28-Year-Old Man With Recurrent Vertigo, Syncope, and Progressive Memory Impairment

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A 28-year-old man with past medical history of long-standing normocytic anemia of unknown etiology presented to a local emergency department for evaluation of vertigo and recurrent syncope. Leading up to his presentation, he had been experiencing several months of episodic vertigo, transient visual deficits, cognitive slowing, and new memory difficulties. He had no prodromal symptoms, incontinence, tongue biting, or convulsions. He was on no medications before presentation. His vital signs were normal at presentation. Physical exam was notable for livedo reticularis, left side hyperreflexia, and a mildly reduced Kokmen score (short mental status examination) identifying deficits in executive functioning. Laboratory studies were notable for the following (reference ranges shown parenthetically): hemoglobin, 10.7 g/dL (13.5 to 17.5 g/dL); mean corpuscular volume, 93.8 (78.2 to 97.9 fL); white blood cell count, 4.5 (3.4 to 9.6×10^9/L); platelets, 212 (135 to 317×10^9/L); creatinine, 1.02 (0.84 to 1.21 mg/dL); activated partial thromboplastin time, 53 seconds (25 to 37 seconds); and prothrombin time, 14.8 (12 to 15.5) with an international normalized ratio (INR) of 1.2 (0.9 to 1.1). Noncontrast head computed tomography showed multiple foci of encephalomacia involving the right frontal, temporal, and parietal lobes with ill-defined loss of gray-white matter differentiation in the bilateral parietal and left occipital lobes, concerning for multifocal ischemic strokes. Conventional angiogram of the head and neck confirmed normal vasculature. Electrocardiogram (ECG) and Holter monitoring showed sinus rhythm. Transthoracic echocardiogram showed nodular mitral valve thickening, moderate mitral regurgitation (MR), and absence of intracardiac shunt. Blood cultures were negative.

1. Given this patient’s constellation of symptoms, which one of the following is the most likely diagnosis?
   a. Infective endocarditis
   b. Central nervous system (CNS) vasculitis
   c. Antiphospholipid syndrome (APS)
   d. Paroxysmal atrial fibrillation
   e. Small vessel cerebrovascular disease

This patient presented with findings of multifocal ischemic strokes, raising concern for a thromboembolic process. Infectious endocarditis should be ruled out in the presence of vegetations on echocardiogram. However, the absence of fever, which is present in nearly 90% of cases, negative blood cultures, and lack of other systemic manifestations, makes this diagnosis unlikely.

Primary CNS vasculitis is a rare autoimmune disease generally limited to the brain and meninges. Headache and cognitive dysfunction are common findings and patients typically present with neurologic deficits secondary to ischemic strokes in multiple vascular territories. The diagnosis is frequently made through imaging studies, such as brain MRI/MRA with black blood imaging, which show thickening and late gadolinium enhancement in the affected territories; conventional angiogram is the preferred method to confirm this pathology,
although biopsy may be required. Normal vasculature by both brain MRA and angiogram in this case rules out CNS vasculitis.

Antiphospholipid syndrome is a systemic autoimmune process that is characterized by vascular thrombosis and/or pregnancy morbidity in association with abnormalities in antiphospholipid (aPL) antibody testing.\textsuperscript{1} Non-criteria manifestations of the disease, as seen in this case, include livedo reticularis and nonbacterial thrombotic endocarditis (NBTE), also known as Libman-Sacks endocarditis.\textsuperscript{2} The presence of arterial thrombosis (stroke) in a young patient, NBTE, and livedo reticularis combined with prolonged partial prothrombin time, negative blood cultures, ECG, and cerebral angiogram makes APS the most likely diagnosis in this patient.

Atrial fibrillation is the most common persistent arrhythmia in the general population. Its prevalence approaches 10% by the age of 80 years. It is the most common cause of embolic stroke, making it imperative to rule out in the case of multifocal ischemic strokes. This patient's young age, normal ECG, and negative Holter make atrial fibrillation less likely.

Small vessel disease underlies perhaps 20% of ischemic strokes. Strokes occur due to occlusion of a deep penetrating branch of a large cerebral artery and most often affect the basal ganglia, subcortical white matter, or pons. Patients are typically older and possess risk factors for small vessel disease such as chronic hypertension, diabetes mellitus, hyperlipidemia, and smoking.

Additional workup in this patient revealed a positive lupus anticoagulant based on an abnormally elevated dilute Russell viper venom time screening and confirmatory test, elevated anti-beta2-glycoprotein I (anti-\beta2GPI) immunoglobulin G (IgG) antibodies, 146.8 (<15.0); elevated anticardiolipin (aCL) IgM, 55.7 (<15.0); and IgG, 98.8 (<15.0).

