Case Report

Unexplained Multi-Site Thrombosis: A Step-by-Step Strategy for Factor V Leiden Detection in a Hypercoagulable Patient

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Abstract

Thrombotic manifestations involve the development of blood clots within blood vessels. These conditions can occur unexpectedly in different areas and are often linked to life-threatening situations, presenting challenges for both diagnosis and treatment.

We present a case of multi-site thrombosis in a patient with a confirmed hypercoagulable state, resulting from a positive factor V Leiden mutation. The patient's medical history included hypertension, chronic obstructive pulmonary disease, previous thrombotic events, and changes in anticoagulant therapy.

This case highlights the challenges associated with multisystem thrombosis and underscores the necessity of employing various diagnostic techniques, such as echocardiography, computed coronary angiography, and Doppler ultrasonography. In this instance, the patient presented with a history of unprovoked lower limb deep vein thrombosis and multiple arterial thromboses.

The patient's treatment regimen comprised anticoagulants, antiplatelet drugs, and vasodilators. While a reduction in thrombus size was noted, complete revascularization could not be attained.

Effective diagnosis and treatment of venous and arterial thrombosis often require multimodal imaging. Selective blood test screening can be beneficial in diagnosing or detecting inherited or acquired abnormalities linked to thrombosis development.

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Introduction

Thrombosis is the formation of a blood clot (thrombus) within a blood vessel or heart chamber. Thrombotic manifestations can develop in various locations, such as the cerebral, splanchnic, upper-extremity, coronary, renal, ovarian, or retinal veins.[1] It is estimated that arterial and venous thrombotic conditions constitute the primary cause of global mortality.[2] Clinical signs, symptoms, and risk factors linked to atypical thrombotic manifestations differ from those found in the typical presentation of venous thrombosis in the lower extremities.[3,4] Multiple factors contribute to the risk of thrombosis, including a history of deep vein thrombosis, use of birth control pills or hormone therapy, pregnancy, vein injury, immobility, inherited blood clotting disorders, central venous catheter presence, advanced age, smoking, overweight or obesity, and certain medical conditions such as cancer, heart disease, lung disease, or Crohn's disease.[5,6] Preventing thrombosis is crucial, and recognizing its symptoms can help determine when immediate medical care is needed.[7] Treatment strategies can vary significantly based on the affected region, whether it involves cerebral, abdominal, or extra-abdominal areas.[8] Anticoagulant medication is a well-established treatment option for thrombosis. Interventional therapies also play a significant role in site-specific cases, such as coronary or vascular angioplasty.[9] These treatments involve catheter-based vessel dilation, anticoagulant drugs to thin the blood, and clot-dissolving medications.[8]

The purpose of this study is to present a complex case involving thrombotic manifestations and multidisciplinary management in a patient with a hypercoagulable state and cardiovascular risk factors.

Case Report

The patient was a 61-year-old driver with a history of smoking and several medical conditions. These included chronic obstructive pulmonary disease, hypertension, and a previous episode of unprovoked lower limb thrombosis dating back to 2006. Furthermore, he was a smoker, and his long-term warfarin therapy of approximately 8 or 9 years had recently been changed to rivaroxaban. About a month before the visit, the patient experienced a sudden episode of loss of consciousness and syncope. Initially referred for neurological consultation, he reported chest pain and elevated blood pressure upon direct questioning, prompting a simultaneous referral to a cardiologist for further assessment.

The patient's ECG indicated left ventricular hypertrophy and nonspecific changes, while the troponin assay yielded negative results. A transthoracic echocardiography was performed, which revealed normal biventricular systolic function, mild left ventricular diastolic dysfunction, no significant valvular disease except for a thickened aortic valve with no apparent gradient or regurgitation, and no signs of pulmonary hypertension (systolic pulmonary artery pressure =25 mm Hg). The transthoracic echocardiogram also showed no evidence of left ventricular outflow tract obstruction or aortic stenosis.

