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CANCER – ASSOCIATED THROMBOSIS – A STUDY OF CASES

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ABSTRACT

Research shows that the presence of cancer increases the likelihood of developing venous thromboembolism (pulmonary thromboembolism and deep vein thrombosis) from as much as fourfold up to sevenfold. It is imperative that after early diagnosis we treat cancer-associated thrombosis with grave seriousness in order to reduce its morbidity and mortality.

We present 14 case reports of patients with cancer-associated thrombosis including thrombosis related to malignant hemopathies.

Keywords: cancer-associated thrombosis (CAT), malignant hemopathies, venous thromboembolism (VTE)

INTRODUCTION

The association between cancer and venous thromboembolism (VTE) is likely to be multifactorial, as patients with malignancy tend to have several other risk factors for venous thrombosis including advanced age, immobility, smoking history, chronic central venous catheterization, and exposure to chemotherapeutic agents. Additionally, there appears to be a procoagulant state associated specifically with malignancy. [1]

Pulmonary thromboembolism (PE) and deep vein thrombosis (DVT) are some of the early postoperative complications following oncological surgery. PE is common in patients with any form cancer and incidence is increased not only by surgery, but also with chemotherapy, radiotherapy, and disease progression. Additionally, the risk of PE and DVT increases relatively in patients with advanced chronic diseases. [2]

We present fourteen case reports of patients with cancer-associated thrombosis including thrombosis related to malignant hemopathies.

Case 1. A rare location of cancer-associated thrombosis

This case concerns a 49-year-old woman with radical mastectomy due to breast cancer (ductile, stage IIIA, hormone-dependent Luminal type B). She received four cycles of chemothera-

py, followed by local radiotherapy and hormonal therapy with Tamoxifen. She was free of symptoms for the next 4 years. Suddenly, she experienced loss of consciousness for a few minutes and was admitted to the emergency room. It was her first episode of syncope without having any previous history of epilepsy. Her BP on admission was 180/100mmHg, sinus rhythm on heart auscultation (no electrocardiogram (ECG) attached). She was referred to the neurology department and urgent brain CT (native plus contrast), where she showed thrombosis of superior sagittal sinus, followed by magnetic resonance imaging (MRI). This revealed secondary meningeal deposits with vein thrombosis of SSS. After the initial tests of hemostatic system (platelets of 222x 10^9/L, hematocrit of 44.8%, prothrombin time (PT) of 9.5 seconds, activated partial thromboplastin time (aPTT) of 17.8 seconds, thrombin time (TT) of 23 seconds), as well as the fibrinolytic system (significantly elevated D-Dimer of 19278 ng/ml), treatment with anticoagulant therapy (subcutaneously administered low-molecular weight heparin (LMWH) of 60 mg twice daily for 3 weeks. This treatment led to a decrease of D-Dimer values (D-Dimers of 190ng/ml), and a slightly prolonged aPTT of 33 seconds. This was followed by oral anticoagulant therapy with a vitamin K antagonist (VKA) with an international normalized ratio (INR) within the range of 2-3. Unfortunately, progression of the disease upon observation of the MRI was seen, as compared with the previous brain MRI. At the same time, extended hormonal therapy was prescribed. The patient was entered into the "watch and wait" condition. She has not had any new episodes of syncope nor seizures since 2019. After 1 year, in November of 2020, the patient was infected with COVID-19, and because of high D-Dimers, she was started on LMWH for 10 days, followed by Apixaban of 2.5 mg twice daily, as well as Acetylsalicylic acid of 100 mg once daily. The last control MRI of the brain was done in December of 2020, and it showed that thrombosis of the superior sagittal sinus was still present.

