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Arterial Embolism Caused by Large Mobile Aortic Thrombus in the Absence of Atherosclerosis, Associated with Iron Deficiency Anemia

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Case 1

A 42-year-old Hispanic female with a history of severe menorrhagia presented with sudden onset and progressively worsening severe right leg pain and numbness. Six months previously, she had an embolic right popliteal artery occlusion. A trans-esophageal echocardiogram performed to search for an embolic source was normal at that time but she had hypochromic anemia with hemoglobin of 6.6 g/dL. There was a negative work up for hypercoagulable condition (including prothrombin G20210A, Factor V Leiden, antithrombin III, anticardiolipin antibody IgG, IgM, lupus anticoagulant, homocysteine, Protein C activity), performed a few weeks after the event, prior to starting warfarin.

She had no risk factor for cardiovascular disease, did not smoke, and her family history was unremarkable. She was intolerant of oral iron due to severe constipation. At the time of the current presentation she was not on anticoagulation or birth control pills.

On the current admission, there was decreased perfusion of right lower extremity; and, weak right femoral, absent popliteal, dorsalis pedis, and posterior tibial pulsations, with normal left leg pulsations. There were no associated neurological deficits.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Movie clip for Figure 1.

Movie clip for Figure 2.

Movie clip for Figure 3.

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She had severe microcytic hypochromic anemia with hemoglobin of 7.7 g/dL, hematocrit of 26%, mean corpuscular volume (MCV) of 65, and serum ferritin of 9 ng/mL. Her platelet count was 465,000 /mL. The electrocardiogram (EKG) was normal.

Right lower extremity angiogram showed an abrupt cutoff of the right external iliac artery suggesting an embolus. There were also emboli to the proximal to midsuperficial femoral arteries and the bilateral profunda femoris arteries. Right hypogastric, popliteal and anterior tibial arteries were also occluded. She was anticoagulated with unfractionated heparin.

Transthoracic echocardiogram was normal. Transesophageal echocardiogram (TEE) revealed a 1 cm × 3 cm long mobile thrombus in the descending thoracic aorta attached distal to the origin of the left subclavian artery. There was no atherosclerotic thickening of the thoracic aorta (Fig. 1A and B, movie clip 1). There was no patent foramen ovale. Additional hematological workup showed a plasminogen activator inhibitor-1 antigen level of 624 ng/mL (normal 4–43), and mildly decreased Protein S activity of 33 (normal 52–151) thought to be associated with consumption of coagulation proteins due to the hypercoagulable state. Upper and lower gastrointestinal endoscopy was unremarkable and gynecologic evaluation was negative. She was treated with intravenous iron therapy with improvement in hemoglobin to 10 g/dL and hematocrit to 34% after a course of 4 weeks. Anticoagulation therapy was continued with warfarin. A repeat TEE performed 4 weeks later showed resolution of aortic thrombus (Fig. 2A and B, movie clip 2).

Case 2

A 49-year-old Caucasian female with a history of menorrhagia presented with new onset of left hemiparesis. She did not smoke and was not on birth control pills. On the day of admission she suddenly developed left side weakness and fell to the ground. In the emergency department, she had left sided hemiparesis and neglect, absence of left deep tendon reflexes, and positive left Babinski response.

An EKG was normal. Computed tomography (CT) of the brain showed no evidence of intracranial hemorrhage or acute infarct. CT angiogram of the head showed no evidence of intracranial arterial stenosis. Magnetic resonance imaging (MRI) of the brain showed multiple small infarcts with restricted diffusion throughout the right cerebral white matter and cortex. Carotid arteries were patent and showed no significant abnormalities.

Routine laboratory studies showed only iron deficiency anemia, with hemoglobin of 8.4 g/dL, MCV of 68 fL, mean corpuscular hemoglobin (MCH) of 20, elevated platelets of 567,000/mL. Iron studies showed: ferritin of 15ng/mL, serum iron of 20 µg/dL, and transferrin of 263 mg/dL.

The patient was started on anticoagulation using unfractionated heparin and a TEE was performed that showed normal size chambers, normal left and right ventricular function, without valvular abnormalities. A large mobile thrombus of 1.0 cm × 0.6 cm was visualized in the mid portion of the aortic arch, in the absence of significant atherosclerosis (Fig. 3, movie clip 3). There was no patent foramen ovale (PFO).

There was a negative work up for hyper-coagulable condition (including prothrombin G20210A, Factor V Leiden, antithrombin III, anticardiolipin antibody IgG, IgM, lupus anticoagulant, homocysteine, Protein C, and Protein S activity). Plasminogen activator inhibitor-1 activity level was normal, 7.6 IU/mL (normal 0–22). No gastrointestinal bleeding was discovered and gynecological evaluation was negative.

The patient's neurological status improved rapidly and she was transferred to the inpatient rehabilitation unit. Ten days after admission she was discharged on warfarin anticoagulation and oral iron therapy and was able to ambulate independently.

