

SPECIAL CONDITIONS IN VENOUS THROMBOEMBOLISM – CASE SERIES

Marijan Bosevski¹, Irena Mitevska¹, Marica Pavkovic², Milka Klincheva³, Emilija Trajkovska Lazarova¹, Emilija Velkova⁴, Zlate Stojanoski², Nela Kostova¹, Savetka Paljoskovska Jordanova¹, Danica Petkoska¹, Mimi Mancheva¹, Aleksandra Gulevska⁵, Marjan Baloski⁵, Vasko Hadjiev⁶, Gorjan Krstevski¹, Viktorija Krlevska¹, Ivica Bojovski¹, Mario Jovanovski¹, Vesna Nedelkovska⁷, Atanas Gjorgievski¹

¹ University Cardiology Clinic, Faculty of Medicine Skopje

² University Clinic of Hematology Skopje

³ Zan Mitrev Clinic Skopje

⁴ Institute for Transfusion Medicine Skopje

⁵ General Hospital 8th September

⁶ Private Outpatient Health Facility “D-r. Hadjiev”, Bitola

⁷ General Hospital Veles, R.N. Macedonia

Corresponding author: Marijan Bosevski, Address: University Cardiology Clinic, 16 Vodnjanska Street, postal code: 1000, city: Skopje, country: Macedonia, Telephone number: 0038923147184 ; E-mail: marijanbosevski@yahoo.com

ABSTRACT

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a preventable cause of in-hospital death, and one of the most prevalent vascular diseases. There is a lack of knowledge with regards to contemporary presentation, management, and outcomes of patients with VTE. Many clinically important subgroups (including the elderly, those with recent bleeding, renal insufficiency, disseminated malignancy or pregnant patients) have been under-represented in randomized clinical trials. We still need information from real life data (as example RIETE). The paper presents case series with VTE in special conditions, including cancer associated thrombosis, malignant homeopathies, as well in high risk population.

Keywords: venous thromboembolism, pulmonary embolism, deep vein thrombosis, cancer associated thrombosis, malignant homeopathies, high risk

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a preventable cause of in-hospital death, and one of the most prevalent vascular diseases. There is a lack of knowledge with regards to contemporary presentation, management, and outcomes of patients with VTE. Many clinically important subgroups (including the elderly, those with recent bleeding, renal insufficiency, disseminated malignancy or pregnant patients) have been under-represented in randomized clinical trials [1,2]. Further, design of clinical trials is challenging in some scenarios, such as in those with haemodynam-

ically-unstable PE. RIETE (Registro Informatizado Enfermedad TromboEmbolica) is a large prospective international ongoing registry, designed to address these unmet needs using representative data from multiple centers. RIETE has helped characterize the pattern of presentation and outcomes of VTE, including in the aforementioned understudied subgroups [3]. Its results could be helpful for improving our understanding of the epidemiology, patterns of care and outcomes of patients with thrombotic disease [4].

We have presented 18 cases of Venous thromboembolism in special situations, conditions, includ-

ed cancer associated thrombosis. All of them were presented at Symposium on Venous thromboembolism held in Skopje on April 5th and 6th 2019 and organized by Macedonian Society of Cardiology and endorsed by the European Society of Cardiology.

Case 1. We are presenting the role of transthoracic echocardiography (TTE) in diagnosis of PE in successfully treated critically ill patient. Case report: 72-year-old woman presented in emergency room with severe dyspnea and syncope one hour before admission. Her blood pressure was 90/60mmHg. ECG showed sinus tachycardia and right bundle branch block. Patient had reduced lung breathing, respiratory rate 28/min, SpO₂ 85%. There were no signs of deep vein thrombosis. She has been treated for hypertension and was hospitalized, due to ischemic stroke three months ago with no other comorbidities. Investigations: Urgent 2D echocardiography showed signs of pulmonary artery hypertension (PAH) with dilated right ventricle (RV), D-shaped left ventricle, dilated and incompressible vena cava (23mm), hypokinesia of the mid right ventricle free wall (McConnell's sign), severe tricuspid regurgitation (There were floating thrombotic formations in the right atrium Computed tomography (CT) angiography revealed pulmonary embolism in bilateral main pulmonary artery. The ultrasound of the lower limbs was normal. D-dimers values were 4562 µg/l. Other laboratory findings were within normal limits. Calculate glomerular filtration rate (GFR) was 78 mL/min/1.73 m². Due to high clinical risk (high risk sPESI score) the patient was treated with fibrinolytic therapy (actilisae protocol for PE) with significant clinical improvement. BP normalized to 120/75mmHg, HR 90bpm, SpO₂ 95%. UF Heparin 25.000IE daily (100,000 IU/hour) was given for 5 five days with inclusion of rivaroxaban 15mg bid. Control echocardiography after 7 days showed significant reduction of RV size, reduced tricuspid regurgitation, and no thrombotic formations. Patient was discharged after 10 days, clinically stable with rivaroxaban 15mg bid for 21 days and 20 mg od for the next six months. Conclusion: The case describes the role of emergency transthoracic echocardiography and successful treatment of massive pulmonary embolism in critical care settings.

