Recurrent Pulmonary Thromboembolism in a Patient with Systemic Lupus Erythematosus and HIV-1 Infection Associated with the Presence of Antibodies to Prothrombin: A Case Report

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Background. The coexistence of human immunodeficiency virus (HIV) infection and systemic lupus erythematosus (SLE) is being increasingly reported and, because of the immunological disturbances demonstrated in HIV-infected patients, diagnostic and therapeutic difficulties may arise when the 2 conditions coexist. Antiphospholipid antibodies are demonstrable in patients with both conditions, but clinical manifestations of the antiphospholipid syndrome (APS) in HIV-infected patients, although reported, are uncommon.

Methods. We describe a patient with HIV infection and SLE who manifested 4 episodes of deep vein thrombosis (DVT) complicated by pulmonary embolism. Enzyme-linked immunosorbant assay was used to test for the presence of antiphospholipid antibodies, including anticardiolipin antibodies, anti–β2-glycoprotein I antibodies, and antiprothrombin antibodies (anti-PT). Additionally, we performed a computer-assisted search of the literature (via the Medline database) to identify all reported cases of HIV infection plus SLE.

Results. We document the case of a 35-year-old African woman with HIV infection and SLE who developed recurrent episodes of DVT and pulmonary embolism in the presence of anti-PT and discuss in depth the pathogenic role of these antibodies and the clinical challenges posed to clinicians by the coexistence of HIV and SLE in the same patient.

Conclusions. Immunological reconstitution in HIV-infected patients contributes to the appearance of multiple autoimmune conditions, including SLE and APS. The recognition of the coexistence of these autoimmune disorders in HIV-infected patients has important implications in the treatment of and prognosis for these individuals.

Since the introduction of HAART in the late 1990s, the clinical spectrum of HIV infection has changed dramatically. During the past few years, increased recognition of a variety of autoimmune disturbances has emerged because of better control of HIV disease, which is associated with the constant antigenic viral stimulation and immune reconstitution that follows an increase in the number of circulating CD4+ cells [1]. Some of these disorders, such as inflammatory myopathies, systemic vasculitis, and systemic lupus erythematosus (SLE), may coexist with and overlap with the underlying HIV infection.

Several chronic viral infections (such as those due to HIV, hepatitis C virus, and cytomegalovirus) have been shown to generate widely different types of autoantibodies, including antiphospholipid antibody, that are capable of inducing (in some circumstances) thrombosis, as has been observed in patients with antiphospholipid syndrome (APS) [2]. We describe a 35-year-old African woman with HIV infection and SLE who developed recurrent episodes of deep vein thrombosis and pulmonary embolism in the presence of antiprothrombin antibody (anti-PT), and we discuss in depth the pathogenic role of these antibodies and the clinical challenges posed to clinicians by the coexistence of HIV and SLE in the same patient.

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CASE REPORT

The patient, a 35-year-old African woman, received a diagnosis of HIV-1 infection in 1996 and was being treated with a combination of efavirenz, zidovudine, and lamivudine. There were no concomitant infections present at the time of referral. Between October and December 2002, the patient was admitted to hospital on 4 separate occasions with recurrent lower limb deep vein thromboses complicated by pulmonary emboli. It was noted during this period that she had developed symmetrical nonerosive arthritis in the hands and knees accompanied by progressive hemolytic anemia.

Serological investigations showed antinuclear antibody titers of 1:640 and detected antibodies to extractable nuclear antigens (i.e., anti-Smith antibodies, antiribonucleoprotein antibodies, and anti–Sjögren syndrome A/Ro antibodies). Additionally, the level of the C4 component of complement was reduced to <10 mg/dL (normal range, 10–34 mg/dL), results of the Coombs test were positive, and the erythrocyte sedimentation rate was elevated at 97 mm/h. The patient received a diagnosis of SLE, and high-dose oral steroids were added to her regimen once the thrombosis demonstrated anti-PT and that a strong correlation between anti-PT and thrombosis existed. The level of anti-PT diminished after receipt of anticoagulant treatment. The level of anti-PT remained elevated during the subsequent 3-year period. Long-term antimarial therapy was also added to her regimen (chloroquine, 200 mg daily).

