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Review

The Possible Link Between Tirzepatide and Pulmonary Embolism: A Case Report and a Narrative Review

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Abstract

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent condition with a significant annual incidence, particularly increasing with age. Its pathophysiology is explained by Virchow's triad (venous stasis, vascular injury, and hypercoagulability). Tirzepatide, a dual receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), is approved for type 2 diabetes mellitus (T2DM) and obesity, showing efficacy in lowering HbA_{1c} and promoting weight loss. Recent case reports have linked tirzepatide to VTE events, particularly in patients experiencing significant weight loss, raising concerns about its safety profile. We present a case of a male T2DM subject who developed PE after five injections of tirzepatide in a patient with grade I obesity. We also review emerging literature on VTE associated with tirzepatide, emphasizing the need for further research to clarify the drug's risk and underlying mechanisms.

Keywords: venous thromboembolism; pulmonary embolism; tirzepatide; GIP/GLP-1 receptor agonist; obesity; type 2 diabetes mellitus

1. Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disorder with annual incidence rates of 150 per 100,000 in Western countries [1]. VTE's incidence increases with age and is comparable between sexes, although men exhibit a higher risk of recurrence [1]. The Virchow triad, characterized by venous stasis, vascular injury, and hypercoagulability, along with predisposing factors, explains the pathophysiology of VTE [2]. The risk factors for VTE include immobilization, fracture of a lower limb/hip or knee replacement/spinal cord injury, major trauma, infections, cancer, hospitalization for heart failure or atrial fibrillation/flutter or myocardial infarction (within previous 3 months), obesity, pregnancy, central venous lines/intravenous catheters and leads, and thrombophilia (inherited such as homozygous factor V of Leiden or prothrombin mutation, antithrombin deficiency, or protein C or S deficiency, or acquired such as antiphospholipid syndrome). Different drugs can be a risk factor for VTE, such as hormone replacement/oral contraceptive therapy or chemotherapy [3]. Dyspnea, chest pain, and cough are the most frequent symptoms of PE, while fever, tachycardia, abnormal pulmonary signs, and peripheral vascular collapse are the most common physical findings [4]. Cyanosis, hemoptysis, and syncope are less commonly

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observed [4]. Patients with identifiable risk factors for PE are defined as having provoked PE, whereas others are classified as having unprovoked PE, which requires further workup, including testing for thrombophilia and/or screening for malignancy [3]. Management of PE includes supportive measures, anticoagulation as the mainstay of treatment, and reperfusion strategies (thrombolysis, catheter-directed therapy, and surgical embolectomy) for severe cases [5].

Tirzepatide is the first dual receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) for the treatment of type 2 diabetes mellitus (T2DM) and obesity [6]. It is commercially available in pre-filled single-dose pens for once-weekly subcutaneous injection in doses of 2.5, 5, 7.5, 10, 12.5, or 15 mg/0.5 mL (https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro (accessed on 10 May 2026)). Tirzepatide has been shown to be effective in reducing glycated hemoglobin (HbA_{1c}) levels in adult patients with T2DM in multiple phase III, randomized, double-blind or open-label studies conducted globally (SURPASS 1--) and in promoting weight loss (SURMOUNT 1–6).

The use of GLP-1 receptor agonists (GLP-1 RAs) for weight loss in patients with T2DM has produced mixed outcomes regarding the risk of VTE. A large study involving over 540,000 patients found that those treated with GLP-1 RAs had a lower incidence of VTE compared to those receiving dipeptidyl peptidase-4 inhibitors (DPP-4i) [7]. However, a meta-analysis of trials on semaglutide found an increased risk of DVT compared to placebo [8]. Some case reports concerning tirzepatide have emerged, suggesting a potential link to VTE [9–11]. Cases involving significant weight loss on tirzepatide correlate with the emergence of DVT and PE, raising concerns about the drug's safety profile.

We describe the case of a male T2DM subject who developed PE after five injections of tirzepatide (four injections at a dosage of 2.5 mg and one injection at a dosage of 5 mg) in a patient with grade I obesity. We also conducted a narrative review of the literature on VTE cases associated with tirzepatide to highlight the features of these rare (but sometimes life-threatening) adverse events. We also discuss the possible pathophysiology of how tirzepatide could increase the risk of VTE. Further research is needed to elucidate the underlying mechanisms and confirm these findings in larger populations.