2. Which one of the following testing should be completed to confirm this patient's diagnosis?
   a. No further testing is required
   b. aPL antibody testing should be completed in 12 or more weeks while continuing anticoagulation
   c. aPL antibody testing should be repeated in 12 or more weeks while holding anticoagulation
   d. Rapid plasma reagin or venereal disease research laboratory syphilis testing should be sent
   e. Antinuclear antibodies should be performed

This patient's presentation is suspicious for APS. However, the diagnosis requires additional testing, making answer choice a incorrect. Confirmation of the diagnosis requires persistent abnormality of at least one antiphospholipid test — positive lupus anticoagulation (LA) or elevation of aCL or anti-\beta2GPI (either IgM and IgG) antibodies above the 99th percentile — for 12 weeks or longer.\textsuperscript{3} Repeat aPL antibody testing is required due to transient elevation of aPL antibodies in the setting of infections, acute thrombotic events, use of certain medications, and some malignancies.\textsuperscript{3} Although anticoagulants can affect coagulation and interfere with interpretation of LA, they do not affect testing for aCL or anti-\beta2GPI antibodies. Testing for the presence of LA — such as with dilute Russell vider venom time — requires interpreting clotting time (prolonged in APS) and assessing the respective effects of mixing normal plasma and phospholipids with the patient’s plasma on clotting time (no effect with the first and shortening with the second in APS). Confirmatory testing in 12 or more weeks should be sent as described in answers b and c. Answer b, however, is the correct option as anticoagulation should not be held in this patient given the high risk of thromboembolic events. Because anticoagulation may result in false-positive or indeterminate LA, it would be most cost-effective to repeat only aCL and anti-\beta2GPI antibodies.\textsuperscript{2}

False-positive nontreponemal syphilis tests can raise suspicion for APS, but are not diagnostic. Both venereal disease research laboratory and rapid plasma reagin use an antigen that contains cardiolipin,
explaining why these tests may return positive in this population.3

Antiphospholipid syndrome can occur as a primary disease or be related to an underlying autoimmune condition, most commonly systemic lupus erythematosus (SLE).4 Our patient did not have other features to suggest SLE such as inflammatory arthritis, serositis, or photosensitive skin rashes. Antinuclear antibody testing, although important to identify lupus and other diseases, is not required for diagnosis of APS and therefore will not confirm the diagnosis of our patient.4

This patient had persistent abnormalities of LA, anti-β2GPI IgG, and aCl IgM and IgG 12 weeks after his initial presentation, solidifying the diagnosis of APS. Triple positivity places him in the highest risk for recurrent thrombosis.2 Antinuclear antibodies were negative.

3. Which one of the following would not be appropriate to use for secondary stroke prophylaxis for this patient?
   a. Warfarin with INR goal 2 to 3
   b. Warfarin with INR goal 3 to 4
   c. Low-dose aspirin (LDA) with warfarin (INR goal 2 to 3)
   d. Low molecular weight heparin (LMWH)
   e. Rivaroxaban

Warfarin is the preferred long-term agent for secondary thromboprophylaxis in APS. In patients with definite APS and first arterial thrombotic event, as in this case, an INR goal of 2 to 3 or 3 to 4, or combining standard-intensity warfarin (INR 2 to 3) with LDA are all reasonable options.3 The appropriate INR or the addition of LDA should be decided by balancing the patient’s risk of bleeding and thrombosis.3 Options a, b, and c would all be appropriate. In the case of first venous thrombotic event, standard-intensity warfarin (INR 2 to 3) is recommended.2,3,6 Chromogenic factor X activity testing may be obtained if the patient’s baseline INR is elevated due to LA. Chromogenic factor X activity of 25% to 35% corresponds to therapeutic standard-intensity warfarin.3

Low molecular weight heparin is also recommended in APS for secondary thromboprophylaxis. It is most often used in patients for whom warfarin is contraindicated (eg, during pregnancy) or in those with recurrent thrombotic events on warfarin.3

Rivaroxaban and other direct oral anticoagulants are not recommended for the treatment of APS.3,7,8 A recent randomized control trial comparing rivaroxaban versus warfarin was ended early because the patients on rivaroxaban had higher thrombotic events than those on warfarin.7 Another large randomized controlled trial also had a higher proportion of patients with thrombotic events in those on rivaroxaban compared to those on warfarin.8

This patient was placed on warfarin for secondary stroke prophylaxis with an INR goal of 2.5 to 3.5 (chosen due to his low bleeding risk and high risk of stroke morbidity). Chromogenic factor X activity measured at 23% with concurrent INR of 3.3. As both tests indicated therapeutic anticoagulation, the patient was subsequently followed by INR. Follow-up brain MRI at 3 months showed no new interval strokes.