Discussion

In patients with embolic events, aortic atheromas are often detected by TEE, sometimes with attached mobile thrombus.^{1,2} However, large mobile thrombus in the aortic arch without bulky atheromatous disease is an unusual finding. Laperche et al. found 23 cases in 27,855 (0.08%) examinations.³ These patients were young, mean age 45 years. This contrasts with the substantially older age of patients with severe aortic plaque and superimposed mobile thrombus, mean age 70 described by Kronzon et al. and others.² In the Laperche series, as in the two cases reported here, the attachment of the thrombus was in the aortic arch, or at the isthmus near the origin of the great vessels. Similar to our cases, Laperche et al. also found that atherosclerotic plaque was often not seen on TEE. However, in the 10 surgically treated patients direct inspection and histology showed thin plaque at the thrombus insertion and the removed masses always showed red fibrin thrombus.^{3,4} Since that time, subsequent reports of massive aortic thrombus have appeared.⁴⁻⁹

In the present report we describe two patients in whom profound iron deficiency anemia may have promoted a hypercoagulable state and acted as cofactor for thromboembolism. There is another report of two female patients with severe iron deficiency anemia and brain embolism caused by mobile aortic thrombus, but with no apparent aortic atheroma on TEE or magnetic resonance imaging. The patients, ages 41 and 50 were treated with intravenous heparin and iron, with resolution of aortic thrombus by days 7 and 19, respectively.¹⁰ In addition there are other reports of four female patients (ages 20, 39, 44, 49) with bulky proximal carotid thrombosis and brain embolism who had severe IDA.^{11,12} These patients also had no atherosclerotic thickening of their carotid arteries detected by imaging. These four patients also had successful resolution of their thrombi demonstrated after treatment with intravenous heparin and/or warfarin, and iron. Including our two cases, all eight of the reported cases of bulky aortic or carotid thrombi with iron deficiency occurred in woman, and seven of eight had severe menorrhagia as the cause of the iron deficiency anemia and, three had uterine fibroids as the cause of bleeding.¹⁰⁻¹²

Though severe and complex atherosclerotic aortic plaques are more frequently found in patients with embolic stroke,^{1,2} the association between plaque and embolic stroke is strengthened by blood hypercoagulability.¹³⁻¹⁵ Iron deficiency anemia induces a hypercoagulable state.¹⁶⁻²⁴ Cerebral venous sinus thrombosis has been reported in patients with severe IDA due to menorrhagia secondary to myoma uteri.¹⁶ Several mechanisms have been proposed to explain the association between IDA and thrombogenesis that are pertinent here. First, thrombocytosis and increased platelet adhesion occur secondary to iron deficiency and may be associated with a hypercoagulable state.^{20,23} Modest thrombocytosis was observed in both of our patients. Second, an increase in plasminogen activator inhibitor-1 in anemia may cause decreased fibrinolytic activity in IDA.^{21,24} Plasminogen activator inhibitor-1 was markedly increased in one of our patients, but the second patient had a normal level. Third, increased shear force caused by an anemia-induced hyperdynamic state can cause endothelial disruptions. A small fissure in the endothelium with only thin plaque could serve as nidus for thrombus.

The previously described hypercoagulable state, and the previous cases of IDA with aortic and carotid bulky thrombus lend credence to our contention that IDA is the causative pathophysiological mechanism in these patients.¹⁰⁻¹² A formal study to prove the association of IDA with aortic thrombus would require TEE in patients with IDA but

without embolism, and thus would not likely ever be done given the invasive nature of TEE. It is also possible that the underlying gynecologic cause for menorrhagia was the cause of our patients' hypercoagulable state. Patients found to have uterine fibroids as the cause of menorrhagia will require either hormonal treatment or surgical therapy to prevent recurrent bleeding.

There are no randomized trials comparing therapies in mobile aortic thrombus and there are no current American Heart Association/American Stroke Association guidelines on this issue.²⁵ In nonrandomized observational studies, patients with mobile thrombi experienced benefit from warfarin anticoagulation.^{26,27} In the previously reported cases of massive thrombus and IDA and our two cases antithrombotic therapy with heparin followed by warfarin along with iron was uniformly successful in resolution of the thrombus, and prevention of subsequent emboli.¹⁰⁻¹² Also, the pathologic findings of red fibrin thrombus in the surgically extirpated masses^{3,4} support heparin and warfarin antithrombotic therapy in this unusual pathology. In contrast, in the different pathology of aortic atheroma without massive thrombus, anticoagulant therapy may not be effective in preventing subsequent embolism.²⁸

In conclusion, when embolism occurs in IDA meticulous TEE inspection of the thoracic aorta is indicated. Empiric evidence available at this time supports heparin-warfarin therapy when large mobile aortic thrombus without bulky atheroma is found with iron deficiency anemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Patient 1: TEE of descending thoracic aorta showing **A.** longitudinal and **B.** cross-sectional view of a large mobile thrombus.

Figure 2.
Patient 1: 4 weeks later TEE of descending thoracic aorta showing **A.** longitudinal and **B.** cross-sectional view of resolved large mobile thrombus.

Figure 3.
Patient 2: TEE of mid portion of the aortic arch showing a large mobile thrombus, arrow.