

Multiple Arterial Thrombosis in Anti Thrombin III Deficiency

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Abstract: *Antithrombin III (AT III) inhibits thrombin and activated clotting factors like factor Xa, IXa and VIIa. AT III deficiency increases risk for thromboembolic diseases. Inherited deficiency of AT III is relatively rare with prevalence in general population between 1:500 to 1:5000¹. AT III deficiency is transmitted in autosomal dominant manner. Thrombosis appears at around 20 years of age and by 4th-5th decade majority of the patients are symptomatic. Thrombosis usually occurs in venous system² and arterial thrombosis is less reported³. We report a case of a young male having multiple episodes of arterial thrombosis. First he developed Myocardial Infarction (MI) due to coronary artery thrombosis and had second episode of pulmonary artery thrombosis. He was diagnosed as having AT III deficiency as a cause for these multiple arterial thrombotic events. He was put on anticoagulant therapy with gradual recovery.*

Keywords: Antithrombin III, Myocardial Infarction, Autosomal Dominant

1. Introduction

Antithrombin III, a member of the serine protease super family plays a vital role in coagulation cascade⁴. Despite inhibiting thrombin, AT III also inhibits free factors Xa, IXa and VIIa⁵. Deficiency of AT III increases risk for thromboembolic diseases at a younger age. Hereditary AT III deficiency is relatively rare with incidence of around 1:500 to 1:5000¹ in general population. Acquired deficiency is more common and is found with sepsis, chronic liver disease, nephrotic syndrome, bone marrow transplant recipients, pregnancy etc. Thrombosis in venous system is usual presentation but arterial thrombosis due to AT III deficiency is rarely reported. We describe a case of 22 year old male patient who developed two episodes of arterial thrombosis (MI due to proximal left anterior descending artery thrombosis and pulmonary thromboembolism due to thrombosis of right and left pulmonary artery).

2. Case Presentation

22 year old male presented with complain of chest pain on exertion, breathlessness (Grade III MMRC) and hemoptysis since past 1 month (Fig 3). There was no history of orthopnea/paroxysmal nocturnal dyspnoea/decreased appetite/evening rise of fever/chronic cough/weight loss/chest trauma. On detailed past history, it was found that patient had similar complains of chest pain, breathlessness on exertion and palpitation 2 months back for which he was diagnosed as ST elevation Myocardial Infarction with Anterior wall infarction on previous ECG.

He was posted for angiography and diagnosed as Ischemic Heart Disease with proximal left anterior descending artery (LAD) total occlusion (Fig.1). Angioplasty with bare metal

stenting was done in LAD artery. He was put on dual anti platelet therapy with aspirin and clopidogrel, nitorandil and digoxin. And he was better symptomatically.

At presentation to us this time, on examination, patient was conscious and oriented and his vitals were, Pulse- 114/minute, BP- 100/66 mmHg, Respiratory rate-22/minute and he was having bilateral basal crepitations on respiratory system examination. O₂ saturation (SpO₂) was 85% on 4 litre O₂ on admission. ECG showed right bundle branch block with tachycardia and deep q wave in V2-V6. His (fig.3) reports showed Hb of 9.7 gm%, WBCs 11000/cumm, platelets 3.34 lakh/cumm, creatinine 0.7 mg/dl, Potassium 3.7 mg/dl. His Prothrombin time was 18.0 with an INR of 1.24. Sickle solubility test was negative and Hb electrophoresis did not show any abnormal hemoglobin fraction.

Based on these clinical and laboratory data, suspicion of pulmonary thrombosis was made. To diagnose pulmonary thromboembolism or in view of suspected pulmonary thromboembolism, Computed Tomography (CT) scan of thorax was done which was suggestive of filling defect in upper, middle and lower lobar and segmental branches of right pulmonary artery and lobar and segmental branches of left pulmonary artery suggestive of pulmonary thromboembolism (Fig.5). Bilateral lower limb Doppler did not show any flow limitation in any artery. 2-Dimensional Echocardiography (2D Echo) showed akinetic lateral wall, dilated all chambers with EF of 30% with moderate pulmonary artery hypertension (PASP by TR jet 50 mmHg) (Fig.2).

