CLINICAL VIGNETTE

Antiphospholipid Syndrome

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Case Report

A forty-nine year old previously healthy male presented to the Emergency Room with worsening mental status over two days. There was no history of trauma, smoking, drug use or any other antecedent illness. He had some headache and transient mild chest pain and physical exam was remarkable for splinter hemorrhages and osler nodes. WBC and platelets counts were slightly below normal, at less than 3000 for WBC and the sedimentation rate was elevated at 48 mm/hr. PTT was prolonged at 76.3 s and urinalysis showed microscopic hematuria. EKG was normal but troponin 1 was slightly positive at 5.7. Echocardiogram including trans-esophageal echocardiogram [TEE] showed thickened mitral valve leaflets with vegetations versus thrombotic deposits with minimal mitral regurgitation. MRI scan of brain showed multiple infarct like lesions which appeared to be embolic and mainly in Lt Parietal lobe as well as left insula. Multiple blood cultures were negative and subsequent workup was also negative for other infectious etiologies.

The diagnosis of embolic strokes with Libman-Sacks endocarditis was established with positive tests for anticardiolipin antibodies, IgG(166), IgM(89),IgA(32), Anti Beta 2 Glycoprotein Ab IgG (>150), IgM (57), IgA (30). D Dimer was elevated at 152 and DRVVT was borderline. Other hypercoagulable workup was negative except for a slightly decreased Protein S at 57%. ANA was 1:1280, homogenous pattern with negative ds DNA and positive SSA at 159 and SSB 47. Other rheumatological blood tests were negative. The patient did have a positive RPR on admission, and FTA-ABS was non-reactive. Additional history suggestive of amaurosis fugax was obtained. Other workup for pancytopenia was negative and follow-up antiphospholipid antibody titers remained positive.

The patient was anticoagulated with heparin and bridged to warfarin, with target INR of 3.0. He was also started on low dose aspirin. His neurological symptoms resolved and repeat brain MRI/MRA showed no new lesions. Follow up trans-esophageal echocardiogram showed improvement of mitral valve thickening and myoview was normal. He was treated with beta blockers and a statin. He had an episode of flank pain and gross hematuria after discharge with a supra therapeutic INR which resolved with correction. He met criteria for SLE or Sjogren like syndrome and started on hydroxychloroqine. He has been maintained on warfarin and baby aspirin without any subsequent events. He continues to have persistent high antibodies titers and mild pancytopenia.

Antiphospholipid syndrome is characterized by thrombotic events involving either the venous or arterial system and in some cases causing pregnancy morbidity in presence of antiphospholipid antibodies. This patient's presentation of Antiphospholipid syndrome involved thrombotic vegetation of cardiac valves (Libman Sacks endocarditis) in presence of anti-phospholipid antibodies. Although these patients can have CNS abnormalities through various mechanisms, in this case it was attributed to embolic infarcts. Thrombotic infarcts and vasculopathies can also cause neuropsychiatric symptoms. Cardiac involvement with valvular disease, coronary events and pericardial effusions has been reported and this patient had NSTMI at time of diagnosis. Microscopic hematuria and proteinuria was also present which could be related to endocarditis or SLE like syndrome. Subsequent gross hematuria and pain could have been embolic in nature but was more likely related to over anticoagulation. Nephiritic complications have been often described. He also had mild thrombocytopenia, which is often seen in APS[1, 2].

Anti-phospholipid antibodies are not really directed against phospholipids but to the phospholipid binding plasma proteins These antibodies bind to epitopes exposed or generated when these proteins bind to phospholipids. False positive RPR and VDRL occur because these are serological tests performed using cardiolipin. Specific antitreponemal tests do not show false positivity[3].

Tests to identify antiphospholipids antibodies include Anticardiolipin antibodies, Anti beta 2 glycoprotein antibodies both of which are enzyme linked immunosorbent assay (ELISA) tests. Lupus anticoagulant activity, a functional clotting assay, is routinely performed. These tests vary in their sensitivity and specificity. Specific tests for Antibodies towards prothrombin, AnnexinV, phosphatidylserine and phosphatidylinositol are not reliably tested by current assays and are therefore not recommended[3].