Case 2. Patients with Myeloproliferative Neoplasms-(MPN) have a high risk of rarer form of thrombotic complications. Portal vein thrombosis (PVT) is a severe complication, which in many cases, appears at the onset of the disease; the risk factors are related to the presence of qualitatively altered thrombocytes and leucocytes, leading to their activation

and appearance of leukocytes-platelet-aggregates; anomalies of portal vein endothelial cells are also implicated. The presence of JAK2V617F mutation increases the risk for splahnic thrombosis. A case report: We present a case of a female patient of 35 years with MPN presenting with a portal vein thrombosis and Budd Chiari syndrome. She developed portal vein thrombosis while she was on Interferon and Aspirin therapy for MPN. She was successfully treated with low molecular weight heparins and vitamin K antagonists (VKA). Conclusion: Portal vein thrombosis is rare, but serious complication in patients with MPN. Long-term oral anticoagulation with vitamin K-antagonists (VKA) is recommended in all PVT patients with the MPN-related permanent post-thrombotic state; the benefits of adding aspirin to VKA are uncertain. Cytoereduction is warranted in all PVT patients with an overt MPN, but its appropriateness is doubtful in those with molecular MPN without hypercythaemia.

Case 3. Acute pulmonary thromboembolism is the most serious complication of venous thromboembolism. Pulmonary embolism can cause sudden death. It is a major cause of mortality and morbidity. A Case report: A 47-year-old male patient was admitted to our hospital, due to episode of syncope 7 hours before admission. He had chest pain and dyspnea during the last three days. Two weeks before he had pain in the leg, which he ignored. Echocardiography revealed right ventricular dilatation with moderate pulmonary hypertension. Predisposing factors for deep vein thrombosis were weak (odds ratio < 2), but D-dimers were increased 7574 mg/ml. Urgent 256-MSCT pulmonary angiography revealed massive pulmonary embolism. PESI score was 107 (high risk for mortality 4-11%). Thrombolysis with alteplase was introduced according to protocol. Venous Doppler revealed thrombosis in the popliteal vein. Control MSCT pulmonary angiography performed after 3 days revealed only segmental pulmonary thromboembolism. A 40-year-old female patient was admitted to our hospital due to cough and dyspnea during the last four days. She was taking oral contraceptive therapy for five years; she was active smoker and had BMI > 30. Echocardiography revealed borderline dimensions of the right ventricle, mild tricuspid regurgitation. Predisposing factors for deep vein thrombosis were moderate (odds ratio 2 - 9). D-dimers were increased 4900 ng/ml. 256-MSCT pulmonary angiography revealed massive pulmonary embolism with pulmonary infarction. PESI score was 40 (Class I, Very Low Risk: 0-1.6% 30-day mortality). Anticoagulation with novel anti-coagulation drugs was started. Venous Doppler re-

vealed thrombosis in the popliteal vein. The patient remained hemodynamically stable with clinical improvement in few days. Conclusion: A guidelines for pulmonary embolism encompasses the risk factors for venous thromboembolism, and different clinical pictures with appropriate therapy modalities. This is all applicable in every day practice.

Case 4. Underdiagnosed and untreated pulmonary embolism (PE) is associated with high mortality. We report a case report of high risk PE with evidence based diagnostic and therapeutic approach. A Case report. A 40 years old woman presented in emergency room with dyspnea 1 week ago. She's been on oral contraceptives for 15 years. Symptoms of dyspnea at rest, cough, palpitations, fatigue and signs of tachypnea, tachycardia, loud R2, gallop rhythm and hypotension were present, raising a high clinical suspicion of PTE. ECG findings of acute cor pulmonale, such as S1Q3T3 pattern, RBBB, P-pulmonale, were present on admission. A bed-side echocardiography was performed immediately with signs of right ventricular (RV) overload (dilated D-shape right ventricle with reduced systolic function, positive McConnell' sign) and PAH (SPAP 61mmHg). A positive D-dimer test (4427ng/ml) confirmed our clinical suspicion, so the patient was referred to contrast-enhanced CT angiography, with a finding of central filling defect (a big bifurcation thrombus) with extension in both, right and left pulmonary arteries and their main branches. No signs of pulmonary infarction, nor pleural effusion were seen. Our patient was classified as high-risk, with hemodynamical instability and thrombolysis with actilyse50mg was immediately performed. Vaso-pressor therapy with dopamine and oxygen mask as supportive measurements of shock and hypoxemia were added. The patient was discharged after 10 days of treatment with NOAC (apixaban 2 x 5mg). After 1 month she was asymptomatic with decreased RV diameter and SPAP of 30mmHg. Because of first provoked episode of PTE, the duration of oral anticoagulation therapy is planned to be at least 3 up to 6 months. Conclusion: Prompt diagnosis, risk stratification and clinical assessment are necessary to optimize decision making with regard to the use of thrombolytic therapy. Nevertheless, preventive efforts are crucial for long-term follow-up.