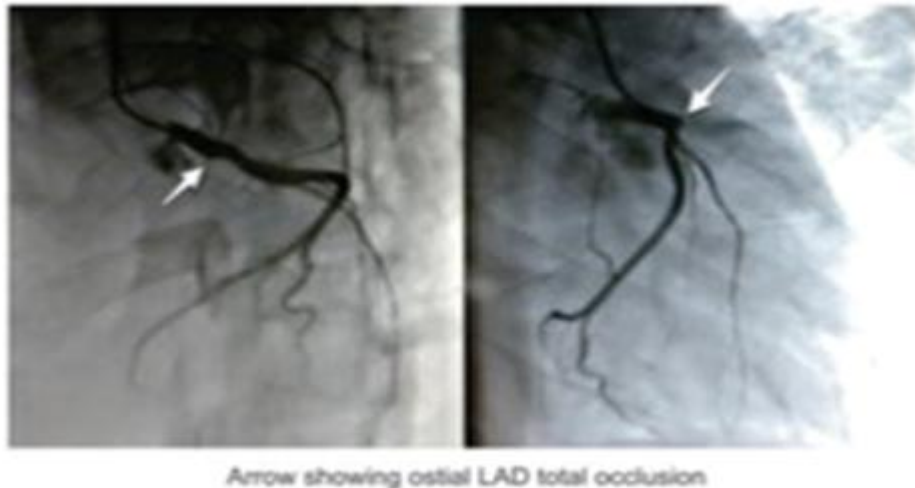


Figure 1

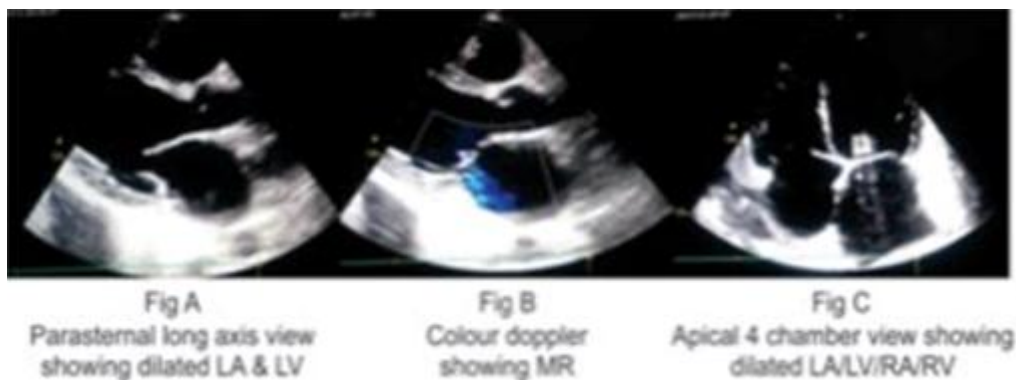


Figure 2

Another incidental finding on USG abdomen was splenic infarcts with occluded splenic artery (Fig.5). With these reports of multiple arterial thrombosis (Coronary artery, multiple sites in Rt and Lt pulmonary artery and splenic artery) in a young patient, an inherited cause for this thrombosis was suspected and his complete coagulation profile was sent. AT III level was low- 54.6% (N =80-120). Anti Phospholipid Antibody Test, Direct and Indirect Coomb's test, Ham test were all negative. Protein C, Protein S were within normal range. Serum Homocystein was 4.98 micromol/litre (N= 5.46-16.20). A diagnosis of hereditary thrombophilia due to anti thrombin III deficiency was made. Patient was started on Injection heparin which was overlapped with warfarin, therapeutic INR was achieved. Patient was discharged on oral warfarin. On follow up at 2 months patient was symptomatically well on oral anticoagulant and his Prothrombin Time (PT) was within therapeutic range.



