Hypercoagulability Due to Protein S Deficiency in HIV-Seropositive Patients

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Abstract

Background: Thrombosis due to a hypercoagulable state is a serious clinical problem in HIV-infected individuals that can lead to life-threatening thromboembolic phenomenon.

Objective: To describe the salient clinical features of dual HIV infection and protein S deficiency.

Design: Retrospective case series.

Subjects: HIV seropositive patients with laboratory-confirmed protein S deficiency.

Results: Three patients had concurrent protein C deficiency. No patient had other primary or secondary risk factors for thrombophilia. Seven subjects had symptomatic thromboembolic manifestations that included deep venous thrombosis (5 subjects), pulmonary embolism (4 subjects), inferior vena cava thrombosis (2 subject), and/or stroke (1 subject). Five additional patients were identified with asymptomatic protein S deficiency. All subjects were African-American.; the mean patient age was 44 years (range, 21 to 60 years). The mean CD4+ cell count was 102 per mm³ (range 0-343), and the mean HIV RNA level was 71,772 copies/mL (range 1,421-554,237 copies/mL). Only three patients were receiving highly active antiretroviral therapy (HAART) at the time of clinical presentation. All symptomatic subjects received heparin, with or without warfarin, for their thromboembolic event and all but one recovered.

Conclusion: HIV-infected patients should be screened for acquired protein S deficiency, which contributes to hypercoagulability and risk of clinical thromboembolic events. Asymptomatic patients with reduced plasma free protein S levels may benefit from aspirin primary prophylaxis.

Keywords: Protein S deficiency, Hypercoagulable, Thromboembolic, HIV/AIDS

Introduction

Infection with the human immunodeficiency virus (HIV) is a type of hypercoagulable state that predisposes to the development of serious and potentially life-threatening thromboembolic disorders such as deep venous thrombosis, pulmonary embolism, and arterial thrombosis. Reported causes of thrombophilia in HIV-infected subjects include antiphospholipid syndrome [1], increased platelet activation [1], elevated homocysteinemia [2], elevated plasma factor VII activity [2], lupus anticoagulant [3], activated protein C resistance [3], protein C deficiency [3,4], and acquired protein S deficiency [4-10]. We herein report our experience with 12 HIV-seropositive subjects with laboratory-confirmed evidence of protein S deficiency, with and without venous or arterial thrombosis, and discuss the diagnostic approach to hypercoagulability in HIV infection, and the clinical management of thromboembolic complications in patients with protein S deficiency.

Patients and Methods

We retrospectively reviewed the medical records of 12 HIV-seropositive patients diagnosed with protein C and S deficiencies at the Lawnwood Regional Medical Center and Heart Institute, Fort Pierce, Florida, from July 2005 through December 2005. All patients were seen by one of the authors (DO), an infectious diseases consultant. Lawnwood Regional Medical Center is a 341-bed, acute care institution and regional referral center for four counties of Treasure Coast, FL.

Hyperoagulability testing was performed on all 12 subjects and included protein C and S assays, lupus anticoagulant, antiphospholipid antibodies, factor V Leiden, antithrombin and homocysteine levels, and prothrombin G20210A mutation. Protein S and C deficiencies were the only coagulopathies detected. All subjects were screened for common risk factors for thrombophilia including family history, immobilization, recent surgery or trauma, pregnancy, malignancy, and thrombogenic medications such as conjugated estrogens or oral contraceptives.

Results

Twelve HIV-seropositive with laboratory-confirmed protein S deficiency were identified, and their clinical features are summarized (Table 1). Isolated protein S deficiency was seen in 9 patients, and combined protein S plus protein C deficiency occurred in 3 subjects. Other primary or secondary risk factors for hypercoagulability were not present. Five patients were asymptomatic, and seven subjects had symptomatic, acute thromboembolic manifestations including: deep venous thrombosis plus pulmonary embolus (4 subjects), inferior vena cava thrombosis (1 subject), deep venous thrombosis plus inferior vena cava thrombosis (1 subject), and stroke (1 subject). Thromboembolic events were diagnosed using venous angiodinograms and high resolution computed tomography (CT) of the lung or abdomen. No patient had previous thrombosis, family history of thrombosis, or prothrombotic conditions. The mean patient age was 44 years (range, 21 to 60 years), and the male:female ratio was 5:7. All subjects were African-American. The mean CD4+ cell count was 102 per mm³ (range 0-343), and the mean HIV RNA level, determined by polymerase chain reaction (PCR) testing, was 71,772 copies/mL (range 1,421-554,237 copies/mL). Only three patients were receiving highly active antiretroviral therapy (HAART) at the time of clinical presentation. All symptomatic subjects received heparin, with or without warfarin, for their thromboembolic event and all but one recovered.