2. Case Report

In August 2025, a 67-year-old Caucasian man presented to the emergency department with a 7-day history of gradually worsening shortness of breath during exertion and an acute onset of pleuritic chest pain for one hour. He described the pain in the base of his left chest, rating it 5 out of 10 in intensity, which was exacerbated by breathing and irradiated to the right upper quadrant. He had T2DM diagnosed in 2019 with concomitant diabetic stage IIIb chronic renal disease (CKD, creatinine 1.66 mg/dL, eGFR according to MDRD 44.3 mL/min) treated with metformin 1000 mg once a day and dapagliflozin 10 mg once a day. In July 2025, to lose weight and improve glycemic control (at June 2025 exams: HbA_{1c} 6.9% with Hb 13 g/dL), therapy with tirzepatide was initiated at a dosage of 2.5 mg weekly for one month and then increased to 5 mg weekly.

His medical history included orthotopic liver transplantation (OLT) in August 2023 secondary to hepatocellular carcinoma and MASLD (metabolic dysfunction-associated steatotic liver disease)-cirrhosis treated with tacrolimus 1 mg once a day and everolimus 0.75 mg once a day, arterial hypertension for which he did not require any regular medication, and dyslipidemia treated with a combination of atorvastatin 20 mg and ezetimibe 10 mg once a day. He underwent middle meningeal artery embolization for bilateral chronic subdural hematomas in February 2022. He also took as medication acetylsalicylic acid

100 mg once a day for primary prevention, pantoprazole 40 mg once a day for gastroprotective purposes and ursodeoxycholic acid 300 mg three times a day. He denied any history of recent travel, trauma, surgery, prolonged immobilization, recent illness or COVID-19 infection. He was a former smoker: he smoked about 40 cigarettes a day from the age of 30 until 2023 (70 pack years). He had no personal or family history of VTE. There were no symptoms suggestive of DVT. His body mass index (BMI) was 30.4 kg/m^2 with a weight of 88 kg and a height of 1.70 m, indicating grade I obesity. A 0.5 kg loss was reported over a one-month period following initiation of tirzepatide. The patients denied recent use of tobacco, alcohol or recreational drugs.

Thirty-three days after the initial injection of tirzepatide (and three days after the first injection of tirzepatide 5 mg), he was admitted to the emergency department due to acute pleuritic chest pain. The physical examination revealed tachypnea, low oxygen saturation on the pulse oximeter (92–93% at FiO_2 21%), and fever (axillary temperature 37.5 °C); blood pressure and cardiac frequency were 150/90 mmHg and 75 beats per minute, respectively. An arterial blood exam revealed a reduction in peripheral oxygen saturation (SpO_2 93.4% with pO_2 of 73.6 mmHg, P/F ratio of 350) and mild HCO_3^- reduction (21.9 mmol/L) with normal pH (7.39) and pCO_2 (36.1 mmHg). Oxygen therapy was initiated at a rate of 2 liters per minute using nasal prongs. There were no signs of right ventricular strain: no jugular venous congestion was present, and there were no parasternal lifts or audible gallops. Respiratory exam revealed a bilateral reduction in murmur at the lung bases, difficult to interpret due to reduced breathing from pain. There were no cardiac murmurs heard. No palpable abdominal masses were noted; a mild abdominal tenderness in the right upper quadrant was reported. The patient no reported diarrhea or vomiting. He had no signs of dehydration (hematocrit 40.1%, BUN/creatinine ratio 11.6). No signs of DVT were detected.

Suspicion of left basal pneumonia led to a chest X-ray, which showed blurred thickening and associated pleural effusion in the lower part of the left lung. As his temperature increased to 38.5 °C, blood cultures, tests for respiratory viruses and bacteria, and urine antigen tests for Legionella and Streptococcus pneumoniae were performed; however, all results were negative. No symptoms or signs of urinary tract infection were detected. Moreover, the Well Score for Pulmonary Embolism [12] was calculated as 3.0 (criteria: PE is first diagnosis or equally likely), identifying the patient in the moderate-risk group with a 16.2% chance of PE in an Emergency Department population. A coagulation profile was performed, with the result of an increase in D-dimer (2366.0 µg/L; reference range age-adjusted < 670.0 mcg/L) and normal international normalized ratio (INR, 1.08) and activated partial thromboplastin time (aPTT, 29.6 s). Troponin-I was negative (5 ng/L). A mild increase in C-reactive protein (CRP; 16.3 mg/L, normal range: <5 mg/L) was detected. ECG demonstrated sinus rhythm at 86 beats per minute, with no evidence of right heart strain such as right axis deviation, right bundle branch block or S1Q3T3 pattern.