Case 2. Hypercoagulable state post-COVID-19 complication reveals cancer-associated thrombosis

A 58-year-old male presented with fatigue and abdominal pain was admitted to the emergency room. The patient had a previous history of non-insulin dependent diabetes mellitus for 8 years and hypertension. He was diagnosed and treated for COVID-19 three months prior in the General Hospital of Struga. A CT angiography revealed a large thrombus in the inferior vena cava (IVC) with a diameter of 14 cm, with an extension proximal to the right atrium and distal to the left renal artery, compromising a renal flow with poor renal function and large amounts of ascitic fluid and a right pleural effusion. He was immediately admitted to the intensive care unit (ICU) for an urgent antithrombotic treatment, with an IVC syndrome determined upon examination. The ECG at admission was normal: sinus rhythm, 87 bpm, left axis deviation, without any pathological ST-T changes. Lab tests were consistent with decreased renal function, with a creatinine of 217 mmol/l, potassium of 5.1 mmol/l, complete blood count (CBC) in normal ranges, glucose at 9.9 mmol/l and high-sensitive cardiac troponin within normal ranges, at 6 ng/l. Hemostasis (PT, aPTT, TT) was in normal ranges, but the D-Dimers were significantly elevated, at 2242 ng/ml. The duplex ultrasound of the low extremity veins was normal, without signs of DVT. A bedside echocardiography revealed normal heart chambers, normal left-ventricular and right-ventricular systolic function. A hyperechogenic mass consistent with a thrombus was seen in right atrium at the IVC connection point. During urgent diagnostics, a heparin drip was started with unfractionated heparin (UFH) of 30000 IU/24h simultaneously started, with an aPTT two to threefold target. The patient was transferred to the clinic Acibadem-Sistina, where the IVC tumor extirpation surgery was performed, followed by an IVC repair with patch plasty successfully performed, without any perioperative complications. Pathophysiological findings were consistent with clear cell renal cell carcinoma fitted in the thrombotic mass. Postoperatively, Amiodarone was given for atrial fibrillation and oral anticoagulation with VKA were added to the previous therapy. The patient was referred to an oncologist for further clinical and radiological investigations of the primary cancer location.

Case 3. Thrombosis as an early postoperative complication after prostate cancer

A 66-year-old man was hospitalized due to dyspnea, fatigue, and anamnestic data from a transurethral resection of the prostate (TURP)

that was performed 6 days prior to hospitalization. Later on, at the same hospital, the patient showed up for an examination, and a transthoracic echocardiogram (TTE) was performed. He was then referred to the Cardiology Clinic for further treatment. TTE was performed again and it showed right ventricular pressure overload, pulmonary hypertension with systolic pulmonary artery pressure (sPAP)-55 mmHg + 8 mmHg = 63 mmHg, pulmonary wedge pressure (PWP) -28 mmHg, with a preserved left ventricular ejection fraction, but with a reduction in stroke volume index (SVi) of 23 mL/m^2. The ECG showed sinus rhythm and heart rate 100 bpm with S1Q3T3 pattern. Lab tests revealed elevated D-Dimer values (5290 ng/ml), aPTT of 120 seconds. The patient was given anticoagulant therapy with LMWH. A computed tomography pulmonary angiogram (CTPA) was performed and showed acute PE. A control echocardiogram was performed within nine days without signs of a right ventricular overload. The patient was discharged in good condition with a VKA. In conclusion, thrombosis is a pervasive and dangerous pathological entity in the field of oncology surgery. The propensity for pathological entities to result in sudden postoperative death highlights the importance of prevention, rapid diagnosis, and expedited treatment of this condition.

Case 4. Deep vein thrombosis in a patient with the diffuse large B cell lymphoma subtype of non-Hodgkin's lymphoma