Case 5. Venous thromboembolism (VTE) is a leading cause of death in patients with cancer. Hematologic malignancies also are associated with thrombus formation, but the magnitude of this risk is unclear. Non Hodgkin Lymphoma (NHL) patients with high-grade disease had the highest rate of

thrombosis (8.3%). The American Society of Clinical Oncology (ASCO) recommends routine assessment of thrombosis risk in patients with newly diagnosed cancer and suggests use of a validated VTE risk prediction model. The rate of VTE differs based on NHL histology, with the highest rates in aggressive lymphomas, such as diffuse large B cell lymphoma (DLBCL). A Case report: We report the case of 38 years old female presenting with right sided neck pain and arm and breast swelling secondary to ipsilateral subclavian-axillary deep vein thrombosis. Investigations revealed it to be secondary to a mediastinal mass shown on CT scan of the chest. Computed tomography (CT) scan of the chest and the neck with contrast showed a singular anterior mediastinal mass with persistent thrombosis of the right subclavian and axillary veins. Mediastinoscopic surgery was done and a biopsy of the anterior mediastinal mass was obtained with no complications. Biopsy showed mediastinal large B-cell lymphoma. Hypercoagulable status work-up was unrevealing and meanwhile the patient was started on enoxaparin subcutaneously with a 1 mg/kg dose every 12 hours. The patient started chemotherapy with R-CHOP-regimen. During a 1 year period she received oral anti-coagulant drugs. Now she is 3 years after completing CHOP regimen in complete remission. Conclusions: VTE diagnosis should be based on age, history, and appropriate clinical history. Understanding VTE risk in NHL can allow for more accurate stratification of VTE and facilitate identification of patients who may benefit from thromboprophylaxis.

Case 6. Pregnant woman with inherited mutations of coagulation factors, or acquired disorders of the hemostatic system, display emphasized physiologic hypercoagulation condition that leads towards thrombophilic state with an increased risk of thromboembolism during pregnancy and after delivery. A Case report: There is a case display of a pregnant woman – 19g.w., at the age of 33, and previously two unsuccessful pregnancies. The hemostasis, thrombophilic conditions and presence of mutations/polymorphisms of thrombophilic genes, as well as screening tests were performed. The results demonstrated decreased values of ATIII, heterozygote mutation of factor V Leiden, heterozygote of PAI-1 and homozygote mutation of MTHFR. Beside the ongoing therapy of: Aspirin 100mg tablets, Folic Acid and amp Clexane at dosage of 40-80 mg, the pregnancy ended with fetus mortuus in the 34 g.w with thromboembolism along the length of the umbilical cord and multiple thromboembolism in the placenta. She came with thrombosis of popliteal vein, 10 years later, with data of one more attack

earlier. The therapy was oral anticoagulant therapy. Unfortunately, five days after the first symptoms the patient is diagnosed with pulmonary embolism and is hospitalized, treated with therapy LMWH and completely rehabilitated after 6 months. Further on ordained by a chronic therapy of rivarixaban 20 mg. Conclusion: Venous thromboembolism related to mutations/polymorphisms of thrombophilia genes during pregnancy is connected to placenta malfunctions, recurrent abortions, fetus mortuus and women thromboembolism. Anticoagulation and antiagregant therapy, before conception and during pregnancy incorporated by haemostatic parameter follow up enables a positive outcome of pregnancy and a healthy newborn. Anticoagulation prophylaxis is recommended only for patients with recurrent thromboembolic attacks related to gene mutations for thrombophilia.

Case 7. The risk of venous thromboembolism as a complication of heart failure is an increasingly common. Evaluation of heart failure patients with suspected acute pulmonary embolism (PE) is challenging, because of the overlap in symptoms and signs of both conditions. A Case report: 53 old male presented with acute dyspnea and substernal chest pain. He had fatigue and mild dyspnea on exertion, since he had untreated cold three months ago. Biochemistry was normal except D-dimmer value of 9832 ng/ml. Echocardiography revealed moderate pulmonary hypertension and left ventricular systolic dysfunction (LVEF 46%). Echo Doppler of lower extremities confirmed right popliteal vein thrombosis. Pulmonary CT angiography didn't detect trombus in dilatated pulmonary arteries. There is evidence of pleural effusion and wedge-shaped area of hyperattenuation in the right lower lobe. Initial treatment begun with heparin and heart failure therapy and continued with Xa anticoagulant. Echocardiography confirmed enlarged right ventricle and pulmonary hypertension. Control CT angiography was performed with findings of massive pulmonary embolism. Previous therapy was continued. Control CT angiography performed 3 months later was normal, but echocardiography still confirmed both ventricle enlargement and mild pulmonary hypertension. 3 months later the patient was admitted with acute worsening of heart failure, pleural effusion, uncontrolled atrial fibrillation. Echocardiography detected lowering of LVEF 35% and septal hypokinesia. There was no signs of acute recurrent venous thromboembolism. Coronary angiography excluded coronary artery disease. Patient was dismissed in NYHA I stage and followed-up. Conclusion: Acute PE is serious, difficult to be recognized condition,

especially accompanied with heart failure. Although dyspnea is the most commonly reported symptom in both conditions, its severity, hypoxemia out of proportion to findings of pulmonary vascular congestion or worsening in right ventricle function should raise concern for acute PE. Early diagnosis and treatment for both disorders are substantial for good prognosis.