Later in his course, he developed anemia and dyspnea on exertion. His laboratory testing showed hemoglobin of 10.7 g/dL (13.5 to 17.5 g/dL) and positive direct antibody (Coombs) test.

4. For which one of the following potential APS manifestations would immunosuppression be beneficial in this patient?
   a. Autoimmune hemolytic anemia (AIHA)
   b. Antiphospholipid nephropathy
   c. Pulmonary hypertension related to pulmonary thromboembolic disease
   d. NBTE
   e. Livedo reticularis

Hematologic complications in APS include antibody-mediated complications such as thrombocytopenia and AIHA, and complement-mediated complications such as thrombotic microangiopathy.4 Antibody or complement-mediated complications are managed with additional immunosuppressive therapy, such as steroids and rituximab for AIHA and eculizumab for thrombotic...
microangiopathy. The patient had hemolytic anemia based on low haptoglobin and elevated indirect bilirubin, and a positive Coombs test. He was diagnosed with AIHA, for which immunosuppression would be beneficial.

Antiphospholipid nephropathy may affect nearly 25% of those with primary APS and is a consequence of noninflammatory occlusion of micro- and/or macrovasculature of the kidney. Those with APS in the setting of SLE may instead have immune complex-mediated lupus nephritis. Anti-phospholipid syndrome nephropathy is managed with anticoagulation while immune complex-mediated renal disease requires immunosuppression. This patient had no evidence of renal involvement.

Pulmonary APS manifestations include pulmonary thromboembolic disease, pulmonary hypertension, and diffuse alveolar hemorrhage (DAH), which the patient did not have. Thromboembolic-related pulmonary manifestations require anticoagulation whereas immunosuppressive therapy may be used in DAH.

Nonbacterial thrombotic endocarditis results from formation of fibrin-platelet thrombi on the leaflets of the cardiac valves leading to thickening and valve dysfunction. The mitral valve is the most commonly affected, followed by the aortic and tricuspid valves. Patients may be asymptomatic or experience thromboembolic phenomena such as in this case. Management consists of anticoagulation; the role of immunosuppression in this setting is unclear. In the case of symptomatic valvular disease or refractory thromboembolic events despite anticoagulation, surgical intervention may be required.

Livedo reticularis — a violet net-like, cyanotic pattern on the skin — seen in APS, as in this patient, does not require specific management. Skin findings can vary in APS and be severe, including digital ischemia and cutaneous vasculitis. Sneddon syndrome is a condition in which patients have widespread livedo reticularis and stroke from thrombotic vasculopathy of dermal and cerebral arteries; this syndrome can affect patients with or without APS.

Given his positive Coombs test and anemia, immunosuppression was recommended. Over the next several months, he continued having progressive exertional dyspnea. His anemia remained stable. His exam showed a 2/6 apical systolic murmur with normal jugular venous pressure, clear lungs, and no peripheral edema. Chest x-ray showed an enlarged cardiac silhouette without consolidation, parenchymal abnormalities, or effusions.

5. Given this patient’s diagnosis of APS, which of the following complications is the most likely cause of his dyspnea?
   a. Catastrophic antiphospholipid syndrome
   b. AIHA
   c. Decompensated congestive heart failure
   d. Valvular insufficiency related to NBTE (Libman-Sacks endocarditis)
   e. DAH

Catastrophic antiphospholipid syndrome is a rare but life-threatening complication of APS. It consists of disseminated thrombosis occurring in 3 or more organs/tissues within a 1-week period in a patient with positive aPL antibodies. Symptoms depend on the organs involved. It is an acute process that would not explain this patient’s gradual progression of dyspnea.

Autoimmune hemolytic anemia symptoms depend on the severity of anemia as well as the acuity of progressive anemia. Autoimmune hemolytic anemia may cause anemia-related symptoms, including dyspnea on exertion and fatigue, as well as jaundice and chest pain. Given that the anemia remained stable after immunosuppressive treatment with rituximab, AIHA would not explain progressive dyspnea.

The patient’s exam shows no elevated jugular venous pressure, pulmonary crackles, or peripheral edema to suggest decompensated heart failure, and his chest x-ray shows no pulmonary edema or effusions to support the diagnosis.

