Splenic infarction secondary to multi-site thrombosis in lung adenocarcinoma with EGFR-L858R mutation: A case report

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Abstract. Venous thromboembolism (VTE) is a well-documented complication in lung cancer; however, the culmination of multi-site thrombosis in splenic infarction remains extremely rare. The present case report highlighted the complex interplay between oncogenic drivers and coagulation abnormalities in advanced non-small cell lung cancer (NSCLC). A 37-year-old man with stage IVA (T3N2M1a) EGFR-L858R-mutated lung adenocarcinoma presented with acute left upper quadrant pain. Despite prophylactic anticoagulation with rivaroxaban (10 mg twice daily), imaging indicated progressive thrombosis involving the splenic artery, superior vena cava, and deep veins of the neck and lower extremities. Contrast-enhanced abdominal CT confirmed splenic infarction without secondary abscess formation. The patient underwent intensified anticoagulation with enoxaparin (8,000 IU twice daily) and anti-infective prophylaxis, which achieved spontaneous splenic infarct resolution on follow-up imaging (December 2024 to May 2025). The present case underscored three critical clinical insights: i) The paradoxical thrombotic risk profile associated with EGFR-mutated NSCLC during disease progression; ii) the limitations of current VTE risk assessment tools in advanced malignancies; and iii) the necessity for dynamic anticoagulation strategies in cancer-associated thrombosis. Clinicians are advised to maintain heightened vigilance for thrombotic complications even in genetically defined NSCLC subsets (such as EGFR-L858R mutant lung adenocarcinoma) receiving targeted therapies in the future.

Introduction

Lung cancer is recognized as one of the most thrombogenic cancer types, wherein venous thromboembolism (VTE) occurs in up to 14% of patients (1). The risk of VTE is particularly high in patients with advanced stages of lung cancer, such as those with adenocarcinoma, which has been associated with a higher incidence of thrombotic events compared with other histological types of lung cancer, such as squamous cell carcinoma or small cell lung cancer (1). The mechanisms underlying the increased risk of thrombogenesis include immobilization, the presence of central venous catheters and the direct activation of the coagulation system by cancer cells, which release procoagulant factors that stimulate platelet activation and coagulation pathways. Following vascular endothelial disruption, factor XII initiates the intrinsic coagulation pathway through contact activation with subendothelial collagen, thereby mediating hemostasis in deep tissue injuries. Concurrently, tissue factor (TF) exposure upon vascular rupture triggers the extrinsic pathway, enabling rapid thrombin generation via TF-factor VIIa complex formation. These two pathways synergistically regulate hemostasis and thrombosis through distinct yet complementary mechanism (2,3). Chemotherapy, a common treatment for lung cancer, further exacerbates the risk of thrombosis. Chemotherapy agents, such as cisplatin, carboplatin, gemcitabine and paclitaxel, have been demonstrated to elevate procoagulant activity in endothelial cells and other blood components such as fibrinogen, antithrombin III and tissue factor pathway inhibitor. The increase in procoagulant activity is primarily mediated through mechanisms that involve TF expression and disulfide bond formation, which contributes to a hypercoagulable state in patients with lung cancer (4). Furthermore, the presence of central venous catheters, which are often used for chemotherapy administration, further increases the risk of thrombosis. A previous study indicated that patients with lung cancer who had peripherally inserted central catheters experienced a high incidence of upper extremity venous thrombosis, particularly when treated with certain chemotherapeutic agents such as etoposide (5). The use of antiangiogenic agents, including bevacizumab, sorafenib, apatinib and amilorotinib, and immunotherapy has also been linked to an increased risk of thromboembolic events (2,3). In a previous study, which included 605 patients diagnosed with non-small cell lung cancer (NSCLC), the presence of EGFR mutations was associated with varying risks of VTE. Specifically, patients with EGFR wild-type status had a higher risk of developing VTE compared with patients with EGFR mutations. The probability of developing VTE was

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8.3% in patients with EGFR mutations after 1 year, compared with 13.2% in patients without EGFR mutations. After 2 years, the probabilities of developing VTE differed significantly (9.7 and 15.5%, respectively; P=0.047) (6). Furthermore, another study highlighted that the mutation of EGFR was associated with a decreased risk of VTE. In a cohort of 310 patients with lung adenocarcinoma, patients with EGFR mutations had a hazard ratio (HR) of 0.46 for VTE, which suggested a protective effect against thrombosis compared with patients with wild-type EGFR with lung adenocarcinoma (7). This finding indicated that the presence of the EGFR-L858R mutation may not only be a driver of tumorigenesis but could also serve a role in modulating the risk of thrombotic events. Splenic infarction, a rare but clinically significant thromboembolic event, arises from the occlusion of the splenic artery or the splenic artery branches by emboli or thrombi. With an incidence of 0.016% in hospital admissions, VTE predominantly results from cardiogenic embolism (62.5%), most notably atrial fibrillation (1). Secondary etiologies include autoimmune disorders (12.5%), infections (12.5%) and hematologic malignancies (6%) (8). Clinically, sudden-onset left upper quadrant abdominal pain (84% of cases) constitutes the classic presentation, although asymptomatic cases (≤16%) and atypical manifestations such as fever and nausea may occur (9). Diagnostic delays are common due to nonspecific symptoms. The prognosis remains favorable with timely intervention (10,11). The median hospitalization duration is 6.5 days, and anticoagulation therapy is initiated in most cases to mitigate thromboembolic risks and promote recovery (12).

The clinical implications of multiple-site thrombosis in patients with lung cancer are notable (13,14). Patients with VTE often experience longer hospital stays, higher rates of inpatient mortality and increased healthcare costs compared with patients without VTE. Furthermore, the presence of thrombosis can complicate cancer treatment, as anticoagulation therapy may increase the risk of bleeding, particularly in patients undergoing chemotherapy or surgery (15). The present case illustrated the complex thrombotic evolution in EGFR-driven NSCLC, which emphasizes the need for precision anticoagulation strategies.

