Mural thrombus of the aorta in association with homozygous plasminogen activator inhibitor type 1 (PAI-1)-675(4G) and heterozygous GP Ia 807C/T genotypes

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Thrombus formation in the thoracic and abdominal aorta without evidence of arteriosclerotic disease is very uncommon. We present a case of a 50-year-old woman with a mural thrombus of the upper abdominal aorta associated with a combination of two mutations predisposing for thrombophilia. The genetic analysis showed a homozygous mutation of plasminogen activator inhibitor type 1 (PAI-1)-675 (4G) and a heterozygous mutation of GP Ia 807C/T. To our knowledge, this is the first report of the combination of both mutations occurring in a patient with isolated thrombus formation of the aorta. (J Vasc Surg 2002;36:632-4.)

Mural aortic thrombi have been recognized more frequently in the past years because of improved diagnostic instruments.[1] Thrombus formation in the thoracic and abdominal aorta is primarily the result of underlying arteriosclerotic or aneurysmatic disease, and can lead to major morbidity and mortality. Visceral and peripheral embolism may lead to surgical emergencies and mandate rapid intervention. However, aortic mural thrombus formation in an aorta without morphologic alterations has been reported rarely.[2] After exclusion of common causes, we report an unusual case of aortic mural thrombus occurring in a relatively young patient with an inherited thrombophilia.

CASE REPORT

An otherwise healthy 50-year-old woman presented with a history of 24 hours of progressive periumbilical and lower abdominal pain. There were no signs of distal limb ischemia, such as pain and pallor. Further, the patient had palpable pulses. She had no personal and no family history of arteriosclerotic or thrombotic disease and was not taking any medication. There were no risk factors for arteriosclerosis or thrombosis: She is a nonsmoker, has normal cholesterol and glucose levels, and is not taking estrogens.

Abdominal computed tomography revealed a localized suprarenal mural thrombus located ventrally in the visceral aorta (Fig). The celiac trunk was completely occluded, and the superior mesenteric artery was partially occluded. In addition, free intraperitoneal fluid, splenic infarcts, and a myoma (diameter, 7 cm) of the uterus were observed. Angiography was not performed, as there was no clinical evidence of other sites of thromboembolism except for the intestine, the kidney, and the spleen as viewed in the computed tomography.

The patient underwent emergency transabdominal thrombectomy of the visceral aorta. After performing a left rotation of the abdominal organs, the aorta was clamped 3 cm cranial to the celiac trunk and just proximal to the renal arteries. The thrombus was removed after longitudinal arteriotomy of the aorta. The surface of the aorta beneath the thrombus was macroscopically normal without any signs of arteriosclerotic or other lesions. The thromboembolic material in the superior mesenteric artery and celiac trunk were removed with use of a Fogarty maneuver.

On histopathologic examination, the thrombus consisted mainly of fresh fibrin. The attached vessel wall was without any histopathologic abnormalities, eg, inflammation, atherosclerosis, or dissection. Approximately 30 cm of necrotic ileum was resected. A repeat procedure to assess the bowel viability was performed 24 hours later and showed no residual necrotic intestine. A computed tomography with contrast of the abdomen and thorax performed 14 days postoperatively revealed no source of thrombus, yet again demonstrated the splenic infarcts. In addition, the evaluation showed small renal infarcts. Echocardiography revealed no abnormality, making a cardiac source unlikely.

Systemic heparin therapy was initiated intraoperatively and continued until therapeutic anticoagulant levels were achieved with phenprocoumon. The patient was asymptomatic at follow-up 6 months after intervention.

An extensive coagulation work-up revealed an increased level of plasminogen activator inhibitor type 1 (PAI-1) in the plasma. The genetic analysis showed a homozygous mutation of PAI-1-675(4G) and a heterozygous mutation of GP Ia 807C/T. The classic, more common, disorders associated with arterial or venous thromboembolic diseases such as hyperhomocysteinemia, antithrombin-III deficiency, activated protein-C resistance, lupus anticoagulant, anticardiolipin antibodies, anti-β2-glycoprotein-1 antibodies, prothrombin mutation, and dysfibrinogenemia were ruled out. Of the tests performed, those for lupus anticoagulant,

