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Antiphospolipid Syndrome in HIV Infection — Report on Four Cases and Review of Literature

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The antiphospholipid antibody syndrome (APS) is a thrombophilic syndrome, defined by the presence of elevated antiphospholipid antibody (aPL). The presence of elevated aPL has been described during the course of human immunodeficiency virus (HIV) infection but has not been commonly associated with thrombosis. Herein, we briefly describe four HIV-infected patients, two children and two adults, with vascular manifestations suggestive of the APS and elevated aPL. In addition, we reviewed the literature regarding APS and APS in the context of HIV infection.

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Background

The antiphospholipid antibody syndrome (APS) is a thrombophilic syndrome, defined by the presence of elevated antiphospholipid antibodies (aPL). Although the presence of elevated aPL has been described during the course of adult human immunodeficiency virus (HIV) infection [3–8], it has not been associated with HIV disease progression, intercurrent infections, malignancy, or positive Venereal Disease Research Laboratory (VDRL) test [9, 10]. During the course of pediatric HIV infection a number of conditions are seen that are present in the APS, such as stroke, cerebral infarction, dementia, thrombocytopenia, and Coombs positive hemolysis, but these have not been evaluated for their association with aPL [11]. Herein, we describe briefly four HIV-infected patients, two children and two adults, with vascular manifestations suggestive of the APS and elevated aPL.

Case Reports

Case 1

A 7-year-old boy with perinatally-acquired acquired immunodeficiency syndrome (AIDS) developed an acute onset of livedo reticularis on the trunk and upper extremities. He was diagnosed with AIDS at 4 years of age when he developed *Pneumocystis carinii* pneumonia (PCP). At diagnosis, his T-helper count was 0 cells/mm^3. Anticardiolipin antibodies (aCL) were elevated: Immunoglobulin G (IgG) 31.0 anti-phospholipid unit (GPL) units (normal 0–22.9) and IgM 16.7 anti-phospholipid unit (MPL) units (normal 0–10.9). A skin biopsy showed interface dermatitis. Three months after the onset, the rash resolved completely; IgG aCL was 9.0 GPL units and IgM aCL 9.2 MPL units. There were no recurrences of livedo reticularis until his death 3 years later.

Case 2

A 4-year-old boy with perinatally acquired HIV infection presented with an acute onset of pain in the left thigh and a limp. He was diagnosed with HIV infection at 4 months of age following an evaluation for perinatal exposure to HIV. At diagnosis, a T-helper cell count was 710 cells/mm^3. A technetium 99m bone scan revealed decreased blood flow to the left femoral head. There was marked clinical improvement within 1 week of the onset and complete resolution of limp within 2 weeks. One month later, aCL was measured and found to be elevated: IgG aCL 46.1 GPL units and IgM aCL 13.3 MPL units. Three months later, IgG aCL was 34.0 GPL units and IgM aCL 8.5 MPL units. There were no recurrences of the limp until his death 16 months later.

Case 3

A 26-year-old male with heterosexually acquired HIV infection was admitted to the hospital with cough and fever. He was diagnosed with HIV infection 8 years prior to this. His T-helper cell count 3 months prior to admission was 10 cells/mm^3. A computed tomography (CT) scan of the abdomen revealed an inferior vena cava thrombus. A ventilation-perfusion scan was suggestive of pulmonary emboli. A coagulation evaluation included a protein S of 58 U/dl (normal 59–147 U/dl activity), protein C of 46 U/dl (normal 70–140 U/dl). Antithrombin III was 140 mg/l (normal 80–120 mg/l). IgG aCL was 46 GPL and IgM aCL 10 MPL. A Greenfield filter was placed into the inferior vena cava, anticoagulation with warfarin was started, and the patient was discharged home in stable condition.