In light of the patient's chest discomfort upon presentation and cardiac risk factors, a computed tomography coronary angiography (CTCA) was performed to rule out coronary artery disease. The CTCA identified a moderate lesion in the obtuse marginal artery. Notably, a mass was also detected on the left coronary cusp of the aortic valve during the examination.

At this point, the patient was admitted for further evaluation and to rule out infective endocarditis on the aortic valve, given the presence of the mass. Upon initial hospital admission, his vital signs were as follows: heart rate of 84 beats per minute, blood pressure of 125/80 mm Hg, respiratory rate of 16 breaths per minute, and oxygen saturation (SO2) of 93%. The patient exhibited an absence of pulses in the lower limbs. Upper limb pulses, while detectable, were mildly diminished. Both lower limbs appeared pale and hairless. A detailed history revealed that despite the sedentary nature of his profession, the patient experienced intermittent claudication.

Transesophageal echocardiography was conducted, which revealed mural thrombosis within the descending aorta (Figure 1). Additionally, a semi-mobile object measuring 0.7×0.7 cm was detected along the anterolateral wall of the right ventricle (Figure 2). Furthermore, a substantial amorphous mass measuring 1.5×1.4 cm, displaying varying opacities with filament-like attachments, was identified near the left coronary cusp of the aortic valve, accompanied by mild aortic regurgitation (Figure 3 A and B). Given these observations, further diagnostic tests were advised to ensure a thorough evaluation.

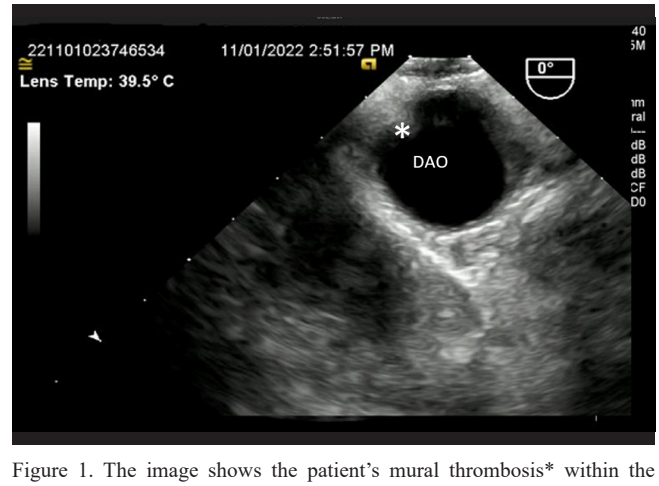

Figure 1. The image shows the patient's mural thrombosis* within the descending aorta.

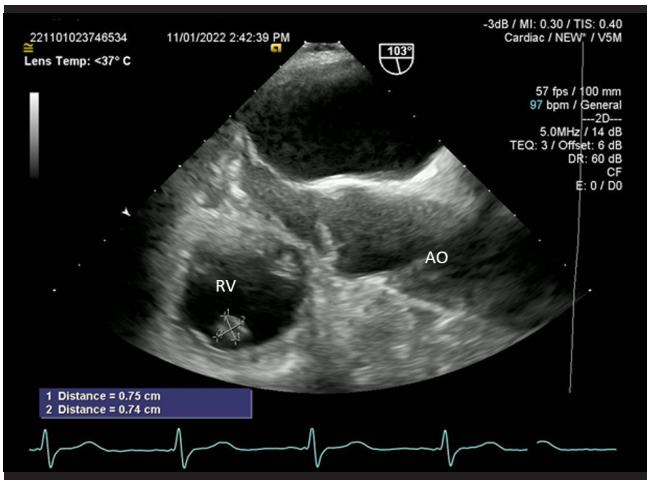

Figure 2. The image illustrates a semi-mobile object along the anterolateral wall of the RV.
RV, Right ventricle; AO, Aorta

