CLINICAL VIGNETTE

45-Year-Old Woman with Antiphospholipid Antibodies

Olga Popel, MD, MBA

Case

A 45-year-old Caucasian female was found to have a positive ANA 15 years prior while living in Europe. It is unclear why the test was ordered as the patient she did not have arthralgias, facial or body rashes, hair loss, lack of energy, Raynaud's, dry eyes, dry mouth, or mouth sores. Further serological evaluation included, high titers of cardiolipin and beta-2-glycoprotein antibodies. Nine years prior she was started on Hydroxychloroquine but did not recall having any symptoms that required medical evaluations. Her first pregnancy 14 years prior ended in fetal death at ten weeks. During her second pregnancy three years later, she was treated with a blood thinner, "Claxon" with her daughter delivered by Caesarean section. A third pregnancy also ended at ten weeks. She was advised to start a baby aspirin, but did not comply.

She moved to the California six months ago and developed shoulder pain with decreased range of motion after morning furniture and presented to establish care with a rheumatologist.

She has no other medical problems. Her only surgeries were a tonsillectomy and the Caesarean section.

She smoked about a quarter pack of cigarettes a day between 1996 and 1998 and rarely drinks alcohol.

Family history is notable for her father with lupus nephritis and a female paternal cousin also with lupus.

Her only medication was hydroxychloroquine 200 mg daily.

Initial labs in 2023: WBC 7.5, Hgb 10.8 gms, MCV 66.5, platelets 175,000. Normal CMP, C3, C4, CRP. ESR 9 mm/hr Negative nDNA, SS-A/B, ENA. Beta-2-glycoprotein IgG >112.0, beta-2-glycoprotein IgM >112.0, beta-2-glycoprotein IgA >65.0Cardiolipin IgG >112.0, cardiolipin IgM >112.0, cardiolipin IgA >65.0

7/05/2023: WBC 7.41, Hgb 10.8 gms, platelets 149,000. Normal CMP, magnesium, TSH, T4. ESR 4 mm/hr B12 317 LDL 85, triglycerides 177. Negative TPO. Vitamin D 23.2 (normal range 30-100)

5/23/2015: WBC 8.39, Hgb 10.8 gms, platelets 99,000. Lupus anticoagulant + at 68.3, beta-2-glycoprotein IgG 40.5, beta-2-glycoprotein IgM 161 CRP 2.20

Physical Exam: BP 109/71 Pulse: 86 Respirations: 16
Temperature: 36.9 degrees Celsius (98.4 degrees F.) SpO2 95% Weight: 171 lb 12.8 oz (77.9 kg) Height: 5' 4.17"
BMI: 29.33 kg/m2
HEENT: PERRLA. Normal saliva pool. No adenopathy
LUNGS: clear to auscultation. No wheezes, rhonchi, or rubs
Cardio: S1S2 no murmurs, gallops, or rubs
ABDOMINAL: Normal bowel sounds. Soft, nontender. No hepatosplenomegaly.
PULSES: Full. No bruits.
NEURO: Right-handed. Motor 5/5. Normal light touch. DTR symmetrical. Negative Tinel's sign.
MUSCULOSKELETAL: Cervical spine restricted movement in all planes. No synovitis in the hand or feet. Shoulders had abduction bilaterally decreased to 80 degrees.
SKIN: no malar rash. No hair thinning or alopecia.

Autoantibodies that interfere with the ability of certain clotting factors to bind to phospholipids have been found in patients who have systemic lupus erythematosus as well as in patients without lupus. Antiphospholipid syndrome is a clinical scenario with venous and/or arterial thrombosis, fetal death or distress, and thrombocytopenia.[1] Primary antiphospholipid syndrome occurs independently of autoimmune diseases and represents 50% of cases. Antiphospholipids syndrome also occurs in association with underlying systemic autoimmune disease, most frequently systemic lupus erythematosus. About 35 % of lupus patients will have antiphospholipid antibodies.[2] These antibodies can also be found in healthy patients who do not have the syndrome.

Antiphospholipid antibodies are a cache of immunoglobulins directed against phospholipids and phospholipid-binding proteins.[3] Antiphospholipid antibodies include anticardiolipin antibodies (IgG, IgM, or IgA), anti-beta-2-glycoprotein I antibodies (IgG, IgM, or IgA), and the lupus anticoagulant. The first two are assayed by ELISA and the third found by a clotting test.

