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VARIOUS CASES OF VENOUS THROMBEMBOLISM

Ivica Bojovski[1, 2], Emilija Lazarova Trajkovska[1, 2], Dimitar Galachev[3], Simona Jovchevska[2], Ivona Bogevska Naumovska[2], Tomislav Konjanovski[2], Elif Vrajnko[1, 2], Vegim Zhaku[4], Ile Kuzmanoski[2], Miroslav Boskovski[5], Irena Bede[6], Bekim Pocesta[1, 2], Marijan Bosevski[1, 2]
Collaborators: Enes Shehu[1, 2], Robert Nikolovski[1, 2], Natasha Skrcheska[6], Mario Jovanoski[1, 2], Valentina Andova[1, 2,] Irena Mitevska[1, 2]

[1] Ss Cyril and Methodius University, Faculty of medicine, Skopje, RN Macedonia
[2] University clinic of cardiology, Skopje, RN Macedonia
[3] PHI Echomedika, Kocani, RN Macedonia
[4] Tetovo University, Faculty of Medicine, Tetovo, RN Macedonia
[5] PHI D-r Goran Denkovski, Kumanovo, RN Macedonia
[6] Special hospital for cardiovascular diseases, Ohrid, RN Macedonia

Corresponding author: Ivica Bojovski, MD, Marijan Bosevski, PhD, Ss. Cyril and Methodius University, Faculty of medicine, University clinic of cardiology, Mother Tereza 17, Skopje, N.Macedonia, email: ivicabojovski@hotmail.com, Phone 078848845

ABSTRACT

Venous thromboembolism (VTE) with its two forms: deep vein thrombosis (DVT) and pulmonary embolism (PE) occurs due to interacting genetic and environmental risk factors. The strongest risk factors are major surgery, major trauma and malignancies. Over the last decade many new risk factors for venous thrombosis have been identified. Even risk factors, clinical signs, symptoms and diagnostic methods of venous thromboembolism (VTE) are well known, there are still uncommon scenarios for this disease. This paper includes eight case reports of venous thromboembolism with different etiologies. Ongoing studies in this field are focused on improving diagnostic strategies for suspected venous thrombosis, comparing different direct oral anticoagulants (DOACs), developing safer anticoagulants, and further individualizing approaches for the prevention and management of VTE.

Keywords: venous thromboembolism, deep vein thrombosis, pulmonary

INTRODUCTION

Venous thromboembolism (VTE) is a disease involving two forms: deep vein thrombosis (DVT) and pulmonary embolism (PE).Venous thrombosis manifests mainly as deep vein thrombosis of the lower extremities and pulmonary embolism. Over the last decade many new risk factors for venous thrombosis have been identified. The causes of venous thrombosis are genetic, acquired, behavioral, and combinations of disease. Risk factors can be distinguished as major (strong association with index venous thrombosis; likely responsible of index event), intermediate (moderate association with index venous thrombosis, probably responsible of index event), or minor (weak association with index VTE; might partly explain index event). Another classification divides the risk factors in *strong* (OR>10): Major surgery (orthopedic and neurological)/major trauma, re-

cent (<3 months) hospitalization for acute heart disease, prior venous thromboembolism, antiphospholipid syndrome, active cancer (depends on type and stage)/chemotherapy; *moderate* (OR 2-9): arthroscopic knee surgery, venous catheters, oral contraception/hormone replacement therapy/ in vitro fertilization (depends on dose and type of hormone), pregnancy or postpartum period, inflammatory and autoimmune diseases, infections, active cancer (depends on type and stage)/chemotherapy, congestive heart or respiratory failure, genetic thrombophilia, superficial vein thrombosis (>3 cm from SFJ or PJ and >5 cm length), stroke with residual hemiparesis/hemiplegia; and *weak* risk factors (OR<2): bed rest (>3 days)/immobility (prolonged sitting position, i.e. travel), age. (Table 1) [1].

Public awareness of thrombosis is low, and fewer people have basic knowledge of its symptoms and risk factors than they have of other major vascular diseases, such as myocardial infarction and stroke. To reduce the burden of thrombosis, it is necessary to know the factors that contribute to its occurrence. This will lead to risk stratification and targeted prevention and treatment.[2]

Diagnosis requires a sequential work-up that combines assessment of clinical pretest probability for venous thromboembolism using a clinical score (e.g., Wells score), D-dimer testing, and imaging. Venous thromboembolism can be considered excluded in patients with both a non-high clinical pretest probability and normal D-dimer concentrations. When required, ultrasonography should be done for a suspected deep vein thrombosis and CT or ventilation-perfusion scintigraphy for a suspected pulmonary embolism. [3]

The duration of anticoagulation therapy in patients with provoked VTE is clear, but in patients with verified genetic inheritance without known risk factors, this duration is still questionable.[4]

Risk factors, clinical signs, symptoms and diagnostic methods of VTE are well known, yet there are still uncommonscenarios for this disease. [5] This paper includes eight case reports of venous thrombosis.

