseau syndrome (TS) refers to spontaneous, recurrent, and wandering arterial and venous thromboembolic events in patients with tumors. It results from abnormalities in coagulation and fibrinolytic mechanisms of varying degrees throughout the course of the disease. It has a high fatality rate, and it is commonly seen in patients with highly invasive tumors, such as lung, pancreatic, gastrointestinal, and breast cancers; however, to date, there has been no report of TS combined with chordoma.

**Case Description:** A 56-year-old male with a diagnosis of chordoma underwent surgery, immunotherapy, immunotherapy combined with antiangiogenic therapy, chemotherapy combined with immunotherapy, and proton therapy for localized metastases. Subsequent to the worsening of chest tightness, a repeat chest computed tomography angiography (CTA) scan suggested pulmonary artery embolisms; eventually, a diagnosis of TS was made. After anticoagulation and synchronized antitumor therapy, the patient's condition remained recurrent, eventually leading to death.

**Conclusions:** TS is a frequent but easily overlooked clinical complication that can occur in a variety of tumors, including chordoma, and is currently diagnosed clinically. Thus, further exploration of its sensitive markers is needed. We have reported a case of chordoma combined with TS and conducted a literature review on TS to increase clinicians' awareness of tumor-related thromboembolism and explore strategies to optimize the diagnosis, treatment, and prevention of TS.

**Keywords:** Trousseau syndrome (TS); venous thrombosis; pulmonary embolism (PE); chordoma; case report

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## Introduction

Trousseau syndrome (TS), the equivalent of cancer-associated thrombosis, is the second leading cause of death in cancer patients, after cancer itself (1). Studies have shown that patients with malignant tumors have a 7-fold increased overall risk of venous thrombosis than those with non-malignant tumors (2), and approximately 15% of patients with tumors experience a thromboembolic event during treatment (3). TS is most commonly seen in patients with highly aggressive tumors, such as lung, pancreatic, breast, and colon cancers, and is usually associated with mucin-producing cancers (4).

The pathogenesis, diagnostic methods, and survival prognosis of TS have not been unanimously determined. Herein, we report for the first time a case of chordoma combined with TS. We also conducted a meta-analysis of the diagnosis and treatment of TS to increase clinicians' awareness of tumor-related thromboembolism and explore anticoagulation treatment strategies. We present this article in accordance with the CARE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1232/rc).

### Highlight box

**Key findings**

- This is the first report of a case of chordoma combined with Trousseau syndrome (TS). A literature review of TS was also conducted.

**What is known and what is new?**

- TS refers to spontaneous, recurrent, and wandering arterial and venous thromboembolic events in patients with tumors that result from abnormalities in coagulation and fibrinolytic mechanisms of varying degrees during the course of the disease. It has a high fatality rate, and is commonly seen in patients with highly invasive tumors, such as lung, pancreatic, gastrointestinal, and breast cancers; however, there has been no previous report of TS combined with chordoma.
- TS is a frequent but easily overlooked clinical complication that can occur in a variety of tumors, including chordoma, which is currently diagnosed clinically.

**What is the implication, and what should change now?**

- We need to raise awareness of TS, particularly emphasizing the importance of early diagnosis and treatment for cancer patients. Early diagnosis and treatment are key factors in preventing the deterioration of TS. Additionally, prevention, diagnosis, and treatment, mainly anticoagulation and related tumor therapies, could help to improve the prognosis of patients with TS.

## Case presentation

A 56-year-old male patient underwent lumbar magnetic resonance imaging (MRI) for what appeared to be lumbosacral pain in October 2017. The results suggested a sacral occupation. He subsequently underwent resection for sacrococcygeal tumor, the postoperative pathology of which showed a sacrococcygeal tumor, Ki-67 5%, CK7(–), CK20(–), CK8/18(–), GFAP(–), EMA(+), Vimentin(+), S100(weak+), and CD10(–) with S100(–), E-cadherin(–), E-cadherin missing, and N-cadherin overexpressed. A diagnosis of chordoma was made. A follow-up examination in August 2018 indicated lung metastasis, and genetic testing suggested that the *PBRM1* gene was mutated and there was an amino acid change of A1209fs. The patient was treated with immunotherapy, immunotherapy combined with anti-angiogenic therapy, chemotherapy combined with immunotherapy, and proton therapy for localized metastases.

An overview of the patient's treatment is shown in *Figure 1*. In March 2023, due to a worsening of chest tightness, a chest computed tomography angiography (CTA) scan was performed (*Figure 2A*) that showed multiple filling defects in the left pulmonary artery, indicating pulmonary embolism (PE). A positron emission tomography/computed tomography (PET/CT) examination showed that the lymph nodes of the hilar region of both lungs, bones, and adrenal glands had high levels of anomalous metabolism, which were considered indicative of tumor progression (progressive disease). On 23 March 2023, the patient was scheduled to commence oral rivaroxaban (20 mg, 1/day) anticoagulant therapy in parallel with antitumor therapy. On 23 March 2023, the patient's pulmonary artery CTA (*Figure 2B*) was repeated, the PE had filled up, and the patient had a TS Composite Score (5) of 3 (infarcts in multiple vascularized areas: 2; active tumor: 1), and a Khorana Score of 1 (infarcts in multiple vascularized areas: 1) (6).