A 71-year-old male patient was referred to our outpatient department in June 2017 due to enlarged abdominal lymph nodes and clinical signs of DVT of the right iliofemoral vein. Clinical examination revealed an edema grade 3/4 with a warm and tense right leg with a 4.5 cm discrepancy compared to the left leg. Distal pulses on both legs were positive. Peripheral lymph nodes were not enlarged. The patient had already been treated for DVT of the right iliofemoral vein confirmed with a Doppler ultrasound, with a LMWH and Acenocoumarol for 6 weeks without significant improvement. Due to a poor clinical response to treatment, an abdominal ultrasound was performed and an abdominal lymphadenopathy was detected. He was then referred to our clinic for further investigation. Abdominal and chest CT scans confirmed significantly enlarged abdominal lymph nodes and a CT guided core biopsy was performed with histological confirmation of the non-Hodgkin's lymphoma (NHL) subtype diffuse large B cell lymphoma (DLBCL), with a high proliferation Ki67 index of 70%. The regular blood counts and biochemical analysis were normal, with elevated lactate dehydrogenase (LDH). A positron emission tomography–computed tomography (PET-CT) was not performed at the beginning due to technical problems. The patient was treated with six cycles of R-CHOP immuno-chemotherapy plus two doses of Rituximab along with oral anticoagulant therapy. After finishing chemotherapy, control PET-CT was normal with signs of complete morphological and metabolical response. Regarding the course of DVT, significant improvement of the deep vein thrombosis was noticed after the first cycle of R-CHOP. After the second cycle, almost complete normalization of the edema and enlargement of the right leg was registered. A control Doppler ultrasound was performed after finishing chemotherapy and normal blood flow in the deep veins of both legs was detected. Acenocoumarol continued for one year with regular controls of prothrombin time. Oral anticoagulant therapy was stopped another six months later and normal deep vein flow and circulation without signs of thrombosis was confirmed with another control Doppler ultrasound. In conclusion, this is a case of a patient with high grade non-Hodgkin's Lymphoma with signs of typical DVT resistant to standard treatment due to an underlying malignant disease. In fact, DVT was the first sign of the disease and due to poor response to anticoagulant treatment, further investigations were performed and histological confirmation of DLBCL was done. Treatment of the underlying malignant disease combined with anticoagulant treatment resulted in clinical improvement and remission of both the lymphoma and the DVT. Idiopathic DVT, especially in older patients, should be approached seriously, with special consideration to malignancy since DVT could be a preceding sign of underlying malignant diseases.

Case 5. Pulmonary thromboembolism in a patient with active breast cancer - case report

A 52-year-old female arrived at our emergency department with gradually worsening dyspnea and cough over a one week period. Lung and heart examinations were normal. Her blood pressure was 130/75 mmHg. An ECG showed sinus tachycardia with heart rate of 110 bpm and incomplete right bundle branch block (RBBB).

There were no signs of DVT. Patient denied any risk factors that would provoke PE. She had no history of previous cardiovascular or respiratory disease, no history of PE or DVT. She has been treated for breast cancer with Trastuzumab (Herceptin), which was started 7 months before the symptoms appeared. Mastectomy was done 8 months before actual complaints. Due to assessed PE likely based on modified Wells score, a TTE was performed immediately, in order to evaluate the cause of the patient's symptoms. An examination showed increased right ventricle (RV) size, reduced RV function (Tricuspid annular plane systolic excursion (TAPSE) of 15, TDI of 8), presence of McConnell's sign, severe tricuspid regurgitation with dilated v. cava, and signs of pulmonary hypertension (PH). D-Dimers values were 4250 ng/ml, Troponin I was 6.5 ng/ml, within normal ranges. The patient was admitted to the ICU, where treatment with LMWH was started. Renal function was normal, with serum creatinine values of 61 nmol/l (Glomerular filtration rate (GFR) of 94 ml/min). The patient was afebrile and oxygen saturation was at 95% on room air. The sPESI score was >1. A CTPA showed segmental and sub-segmental thrombi in the right pulmonary artery. Doppler ultrasound found no signs of deep vein thrombosis. She has been assessed as an intermediate low risk patient with a HAS-BLED score of 2. On the third hospital day, she was started on direct oral anticoagulant (DOAC) therapy with 15 mg of Rivaroxaban, twice daily. The patient remained stable throughout hospitalization. She was discharged on the eighth hospital day with normalized RV function and regression of the PH. The patient received a recommendation for 6 months of anticoagulation therapy, as well as cancer activity assessment. Follow-up visits were performed after one and six months. The patient remained stable, asymptomatic with normal right ventricular function, with no recurrent PE or major bleeding within the six-month period after the thromboembolic event. Good tolerance of the therapy was reported. In conclusion, this case is an example of cancer-associated PE, successfully treated with LMWH and a DOAC. Clinicians should be alert to presentations and high PE risk in cancer patients in order to reduce the misdiagnosis and allow proper patient treatment.

