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Proper diagnosis of antithrombin III deficiency

To the Editor,

We read the article written by Hayıroğlu et al. (1) entitled "Antithrombin III deficiency concomitant with atrial fibrillation causes thrombi in all chambers: 2-D and 3-D echocardiographic evaluation."published Anatol J Cardiol 2016; 7456: 21-2. in which they reported the case of a 62-year-old man who had antithrombin III (AT) deficiency concomitant with atrial fibrillation that caused thrombi in all chambers of the heart. The authors claimed that thrombosis in all chambers of the heart in a patient with atrial fibrillation was associated with AT deficiency. In diagnosis of AT deficiency, it should be considered that the disease is very rare. The estimated prevalence in the general population is thought to be in the range of 0.02% to 0.2% (2).

A study that re-evaluated 59 patients with pre-existing diagnosis of AT deficiency revealed AT deficiency in only 3, none of whom had a personal or family history of thrombosis (3). Above all, in patients with a thromboembolic event, testing is indicated; however, AT levels should not be measured at the time of the acute event because thrombosis may cause a transient reduction in all natural anticoagulants, including AT level, which could be misread to suggest an underlying deficiency. If the level of AT is found to be low during acute thrombosis, measurement should be repeated once the patient has recovered. A variety of commercial assays are available to measure AT level. Functional assays using the chromogenic substrate method are preferable, in order to detect both type I and type II deficiency. The test results should be evaluated according to the lower limit of the method used by the relevant laboratory and abnormal test results should lead to repeat testing with new blood sample (2).

Another subject we would like to point out is that AT deficiency is manifested primarily by recurrent venous thromboembolism. Although almost all vein sites have been reported to be involved with thrombosis in AT deficiency, isolated cardiac thrombosis in both arterial and venous chambers is not an expected clinical picture. The association of natural anticoagulant deficiencies with arterial thrombosis still remains unclear. It has been demonstrated that AT deficiency was not related to a significantly increased risk of arterial thromboembolic events (4).

If someone has inherited a natural anticoagulant deficiency, the clinical problem often occurs at an earlier age. In family studies, venous thrombosis occurred in 85% of AT deficient relatives before 55 years of age. Large patient series with natural anticoagulant deficiency, including AT deficiency, revealed no increased risk of arterial cardiovascular disease in affected family members older than age 55 (5).

In conclusion, it is not proven that AT deficiency is related to an increased risk of arterial thrombosis. Its diagnostic testing should be discouraged in the clinical evaluation of either arterial or venous thrombosis in elderly patients, particularly those with facilitating factors such as atrial fibrillation.

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Author`s Reply

To the Editor,

We are pleased to see the valuable comments and contribution of our colleagues in response to our article entitled "Antithrombin III deficiency concomitant with atrial fibrillation causes thrombi in all chambers: 2-D and 3-D echocardiographic evaluation" published in the December 2016 issue of the Anatolian Journal of Cardiology (1). We have some points to explain further.

In our report, there were many precipitating factors contributing to the thrombi in all chambers. Antithrombin III (AT) deficiency was proposed as a precipitating factor in addition to coronary artery disease and atrial fibrillation. We are aware of the rarity of arterial thrombosis secondary to AT deficiency; it was for this reason that we reported our case. There are case reports in the literature concerning arterial thrombosis due to AT deficiency (2). Other procoagulant precipitating factors accompanying AT deficiency have a role in the time of clinical incidence, as reported by

Emmanuelle et al. (3). The level of AT activity and the type of AT deficiency determine the clinical picture (4). The occurrence of multiple thrombi at the age of 62 made our case interesting.

The criticism about testing the AT level only once makes sense; however, we only had one chance to test the AT activity in our patient. Due to multiple mobile intracardiac thrombi, intravenous anticoagulation therapy was initiated as soon as possible. The patient did not recover, and was under medical therapy throughout the hospitalization period. Therefore, repeat testing for AT activity while under anticoagulation therapy would be misleading. It is known that AT level decreases as a result of anticoagulation therapy (5).

We agree with the opinion that when someone has inherited natural anticoagulant deficiencies, clinical problems often occur at an early age. On the other hand, as you mentioned, it was presented in a cross-sectional study that 3 patients who were demonstrated to have AT deficiency with repeated tests had no personal or family history of thrombosis (6). Precipitating factors play a major role in these circumstances. In our patient, apart from AT deficiency, atrial fibrillation concomitant with severe apical hypokinesia in the left ventricle due to myocardial infarction exacerbated the situation. It is impossible to link the multiple thrombi to only one of the underlying causes in this case report.

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Inflammatory activity of adipose tissue

To the Editor,

There is growing interest in inflammation, adipose tissue, and the atherosclerotic process in vessels. As a result of recent studies, it is known that obesity and increased epicardial adipose tissue are important factors affecting the pathogenesis of atherosclerosis. Adipose tissue releases inflammatory mediators like an endocrine organ. It produces cytokines, such as adiponectin, leptin, resistin, and interleukins, and these mediators cause an increase in inflammatory activation in the arterial wall. Adipose tissue acts as a source of proinflammatory activity, and it is therefore called obesity-related inflammatory activity (1).

We read the article entitled "An increase in epicardial adipose tissue is strongly associated with carotid intima-media thickness and atherosclerotic plaque, but LDL only with the plaque" published in The Anatolian Journal of Cardiology 2017; 17: 56-63 by Kocaman et al. (2) with great interest. The authors sought to investigate whether epicardial adipose tissue (EAT) has proliferative effect on carotid intima-media thickness (CIMT) and carotid plaque. They concluded that EAT had a relationship with both CIMT and the presence of carotid plaque. The authors also said that this finding suggested that EAT thickness may be a risk factor and a biomarker, playing an important role beginning in early stages of atherosclerosis. We congratulate the authors for these valuable results, which are compatible with the literature. They also drew attention to an interesting topic related to the inflammatory capacity of adipose tissue. There are hypotheses related to interactions of the heart and epicardial fat. One suggests that lack of fascia between heart and epicardial fat allows inflammatory mediators to easily diffuse to the vessels and myocardium (1). Having read the authors' report, we want to contribute to a seemingly missing aspect. In the results of the study, it was reported that EAT correlated to BMI, waist circumference, and CRP, in addition to CIMT ($p<0.001$) (Table 2). CIMT, BMI, waist circumference, and presence of carotid plaque increased with increase of EAT thickness ($p<0.001$) (Table 3). These results show that CIMT and carotid plaque formation may also be related to obesity of the study patients, as EAP and BMI are directly proportional in the study. In the limitations section, the authors said that their study group had increased visceral adipose tissue. BMI is a widely used marker of obesity and there are many studies about obesity and inflammatory effect on progression of atherosclerosis (1). So there is a need to differentiate whether these results belong to visceral or epicardial adipose tissue. The authors were also interested in question of if CRP level increased as EAT thickness increased, and if there is a possible inflammatory link between EAT and CIMT. We think there is a need for more studies to investigate the inflammatory pathways of EAT, independent of other clinical variables like obesity, and that there is also a need for a patient group that isolates increase in EAT to obtain more significant results.