Case report

Case summary. A 37-year-old man was admitted to the First People's Hospital of Suining (Suining, China) in December 2024, due to 'pain and discomfort in the left upper abdomen for >3 days'. Furthermore, the patient reported persistent chest tightness accompanied by myocardial discomfort over a 2-week duration. Physical examination revealed a soft abdomen, fullness in the left intercostal space, pronounced tenderness in the left upper quadrant and palpable enlargement of the spleen, accompanied by significant rebound tenderness in the spleen area. In November 2024, the patient developed chest pain, exertional dyspnea and fatigue. An enhanced CT of the abdomen indicated a filling defect and low-density shadow in the pancreatic body segment of the splenic artery, with portions of the splenic parenchyma demonstrating no enhancement, which raised suspicion for splenic artery embolism and splenic infarction. Upon admission, empiric antimicrobial prophylaxis with intravenous cefuroxime (4.5 g/day; treatment duration, 1 week) was initiated to mitigate infectious complications of splenic infarction. Simultaneous therapeutic anticoagulation with subcutaneous enoxaparin sodium (8,000 IU every 12 h; treatment duration, 3 weeks) targeted thromboembolic pathophysiology. The patient was discharged from hospital in December 2024 and followed up until May 2025, and the splenic infarction in the patient had not progressed and had gradually healed spontaneously.

Past medical history. The patient was admitted to the First People's Hospital of Suining in October 2024 due to pleural effusion. Lung adenocarcinoma cells were identified in the exfoliated cells from the pleural effusion, which led to a diagnosis of a malignant tumor in the upper lobe of the left lung, classified as adenocarcinoma T3N2M1a at IVA stage (16) (Fig. 1A and B). On admission, according to the Khorana scoring scale (17), the VTE score of the patient was classified as low-risk. Additionally, malignant pericardial effusion (MPE) was diagnosed at the First People's Hospital of Suining in October 2024 (Fig. 1C and D), which prompted the performance of pericardiocentesis and catheter drainage. A week before presentation in December 2024, color ultrasound examinations of the lower extremity veins and the internal jugular vein demonstrated thrombosis in the popliteal vein, posterior tibial vein, peroneal vein and right internal jugular vein. Following discharge, the patient was prescribed rivaroxaban at a dose of 10 mg twice daily for anticoagulation for 3 months, with dose and frequency adjusted based on lower extremity venous ultrasound review.

Genetic findings. The amplification refractory mutation system-polymerase chain reaction analysis (experiments were carried out by the Pathology Laboratory of Suining Central Hospital, Suining, China; data were obtained from medical records) confirmed a heterozygous activating mutation at exon 21 of the EGFR gene (c.2573T>G, p.Leu858Arg), which corresponded to the canonical L858R substitution (Fig. 2A). The target EGFR gene primer sequences were as follows: Forward, 5'-GCCAGGAACGTACTGGTGAA-3'and reverse, 5'-CCT TCTGCATGGTATTCTTTCTCTTC-3'.

Laboratory test results. Laboratory test results of routine blood tests on admission are shown in Table I.

Changes in D-dimer levels. Numerous studies have established that D-dimer levels serve as an independent risk predictor for VTE in various cancer types such as kidney, breast, rectal and ovarian cancer (18-20). In the present study, the D-dimer levels of the patient were dynamically monitored by detecting the D-dimer levels in the serum. When the patient presented with multiple thrombosis sites, the D-dimer levels (15.57 mg/l) were increased compared with the normal range (<0.5 mg/l) (Fig. 2B). Following anticoagulation treatment, the D-dimer levels gradually returned to normal levels (<0.5 mg/l).

Imaging findings. Complementary vascular ultrasonography (December 2023) demonstrated extensive thromboembolic disease: Acute thrombosis included the distal left superficial femoral vein, popliteal vein, right internal jugular vein and bilateral posterior tibial/peroneal veins, with venostasis evident in the remaining lower extremity vasculature.