CASE REPORTS

Case 1. An unusual case of pulmonary carcinoma associated with multiple thrombotic manifestations

Patients with malignancy may present with significant thromboembolic complications including deep vein thrombosis (DVT), pulmonary

Table 1. *Deep vein thrombosis risk factors*

	Risk factors
Strong risk factors (OR ≥ 10)	• Major surgery (orthopedic and neurological)/major trauma • Recent (<3 months) hospitalization for acute heart disease • Prior venous thromboembolism • Antiphospholipid syndrome • Active cancer (depends on type and stage)/chemotherapy
Moderate risk factors (OR 2–9)	• Arthroscopic knee surgery • Venous catheters • Oral contraception/hormone replacement therapy/in vitro fertilization (depends on dose and type of hormone) • Pregnancy or postpartum period • Inflammatory and autoimmune diseases • Infections • Active cancer (depends on type and stage)/chemotherapy • Congestive heart or respiratory failure • Genetic thrombophilia • Superficial vein thrombosis (>3 cm from SFJ or PJ and >5 cm length) • Stroke with residual hemiparesis/hemiplegia
Weak risk factors (OR < 2)	• Bed rest (>3 days)/immobility (prolonged sitting position, i.e. travel) • Age

embolism (PE), arterial thrombosis (AT) and stroke due to abnormal coagulation cascades. Although these events are typically recognized later in the disease process, complications of a hypercoagulable state can rarely present as the first manifestation of an occult malignancy. We report on a case of a54 year oldfemale who was ultimately found to have an aggressive form of lung adenocarcinoma after the initial presentation of multiple thromboembolic events. A CT scan also revealed extensive infiltration of the left lung and pleura, including soft tissues of the left thoracic wall, in the pectoral muscle and left breast. Extra-thoracic metastases were also found.Screening for occult cancer should be given special consideration, especially in younger patients with no prior risk factors.

Case 2. Pulmonary embolism associated with combined oral contraceptives use after IVF treatment

We present a case of pulmonary embolism (PE) in a 47–year-old woman who was using combined oral contraceptives (COCs) (triptorelin and urofollitropin) containing the fourth generation progestogen (drospirenone) as part of in-vitro fertilization (IVF) treatment.

A 47-year-old woman reported to our clinic with left leg pain and swelling. Prior to this, the patient had undergone two IVF treatments that had failed and she had been taking a combined oral contraceptive pill containing drospirenone until 1 month before presenting to the clinic. The patient did not have any history of previous thrombosis and she was a smoker. There was also no family history of thrombosis. Doppler ultrasound showed left lower extremity deep venous thrombosis (DVT), in the common femoral and popliteal vein. D-Dimer levels were increased. The patient was admitted to the Intensive Care Unit (ICU) of our hospital. A transthoracic echocardiogram revealed normal left ventricle function and dilated right ventricle but with preserved systolic function. Next, computed tomography pulmonary angiogram (CTPA) was performed, showing acute pulmonary embolism, which confirmed the diagnosis of acute bilateral PE. The patient received standard anticoagulation treatment with unfractionated heparin, then was switched to NOAC–Apixabanaccording to the protocol. After a 12-day course of hospital treatment, she was discharged on Apixaban. At 1-year follow-up the patient was well without any new episodes of recurrent DVT or PE. Doppler ultrasound showed residual thrombus in the common femoral vein and complete resolution of thrombus on the popliteal vein. Echocardiographic findings were normal. The patient continued with oral anticoagulation.

Use of COCs due to IVF has been considered a risk factor for venous thrombosis. With increasing use of assisted reproductive techniques, especially in women with advanced age, obesity and smoking, it is important for clinicians to assess risk of VTE in patients and to adopt appropriate modified risk-reduction strategies to make treatment safer.