According to the National Comprehensive Cancer Network (NCCN) guidelines (7) and the American Society of Clinical Oncology (ASCO) study (8), the treatment regimen was changed to naltrexone heparin (0.6 mL, 1/day) via subcutaneous injection in the morning. The patient underwent proton radiotherapy to the left pulmonary artery from April 2023 to May 2023. A follow-up CTA of the pulmonary artery performed in June 2023 (*Figure 2C*) showed that the PE had stabilized. The patient continued to receive anticoagulant therapy with naltrexone heparin.

On 13 October 2023, because of a worsening shortness

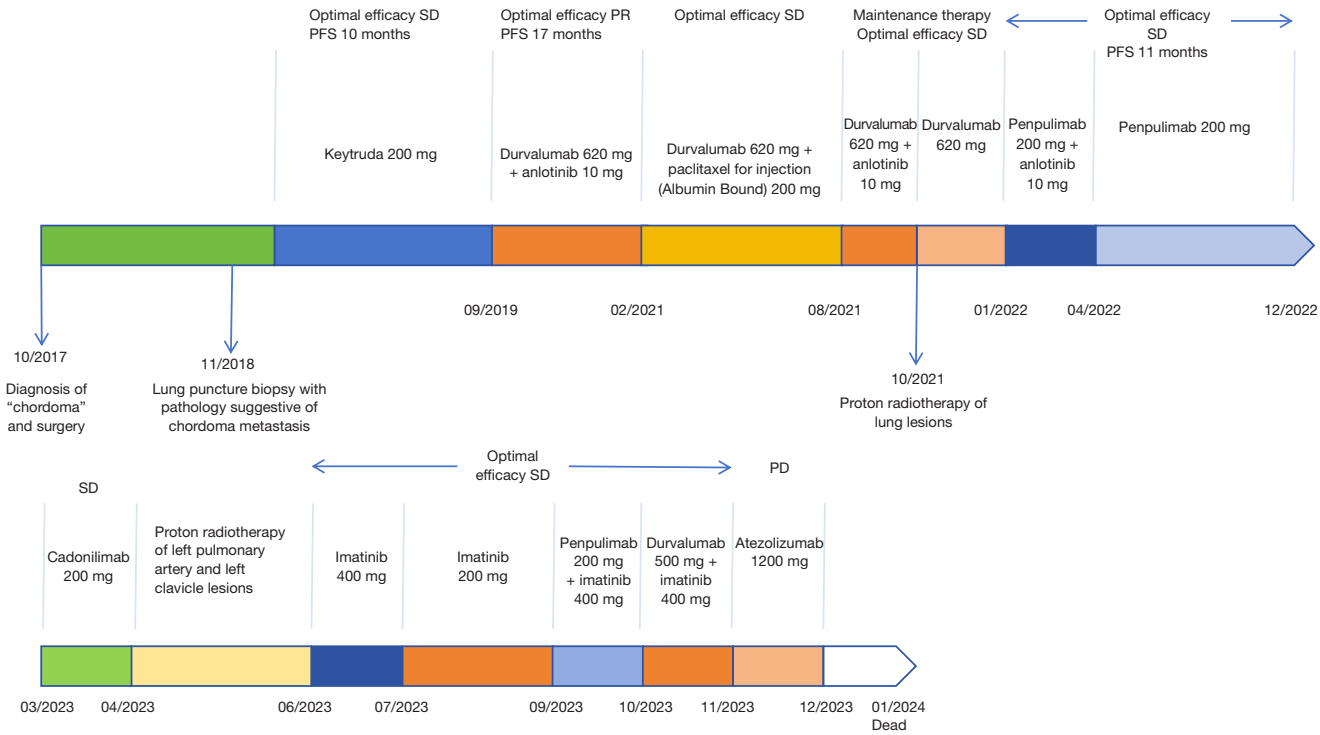


**Figure 1** List of prior treatments. SD, stable disease; PR, partial response; PFS, progression-free survival; PD, progressive disease.

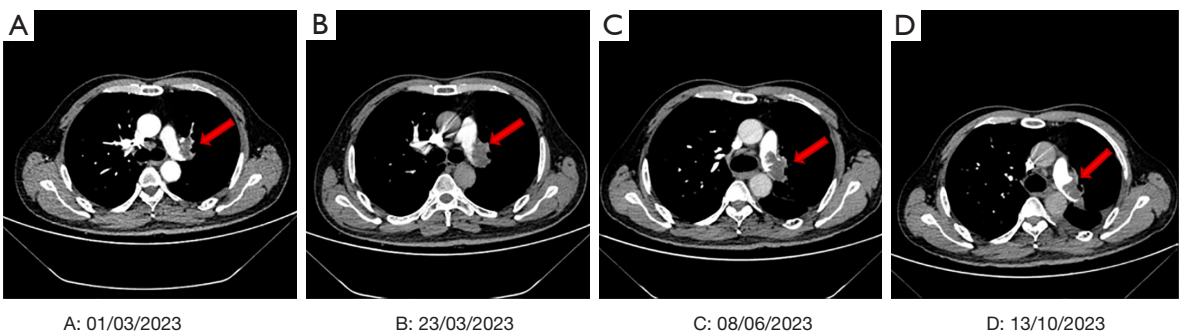


**Figure 2** CTA pulmonary angiography of patient. (A) CTA shows a nodular filling defect in the main trunk of the left pulmonary artery. (B,C) The filling defect is still visible in the main trunk of the left pulmonary artery, which has progressed from the previous one. (D) The filling defect shadow in the trunk of the left pulmonary aorta has narrowed and improved from the previous one. The left pulmonary aortic trunk has a better filling defect shadow than the previous one. Red arrows indicate the location of the thrombus. CTA, computed tomography angiography.