Case 6. Colon cancer associated venous thromboembolism

Our patient is a 60-year-old male, a smoker, with a history of hypertension, diabetes, and colon cancer (with surgical treatment 4 years prior, and chemotherapy prior to admission). He complains of pain in the left leg and fatigue during exertion. Initial investigations showed normal laboratory values except for an increase in white blood cells (11.6x10^9/L) and D-Dimer levels at 3209 ng/ml. Lower extremity Doppler ultrasound showed an occlusive thrombus in the left femoral vein. CTPA was indicated which revealed central filling defects beginning from the principal branching of the pulmonary artery (PA), reaching the right middle lobular branches and segmental branches for the left inferior lobe. The performed abdominal ultrasound result was normal. TTE depicted a normal heart both functionally and structurally. The patient was immediately started on therapeutic doses of continuous UFH (30000 IU/24 hours), on top of the regular therapeutic regimen for his co-morbidities. After 11 days of intravenous therapy, the patient was switched over to a DOAC. During his hospital stay, laboratory values, clotting times, D-Dimer levels, and the Doppler ultrasound were repeated and showed signs of improvement. The patient was discharged after 17 hospital days, with the recommendation to continue treatment with 15 mg of Rivaroxaban twice daily for 21 days, followed by 20 mg of Rivaroxaban once daily. In conclusion, CAT has to be distinguished from ordinary VTE cases in the sense that CAT carries both a high risk of thrombosis as well as a high risk of bleeding. Therefore, LMWH is markedly cemented as the first-line therapy with DOAC proving non-inferior, with the advantage of better therapy adherence.

Case 7. Pulmonary thromboembolism associated with cancer

A 65-year-old patient was diagnosed with bladder cancer. She underwent a diagnostic biopsy and bladder surgery. The patient was hospitalized on May 28, 2017 in the ICU, due to a fast and irregular heartbeat. During hospitalization, laboratory and D-Dimers were taken, which were elevated at 9055 ng/ml. TTE found a right enlarged ventricle and presence of PAH, and the coronary angiography was normal, as well as hemostasis, showing prolonged PT, prolonged aPTT and prolonged TT. PE was suspected, and a CTPA was performed. The diagnosis of PE was then confirmed. Due to the confirmed diagnosis, anticoag-

ulant therapy with a subcutaneous LMWH dose was started during the hospitalization, whereupon the condition significantly improved, and the patient was subsequently discharged. The patient was given anticoagulant therapy with an DOAC at home. The patient was also tested for protein C, protein S, both of which came back normal, as well as protein V Leiden, where a genetic mutation was found. In conclusion, in the daily practice of medical oncology treatment of patients with a diagnosis of thromboembolism is not rare. Due to the focus on anticancer therapy, the possibility of health deterioration or even imminent danger to life caused by thromboembolic disease may be underestimated. Ignorance of the symptoms of such life threatening conditions makes it impossible to establish the correct diagnosis, resulting in the lack of timely implementation of appropriate treatment. The priority of treatment for cancer might result in overlooking the symptoms that are the real cause of the poor effect of the anticancer therapy.

Case 8. Lung cancer-associated thrombosis

A 47-year-old patient was presented to the University Cardiology Clinic with symptoms of severe dyspnea and shortness of breath. A CTPA was performed, and it revealed PE. The patient was hospitalized and immediately had LMWH. The patient underwent 10 days of continuous treatment with a DOAC and was discharged in a stable condition. He was scheduled for a follow-up examination after three months. After approximately 3 months, the patient was presented with reduced intensity of his dyspnea, decreased appetite as well as present general malaise, despite secondary thromboprophylaxis. The patient had almost normal values of D-Dimers, and a high RIETE score of three. A repeat CTPA was done, negative for a new PE, yet it indicated a malignant neoplasm of the lungs. After the bronchoscopy, the diagnosis of small-cell lung cancer was made (SCLC). With regards to the patient's age, and his normal left ventricular ejection fraction, there was an opportunity and possibility to treat him utilizing more aggressive treatment. The patient underwent chemoradiotherapy. Radiation was administered in adjunct to the combination chemotherapy with Etoposide and Cisplatin. In conclusion, we presented a case with lung cancer and a first occurrence of a thrombotic event. Physicians should think of occult cancer in patients with unprovoked thrombosis, especially ones with high-risk profiles.

