Massive SVC Thrombus in a Woman With Heterozygous Methyl-Tetrahydrofolate Reductase A1298C Genetic Mutation

Abdelkarim Waness a, d, Hiba Chehade b, Mohamed El Sheikh c

Abstract

Some genetic mutations are known to be thrombophilic. Methyl-tetrahydrofolate reductase (MTHFR) mutations are among the most recently described. Further, large Superior Vena Cava thrombi are a rare occurrence. They are usually discovered in the setting of invasive venous procedures or in patients afflicted with malignancies. Their presentation can be dramatic in the form of Superior Vena Cava Syndrome requiring urgent therapeutic intervention. We present a unique case of a covert large Superior Vena Cava thrombus in a woman diagnosed with heterozygous Methyl-tetrahydrofolate reductase A1298C genetic mutation. She presented with symptoms of bilateral pulmonary embolism requiring urgent thrombolytic intervention. A discussion about the prevalence of Superior Vena Cava thrombi, their risk factors, their possible presentations, diagnostic modalities and therapeutic options follows the presentation.

Keywords: Methyl-tetrahydrofolate reductase A1298C mutation; Superior vena cava thrombus; Pulmonary embolism; Computerized tomography scan; Thrombolysis; Anticoagulation

Introduction

SVC thromboembolism is a rare form of venous thromboembolic disease. Classic forms of this condition are described in patients suffering from malignancies, thrombophilia, or following central venous catheter insertion. Methyl-tetrahydrofolate reductase is an enzyme responsible for re-methylation of homocysteine to methionine. This enzyme can have two mutations-C677T and A1298C- which can lead to thrombophilia and fetal loss usually in the homozygous mutations. The occurrence of recurrent VTE in patients with heterozygous Methyl-tetrahydrofolate reductase A1298C genetic mutation is extremely rare.

Case Report

A 47 year- old Caucasian female was brought to the department of Emergency Medicine with one-day history of chest pain, worsening dyspnea and presyncope. She was treated 12 years ago for lower extremity deep venous thrombosis while pregnant. She denied any prior spontaneous abortions. The patient is also known to have premature ovarian failure and has never received estroprogestative treatment. She was not taking any medication when seen. Physical examination revealed a diaphoretic patient in clear respiratory distress. Her vital signs were: heart rate 128 beats/minute, respiratory rate 32 breaths/minute, blood pressure was 126/72 mmHg, and temperature 36.8 °C. She was normocephalic with no evidence of facial edema, or cyanosis. Her neck veins were not distended. Her upper extremities were normal in size with no obvious discoloration. Chest examination revealed tachycardia and reduced breath sounds bilaterally. She has extensive varicose veins below knees bilaterally without superficial skin or deep calf tenderness. The circumference of both legs was equal. Arterial blood gases on room air showed: pH = 7.38, PO2 = 58 mm Hg and oxygen saturation at 90%. D-Dimer level was elevated at 7.4 mcg/mL. Serum troponin-I, electrolytes, blood counts, coagulation profile, kidney and liver functions were normal. Electrocardiogram shows only sinus tachycardia. Chest X-ray was unremarkable. A quick

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aConsultant, Medicine Institute, Sheikh Khalifa Medical City, Abu Dhabi, UAE
bResident, Medicine Institute, Sheikh Khalifa Medical City, Abu Dhabi, UAE
cSpecialist, Medicine Institute, Sheikh Khalifa Medical City, Abu Dhabi, UAE
dCorresponding author: Abdelkarim Waness, Consultant, Internal Medicine, Sheikh Khalifa Medical City, P.O. Box: 51900, Abu Dhabi, UAE. Email: n4a1w@yahoo.com
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on-site trans-thoracic echocardiogram revealed mild elevation of pulmonary artery pressure at 42 mmHg with normal left ventricular function. Chest Computed Tomography - Pulmonary Angiogram showed extensive pulmonary embolism seen in both pulmonary arteries extending into upper and lower lobe branches with mild enlargement of the right ventricle. This imaging modality also accidentally revealed severe incomplete filling of the superior vena cava extending upward into the right innominate vein (Fig. 1). The patient was emergently treated with intravenous alteplase and transferred to the Intensive Care Unit. A Doppler scan of her legs showed normal blood flow with normal velocities and no evidence of deep thrombosis. The patient was also started on therapeutic dose of low-molecular weight heparin. After clinical improvement, she was transferred to the ward where she had successful anticoagulation bridging to warfarin. Thrombophilia panel was negative. She was however found to be heterozygous for the Methyl-Tetrahydrofolate Reductase (MTHFR) A1298C genetic mutation. The patient was discharged home and has been regularly following with the anticoagulation clinic.