Case 4

A 26-year-old male was admitted to the hospital for evaluation of a 2-day history of sudden onset of sharp chest pain, difficulty breathing, fever, and chills. On the third hospital day, the patient developed massive hemoptysis. He underwent a lung resection of an infarcted segment of the right lower lobe because of persistent bleeding. Bacterial, fungal, and viral cultures from the surgical specimen were negative. There was no evidence of neoplasm within the hilar lymph nodes but there was enlargement with lymphocyte depletion. The patient was found to be HIV-infected. T-helper cell count was 110 cells/mm^3. Serum IgG was elevated (3050 mg/dl), IgA was 360 mg/dl, and IgM was 105 mg/dl. Lupus anticoagulant tests were negative. An erythrocyte sedimentation rate was 100 mm/h. Protein S was 85 U/dl and protein C was 65 U/dl. Antithrombin III was mildly elevated (165 mg/l). IgG aCL was 52 GPL and IgM aCL was 4.9 MPL. A VDRL screen was negative. The patient was treated with warfarin and had no further thrombo-embolic events during the next 6 months of follow-up.

Table 1
The Antiphospholipid Syndrome

Venous Thrombosis	Arterial Thrombosis
– Deep venous thrombosis	– Strokes
– Mesenteric, renal, hepatic, splenic, caval thrombosis	– Transient ischemic attacks
– Cerebral venous thrombosis	– Multi-infarct dementia
Thrombocytopenia	Neurological Abnormalities – Guillian-Barré syndrome – Transverse myalitis – Chorea
Coombs + hemolysis	Livedo reticularis
Recurrent fetal loss	Addison's disease
Valvular heart disease	Avascular necrosis of bone

Clinical Presentation and Complications of APS

The APS is associated with a variety of clinical disorders, as shown in Table 1. aPL also are of considerable clinical importance because of their association with the APS. aPL may occur in association with autoimmune diseases, most commonly SLE, but may also be associated with various other conditions as shown in Table 2.

Complications associated with the APS are thrombosis, including gangrene, myocardial infarction, stroke, recurrent pregnancy loss, or thrombocytopenia. Vasculitis, rashes, and arthralgia are also noted in approximately 50% of patients. Other manifestations include migraine headaches, livedo reticularis, hemolytic anemia, cardiac abnormalities, e.g., bland verrucous endocardial lesions causing mitral valve thickening, amaurosis fugax, and transient neurological deficit.

Pathogenesis of aPL and Thrombosis

The mechanism of the association of aPL with thrombosis has not been established [4, 14, 19]. Proposed mechanisms include interference with the activation and function of protein S [20, 21], inhibition of prostacyclin production and induction of platelet activation [22], interference with the formation of heparin-antithrombin III complexes [23], and reduced expression of the potent anticoagulant protein, annexin-V [24]. Initially it

Table 2
Clinical Conditions Associated with Antiphospholipid Antibodies

Autoimmune Diseases	Infections
Systemic lupus erythematosus (SLE)	*M. tuberculosis*
Rheumatoid arthritis	*M. leprae*
Scleroderma	*T. pallidum*
Dermatomyositis	*B. burgdorferi*
	P. carinii
	Human immunodeficiency virus (HIV)
	Epstein Barr virus (EBV)
	Rubella virus
Drug Exposure	**Lymphoproliferative Disorders**
Clorpromazine	Hairy cell leukemia
Procainamide	Lymphoma
Hydralazine	Macroglobulinemia
Quinidine	
Phenytoin	

was thought aPL were simply markers for other antibodies [19] but recent observations suggest that aPL are not merely epiphenomena of thrombi arising for other reasons, but in some cases play a direct role in initiation, propagation, or maintenance of thrombosis. It is possible that in some circumstances, aPL might somehow augment or maintain a thrombotic process that is underway. For example, conformational changes of platelet phospholipids may influence β_2-glycoprotein I (β_2GPI) binding and activity. Anionic phospholipids are asymmetrically located in the inner leaflet of the resting platelet membrane. Loss of this asymmetry occurs upon platelet activation, and newly exposed anionic phospholipids may then bind the IgG aPL antibodies [25]. It appears that when β_2GPI is bound to anionic phospholipids or other suitable surfaces, a cryptic epitope is then expressed, and antibodies then bind to the β_2GPI-phospholipid complex [26].