Figure 3

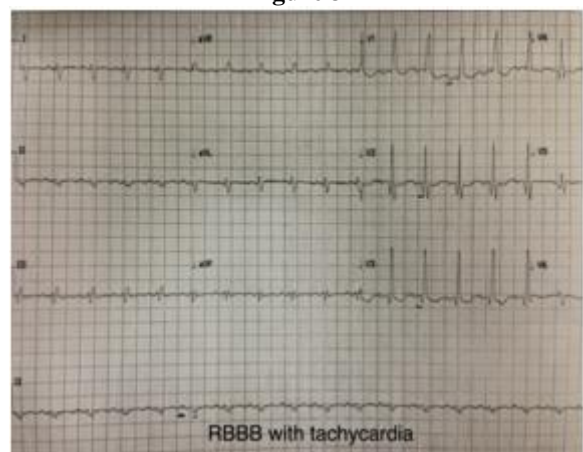


Figure 4

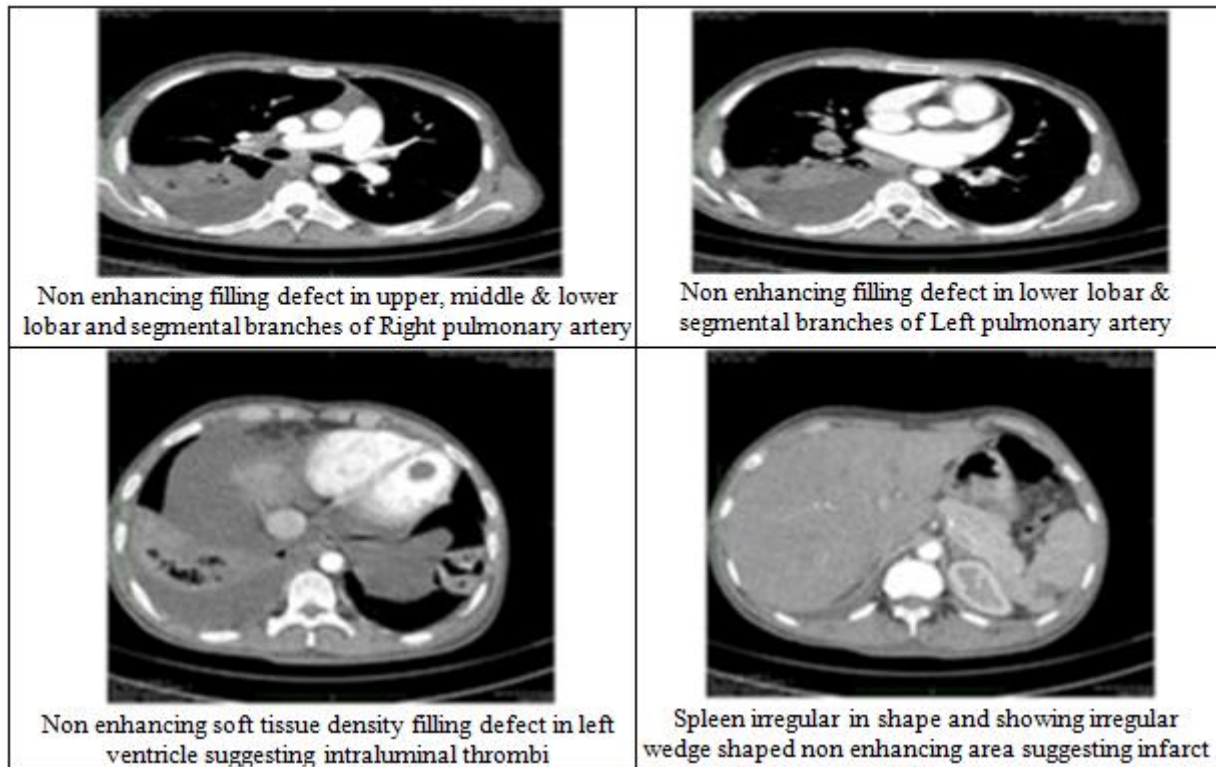


Figure 5

3. Discussion

Antithrombin (AT) deficiency was first described in 1965 by Olav Egeberg in a Scandinavian family in which several family members had venous thrombo-embolism. Egeberg established the deficiency to be an autosomal dominant disorder. Antithrombin III (AT III) is a 58-kDa molecule of serine protease inhibitor superfamily which plays an important role in anticoagulation and in regulation of wound healing. AT III deficiency, which may be congenital or acquired, results in increased risk for venous thrombosis and, far less commonly, arterial thrombosis. AT III also has anti-inflammatory and anti-proliferative actions that are independent of its effects on regulating coagulation⁶. AT is synthesized primarily in liver and then secreted in plasma. Its normal plasma level is 150 mcg/ml and plasma half-life is approximately 3 days. The major physiologic role of AT III is inhibition of thrombin (Factor IIa). Additional targets are activated factor X, IX, XI and XII.