Lupus anticoagulant is a misnomer as it is a risk factor for thrombosis and does not act as anticoagulant in vivo. Some of the Antiphospholipid [aPL] antibodies act as LA by blocking in vitro assembly of prothrombin complex, resulting in prolongation of aPTT, dilute Russell viper venom time and kaolin clotting time and infrequently prothrombin time. In vitro coagulation assays abnormalities can be reversed by incubating patient plasma with hexagonal phase phospholipid.

Beta 2 glycoprotein- 1 (apolipoprotein H) is naturally occurring inhibitor of coagulation and platelet aggregation by maintaining free protein S level and activity as well effecting certain aggregation associated receptors binding on platelets. Therefore antibodies to Beta 2 glycoprotein increases clotting risk[4, 5]. Anticardiolipin Ab assay detect antibodies directed towards cardiolipin as well as beta 2 glycoprotein and other targets. IgG Antibodies confer the highest risk although IgM and IgA Antibodies have also been associated with APS.

Antibodies with cross reactivity against prothrombin may also increase bleeding risk with anticoagulation at high levels although they primarily increase clotting risk. The LA test is a clotting based assay and should be collected before start of anticoagulation. Drug induced (procainamide and hydralazine) antiphospholipid antibodies generally do not significantly increase clotting risk[6, 7].

Although there may be cross reactivity for different antigens discussed, testing is limited to aCL and anti bet2 GPI and LAC. Prolongation of PTT, decreased platelet count and increase of FDP in various forms are often noted. The high level of antibody titers and multiplicity of positive antibody tests for aPL antibodies in the setting of APS clinical syndrome supports the diagnosis as does persistence of antibodies beyond 6 -12 weeks. Although slight increase of antibodies can be seen with certain medications and infections, all the criteria need to be met to establish the diagnosis and exclude diagnosis of other clinical syndromes. There are multiple mechanisms of action of these antibodies on coagulation through protein C and S and annexin V, platelets, serum proteases, tissue factors and through impaired fibrinloysis. In addition to vascular thrombosis aPL also increase vascular tone and tendency for atherosclerosis, fetal loss and neurological damage[6,7].

Besides autoimmune conditions like SLE, other causes of aPL antibodies are not well understood. The second hit hypothesis is favored as mechanism of development of APS with vasculopathies or risk factors that promote vasculopathies[7]. Patients with SLE-like conditions have higher risk of thrombosis as well as women on hormonal replacement, and patients with venous stasis, smoking, hyperlipidemia or hypertension. Patients with prior vascular events are more likely to have secondary events than previously asymptomatic individuals[8].

Initial treatment is similar to other thrombotic events with heparin (fractionated or unfractionated) anticoagulation bridging to warfarin, although lab testing results with underlying prolonged PTT or abnormal Xa level should be carefully interpreted. Consensus about target INR is lacking and includes targeting INR 3-4 instead of 2-3[9,10]. Also PT testing may be affected by technique and whether standardization is done with the patient's own baseline[11].

Antiplatelet agents are also not clearly established. Studies examining antiplatelet therapy in patients with prior thrombotic events showed minimal if any benefits. Antiplatelet use should generally be guided by cardiovascular risk factors. Addition of low dose ASA is better supported in patients with arterial events, or patients with treatment failure on therapeutic warfarin. Lifelong anticoagulation is generally accepted since secondary events are frequent. However preventive treatment of aPL antibody carriers is not warranted except possibly ASA in patients with SLE. SLE patients with high titers carry high risk of events and should be carefully evaluated. Hydroxychloroquine may directly affect platelet activation by IgG aPL in addition to decreasing titers of antibody production[12,13]. Patients with cardiac valvulopathy due to nonbacterial endocardial deposits are at risk for systemic embolic events (as in this patient). Antiplatelet agents and

warfarin cab prevent clinical events but do not necessarily cause regression of valvular lesions[8].