Case 3. Bilateral massive pulmonary embolism with co-existing massive pneumonia and distal deep venous thrombosis following arthroscopic meniscus surgery

A 50-year-old patient was admitted to our hospital experiencing chest pain, dyspnea, and hemoptysis. One month prior, the patient underwent a successful arthroscopic meniscus repair without any complications during the procedure. Upon admission, the patient's vital signs were recorded as follows:heart rate: 150 beats per minute, respiratory rate: 20 breaths per minute, and oxygen saturation (SaO2) 85%. The blood pressure and the body temperature were normal. The ECG findings showed sinus tachycardia, T wave inversion in D1, aVL, and ST depression in V5-V6 leads. Common inflammatory biomarkers and D-dimers were significantly elevated. An echocardiogram showed normal dimensions and longitudinal function of the right ventricle. A CT angiography of the lungs revealed a massive bilateral PE with co-existing pneumonia. Workup for DVT was initiated, and doppler ultrasound on the lower extremities confirmed deep vein thrombosis in the right popliteal vein. The patient had no risk factors except for anxiety-depressive disorder and prior use of antidepressant medications. Due to hemodynamic deterioration, fibrinolytic treatment with alteplase 100mg over 2 hours was initiated, followed by a 24-hour infusion of unfractionated heparin. Subsequently, the patient received therapeutic doses of apixaban according to the PE protocol. After a two-week hospitalization period, the patient was discharged in an improved condition. A follow-up lung CT angiography conducted three months later revealed significant improvement in the local findings, while doppler ultrasonography de-

tected no signs of deep vein thrombosis between the common femoral and popliteal veins.

Arthroscopic meniscus surgery is a minimally invasive procedure that elevates the risk of developing DVT and PTE due to immobility and increased blood coagulation. The coexistence of pulmonary thromboembolism and pneumonia continues to account for an important proportion of early deaths. Prioritizing prompt and adequate anticoagulation therapy is crucial for decreasing mortality associated with venous thromboembolism.

Case 4.Obesity and bariatric surgery as risk factors for thrombotic events

Obesity is a well-known risk factor for thrombotic events. Bariatric surgery, although effective for weight loss, may also introduce additional risks for thrombosis. Understanding the association between obesity, bariatric surgery, and thrombotic complications is crucial for effective management and prevention.

This case report aims to elucidate the potential link between obesity, bariatric surgery, and thrombotic events, focusing on the presentation, management, and outcomes of a woman who developed thrombosis post-bariatric surgery. A 37-year-old woman with a BMI of 34 presented with swelling in the right leg one and a half months after undergoing bariatric surgery. Doppler ultrasonography of the lower extremities revealed a dilated right great saphenous vein and multiple thrombi in the right great and small saphenous vein, along with spontaneous echo contrast on both legs. Treatment with therapeutic dose of low molecular weight heparin (LMWH) - Enoxaparin 1mg/kg BW daily) was initiated for ten days and then continued with direct oral anticoagulant(DOAC). On the follow-up Doppler after one month, there were no more thrombi present in the right great and small saphenous veins; however, evidence of spontaneous echo contrast persisted in the left great and small saphenous veins. The patient continuedwithfull dose DOAC for 4 months.

This case highlights the importance of recognizing obesity and bariatric surgery as significant risk factors for thrombotic events. Prompt diagnosis, initiation of anticoagulation therapy, and vigilant monitoring are essential in managing thrombotic complications post-bariatric surgery. Further research and awareness are warranted to optimize preventative strategies in this high-risk population.

Case 5. Pulmonary embolism in moderate high-risk patient complicated with obstructive shock

Pulmonary thromboembolism (PE) has a high morbidity and mortality rate, in spite of its early diagnosis and treatment. Moderately high-risk patients are a therapeutic challenge due to the possibility of deterioration during hospitalization. Early detection of hemodynamic deterioration and the initiation of fibrinolytic treatment are crucial for the outcome of these patients.

A 57-year-old diabetic patient was hospitalized at theintensive cardiac care unit(ICCU) of thecardiology clinic, with an admission diagnosis of acute coronary syndrome. Uponadmission, the patient had chest pain, dyspnea, ECG changes with inverted T waves in the inferior leads, sinus rhythm with a heart rate of 90/min, slightly elevated troponin, normal blood pressure, and an oxygen saturation of 89%. Treatment with low-molecular-weight heparin (LMWH), antiplatelet therapy, statins, and ACE inhibitors was started. Laboratory analyses on admission showed elevated values of D-dimer=2593ng/mL, troponin 60 ng/L, NT-proBNP 3077 pg/mL, CRP 27.9 mg/l. Transthoracic echocardiography was performed with findings of dilated right heart cavities, D-shape of the left ventricle, signs of PAH, reduced right ventricular function, and TAPSE 15, with normal global and regional left ventricular function. The signs were highly suspected for acute PE. A CT pulmonary angiography (CTPA) was performed, which showed acute PE with a high pulmonary obstructive index (>25) of mainly central and lobar type. The estimated simplified pulmonary embolism severity index (sPESI) score was >1. Continuous UFH therapy was initiatedaccording to protocol. On the second day after admission, due to the worsening of the clinical condition with dyspnea, a drop in SpO2 of 85%, and a lower blood pressure of 90/60 mmHg, fibrinolytic therapy was initiated with Actilyse according to the protocol. Hemodynamic stability occurred after several hours, with normalizing of BPand HR. SpO2 was 93%. The patient was stable during the following days, without bleeding complications. After fibrinolytic therapy, UFHwas continued, and after that was switched to DOAC. After a18-day hospital stay, the patient was discharged in stable condition

with normalized right ventricular function and a recommendation to continue DOAC for a period of 6 months due to the absence of a major precipitating factor for acute BTE.