Discussion

Infection with HIV is an independent risk factor for developing venous thromboembolic events. But HIV is also associated with a variety of acquired coagulopathies that increase the incidence of venous and arterial thrombosis, including antiphospholipid-anticardoplipin antibodies, increased platelet activation, elevated serum homocysteine levels, lupus anticoagulant, elevated plasma factor VII activity, activated protein C resistance, protein C deficiency, and protein S deficiency [1-10].

The prevalence of protein S deficiency among persons with HIV infection has been reported in 33% to 94% of patients with HIV infection [4-10]. A study of protein S deficiency among 25 randomly-selected HIV-seropositive men found 19 subjects (76%) with decreased plasma free protein S levels, and this was a statistically significant difference compared to healthy A decrease in protein S levels did not correlate with CD4+ cell count, male controls [9]. CDC class, p24 antigen positivity, zidovudine use, or *Pneumocystis carii* prophylaxis, but a linear correlation was seen with duration of HIV infection. Sugerman and coworkers conducted a prospective laboratory evaluation of 34 HIV-infected children and detected free protein S deficiency in 76.5% of subjects; 55.9% had functional protein S deficiency levels < 2SD below the mean of laboratory controls [6]. These authors found no association between protein S deficiency and CD4+ lymphocyte count, cy (CMV) status, HIV p24 antigen, von Willebrand factor antigen, IgG anti-cardiolipin antibodies, or serum beta-2-microglobulin levels. Similarly, a prospective study of 74 HIV-seropositive men found protein S deficiency in 33% of the cohort, with no significant association seen between protein S deficiency and medication use, opportunistic infection, or CD4+ cell count [7]. Bissuel et al. found plasma free protein S deficiency in 41 of 61 (65%) symptomatic and asymptomatic patients infected with HIV-1, and a significant decrease in plasma free protein S levels was observed in HIVseropositive subjects compared with healthy controls (p = 0.0001) [10]. In contrast to the above authors, however, protein S deficiency was associated with disease severity, namely CD4+ lymphocyte count and CDC class. Sorice and coworkers also found that protein S levels were significantly lower in patients with < 100 CD4+ cells/ul compared to those with higher counts [8].

Protein S deficiency may result in venous thromboembolic phenomena including deep venous thrombosis, pulmonary embolus, inferior vena cava thrombosis, renal or hepatic vein thrombosis, and intracranial venous and dural sinus thrombosis [2,3,11,12], as well as arterial thrombosis leading to stroke [3,13-17]. Still, there is a paucity of data on the incidence of clinical thrombosis in HIV-infected individuals with protein S deficiency. Previous literature studies have reported thrombotic events in 1.52% to 18% of HIV-infected patients with protein S deficiency [3,7], but we found a 58% incidence of clotting complications in our small study cohort. Hassel et al reported an overall incidence of thrombosis of 18% among 74 HIV-infected men, and thrombosis developed in 6.6% of subjects followed prospectively over a median follow-up of 12 months [7]. Development of thrombosis was not significantly correlated with protein S levels. In a case-control study, Mochan and colleagues found protein S deficiency to be an epiphenomenon associated with HIV infection, and it occurred significantly more frequently in HIV-seropositive subjects compared to HIV-seronegative patients with ischemic stroke (p < 0.001) [13]. However, when they included HIV-positive patients without stroke as a control group and compared them with the HIV-seropositive stroke group they found that protein S deficiency was statistically related to HIV infection but not to stroke occurrence. Among 35 black South African heterosexuals with stroke, protein S deficiency was the most common coagulopathy causing clinical clotting abnormalities [14].