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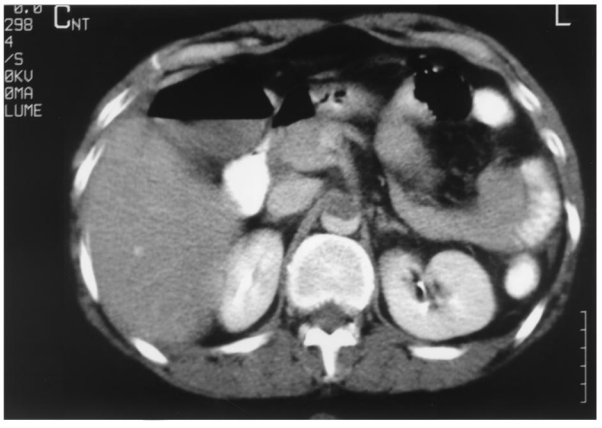
protein C, and protein S are altered by oral anticoagulation, whereas antithrombin III is decreased by heparin therapy. The results of the other tests are not influenced by anticoagulation, as they are based mainly on molecular biology and performed by extraction of deoxyribonucleic acid (DNA) from leukocytes.

In addition, an inflammatory cause was ruled out by normal blood sedimentation rate, baseline C-reactive protein level, absence of antineutrophil cytoplasmatic antibodies, normal serum protein electrophoresis, absence of fragmentocytosis, normal platelet count, normal hemogram, and no histologic pathology in the few fragments attached to the excised thrombus. Tissue factor pathway inhibitor (TFPI) and human platelet antigen (HPA) genotype were wildtype.



Computed tomography of the abdomen. Note the semicircular thrombus at the level of the celiac trunk and superior mesenteric artery.

DISCUSSION

Mural aortic thrombus formation without signs of arteriosclerosis or aortic aneurysm is unusual. The largest series were presented by Hahn and coworkers,[2] with six cases over a period of 3.5 years of which one patient had a positive Ham test and in another a positive anticardiolipin immunoglobulin (Ig)G was found.

Celiac axis compression syndrome was clinically ruled out because the patient did not have chronic abdominal pain. Furthermore, thrombus formation in the aorta and superior mesenteric artery is very atypical in celiac axis compression syndrome.

In the case we described, we found two polymorphisms: homozygous PAI-1-675(4G) and heterozygous GP Ia 807C/T genotypes. Other disease entities such as paroxysmal nocturnal anemia and most recently described thrombophilic autoantibodies against annexin V, factor II, and protein S were not addressed. However, there was little evidence for presence of these disorders with a patient observation time of more than 15 months.

The main function of PAI-1 is inhibition of tissue plasmin activator (tPA). In healthy individuals the interaction of PAI-1 and tPA inhibits the development of systemic fibrinolysis and systemic bleeding while permitting local clot lysis. Mutation of the PAI-1 gene is weakly associated with elevated plasma levels of PAI-1, leading to impaired fibrinolysis. Mutations of PAI-1 have been related to coronary artery disease, usually in association with other cardiovascular risk factors.[3-5] A metaanalysis revealed a weak significant effect of PAI-1 genotype on myocardial infarction.[6] GP Ia polymorphism 807C/T increases platelet receptor density of the collagen receptor glycoprotein Ia/IIa.[7] An association of this polymorphism and the risk of myocardial infarction with an odds ratio of 3.3 has been demonstrated.[8] Because GP 1a polymorphism results in an increased binding of platelets to collagen, which is exposed during vascular damage, it can be assumed that there will be a greater influence on arterial than on venous thromboembolism. The genotype frequency in healthy Caucasian controls of the homozygous 4G/4G polymorphisms of PAI-1-675 is 26% and of the heterozygous GP Ia 807C/T is 47%.[4,8] At present, no data exist about the frequency of the combination of these polymorphisms. Mutations of PAI-1 and GP Ia alone are associated with weak increased risk of arterial thrombotic disease. The frequencies for the combined genetic states as seen in our case, can be calculated, and amount to approximately 2.9%. Thus, it can be concluded that the association of these two mutations will significantly increase the hypercoagulable risk. Case-control studies are needed to show the incidence and significance of this combination in patients with arterial thrombotic disease. In addition, the combination of these two mutations could be responsible for additional arterial thromboembolic disorders with unknown etiology.

On the basis of the relatively young age of the patient and the severity of the arterial thrombotic event, we advocated life-long oral anticoagulation. Furthermore, the genetic defects found will constitute a permanent risk for future thromboembolic events and outbalance the risk for major bleeding due to long-term oral anticoagulation.

In conclusion, in a rare event such as mural aortic thrombus formation in a relatively young patient, the classic coagulation disorders have to be excluded first. If these tests are negative, further investigation for more unusual coagulation disorders such as GP Ia and PAI-1 polymorphisms; TFPI; HPA; and autoantibodies against annexin V, factor II, and protein S should be considered.

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