of breath and fluctuating oxygen saturation of 88–93% under nasal cannula oxygenation, a follow-up CTA of the pulmonary arteries (*Figure 2D*) was conducted, revealing multiple irregular filling defects of the left pulmonary arterial trunk and its branches, as well as the right pulmonary arterial branches, which were indicative of PE. A diagnosis of PE was considered, with the right-side lesion having progressed and the left side lesion having improved compared to the previous scan.

At the same time as synchronous anticoagulation, the patient received antitumor treatment with atilizumab, and the Department of Radiotherapy was consulted about the patient. It was recommended that proton therapy of the right lung lesion be carried out again, which the patient

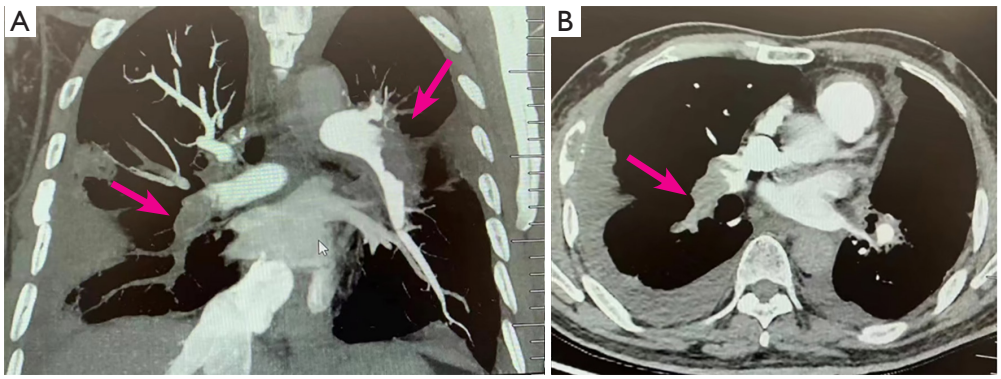


**Figure 3** 01/2024 pulmonary artery CTA. (A) Coronal view shows filling defects in both the right and left pulmonary arteries. (B) Axial view shows filling defects in the right pulmonary trunk and its branches. Red arrows indicate the location of the thrombus. CTA, computed tomography angiography.

refused. His activity endurance gradually deteriorated, and the CTA of the pulmonary artery was reviewed in January 2024 by another hospital (*Figure 3*), which suggested the following: complete embolism of the right middle and lower pulmonary arteries and their branches; left distal pulmonary artery trunk, left upper pulmonary artery branch, and left upper pulmonary artery branch, distal pulmonary trunk, left upper and lower pulmonary arteries and their branches, right upper pulmonary posterior dissection, and multiple incomplete PEs in the anterior pulmonary arteries; multiple solid lesions in both lungs, which were considered pulmonary infarction.

Given that the interventional therapy could not produce any survival benefits, the patient returned to our hospital to continue supportive treatment. The patient died on 16 January 2024, after a progressive decrease in oxygen saturation.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## International Multidisciplinary Team (iMDT) discussion

### *Definition of TS*

TS is a paraneoplastic syndrome that occurs in patients with malignant tumors due to hypercoagulability, which is equivalent to cancer-related thrombosis (1). In 1865, Trousseau first suggested that patients with gastric cancer were prone to venous thrombosis (9). All clinical manifestations of malignant tumors that occur in patients during their pathogenesis due to abnormalities in coagulation and fibrinolytic mechanisms have since been collectively referred to as TS. TS is characterized by venous thromboembolism (VTE), including deep vein thrombosis, and PE, chronic disseminated intravascular coagulation (DIC) combined with non-bacterial infective thrombotic endocarditis (NBTE), and arterial thromboembolism (ATE) formation, of which VTE is the most common clinical manifestation of cancer-associated thrombosis, with an incidence of 4–20% (2).

