

## A huge intracardiac thrombus developed in the presence of antithrombin III deficiency in a patient with end-stage renal failure

### Son dönem böbrek yetersizliği olan hastada antitrombin III eksikliğine bağlı olarak gelişen büyük kalp içi trombus

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**Summary**– In this study, we report a 15-year-old female with end-stage renal disease undergoing hemodialysis, who admitted with acute respiratory failure and generalized edema. Abdominal tomography detected thrombi in the right renal vein, in the hepatic segment of the inferior vena cava and in iliac veins. Levels of proteins C and S, antinuclear antigen, anti-dsDNA, C3, and C4 were in normal limits. The thrombi persisted despite treatment with nadroparin, heparin with fresh frozen plasma and warfarin. Due to heparin resistance, antithrombin III levels were measured and were found abnormally low. The first echocardiographic examination was in normal limits but the second echocardiography revealed a huge thrombus occluding the tricuspid valve. Urgent thrombectomy was planned but the patient died in the intensive care unit due to severe pulmonary edema.

In pediatric patients, intracardiac thrombi are relatively rare. The main underlying causes of thrombosis in children are acquired risk factors, such as central venous catheters, malignancy, infections, cardiac diseases, trauma, and surgery, or inherited risk factors, such as factor V Leiden (FVL) and prothrombin (PT) G20210A mutations, deficiencies of protein C (PC), protein S (PS), and antithrombin III (AT3), some dysfibrinogenemias, and fibrinolytic defects.<sup>[1,2]</sup> In this study, we report a 15-year-old patient with end-stage renal disease who had a huge right atrial thrombus that was obstructing the tricuspid valve, which developed in the presence of AT3 deficiency.

**Özet**– Bu yazıda son dönem böbrek yetersizliği nedeniyle hemodiyaliz uygulanan ve akut solunum yetersizliği ve yaygın ödem ile başvuran 15 yaşında bir kız çocuğu sunuldu. Batın tomografisinde sağ renal vena, vena kava inferiorun hepatic segmentinde ve iliak venlerde yaygın trombüsler görüldü. Protein C, S, antinükleer antijen, anti-Ds DNA, C3 ve C4 değerleri normal bulundu. Nadroparin, heparinle beraber taze donmuş plazma ve varfarin tedavilerine rağmen trombüsler kaybolmadı. Heparin direnci nedeniyle bakılan antitrombin III değeri düşük saptandı. İlk ekokardiyografik incelemesi normal olan hastanın tekrarlanan ekokardiyografisinde triküspit kapağı tıkanan dev trombüs görüldü. Acil trombektomi planlanan hasta ameliyat edilemeden ağır akciğer ödemi nedeniyle kaybedildi.

#### CASE REPORT

A 15-year-old gypsy girl was admitted to our emergency department because of right-sided abdominal pain, bilious vomiting and anuria. She had a history of pyelonephritis and agenesis of the left kidney associated with an enlarged right kidney, detected in an outside clinic. At first admission, her weight was 35 kg (<3p) and height 140 cm (<3p). Blood pressure was 140/90 mmHg and heart rate was 84 beats/minute. She had pretibial edema and reduced respiratory sounds on the right lung. Abdominal tomography confirmed agenesis of the left kidney and detected throm-

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**Abbreviations:**

APTT	Activated partial thromboplastin time
AT3	Antithrombin III
INR	International normalized ratio
PC	Prothrombin
PS	Protein S
PT	Prothrombin time

bi in the right renal vein, in the hepatic segment of the inferior vena cava and in the iliac veins.

The echocardiography on the first admission did not reveal any thrombus in the cardiac chambers. Cardiac dimensions and systolic functions were in normal limits. In the complete blood count, the patient's hemoglobin was 10.1 g/dl, white blood count was 31,300/mm<sup>3</sup>, and platelet count was 163,000/mm<sup>3</sup>. The sedimentation rate was 13 mm/h, and C-reactive protein was 23.4 mg/dl. Sodium was 125 mEq/L. Total serum protein, albumin and lipid profile were in normal limits. Other findings were: serum glucose 118 mg/dl, blood urea nitrogen 41.6 mg/dl, creatinine 6 mg/dl, uric acid 5 mg/dl, serum aspartate aminotransferase 90 IU/L, alanine aminotransferase 61 IU/L, fibrinogen 2.05 g/L, international normalized ratio (INR) 1.78, prothrombin activity 54%, PT 19.3 seconds, and activated partial thromboplastin time (APTT) 45.4 seconds, and levels of PC, PS, antinuclear antigen, anti-Ds DNA, C3 and C4 were in normal limits. Once daily subcutaneous dose of 100 IU/kg nadroparin was started. Therapeutic anti-factor Xa levels could not be achieved despite increasing the doses of nadroparin. Finally, unfractionated heparin was started with a bolus of 50 units/kg intravenously and maintained with a dose of 25 units/kg/hour; however, APTT did not prolong. Due to heparin resistance, AT3 levels were measured, and were found abnormally low (10%). Three units of fresh frozen plasma were transfused along with unfractionated heparin to increase AT3 levels, but PT and APTT levels did not increase. Finally, heparin was withdrawn and warfarin was started with a loading dose of 0.1 mg/kg/day. She was discharged with an INR of 2.42. Six months later, she was admitted to our emergency department with respiratory distress, generalized edema and increased levels of creatinine despite hemodialysis. Echocardiography confirmed a huge thrombus (40.7x36 mm) obstructing the tricuspid valve (Figure 1).