In the suspicion of PE and to clarify the origin of the pain, a chest and abdominal enhanced computed tomography (CT) scan was performed, which revealed multiple filling defects affecting the main left pulmonary artery, the lobar and segmental branches for the upper lobe (especially for the lingula) and partial for the lower lobe on the same side, and a further focal filling defect affecting a segmental branch for the upper lobe on the right lung. Additionally, a focal peripheral wedge of airspace opacity was identified at the lingula. These findings were consistent with PE, accompanied by an ischemic infarction. There was also a left dorsobasal pleural effusion (maximum thickness 12 mm) with minimal consensual parenchymal atelectasis. The abdominal enhanced CT scan showed the previous OLT with no recurrent lesions.

To investigate whether PE was provoked, a lower limb venous Doppler study was performed, but excluded bilateral DVT. No central venous catheter was placed. Echocardiography revealed normal findings without any evidence of right ventricular strain pattern, valvular defects or atrial thrombosis. Screening for hepatitis B and hepatitis C was negative. No signs of inflammatory bowel disease were found on the abdominal enhanced CT scan. Complete blood count showed a mild normochromic normocytic anemia (Hb 13.2 g/dL, MCV 87.4 fL, MCH 33 g/dL) and mild thrombocytopenia (PLT 112 $\times$ 10^9/L). Given the unprovoked multifocal PE, further investigations, including thrombophilia screening (activated protein C resistance, antithrombin III, protein C, free protein S, antiphospholipid antibodies and homocysteine are normal; factor V Leiden and factor II do not present mutations), were performed, and all were negative, except a non-specific ANA (antinuclear antibodies) positivity (ANA titer 1:320, spindle fibers pattern) with ENA (extractable nuclear antigen antibodies) and ANCA (antineutrophil cytoplasmic antibodies) negative and complement components C3 and C4 not reduced.

The Pulmonary Embolism Severity Index was calculated at 107 points, placing the patient in Class IV (high risk) with an estimated 30-day mortality of 4.0–11.4%. Therefore, the patient was hospitalized and anticoagulation therapy was initiated with subcutaneous low-molecular-weight heparin (enoxaparin 100 UI/kg twice daily), subsequently switching to oral anticoagulation with edoxaban 30 mg (reduced dose for creatinine clearance 15–49 mL/min) once daily upon discharge. At discharge, tirzepatide had not been restarted, as well as metformin and dapagliflozin.

After three days of hospitalization, CRP increased (160.8 mg/L), while white blood cells remained normal (6.15 $\times$ 10^9/L) and procalcitonin was negative (0.11 µg/L). Beta D-glucan and galactomannan were negative. Virus serology evidenced a previous CMV infection (IgM negative, IgG positive and CMV DNA negative); no EBV infection was detected. For the persistence of increased CPR, an empirical antibiotic therapy with ceftriaxone was initiated for eight days. A new fever peak occurred, and new blood cultures were performed, but were negative. Due to the persistence of pleuritic chest pain and abolition of murmur in the left lung base, a non-enhanced CT scan was performed, and an increase in left apical-basal pleural effusion (maximum thickness 45 mm) with consensual parenchymal atelectasis without modification of findings in the lingula was reported. So, a pulmonology consultation was requested, and furosemide 25 mg once a day and ex adiuvantibus dexamethasone 25 mg once a day were started for one week. Ten days after discharge, a CT scan showed a reduction in pleural effusion (maximum thickness 8 mm) with persistent thickening in the lingula.

At one-month follow-up after discharge, the patient reported complete resolution of symptoms and no adverse effects from edoxaban. Dapagliflozin was restarted two weeks after discharge, while metformin was restarted one month later.

A Naranjo nomogram with a score of 5 indicated a probable relationship between tirzepatide and PE.

3. Discussion

This case report presents an interesting example of the challenges faced in managing PE and evaluating its causes in a former smoker T2DM patient who has recently started treatment with a tirzepatide. In our patients, a definite cause of PE was not identified; however, it is likely that tirzepatide may have contributed to this event.