### *Current status of TS*

Results from the Global Registry of Anticoagulant Drugs (GARFIELD)-VTE Registry reported that 10,315 patients with VTE from 419 centers in 28 countries had an overall mortality rate within 6 months of 9.7%, with 54.3% of these deaths attributed to cancer (10). A study has shown that the primary site of the tumor is a risk factor for VTE (11). In a study of more than 1 million cancer hospitalizations, the incidence of VTE increased by 28% from 1995 to 2003, with an overall prevalence of 4.1%, and the cancer sites with the highest rates of VTE included the pancreas (8.1%), kidneys (5.6%), ovaries (5.6%), lungs (5.1%), and stomach (4.9%) (12). In several studies (13-15), we have found (*Table 1*) that although the specific incidence of VTE may vary depending on the clinical situation, patients with

**Table 1** Incidence of VTE in each tumor

| First author | Type of study | No. of patients | Cancer setting | VTE incidence (IR/%) | Median follow-up | Death rate (cancer-related VTE) (IR/%) |
|---|---|---|---|---|---|---|
| Crobach (13) [IR (95% CI) per 100 py] | Cohort study | 144,952 | Cancer | 4.8 (4.7–4.9) | Cancer diagnosis to VTE diagnosis 1.2 years. VTE diagnosis to death 0.7 years | 45.3 (41.1–50.0) |
| | | | Lung | 7.4 (6.9–7.8) | | 112.0 (89.5–140.0) |
| | | | Colorectal | 3.6 (3.4–3.9) | | 32.8 (24.8–43.3) |
| | | | Upper GI | 8.1 (7.3–8.9) | | 53.6 (33.7–85.0) |
| | | | Pancreas | 8.0 (7.1–8.7) | | 197.0 (134.1–289.3) |
| | | | Breast | 1.2 (1.1–1.3) | | 26.0 (18.0–37.7) |
| | | | Prostate | 2.0 (1.9–2.1) | | 28.7 (20.9–39.5) |
| | | | Bladder | 3.3 (2.9–3.8) | | 59.7 (39.3–90.7) |
| | | | Uterus | 1.7 (1.4–2.1) | | 50.6 (27.2–94.0) |
| | | | Cervix | 2.7 (2.0–3.7) | | NA |
| | | | Ovary | 5.6 (4.8–6.4) | | 98.6 (57.2–169.8) |
| | | | Kidney | 4.4 (3.8–5.1) | | 34.4 (20.8–57.1) |
| Khorana (12) | Retrospective cohort study | 1,015,598 | Cancer | 4.1% | NA | 16.3% |
| | | | Lung | 5.1% | | |
| | | | Breast | 2.3% | | |
| | | | Esophagus | 4.3% | | |
| | | | Stomach | 4.9% | | |
| | | | Pancreas | 8.1% | | |
| | | | Colon | 4.0% | | |
| | | | Rectum | 3.5% | | |
| | | | Other abdominal | 6.6% | | |
| | | | Ovary | 5.6% | | |
| | | | Endometrium and cervix | 3.5% | | |
| | | | Bladder | 2.9% | | |
| | | | Kidney | 5.6% | | |
| | | | Prostate | 1.9% | | |
| | | | Testes | 3.3% | | |
| | | | Brain | 4.7% | | |
| | | | Head and neck | 1.4% | | |
| | | | Sarcoma | 2.9% | | |
| | | | NHL | 4.8% | | |
| | | | HL | 4.6% | | |
| | | | Myeloma | 5.0% | | |
| | | | Leukemia | 4.2% | | |
| | | | Multiple sites | 5.1% | | |
| | | | Other sites | 4.5% | | |

**Table 1** (*continued*)

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| First author | Type of study | No. of patients | Cancer setting | VTE incidence (IR/%) | Median follow-up | Death rate (cancer-related VTE) (IR/%) |
|---|---|---|---|---|---|---|
| Mulder (14) [6 mo after cancer diagnosis, cumulative incidence (95% CI)] | Cohort study | 499,092 | Cancer | 1.69 (1.66–1.73) | NA | NA |
| | | | Pancreatic | 4.43 (4.12–4.76) | | |
| | | | Ovarian | 3.10 (2.78–3.44) | | |
| | | | Biliary | 2.90 (2.31–3.60) | | |
| | | | HL | 2.88 (2.27–3.61) | | |
| | | | MM | 2.84 (2.46–3.26) | | |
| | | | Liver | 2.82 (2.42–3.26) | | |
| | | | NHL | 2.66 (2.43–2.90) | | |
| | | | NSCLC | 2.60 (2.48–2.73) | | |
| | | | Stomach | 2.48 (2.19–2.80) | | |
| | | | Colon | 2.21 (2.09–2.34) | | |
| | | | Brain | 2.18 (1.88–2.51) | | |
| | | | Kidney | 2.17 (1.92–2.44) | | |
| | | | Esophageal | 2.16 (1.86–2.50) | | |
| | | | Rectal | 2.07 (1.90–2.25) | | |
| | | | Bladder | 1.66 (1.47–1.87) | | |
| | | | SCLC | 1.50 (1.29–1.73) | | |
| | | | Cervical | 1.49 (1.24–1.79) | | |
| | | | Uterine | 1.43 (1.24–1.65) | | |
| | | | Leukemia | 1.27 (1.10–1.47) | | |
| | | | Prostate | 0.80 (0.73–0.87) | | |
| | | | Testicular | 0.80 (0.60–1.05) | | |
| | | | Breast | 0.64 (0.59–0.70) | | |
| | | | Melanoma | 0.36 (0.30–0.43) | | |
| Khorana (15) | Retrospectively | 1,700,000 | Cancer | 6.2% | Cancer diagnosis to VTE diagnosis 181 days | NA |
| | | | Lung | 12.6% | | |
| | | | Breast | 4.2% | | |
| | | | Prostate | 4.1% | | |
| | | | Stomach | 12.1% | | |
| | | | Colon/rectum | 8.3% | | |
| | | | Pancreatic | 17.5% | | |
| | | | Genitourinary | 5.9% | | |
| | | | Gynecologic | 8.2% | | |
| | | | Brain | 10.9% | | |

IR, incidence rate; CI, confidence interval; py, person-years; mo, months; Upper GI, upper gastrointestinal; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; NSCLC, non-small cell lung carcinoma; SCLC, small-cell lung carcinoma; VTE, venous thromboembolic event; NA, unknown.

