Behçet's Disease in an HIV-1-Infected Patient Treated with Highly Active Antiretroviral Therapy

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Behcet's disease is a systemic vasculitis of unknown etiology, characterized by recurrent oral and genital ulcers and uveitis. In addition, cutaneous, articular, neurologic, intestinal, pulmonary, urogenital and vascular manifestations have been observed in these patients [1]. Since the introduction of protease inhibitor-based antiretroviral therapy in 1996, the natural history of human immunodeficiency virus infection changed dramatically, with a decrease in disease progression and mortality. Simultaneously, a wide variety of autoimmune diseases emerged in this group of patients although the number of reports of HIV patients with Behcet's disease seems to remain stable [2]. The diagnosis of Behcet's disease in HIV patients may be difficult to establish, mainly because some clinical manifestations of infections related or not with HIV may mimic the clinical features of Behcet's. We describe here an HIV-infected patient who developed Behcet's disease 10 years after contracting HIV infection. In addition, we review the literature and describe the clinical characteristics of patients with this association [Table 1].

Patient Description

A 38 year old Caucasian man with HIV infection (stage C3) due to a pulmonary tuberculosis episode in 1992 and a transfusional exposure in 1984 for a surgical procedure was admitted. His medical history revealed a previous hepatitis B infection and positive hepatitis C serology, but with normal transaminase levels, negative RNA-HCV in plasma, and normal ultrasound. He started antiretroviral treatment with zidovudine in 1993, presenting ophthalmic Herpes zoster infection a few months later. Didanosine therapy was added in 1994. A new episode of pulmonary tuberculosis was diagnosed by bronchoscopy in 1995. Highly active antiretroviral therapy was begun in 1996 with indinavir, zidovudine and lamivudine, with good response, including CD4 level restoration to 790 cells/mm^3 (nadir CD4 cell count was 39 cells/mm^3 in 1997) and persistent undetectable plasma RNA-HIV viral load. In 2000, antiretroviral treatment was simplified to nevirapine, lamivudine and abacavir due to sustained good virologic control and the presence of lipodystrophy and renal lithiasis.

The patient was referred to our Unit in January 2003 because of oral ulcers that persisted for 1 month without response to acyclovir therapy (1.5 g oral daily for 10 days). In addition, he presented genital ulcers, knee and elbow arthritis, erythema nodosum lesions on the forearms, and retinal vein thrombosis. HLA-B51 was positive, viral load was 19 copies/ml and CD4 count was 480 cells/mm^3. Behcet's disease was diagnosed according to criteria of the International Study Group [3].

Prednisone treatment with 1 mg/kg/day was started with good initial response and a slow tapering of doses. Three weeks later (while on 45 mg prednisone per day), a new flare-up of the disease appeared, with panuveitis, arthritis and folliculitis. Colchicine and cyclosporine A (400 mg per day) treatment was added with transient amelioration of symptoms. During follow-up the CD4 cell count was above 500 cells/mm^3 in all determinations and viral load was < 50 copies/ml in all but one control (690 copies/ml in July 2003). Currently, the patient's clinical condition has remained stable, with neither relapses of Behcet's disease nor HIV symptoms.

Comment

Behcet's disease is a systemic vasculitis of unknown origin. In predisposed patients (i.e., those with HLA-B51), bacterial or viral infection could trigger cross-reactive autoimmune responses resulting in Behcet's disease. The multiple clinical similarities between Behcet's and HIV confront the clinician with a diagnostic challenge. The classical common symptoms of Behcet's disease (recurrent oral aphthous ulcers, genital ulcers, arthritis, uveitis, aseptic meningitis and folliculitis) are routinely found in some HIV-related complications. Cuellar and Espinoza [4] reported that none of the more than 1000 HIV-infected patients attending their clinics fulfilled the diagnostic criteria for Behcet's disease. This limited absence of information is not evidence of the absence of a possible role of HIV infection as a potential pathogenic factor in the development of Behcet's disease at the present time, but it strongly argues against it. Finally, an important aspect in Behcet patients with concomitant HIV infection is immunosuppressive therapy. Clinicians are used to being cautious with the use of immunosuppressive agents in HIV patients, mainly due to the potential

