Teaching Case Report

Spontaneous aortic thrombosis and embolization: antithrombin deficiency and the work-up of hypercoagulable states

The Case: A previously healthy 24-year-old man presented to the emergency department with sudden onset of severe periumbilical and right costovertebral pain accompanied by nausea and vomiting. His vital signs, including oxygen saturation, were normal. His physical exam was remarkable for decreased abdominal sounds with epigastric and right costovertebral tenderness. The patient had no history of tobacco or illicit drug abuse. His mother had died at age 41 from a pulmonary embolism believed to have been caused by an unspecified hypercoagulable disorder.

Except for leukocytosis (leukocyte count 15.0 [normal 4.0–11.0] × 10^9/L), his complete blood count, serum blood chemistry, and liver and renal function test results were normal. An abdominal CT scan with contrast medium showed a wedge-shaped hypodense lesion in the right kidney, indicating infarction (Fig. 1A, arrow), as well as a filling defect in the lumen of the superior mesenteric artery (SMA), consistent with a thrombus or thromboembolus (Fig. 1B, arrowhead), and edema of the wall of the small intestine (Fig. 1B, arrow).

Embolectomy with patch angioplasty (dissection of the native artery with removal of the thrombus followed by arterial repair using a patch of bovine arterial material) of the SMA was performed. Intraoperative transesophageal echocardiography (TEE), performed to search for the source of the SMA embolus, showed a mobile thrombus 1.5 × 2 cm in size in the descending thoracic aorta near the origin of the left subclavian artery (Fig. 2, arrow). Intravenous heparin therapy was begun; higher than usual doses were required to achieve adequate anticoagulation (an activated partial thromboplastin time > 2.5 × control). Therefore, a presumptive diagnosis of antithrombin deficiency was made, which was confirmed by an antithrombin–heparin cofactor level of 65% (normal pooled plasma activity 80%–120%). Results of all other tests for prothrombotic states, including measurement of protein C and S, homocysteine, antinuclear antibodies and antiphospholipid antibodies, were negative. Warfarin was added to the anticoagulation therapy on postoperative day 2, and after 3 days of concomitant administration it replaced the heparin therapy.

The patient had an uneventful recovery, with resolution of the aortic thrombus seen on TEE at 8 weeks' follow-up. The antithrombin–heparin cofactor level at that time was 65%, which confirmed the diagnosis of antithrombin deficiency. The patient was informed that he would have to continue the warfarin therapy indefinitely.

Clinically significant thrombotic processes may result from a primary hypercoagulable state caused by deficiencies in one of the components in the coagulation–anticoagulation sys-
tem or from an acquired hypercoagu-
lable state caused by precipitating fac-
tors such as trauma, immobilization
or advanced age. Genetically suscepti-
ble people may have thrombosis after
exposure to exogenous stimuli such as
pregnancy, surgery or estrogen use.
When testing for primary (inherited)
hypercoagulable disorders in patients
presenting with thrombosis, physi-
cians should take into consideration
whether the thrombosis is arterial or
venous (Box 1) and whether there are
precipitating factors or a family his-
tory of thrombosis (Box 2). Initial lab-
atory evaluation should include a
complete blood count and peripheral
blood smear to rule out polycythemia
vera, essential thrombocythemia and
disseminated intravascular coagulo-
pathy; renal function tests and urinaly-
sis to rule out nephrotic syndrome;
liver function tests to rule out im-
paired protein synthesis; and pro-
thrombin and partial thromboplastin
times. Antinuclear antibody testing
and measurement of the erythrocyte
sedimentation rate should be per-
formed if autoimmune diseases such
as systemic lupus erythematosus or
vasculitides (giant cell arteritis, Takay-
asu’s arteritis) are suspected as the
cause of the thrombosis. Tests for spe-
cific hypercoagulable disorders should
include a screening clotting assay for
factor V Leiden mutation (using
plasma deficient in factor V) and, if
needed, confirmatory genetic testing,
genetic testing for prothrombin gene
G20210A mutation, functional assays
for protein C and S deficiencies, tests
for antiphospholipid antibody syn-
drome (lupus anticoagulant, anti-
cardiolipin and, if available, anti-β2
glycoprotein I antibodies) and an-
tithrombin–heparin cofactor assay
for antithrombin deficiency. Patients
who present with spontaneous, un-
explained, arterial thrombosis should
be tested for the presence of anti-
phospholipid antibody syndrome (pri-
mary, or secondary to other auto-
immune disorders such as systemic
lupus erythematosus and hyperho-
mocysteinemia.