The most common features of antiphospholipid syndrome are deep vein thrombosis, thrombocytopenia, livedo reticularis, stroke, superficial phlebitis, pulmonary embolism, fetal loss, and transient ischemic attack.[4] What causes some patients to have arterial clots and others venous is not understood. However, patients with initial arterial clot are more likely to have a second arterial clot. Patients with an initial venous clot are more

likely to have subsequent venous clots. Snedden syndrome refers to occurrence of a stroke in patients with widespread livedo reticularis. Half of patients with Sneddon syndrome have antiphospholipid antibodies.[5]

Pregnancy complications of antiphospholipid syndrome include fetal death after ten weeks gestation, fetal loss before ten weeks gestation, and premature birth due to placental insufficiency or severe preeclampsia. Antiphospholipid antibodies have been found in about 9 percent of patients with miscarriages without diagnosed autoimmune disease.[6] Patients with antiphospholipid antibodies and preeclampsia have risk of developing catastrophic antiphospholipid syndrome. Patients with a history of miscarriages or thromboses are at higher risk.[7]

Catastrophic antiphospholipid syndrome involves multiorgan failure and generalized thrombosis. The diagnosis requires pathology in 3 or more organs, simultaneously or within seven days, histologic evidence of small vessel thrombosis, and presence of antiphospholipid antibodies.[8]

Antiphospholipid syndrome may include: skin findings such as livedo reticularis and racemose, ulcerations, and "pseudovasculitic" nodules, valvular disease, especially in patients with lupus anticoagulant anticardiolipin IgG; cognitive deficits, hemolytic anemia, pulmonary thromboembolic disease with subsequent pulmonary hypertension, and gastrointestinal ischemia.

The criteria for diagnosing antiphospholipid syndrome include clinical events and laboratory findings. The patient must have a history of large vessel venous thromboembolism, large vessel arterial thromboembolism, microvascular phenomena such as livedo racemose or livedo reticularis, three or more consecutive fetal losses, hematologic abnormalities, and cardiac valve thickening or vegetations.[9] Patients must fulfill three or more weighted criteria.

Laboratory criteria must include two positive tests for antiphospholipid antibodies at least twelve weeks apart, presence of lupus anticoagulant, positive IgG and/or IgM cardiolipin antibodies and/or beta-2-glycoprotein antibodies. Moderate titers are considered to be 40 to 79 units and high titers are equal to or greater than 80 units as measured by enzyme-linked immunosorbent assay (ELISA). Presence of IgA cardiolipin or beta-2-glycoprotein antibodies has not been definitely established as clinically significant. Finding of IgA cardiolipin or beta-2-glycoprotein antibodies also does not establish the diagnosis of antiphospholipid syndrome. The thrombocytopenia associated with antiphospholipid syndrome can vary from 20,000 to 130,000.

Several infections have been associated with the creation of antiphospholipid antibodies. These include bacterial sepsis, syphilis, Lyme disease, tuberculosis, COVID-19, parvovirus, hepatitis A and B, cytomegalovirus, and Epstein-Barr virus amongst others. Parasite such as malaria, *Pneumocystis jirovecii*, and visceral leishmaniasis may also generate antiphospholipid antibodies.

Drug-induced antiphospholipid antibodies have been found with phenytoin, hydralazine, alpha interferon, amoxicillin, oral contraceptives, and propranolol.[10] These are usually IgM and are transient.

Testing performed close to the suspicious clinical event, may have a deceivingly normal aPTT. A normal aPTT or other lupus anticoagulant test in the acute setting should be repeated later.

Antiphospholipid antibody positive patients who have not had any thrombotic history or history of antiphospholipid syndrome-associated pregnancy loss, may not need routine counselling for aspirin or other anticoagulants. Patients who are being evaluated for a suspicious antiphospholipid-related event are generally given warfarin in the acute phase. To prevent recurrent venous thrombosis, warfarin dosed to achieve an INR of 2 to 3.[11] For patients with arterial thrombosis, aspirin is recommended along with warfarin with an INR of 2 to 3. Patients without cardiovascular risk factors, may be treated with warfarin. Generally, anticoagulation is lifelong. In situations where the titer of antiphospholipid antibody is low with other reasons for a venous thromboembolic event could consider terminating the anticoagulation after six months.

Our patients prescribed hydroxychloroquine for arthralgias or perhaps fatigue was not appropriate for high titer antiphospholipid antibody syndrome.

