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Complex Combination of Pulmonary Embolism, Stroke, and ST-Segment Elevation Myocardial Infarction in Young Patient with Recent COVID-19 Infection and Newly Diagnosed Lung Carcinoma

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Abstract

BACKGROUND: Ischemic stroke, pulmonary embolism (PE), and acute ST-segment elevation myocardial infarction (STEMI) are very rarely all present in younger patients without classical risk factors or a family history of dyslipidemia or cardiovascular disease. They represent a medical emergency and necessitate fast diagnosis, treatment, and search for etiology, not explained purely by atherosclerosis. Thrombophilia testing should be considered in younger patients with several major thrombotic episodes, although there is much disagreement concerning the importance of homocysteine level testing in patients with arterial and venous thrombotic events, including PE. COVID-19 infection may trigger several thrombotic complications caused by unique immunothrombotic processes.

CASE PRESENTATION: A 44-year-old patient complaining of chest pain was admitted at our clinic due to acute anterior STEMI. He has a previous medical history of ischemic stroke, COVID-19 infection, and PE in the past 2 months. Newly, diagnosed lung adenocarcinoma was confirmed by biopsy 10 days before STEMI admission, without surgical or previous hemotherapy. The patient was on regular anticoagulant therapy with rivaroxaban 20 mg OAD and antiplatelet therapy with Aspirin due to previous PE and ischemic stroke. Patient denied standard risk factors, family history for cardiovascular disease or any previous minor or major bleedings, history of anemia, liver, or renal dysfunction. Acute stroke was confirmed by brain computed tomography imaging. Thrombophilia panel testing revealed homozygote mutations for MTHFR 677 gene, heterozygote mutation for integrin subunit alpha 2, and fibrinogen B beta chain) genes. The patient was treated with low molecular weight heparin, aspirin, clopidogrel, and heart failure therapy in the acute phase. Clinical consultations were performed with a team of doctors which included a cardiologist, neurologist, and oncologist. Patients have a high bleeding risk, assessed by HAS-BLEED score of 4.

CONCLUSION: Our patient is a rare case of serious multi-vascular thrombotic events with underlying thrombophilia, lung cancer, and past COVID-19 infection complicated by pulmonary embolism, ischemic stroke, and STEMI.

Introduction

The cluster of several major venous and arterial thrombotic events including ischemic stroke, pulmonary embolism (PE), and acute ST-segment elevation myocardial infarction (STEMI) are very rarely all present in younger patients without classical risk factors or family history of dyslipidemia or cardiovascular disease. They represent a medical emergency and necessitate fast diagnosis, treatment, and search for etiology, not explained purely by atherosclerosis. Thrombophilia testing should be considered in younger patients with several major thrombotic episodes, although there is much disagreement concerning the importance of homocysteine level testing in patients with arterial and venous thrombotic events, including PE. COVID-19 infection may trigger several thrombotic complications caused by unique immunothrombotic processes. We are presenting a complex rare case of young male patient with acute STEMI and stroke, confirmed thrombophilia, previous COVID-19 infection, and PE. In addition, before STEMI, pulmonary adenocarcinoma was diagnosed. Management and balance of both thrombotic and bleeding risk in these patients are challenging and important for the choice of antithrombotic treatment and duration.

Case Report

A 44-year-old patient complaining of chest pain was admitted at our clinic due to acute anterior STEMI. He has previous medical history of ischemic stroke, COVID-19 infection, and PE in the past 2 months. Newly, diagnosed lung adenocarcinoma was confirmed by biopsy 10 days before STEMI admission, without surgical or previous hemotherapy. The patient was on regular anticoagulant therapy with rivaroxaban 20 mg OAD and antiplatelet therapy with aspirin due to previous PE and ischemic stroke. Patient denied standard risk factors, family history for cardiovascular disease or any previous minor or major bleedings, history of anemia, liver, or renal dysfunction.

