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Pernicious Emboli: An Uncommon Cause of a Common Problem

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PRESENTATION

A 51-year-old woman with a history of hypertension presented to an emergency room with sudden-onset shortness of breath that began while walking with her family. She became sweaty and lightheaded and returned home to rest. She could not catch her breath after sitting down for several minutes, so her family drove her to the hospital.

The patient reported increased swelling of both legs for 2 weeks before admission. She had no chest pain, orthopnea, paroxysms of nocturnal dyspnea, palpitations, cough, wheezing, sputum production, melena, hematochezia, vomiting, fevers, or chills.

In addition to shortness of breath, the patient had been experiencing a tingling sensation in her hands and feet for approximately 3 weeks. She also complained of progressive weakness and unsteadiness on her feet. Her appetite had waned, and her daughter worried that she was not eating enough. Family members reported that she seemed fatigued, drowsy, and forgetful.

ASSESSMENT

On presentation to the emergency room, the patient's heart rate was 112 beats per minute. Oxygen saturation was 94% on ambient air. Other vital signs were normal. On examination, she was alert and in no acute distress. Her conjunctivae were pale, but the head and neck examination results were otherwise normal. The jugular venous pulse was not seen with the head of the bed at 30°. No right ventricular heave was present, and the point of maximal cardiac impulse was not displaced. No cardiac murmurs were present, and pulmonary examination results were normal. Her extremities were warm with full distal pulses, and shallow pitting edema extended to the knees on the left and right. There was no loss of sensation to light touch in the distal extremities. Deep tendon reflexes were normal, and the Babinski sign was not present. She was able to walk without assistance, but her gait was slightly wide-based and showed a tendency for retropulsion. Her mental status examination was notable for an inability to recall 3 objects at an interval of three minutes.

Initial laboratory evaluation of the serum was notable for glucose 112 mg/dL, creatinine 1.0 mg/dL, total bilirubin 2.5 mg/dL, tropinin 0.6 ng/mL, platelet count 170 K/mL, hemoglobin 7.7 g/dL, mean corpuscular volume 107 fL, red cell distribution width 16.7%, reticulocyte count 0.6 K/mL, and lactate dehydrogenase 650 U/L. Coagulation studies were notable for an international normalized ratio of 1.4, prothrombin time 14.3 seconds, and activated partial thromboplastin time 23.7 seconds. A chest radiograph revealed faint bibasilar opacities consistent with atelectasis, but no other abnormalities. An electrocardiogram revealed sinus tachycardia with an RSR' pattern in leads V1 and V2. Duplex ultrasound examination of the lower extremities revealed no thrombi. Given the lack of an explanation for the patient's dyspnea, she was admitted to the general medicine service for further evaluation.

DIAGNOSIS

The patient's dyspnea, tachycardia, and electrocardiogram findings prompted evaluation for pulmonary embolism with spiral computed tomography of the chest. This revealed extensive pulmonary emboli within segmental branches of pulmonary arteries of both lungs (**Figure 1**). A transthoracic echocardiogram showed evidence of mild pulmonary hypertension but no signs of right ventricular strain.

The findings of elevated bilirubin and lactate dehydrogenase raised concern for hemolytic anemia, which is commonly associated with thrombotic complications.[1] However, results from direct Coombs testing and from flow cytometric testing for paroxysmal nocturnal

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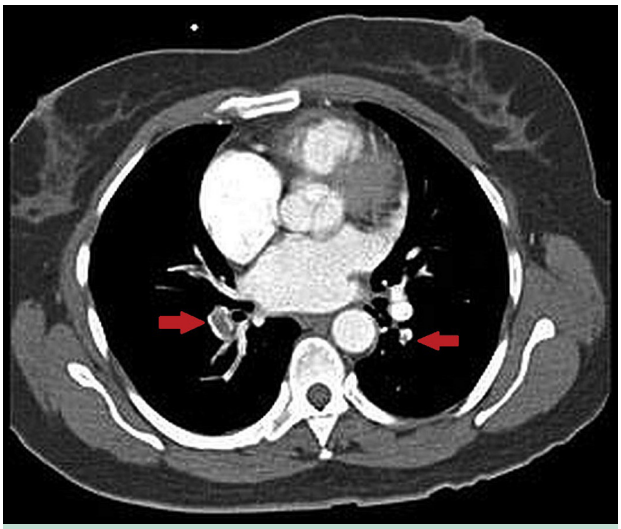

Figure 1 Contrast-enhanced CT scan showing bilateral pulmonary emboli.

hemoglobinuria were negative. Hemolytic anemia due to G6PD deficiency has also been associated with venous thromboembolism (VTE),[2] but initial review of the peripheral blood smear showed no blister cells characteristic of this diagnosis. Moreover, the absence of an appropriate reticulocyte response suggested that the primary process involved bone marrow dysfunction with intramedullary cell turnover and destruction rather than intravascular hemolysis.

The constellation of paresthesia, impaired memory, gait instability, macrocytosis, and low reticulocyte count raised concern for a hypoproliferative anemia caused by vitamin B12 or folate deficiency. A red blood cell folate level was normal. Serum levels of B12, homocysteine, and methylmalonic acid levels were 33 pg/mL (normal 211-946), 200 umol/L (normal 4.0-15.2), and 8770 nmol/L (normal 45-325), respectively. A blood smear review demonstrated hypersegmented neutrophils (**Figures 2 and 3**), macrocytes, and macroovalocytes.