Highly active antiretroviral therapy (HAART) has altered the expected frequency of hematologic complications in HIV/AIDS [18]. Today, acquired protein S deficiency is a relative rare complication of HIV in the US among persons taking HAART, but is much more common in developing regions of the world where antiretroviral treatment is not as widely available. Interestingly, however, the use of protease inhibitors (PIs) has been implicated as the cause of a hypercoagulable state in HIV-infected with myocardial infarction [1]. Majluf-Cruz et al. reported a rate of thrombosis of 1.52% (cumulative incidence = 0.30% per year) during the 42-month follow-up period of their study of 28 HIV-positive male homosexuals with venous thrombosis, compared to a rate of 0.33% (cumulative incidence = 0.055% per year; p < 0.001) in 600 patients in the pre-PI era [3]. Protein C and protein S deficiency was detected in nine and two patients, respectively, and lupus anticoagulant in one.

There is almost no literature on the management of HIV-seropositive patients with protein S deficiency and thromboembolism. In subjects with clinical thromboembolic events, we noted a good response to treatment with heparin, with or without warfarin. One previous study noted a high incidence of thrombotic recurrences and hemorrhagic complications using oral anticoagulants, and acetylsalicylic acid secondary prophylaxis was successfully employed [3]. In view of the 58% risk of thromboembolism in our small series of HIV-seropositive patients, we suggest that screening of asymptomatic individuals may be indicated, and those with documented protein S deficiency may benefit from aspirin primary prophylaxis, at least.

The pathogenesis of this HIV-related protein S deficiency is poorly understood. Sorice and colleagues screened for specific anti-protein S antibodies using immunoblotting and showed an overall positivity of 28.6% in HIV-seropositive patients, with a higher prevalence in symptomatic than in asymptomatic patients [8]. Furthermore, the prevalence of positivity for anti-protein S antibodies was higher in HIV-positive subjects with protein S levels < 50%. Another group evaluated the possible role of autoimmune mechanisms in the pathophysiology of HIV-related acquired protein S deficiency and detected anti-protein S antibodies in 31 (56.36%) of 55 HIV-1-positive patients vs. three (20%) of 15 control subjects (p = 0.012) [19]. These antibodies were associated with a significantly low protein S activity compared to controls. Hooper and colleagues postulated that tumor necrosis factor (TNF)-downregulation of protein S may be a mechanism for local and procoagulant activity and thrombosis in patients with HIV/AIDS [20].

Conclusion

HIV-infected patients should be screened for acquired protein S deficiency, which contributes to hypercoagulability and risk of clinical thromboembolic events. Asymptomatic patients with reduced plasma free protein S levels may benefit from aspirin primary prophylaxis.

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| Table 1: | HIV-seropositive patients with protein S deficiency, with and without | | | | | | | | |
|-------------------------|---|--|--|--|--|--|--|--|--|
| thromboembolic features | | | | | | | | | |

| Pt No. | Age (yrs) | Sex | CD4+ count (/mm ³) | Viral load (copies/ml) | HAART* | Thromboembolic features | Anticoagulation | Outcome |
|-----------|--------------|-----|--------------------------------------|---------------------------|--------|------------------------------------|--|-------------------------------|
| 1 | 60 | М | 69 | 159,723 | Yes | DVT ^a ; PE ^b | Heparin/ warfarin ^c | Recovered |
| 2 | 51 | М | - | 1,421 | Yes | IVC ^d thrombus | Heparin | Hematuria; hospice care |
| 3 | 31 | М | 21 | - | No | DVT; PE | Heparin/ warfarin w/ maintenance | Recovered |
| 4 | 37 | F | 132 | 66,761 | No | DVT; PE | Heparin/ warfarin | Recovered |
| 5 | 49 | F | 40 | 28,100 | No | Stroke | Heparin/ warfarin | Recovered |
| 6 | 46 | F | 0 | 554,237 | No | DVT; PE | Heparin | Died |
| 7 | 35 | F | 12 | 33,191 | No | DVT; IVC thrombus | Heparin/ warfarin | Recovered |
| 8 | 44 | F | 343 | 231,411 | No | None | - | - |
| 9 | 44 | F | 24 | 60, 856 | No | None | - | - |
| 10 | 33 | F | 2 | 126,767 | Yes | None | - | - |
| 11 | 48 | Μ | 170 | 43,114 | No | None | - | - |
| 12 | 51 | Μ | 106 | 21,721 | No | None | - | - |

* Highly active antiretroviral therapya Deep venous thrombosis

b Pulmonary embolism

c Heparin followed by warfarin

d Inferior vena cava