The recently popularized concept of hexagonal phase configuration is thought to arise *in vivo* in response to membrane damage [27]. Normally, polar heads of the phospholipids exist on the external surface, whereas in the hexagonal phase, lipid cylinders exist with internal aqueous channels formed by polar head groups [28]. Lupus anticoagulant (LA) and aPL may represent antibodies generated in response to these neoantigens. aPL have been generated in mice immunized with hexagonal phase phospholipid [29]; these antibodies reacted with cardiolipin and possessed functional LA activity. Recently a summary of thrombogenic mechanisms of aPL has been reported [30].

Laboratory Evaluation of aPL

aPL are detected through their interaction with negatively charged phospholipids, such as, cardiolipin or phosphatidylserine [31, 32]. Targets of aPL include anionic phospholipids and phospholipid binding plasma proteins, prothrombin, protein C, protein S or β_2 glycoprotein [8, 10–12]. β2GPI inhibits the intrinsic pathway of blood coagulation, adenosine diphosphate-mediated platelet aggregation, and prothrombinase activity associated with activated platelets [12, 33].

aPL are detected with lupus anticoagulant assays, aCL assays, and biologic false positive serologic tests for syphilis. It is not yet clear which antigens are recognized by aCL. aCL may directly recognize phospholipids or may recognize phospholipid-associated proteins, such as β2GPI antigen or combinations of phospholipid-protein antigens [12, 13]. Although aCL may be associated with the presence of a lupus anticoagulant, the level of lupus anticoagulant activity does not correlate directly with the aCL level [8, 9]. In autoimmune-associated, i.e., secondary aPL, high titer IgG antibodies predominate and anticoagulant activity is often present [4, 14]. In infection-induced and drug-induced aPL, IgM antibodies predominate, where they are generally low in concentration and anticoagulant activity is rare [1, 2, 4].

HIV-aPL Association

Several studies reported the presence of various coagulation test abnormalities in HIV patients but the significance of these laboratory anomalies has not been established [3, 7, 9, 10, 23, 35]. Despite the recognition of potentially prothrombotic coagulation changes in HIV infection, there are only few reports of HIV-infected adults with various forms of thrombosis [11, 15, 36–38]. It is possible that some patients may have only nonspecific increases which are associated with hypergammaglobulinemia, but not thrombosis [5–7].

No explanation for the elevation of aCL in HIV infection is yet known. Possibilities include elevated titers of various self-antigens attributed to B-cell functional abnormality and refractory T-cell-independent B-cell activation. Furthermore, elevated IgG aCL in HIV-infected patients who have various infections could result from polyclonal activation of B cells. Several groups tried to define an association between these laboratory anomalies and underlying conditions in HIV including PCP [17], duration of HIV infection, CD4 cell counts, or zidovudine use [35] but there is as yet no consensus on this matter.

Treatment of APS

The optimal treatment of patients with APS has not been defined [40]. Depending upon the severity of the clinical manifestations, patients may need no treatment or may need anticoagulants or immunosuppression. Approximately 10%–15% of patients with aPL will develop APS. Because of the uncertainty in predicting when thrombotic events might occur, most investigators do not treat asymptomatic patients prophylactically except in situations when the risk of thrombosis is increased, such as during prolonged immobilization or when surgery is anticipated.

In patients with significant thrombotic events, anticoagulation with warfarin is recommended [41]. Treatment should continue with warfarin or low molecular weight heparin for life or until aPL are undetected for more than 6 months. Recurrences have been reported to occur as late as 8 years after a thrombotic event [42]. The role of steroids, immunosuppressants, or aspirin is uncertain in this patient population. In patients with multisystem involvement these agents and plasmapheresis may have a role [43].

Conclusions

Our report is one of few to report the development of thrombosis in HIV-infected adults and children and points out to an association with the presence of elevated aPL. The significance of aPL in HIV infection needs to be determined. It has been

suggested that HIV-infected patients might have antibodies associated with anti-endothelial cell antibodies and may form a distinct group of patients with a low thrombotic complication tendency. Further studies are warranted to define the specificity of aPL in HIV infection.

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