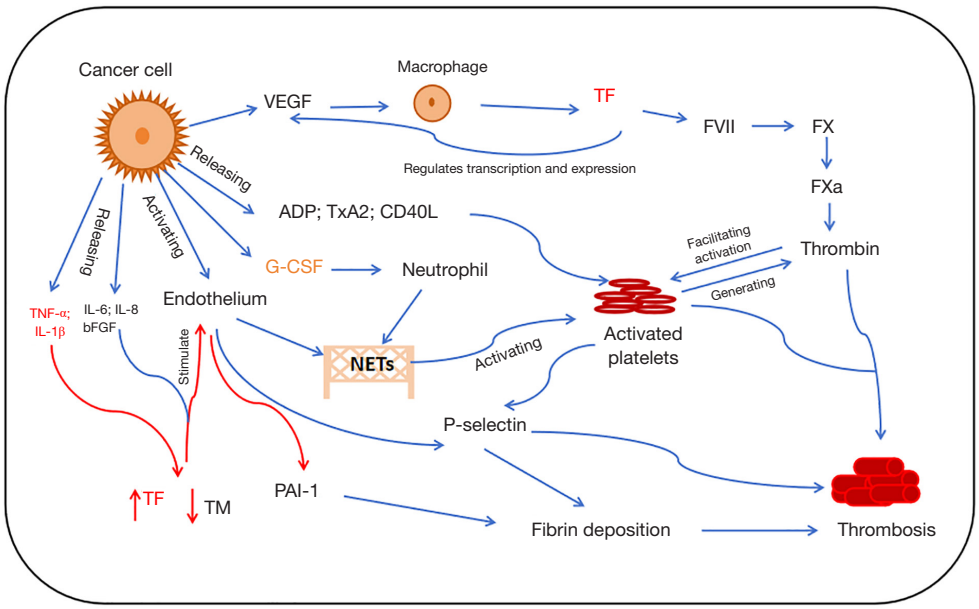


**Figure 4** Mechanisms associated with Trousseau syndrome. Mechanisms of tumor-associated thrombosis include activation of coagulation, dysregulation of the fibrinolytic system, inflammation, and cytokine production. TF is a procoagulant protein that initiates the extrinsic pathway of the coagulation cascade by forming a complex with coagulation factor VII, which promotes the activation of coagulation factor X and the formation of coagulation factor Xa. Tumor cells release platelet-activating factors such as ADP, TxA2, and CD40L, which activate vascular endothelial cells. Activated neutrophils form NETs, while circulating G-CSF in tumor patients increases the number of neutrophils and induces their activation, which promotes NET formation. Additionally, soluble mediators released from tumor cells, including TNF-α, IL-1β, IL-6, IL-8, and bFGF, can stimulate vascular endothelial cells to generate NETs. Histones in NETs activate platelets to generate thrombin, which promotes thrombosis. TNF-α and IL-1β can upregulate TF and downregulate TM, stimulating endothelial cells to produce the fibrinolytic inhibitor PAI-1, which promotes fibrin deposition and thrombosis. P-selectin, an important cell adhesion molecule expressed by stimulated endothelial cells and activated platelets, mediates the aggregation of activated platelets with cancer cells, as well as the adhesion of cancer cells to stimulated endothelial cells and the intercellular transfer of activated platelets with procoagulant MPs, promoting fibrin deposition and microthrombosis. TNF-α, tumor necrosis factor α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; ADP, adenosine diphosphate; TxA2, thromboxane A2; CD40L, platelet-derived CD40 ligand; G-CSF, granulocyte colony-stimulating factor; TF, tissue factor; FVII, factor VII; FX, coagulation factor X; FXa, coagulation factor Xa; NETs, neutrophil extracellular traps; TM, thrombomodulin; PAI-1, plasminogen activator inhibitor-1.

pancreatic, gastric, uterine, ovarian, renal, lung, and primary brain tumors have the highest rates of VTE. Compared with patients with cancer alone, patients with a combination of cancers with VTE had an increased risk of death, with pancreatic, lung, and upper gastrointestinal tract cancers having the highest risk. In this case, multiple PEs occurred simultaneously and in multiple branches of the pulmonary artery. There was no compression or stenosis of the arterial wall caused by infiltration of metastatic lesions or tumor masses in the proximal pulmonary arterial branch, so arteriogenic embolism could be excluded. Meanwhile, the patient was evaluated as having a TS Composite Score of 3, making this is the first reported case of chordoma combined with TS in a patient.