On admission patient was hemodynamically stable, eupneic, with blood pressure 120/80 mmHg, oxygen saturation 94% on room air, and no signs of heart failure. The patient had moderately reduced cognitive function which worsened shortly after the admission. Worsening of neurological status and signs of new stroke with the left hemiparesis and disorientation dominate the clinical presentation.

The electrocardiogram revealed sinus rhythm with heart rate 98 bpm, and 20 mm ST segment elevation in the anterior leads (Figure 1).



Figure 1: Admission electrocardiogram with 20 mm ST segment elevation in anterior leads

Laboratory findings showed elevation in the high-sensitive troponin I (50000 ng/L, referent values for male individuals 16.5 ng/L), leukocytes values (20.4; 9.9; 7.3 × 10^9 -ref values 9 × 10^9), increased CRP (28.5; 129.8; 112.2 mg/L; referent values 6 mg/L) and D-dimer values (6623 ng/ml – referent values up to 500 ng/mL), and hemoglobin of 92 g/L. Other laboratory parameters were within referent limits.

Echocardiography showed moderately reduced left ventricular function, with an ejection fraction of 45% and akinesia of the apex and apical septal wall, and mild functional mitral regurgitation (Figure 2).

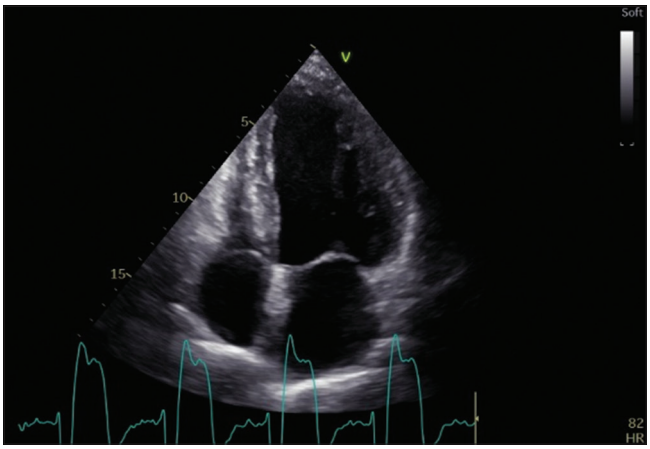


Figure 2: 2D transthoracic echocardiography showed moderately reduced global left ventricular function, with the left ventricular ejection fraction of 45% and apical and distal septal wall hypokinesia

Brain computed tomography revealed a large zone of ischemic stroke in the area of the right cerebral artery. Examination by neurologist confirmed left site hemiparesis with moderate neurological impairment and recommendation for anticoagulation therapy. Due to the worsened neurological state of the patient, coronary angiography was not performed. The patient continued with medical therapy with low molecular heparin 1 mg/kg BID, dual antiplatelet therapy with aspirin and clopidogrel, and a high dose of statin (rosuvastatin 40 mg). Additional therapy for heart failure was introduced which included AKE inhibitor-Perindopril, 4 mg OAD, beta-blocker Bisoprolol 2.5 mg OAD, Spironolactone 25 mg OAD, and Empagliflozin 10 mg OAD. Clinical consultations were performed with a team of doctors which included cardiologist, neurologist, and oncologist. Patients have high bleeding risk, assessed by HAS-BLEED score of 4.

The thrombophilia panel revealed homozygote mutations for MTHFR 677 gene, heterozygote mutation for *ITGA2* (integrin subunit alpha 2), and fibrinogen B beta (Bβ) chain (FGB) genes. Immunological tests antiphospholipid antibodies were negative. Doppler ultrasound did not show signs of deep venous thrombosis.