Results of ELISA (Cheshire Diagnostics) for detection of anticardiolipin antibody (aCL) and anti–β2-glycoprotein 1 antibody (β2GP1) were negative on several occasions. Results of solid-phase ELISA (Cheshire Diagnostics) for detection of anti-PT were positive, and anti-PT levels remained elevated during each the following 2 years (means of 25.3 AEU during the first year and 30.3 AEU during the second year; normal level, <12 AEU). Despite achievement of an international normalized ratio of 3 during anticoagulation therapy, she nevertheless had 3 additional peripheral venous thromboses, all of which were complicated by pulmonary emboli. Each thrombosis episode was treated with unfractionated heparin and required hospital admission. The level of anti-PT diminished after receipt of appropriate therapy for HIV infection for 2 years; however, titers of β2GP1 became positive 6 months later in 2004.

At the time of writing, the patient has remained healthy while receiving the antiretroviral regimen specified above, warfarin (international normalized ratio, 2.5–3), antimalarial treatment (chloroquine phosphate, 200 mg daily), and prednisone (5 mg daily). The hemoglobin level has remained stable, with an HIV load of <50 copies/mL and a CD4+ cell count of 260 cells/mm³. She is working full-time.

DISCUSSION

Thrombosis and HIV infection. Patients with HIV infection have increased thrombosis risk, with an incidence as high as 8% reported in one series [3]. The causes of thrombosis in patients with HIV infection include opportunistic infection (mainly that due to cytomegalovirus), related malignancies, receipt of drugs (e.g., protease inhibitors, abacavir, and megestrol acetate), injection drug use, acquired hematological disorders (protein S and protein C deficiency, protein C resistance with factor V Leiden mutation, lupus anticoagulant positivity, and aCL), and HIV infection itself. Additionally, there is a significant correlation between thrombotic disease and a CD4+ cell count of <200 cells/mm³ [4–7].

Antiphospholipid and HIV infection. Our patient clearly had an episode of APS that met the definition originally introduced by Harris et al. [8]. APS may be associated with either lupus anticoagulant positivity or the presence of aCL and/or antibodies against β2GP1 [9]. Our case is most unusual in that, during the first years, the only autoantibodies to phospholipid detected were those against prothrombin. Of interest was that the initial antibody response was directed against prothrombin, whereas later, after control of the HIV infection, the usual finding associated with lupus (i.e., detection of β2GP1) was then evident.

Recently, there has been much interest in the detection of anti-PT as a further means of detecting antiphospholipid antibody, which might be useful in patients who had previously been found to be antiphospholipid antibody negative by means of repeated testing with conventional methods. In 1995, Arvieux et al. [10] first designed an ELISA for the detection of anti-PT on γ-irradiated plates. They found a good correlation with lupus anticoagulant positivity, particularly in serum samples from autoimmune patients. In the following year, Puurunen et al. [11] reported that 50% of patients with SLE and thrombosis demonstrated anti-PT and that a strong correlation existed between anti-PT and anti-β2GP1. Anti-PT were usually accompanied by positivity for antibodies against β2GP and almost never seemed to occur alone. These results have subsequently been confirmed by some investigators [12] but not by others. For example, Swadzba et al. [13] found that IgG and IgM anti-PT did not associate significantly with thrombosis in patients with SLE or “lupus-like” disease. In recent reviews, Galli and Barbui [14] and Galli [15] also could not confirm any significant correlation between anti-PT and thrombosis in patients with both SLE and primary APS. However, Salcido-Ochoa et al. [16], in a recent study from Mexico involving patients with SLE and primary APS, found a higher frequency of anti-PT among patients with SLE and primary APS who had thrombosis, but no patients demonstrated anti-PT as the sole antiphospholipid antibody. Their conclusion was that the es-
timation and measurement of the anti-PT response did not provide additional clinical information.

Elevated levels of anti-PT have been reported in 2%–12% of HIV-infected patients, 6%–45% of patients with leprosy, and only 4% of patients with syphilis, as well as <10% of hepatitis C virus–positive serum specimens [17]. The occurrence of anti-PT and, indeed, APS in HIV-infected patients has been well reviewed. Loizou et al. [18] found a high prevalence of anti-PT in a selected group of 100 HIV-infected patients from South Africa. However, de Larrañaga et al. [19] found a lower prevalence of anti-PT in 61 HIV-infected Argentine patients. The frequency of anti-PT, therefore, may be associated with ethnicity.