### *Mechanisms associated with TS*

The pathogenesis of TS is complex (*Figure 4*) with diverse etiologies. First, tumor cells can promote blood hypercoagulation and activate coagulation by promoting tissue factor (TF) expression, inflammatory mediator release, and multiple mechanisms associated with cancer pro-coagulation (16). Additionally, the presence of an inflammatory response in the host, such as monocyte TF

expression, factor VII, and elevated levels of fibrinogen, are important factors influencing the hypercoagulable state of malignant tumors (3). The treatments received by tumor patients, such as surgery, chemotherapy, and radiotherapy, also affect the coagulation function radicalization to a certain extent. Further, platelets are activated in oncology patients because venous thrombosis is caused by the hypercoagulability of the blood, blood flow vortex, and stasis, and the activation of endothelial cells (17). Malignancy increases the coagulation cascade reaction and platelet activation, with appositionally activated platelets releasing procoagulant agents, which further promotes fibrin deposition and microthrombosis (18). In addition, age, gender, a previous history of thrombosis, comorbidities, such as anemia, renal and hepatic impairment, and sepsis, are influential factors in the hypercoagulable state of cancer patients (19). However, in this case, our patient had no previous history of thrombosis and had not developed any of the aforementioned complications.

### *Diagnosis of TS*

The clinical manifestations of TS are diverse and can manifest as wandering phlebitis, PE, cerebral embolism, myocardial infarction, and diffuse intravascular coagulation. However, there are no clear criteria for the diagnosis of TS, which makes the diagnosis and treatment of clinical tumor-related thromboembolism difficult. The current diagnosis of TS is mainly based on the presence of multifocal simultaneous high-intensity lesions on diffusion-weighted MRI and hypercoagulability suggested by elevated levels of D-dimer in the acute phase (20). Ito *et al.* (21) found that serial D-dimer levels may be a good biomarker for TS as well as a useful predictor of the prognosis of TS patients. Elderly patients with unexplained D-dimer elevation, multiple cerebral vascular lesions detected on MRI, and an absence of typical stroke risk factors need to be monitored for TS (22). However, this case did not exhibit multiple cerebral embolisms or elevated D-dimer levels. However, the simultaneous multiple cerebral embolisms in multiple cerebral artery territories and the persistent elevated D-dimer level, which are usually very useful for diagnosing Trousseau's syndrome, may not be diagnostic biomarkers for multiple embolisms caused by chordoma. Therefore, there are also limitations in the efficacy of D-dimer detection, which makes accurate diagnosis and treatment difficult.

Shi *et al.* (23) analyzed the multicellular ecosystem of venous tumor thrombus in renal cell carcinoma (RCC) by single-cell RNA sequencing and found phenotypic heterogeneity of the primary tumors and tumor thrombus in terms of the tumor cells, immune cells, and stromal cells, which extended understandings of the mechanisms related to tumor thrombus, and helped to develop more effective neoadjuvant molecular therapies and biomarkers for patients with advanced clear cell RCC. Single-cell sequencing methods might be able to be used to explore the mechanisms of thrombosis in tumor patients and identify specific markers to provide faster and more favorable support for the diagnosis of TS.

### *Treatment of TS*

The NCCN guidelines and ASCO reports indicate that the conventional treatment for TS is preferred to anticoagulation therapy and aggressive treatment of the primary tumor. However, the prognosis of TS patients is poor, and a study has reported that the mortality rate of cancer-related stroke is as high as 25–30% (24). In oncology patients, the long-term management of cancer thrombosis, which frequently recurs, is particularly important. Current pharmacological options for VTE treatment and prophylaxis include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), sodium sulphadoxine (an indirect synthesis inhibitor of activated factor Xa), vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs), including direct thrombin inhibitors and direct factor Xa inhibitors (e.g., rivaroxaban) (25). A meta-analysis (26) that included 7 randomized controlled trials showed that LMWH produced no statistically significant survival benefit compared with VKAs [hazard ratio (HR) =0.96; 95% confidence interval (CI): 0.81–1.14], but a statistically significant reduction was observed in VTE (HR =0.47, 95% CI: 0.32–0.71). In a review that included 12,352 cancer outpatients receiving chemotherapy (27), compared with a placebo, LMWH was associated with a significant reduction in VTE recurrence [relative risk (RR) =0.54, 95% CI: 0.38–0.75], but an increased risk of major bleeding (RR =1.44, 95% CI: 0.98–2.11). However, there was no significant difference in 1-year mortality between the two groups (RR =1.02, 95% CI: 0.96–1.08). Therefore, current clinical practice guidelines do not recommend routine thromboprophylaxis for outpatient cancer patients.

A meta-analysis that included nine clinical studies involving a total of 1,952 patients showed that the rates of VTE recurrence were 5.4% and 5.9%, and the rates of hemorrhage were 10.8% and 11% in cancer patients

 

receiving DOCAs and conventional therapy (heparin/VKA), respectively. The patients who received DOCAs had a higher rate of bleeding than those who received LMWH (odds ratio =2.72, 95% CI: 1.05–7.01, P=0.04) (28). A meta-analysis of 12 studies with 4,720 patients (29) showed no significant difference in VTE recurrence in patients treated with LMWH compared to those treated with DOACs (RR =1.3, 95% CI: 0.91–2.0), but significantly fewer VTE recurrences were observed in patients treated with both LMWH and DOACs compared to those treated with VKAs. There was no significant difference in the incidence of major bleeding among the DOAC, LMWH, and VKA groups with rates of 4.9%, 4.3%, and 4.1%, respectively. Another meta-analysis (30) showed that in the initial treatment of VTE in cancer patients, LMWH reduced mortality and might reduce VTE recurrence compared with UFH.