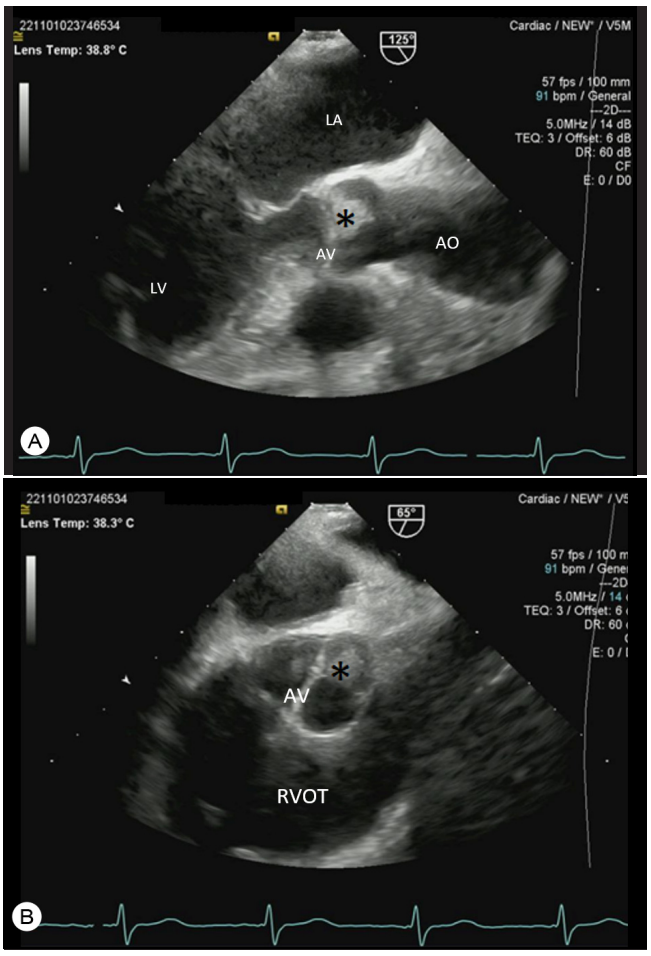

Figure 3. A significant non-homogeneous mass can be observed adjacent to the left coronary cusp of the aortic valve in the long-axis view (A) and the enface AV valve view (B).
AV, Atrioventricular; AO, Aorta; RVOT, Right ventricular outflow tract; LV, Left ventricle

Aortic CT angiography was conducted for the thoracic and abdominal aorta (Figure 4). The angiogram revealed a mural thrombus along the entire descending aorta and the complete blockage of the infrarenal abdominal aorta, the common iliac artery on both sides, and the external and internal iliac arteries on both sides, except the distal portion.

