

## CASE REPORT

### Familial antithrombin III deficiency in a Malay patient with massive thrombosis

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#### Abstract

Patients with low antithrombin III (AT III) has increased risk for arteriovenous thromboembolic (TE) disease. We report a 28-year-old Malay lady who presented with spontaneous right calf pain and swelling of one week duration. She was on oral contraceptive pills and had a history of travelling for a long distance prior to the presentation. Her brother who was diagnosed with AT III deficiency had arterial thrombosis at a young age. She was diagnosed as having right popliteal vein thrombosis by ultrasound and treated with subcutaneous fondaparinux. While on treatment, she developed massive bilateral pulmonary embolism (PE). Thrombophilia study showed reduced AT III activity (38µl/dl) and normal results for protein C, protein S, activated protein C resistance and lupus anticoagulant assays. This patient has heterozygous AT III deficiency added with significant acquired factors responsible for the TE events. Those with AT III deficiency may have resistance to heparin therapy and require higher doses of heparin.

**Keywords:** antithrombin III, heparin, thrombophilia, thrombosis, venous thromboembolism

#### INTRODUCTION

Antithrombin (AT) is a serine protease inhibitor which inactivates many activated coagulation factor in the coagulation cascade, mainly thrombin and factor Xa.<sup>1,2</sup> AT deficiency occurs in 1 in 500 to 1 in 5000 overall populations.<sup>3</sup> Among Asians, 0.15% of individuals in the healthy Japanese populations was estimated to have antithrombin deficiency, which is relatively similar to that for Caucasian populations.<sup>4</sup> It is inherited as a rare autosomal dominant disorder. Patients with low AT III has increased risk for thromboembolic disease.<sup>5,6</sup> Homozygous are rare as compared to heterozygous type and majority of homozygosity was reported to be associated with intrauterine death.

We describe a young woman, 8 months postnatal who presented with unilateral leg swelling, attributed to right popliteal vein thrombosis complicated by massive bilateral pulmonary embolism while on treatment. She had heterozygous AT III deficiency. Her brother

had cerebrovascular accident at a young age and was diagnosed to have AT III deficiency.

#### CASE REPORT

##### Case 1

A 28-year-old Malay woman, (para 1) at 8 months postpartum, presented with spontaneous right calf pain and swelling of one week duration. She was on oral contraceptive pills for 2 weeks and had a history of travelling by car for a long distance prior to the presentation. She was diagnosed as having right popliteal vein thrombosis by ultrasound. She has a strong family history of arterial and venous thrombosis. Her brother had stroke and ischaemic heart disease at the age of 39 years old. Her cousin had sudden death at the age of 27 years old due to cerebrovascular accident. Physical examination revealed a normal blood pressure and pulses. She was afebrile. Her right leg was swollen, warm and tender and Homan's sign was positive. Her cardiorespiratory examination was unremarkable.

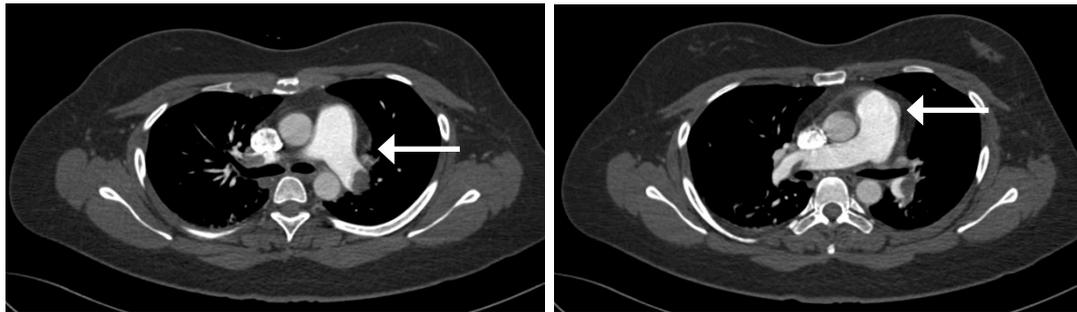


FIG. 1: Axial images of CTPA showing filling defects (arrow) in the main and segmental branches of both pulmonary arteries in keeping with thrombus

She was diagnosed as having right popliteal vein thrombosis by ultrasound and was treated with subcutaneous fondaparinux.

While on treatment in the ward, she developed sudden shortness of breath. Her oxygen saturation was documented low and lung examination revealed reduced air entry bilaterally. Computed tomography pulmonary angiography (CTPA) showed massive bilateral pulmonary embolism (Figs. 1 & 2). She was scheduled for a lifelong warfarin therapy. Investigation revealed that her full blood count, fasting lipid profile, liver function and renal function were within range. Thrombophilia study done 3 months post acute event showed reduced AT III activity (38µl/dl); and normal result for protein C, protein S, activated protein C resistance and lupus anticoagulant assays.

*Sibling 1*

Her brother, a 46-year-old Malay man, a chronic smoker, presented with sudden onset of left hemiparesis at the age of 31 years old. Carotid Doppler ultrasound revealed a complete occlusion of the right common carotid artery and internal

carotid artery. He had recurrent admissions for worsening of left sided hemiparesis due to a new right parietal cerebral infarct. His central nervous system examination revealed reduced muscle power with increased muscle tone over left upper and lower limbs. Blood investigation results showed his full blood count, fasting lipid profile, liver function and renal function were within normal range. Thrombophilia study showed similar findings of reduced AT III activity (38 µl/dl) and normal results for protein C, protein S, activated protein C resistance and lupus anticoagulant assays.