Obesity is a known risk factor associated with an increased risk of VTE; however, the effect of weight loss on thrombotic risk is conflicting. A large population-based cohort, the Tromsø Study, reported that individuals with obesity who increased their body weight $\geq$ 7.5 kg over time had a 1.9-fold higher risk of VTE when compared to those with

no or a moderate (0–7.4 kg) weight gain (hazard ratio [HR] 1.92; 95% confidence interval [CI] 1.38–2.68) and the VTE risk at ≥7.5 kgs weight gain was highest (HR 3.75; 95% 1.83–7.68) in subjects with baseline BMI ≥ 30 kg/m^2 [13]. Moreover, authors observed an unexpectedly slightly increased risk of provoked VTE with weight loss in overweight and obese subjects (HR 1.38; 95% CI 0.94–2.03), suggesting that a rapid weight fluctuation may exert a prothrombotic effect [13]. Weight loss resulting from bariatric surgery reduces the long-term risk of VTE by ~40% [14]. The mechanism by which obesity increases the risk of VTE is thought to be based on the presence of chronic inflammation, which stimulates the synthesis of plasminogen activator inhibitor 1 (PAI-1), tissue factor (TF), fibrinogen and potentially other factors involved in the coagulation cascade [15].

Pharmacologically inducing weight loss with GLP-1 RAs has also yielded conflicting results. A large-scale target trial emulation involving 540,258 patients with T2DM showed that over 12 months of follow-up, patients who received GLP1-RAs, after propensity score matching, had a lower incidence of VTE compared with patients who received DPP4 inhibitors (DPP4i; 6.1 vs. 7.6 events per 1000 patient-years; HR 0.78; 95% CI 0.73–0.83) and similarly for PE (2.9 vs. 3.8 events per 1000 patient-years; HR 0.74; 95% CI 0.68–0.82) and DVT (3.9 vs. 4.7 events per 1000 patient-years; HR 0.81; 95% CI 0.75–0.88) [7]. A subgroup analysis suggested that the VTE risk was reduced in all patients, regardless of their obesity status at the time of initiation. Although the study does not allow for examining the underlying mechanisms by which GLP1-RAs reduce VTE risk, preclinical data reported that liraglutide reduced thromboxane-induced platelet aggregation by ~50% compared with DPP4i in platelet-rich plasma from whole blood of adults with obesity and prediabetes stimulated with thromboxane receptor agonists [16]. Conversely, a meta-analysis of the SUSTAIN and PIONEER trials showed that semaglutide therapy significantly increased the risk of DVT (RR 3.66, 95% CI 1.09–12.25) compared with placebo, with a 266% increased risk [8]. Different mechanisms have been proposed to explain how GLP-1 RAs could increase the risk of VTE, including an increase in blood viscosity secondary to dehydration and hemoconcentration due to vomiting or diarrhea, as well as endothelial dysfunction or alterations in regional blood flow resulting from changes in vascular tone [10]. Evidence from randomized controlled trials (RCTs) and recent meta-analyses does not support an impact on VTE risk of GLP-1 RA therapy in patients with T2DM or obesity. A recent systematic review and meta-analysis of 27 RCTs with 84,003 patients found no statistically significant difference in overall VTE risk between GLP-1RA and placebo groups (RR 0.70, 95% CI 0.46–1.07), although GLP-1RAs were associated with a significantly lower risk of PE (RR 0.60, 95% CI 0.39–0.94), but not DVP [17]. Another meta-analysis of 39 RCTs, involving 70,499 participants, observed a nonsignificant upward trend in VTE risk (OR 1.19, 95% CI 0.94–1.50) and a significant increase in DVT risk (OR 1.64, 95% CI 1.14–2.36), especially with longer treatment duration (>1.5 years), but no significant effect on PE [18].

In preclinical studies, GLP-1 RAs have shown antiplatelet and antithrombotic properties. Multiple mechanistic studies demonstrate that GLP-1 RAs inhibit platelet function and thrombus formation. Native GLP-1 (7–36) and GLP-1 RAs (exenatide and liraglutide) reduce platelet aggregation induced by thrombin, ADP, collagen, and arachidonic acid [19,20]. Native intact GLP-1 suppresses thrombus growth under physiological flow conditions, reducing thrombus volume by 32% at both venous and arterial shear rates [21]. These antiplatelet effects occur largely independent of the GLP-1 receptor on platelets themselves, suggesting alternative mechanisms [20,21]. No direct preclinical studies of tirzepatide on platelet aggregation are available.