This patient has a murmur characteristic of MR. Patient’s with NBTE or Libman-Sacks endocarditis can have associated valvular insufficiency that progresses over time,
causing progressive dyspnea.\textsuperscript{8} Option d, or worsening MR from NBTE, best explains this patient’s presentation.\textsuperscript{8}

Diffuse alveolar hemorrhage is typically an acute process that has been well described in APS. However, patients present with cough, dyspnea, hemoptysis, and sometimes fever. Chest x-ray often shows diffuse lung opacities. This patient’s signs and symptoms do not fit DAH.

This patient underwent repeat transthoracic and transesophageal echocardiogram, showing irregular thickening of the mitral valve with a focal, “stuck on” soft echodensity at the mitral leaflet tips associated with severe MR. He is awaiting mitral valve replacement surgery. He will require bridging anticoagulation in the perioperative period due to his APS.\textsuperscript{7}

**DISCUSSION**

Antiphospholipid syndrome is an autoimmune disease characterized by circulation of autoantibodies to phospholipid-binding proteins, which leads to vascular complications including arterial/venous thrombosis, small vessel thromboembolic events, and obstetric complications.\textsuperscript{7} Epidemiologic studies have estimated the incidence of APS to be 2.1 in 100,000.\textsuperscript{12}

Clinical presentation and symptoms are variable, with deep venous thrombosis, thrombocytopenia, and livedo reticularis being the most common clinical features.\textsuperscript{4} Thrombosis can affect any organ system and stroke may be the presenting feature in up to 13% of patients.\textsuperscript{9} Baseline thrombocytopenia and elevated activated partial thromboplastin time may be supportive findings.\textsuperscript{2}

Classification of definite APS requires the presence of 1 clinical and 1 laboratory criteria (positive LA, elevated aCL IgG and/or IgM, and elevated anti-β2GP1 IgG and/or IgM). Clinical criteria include vascular thrombosis and pregnancy morbidity. The positive laboratory test should be present on 2 occasions 12 or more weeks apart to meet the classification criteria for APS.\textsuperscript{1,2}

There are various clinical features outside of thrombosis seen in APS. These are referred to as “non-criteria” manifestations and can involve various organ systems including hematologic, renal, pulmonary, cardiovascular, and cutaneous. Manifestations such as isolated (non-immune) thrombocytopenia or livedo reticularis require no specific management. Autoimmune hemolytic anemia and DAH may respond well to immunosuppression with steroids and rituximab.\textsuperscript{4,6} Other manifestations have not been shown responsive to immunosuppressant therapy. These include APS nephropathy and NBTE; both are managed primarily with anticoagulation. Anticoagulation with or without antiplatelet therapy in patients with NBTE prevents clinical embolic events but does not necessarily induce regression of fibrinous vegetations; immunosuppression has similarly not been shown to resolve vegetations.\textsuperscript{9}

For secondary prevention, warfarin is first-line treatment for anticoagulation whenever possible. For patients with recurrent thrombosis, guidelines recommend intensifying warfarin therapy, adding antiplatelet therapy, or switching to LMWH.\textsuperscript{5} Data do not support the use of novel oral anticoagulants in APS, in particular, those with a high-risk profile such as triple positivity.\textsuperscript{8}

Antiphospholipid syndrome may be primary or secondary in the setting of an underlying autoimmune disease, most often SLE. Approximately 1 in 5 APS patients has SLE.\textsuperscript{4} In SLE, hydroxychloroquine use is recommended in all the patients and can be considered in primary APS cases with refractory disease.

A rare but severe complication of APS is known as catastrophic antiphospholipid syndrome. Patients present with thrombosis affecting 3 or more organs in the span of 1 week. The condition has a mortality that approaches 50% and requires rapid recognition and treatment.\textsuperscript{2,10} Guidelines recommend treatment with high-dose steroids, intravenous heparin, and plasma exchange (and/or intravenous immunoglobulins).\textsuperscript{5,11} In patients with poor response to initial therapy, additional agents such as rituximab for B-cell depletion, eculizumab for complement inhibition, and pulse dose cyclophosphamide in SLE patients are considered.\textsuperscript{4,5,6,11}
Females of reproductive age are a unique population in APS. Estrogen-based contraception should be avoided. Appropriate anticoagulation treatment during pregnancy and postpartum is crucial as these are hypercoagulable states. Warfarin is teratogenic and should be switched to LMWH or unfractionated heparin during pregnancy. Low molecular weight heparin is preferred for practical reasons. Warfarin can be restarted postpartum.5

Antiphospholipid syndrome should be considered in the setting of early-age stroke, atypical thrombosis, and pregnancy morbidity. Anticoagulation is the mainstay of treatment. Immunosuppressive therapy may be beneficial in nonthrombotic manifestations of APS.

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REFERENCES

Correct Answers: 1. c. 2. b. 3. e. 4. a. 5. d.