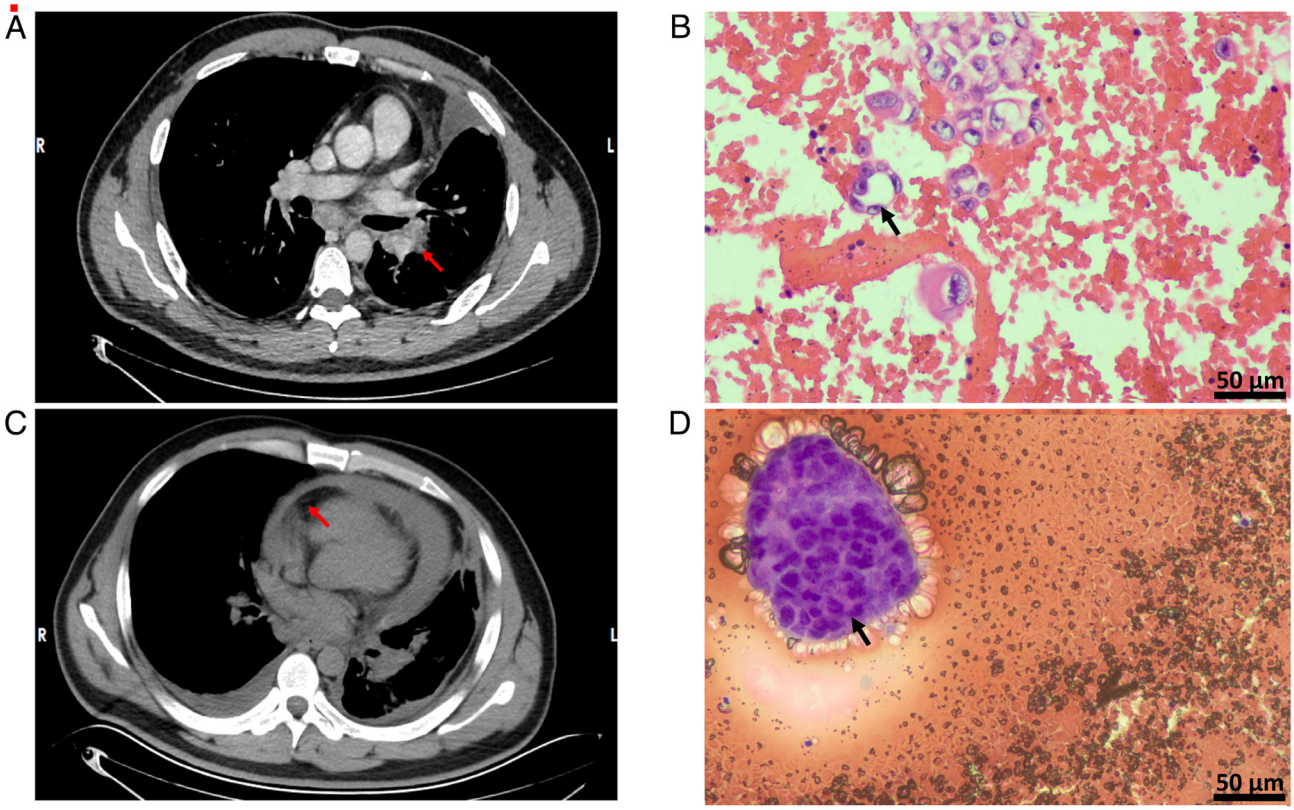

Figure 1. Chest CT revealing a lung mass and pericardial effusion, which was confirmed by H&E staining for lung adenocarcinoma and pericardial metastases. (A) Contrast-enhanced chest CT identified a pulmonary mass in the left upper lobe, indicated by the red arrow, which exhibited characteristic neoplastic morphology. (B) Analysis via H&E staining of the pleural effusion confirmed metastatic lung adenocarcinoma. Tumor cells are indicated by the black arrow (H&E staining; scale bar, 50 μm). (C) Chest CT demonstrated pericardial effusion. The red arrow indicates thrombosis of the splenic artery. (D) H&E staining of the pericardial effusion also revealed lung adenocarcinoma cells. Tumor cells are indicated by the black arrow (H&E staining; scale bar, 50 μm).

Cervical venous evaluation identified aneurysmal dilatation of the right internal jugular vein containing intraluminal thrombus (Fig. 3A-C). Contrast-enhanced abdominal CT demonstrated a filling defect and hypodense intraluminal shadow within the splenic artery distal to the pancreatic body segment (Fig. 3D). Concomitant absence of parenchymal enhancement in a portion of the spleen confirmed the diagnosis of splenic artery embolism with resultant splenic infarction (Fig. 3E).

VTE score. The patient received anticoagulant treatment prior to admission. According to the 'Guidelines for the Quality Evaluation and Management of VTE Prevention and Treatment in Hospitals (2022 Edition)' (17), the patient did not require a VTE score assessment.

Pathological examination

Cytopathological analysis of left pleural effusion. Malignant tumor cells were identified via left bloody pleural effusion analysis.

H&E staining and immunohistochemistry. Histological analysis was performed on tissue sections fixed in 10% neutral buffered formalin at room temperature for 24 h. The tissue was processed, embedded in paraffin and sectioned at a thickness of 5 μm. Sections were stained with hematoxylin and eosin for 5 min at room temperature, following standard protocols. The slides were examined using a light microscope (Leica DM3000; Leica Microsystems GmbH) at a magnification of x400. After H&E staining, the following results were observed: Tumor cells were found in the pleural fluid, with an enlarged nucleoplasm ratio, deviated nuclei, pronounced nucleoli and sparse vacuolated cytoplasm (Fig. 1B). Immunohistochemistry (data were obtained from medical records and are not shown) showed the following: Transcriptional intermediary factor 1 (+); NapsinA (+); P40 (-); cytokeratin 5/6 (-); cytokeratin (+); calretinin mesothelium (+); desmin mesothelium (+); Wilms' tumor protein 1 (-); and Ki67-positive rate, ~10%.

Pericardial effusion analysis. Adenocarcinoma was identified via pericardial effusion analysis.

H&E staining and immunohistochemistry. Histological analysis was performed on tissue sections fixed in 10% neutral buffered formalin at room temperature for 24 h. The tissue was processed, embedded in paraffin and sectioned at a thickness of 5 μm. Sections were stained with hematoxylin and eosin for 5 min at room temperature, following standard protocols. The slides were examined using a light microscope (Leica DM3000; Leica Microsystems GmbH) at a magnification of x400. After H&E staining, the following results were observed: Tumor cells were found in the pericardial effusion cell block, the tumor cells were arranged in an adenoidal/papillary pattern with deeply stained, enlarged nuclei with prominent nucleoli and cytoplasm containing mucus vacuoles (Fig. 1D). Immunohistochemistry (data were obtained from medical records and are not shown) revealed