Case 9. Cancer-associated thrombosis in a patient with recto-sigmoid cancer

A 67-year-old woman was diagnosed with a rectal neoplasm. She underwent diagnostic biopsy and pre-surgical examinations in March of 2015. A CT scan was done in April of 2015, and it showed a malign neoplasm of the recto-sigmoid junction, along with vaginal infiltration. While still awaiting surgery, the patient presented with lower right leg swelling. She is suspected of having DVT, and was started on a therapeutic subcutaneous LMWH dose. The patient was subsequently hospitalized and treated as an inpatient for DVT. DVT of the common femoral vein, the femoral vein and the popliteal vein of the left leg was confirmed by compression ultrasound (CUS). The patient was initially treated with therapeutic doses of Enoxaparin. When the patient was switched over to a VKA, the INR values were shown to be unsatisfactory. With the therapy found lacking, and with a slightly increased risk of bleeding in cancer patients with VTE, our patient was started on Rivaroxaban. After discharge, she continued with surgery and oncology treatment. In conclusion, the diagnosis of DVT was made relatively early. The patient was started on anticoagulant therapy, with the aim to improve prognosis. At that point in time, there was no sure-fire data regarding the safety of use of DOACs for CAT, provoked by gastrointestinal and genitourinary malignancies. Now we know that the bleeding risks are higher for such cancers, so patients might be better off with prolonged LMWH therapy instead of a DOAC.

Case 10. Cancer-associated thrombosis in a patient with mucinous adenocarcinoma

A 67-year-old woman started having gastrointestinal complaints in February of 2017. By March of 2017, she had been diagnosed with an intrahepatic cholangiocarcinoma. She underwent six rounds of chemotherapy under the gemcitabine/cisplatin (Gem-Cis protocol). A partial remission of the cancer was achieved. Next, the patient underwent outpatient CUS for left leg pain in August of 2017. That ultrasound came back negative. In October of 2017, the patient was pre-

sented to the Institute of Transfusion Medicine in Skopje, once again with left leg pain. Her CUS was again negative. She was treated as an outpatient with Diosmin. A week later, she was presented to the University Cardiology Clinic with erythematous and a painful and swollen left thigh and lower leg. Her CUS revealed left iliac and left femoral thrombosis. She was admitted and started on therapeutic doses of Enoxaparin. Her echocardiography was non-contributory. At admission, she had paroxysmal atrial fibrillation, but this was converted into sinus rhythm. She was switched over from LMWH to the DOAC Rivaroxaban. After discharge, she continued with Rivaroxaban. In December of 2018, the patient underwent a liver biopsy which showed metastases, which reclassified the cancer as mucinous adenocarcinoma. Further examination elucidated bone metastases. She underwent palliative care and unfortunately passed away in March of 2019. In conclusion, the diagnosis of mucinous adenocarcinoma is a grave one, and it carries a low chance of survival. Some studies single out mucinous adenocarcinoma as the cancer most likely to be associated with the development of VTE, with a calculated incidence of 66.7 per 1000 years. As a comparison, squamous cell carcinoma is widely considered to be likely associated with VTE, while its incidence is 21.2 per 1000 years, more than three times lower that mucinous adenocarcinoma.

Case 11. Comorbidities as risk factors for precipitated cancer-associated thrombosis