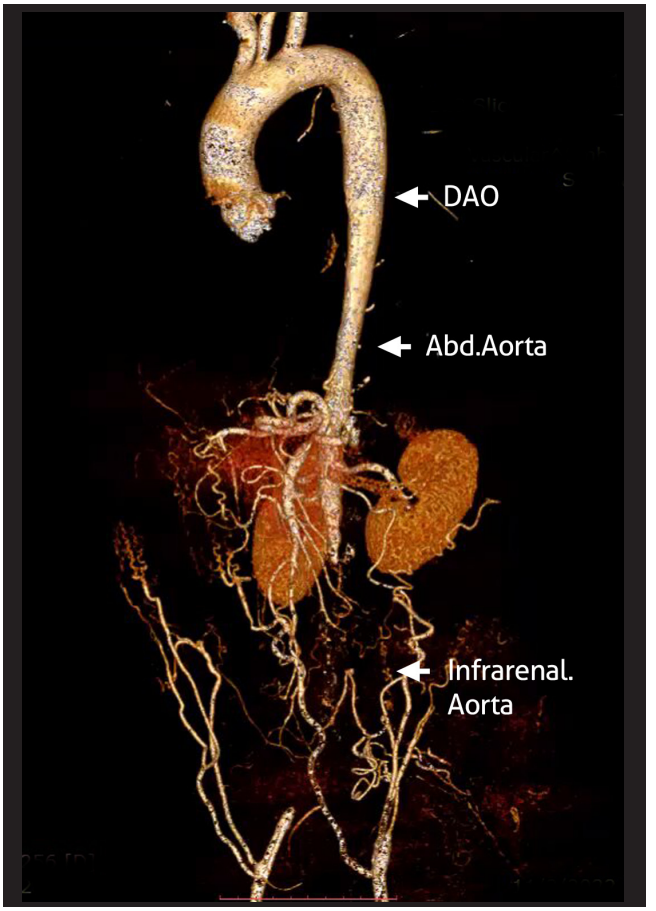

Figure 4. The patient's aortic computed tomography angiography, conducted for the thoracic and abdominal aorta, demonstrates a mural thrombus along the entire descending aorta and the complete blockage of the infrarenal abdominal aorta, the common iliac artery on both sides, and the external and internal iliac arteries on both sides, except for the distal portion.

Color Doppler ultrasound was employed to assess the lower limbs, which showed the presence of atherosclerotic plaques in the arteries with minimal narrowing. Importantly, all lower limb arteries demonstrated monophasic waveforms, suggesting impaired blood supply. Concerning venous evaluation, Duplex ultrasonography revealed heterogeneous and hypoechoic thrombotic material in both femoral veins. Additionally, recanalization pathways with venous flow maintained through partial occlusion were observed, indicating chronic venous thrombosis.

Considering the patient's negative blood cultures on 3 separate occasions, normal inflammatory marker

(erythrocyte sedimentation rate), and slightly elevated serum D-dimer level, the mass attached to the aortic valve was likely a thrombosis. Moreover, the mass in the right ventricle was also suspected to be a thrombosis within the venous system.

In light of the patient's reported loss of consciousness lasting 5 minutes 1 month before admission, a neurological evaluation was conducted. No focal neurological deficits were found. Both the brain CT scan and brain magnetic resonance imaging showed no indications of brain injury and were considered normal. Nonetheless, the electroencephalogram displayed abnormal wave patterns potentially linked to seizure activity. Based on the recommendations of the neurological consultation, the patient was prescribed valproic acid to be taken every 12 hours and encouraged to seek further evaluation and care from the neurology division.

In view of the patient's hypercoagulable condition and recurrent thrombotic episodes affecting both arterial and venous systems, an internal medicine consultation was sought. A comprehensive set of laboratory tests was conducted utilizing ELISA and a fully automated STAGO coagulometer, which employs a viscosity-based detection system to evaluate coagulation. The tests encompassed analyses for several antibodies and activities, including perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA), antinuclear antibodies (ANA), anti-Ro and anti-La antibodies, cardiolipin antibodies (both immunoglobulin M [IgM] and immunoglobulin G [IgG]), lupus anticoagulants (LACs), anti-B2 glycoprotein antibodies (IgG and IgM), anti-double-stranded DNA (anti-dsDNA), complement levels (C3, C4, and CH50), protein C activity, protein S activity, and antithrombin III levels.

The test results were largely within normal ranges, except for a confirmed positive Factor V Leiden mutation.

Factor V Leiden mutation is a genetic variation that impacts human factor V, a crucial substance in the blood clotting process. This mutation leads to an increased likelihood of blood clot formation. The mutation interferes with the binding of protein C—an anticoagulant protein responsible for counteracting the clot-forming activity of factor V—to factor V, resulting in a predisposition to clotting.[10]

Factor V Leiden mutation is the most prevalent inherited thrombophilia among the unselected White population, affecting approximately 1% to 5% of individuals. Moreover, it is considered the most common inherited thrombophilia in those with venous thromboembolism, with a prevalence of roughly 10% to 20%.[11] Consequently, individuals with Factor V Leiden mutation are more prone to developing hazardous blood clots in both arterial and venous systems.

Upon admission, hemoglobin, WBC count, platelet count, C-reactive protein, erythrocyte sedimentation rate, urea, creatinine, and electrolytes were all within normal ranges. Subsequent tests showed no significant changes in any of these parameters. Both baseline partial thromboplastin and prothrombin times were normal, while the D-dimer level was measured at 0.52.