With the lower efficacy and higher recurrence rates of warfarin, DOACs have emerged as a superior alternative to warfarin in some cases (31). DOACs have been shown to have more predictable and reliable pharmacologic evidence, and frequent monitoring of anticoagulation is not required. Novel oral anticoagulants that directly inhibit factor Xa or thrombin are expected to be used in the prevention of high-risk cancer patients and in the long-term treatment of VTE; however, more clinical evidence is needed to support the use of these anticoagulants.

In our TS patient, VTE was mainly manifested by PE. For the anticoagulation of cancer-related VTE, LMWH anticoagulation is the preferred method recommended by international guidelines (32). The ASCO guidelines recommend the use of LMWH over UFH in patients with good renal function (8). For the initial treatment of VTE in cancer patients, the American Society of Hematology (ASH) guidelines (25) recommend the use of LMWH rather than plain heparin; for the short-term treatment of VTE in patients with active cancer (3–6 months), the guidelines suggest that LMWH is preferable to VKA, whereas for the long-term anticoagulation treatment (>6 months) of VTE in patients with active cancer, the guidelines recommend DOAC or LMWH. Meanwhile, the 2022 International Initiative on Thrombosis in Cancer (ITAC) Clinical Practice Guidelines (33) also recommend LMWH as the standard anticoagulation therapy for the first 3 months after diagnosis of VTE.

### *Discussion among physicians from the 900th Hospital, Joint Logistic Support Force, People's Liberation Army of China*

#### Respiratory Department

***Aggressive tumor treatment***

Given the signs of tumor progression, it is recommended to continue intensifying antitumor therapy, such as targeted therapy, immunotherapy, and combined radiotherapy. The treatment plan should be further adjusted based on the patient's specific genetic mutations to slow down tumor progression. Close attention should be paid to the patient's tolerance to the current antitumor treatment, especially considering the worsening PE and respiratory symptoms, to ensure that the treatment does not exacerbate the patient's respiratory burden.

***Aggressive anticoagulation for PE***

Given the patient's history of recurrent PE, it is necessary to continue and possibly intensify anticoagulant therapy. Low molecular weight heparin is currently in use; however, the anticoagulation strategy should be adjusted according to the disease progression. Consideration should be given to combining other anticoagulant drugs or thrombolytic therapy to reduce the pulmonary arterial thrombus load. Regular pulmonary artery CTA follow-up is advised to monitor changes in embolism and ensure the effectiveness of anticoagulant therapy.

***Respiratory support and management***

As the patient's condition worsens and oxygen saturation decreases, it is recommended to escalate respiratory support. Transitioning from low-flow oxygen therapy to high-flow nasal cannula oxygen therapy, or even non-invasive positive pressure ventilation (NIV), should be considered to improve gas exchange. If the patient's respiratory failure continues to worsen, preparation for escalation to intubation and mechanical ventilation should be made, with careful consideration of the patient's overall prognosis and disease progression.

***Comprehensive symptom management and palliative care***

For cancer patients experiencing symptoms such as chest tightness and shortness of breath, appropriate pharmacological and non-pharmacological therapies should be used to improve the patient's quality of life. Given the patient's prognosis and disease progression, it is important to enhance humane care and prioritize palliative care,

ensuring the patient's comfort in the late stages of the disease.

**Interventional Department**

Considering the extensive PE and recurrent embolism, the benefits of interventional therapy may be limited. It is recommended to prioritize non-interventional conservative treatment options, such as optimizing anticoagulant therapy and strengthening respiratory support. By adjusting the types and dosages of anticoagulants, efforts should be made to reduce the pulmonary arterial thrombus load as much as possible, while closely monitoring the progression of the embolism. An individualized treatment plan should be developed, taking into account the patient's overall condition, tumor progression, and the severity of PE. Combining anticoagulant drugs with other supportive therapies may be considered to improve the patient's quality of life and survival time. Continuous assessment of the disease's evolution is necessary, and if new therapeutic opportunities or technological advancements arise, the feasibility of interventional therapy should be reevaluated.

This case is complex with multiple coexisting conditions, requiring a joint effort from the Respiratory and Interventional Departments to formulate a personalized treatment plan aimed at extending the patient's survival time and improving their quality of life. Careful consideration must be given to balancing anticoagulant therapy, pulmonary symptom management, and interventional therapy to achieve the best possible treatment outcomes.

***Several issues on the treatment of these patients were further discussed as follows***

We have reported on TS with multiple PE as the main feature; however, TS with cerebral infarction is now more commonly reported, so we discussed some of the current issues with Shinji Ito and Tatsuro Mutoh online. The contents are as follows.

(I) Should patients with tumor-combined TS be treated with conventional thrombolytic and anticoagulation therapy or is a more aggressive anticoagulation regimen needed?