Our patient is an example of a patient with PE, initially moderate-high-risk, who was successfully treated despite the worsening of the clinical condition and the development of obstructive shock. Treatment should be considered according to the cost-benefit effect of the medical condition. Timely initiation of fibrinolytic therapy in cases of hemodynamic deterioration is of crucial importance for the outcome in these patients.

Case 6. Gallbladder cancer, metastatic adenocarcinoma and peritoneal carcinosis presented with cancer-associated thrombosis

Gall bladder cancer (GBC) is a rare malignancy originating from the gallbladder epithelium, and its association with cancer-associated thrombosis (CAT) remains poorly understood. The incidence of CAT fluctuates depending on the patient demographics, duration of surveillance, and methodologies employed for detecting and documenting thrombotic occurrences.

We describe a case of a 69-year-old female with a history of GBC with metastatic adenocarcinoma, carcinosis peritonei and ascites, who presented with pain and left arm swelling. Laboratory findings right before hospitalization revealed leukocytosis (17.3 x 10^9/L) and elevated d-dimer (>10.000 ng/ml). Doppler ultrasound of the upper extremities showed total occlusion of the axillary and brachial vein, along with thrombotic particles observed in the subclavian vein. During hospitalization the patient complained about chest pain and a CT angiography showed discrete central defects in opacification of the distal segmental arteries for both lower lobes, consistent with CAT. Management included therapeutic anticoagulation and initiation of chemotherapy. Despite the treatment, the patient passed away dueto complications of advanced malignancy. This case highlights the importance of recognizing CAT as a potential complication of GBC and underscores the challenges in its management, necessitating a multidisciplinary approach for optimal outcomes.

Further research is warranted to elucidate the underlying mechanisms and develop targeted therapeutic strategies for CAT in GBC patients.

Case 7. Varicose veins as a predisposing factor for deep venous thrombosis and PE

Varicose veins are a very common finding amongthe general population. Although they present as a weak risk factor for the development of DVT and PE, some studies show that they can cause a 5.3-fold increased risk of the above-mentioned diseases. With this case report, we want to highlight the importance of recognizing these risk factors in the absence of others, as they could majorly contribute to clot formation.

We present the case of a 63-year-old female patient who presented in our clinic with pain in the left calf that started one week before hospitalization. The patient also had elevated d-dimers (14714g/ml). The patient's medical history also revealed paroxysmal atrial fibrillation, with a CHA2DS2-VASc Score=1, so anticoagulation therapy hadnot been initiated. The patient had a history of varicose veins for several years. The laboratory findings showed moderately elevated inflammation markers. The echocardiography findings were within normal values. The Doppler ultrasonography excluded DVT, but showed saphenous-femoral reflux on the left extremity. The patient was stratified in the moderate risk group for DVT, according to Wells' criteria. Two weeks after the initial symptoms, a CT scan for PE was performed. The patient had a Geneva score of 7 points which stratified the patient in the moderate risk group for PE. The CT findings confirmed the diagnosis of PE, which additionally supports the theory of thrombus formation in the deep veins and its passage in the pulmonary trunk, in the absence of other risk factors other than varicose veins. The patient was treated with anticoagulant therapy with subsequent improvement of the patient's condition.

Weak risk factors, such as varicose veins, might be underestimated in the absence of major risk factors. The stasis in the varicose veins is an important pathophysiological mechanism, that can initiate more severe complications. The risk is the highest during the first year of diagnosis, and even higher if other predisposing factors are present. Stasis and venous reflux play a key role in clot formation. Patients with C3 or higher CEAP grade represent a higher risk factor for concomitant DVT. Early recognition and treatment of varicose veins, as early as in the phase of venous reflux, plays an important role in the prevention of such complications.