Whether GIP receptor agonism contributes to thrombotic risk remains uncertain. Tirzepatide differs from pure GLP-1 RAs because it is a dual GIP/GLP-1 receptor agonist. GIP may exert some vascular and inflammatory effects. Chen et al. reported that GIP in-

creased expression of inflammatory or fibrinolytic mediators, such as IL-6 and plasminogen activator inhibitor-1, in experimental obesity-related models [22]. GIP has also been shown to induce the expression of the proatherogenic cytokine osteopontin in the vasculature [23]. Further clinical evidence is needed to demonstrate whether agonism on the GIP receptor has a prothrombotic effect.

To date, several case reports have been published regarding the potential risk of tirzepatide, a dual receptor agonist of GIP and GLP-1, as a risk factor for VTE [10]. Farooqi and colleagues reported a case of a 20-year-old young man who developed unprovoked extensive left leg DVP following a 12 kg weight loss over 6 weeks of 7.5 mg tirzepatide [9]. Alsararatee reported a case of a 40-year-old young woman who developed PE following 2 kg weight loss over 20 days of tirzepatide 2.5 mg without an identifiable provoked or unprovoked risk factor for VTE [10]. Sonavane et al. described a case of a 57-year-old obese woman who developed a left subclavian vein following weight loss after 8 months of tirzepatide 10 mg once without provoked or unprovoked risk factors for DVT [11]. Aleem et al. described a case of a 35-year-old obese woman with heterozygosity for prothrombin G20210A mutation who developed PE 3 weeks after initiating tirzepatide without weight loss [24]. We reported a case of a 67-year-old man who developed PE over 33 days of tirzepatide (after 3 days of increasing tirzepatide to 5 mg) with a negligible weight loss (0.5 kg).

Data from clinical trials on the use of tirzepatide in patients with T2DM and/or obesity report a few cases of PE and DVT (Table 1).

Table 1. Randomized clinical trials on the use of tirzepatide in patients with T2DM and/or obesity (the SURPASS and SURMOUNT trials) and associated VTE (PE and DVT).

Study	Study Characteristics	Population	Mean Age (Years)	Baseline Weight (kg)	Control Type	Tirzepatide Dose	Weight Loss vs. Control	PE Tirzepatide *n* (%)	PE Control *n* (%)	DVT Tirzepatide *n* (%)	DVT Control *n* (%)	Total VTE Tirzepatide *n* (%)	Total VTE Control *n* (%)
SURPASS-1 (NCT03-954834) [25]	Phase 3, randomized, double-blind, placebo-controlled	T2DM, drug-naïve, inadequately controlled by diet and exercise alone	54.1	85.9	Placebo	5–10–15 mg	−7.0/−7.8/−9.5 kg vs. −0.7 kg	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SURPASS-2 (NCT03-987919) [26]	Phase 3, randomized, open-label, active comparator	T2DM, inadequately controlled on metformin at a dose of at least 1500 mg per day	56.6	93.7	Semaglutide 1 mg	5–10–15 mg	−7.6/−9.3/−11.2 kg vs. −5.7 kg	1 (0.07)	0 (0)	1 (0.07)	0 (0)	2 (0.14.)	0 (0)
SURPASS-3 (NCT0-3882970) [27]	Phase 3, randomized, open-label, active comparator	T2DM, inadequately controlled on stable treatment with metformin alone or in combination with an SGLT2 inhibitor	57.4	94.3	Insulin degludec	5–10–15 mg	−7.5/−10.7/−12.9 kg vs. +2.3 kg	0 (0)	1 (0.28)	1 (0.09)	0 (0)	1 (0.09)	1 (0.28)
SURPASS-4 (NCT0-3730662) [28]	Phase 3, randomized, open-label, active comparator	T2DM and high cardiovascular risk inadequately controlled on oral glucose-lowering medications	63.6	90.3	Insulin glargine	5–10–15 mg	−7.1/−9.5/−11.7 kg vs. +1.9 kg	1 (0.10)	3 (0.30)	1 (0.10)	2 (0.20)	2 (0.2)	5 (0.5)