Antithrombin deficiency was found
to be the cause of the thrombosis in
our patient. Antithrombin is the main
inhibitor of thrombin and the other
clotting factors involved in the intrin-
sic and common coagulation path-

Antithrombin deficiency may be inherited or acquired. The inherited form, first described in 1965 in a Norwegian family,\(^2\) is an autosomal dominant trait with a prevalence of about 1 per 2000 and presents early in life with venous and, rarely, arterial thrombosis.\(^1,3\) A family history of thrombotic disorders is present in most cases.\(^1\) Secondary pathophysiologic conditions associated with reduced antithrombin concentration should be excluded before a diagnosis of inherited deficiency can be established (Box 3). Inherited antithrombin deficiency can be one of 2 types: type 1 (quantitative abnormality) is the result of reduced synthesis of biologically normal protein, and type 2 (qualitative abnormality) is the result of normal synthesis of a deficient protein.

The best screening test for inherited antithrombin deficiency is the antithrombin–heparin cofactor assay. This assay measures factor Xa inhibition, which is reduced in both quantitative and qualitative antithrombin defects.\(^1\) Ideally, blood for investigation of coagulation disorders should be obtained before the initiation of heparin or warfarin therapy. In addition, warfarin may decrease protein C and S levels and transiently increase antithrombin levels. Heparin increases the anticoagulant activity of antithrombin and thus may decrease its levels by 30%, which may lead to erroneous diagnosis of antithrombin deficiency. Because of the reduced levels or biological activity of antithrombin, large quantities of heparin are often required to achieve adequate anticoagulation. Such “heparin resistance” may alert the clinician to consider antithrombin deficiency as the underlying cause of thrombosis before the results of confirmatory tests become available. Patients with thrombosis due to inherited antithrombin deficiency should receive life-long anticoagulation with warfarin, which impairs the synthesis of vitamin K–dependent clotting factors (factors VII, IX and X), thus allowing appropriate anticoagulation irrespective of the antithrombin level.\(^1,3\) The infusion of antithrombin concentrates may be useful in patients with antithrombin deficiency who have recurrent thrombosis despite adequate anticoagulation.\(^3\) However, prophylactic anticoagulation is not generally indicated in asymptomatic cases unless the patient has been exposed to prothrombotic situations such as surgery or prolonged immobilization.\(^1,3\)

### References

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2. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 1965;13:356.

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### Box 3: Secondary causes of antithrombin deficiency\(^1,3\)

| Cause               | Mechanism                                                                 |
|---------------------|---------------------------------------------------------------------------|
| Neonatal period     | Antithrombin concentration is half the normal adult concentration in the first 6 mo of life |
| Complicated pregnancy | Especially in women with pregnancy-induced hypertension or pre-eclampsia, increased consumption of antithrombin is initiated by platelet activation, renal loss or decreased hepatic function |
| Liver disease       | Decreased protein synthesis                                               |
| Disseminated Intravascular coagulation | Pathologic consumption of antithrombin                                    |
| Nephrotic syndrome  | Renal protein loss                                                        |
| Major surgery       | Increased consumption of antithrombin                                     |
| Infectious state (sepsis, plant cell arthritis and possibly Behçet’s syndrome) | Increased consumption of antithrombin                                     |
| Acute thrombosis    | Increased consumption of antithrombin                                     |
| Medication use (heparin, estrogen, L-asparaginase) | Heparin accelerates in vivo clearance of antithrombin; estrogen decreases antithrombin; L-asparaginase decreases antithrombin synthesis |

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