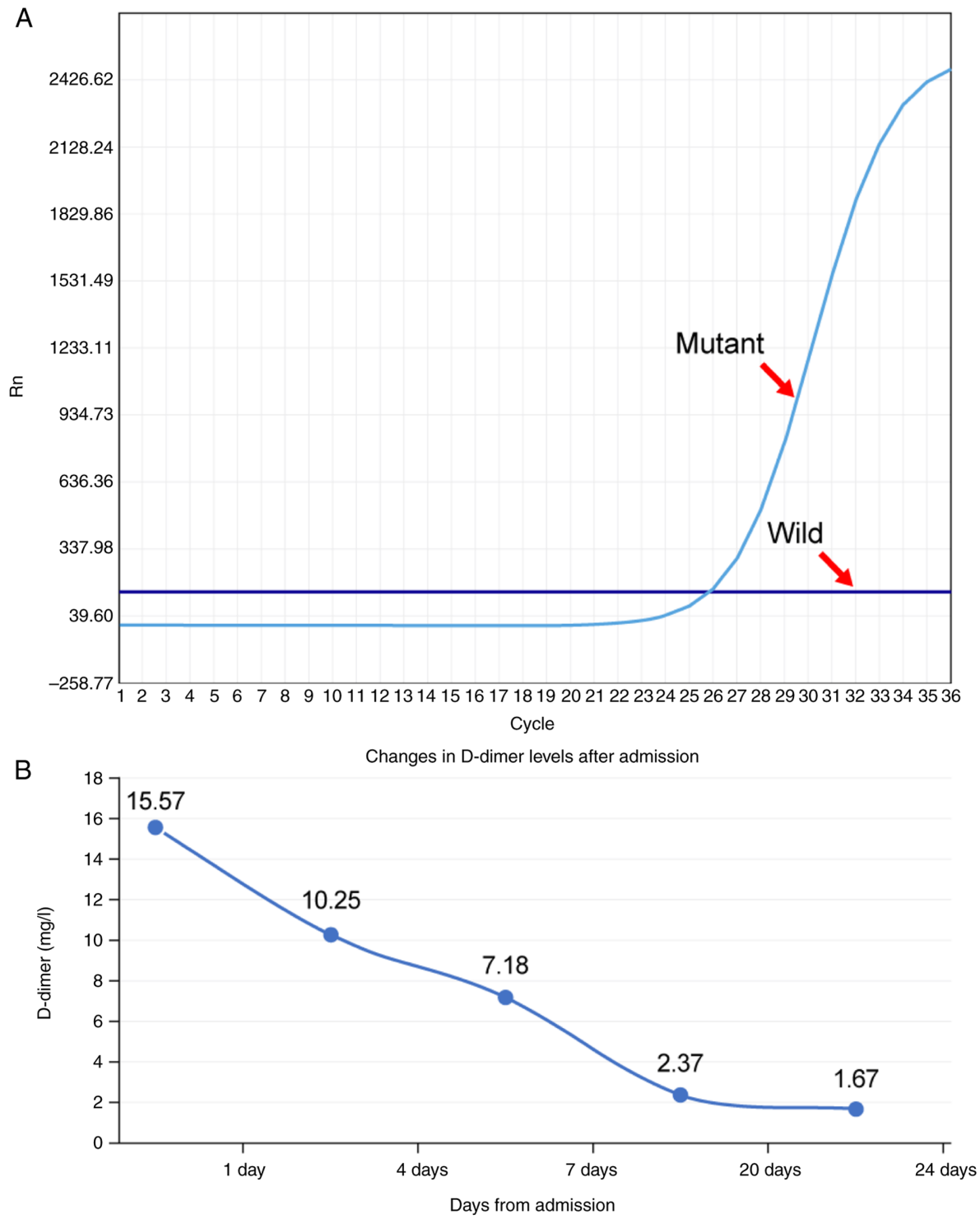

Figure 2. Genetic test results and D-dimer trend changes. (A) Amplification refractory mutation system-PCR analysis confirmed a heterozygous activating mutation at exon 21 of the EGFR gene (c.2573T>G, p.Leu858Arg). The purple horizontal line represents wild-type; the blue horizontal line represents mutant-type. (B) Following admission, the D-dimer levels of the patient exhibited a decreasing trend. Rn, normalized reporter.

the following: Cytokeratin 7 (+); thyroid transcription factor 1 (weak +); NapsinA (+); p40 (-); and Wilms' tumor protein (-).

Treatment method. Following the diagnosis of a malignant tumor in the upper lobe of the left lung (adenocarcinoma; T3N2M1a and IVA stage), the patient received regular chemotherapy at the First People's Hospital of Suining. The chemotherapy regimen consisted of carboplatin (0.7 g) and pemetrexed (1.0 g), which were administered intravenously (21 days for one cycle, and 6 cycles of continuous chemotherapy). Concurrently, based on the genetic test results (Fig. 2A) of the patient, targeted therapy was initiated with the third-generation tyrosine kinase inhibitor (TKI) osimertinib (80 mg; oral once a day; long-term maintenance therapy). Subsequently, after the patient was diagnosed with thrombosis affecting the popliteal vein, posterior tibial vein, peroneal

Table I. Laboratory test findings on admission of the patient.

Blood parameters	Value	Normal range
WBC, x10^9/l	4.79	4.0-10.0
Neutrophil, %	63.8	50-70
Lymphocyte, %	19.7	20-40
Monocyte, %	12.9	3-8
Eosinophil, %	3.5	1-4
Basophil, %	0.1	0.5-1
RBC, x10^{12}/l	4.36	3.5-5.5
HGB, g/l	134	120-160
PLT, x10^9/l	168	100-300
TG, mmol/l	1.85	0.56-1.7
TC, mmol/l	5.24	<5.2
Na, mmol/l	138.2	135-145
K, mmol/l	4.36	3.5-5.0
CL, mmol/l	103.4	96-108
TP, g/l	73.6	60-80
ALB, g/l	42.1	35-55
AKP, U/l	134	45-125
AST, U/l	24	10-40
ALT, U/l	37	10-40
CK-MB, ng/ml	2.2	<5
BNP, pg/ml	82	<100
TNT-HS, ng/ml	0.007	<0.1
D-dimer, mg/l	15.57	<0.5
Fibrinogen, g/l	6.01	2-4
PT, sec	17.9	11-14
APTT, sec	47.4	25-37
FDP, μg/ml	74.73	<5
R, min	3.5	5-10
K, min	2.2	1-3
MA, mm	44.5	50-70
CI	-0.7	-3-+3
EPL, %	0	<15
Solidification angle, °	63.6	53-72
pCO_2, mmHg	34	35-45
pO_2, mmHg	99	80-100
PROGRP, pg/ml	29.7	<63
NSE, ng/ml	15.9	<16.3
CYFRA21-1, ng/ml	12.1	<3.3
mSCC, ng/ml	1.14	<5
CEA, ng/ml	1.23	<1.5
PT-INR	1.1	0.8-1.2
PA, g/l	3.2	1.5-2.5