Table 1. *Cont.*

Study	Study Characteristics	Population	Mean Age (Years)	Baseline Weight (kg)	Control Type	Tirzepatide Dose	Weight Loss vs. Control	PE Tirzepatide *n* (%)	PE Control *n* (%)	DVT Tirzepatide *n* (%)	DVT Control *n* (%)	Total VTE Tirzeptide *n* (%)	Total VTE Control *n* (%)
SURPASS-5 (NCT04039503) [29]	Phase 3, randomized, double-blind, placebo-controlled	T2DM and inadequate glycemic control while treated with once-daily insulin glargine with or without metformin	60.6	95.2	Placebo + insulin	5–10–15 mg	−5.4/−7.5/−8.8 kg vs. +1.6 kg	0 (0)	1 (0.83)	n.a.	n.a.	0 (0)	1 (0.83)
SURPASS-CVOT (NCT04255433) [30]	Phase 3 CVOT, randomized, double-blind, active comparator	T2DM + atherosclerotic CV disease	64.1	92.6	Dulaglutide 1.5 mg	Up to 15 mg	−11.6 kg vs. −4.8 kg	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SURMOUNT-1 (NCT04184622) [31]	Phase 3, randomized, double-blind, placebo-controlled	Obesity or BMI $\geq$ 27 kg/m^2 and at least one weight-related complication	44.9	104.8	Placebo	5–10–15 mg	−15.0/−19.5/−20.9% vs. −3.1%	2 (0.11)	3 (0.47)	1 (0.05)	0 (0)	3 (0.16)	3 (0.47)
SURMOUNT-2 (NCT04657003) [32]	Phase 3, randomized, double-blind, placebo-controlled	BMI $\geq$ 27 kg/m^2 + T2DM with HbA_{1c} of 7–10% on stable therapy, either diet and exercise alone or oral antihyperglycemic medication	54.2	100.7	Placebo	10–15 mg	−12.8/−14.7% vs. −3.2%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SURMOUNT-3 (NCT04657016) [33]	Phase 3, randomized, double-blind, placebo-controlled (after lifestyle run-in)	Obesity or BMI $\geq$ 27 kg/m^2 and at least one weight-related complication (excluding diabetes) post intensive lifestyle	45.6	101.9	Placebo	10–15 mg	−18.4% vs. −2.5%	0 (0)	1 (0.34)	n.a.	n.a.	0 (0)	1 (0.34)
SURMOUNT-4 (NCT04660643) [34]	Phase 3, randomized, double-blind, withdrawal design	Obesity or BMI $\geq$ 27 kg/m^2 and at least one weight-related complication (excluding diabetes)	48	85.2	Placebo	10–15 mg	−5.5% vs. +14.0%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SURMOUNT-5 (NCT05822830) [35]	Phase 3b, randomized, open-label, head-to-head	Obesity or BMI $\geq$ 27 kg/m^2 and at least one weight-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)	44.7	113.0	Semaglutide (1.7 or 2.4 mg)	10, 15 mg	−20.2% vs. −13.7%	1 (0.27)	0 (0)	n.a.	n.a.	1 (0.27)	0 (0)

Legend: BMI: body mass index; CV: cardiovascular; HbA_{1c}: glycated hemoglobin; *n*: number; n.a.: not available; T2DM: type 2 diabetes mellitus; vs.: versus.

The role of anti-diabetic drugs, such as sodium–glucose cotransporter type 2 inhibitors (SGLT2i) or metformin, in VTE has also been investigated. A population-based cohort study assessed whether SGLT2 inhibitors are associated with a higher incidence rate of VTE in 219,538 patients with T2DM [36]. Compared with DPP-4i, the use of SGLT2i was associated

with a lower rate of VTE (relative risk [RR] 0.75; 95% CI 0.59–0.94), despite SGLT2i causing volume depletion and increasing hematocrit values, which could lead to a consequent increased risk of VTE. Conflicting evidence is reported about the role of metformin as a risk factor for VTE. A general-population-based cohort study evaluated the risk of VTE among individuals initiating metformin compared to those initiating sulfonylurea [37]. A lower risk of VTE was observed after initiation of metformin (1.3/1000 person-years) compared with sulfonylureas (2.1/1000 person-years). The protective effect of metformin can be exerted through various mechanisms. Metformin enhances endothelial cell integrity and adherence [38], inhibits platelet adhesion and aggregation [39], and reduces fibrinogen levels, thereby decreasing the activity of coagulation factors such as factor VII and factor XIII [40]. Conversely, some authors have demonstrated that metformin leads to hyperhomocysteinemia, which causes oxidative damage to endothelial cells [41].