Cardiac chambers and the inferior vena cava were dilated and ejection fraction was diminished (45%). Urgent thrombectomy was planned under antithrombin replacement despite high risk. However, signed written consent could not be obtained and she died in the intensive care unit due to severe pulmonary



**Figure 1.** 2D echocardiographic image of huge right atrial thrombus obstructing the tricuspid valve.

edema. Genetic study for mutation of congenital AT3 deficiency could not be done. In the following year, two more gypsy adolescents from different families presented with spontaneous deep venous thrombosis. These patients also had AT3 deficiency, and homozygous p.Leu131Phe mutation, which is a type II heparin binding site deficiency, was detected. The asymptomatic parents had heterozygous deficiency, and we learned later that the presented patient was related to one of these families.

## DISCUSSION

Intracardiac thrombi are rare pathologies in pediatric patients. In addition to patients with thrombophilia, right heart thrombus can also occur in patients with endocarditis, polycythemia, congenital heart defects, respiratory distress syndrome, and persistent fetal circulation.<sup>[3,4]</sup>

Anti-thrombin III is one of the most important inhibitors of blood coagulation, and it inactivates thrombin and several serine proteases, including factors IXa, Xa, Xia, and XIIa. In addition, recent reports suggest that antithrombin also plays a role in the inhibition of inflammation in the vascular endothelium. Reduced plasma antithrombin may result from congenital deficiency or arise secondarily from a range of disorders such as liver dysfunction, disseminated intravascular coagulation, drugs such as L-asparaginase, or as a result of interventions such as major surgery or cardiopulmonary bypass.<sup>[5]</sup> The most important complication of AT3 deficiency is severe

veno-occlusive disease. Some congenital AT3- deficient patients suffer from renal failure because of fibrin deposition in the kidney glomeruli or in the renal vein and need renal replacement therapy for end-stage renal disease.<sup>[6]</sup> We consider that this patient had congenital AT3 deficiency because she did not have any acquired risk factor for thrombosis, and her relative with deep venous thrombosis also had AT3 deficiency and homozygous AT3 mutation.

Right atrial thrombus may also be seen in patients with cancer or indwelling catheter.<sup>[7]</sup> In the report of Atalay et al.,<sup>[8]</sup> 9 of 13 patients with intracardiac thrombus had right atrial thrombus. Eleven patients were evaluated for PS, PC and AT3 deficiencies. PC deficiency was found in 8 patients, PS deficiency in 5 patients and AT3 deficiency in 3 patients. However, their parents had normal levels of PC, PS and AT3.

Ozkutlu et al.<sup>[9]</sup> evaluated 11 patients with intracardiac thrombi. Four patients had dilated cardiomyopathy. Three patients had no heart disease but had PC deficiency. AT3 levels were measured in only 3 patients and were within normal limits.

Erbay et al.<sup>[10]</sup> evaluated 60 patients with dilated cardiomyopathy. Activated protein C resistance was found in 12 of 22 patients (54%) with left ventricular thrombus and in 4 of 38 patients (9.5%) without cardiac thrombus, but none of his patients had PS or AT3 deficiency.

The optimal treatment of intracardiac thrombi in children is unclear. Thrombolysis, thrombectomy, anticoagulation, and observation are the therapeutic options. There are reports about treatments with urokinase and tissue plasminogen activator in children. Patients with heterozygous AT3 deficiency generally respond to standard doses of heparin infusion, but occasional patients with congenital AT3 deficiency as well as patients with severe acquired AT3 deficiency (<10% of normal) may be resistant to heparin.<sup>[6]</sup> However, some reports recommend not using heparin alone to treat thrombotic episodes in patients with congenital AT3 deficiency because heparin may decrease AT3 levels. Treatment with recombinant or purified AT3 in combination with heparin seems optimum, although there are reported cases that were treated with heparin alone with appropriate prolongation of APTT and no evidence of thrombus activation.

Thrombolytic therapy offers the possibility of

achieving more rapid relief of vessel occlusion compared to anticoagulant therapy, but carries increased risk of bleeding. In children, indications for treatment and optimal dosing regimens have not yet been established.

Our patient could not receive ambulatory peritoneal dialysis due to their low socioeconomic status and the poor sanitary conditions. Hemodialysis and intravenous catheter were essential for the patient, and this therapy carried additional risk factors for thrombosis.

In conclusion, we suggest that AT3 deficiency should also be investigated in all patients with intracardiac thrombi. We also suggest that in addition to lifelong oral warfarin, periodic 2-D echocardiographic examination should be performed in all patients with congenital AT3 deficiency and in conditions that may cause acquired AT3 deficiency in order to detect possible intracardiac thrombus formation.

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**Anahtar sözcükler:** Antitrombin III; kardiyovasküler hastalıklar/eti-yoloji; böbrek yetersizliği, kronik/fizyopatoloji/komplikasyonlar; böbrek diyalizi; tromboz.