Case 8. Cancer associated thrombosis and Hodgkin lymphoma

Cancer associated thrombosis (CAT) is a frequent complication in patients with malignancy. Not infrequently, however, it can be the first and only symptom in patients with malignancy – Hodgkin lymphoma. The first manifestation of the disease was superficial venous thrombosis on the right great saphenous vein (GSV). A 35-year-old man arrived at the clinic with an elevated temperature of 39C, malaise and sweating in the previous week. One day before, he experienced pain in the lower back right part of the abdomen, as well as swelling, pain, redness along the right leg. Laboratory findings showed increase inflammatory markers: leukocytosis - 33x10 9 /L with neutrophil predominance and high CRP. Doppler ultrasound of arterial and venous blood vessels of the legs finds dilated, tortuous, varicose right great saphenous vein along its entire length, and thrombus in the proximal segment. Ultrasound of the abdomen showed several enlarged lymph glands in both groins, the largest in right (up to 70mm), with a compressive effect on the great saphenous vein. Low molecular weight heparin(LMWH), according to protocol, was initiated. CT of abdomen and small pelvisand diagnostic puncture of the right lymph gland were performed. The patient had previously had an episode of thrombosis on the same leg several years ago. Phlebectomy and stripping of the right GSV with occlusion of the present perforatorsby vascular surgeon was performed. In the same act the lymph gland on the right side has been extirpated. Pathohistological finding showed Hodgkin lymphoma with nodular lymphocytic predominance. According to the Ann-Arbor classification, this patient was classified in stage 3 and started therapy per ABVD protocol. For the entire time the patient was on a prophylactic dose of LMWH.

Carcinoma-associated thrombosis (CAT) is one of the main causes of morbidity and mortality in patients with malignancy. About 4-20% of patients with malignancy develop CAT in one of the stages of the disease. The rate of recurrent venous thromboembolism in patients with malignancy is three times higher compared to patients without malignancy, while the risk of bleeding is 2–6 times higher.

CONCLUSION

The differences in risk factors, clinical manifestations, and clinical outcomes in patients with venous thrombosis are still interesting areas for research [5]. Future aims to come to targeted prevention, and treatment will follow from the integration of the large number of risk factors in individual risk prediction tools. Ongoing studies focus on improving diagnostic strategies for suspected venous thrombosis, comparing different DOACs, developing safer anticoagulants, and further individualizing approaches for the prevention and management of venous thromboembolism.

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Резиме

РАЗЛИЧНИ СЛУЧАИ НА ВЕНСКИ ТРОМБЕМБОЛИЗАМ

Ивица Бојовски[1, 2], Емилија Лазарова Трајковска[1, 2], Димитар Галачев[3], Симона Јовчевска[2], Ивона Богевска Наумовска[2], Томислав Коњановски[2], Елиф Врајнко[1, 2], Вегим Жаку[4], Иле Кузмановски[2], Мирослав Бошковски[5], Ирена Беде[5], Беким Поцеста[1, 2], Маријан Бошевски[1, 2]
Соработници: Енес Шеху[1, 2], Роберт Николовски[1, 2], Наташа Скрческа[5], Марио Јованоски[1, 2], Валентина Андова[1, 2], Ирена Митевска[1, 2]

[1] Универзитет „Св. Кирил и Методиј“, Медицински факултет, Скопје, РС Македонија
[2] Универзитетска клиника за кардиологија, Скопје, РС Македонија
[3] ПЗУ „Ехомедика“, Кочани, РС Македонија
[4] Медицински факултет на Универзитетот во Тетово, Тетово, РС Македонија
[5] ПЗУ „Д-р Горан Денковски“, Куманово, РС Македонија
[6] Специјална болница за кардиоваскуларни болести, Охрид, РС Македонија

Венскиот тромбоемболизам (ВТЕ), со неговите два ентитета: длабока венска тромбоза (ДВТ) и белодробната емболија (БЕ), се јавува како резултат на интеракција на генетски фактори и фактори на околината. Најсилните фактори на ризик се: поголеми хируршки интервенции, поголеми трауми и малигнитетите. Во текот на последната деценија идентификувани сев ногу нови фактори на ризик за венската тромбоза. Иако факторите на ризик, клиничките знаци, симптомите и дијагностичките методи на венскиот тромбоемболизам (ВТЕ) се добро познати, сè уште има невообичаени сценарија за оваа болест. Овој труд вклучува осум приказина случаи на венски тромбемболизам со различни етиологии. Тековните истражувања на ова поле се фокусирани на подобрување на дијагностичките стратегии за суспектна венска тромбоза, споредување различни директни орални антикоагуланси, развој на побезбедни антикоагуланси и понатамошно индивидуализирање на пристапите за превенција и управување со ВТЕ.

Клучни зборови: венски тромбоемболизам, длабока венска тромбоза, белодробна емболијаа