WBC, white blood cell; RBC, red blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PT-INR, prothrombin time international normalized ratio; APTT, activated partial thromboplastin time; TP, total protein; TC, total cholesterol; TG, triglyceride; AKP, alkaline phosphatase; CK-MB, creatine kinase isoenzyme; BNP, B-type natriuretic peptide precursor; TNT-HS, high-sensitivity troponin T; FDP, fibrinogen degradation products; PA, plasminogen activity; R, coagulation time; K, clot formation time; MA, clot strength; CI, coagulation composite index; EPL, fibrinolytic index; pCO_2, carbon dioxide partial pressure; pO_2, partial pressure of oxygen; PROGRP, gastrin-releasing peptide precursor; NSE, neuron-specific enolase; CYFRA21-1, cytokeratin 19 fragment antigen; mSCC, squamous cell carcinoma-associated antigen; ALB, albumin; CL, chlorine; HGB, hemoglobin.

vein and right intravenous vein, the patient was prescribed rivaroxaban (10 mg twice daily; duration, 3 weeks) for anticoagulation. Upon diagnosis of splenic artery thrombosis with infarction, a dual therapeutic strategy was implemented: i) Anti-infective prophylaxis, cefuroxime (4.5 g/dose every 8 h; duration, 1 week), was empirically administered intravenously, which targeted the encapsulated organisms [the encapsulated microorganisms in splenic abscesses after splenic infarction are predominantly gram-positive (staphylococci and streptococci) and anaerobic (anaplastic bacilli and clostridia), with gram-negative (salmonella and *Escherichia coli*) and fungal (*Candida*) bacteria being the next most common (21)] associated with post-infarction splenic abscess formation; and ii) weight-adjusted therapeutic enoxaparin (8,000 IU subcutaneously every 12 h; duration, 3 months) was initiated for anticoagulation to prevent thrombus propagation, following International Society on Thrombosis and Hemostasis guidelines for splanchnic vein thrombosis (22). After discharge, the patient continued with rivaroxaban (15 mg twice daily) to maintain anticoagulation, and based on the condition of the patient, permanent maintenance anticoagulation was chosen.

Post-treatment results. The left lower abdominal pain in the patient was markedly reduced, the splenic infarction did not progress further and there was no secondary splenic abscess.

Abdominal CT. Contrast-enhanced abdominal imaging demonstrated persistent non-enhancement of splenic parenchyma consistent with established infarction. Comparative volumetric analysis indicated interval reduction (23.4%) in the infarcted volume compared with the baseline (December 2024; Fig. 3D and E), which suggested partial splenic reperfusion (Fig. 3F).

Ultrasound of neck veins. Color Doppler ultrasonography identified a persistent non-occlusive thrombus within the right internal jugular vein (data not shown), unchanged from prior examinations (Fig. 3A).

Lower extremity vasculature. Color Doppler ultrasonography identified residual thrombosis in the left popliteal vein and segmental branches of the posterior tibial/peroneal veins (data not shown), indicative of chronic thromboembolic remodeling.

Follow-up results. Following discharge, the patient remained asymptomatic with complete resolution of abdominal pain. Serial monitoring demonstrated progressive regression of multi-territory thromboembolic events, with no clinical or radiographic evidence of new thrombus formation. The last follow-up was in May 2025, and the follow-up was conducted every 2 weeks in the form of outpatient follow-up, and changes in the condition of the patient were clarified by reviewing the CT of the chest and ultrasound of the veins of the lower limbs and neck at 1-month intervals.

Discussion

Patients with lung cancer are particularly susceptible to multi-site thrombosis due to a combination of factors that create a hypercoagulable state (23-25). Multi-site thrombosis