Shinji Ito and Tatsuro Mutoh: If "conventional thrombolytic therapy" includes usage of t-PA, it is applicable in the hyperacute phase of multiple cerebral infarction in the cases where t-PA is surely indicated. However, the thrombolytic therapy should be exercised with caution if the tumor itself has a high risk of bleeding. Anticoagulation therapy must be considered separately for the acute phase and for preventing recurrence. In the acute phase, continuous intravenous infusion of heparin is recommended. Regarding the prevention of recurrence, some reliable clinical studies (34-36) have reported that subcutaneous injection of LMWH is the standard. Meanwhile, considering the pain, local bleeding, and initiative of the patients, several studies (37-41) have been conducted comparing oral administration of DOAC, which has a higher adherence, with subcutaneous injection of LMWH, but unfortunately the superiority of DOAC has not been validated. If consent from the patient and family is obtained, and there are no issues of burden of medical expenses, or side effects such as bleeding complications or HIT, heparin should be selected rather than oral administration of DOAC or warfarin at this time. In our opinion, DOAC is the next best option. If there is a possibility of shrinking or treating the primary cancer, it could be a positive indication.

(II) How can we better assess the risk of bleeding and thrombotic progression in patients with tumor-combined TS?

Shinji Ito and Tatsuro Mutoh: Based on our previous study (21,42) and review (43), we recommend monitoring serial D-dimer. D-dimer values at the onset not only correlate with the risk of cerebral infarction, but also reflect the progression of the tumor and are a predictor of life prognosis. Furthermore, the subacute D-dimer value 7–28 days after onset reflects the effectiveness of anticoagulant therapy, and if the subacute value is clearly lower than the acute value, it suggests that the risk of recurrent cerebral infarction has been temporarily reduced. However, if treatment of the primary cancer is ineffective and the tumor will be tending to grow, the D-dimer value will increase continuously, or will decrease temporarily but then rise again, correlating with the increasing of the D-dimer value and further increasing the risk of cerebral infarction. The risk of primary brain hemorrhage increases with DIC and is associated with more advanced cancer. Secondary hemorrhage associated with cerebral infarction (hemorrhagic infarction) associated with infarction is more likely

 

to occur and is more massive hemorrhage with the larger the infarct.

In addition, the D-dimer was not elevated in this case, it may be related to the fact that the primary lesion was chordoma and not mucin-producing adenocarcinoma. Among the cancer-related multiple embolisms collectively known as TS, there would be subgroups that are caused by mucin-producing adenocarcinoma and, as in the case presented here, those that are caused by non-adenocarcinoma. The possibility that the diagnostic markers and treatment methods may differ among those subgroups is an important issue that remains to be elucidated.

(III) What difficulties and considerations could arise in the treatment of patients with advanced tumors combined with TS?

Shinji Ito and Tatsuro Mutoh: Depending on the symptoms of cerebral infarction, if the performance status of cancer declines due to the onset of cerebral infarction, the doctor in charge of cancer treatment may reduce the treatment. In addition, regular intravenous administration of anticancer drugs may be discontinued if the patient has motor impairments that make it difficult for them to visit the hospital, or oral anticancer drugs may not be taken due to dysphagia. Such situations become even more serious if there are recurrences of cerebral infarction. There is also a risk that anticoagulant therapy may promote bleeding complications due to the growth of the tumor. For patients with adenocarcinoma, who are considered particularly susceptible to TS, we recommend that regular brain MRI, especially diffusion-weighted imaging, is performed to check for acute asymptomatic cerebral infarction in addition to screening for brain metastases, and that early anticoagulant therapy is introduced to prevent symptomatic cerebral infarction. There have been many reports (44-46) that acute multiple cerebral infarctions that occur simultaneously in multiple vascular territories on MRI suggest the possibility of TS, even if the lesions are small and asymptomatic.

(IV) How can we better identify patients with advanced tumors presenting with the complication of TS?

Shinji Ito and Tatsuro Mutoh: It is considered useful to detect the onset and increase of acute cerebral infarcts and old infarcts by monitoring D-dimer as described in II) and conducting brain MRI as described in III). Ito *et al.* demonstrated (42) that when D-dimer is 2.0 μg/mL or higher and acute multiple cerebral infarction is observed on MRI (including cases where there is no stenosis that could be an embolic source in the proximal side even in a single cerebral artery territory), the possibility of TS will be significantly higher, and latent cancer might be identified even in patients who have not been diagnosed with cancer in the past; some other similar reports have also been published.

## Conclusions

TS is a frequent but easily overlooked clinical complication that can occur in a variety of tumors, including chordoma, and is currently diagnosed clinically. Thus, further explorations of its sensitive markers are necessary.

Early diagnosis and treatment are key factors in preventing the deterioration of the condition. Prevention, diagnosis, and treatment, mainly anticoagulation and related tumor therapies, can help improve the prognosis of patients with TS. In addition, the rapid development of emerging technology is now a part of research in TS, and single-celled sequencing technologies have become more mature. The use of single-cell sequencing to explore the mechanism of thrombosis in tumor patients may show that biomarkers play an important role in the diagnosis of TS and can be used to predict treatment effects in the future.

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*Ethical Statement:* The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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