Case 8. Pulmonary embolism is a condition in which one or more of the lung arteries become obstructed by a blood clot that has been formed somewhere in the body and has travelled to the lungs. Common predilection places for blood clotting are the limbs. Acute pulmonary embolism (PE) is a frequent life-threatening condition in emergency departments. Although ECG is a cheap and rapid diagnostic test for pulmonary embolism, it has some limitations in the differential diagnosis of acute coronary syndrome and acute PE. Herein, we report results of a patient diagnosed with acute PE mimicking acute coronary syndrome. A Case report: We present a clinical case of 62-year-old woman that was hospitalized in the University Clinic of Cardiology, because of symptoms of chest pain, dyspnea, fatigue that was provoked with physical exertion. The onset of the symptoms started one month ago and got high intensive 4 days before she was hospitalized. The patient has a history of arterial hypertension and diabetes mellitus. ECG on admission showed sinus rhythm, with down sloping ST segment depression in leads DI, DII, DIII, aVF of 2 mm, in V5-V6 of 1.5 mm, aVR elevation, biphasic T waves in precordial leads. Laboratory findings showed increased leukocytes counts, levels of hs-Troponin and D-dimmers. Immediate coronary angiography was performed and only plaque to RCA was found. The echocardiography done after angiography was suggestive for right ventricular dysfunction. Doppler ultrasound showed deep venous thrombosis in the right popliteal vein. CT angiography confirmed PE. Conclusion: Although certain elements of the chest pain history are associated with increased or decreased likelihoods of a diagnosis of acute coronary syndrome (ACS) or PE, none of them, alone or in combination, identify a group of patients that can be safely discharged without further diagnostic testing.

Case 9. Major operation is a strong risk factor for VTE, especially for thromboembolic complications during the first three months after surgery. A Case report: We present a 54-year-old female with fatigue onset five days before admission. She underwent Bentall operation with CABG one month ago, because of aortic dissection, type Stanford A. She had a positive family history for cardiovascular

disease and no other risk factors. ECG on admission was with partial McGine and White sign-Q form and inverse T wave in lead DIII and also as an additional sign there were inverse T waves in precordial leads. INR value (6 days before admission) was in sub-therapeutic range (1.41). D-dimer was positive and that led to a suspicion of pulmonary thromboembolism (PE). Echocardiography that was performed showed dilated right ventricle with mild tricuspid regurgitation and without sign for PAH. Computed tomography angiography of thorax was done, which revealed pulmonary embolism in left pulmonary artery and segmental arteries filling defect. Lower extremity venous duplex was without any direct or indirect signs for DVT. The patient was treated with unfractionated heparin for the first three days, when concomitant use with acenocoumarol had achieved an international normalized ratio than continued with it. Conclusion: In patients having undergone major surgery, especially those with an implanted mechanical valve, there is a need for proper anticoagulation to minimize the postoperative thrombotic complications. Vitamin K antagonists are the only appropriate long term therapy for those patients at the moment, maintaining the INR value in optimal therapeutic ranges.

Case 10. Both, deep vein thrombosis (DVT) and pulmonary embolism (PE) are manifestation of the vein thromboembolism (VTE). PE if significant, is serious life-threatening condition. Despite progress in imaging techniques, its medical diagnosis is still one of the most difficult challenges. Although echocardiography is not routinely used for diagnosis of PE, in patients with proven DVT and signs of PE, combined ultrasonographical methods (echocardiography associated with venous ultrasonography) are very useful diagnostic approach for the outpatient early diagnosis of PE and further risk stratification and management. A Case report: Patient aged 42, came for consultation for vascular ultrasound (VUS) because of pain and swelling in the right calf for 10 days. Also complaining for sudden appearance of dry cough with pleurodynia, fatigue, breathlessness, tachycardia. She had an episode of thrombophlebitis one year ago. She has had obesity and diabetes as comorbidities. VUS shows dilatation of both, femoral and popliteal veins, completely uncompressible i.e. extensive proximal DVT. Her blood pressure was 95/60 mmHg. Echocardiography shows right to left ventricular end-diastolic area ratio 0.61, positive McConnell's sign, dilated RVOT (38mm), pressure overload of RV (D-shaped LV), mid-systolic separation of PW Doppler signal with 60/60 sign - acceleration time (AT 54 ms), moderate tricuspid

regurgitation (3.5 m/s), RVSP (57 mmHg), VCI 2.2 cm, eRAP 8 mmHg, limited longitudinal regional RV function (TAPSE 17 mm). Results highly suggestive of acute PE, still hemodynamically stable. Because of signs of imminent acute cor pulmonale we indicated prompt hospitalization and further inpatient management. CT angiography confirmed PE with several emboli in both pulmonary arteries. Conclusion: Echocardiography combined with VUS is a very useful approach for outpatient early diagnosis of PE and further risk stratification and management, considering that up to 40% of all major DVT, are complicated by "silent" PE.