We present a case of a 51-year-old female, admitted for the first time at our Clinic with symptoms of dyspnea, cough, fever, and fatigue. Her visit was four days in duration. One day before being admitted to our hospital, she was examined at another hospital, where the investigations revealed leukocytosis and a bilateral bronchopneumonia on the chest X-ray (CXR). After the CXR, she was given antibiotics and sent home, with a plan of outpatient follow-up. The symptoms persisted on the day of the admission, hence the examination at our emergency department. The patient's past medical history included chronic obstructive pulmonary disease (COPD), managed via medication, as well having underwent previous left breast mastectomy due to breast cancer five years prior. The patient was on regular therapy with Tamoxifen. The physical examination showed impaired vesicular breathing with present bilateral crepitations. Her blood pressure was 90/60 mmHg, and her ECG showed a sinus tachycardia at 107 bpm and a QRS morphology of RBBB. Her lab work came back remarkable for elevated white blood cells (WBC) at 31.9x10^9/L, neutrophils at 27.9x 10^9/L, elevated D-Dimers at 5146.7 ng/ml, elevated cardiac troponin at 663.9 ng/l, as well as elevated CRP at 129.7 mg/l. Blood gasses showed hyposaturation, hypoxemia and normocapnia, with compensated metabolic acidosis. TTE showed tricuspid regurgitation with enlargement of the right chamber, as well as a high probability of PE. Doppler ultrasound of the lower extremities revealed a DVT of the common femoral vein, as well as the popliteal vein of the left lower extremity. CTPA showed a central filling defect on the bifurcation of the left principal pulmonary artery and on the lobar and segment branches as well as pulmonary infarction zones in apicoposterior segment. The right lung notably had filling defects at the subsegmental branches, as well infarction zones in the middle and upper lobe. These findings effectively meant that the patient has a massive PE with zones of infarction bilaterally. The patient was treated with anticoagulation (LMWH), an antibiotic, and antipyretics. On the fifth day of hospitalization, the patient's general state deteriorated and she became hemodynamically unstable. Vasopressor therapy was initiated to correct a low blood pressure, with unsatisfactory response. Subsequently, advanced CPR measures failed and the patient died. In conclusion, cancer is a well-known risk factor for VTE by itself, but cancer in combination with established pulmonary disease and acute pulmonary infection clearly increases the risk for developing VTE and brings with it a grave prognosis.

Case 12. Deep Vein Thrombosis as a first presentation of large B-cell lymphoma

We present a case of a 39-year-old patient with clinical signs and symptoms of DVT located at the saphenofemoral junction. The patient was diagnosed with ultrasound and treated initially with LMWH, and subsequently with VKA. The patient was discharged from hospital stay in stable condition. One month later, the patient was diagnosed with a large B-cell lymphoma, and started on R-CHOP cycles of therapy and two doses of Mabthera. The oncologic disease is in remission, with normal findings on positron emission tomography (PET). The control ultrasound revealed the

presence of post thrombotic syndrome (PTS), and Diosmine was prescribed. In conclusion, VTE is not a rare complication of malignant hemopathies. This case raises a question regarding the association of these two conditions.

Case 13. Cancer-associated thrombosis is the setting CD20-positive small lymphocytic lymphoma

A 41-year-old male patient was diagnosed with a low grade, CD20-positive small lymphocytic lymphoma (SLL), after an axillar lymph nodes biopsy in April of 2005. Abdominal and thoracic CT scans were normal. His bone marrow biopsy was also normal, without infiltration with lymphoma. The patient was followed-up with and no treatment was necessary for the next four years. In May of 2009 there was a noted progression in the disease, and immunochemotherapy was undertaken, with six cycles of the fludarabine and cyclophosphamide (FCR) regiment. Shortly after finishing FCR treatment, enlargement of abdominal lymph nodes was registered and the patient received eight cycles of R-CHOP and radiotherapy. Due to the refractory and progressive state of the patient's disease, he underwent treatment with six cycles of FCR in 2013, eight cycles of R-CVP as well as maintenance therapy with Rituximab for two years. In 2019, he was treated with four cycles of R-Bendamustine. In 2020, the patient was presented to our outpatient department with left calf edema, subsequently confirmed with Doppler ultrasound to be a left popliteal DVT. His abdominal ultrasound was normal with no enlarged abdominal lymph nodes. Treatment was initiated with LMWH, followed by the VKA Acenocoumarol, with noted significant clinical improvement. The patient still takes the oral anticoagulation and has regular INR check-ups.