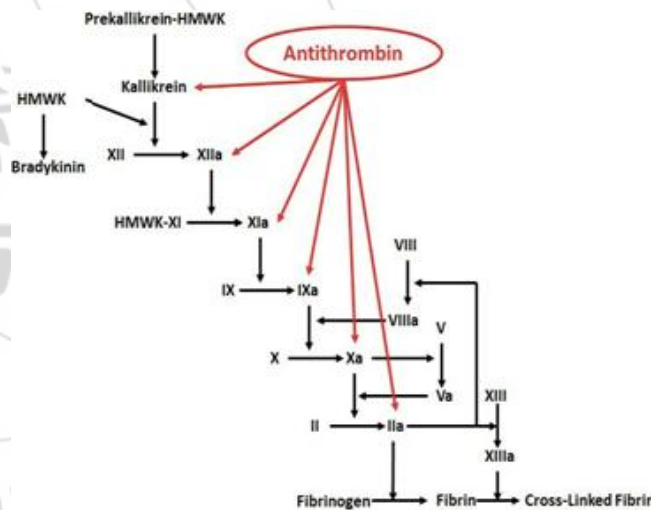


Figure 6

AT III deficiency has a prevalence of 1:500 to 1:5000 in general population. Secondary or acquired deficiency of AT III is more commonly recognized. Acquired causes of AT III deficiency include liver diseases, kidney diseases like nephrotic syndrome, sepsis and disseminated intravascular coagulation (DIC), pregnancy, drugs like heparin. AT III deficiency results in recurrent thromboembolic events. Incidence of venous thrombosis far exceeds those of arterial thrombosis. Diagnosis of AT III deficiency is made by laboratory assay of AT III. All cases reported in literature are of isolated venous thrombosis or associated venous and arterial thrombosis. There are very few reported cases of sole arterial thrombosis in AT III deficiency⁷. Our patient presented with recurrent episodes of arterial thrombosis (Myocardial Infarction, Pulmonary artery thrombosis, splenic artery thrombosis) highlighting the fact that arterial

thrombosis and its serious consequences can also be presenting feature of coagulation cascade defects.

The initial management of venous thromboembolism (VTE) in patients with AT deficiency is not different from that of VTE in any other patient, including thrombolysis, initial therapy with heparin or fondaparinux and transition to a vitamin K antagonist⁸. These patients can be managed with standard intensity oral anticoagulants with a therapeutic International Normalized Ratio (INR) target between 2.0-3.0. In determining the length of vitamin K antagonist therapy, patient's risk factors for recurrence and other risk factors like bleeding and patient's preference regarding longterm treatment should be considered. The risk of recurrent VTE in patients with AT deficiency who are on anticoagulants is low. So long term anticoagulation is recommended for such patients. Similarly for arterial thromboembolism, longterm anticoagulation is appropriate. Though this approach is not derived from clinical studies, anticoagulants will be more effective for such patients than antiplatelets based on known physiologic role of AT in coagulation cascade. Two types of AT concentrates are available: Plasma human AT concentrates manufactured from random donor pooled plasma⁹ and recombinant human AT which can be used in very severe situations but high cost and availability are limiting factors.

In our patient, first attack of arterial thrombosis in form of acute myocardial infarction (MI) was managed as per routine protocol for MI management and the patient was not investigated for secondary cause nor was given longterm anticoagulant. High level of clinical suspicion must be exerted while searching for primary cause in such a young patient developing MI, so that such further life threatening thrombotic episodes can be prevented by giving lifelong oral anticoagulation therapy. Our patient had second thrombotic episode in the form of pulmonary artery thrombosis within 2 months of developing coronary artery thrombosis. Now patient is on regular oral anticoagulant and is symptom free. Patient is counseled about long term monitoring and follow up.

4. Conclusion

Multiple arterial thrombosis in a young patient without any apparent risk factors for the same should warrant a physician to search for the heritable cause for such thrombosis. Although most commonly involving venous system, AT III deficiency should always be put in differentials whenever evaluating such patients.

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Volume 5 Issue 8, August 2016

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