Case 11. We look at an interesting patient treated for deep venous thrombosis (DVT) and for pulmonary embolism (PE), and we examine the efficacy of the therapy used.

A Case report: The patient 58-years of age, extremely physically active, in a great shape, who actively weight lifts and regularly runs marathons. His body mass index was 26.6 kg/m². He had no comorbidities, but had a family history for DVT, with both parents having suffered from DVT during their lifetimes. The initial complaint was right lower leg pain for two weeks, dyspnea and malaise. D-Dimers were elevated, and the patient was hospitalized and started on unfractionated heparin. Initial echocardiography was unremarkable. Color duplex of the lower extremities showed a non-occlusive thrombosis of the left femoral vein. Two days after admission, a CT angiography of the pulmonary arteries was positive, with thrombi in multiple major branches of both pulmonary arteries. Activated partial thromboplastin time (APTT) on the sixth day of hospitalization came in unsatisfactory, and the patient was started on direct oral anticoagulants, specifically rivaroxaban. Control duplex revealed an occlusive thrombus in the left iliac, femoral and popliteal veins. The patient was discharged after 18 days of hospitalization. Three weeks later, the patient underwent tests at a different hospital, for his new symptom of intermittent claudication. CT angiography of lower extremities arteries revealed right-sided occlusion of the tibialis posterior artery. Follow-up one and two months after resulted in persistent arterial occlusion and DVT. The patient then revealed a history of anabolic steroid use. Long-term anticoagulation is planned, as well as genetic testing for a thrombosis panel. Conclusion: Our patient was on adequate therapeutic doses of anticoagulants for DVT when he developed occlusive peripheral arterial disease. The patient probably has some genetic predisposition, despite the anabolic steroid use. We

demonstrate that arterial and venous thrombosis do share some risk factors.

Case 12. Khorana risk stratification score is a new implemented score that can stratify the risk of VTE in ambulatory cancer patients and select those ones with high risk for thromboprophylaxis. A Case report: Our patient was 57-year-old female with symptoms of chest pain, dyspnoea, syncope with epileptiform cramps 2 days prior admission and history of significant risk factors present- cured cervical carcinoma 18 y.a. and obesity (BMI 37.1 kg/m²). Physical examination was with no clinical signs suggestive for VTE. There were neither ECG signs for PTE, sPO₂ was normal. Laboratory findings showed positive level of D-dimmers and elevated troponin level. Echocardiography was strongly suggestive for PTE, with dilated right ventricle, D-shaped left ventricle, moderate TR and moderate PAH (sPAP 55 mmHg). CT angiography confirmed the diagnosis, with present filling defects on the level of pulmonal trunk bifurcation. Lower extremity venous ultrasound detected co-existing unilateral iliac and femoral DVT and bilateral popliteal DVT. Ethyological examinations were also performed, thrombophilic factors were without DNA mutations and for excluding occult metastatic cancer as an underlying cause, tumor markers were evaluated, they were negative. The patient was classified as non-high risk PTE, so the treatment included unfractionated heparin over the first 3 days followed by DOAC (apixaban), in the day forth. As the calculated risk score for our patient was 1, she belongs in the intermediate risk group. Following the Khorana score recommendations, we wouldn't start with thromboprophylaxis in this patient, if it was calculated before the episode of VTE. Conclusion: We could use the Khorana score in patients with non-active carcinoma, but the score should be reclassified, taking into account other risk factors, in a way of their proper risk stratification and thromboprophylaxis.

Cases 13 and 14. Patients with malignancy are at high probability to develop venous thromboembolism (VTE). We report two cases of VTE, where malignancy was detected later. Cases: The first case was about a 53-year-old male. He was admitted in a hospital with chest pain, dyspnea, hemoptysis. Biochemistry tests have shown increased level of D-dimers and leukocytosis counts. CT angiography of the chest have shown a filling defect in the lower right pulmonary artery. After 48h intravenous anticoagulant use, the anticoagulant was then shifted to rivaroxaban. During admission the patient had a non-traumatic fracture of the femur neck, who was

treated conservative, because of the severity of the diagnosis. After two months he had another repetitive episode of VTE, with the same symptoms. The orthopedic team did the operation, replacement with bioprosthesis after six months, and the biopsy material was taken. Differential diagnosis was a metastatic deposits in the bone with origin of connective tissue. CT of the small pelvis was performed and noticed oval shaped tumor in the right iliac region.