The patient was discharged from our hospital clinically stable with left site hemiparesis after 10 days and transferred in other hospitals for oncology evaluation and treatment. The following treatment was prescribed: Rivaroxaban 20 mg OAD, clopidogrel 75 mg OAD (dual antiplatelet therapy [DAPT] due to high bleeding risk and thrombosis risk), rosuvastatin 40 mg OAD, perindopril 4 mg OAD, spironolactone 25 mg OAD, bisoprolol 5 mg OAD, and empagliflozin 10 mg OAD. The patient was advised to continue DAPT for 1 month, then to use rivaroxaban as long-term therapy if it is tolerated well without major bleedings in consultation with oncologist. Clinical revision for prolonged anticoagulation therapy was also advised based on the patient clinical state, cancer treatment and activity, and bleeding risk. Cardiology control was scheduled after 2 weeks, depending on the oncological treatment and outcome.

Discussion

We have presented very rare complex case of a young patient with the presence of arterial and venous major thrombotic complications. Several factors explain the unfortunate constellation of complications in our patients. The presence of thrombophilia, active cancer, and previous COVID-19 infection, might be causes or triggers for thrombotic events based on genetic thrombophilic state. Is well established that COVID-19 infection leads to generalized endothelial dysfunction, micro immunothrombosis, prolonged

activation of cytokines, coagulation, disturbances, and activation on antiphospholipid antibodies, all together increasing the thrombotic risk [1]. The risk declines several weeks after infection, although the risk can persist for a year or even longer, particularly in cases with venous thromboses. Ischemic stroke with hemorrhagic complication and prolonged bed rest additionally contribute to increase both thrombotic and bleeding risk. MTHFR enzyme deficiency is linked with mild-to-moderate hyperchomocysteinemia, a factor that is positively associated with atherosclerosis, arterial and venous thrombotic events at a young age [2]. Mutations in fibrinogen (FGB) lead to several disorders, including afibrinogenemia, dysfibrinogenemia, hypo dysfibrinogenemia, and thrombotic tendency [3], [4], [5]. There are several contrary data on the role of hyperhomoysteinemia and thrombotic complications. Italian study confirmed that MTHFR gene 677TT mutation increased the risk of venous thromboembolism (VTE) in the cases without known clinical provoking factor and without other thrombophilia (i.e. Factor V Leiden, prothrombin gene mutation G20210A, Protein C, Protein S, or antithrombin deficiency) [6]. Contrary, a Japanese study reported that MTHFR gene mutation 677TT is a VTE risk factor only in the presence of other thrombophilia with OR 5.99 (95% CI 1.56–22.96), compared to a control group [7]. At present, there is not enough evidence to support the necessity of testing homocysteine level in PE patients, neither is sufficient evidence of the benefit of vitamin supplementation in mild or moderate hyperhomocysteinemia.

The presence of lung carcinoma in our patient additionally increase thrombotic risk for both arterial and venous thrombosis and complicate clinical outcome, underlying the need of properly balanced long-term anticoagulation. The risk of developing PE in cancer patients is increased up to seven-fold as compared to the general population [8]. PE risk factors in cancer patients depend on patient-related factors, cancer-related factors, and treatment- related factors [9]. Identification of multiple factors, including biomarkers, associated with the risk of cancer-associated PE has prompted the development of risk scores for predicting PE and its complications [10]. Long-term therapy in cancer patients with thrombotic events depends on event type, cancer activity, bleeding risk, and underlying combinations of thrombophilia's and its thrombogenic potential. The last serious thrombotic event in our patient was STEMI accompanied by stroke [1], [10], [11]. This further complicated the clinical course and our treatment decision. The choice and duration of antiplatelet therapy in patients with STEMI and high bleeding risk necessitate an individual approach based on assessment of both bleeding and ischemic risk. Our patient had a triple jeopardy combination: Increased thrombotic, ischemic, and bleeding risk, which put the patient out of the box of the current guidelines.

Conclusion

To the best of our knowledge, our patient is a rare case of serious multi-vascular thrombotic events with underlying thrombophilia, lung cancer, and past COVID-19 infection complicated by PE, ischemic stroke, and STEMI. This underlines the importance of multidisciplinary approach, parallel treatment of all conditions, and individual balance of thrombotic, ischemic, and bleeding risk.

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