Additional history revealed no chronic gastrointestinal symptoms suggestive of a chronic malabsorptive process. The patient had never undergone gastrointestinal surgery. This raised suspicion for pernicious anemia, and an assay for intrinsic factor antibodies was sent on the second day of her hospitalization. This ultimately returned a positive result.

MANAGEMENT

When her spiral computed tomography scan revealed bilateral pulmonary emboli, the patient was started on an intravenous heparin infusion. On the second hospital day, her hemoglobin dropped to 6.7 g/dL, and 2 U of packed red blood cells were transfused. The remainder of her hospital course was uneventful. At the time of discharge, she was transitioned to warfarin with an overlapping regimen of low molecular weight heparin. The patient's pernicious anemia was managed with intramuscular vitamin B12 repletion. To

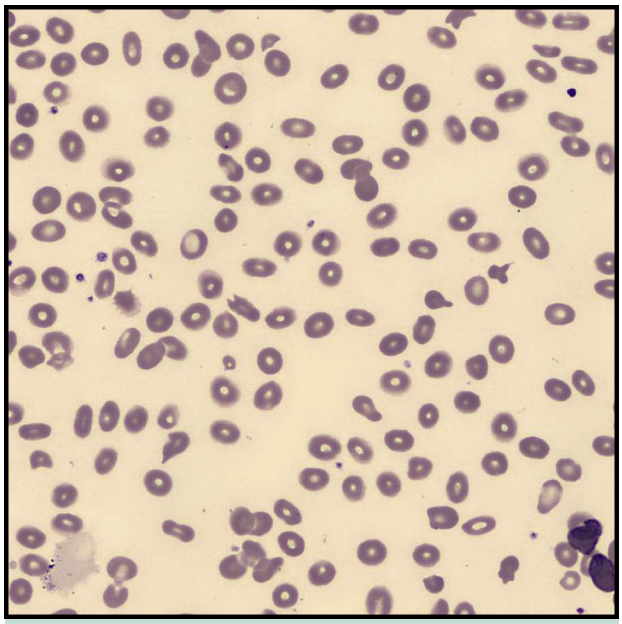

Figure 2 Peripheral blood smear showing macrocytosis and macroovalocytes, characteristic of megaloblastic anemia.

enhance erythropoiesis, thiamine and folate supplements were also prescribed at discharge.

The patient returned to clinic 7 months later, having continued vitamin B12 supplementation. Her anemia, dyspnea, and neurologic symptoms had all resolved, and she had returned to work.

We describe above a unique case of pulmonary embolism associated with pernicious anemia, hyperhomocysteinemia, and pseudomicroangiopathic hemolytic anemia.

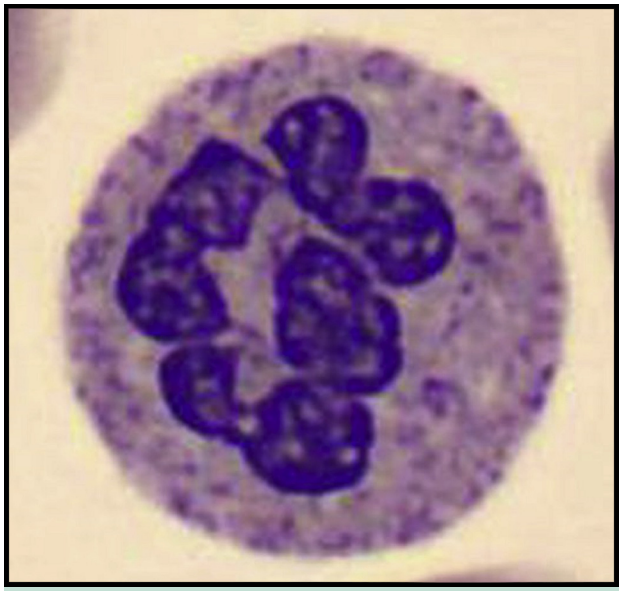

Figure 3 Magnified view of peripheral blood smear showing hypersegmented neutrophil.

Vitamin B12 plays an important role as a cofactor for methionine synthase, which is responsible for the conversion of the amino acid homocysteine to methionine. Consequently, vitamin B12 deficiency leads to an increased plasma homocysteine level, a well-recognized risk factor for VTE. Elevated levels of homocysteine are thought to precipitate thromboembolism through multiple mechanisms. Homocysteine interferes with the inactivation of factor Va by activated protein C in a dose-dependent fashion.[3] It also increases monocyte expression of tissue factor[4] and suppresses the anticoagulant activity of endothelial heparan sulfate.[5] Other proposed mechanisms linking hyperhomocysteinemia to thrombosis include increased hydrogen peroxide production, impaired endothelial antioxidant activity, and increased platelet activation.[6]

Case-control studies of hospitalized patients with VTE suggest that vitamin B12 deficiency is also independently associated with VTE. However, the causal mechanism for this association remains unclear.[7,8]

This case highlights 2 underappreciated features of vitamin B12 deficiency: its thrombotic potential and its ability to mimic microangiopathic hemolytic anemia. Differentiation between thrombotic microangiopathies and pseudothrombotic microangiopathic anemias is crucial: the former entities often require emergent plasmapheresis, whereas the latter can be treated effectively with vitamin supplementation. On the basis of our experience, any patient with macrocytosis and evidence of shortened red blood cell survival merits evaluation for vitamin B12 and folate deficiency. While such tests are pending, the reticulocyte count can be used to differentiate between hemolytic processes, which present with elevated reticulocyte counts, and pseudothrom-botic microangiopathic anemias, which present with decreased reticulocyte counts.

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