The second case is about 44-year-old female. She was admitted in the same hospital with high fever, cough, severe abdominal pain and dyspnea. Blood tests showed increased levels of D-dimmers and leucocytes counts. CT angiography of the chest showed a massive bilateral thrombi and sign of consolidation. During admission the patient was treated with heparin for three days and shifted with rivaroxaban and dual antibiotic therapy. CT scan of the abdomen showed a retrocecal mass that compressed distal ileum and cecum, thrombosis of hepatic and splenic vein. We suspected that the origin of the tumor was from the ovary. Conclusion: Patients with VTE are at significant risk for occult malignancy and later development overt malignancy. Aggressive workup for occult malignancy has not prospectively improved the outcomes, but age appropriate malignancy screening should be recommended.

Case 15. Pulmonary embolism is the occlusion of pulmonary arteries by thrombi that originate elsewhere, typically in the large veins of the legs or pelvis. Risk factors for pulmonary embolism are conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulable states. A Case report: 36 y.o., male, smoker, hospitalized in the psychiatry department, because of bipolar affective disorder two weeks ago. The last few days he was complain on dyspnea, syncope and breathlessness on exertion. The symptoms were understood by the underlying disease, but the condition had not improved with the therapy. Than he was sent for investigations to the department for internal medicine. He had a blood pressure of 100/70 mmHg and pulse of 110 beats/min. From examination: ECG: Right axis, S1Q3T3, negative T in DIII, aVF, V1-V6. Laboratory examination: Hb-13.1, Le-11.6, CK-488, Troponin I-67, D-Dimers-2382 ng/ml. Echocardiography: Enlarged RV-3.71 cm, normal LV and LVEF, SPAP with value of 76 mmHg, He was suspected on pulmonary embolism, started on Low molecular weight heparin (LMWH) and further for CT angiography on chest : The post contrast CT series of thorax is followed by a dilatation of the pulmonal trunk and the main

pulmonary arteries for the right and left side of lungs. Follow of the both sides with concave defects in filling. Filling defects are also observed in the lobar branches of the pulmonary arteries, especially pointed at the arteries for the lower limbs. Segmental and lobular arteries on the lower lobe and upper lobe are irregularly structured. The CT scan shows bilateral pulmonary embolism. In parallel with CT scan one week ago, discrete reduction of defects in filling of pulmonary arteries has been followed. Conclusion: He started to receive oral anticoagulant therapy. After two weeks, LMWH was excluded. After one week, his condition was significantly improved.

Case 16. After an initial 3 to 6 months of anticoagulation for venous thromboembolism (VTE), clinicians and patients face an important question: “Do we stop anticoagulants or continue them indefinitely?” A Case report: We present a case of 36 y.o. male, admitted at our Clinic with symptoms of pain and oedema of the left leg below the knee last couple of days, subfebrile and also symptoms of dyspnea last two days. On physical examination edema of the left leg was noticed. On ECG, we noticed sinus rhythm and incomplete right branch bundle block-RBBB. Doppler ultrasound of the femoro-popliteal veins was made, and thrombotic masses were noticed. Anticoagulation therapy with unfractionated heparin was started. On the echocardiography, no signs for pulmonary hypertension were noticed. Laboratory exam: WBC: 12.3, CRP=150, D-dimer 4427 mmol/L. CT angiography of the pulmonary blood vessels: Extensive central filling defect on the right principal pulmonary artery, on the bifurcation, and also on the lobar and segment branches for middle and lower lobe. The finding fits for massive central pulmonary thromboembolism on the right lung. After one week, new vein Doppler of the legs was made and we noticed still presence of thrombus in femoral superficial vein, but we also found presence of floating thrombus on the right VFS. The patient was switched to direct oral anticoagulant (DOA) therapy. Before discharge ultrasound showed improvement in the findings. Genetic investigations for mutation showed presence of heterozygosity of Factor V Leiden mutation and of factor XIII V34L, PAI-1 5G/4G, MTHFR A1298C and MTP A2756G polymorphisms. After 8 months Doppler ultrasound showed resolution of the thrombus in the right popliteal vein, and nonocclusive organized thrombus in left VP. We decided to continue with the DOAC therapy. Conclusion: Patients with unprovoked VTE have substantial long-term risk for recurrent VTE. To reduce the risk of recurrent VTE and complica-

tions, many patients will require long-term or even extended anticoagulation therapy.