Our patient had OLT secondary to hepatocellular carcinoma (HCC) and MASLD-cirrhosis. Cancer-associated thrombosis is a well-recognized complication of malignancy, with the highest risk occurring within the first 3 to 6 months after cancer diagnosis [42]. HCC is characterized by a complex disruption of hemostatic balance, increasing the risk of both thrombotic and hemorrhagic events [43]. Multifactorial mechanisms are implicated in thrombotic risk: HCC often develops in the setting of cirrhosis, characterized by rebalanced but unstable hemostasis, in which both procoagulant and anticoagulant pathways are concurrently impaired [43]. Increased thrombin generation, platelet activation, hypofibrinolysis, and increased fibrinogen levels are among the processes underlying hypercoagulability; also, endothelial dysfunction and systemic inflammation contribute [43]. OLT is associated with a postoperative risk of vascular and systemic thrombotic complications. In a cohort of 430 patients who underwent OLT for HCC, Martinelli et al. reported thrombotic events in 6% of recipients after a median time of 19 days (IQR 12–731) from OLT [44].

Immunosuppressive drugs, used in solid organ transplant recipients (liver, kidney, lung), such as tacrolimus, everolimus, cyclosporine, sirolimus and mycophenolate mofetil, have been associated with variable effects on the risk of PE. A retrospective study considered 999 solid organ transplant recipients (661 renal and 338 liver transplant recipients) to evaluate the frequency of PE in solid organ transplant recipients during the first 10 years after transplantation and the risk factors for its development [45]. Twelve renal (1.2%) and 1 liver transplant recipient (0.3%) were diagnosed with PE, mainly in the first year after transplantation, with 5 patients receiving tacrolimus. Evidence on the role of tacrolimus, a calcineurin inhibitor used after organ transplantation to prevent rejection, in the development of VTE events is not conclusive. It has been reported that in vitro tacrolimus has antithrombotic effects, reducing platelet aggregation and thrombus formation [46]. In contrast, there is also evidence associating tacrolimus with thrombotic disorders, such as drug-induced thrombotic microangiopathy following solid organ transplantation, suggesting a direct endothelial injury caused by tacrolimus [47]. It is possible that the prothrombotic effect observed in patients undergoing solid organ transplantation is secondary to concomitant long-term corticosteroid therapy, which leads to a state of hypercoagulation and hypofibrinolysis similar to that seen in Cushing's disease [48]. Also everolimus, an mTOR inhibitor, has been associated with an increased risk of VTE as reported by a case report in a kidney transplantation recipient [49]. Moreover, in a retrospective case–control study in 55 lung transplant recipients, a higher proportion of VTE in the group treated with everolimus compared to the control was observed [9 (16%) vs. 1 (2%), $p = 0.02$], suggesting that everolimus may trigger VTE via a class effect of sirolimus and on PAI-1 expression. Further evidence from prospective studies is needed to evaluate the role of tacrolimus and everolimus as a risk factor for PE [50].

About the PE episode, our patient had started immunosuppressive therapy with tacrolimus and everolimus 24 months earlier, initially combined with corticosteroid therapy (for a duration of four months), metformin for 20 months, dapagliflozin for 20 months and tirzepatide for 33 days. We consider it unlikely that immunosuppressive drugs could have caused PE, particularly in view of the inconclusive evidence for tacrolimus, the lack of evidence of an increased risk of VTE in patients undergoing liver transplantation and the occurrence of PE with a stable immunosuppressive dose associated with an increase in tirzepatide dose. Similarly, we do not believe that either metformin or dapagliflozin is a causal factor. The relationship between tirzepatide initiation and symptom onset supports the possibility of a drug-related adverse effect.