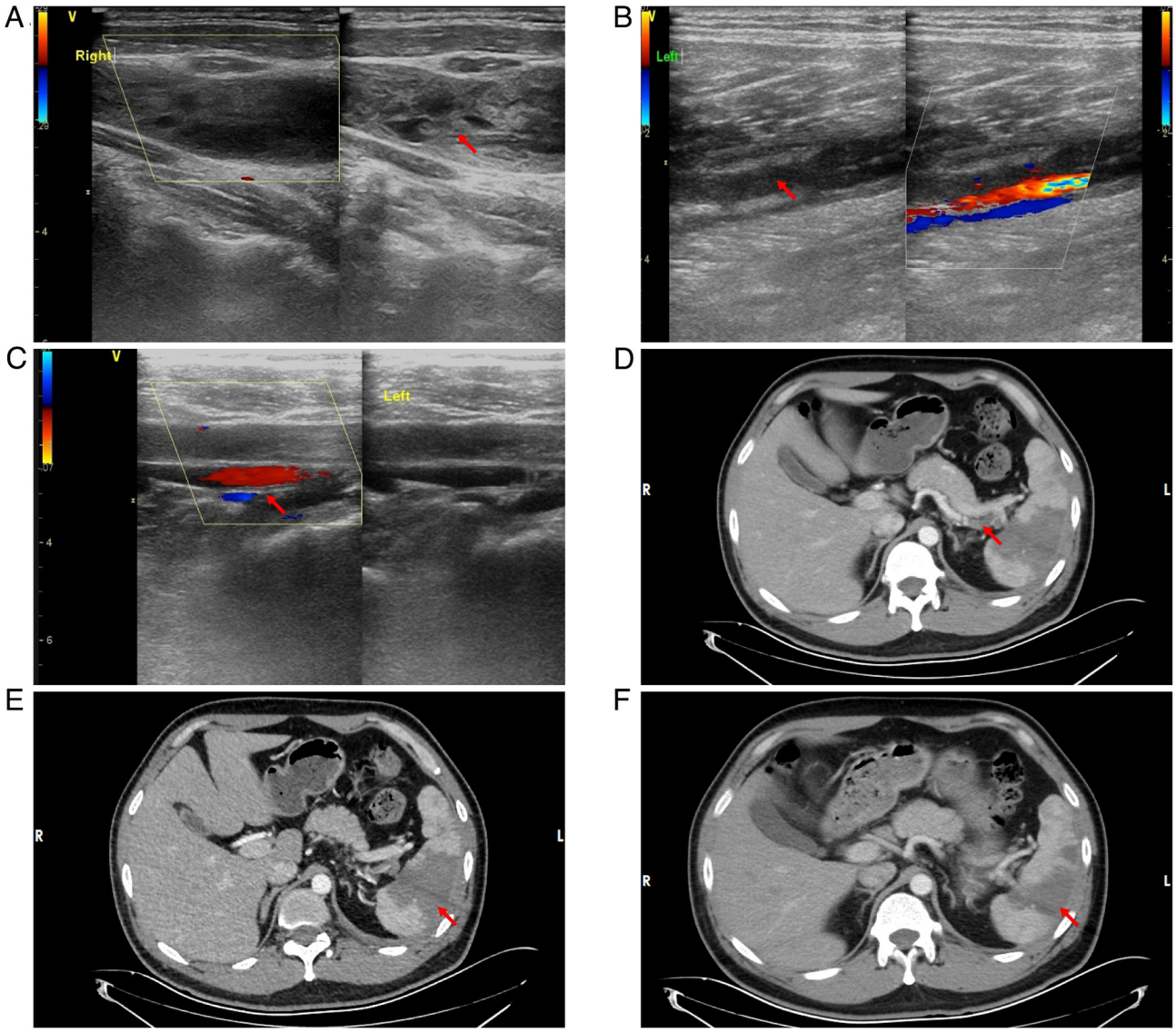

Figure 3. Ultrasound findings indicating multiple thrombi formation in multiple locations and contrast-enhanced abdominal CT revealing splenic infarction. A colored scale is used to indicate the direction and relative velocity of the blood flow signal, with red indicating blood flow towards the ultrasound probe and blue indicating blood flow away from the ultrasound probe. (A) Color Doppler ultrasound indicated thrombosis in the right internal jugular vein. The red arrow indicates a thrombosis. (B) Color Doppler ultrasound demonstrated thrombosis in the left popliteal vein. The red arrow indicates a thrombosis. (C) Color Doppler ultrasound indicated thrombosis in the left peroneal vein. The red arrow indicates a thrombosis. (D) Contrast-enhanced abdominal CT demonstrated splenic artery thrombosis and the red arrow indicates the thrombus. (E) Contrast-enhanced CT demonstrated wedge-shaped hypodensity in the splenic parenchyma, indicated by the red arrow, consistent with ischemic infarction. No evidence of liquefactive necrosis or abscess formation was observed. (F) Following a standard anticoagulation regimen (8,000 IU subcutaneously every 12 h), at 1 month post-treatment, contrast-enhanced CT revealed a slight reduction in the extent of the splenic infarction. The red arrow indicates the infarcted spleen.

is characterized by an increased tendency for blood clot formation, which can result in thromboembolic events in both the venous and arterial systems. A primary reason for this heightened risk is the presence of procoagulant factors associated with malignancy (26,27). Cancer cells, including those from lung cancer, can express various procoagulant substances such as TF, cancer procoagulant and heparanase. These factors serve a key role in the activation of the coagulation cascade, which leads to increased thrombin generation and subsequent clot formation (3,28). Additionally, tumor cells can secrete inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β, which further stimulate the coagulation process and promote thrombosis. The presence of a tumor can disrupt normal blood flow, which leads to stasis, while chemotherapy and other cancer treatments may cause damage to the vascular endothelium and thereby increase the risk of clot formation. The hypercoagulable state observed in patients with cancer is also influenced by the inflammatory response associated with malignancy. Inflammation can lead to alterations in the balance between procoagulant and anticoagulant factors, which shifts the equilibrium towards increased clotting (29-31). This phenomenon is particularly relevant in lung cancer, where the inflammatory environment created by the tumor can heighten the risk of thromboembolic events (3,32). Additionally, elderly patients with lung cancer may have comorbid conditions, such as chronic obstructive pulmonary disease or cardiovascular disease, which can further elevate the risk of thrombosis (32,33). The interplay of these factors

leads to a markedly increased incidence of VTE among patients with lung cancer, where previous studies (24,27) have shown that patients with lung cancer are four to seven times more likely to develop VTE than the general population (34). In summary, the elevated risk of multi-site thrombosis in patients with lung cancer is multifactorial and arises from the direct effects of tumor biology, the influence of cancer treatments and the presence of comorbid conditions. According to the Khorana scoring scale (17), which assesses the risk of VTE in patients with cancer, the current patient was classified as low risk on admission. The current case highlighted limitations of the Khorana risk assessment model in the prediction of VTE among patients with cancer. Despite being classified as low risk using this validated scoring system, the patient developed multi-site thrombosis, which highlighted the insufficient sensitivity of the model in certain clinical scenarios. This finding emphasizes the urgent need for the development of a novel VTE risk stratification tool that incorporates dynamic variables, including tumor histology (such as the association between lung cancer and hypercoagulability), treatment heterogeneity and biomarkers that reflect individual thrombotic potential. Further research is warranted to enhance predictive accuracy for high-risk populations such as patients with lung cancer, who exhibit high thrombotic event rates. Vigilant thromboprophylaxis monitoring is advised for patients with cancer, including patients stratified as low-risk, due to the life-threatening consequences of VTE.