Considering the presence of chronic, multi-site thrombosis, the patient was initially treated with a combination of intravenous unfractionated heparin for 5 days and warfarin. On the sixth day, heparin was discontinued, and warfarin treatment was maintained. The patient was discharged on the tenth day with a normal international normalized ratio (INR=2.48). Furthermore, atorvastatin, varenicline, valsartan, and valproic acid were added to the patient's medication regimen. During subsequent outpatient visits, the treatment plan was modified to include cilostazol after discontinuing varenicline. Given the chronic nature of multi-site thrombosis, a dual therapy consisting of aspirin and warfarin was chosen as the most appropriate treatment plan. The patient's final at-home medication regimen included 20 mg of rosuvastatin daily, 80 mg of aspirin daily, a half-tablet of cilostazol to provide additional antiplatelet and vasodilatory effects, warfarin with dosage adjusted according to INR levels, and a single daily dose of valsartan/amlodipine at 80/5 mg. Follow-up valve surveillance was also scheduled in accordance with established guidelines.

Following the prescribed treatment regimen, the patient's condition significantly improved, and he was discharged in good health. After approximately 5 months of medical therapy, a follow-up aortic CT angiography revealed a reduction in the size of focal thrombosis attached to the aortic valve and a decrease in the extent of the thrombotic segment of the abdominal aorta without complete recanalization (Figure 5). A comparison of the initial aortic CT angiography with the follow-up imaging revealed the development of new runoff in the external iliac arteries, originating from the pelvic collaterals and the paravertebral arteries. Notably, collateral flow around the lower portion of the thoracic aorta was observed in both the aortic CT angiography and echocardiography.

After one year of follow-up, the patient demonstrated an overall positive outcome, maintaining good general health.

Control echocardiography demonstrated that the right ventricular vegetation was no longer visible, and the aortic valve mass had reduced in size (1 cm). Nevertheless, it caused moderate aortic insufficiency, with a higher degree of regurgitation than that recorded in previous assessments. Peripheral pulses showed improvement, as a faint (1+) posterior tibial pulse could be detected bilaterally. Leg claudication demonstrated improvement following treatment with warfarin and cilostazol (Figure 6 A and B).

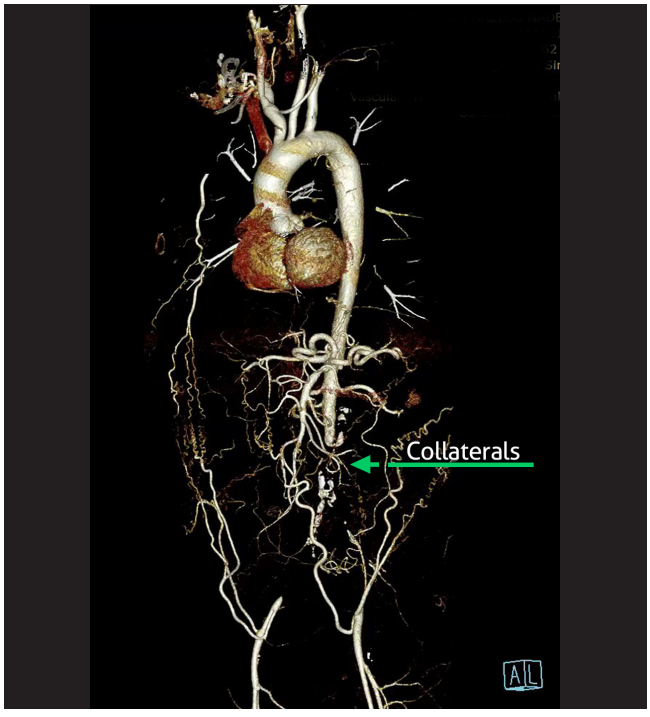

Figure 5. The patient's follow-up aortic computed tomography angiography shows partial mural thrombosis with sufficient flow in the thoracic aorta and the proximal innominate artery, as well as a new runoff in the external iliac arteries from the pelvic collateral and paravertebral arteries.