Discussion

Venous thromboembolism (VTE) remains prevalent and can be deadly despite recent diagnostic and therapeutic advances. According to the American College of Physicians, the yearly incidence of VTE in the United States alone is more than a half million cases, with up to 200,000 of them ending up dying from it [1]. Thromboembolic disease located at the Superior Vena Cava (SVC) and brachiocephalic veins (BCV) is a very rare form of VTE. According to Oymak and colleagues, its prevalence is 0.03% among hospitalized patients [2]. This recent Turkish study confirmed that SVC and BCV thromboses are usually secondary to specific risk factors namely: malignancy, thrombophilia, chronic disorders, or iatrogenic following insertion of peripheral venous lines or central venous catheters (CVC). It has been shown that the location of CVC is crucial to the development of SVC thrombus. Indeed, Cadman et al showed that proximally-placed CVC (proximal third SVC or thoracic inlet veins) are 16 times more likely to thrombose than the ones placed distally (distal third of the SVC or right atrium) [3]. In case of malignancy, the pathogenesis of thrombus formation in the SVC can be complex related to many factors such as humoral ones, mechanic obstruction, or even fibrosis caused by radiotherapy [4]. Collagen vascular diseases and Behçet’s disease are among rare risk factors for SVC thrombosis [5]. It is currently well-documented that certain inherited genetic mutations, such as factor V Leiden, factor V Hong Kong, or factor II G20210A can predispose to venous or arterial thrombosis [6]. Methyltetrahydrofolate reductase is an enzyme responsible for remethylation of homocysteine to methionine [7]. Two major mutations - C677T and A1298C - were discovered in many ethnic groups [8]. These two MTHFR mutations are prevalent in the Middle East. In a large series of 188 patients, Tug et al reported MTHFR C677T and A1298C frequencies of 30.4% and 39.1% respectively. The former was frequently associated with pulmonary embolism (37%), while the latter was pervasive in patients having recurrent spontaneous abortions (55.9%) [9]. These thrombophilic complications are described mostly in homozygous subjects. Our patient however was found to be heterozygous for the MTHFR A1298C genetic mutation. The uniqueness of her presentation is not only the SVC location but also her thrombophilic inclination (two documented episodes) with only heterozygous status.

Symptomatology of SVC thrombosis stems from the progressive increase in the venous pressure within this large vessel. The hallmark of this presentation is “SVC syndrome” with its varying degree of severity. Indeed, neck and facial edema with venous hyperemia can be observed. These changes can manifest themselves in the upper extremities also. Increasing pressure can compromise breathing and swallowing. Patients can present with dyspnea, hoarseness, or dysphagia. If the venous pressure is persistently and extremely elevated, it can cause cerebral edema resulting in confusion, coma and even death [10]. Our patient sought medical care relatively early and did not have any verifiable symptom of SVC syndrome. She had obvious dyspnea at presentation explained by her massive pulmonary embolism. This complication is encountered with more than a third (36%) of patients with SVC thrombus [2].

SVC thrombosis can be relatively easy to diagnose if presented with the clinical picture of SVC syndrome. In the absence of such presentation or symptoms of pulmonary

Figure 1. Large filling defect of the Superior Vena Cava extending upward to the Right Innominate Vein after contrast infusion.
embolism, its diagnosis can be more elusive. Recent guidelines, such as the one established by the American Academy of Family Physicians and the American College of Physicians, stress the importance of adhering to clinical prediction based on guidelines that have good-quality evidence in the diagnosis of VTE [11]. The Wells prediction rules were validated to measure the probability of VTE and therefore guide further investigations. D-dimer assays, a highly sensitive but nonspecific plasma coagulation marker, are helpful in confirming acute deep venous thrombosis (DVT) [12]. Nowadays, there is a formidable array of imaging techniques available for diagnosing VTE. In case of SVC thrombosis, computer axial tomography (CT) is readily available and easy to perform. Magnetic Resonance Angiography imaging (MRA) offers another solid option for the evaluation of the SVC [13]. Occasionally, transesophageal echocardiography (TEE) can diagnose SVC thrombosis [14]; the radiologic gold-standard test for this condition remains contrast venography however [11].

Many therapeutic alternatives are currently available for the treatment of VTE. They are usually well-detailed in evidence-based guidelines recommended by renowned professional medical organizations, such as the “antithrombotic and thrombolytic therapy 8th edition: ACCP guidelines” by the American College of Chest Physicians [15]. These recommendations can generally apply to SVC thrombus. The treatment mainstay is made of low molecular weight heparin or vitamin K antagonists such as warfarin. In life-threatening situations however, thrombolytic therapy is used to dissolve massive clots obstructing the superior vena cava and its tributaries [4]. Placing SVC filters is very controversial and carries the risk of severe complications such as cardiac tamponade, pneumothorax, SVC perforation, or filter migration [16]. Occasionally, and depending on the underlying condition, other rare therapeutic modalities might be undertaken. Examples include: SVC metallic stent placement [17], or surgical SVC reconstruction using autologous tissue [18].

It is always important to apply deep venous thrombosis preventive measures, according to current guidelines, especially for patients at higher risk for VTE [19]. Finally, some authors advocate thrombophilia screening in selected populations, such as Eastern Mediterranean or Hispanic, where these forms of genetic mutations are prevalent [8-20].

**Conclusion**

Superior Vena Cava thrombosis is an extremely rare medical occurrence. It is usually present in the setting of malignancy, invasive catheterization, or thrombophilia. Methyl-tetrahydrofolate reductase A1298C genetic mutation, especially in its homozygous form, can rarely and potentially cause SVC thrombosis. Its manifestations vary from completely silent to SVC syndrome. It has high risk of pulmonary embolism requiring thrombolysis in life-threatening situations. Long-term anticoagulation remains the therapeutic cornerstone for this relatively severe pathology. Preventing thromboembolism is a high medical priority, while screening for thrombophilia might be beneficial in selected populations.

**Conflict of Interest**

None.

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