The L858R mutation results in the continuous activation of EGFR, which in turn activates several downstream signaling pathways. These include the Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways (35,36). The Ras pathway is particularly important as it regulates cell proliferation, survival and migration, which are key processes in cancer progression and metastasis (35,36). The activation of these pathways can lead to increased expression of pro-coagulant factors, which contribute to a hypercoagulable state.

Previous studies have suggested that the interaction between EGFR signaling and coagulation pathways can influence cancer progression. For example, the activation of EGFR can lead to the upregulation of ligands that promote TF expression and thereby enhance the pro-coagulant state in tumors (37,38). The crosstalk is particularly relevant in the context of KRAS mutations, where both mutations (KRAS and EGFR) can synergistically promote tumor growth and thrombosis (39). The presence of the EGFR-L858R mutation in patients with NSCLC may be associated with an increased risk of thromboembolic events. This association is particularly important for clinicians to consider when managing patients with the EGFR-L858R mutation, as the hypercoagulable state can complicate treatment and increase the risk of adverse outcomes. However, a previous study, which included 310 patients diagnosed with lung adenocarcinoma, reported that patients with EGFR mutations had a HR of 0.46 (95% CI, 0.23-0.94) for VTE, which suggests a protective effect against thrombosis compared with patients with wild-type EGFR. Additionally, treatment with TKIs further reduced the risk of VTE, with an HR of 0.42 (95% CI, 0.29-0.79) when compared with other treatment strategies that did not include TKIs. This finding suggested that the presence of the EGFR mutation was associated with a lower incidence of thrombosis and the therapeutic approach using TKIs may enhance this protective effect (7). The current patient was diagnosed with lung adenocarcinoma in October 2024, following the identification of lung adenocarcinoma cells in pleural effusion via immunohistochemistry. The patient exhibited pleural and lymph node metastases, which indicated advanced lung cancer. Subsequent genetic testing demonstrated the presence of the EGFR-L858R mutation, which prompted the initiation of targeted therapy with the TKI osimertinib. However, in October 2024, chest CT indicated tumor progression and the emergence of pericardial metastasis, which led to the conclusion that single-agent targeted therapy had failed. Consequently, the treatment plan was modified to include a combination of chemotherapy (carboplatin and pemetrexed) and targeted therapy (osimertinib). At this juncture, a venous color Doppler ultrasound of the lower limbs had already detected thrombosis, and rivaroxaban (10 mg twice daily) was prescribed for anticoagulation. The anticoagulation strategy proved ineffective, as novel thrombosis was identified when the patient was admitted to the First People's Hospital of Suining in November 2024. The role of the EGFR-L858R mutation in thrombosis among patients with lung cancer remains unclear. A previous study has suggested that the EGFR-L858R mutation may reduce the incidence of thrombotic events, while other studies have indicated an increased incidence associated with the EGFR-L858R mutation (40). Based on the observations in the current patient, we hypothesized that the EGFR-L858R mutation may exert a protective effect in thrombosis among patients with lung cancer. Notably, the patient did not experience thrombosis prior to the initiation of treatment with TKI inhibitors; however, following the commencement of TKI therapy, venous thrombosis developed in the lower extremities, despite treatment with anticoagulants. This phenomenon may arise from two potential factors: Firstly, the condition of the patient progressed during treatment, which led to pericardial metastasis and notable pericardial effusion. This prolonged state likely impaired systemic circulation, which resulted in slowed blood flow and increased coagulability. Secondly, the treatment approach for the patient was modified following the development of pericardial effusion. The patient was transitioned to a regimen that included chemotherapy (carboplatin and pemetrexed) combined with targeted therapy (osimertinib). Previous studies have indicated that platinum-based antitumor agents such as cisplatin, carboplatin, oxaliplatin and lopatin may elevate the risk of VTE in patients with lung cancer, particularly with regard to catheter-related thrombosis (41,42). In summary, the antithrombotic effect of the EGFR-L858R mutation appears to be counteracted by TKI-induced endothelial dysfunction and pharmacokinetic disturbances. Based on the observations from the present case, it is necessary to revise current guidelines (17) to include the following: i) EGFR mutation status in VTE risk models; ii) TKI-specific anticoagulation algorithms; and iii) protocolized cytokine monitoring during metastasis.

MPE markedly impacts hemodynamics and coagulation properties in patients with lung cancer. The presence of MPE can lead to alterations in blood flow dynamics due to the accumulation of fluid in the pericardial space, which can compress the heart and impede its ability to pump effectively (43-45). This condition can result in cardiac tamponade, where the pressure from the fluid prevents the heart chambers from filling properly, which leads to reduced cardiac output and compromised blood flow to vital organs (46). In terms of