Thrombocytopenia, in setting of thrombotic events, is usually treated with anticoagulation. Some data suggest other treatments for significant thrombocytopenia in setting of APS with agents like glucocorticoids, intravenous immunoglobulin or rituximab in the case of immune thrombocytopenia. Catastrophic APS involves treating underlying triggering disorders, e.g. infection, anticoagulation, treatment with high doses glucocorticoids and if there are features of microangiopathies IV IG or plasma exchange. In patients resistant to these approaches, addition of anti CD20 antibody (rituximab) or monoclonal Ab to Complement 5 (ecalizumab) has shown dramatic benefits[14,15,16].

REFERENCES

1. **Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA**. Antiphospholipid syndrome. *Lancet*. 2010 Oct 30;376(9751):1498-509. doi: 10.1016/S0140-6736(10)60709-X. Epub 2010 Sep 6. Review. PubMed PMID: 20822807.
2. **Giannakopoulos B, Passam F, Ioannou Y, Krilis SA**. How we diagnose the antiphospholipid syndrome. *Blood*. 2009 Jan 29;113(5):985-94. doi: 10.1182/blood-2007-12-129627. Epub 2008 Aug 28. Review. PubMed PMID: 18755986.
3. **Roubey RA**. Autoantibodies to phospholipid-binding plasma proteins: a new view of lupus anticoagulants and other "antiphospholipid" autoantibodies. *Blood*. 1994 Nov 1;84(9):2854-67. Review. PubMed PMID: 7949161.
4. **Ginsberg JS, Wells PS, Brill-Edwards P, Donovan D, Moffatt K, Johnston M, Stevens P, Hirsh J**. Antiphospholipid antibodies and venous thromboembolism. *Blood*. 1995 Nov 15;86(10):3685-91. PubMed PMID: 7579334.
5. **Santoro SA**. Antiphospholipid antibodies and thrombotic predisposition: underlying pathogenetic mechanisms. *Blood*. 1994 May 1;83(9):2389-91. PubMed PMID:8167328.
6. **Levine JS, Branch DW, Rauch J**. The antiphospholipid syndrome. *N Engl J Med*. 2002 Mar 7;346(10):752-63. Review. PubMed PMID: 11882732.
7. **Bick RL**. Antiphospholipid thrombosis syndromes. *Hematol Oncol Clin North Am*. 2003 Feb;17(1):115-47. Review. PubMed PMID: 12627666.
8. **Muscal E, Brey RL**. Neurologic manifestations of the antiphospholipid syndrome: integrating molecular and clinical lessons. *Curr Rheumatol Rep*. 2008 Jan;10(1):67-73. Review. PubMed PMID: 18457615.
9. **Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, Laskin C, Fortin P, Anderson D, Kearon C, Clarke A, Geerts W, Forgie M, Green D, Costantini L, Yacura W, Wilson S, Gent M, Kovacs MJ**. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003 Sep 18;349(12):1133-8. Erratum in: N Engl J Med. 2004 Jul 8;351(2):200. *N Engl J Med*. 2003 Dec 25;349(26):2577. PubMed PMID: 13679527.
10. **Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T**. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005 May;3(5):848-53. PubMed PMID: 15869575.
11. **Moll S, Ortel TL**. Monitoring warfarin therapy in patients with lupus anticoagulants. *Ann Intern Med*. 1997 Aug 1;127(3):177-85. PubMed PMID: 9245222.
12. **Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR**. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995 Apr 13;332(15):993-7. PubMed PMID: 7885428.
13. **Ruiz-Irastorza G, Hunt BJ, Khamashta MA**. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2007 Dec 15;57(8):1487-95. Review. PubMed PMID: 18050167.
14. **Atsumi T, Furukawa S, Amengual O, Koike T**. Antiphospholipid antibody associated thrombocytopenia and the paradoxical risk of thrombosis. *Lupus*. 2005;14(7):499-504. Review. PubMed PMID: 16130503.
15. **Lockshin MD, Erkan D**. Treatment of the antiphospholipid syndrome. *N Engl J Med*. 2003 Sep 18;349(12):1177-9. PubMed PMID: 13679533.
16. **Erkan D, Cervera R, Asherson RA**. Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum*. 2003 Dec;48(12):3320-7. Review. PubMed PMID: 14673983.

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