REFERENCES

1. **Lockshin MD**. Anticardiolipin antibodies and lupus anticoagulants. *Curr Opin Rheumatol*. 1990 Oct;2(5):708-11. doi: 10.1097/00002281-199002050-00005. PMID: 2124814.
2. **Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, Buonaiuto V, Jacobsen S, Zeher MM, Tarr T, Tincani A, Taglietti M, Theodossiades G, Nomikou E, Galeazzi M, Bellisai F, Meroni PL, Derksen RH, de Groot PG, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quéré I, Hachulla E, Vasconcelos C, Fernández-Nebro A, Haro M, Amoura Z, Miyara M, Tektonidou M, Espinosa G, Bertolaccini ML, Khamashta MA; Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies)**. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis*. 2015 Jun;74(6):1011-8. doi: 10.1136/annrheumdis-2013-204838. Epub 2014 Jan 24. PMID: 24464962.
3. **Khamashta MA, Amigo MC**. Antiphospholipid syndrome: overview of pathogenesis, diagnosis, and management. In: *Rheumatology*, 6th Edition, Volume 2. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (eds). Elsevier 2015.

4. **Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Lakos G, Tincani A, Kontopoulou-Griva I, Galeazzi M, Meroni PL, Derksen RH, de Groot PG, Gromnica-Ihle E, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quéré I, Hachulla E, Vasconcelos C, Roch B, Fernández-Nebro A, Boffa MC, Hughes GR, Ingelmo M; Euro-Phospholipid Project Group**. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002 Apr;46(4):1019-27. doi: 10.1002/art.10187. PMID: 11953980.
5. **Francès C, Piette JC**. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. *J Autoimmun*. 2000 Sep;15(2):139-43. doi: 10.1006/jaut.2000.0418. PMID: 10968900.
6. **Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D**. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res (Hoboken)*. 2013 Nov;65(11):1869-73. doi: 10.1002/acr.22066. PMID: 23861221.
7. **Gómez-Puerta JA, Cervera R, Espinosa G, Asherson RA, García-Carrasco M, da Costa IP, Andrade DC, Borba EF, Makatsaria A, Bucciarelli S, Ramos-Casals M, Font J**. Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases. *Ann Rheum Dis*. 2007 Jun;66(6):740-6. doi: 10.1136/ard.2006.061671. Epub 2007 Jan 12. PMID: 17223653; PMCID: PMC1954660.
8. **Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, Khamashta MA, Shoenfeld Y; Catastrophic Antiphospholipid Syndrome Registry Project Group**. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12(7):530-4. doi: 10.1191/0961203303lu394oa. PMID: 12892393.
9. **Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, Amoura Z, Andrade D, Andreoli L, Artim-Esen B, Atsumi T, Avcin T, Belmont HM, Bertolaccini ML, Branch DW, Carvalheiras G, Casini A, Cervera R, Cohen H, Costedoat-Chalumeau N, Crowther M, de Jesus G, Delluc A, Desai S, De Sancho M, Devreese KM, Diz-Kucukkaya R, Duarte-Garcia A, Frances C, Garcia D, Gris JC, Jordan N, Leaf RK, Kello N, Knight JS, Laskin C, Lee AI, Legault K, Levine SR, Levy RA, Limper M, Lockshin MD, Mayer-Pickel K, Musial J, Meroni PL, Orsolini G, Ortel TL, Pengo V, Petri M, Pons-Estel G, Gomez-Puerta JA, Raimboug Q, Roubey R, Sanna G, Seshan SV, Sciascia S, Tektonidou MG, Tincani A, Wahl D, Willis R, Yelnik C, Zuily C, Guillemin F, Costenbader K, Erkan D; ACR/EULAR APS Classification Criteria Collaborators**. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. *Arthritis Rheumatol*. 2023 Oct;75(10):1687-1702. doi: 10.1002/art.42624. Epub 2023 Aug 28. PMID: 37635643.
10. **Cervera R, Asherson RA**. Clinical and epidemiological aspects in the antiphospholipid syndrome. *Immunobiology*. 2003;207(1):5-11. doi: 10.1078/0171-2985-00213. PMID: 12638896.
11. **Keeling D, Mackie I, Moore GW, Greer IA, Greaves M; British Committee for Standards in Haematology**. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol*. 2012 Apr; 157(1):47-58. doi: 10.1111/j.1365-2141.2012.09037.x. Epub 2012 Feb 8. PMID: 22313321.