Case 17. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is acquired, immune-mediated condition affecting the peripheral nervous system. Studies have shown that despite prophylactic anticoagulants being used in patients with major problems of mobility still some of them developed clinically detected deep vein thrombosis (DVT) and pulmonary embolism (PE). A Case Report: A 65-year-old female patient presented with progressive dyspnea, tachycardia and bilateral lower extremities swelling which had worsened in the last 10 days. She was suffering from flaccid quadriparesis because of CIDP. On admission she was hemodynamically stable. Echocardiography revealed dilated right ventricle, tricuspid regurgitation and dilated pulmonary trunk (PT). The D-dimer test was positive ($>10\,000$ ng/mL) and blood analysis revealed moderate renal impairment. Computed tomography pulmonary angiography (CTPA) showed massive PE with saddle thrombus in TP and subocclusive thrombi in the main pulmonary arteries. Colour Doppler ultrasound revealed non-obstructive thrombi in the popliteal veins bilaterally. Unfractionated heparin (UFH) was administered for 5 days and overlap with vitamin K antagonist (VKA) was made. After 12 days of hospitalization the patient's condition improved and she was discharged. Three months later the patient was readmitted and treated because of persistent dyspnea. CTPA showed eccentric filling defects in the lobar pulmonary arteries bilaterally with evidence of its recurrence. She was advised to continue with VKA and heart failure therapy. Conclusion: The patient presented as a challenging case of provoked massive PE and bilateral DVT developed in the setting of blood stasis and consequential hypercoagulability. Because of CIDP, she had also received moderate doses of glucocorticoids for prolonged period of time, which in studies was shown to increase the risk of venous thromboembolism, particularly PE. Considering patient comorbidity, the anticoagulation therapy consisted of UHF and VKA. Despite the initial improvement she developed recurrent pulmonary thromboembolism, placing her at risk of developing chronic thromboembolic pulmonary hypertension.

Case 18. Acute pulmonary embolism (PE) is the third most frequent cardiovascular disease and it may be lethal in the acute phase leading to a sudden death even at presentation or lead to chronic disease and disability, but it is often preventable. Although the general risk factors for DVT and PE are well

known, a few cases of sports related trauma pulmonary embolism have been reported. A Case report: Our patient is a 32-year-old male hospitalized at the University Clinic of Pulmology due to symptoms of intensive cough and hemoptysis. The symptoms started two days ago and increased in the following days. The patient denies previous diseases and family history of any cardiovascular disease. He is an active sportsman, training martial arts regularly, not taking any supplements. He gave us an information about a chest injury during training one month ago. ECG was normal. Chest X ray, ultrasound of the lungs, fibernasal epipharyngoscopy, bronchoscopy were also normal. Laboratory findings showed slightly increased D-dimers level. Immediate CT angiography was performed which showed filling defect in the right low lobe confirming PE. Doppler ultrasound of the veins of lower limbs showed no signs of vein thrombosis. Patient was successfully treated with low molecular weight heparin and Vitamin K antagonists. Conclusion: We can not exclude PE as a differential diagnosis in young fit patients and active sportsmen without any history of disease of any kind and without a family history of DVT or PE. Sports trauma may cause vascular endothelium injury, which may trigger formation of thrombus on that site.

DISCUSSION

The overall average venous thromboembolism (VTE) incidence rate in adults ranges from 0.7 to 1.9 events per 1000 persons-years.⁵ It increases sharply with age: up to 1% per year in the elderly. This indicates that ageing is one of the strongest and most prevalent risk factor for VTE and although the underlying mechanism is unknown, it represents a mix of unknown and known risk factors that either become stronger with age or become more prevalent with age. In the elderly, population attributable risk (PAR) of malignancy is 35%, for co-morbidities- 25% and the contribution of genetic risk factors to the thrombosis incidence about 7-22%. Age- specific risk factors of thrombosis, such as endothelial dysfunction, muscle strength, female sex, institutionalized living and frailty may be important in the explanation of the increased incidence of VTE in the elderly.⁶

Also, end stage renal disease (ESRD) patients have higher risk for VTE and bleeding. Recent results of the Longitudinal Investigation

of Thromboembolism Etiology (LITE) trial confirmed that middle-aged and elderly patients with chronic kidney disease (CKD) (stages 3 through 4) are at increased risk for incident VTE, suggesting that VTE prophylaxis may be particularly important in this population.⁷ Renal failure patients have high risk for major bleeding which together with higher VTE risk further aggravates prognosis and all-cause mortality among them.

Venous thrombosis is a well-described complication of cancer and its treatment. Thrombotic events complicate cancer treatment and worsen patient prognosis. Thrombosis mechanisms include disease- and chemotherapy-related vascular damage and involve activation of the thrombotic cascade coagulation pathway. The risk factors depend on patient-, disease- and treatment-associated factors. Khorana score has been developed to identify patients at high risk, although its utility is still limited.⁸ In case of venous thromboembolism diagnosis, the preferable treatment is low molecular weight heparin. However, lately direct oral anticoagulants have been proved as an efficient and safe option.