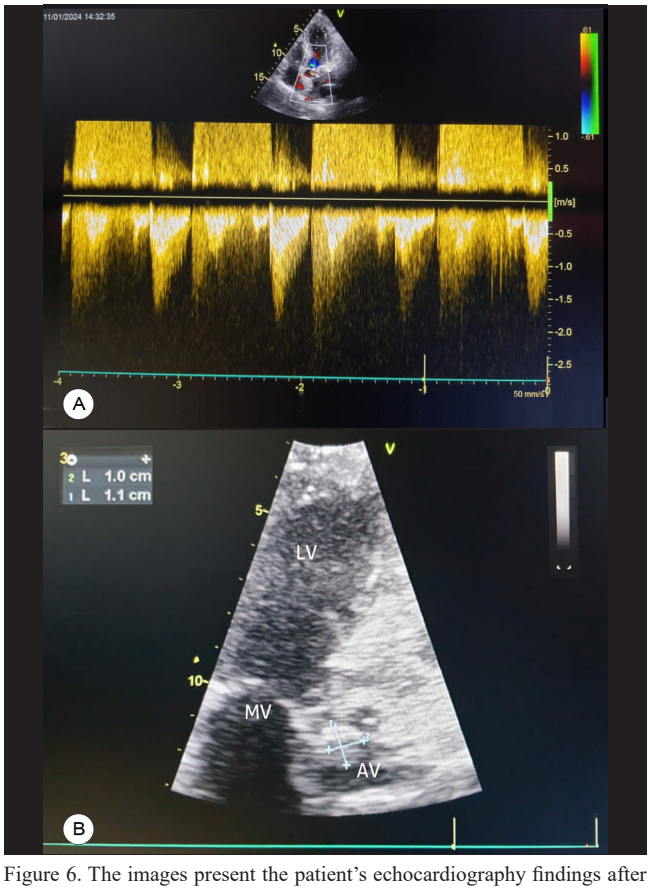

Figure 6. The images present the patient's echocardiography findings after 1 year of follow-up. They show moderate aortic insufficiency as detected by continuous Wave Doppler (A) and the presence of an organized clot on the aortic valve (B).

Discussion

The present case highlights the intricate nature of managing thrombotic symptoms in a patient grappling with both hypercoagulability and concomitant cardiovascular risk factors. Thrombosis, the formation of blood clots within blood vessels, can arise in a multitude of anatomical locations, potentially giving rise to life-threatening circumstances. This case study elucidates the occurrence of thrombotic events in both veins and arteries across diverse regions, including cerebral, splanchnic, upper-extremity, renal, ovarian, or retinal sites, in addition to more common locations.

A comprehensive understanding of thrombotic processes and therapeutic interventions is underscored by the substantial global impact of thrombotic disorders and their considerable contribution to worldwide mortality rates. According to a study, thrombotic events play a pivotal role in the development of underlying conditions such as ischemic heart disease, ischemic stroke, and venous thromboembolism. Further, these events significantly contribute to the overall global burden of disease.[12] In a notable study conducted by Pemmaraju et al[13] (2022), it was emphasized that thrombotic events were linked to an increased mortality risk in individuals recently diagnosed with conditions such as polycythemia vera or essential thrombocythemia.

Our patient's extensive medical history, encompassing thrombosis, chronic obstructive pulmonary disease, hypertension, and previous anticoagulant use, underscores the complex interplay between thrombotic events and traditional cardiovascular risk factors. These risk factors increase the probability of blood clot formation, potentially resulting in conditions such as deep vein thrombosis, ischemic stroke, and myocardial infarction. The recurrence of thrombotic events following the discontinuation of warfarin therapy raises questions about the efficacy of novel oral anticoagulants (NOACs) in managing hypercoagulopathies. As emphasized by a study, the importance of extended preventive measures is crucial for individuals with a predisposition to thrombosis, who should continue to be regularly monitored even after anticoagulant therapy has been discontinued.[14]

A study conducted by Braekkan et al[15] (2012) revealed that smoking was the only factor associated with an increased risk of venous thrombosis. In contrast, atherosclerotic risk factors such as smoking, hypertension, and high cholesterol were linked to an increased risk of arterial thrombosis.