In our patients, it is challenging to determine whether an infectious/inflammatory disease was present simultaneously and may have been a risk factor for VTE. The presence of fever and an increase in CRP suggest an infectious/inflammatory event; however, no viral, bacterial, or fungal isolation was detected in blood, urine, or respiratory swabs. A rise in CPR may be secondary to pulmonary embolism due to lung tissue damage and ischemic infarction. Moreover, PE may be accompanied by fever and show evidence of pulmonary infiltrates on X-ray, making the differential diagnosis from pneumonia challenging [4]. PE has a more sudden onset, and dyspnea is more prominent than cough and sputum, with chest pain usually present. In addition, dyspnea-related PE has no radiological features and is not responsive to antibiotics, with fever typically occurring later in the disease [4]. Pneumonia typically has a progressive onset, characterized by a more prominent cough, sputum production, and a fever that often appears earlier [4]. CT alterations demonstrated a focal peripheral wedge of airspace opacity at the lingula, compatible with ischemic infarction. The persistence of CT alteration after one month makes concomitant pneumonia less likely.

Our patient was a former smoker who smoked 40 cigarettes a day for 35 years (70 pack years). Smoking is a known risk factor for VTE. Evidence from large meta-analyses and prospective cohort studies indicates that former smokers have a risk of VTE that is either only slightly elevated or like that of never smokers. A systematic review and meta-analysis found a relative risk of 1.17 (95% CI 1.09–1.25) for ever smokers, 1.23 (95% CI 1.14–1.33) for current smokers, and 1.10 (95% CI 1.03–1.17) for former smokers compared to never smokers [51]. On the other side, several large prospective studies report no significant difference in VTE risk between former and never smokers, suggesting that the increased risk associated with smoking is largely reversible after cessation [52,53]. The residual risk of VTE in former smokers is influenced by both the cumulative smoking exposure (pack-years) and the duration since smoking cessation. The meta-analyses cited above reported a dose–response relationship: the risk increased by 10.2% (95% CI, 8.6–11.8%) for every additional ten cigarettes per day smoked or by 6.1% (95% CI, 3.8–8.5%) for every additional ten pack-years. A recent Mendelian randomization analysis suggests a causal link between pack-years and an increased risk of VTE [54]. Despite this, and even if our patient is a former smoker, smoking may not be a strong risk factor for VTE in this specific clinical case.

4. Conclusions

Our clinical case describes the occurrence of PE following the initiation of tirzepatide: despite the presence of multiple concomitant factors, the temporal relationship between the start of tirzepatide and the PE suggests a possible link. Awareness of VTE/PE symptoms remains clinically important, and suspected cases should be recognized and assessed according to standard clinical practice. The mechanisms by which tirzepatide might cause VTE are currently unclear: further studies are needed into the in vitro and in vivo effects

of tirzepatide on coagulation and fibrinolysis pathways and whether tirzepatide plays any role in thromboembolic risk. Patients should be informed about the characteristic signs and symptoms, and a risk assessment, evaluating the presence of risk factors and family history of VTE, should be performed before initiating tirzepatide therapy. Further research is needed to elucidate the underlying mechanisms and confirm these findings in larger populations.

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Abbreviations

The following abbreviations are used in this manuscript:

ANA	Antinuclear Antibody
ANCA	Antineutrophil Cytoplasmic Antibodies
APCR	Activated Protein C Resistance
aPTT	activated Partial Thromboplastin Time
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Renal Disease
CMV	Cytomegalovirus
CRP	C-Reactive Protein
CT	Computed Tomography
CV	Cardiovascular
DDP-4i	Dipeptidyl Peptidase-4 inhibitors
DVT	Deep Vein Thrombosis
EBV	Epstein–Barr Virus
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENA	Extractable Nuclear Antigens
FiO2	Fraction of inspired Oxygen
FDA	Food and Drug Administration
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP-1 RAs	GLP-1 Receptor Agonists
Hb	Hemoglobin
HbA_{1c}	Glycated Hemoglobin
HCO_3^-	Bicarbonate
HR	Hazard Ratio
INR	International Normalized Ratio
MASLD	Metabolic dysfunction-Associated Steatotic Liver Disease
MCH	Mean Corpuscular Hemoglobin

MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
OLT	Orthotopic Liver Transplantation
PAI-1	Plasminogen Activator Inhibitor 1
PCO_2	Partial pressure of Carbon Dioxide
PLT	Platelet count
pO_2	Partial pressure of Oxygen
PE	Pulmonary Embolism
RCTs	Randomized Controlled Trials
RR	Relative Risk
SGLT2i	Sodium–Glucose co-transporter-2 inhibitors
SpO_2	Peripheral Oxygen Saturation
T2DM	Type 2 Diabetes Mellitus
TF	Tissue Factor
VTE	Venous Thromboembolism

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