**DISCUSSION**

AT deficiency is a rare autosomal dominant inheritance, affecting men and women equally. There are 2 types of AT III deficiency which are classified as type I and type II deficiencies. Type I causes reduction in both functional activity and antigenic levels of AT proportionately (quantitative deficiency). In contrast, type II deficiency shows low AT activity despite normal antigen levels due to a dysfunctional protein (qualitative deficiency).<sup>7</sup> Type II deficiency is

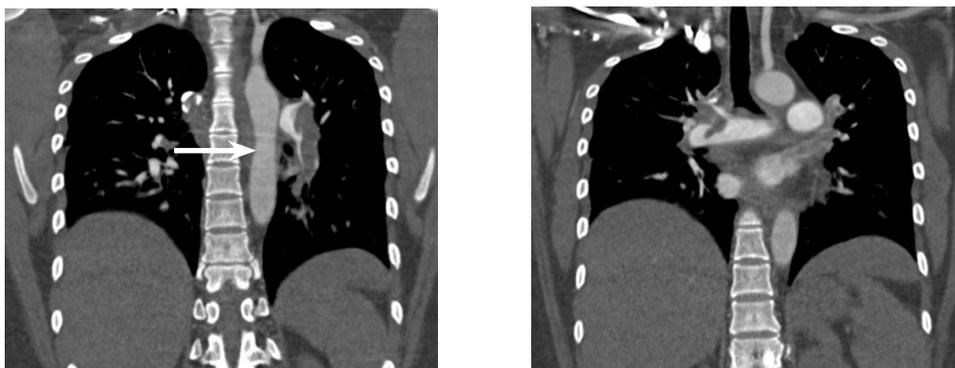


FIG. 2: Sagittal and coronal reformatted images of CTPA show extension of thrombus within the pulmonary arteries

further subdivided into IIa, IIb, and IIc, based on the location of the mutations. Patients with type I AT deficiency is commonly symptomatic, often representing 80% of all thromboembolic events.<sup>8</sup> Before a patient is diagnosed as having hereditary AT deficiency, acquired causes of protein deficiency should be considered. These acquired causes include liver cirrhosis, nephrotic syndrome, sepsis with disseminated intravascular coagulation, burn injuries, polytrauma, large haematomas, and metastatic tumours. A few drugs can induce AT deficiency, such as L-asparaginase and heparins.<sup>9</sup>

#### *Clinical manifestation*

Based on the results, both patient and her brother (and probably their cousins) have inherited, heterozygous AT III deficiency and no acquired cause has been identified in addition to considering similar thrombotic presentation in the same family. Although oral contraceptive pills can slightly reduce AT III level, however, these variations are mild and reported to be not clinically significant. Based on previous studies, most patients in this group have AT activity levels in the range of 40-60%.<sup>7</sup> So far, there is no routine DNA test available for definitive diagnosis, therefore family screening demonstrating AT III deficiency is highly beneficial for diagnosis.<sup>10</sup> A recent study in India detected a known polymorphism previously related to thrombotic risk in 2 families and associated with low AT III levels.<sup>11</sup>

AT III deficiency patients have a significantly increased risk of thromboembolism, especially in the venous circulation. Forty percent of them are precipitated with transient risk factors such as oestrogenic treatment and prolong immobilization.<sup>12</sup> Venous thromboembolism (VTE) usually manifest around the age of 20 years. This is probably as a result of protective effects by alpha2 macroglobulin, one of the naturally occurring thrombin inhibitors during the first 2 decades.<sup>13,14</sup> Those with AT deficiency may have resistance to heparin therapy and required higher heparin doses, which may give the clue to the underlying AT deficiency state.<sup>8</sup> This patient developed another event of thromboembolism when she was on fondaparinux, a synthetic pentasaccharide which is a type of low molecular weight heparin (LMH).

Arterial thromboembolism is reported to have weak association with AT deficiency and not many cases has been reported so far. There is an epidemiological study that supports a

role for antithrombin deficiency in arterial thrombosis. The study suggested that deficiency of antithrombin may be an independent risk factor for myocardial infarction (MI) that has been underestimated.<sup>15</sup> Another study reported a nephrotic syndrome patient with right lower extremity arterial thrombosis associated with decreased levels of serum AT III.<sup>16</sup>

So far, there is no consensus as to which patients should be screened for hereditary thrombophilia.<sup>17</sup> Functional assays and antigenic assays were used to diagnose AT deficiency. However, genetic analysis was useful to further classify AT deficiency. A study done to compare activity assays and direct genetic analysis for identifying individuals with AT deficiency, found 16 patients with decreased AT activity and confirmed 13 mutations in 14 patients.<sup>18</sup>

#### *Treatment*

The initial management of patients with AT III deficiency is similar to any patient with venous thromboembolism. Consideration of thrombolytics, initiation of Heparins or Fondaparinux therapy and later converting to vitamin K antagonist is the treatment given to all patients with AT III deficiency.<sup>8</sup> Women with this problem should avoid taking oral contraceptive pills.<sup>19</sup> For management of arterial thrombotic event, there has been no data to support the best treatment for these patients. Ideally, in the absence of arteriosclerosis in a young patient with suspicion of AT deficiency related thrombotic event, a longer-term anticoagulation therapy may be appropriate.<sup>8</sup> The combination of AT concentrate and LMH has been reported to be safe and efficacious for mother and child in preventing thromboembolism and pregnancy loss.<sup>20</sup>

#### *Conclusion*

Inherited AT deficiency must be considered in a young patient presented with spontaneous venous thrombosis, especially when complicated by another venous thromboembolism while on heparins or indirect anti-Xa treatment. Prolonged immobilisation and oral contraceptive usage may precipitate the thrombotic episodes and should be avoided. A positive family member with arterial thrombotic events is unusual but has been linked to AT III deficiency requiring thrombophilic investigation to confirm the underlying disorder especially in young patients.

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