The multisystem implications of this case, which involve cardiac, arterial, and venous thrombotic events, demonstrate its complex nature. The coexistence of a mass lesion attached to the left coronary cusp of the aortic valve, an intramural hematoma within the descending aorta, and a semi-

mobile mass within the right ventricle presents diagnostic challenges that require a multidisciplinary approach. The synergistic utilization of various diagnostic techniques, including echocardiography, CT angiography, and Doppler ultrasound, emphasizes the multifaceted nature of thrombotic conditions. A study by Opitz et al[16] (2022) explored the utility of echocardiography and Doppler ultrasound in identifying right ventricular failure and pulmonary hypertension in acute pulmonary embolism and chronic thromboembolic pulmonary hypertension. Another study underscored the role of Doppler ultrasound in the lower extremities to confirm the presence of deep vein thrombosis and the use of CT pulmonary angiography to visualize bilateral pulmonary embolism.[17]

The presence of a hypercoagulable state in this scenario is significant, as indicated by the positive factor V Leiden mutation. The patient's inclination toward thrombosis was exacerbated by this genetic predisposition, compounded by supplementary risk factors such as smoking and underlying cardiovascular risk factors. According to Kujovich[18] (2011), factor V Leiden can be identified through laboratory testing, particularly blood tests. It was advised that healthcare providers consider the possibility of factor V Leiden in patients with a history of venous thromboembolism or those exhibiting one or more associated complications. In this case, the patient's thrombophilia indicators appeared predominantly within normal ranges despite extensive laboratory testing, underscoring the challenges in detecting hypercoagulability and emphasizing the significance of clinical suspicion.

The intricate nature of thrombotic disorders necessitates a multidisciplinary therapeutic approach, as exemplified in this patient's case. The concurrent use of anticoagulants, antiplatelet agents, and vasodilators underscores the need for tailored treatments to address the various thrombotic events observed. Gaddh and Maier[19] (2021) found that the efficacy of preventive and therapeutic strategies for thrombosis remained uncertain, advocating for an interdisciplinary approach to thrombosis management. This study also emphasizes the crucial role of a comprehensive clinical assessment in raising suspicion of pulmonary embolism and establishing appropriate diagnostic protocols. Moreover, it sheds light on potential thrombus removal techniques, such as localized infusion of lower doses of thrombolytic drugs, catheter-based thrombus fragmentation and aspiration, or a combination of these modalities, as well as surgical embolectomy.

The management of thromboembolism in patients with the Factor V Leiden mutation follows the same general guidelines as for the general population. The choice between direct oral anticoagulants and warfarin as the preferred anticoagulant is guided by several factors, including the patient's preferences, adherence to the treatment regimen, the severity of the thrombotic event, and possible interactions with other medications. The treatment duration is determined based on the risk of recurrent thrombosis. Long-term anticoagulation therapy is frequently recommended for patients who have suffered from a severe, unprovoked blood clot or experienced recurrent clotting episodes, particularly in unusual locations. The decision to continue anticoagulation indefinitely hinges on striking a balance between the risk of recurrent clotting and the risk of bleeding complications.[11] In the discussed patient's case, the observed recurrence of thrombosis and its dissemination through both arterial and venous systems warrants lifelong warfarin treatment as the preferred therapeutic option.

Conclusion

This case report offers valuable insights into the multiplex dynamics among thrombotic manifestations, hypercoagulable states, and cardiovascular risk factors. The focus on a multidisciplinary approach in diagnosis and treatment exemplifies the importance of cross-disciplinary collaboration in managing complex cases. The various challenges encountered during patient management underscore the necessity for further research to establish optimal therapeutic strategies and preventive measures for complex thrombotic scenarios.

Given the enduring effects of thrombotic events on health outcomes and mortality, in-depth studies, like this one, significantly contribute to our growing comprehension of their multifaceted presentations and the complexities associated with their treatment.

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