Case 14. Deep vein thrombosis in a patient with the T-lymphoblastic lymphoma subtype of non-Hodgkin's lymphoma

A 24-year-old male patient was presented for a first-time visit to the University Hematology Clinic in November of 2020 with left arm edema and pain. A multi-slice computer tomography (MSCT) showed signs of thrombosis of the left jugular vein, as well as a large expansive tumor in the upper and medial mediastinum. CT guided biopsy of the tumor confirmed the diagnosis of the non-Hodgkin's lymphoma subtype T-lymphoblastic lymphoma (T-LBL), with cell types CD3+++ with a high proliferative index (Ki67 95%). PET-CT was confirmed metabolically active lymph nodes in the thorax and bone marrow, evaluated as stage IV disease. A bone marrow biopsy confirmed infiltration with lymphoblastic T-cells. His blood cell count and routine biochemical analysis were normal with the only abnormality being elevated LDH levels. Anticoagulant therapy with LMWH was started immediately and after histological confirmation and staging procedures, therapy was continued with chemotherapy, following the BFM protocol. He received course A and B of the BFM regiment. Before continuation with the BFM protocol chemotherapy, the patient suddenly developed left sided hemiparesis. Brain CT with venography was performed, and thrombosis of the right parietal vein was confirmed. Anticoagulant therapy with LMWH in a therapeutic dose of 80 mg twice daily was initiated, with significant improvement of the symptoms of left hemiparesis. Due to this serious complication, we had to postpone further chemotherapy until the resolution of symptoms and a control MRI was able to be completed. The control MRI has confirmed thrombosis of right parietal vein with radiological signs of improvement. Control abdominal and thoracic CT scans were normal, as well as the control bone marrow biopsy.

DISCUSSION

Cancer-associated thrombosis is present in 0.5% of patients with cancer, as opposed to a presence of 0.1% of venous thromboembolism in the general population, and a significant 20% VTE incidence in cancer patients. [3, 4] PE is the second leading cause of death in cancer patients.

The incidence of DVT and PE is more common in patients with different types of cancer and lymphoproliferative disorders, such as lymphoma and chronic lymphocytic leukemia. Hypercoagulability as well as the enlargement of lymph nodes or tumors leading to venous or lymphatic obstruction can contribute to higher incidence of deep vein thrombosis in patients with lymphoproliferative neoplasms. [5]

The mechanism behind this includes the activation and accentuation of the coagulation cas-

cade, increased platelet activation, and aggregation, as well as the procoagulant properties of both immobilization and potential chemotherapy. It is imperative that after early diagnosis, we treat cancer-associated thrombosis with anticoagulation. According to Prandoni et al., patients with CAT who are not receiving anticoagulation are at high risk for recurrent thrombotic events, more so than bleeding patients. [6]

LMWH is associated with a significant reduction in the risk of recurrent VTE without a significant increase in major bleeding episodes, as opposed to VKA. Recent developments have shown DOACs to be as effective as LMWH in the treatment of CAT. DOACs are associated with a non-significant lower risk of recurrent VTE, and non-significantly higher risk of major bleeding versus LMWH. [7]

The DOACs (Edoxaban and Rivaroxaban) as well as LMWH are the preferred first-line treatment agents by the International Society of Thrombosis and Hemostasis (ISTH). LMWH treatment is preferred in patients with a high risk of bleeding and a potential for drug-drug interactions.

The European Society of Cardiology (ESC) has proposed weight-adjusted LMWH in patients with both PE and cancer, with a recommendation to consider Rivaroxaban and Edoxaban as alternatives to weight-adjusted LMWH, in patients without gastrointestinal cancer. Anticoagulation with NOACs or LMWH should be considered superior to VKA during the first six months. Extended anticoagulation (more than six months) should be considered for an indefinite period of time, or until the cancer is cured. No recommendation is provided for anticoagulation duration in CAT by ISTH. [8, 9'

We presented 14 various and diverse cases, all of which explored some form of CAT or a malignant hemopathy. It is clear that the first-line therapy utilized in the treatment of such patients should be with either a LMWH, Rivaroxaban or Edoxaban, as per the recommendations from the ESC and the ISTH. From our 14 cases, three patients were treated with LMWH, four were treated with a DOAC, one was treated with a LMWH initially followed by a VKA, four were treated with a VKA, and two were initially treated with LMWH, followed by a NOAC in the same therapy course.