coagulation properties, patients with lung cancer and MPE often exhibit a hypercoagulable state. A hypercoagulable state is characterized by changes in plasma fibrin clot properties, which can include increased clot density and altered permeability (47-49). A single study has reported that patients with lung cancer undergoing chemotherapy exhibited higher levels of D-dimer, a marker of fibrin degradation, which indicated increased fibrinolytic activity (50). Additionally, chemotherapy has been associated with changes in clot structure, such as increased clot permeability and prolonged clot lysis time, which can contribute to thromboembolic complications (51). The presence of MPE can also influence the activity of TF, which is a key initiator of the coagulation cascade. In patients with lung cancer, the activity of microparticle-associated TF can be altered, which leads to an imbalance between coagulation activation and fibrinolytic potential. This imbalance may predispose patients to VTE, which is notably more common in patients with lung cancer compared with the general population (52). The hypercoagulable state is further exacerbated by the presence of tumor-derived factors that promote clot formation and inhibit fibrinolysis, which contributes to the overall risk of thrombotic events in patients with lung cancer (53). In November 2024, the patient developed chest pain, exertional dyspnea and fatigue. Pericardiocentesis and catheter drainage were performed following detection of a notable amount of pericardial effusion via chest CT. Lung adenocarcinoma cells were identified in the pericardial effusion. The pericardial metastasis of the patient resulted in a substantial accumulation of pericardial effusion. This process was gradual and continuous, which markedly impacted the systemic circulation of the patient, and exacerbated the hypercoagulable state commonly associated with lung cancer. Consequently, the process led to thrombosis in multiple locations, particularly arterial thrombosis, including splenic artery thrombosis. Although pericardiocentesis and catheter drainage were performed to alleviate the cardiac tamponade in the patient, the effects on the circulatory state are unlikely to improve in the short term.

In some cases, patients with lung cancer undergoing chemotherapy may experience acute complications such as splenic infarction due to embolic events, which can be precipitated by the underlying malignancy and the treatment (54). Furthermore, the anatomical and physiological characteristics of the spleen, along with the vascular supply, can make it susceptible to thrombotic events. The spleen is typically well-protected from non-hematological metastasis and splenic artery thrombosis is a rare occurrence (21,55). However, when splenic artery thrombosis does occur, it is often part of a broader pattern of vascular complications associated with malignancies, including lung cancer (56). In summary, lung cancer can cause splenic artery thrombosis primarily through the induction of a hypercoagulable state, either due to the malignancy itself or as a consequence of chemotherapy. This can lead to thrombus formation in the splenic artery, which results in complications such as splenic infarction. The splenic artery, which is a singular vessel, is particularly susceptible to thromboembolism, which can result in splenic infarction (10). The current patient experienced splenic artery thromboembolism and subsequent splenic infarction, a clinical occurrence that is extremely rare. Notably, splenic artery thromboembolism and splenic infarction occurred despite anticoagulation therapy. To the best of our knowledge, there is a lack of pertinent research reports on this phenomenon, which necessitates further research on the underlying causes. The causes of this phenomenon were analyzed and summarized as follows: i) Hypercoagulable state: Lung cancer may influence the coagulation status of patients through various mechanisms, which leads to a persistent hypercoagulable state; ii) cardiac embolism resulting from pericardial effusion: The patient had a notable history of MPE, which severely compromised blood circulation and contributed to thrombosis formation at multiple sites, including the splenic artery; and iii) treatment modalities: TKIs and platinum-based chemotherapy agents can elevate the risk of thrombosis in patients with lung cancer. Additionally, the use of deep vein catheterization for chemotherapy may lead to catheter-related thrombosis, as evidenced by the current patient undergoing internal jugular vein catheterization for chemotherapy. Subsequent cervical venous color ultrasound revealed thrombosis in the internal jugular vein.

Venous thrombosis was identified in the lower extremity and jugular veins in December 2024 via color ultrasound. In response, anticoagulation with rivaroxaban at a dosage of 10 mg twice a day was initiated; however, new thrombotic sites continued to emerge. Following an adjustment of the anticoagulant dosage to 15 mg rivaroxaban twice a day, marked dissolution and disappearance of the thrombus were observed, with no further occurrences of thrombosis. This observation led to the conclusion that the initial anticoagulant dosage was insufficient. Additionally, as the anticoagulant dosage was modified, the D-dimer levels of the patient gradually decreased to normal levels, which indicated a positive association between D-dimer levels and thrombosis, as well as a potential predictive value regarding anticoagulant efficacy. Nonetheless, further research is necessary to substantiate the findings of the present case report.

It is extremely rare for patients with lung adenocarcinoma and EGFR-L858R mutations to develop multiple thromboses that lead to splenic infarction. This phenomenon may be associated with hypercoagulability, cardiac tamponade and genetic mutations inherent to patients with lung cancer, exacerbated by factors such as chemotherapy, targeted therapy and insufficient anticoagulation dosing. The present case highlights the complex interplay between oncogenic drivers and hemostatic regulation. The authors propose three clinical practice modifications: i) Mandatory thrombophilia screening for patients with EGFR-mutant NSCLC initiating TKIs; ii) implementation of quantitative anti-factor Xa monitoring for patients with direct oral anticoagulants-treated cancer; and iii) development of EGFR mutation-specific VTE risk assessment tools. Further research is warranted to explore the role of PI3K inhibitors in mitigating TKI-associated thrombosis while preserving antitumor efficacy.

The present case underscored the paradoxical thrombotic risk in patients with EGFR-mutant NSCLC undergoing targeted therapy, highlighted the insufficiency of the Khorana score in molecularly defined cohorts, and established visceral thrombosis screening as a critical component of care in EGFR-mutant patients with pericardial effusion. It mandates revision of VTE risk stratification frameworks to incorporate oncogenic driver status, treatment-specific factors and dynamic biomarkers, while advocating for intensified anticoagulation protocols in this high-risk subgroup.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YM, MW, HZ and XW conributed to the conception and design of the study. QW and ZW performed the acquisition, analysis and interpretation of data. QW and ZW confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent was obtained from the patient to publish the present case report findings and process medical records.

Competing interests

The authors declare that they have no competing interests.

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