HIV = human immunodeficiency virus

HCV = hepatitis C virus

Table 1. Clinical characteristics of patients with Behcet's disease and HIV infection

Author (year)	Gender/ Age	HIV transmission	Stage	Behcet manifestations	HIV manifestations	Treatment	Behcet clinical response	Outcome
Routy (1989)	M/69	Heterosexual	A2	Oral & genital ulcers, arthritis		Colchicine	Yes	Recovered
Stein (1991)	M/33	Heterosexual	B1	Genital ulcers, folliculitis, uveitis, pulmonary embolism	Lymphadenopathy	Prednisone	Partial	Died*
Buskila (1991)	F/27	Heterosexual	C2	Oral & genital ulcers, arthritis, episcleritis, erythema nodosum	Oral hairy leukoplakia	Thalidomide, prednisone, colchicine, zidovudine	Yes	Recovered
Chahade (1994)	F/31	Unknown	C1	Oral & genital ulcers, DVT, arthritis, positive pathergy, lymphocytic meningoencephalitis	CNS toxoplasmosis, pulmonary TB, oral candidiasis	Prednisone	No	Died**
Belzunegui (1994)	M/25	IV drug abuser	C2	Oral & genital ulcers, arthritis, uveitis, necrotizing vasculitis	Esophageal candidiasis, lymphopenia, pulmonary infection	Prednisone, dapsone, methotrexate, zidovudine	No	Died **
Olive (1999)	F/40	IV drug abuser	A3	Oral & genital ulcers, arthritis, leukocytoclastic vasculitis		HAART	Partial	Recovered
McDonald (2001)	M/61	Unknown	A1	Oral & genital ulcers, uveitis, central retinal artery occlusion, retinal vasculitis		Prednisone, chlorambucil	Yes	Recovered
Mercie (2002)	M/41	Homosexual	A2	Oral & genital ulcers, arthritis		Colchicine, thalidomide, HAART	Yes	Recovered
Cicalini (2004)	F/34	Unknown	A3	Oral & genital ulcers, folliculitis, skin ulcer, erythema nodosum	Keratoconjunctivitis sicca	HAART	Yes	Recovered
Present case	M/38	Transfusion	C3	Oral & genital ulcers, uveitis, arthritis, erythema nodosum, retinal vasculitis, folliculitis	Pulmonary TB, Herpes zoster	Prednisone, cyclosporine, colchicine, HAART	Yes	Recovered

* Not AIDS-related

** AIDS-related

risk of development of opportunistic infections. However, there is some evidence from other scenarios (e.g., solid organ transplant) that these agents are not as deleterious as might be suspected. Currently, anti-tumor necrosis factor-alpha therapies and interferon-alpha are good alternatives for the treatment of severe recalcitrant manifestations of Behcet's disease. HIV healthcare providers should be aware of the potential interactions between immunosuppressive agents used in Behcet's disease and HAART therapy. In general terms, nucleoside reverse transcriptase inhibitors do not alter the plasmatic levels of prednisone or CsA, although tenofovir may increase the nephrotoxic effects of CsA. Among non-nucleoside reverse transcriptase inhibitors, efavirenz can alter (increase or decrease) plasma levels of prednisone and CsA, while nevirapine decreases plasma levels of both drugs. Finally, protease inhibitors increase plasma levels of prednisone and CsA [5].

In conclusion, occasional patients can present with these two chronic disorders that share many clinical features – oral and genital ulcers, arthritis, uveitis, skin lesions and vasculitis – which makes the approach and treatment of these patients difficult. Expanding knowledge on the pathogenesis, management and evolution of HIV and Behcet's disease will shed light on the real link between these diseases and their treatment. Until then, the association between Behcet's disease and HIV must be considered casual.

HAART = highly active antiretroviral therapy
CsA = cyclosporine A

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