Venous thromboembolism particularly pulmonary embolism is often urgent condition with high rate of mortality, Early diagnosis, risk stratification and treatment is necessary in high risk pts with VTE. We also described less common situation as neurological condition or sport trauma as risk factor for VTE.⁹

In conclusion, our knowledge on predisposing factors, prevention and treatment for venous thrombosis is extensive, but the patient will benefit most when we properly integrate this knowledge, depending on the clinical situation.

REFERENCES

1. Moustafa F, Giorgi Pierfranceschi M, Di Micco P, Bucherini E, Lorenzo A, Villalobos A, Nieto JA, Valero B, Sampériz ÁL, Monreal M; RIETE Investigators. Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism. *Res Pract Thromb Haemost*. 2017 Sep 4; 1(2): 172–179.
2. Mastroiacovo D, Dentali F, di Micco P, Macestre A, Jiménez D, Soler S, Sahuquillo JC, Verhamme P, Fidalgo Á, López-Sáez JB, Skride A, Monreal M; RIETE Investigators; Rate and duration of hospitalisation for acute pulmonary

- embolism in the real-world clinical practice of different countries: analysis from the RIETE registry. *Eur Respir J*. 2019 Feb; 21: 53(2)
3. Mahé I, Chidiac J, Bertolotti L, Font C, Trujillo-Santos J, Peris M, Pérez Ductor C, Nieto S, Grandone E, Monreal M; RIETE investigators. The Clinical Course of Venous Thromboembolism May Differ According to Cancer Site. *Am J Med*. 2017 Mar; 130(3): 337–347.
 4. Bosevski M, Srbinovska-Kostovska E. Venous Thromboembolism - Current Diagnostic and Treatment Modalities. *Open Access Maced J Med Sci*. 2016 Sep 15; 4(3): 523–525.
 5. Bosevski M, Krstevski G, Gjorgievski A, Mitevska I, Kostovska ES. Predictors for Prognosis in Patients With Nonfatal Pulmonary Embolism: A Registry-Based Cohort Study. *Clin Appl Thromb Hemost*. 2018 Jul 26; 1076029618786577. doi:10.1177/1076029618786577.
 6. Gregson J, Kaptoge S, Bolton T, Pennells L, Willett P, Burgess S, et al. Cardiovascular Risk Factors Associated With Venous Thromboembolism. *JAMA Cardiol*. 2019 Feb 1; 4(2): 163–173. doi: 10.1001/jamacardio.2018.4537.
 7. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol*. 2008 Jan; 19(1): 135–40.
 8. Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, Smit K, Büller HR, van Es N; CAT prediction collaborators; CAT-prediction collaborators. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica*. 2019 Jan 3. pii: haematol.2018.209114. doi: 10.3324/haematol.2018.209114.
 9. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. (2014). *European Heart Journal*, 35(43), 3033–3073. doi:10.1093/eurheartj/ehu283.

Резиме

СПЕЦИЈАЛНИ СОСТОЈБИ

ВО ВЕНСКИОТ ТРОМБОЕМБОЛИЗАМ – СЕРИЈА СЛУЧАИ

Маријан Бошевски¹, Ирена Митевска¹, Марица Павковиќ²,
Милка Клинева³, Емилија Лазарова Трајковска¹, Емилија Велкова⁴,
Злате Стојаноски², Нела Костова¹, Советка Паљошковска Јорданова¹,
Даница Петкоска¹, Мими Манчева¹, Александра Гулевска⁵, Марјан Балоски⁵,
Васко Хациев⁶, Горјан Крстевски¹, Викторија Кралевска¹, Ивица Бојовски¹,
Марио Јовановски¹, Весна Неделковска⁷, Атанас Ѓорѓиевски¹

¹ Универзитетска клиника за кардиологија, Медицински факултет, Скопје

² Универзитетска клиника за хематологија, Скопје

³ Клиника Жан Митрев, Скопје

⁴ Институт за трансфузиона медицина, Скопје

⁵ Општа болница 8 Септември

⁶ Приватна амбуланта „Д-р Хациев“, Битола

⁷ Општа болница Велес, РС Македонија

Венскиот тромбемболизам (ВТЕ), вклучувајќи ја длабоката венска тромбоза (ДВТ) и белодробната емболија (ПЕ), е превентабилна причина за болничка смрт и една од најраспространетите васкуларни болести. Постои недостиг на знаење во однос на современата презентација, третман и исход на пациентите со ВТЕ. Многу клинички важни подгрупи (вклучувајќи ги и постарите лица, оние со неодамнешно крвавење, бубрежна инсуфициенција, дисеминиран малигнитет или бременни пациенти) биле недоволно застапени во рандомизираниите клинички испитувања. Ние сè уште црпиме информации од регистрите од реалниот живот (пример РИЕТЕ). Во трудот е дадена серија случаи со ВТЕ во посебни услови, вклучувајќи и тромбоза поврзана со рак, малигни хемопатии, оние кај високо ризична популација.

Клучни зборови: венски тромбемболизам, белодробна емболија, длабока венска тромбоза, тромбоза поврзана со рак, малигни хемопатии, висок ризик