Lupus anticoagulants were first described in 44% of patients with AIDS and in 43% of asymptomatic HIV-infected individuals (in whom they could be transient) by Bloom et al. [20] in 1986. In 1997, Canoso et al. [21] reported aCL positivity in association with human T cell lymphotropic virus type 3 infection. In 1991, the association between aCL and HIV infection in men who have sex with men was reported [22], and several studies since then have confirmed these original findings. Coll et al. [23] evaluated 84 HIV-infected patients in the same year and found that 59.5% were IgG aCL positive. None of these patients had any thromboembolic phenomena, and no significant differences with respect to sex, risk factors, and stage of the disease were observed. Coll et al. [23] stated that aCL did not appear to be a prognostic marker in HIV-infected subjects but was rather indicative of a state of impaired humoral immunity. Falco et al. [24], in 1993, examined 39 HIV-positive serum samples and 20 aCL- and SLE-positive serum samples and found that, in the HIV-positive specimens, reduced aCL binding capacity was evident if the cofactor (i.e., β2GPI) was added. On the contrary, in SLE-positive serum samples, addition of the cofactor improved the binding capacity of aCL. Falco and colleagues concluded that aCL in patients with HIV infection appeared to have a different specificity than aCL found in patients with SLE. In 1995, Weiss et al. [25] found aCL in 47% of HIV-positive individuals, and other authors have confirmed this association [26–28].

**SLE and HIV infection.** The presence of SLE and HIV infection in the same individual is being increasingly reported as the incidence of HIV increases dramatically, particularly in Africa and Asia. SLE is not uncommon in the black population in South Africa and is associated with significant morbidity and mortality [29]. The coexistence of SLE and HIV infection in the same individual has, in some cases, previously been associated with remissions or amelioration of SLE symptoms occurring with advancing HIV infection during the pre-HAART era, whereas in other cases, it has been associated with “flares” in immune reconstitution, as was observed in patients during receipt of effective HAART [30]. A recent article from South Africa has drawn attention to the significant overlapping clinical and serological features between SLE and HIV infection, and the authors note that this overlap may lead to diagnostic difficulties and, indeed, to the institution of appropriate therapy in the black population of South Africa [31]. Arthralgias and frank arthritis, such as were seen in our patient, are only one such feature which may be seen in both conditions. Nonerosive symmetrical inflammatory arthritis occurs in both conditions, and a differential diagnosis may be impossible clinically. Polyclonal B cell activation is, of course, seen with HIV infection and is responsible for the wide range of autoantibodies observed in persons with this condition. The range even includes antibodies against double-stranded DNA, anti-Smith antibodies, as well as antiphospholipid antibodies. Additionally, autoimmune hemolytic anemia in association with positive results of the Coombs test is increasingly being recognized in HIV-infected patients [32]. Low complement levels are, however, not detected in patients with HIV infection.

The pathogenesis of SLE is still unknown. Several factors, however, have been observed, including a genetic predisposition, as well as environmental influences (including drugs and infectious agents). Endogenous retrovirus infections in humans are capable of integrating in key sites involved in immune regulation, generating an abnormal autoimmune response with the subsequent generation of antiretroviral antibodies that are cross-reactive with common nuclear antibodies [33]. For this reason, it is not uncommon that patients with SLE without previous exposure to retroviral infection may express antibodies against retroviral proteins, including gag, env, nef, and the p24 capsids of HIV-1 and human T cell lymphotropic virus type 3. Deas et al. [34] found that one-third of patients with SLE who had no previous exposure to HIV had a false-positive results of ELISA and Western blot for detection of HIV. Furthermore, some authors have suggested that these antibodies directed against HIV proteins may protect SLE subjects from exogenous infection [33].

Recently, Palacios et al. [30] described a 28-year-old white woman who received simultaneous diagnoses of SLE and HIV infection. This woman had malar rash, adenopathies, ascites, and mesangial glomerulonephritis in the presence of antinuclear antibodies, hypocomplementemia, anti-DNA antibodies, and positive serologic test results for HIV. Additionally, Palacios and colleagues described, in detail, 29 previously documented cases of the coexistence of these 2 disorders. They highlighted the fact that only 18 of 30 diagnoses labeled as SLE fulfilled the classification criteria of lupus. The remaining 12 patients had clinical features induced by HIV that simulate lupus. We are aware of only 5 new reports of patients with HIV infection and SLE that have been published since 2002 [31, 35–37].

Although these 2 diseases traditionally tend to affect different
population groups (homosexual transmission [in the case of HIV infection] and females of childbearing age [in the case of SLE]), with the increasing number of new cases in the heterosexual population and the clinical similarities (malar rash, oral ulcers, lymphadenopathies, fever, sicca symptoms, arthralgias, arthritis, and pancytopenia), it is mandatory to rule out HIV infection in black South African patients with SLE who seem to be pursuing an unsatisfactory course. Currently, during the HAART era, many questions are still unresolved in this field, including the real effect of immunosuppressive treatment for SLE on HIV infection and the effect of HIV treatment on SLE, as well as the pathogenic effects of a chronic viral infection during the course of SLE.

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