Tumor site, tumor histology, and molecular classification, tumor stage, the type of chemotherapy used in treatment, the patient's history and comorbidities, the patient's age and gender may all play a crucial role in the development of thrombosis in the setting of cancer. [8] As Ferrer Galván et al. state, the future of predicting CAT may rely on designed composite scales that would include multiple biomarkers, both more "classic" biomarkers, such as D-Dimers, P-selectin, leukocytosis, thrombocytosis, soluble tissue factor, endogenous thrombin generation, hypoalbuminemia and Leiden factor V, together with novel promising biomarkers, such as tissue-factor-bearing microparticles or microvesicles (MPs-TF) and neutrophil extracellular traps (NETs). [8]

While keeping an eye on novel composite scales, it is wise for us, as clinicians treating CAT in North Macedonia, to utilize two benchmarks: The first is to use a validated scale in predicting CAT, depending on the biomarkers and genetic data available, such as the Khorana index, which requires only D-Dimers, or alternatively the Vienna CATS Score which requires the biomarker soluble P-selectin as well as genetic parameters, or possibly even the ONCOTHROMB12-01 study score called ThromboinCode-Oncology (TiC-Onco), which requires genetic parameters. The second benchmark is to reiterate that the best first-line treatment of CAT is LMWH, Edoxaban or Rivaroxaban. [9]

CONCLUSION

CAT remains a close second cause of mortality in patients with cancer and as such should always be one of the goals in the holistic treatment of this group of patients. Early detection, or better, prevention of thrombotic events is of vital importance and tremendously impacts the overall prognosis. Novel oral anticoagulants have proven equal in comparison with the older well known heparin agents and their use, individually tailored to the patient, has proven to provide effective anticoagulation while minimizing the risk of bleeding.

REFERENCES

1. 1. Iorga RA, Bratu OG, Marcu RD, et al. Venous thromboembolism in cancer patients: Still looking

for answers. Exp Ther Med. 2019;18(6):5026-5032. doi:10.3892/etm.2019.8019
2. 2. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;16(9):1891-1894. doi:10.1111/jth.14219
3. 3.Streiff MB, Holmstrom B, Angelini D, et al. NCCN Guidelines Insights: Cancer-Associated Venous Thromboembolic Disease, Version 2.2018. J Natl Compr Canc Netw. 2018;16(11):1289-1303. doi:10.6004/jnccn.2018.0084
4. 4. Trujillo-Santos J, Casas JM, Casado I, et al .RIETE Investigators. Thirty-day mortality rate in women with cancer and venous thromboembolism. Findings from the RIETE Registry. Thromb Res. 2011 Feb;127 Suppl 3:S1-4.
5. 5. Horowitz NA, Brenner B . Thrombosis in hematological malignancies: mechanisms and implications. Thromb Res. 2020 Jul;191 Suppl 1:S58-S62.
6. 6. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-3488. doi:10.1182/blood-2002-01-0108
7. 7. Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood. 2020;136(12):1433-1441. doi:10.1182/blood.2020005819
8. 8. Carrier M, Prandoni P. Controversies in the management of cancer-associated thrombosis. Expert Rev Hematol. 2017;10(1):15-22. doi:10.1080/17474086.2017.1257935
9. 9. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405

Резиме

ТРОМБОЗА ПОВРЗАНА СО КАРЦИНОМ – СЕРИЈА СЛУЧАИ

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Научните трудови посочуваат дека присуството на карцином ја зголемува веројатноста за развивање венски тромбоемболизам (пулмонална тромбоемболија и длабока венска етромбоза) четирикратно до дури седумкратно. По раното поставување дијагноза, оваа тромбоза поврзана со карцином треба да се сфати многу сериозно со цел да се намали нејзиниот морбидет и морталитет.

Претставуваме четиринаесет случаи од пациенти со тромбоза поврзана со карцином, вклучувајќи и тромбоза поврзана со малигни хемопатии.

Клучни зборови: тромбоза асоцирана со карцином, малигна хемопатија, венски тромбоемболизам (ВТЕ)