Thalidomide-Associated Thrombosis in the Treatment of HIV-Associated Severe Aphthous Disease: A Case Report and Review of the Literature

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Abstract
Venous thrombosis is a well-described complication of thalidomide therapy in patients with multiple myeloma (MM). However, an association between thalidomide use and thrombosis in HIV-positive patients has not been previously described. We present the case of a 48-year-old HIV-positive man who developed a deep venous thrombosis while on thalidomide for the treatment of severe aphthous ulcers. We review the management of severe aphthous disease and the potential adverse effects of thalidomide therapy. We examine the association between thalidomide and thrombosis in patients with MM and discuss how the same relationship may or may not exist in HIV-positive patients. Although the strength of the association between thalidomide use and thrombosis in HIV-positive patients being treated for aphthous disease remains unclear, HIV providers should be aware of the potential risk of thrombosis in all patients receiving thalidomide.

Keywords
HIV, adverse effect, aphthous

Introduction
Recurrent aphthous stomatitis (RAS) is a disease associated with painful oral ulceration that occurs with increased frequency in HIV-positive patients. The etiology of these ulcers is poorly understood. Elevated cytokines likely play a key role as corticosteroids and the anti–tumor necrosis factor (TNF) α agent thalidomide can be useful treatments, and disease recurrences typically stop or diminish in frequency following the initiation of highly active antiretroviral therapy (HAART).1 In patients with advanced HIV, aphthous ulcerations can be severe and recurrent, resulting in wasting and malnutrition. Additionally, oroepophageal disease can impede effective HAART if it precludes swallowing oral medications. A study by Jacobson et al found that 200 mg of thalidomide daily is an effective treatment for RAS in HIV-infected patients.1 However, there are a variety of adverse effects associated with thalidomide use. Thrombosis is one such potential side effect which many HIV providers may be unaware. We describe an HIV-positive patient who developed a lower extremity deep venous thrombosis (DVT) while receiving thalidomide for the treatment of aphthous disease.

Case Report and Case Series
A 48-year-old, previously healthy man presented to our emergency department reporting chest pain and odynophagia for approximately 2 months. His examination was notable for temporal wasting and an absence of lesions in the oropharynx. His cardiac enzymes were negative and his electrocardiogram was unremarkable. A rapid HIV test was performed in the emergency department and was positive. The patient was ultimately found to have a CD4 count of 4 cells/mm3 and an HIV viral load of 7174 copies/mL. He underwent esophagastroduodenoscopy, and multiple clean-base, 2- to 3-cm ulcers were identified in the middle third of the esophagus. Multiple biopsy specimens were collected. The pathology revealed acute inflammation and granulation tissue. Viral, fungal, and acid-fast cultures were negative. Giemsa stain as well as

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immunostains for herpes simplex virus and cytomegalovirus was negative. Additionally, urine histoplasma antigen and serum cryptococcal antigen were both negative.

After infectious etiologies for the ulcers had been excluded, the patient was given a presumptive diagnosis of aphthous stomatitis. He was started on an antiretroviral regimen consisting of abacavir (ABC), nevirapine (NVP), and lamivudine (3TC; all available as a solution), as well as thalidomide 100 mg by mouth daily. Approximately 2 weeks after starting thalidomide therapy, the patient developed left lower extremity swelling, and venous doppler revealed a DVT in the left femoral and popliteal veins. The patient had not been receiving any DVT prophylaxis while on thalidomide. Upon diagnosis of the DVT, thalidomide was discontinued and the patient was started on anticoagulation therapy. He was then prescribed a tapering course of prednisone and the symptoms pertaining to his aphthous ulceration improved.

Upon review of pharmacy records at the HIV clinic where this patient was followed, there were an additional 11 HIV-positive patients identified who had received thalidomide therapy over a 10-year period. One of these patients was receiving thalidomide for the treatment of the tuberculoid form of Hansen disease, and the remaining 10 were receiving the drug for the management of aphthous ulcers. Of these 11 patients, none were diagnosed with a DVT or pulmonary embolism (PE) within our health care system.

Discussion

Fortunately, aphthous ulceration is an uncommon diagnosis in patients infected with HIV in the era of HAART. However, for the few patients with aphthous ulcers, the condition can be debilitating. It has been shown that lower CD4 counts correlate with increased severity of aphthous disease. Therefore, initiation of antiretroviral therapy is crucial in the management of RAS. In our experience, RAS often resolves long before immune reconstitution occurs, implicating inflammatory cytokines rather than immunodeficiency per se. More specifically, TNF-α has been implicated in the pathogenesis of RAS by activating cytotoxic T cells, recruiting neutrophils, and release of stimulating cytokine. Thalidomide, a TNF-α inhibitor, has been shown to decrease odynophagia and to improve the overall quality of life in HIV-positive patients with RAS. Jacobson et al observed that of the 29 patients treated with a 4-week course of 200 mg of oral thalidomide, 55% had complete healing of the ulcerations at 4 weeks, compared to 7% of 29 patients receiving placebo. The main side effects of thalidomide in this study were somnolence and rash. No thromboembolic events were reported. Many experienced HIV providers are aware of the utility of thalidomide in treating RAS but are unaware of the potential risk of thrombosis.

After its association with birth defects was recognized in the 1960s, thalidomide was temporarily removed from the market. The drug was later reintroduced to the US market with a black box warning for its known teratogenicity. Recently, there has been a revival of interest in using this drug to treat multiple myeloma (MM), various other malignancies, and inflammatory dermatologic conditions, including inflammatory forms of Hansen’s disease. As experience with this drug has grown, thromboembolic events have emerged as a significant side effect. The incidence of thrombosis is 3% to 58% among the patients with MM taking thalidomide and 20% among patients with inflammatory dermatoses receiving thalidomide. Comparatively, the rate of thrombosis in the general population is estimated at 1%.8

Single-agent thalidomide therapy in patients with MM has not been found to increase the incidence of thrombotic events. It is the concurrent use of corticosteroids or chemotherapy with thalidomide that appears to significantly increase a patient’s risk of thrombosis. In a study examining 256 patients with MM receiving chemotherapy with or without thalidomide, the patients in the thalidomide arm (400 mg daily) had a greater than 3-fold increased risk of DVT during induction chemotherapy. Risk factors associated with thrombosis in patients with myeloma receiving thalidomide therapy include age, history of PE/DVT, central venous catheter, active infections, diabetes, cardiac disease, immobilization, inherited thrombophilia, hyperviscosity, and concomitant use of high-dose dexamethasone or chemotherapy. It is recommended that patients with myeloma receiving thalidomide be given aspirin if they have ≤1 risk factor and low-molecular-weight heparin if they have ≥2 risk factors, or if they are receiving concurrent dexamethasone or doxorubicin.

A careful review of the literature did not reveal any cases of DVT/PE in HIV-infected individuals receiving thalidomide for the management of aphthous ulcers. The adverse events most commonly described in this population include peripheral neuropathy, rash, somnolence, and neutropenia. There is one case report of an HIV-infected individual who was receiving steroids in addition to thalidomide for treatment of severe erythema nodosum leprosum and developed a DVT. HIV infection is known to be an independent risk factor for venous thromboembolism, with HIV-infected patients being at an approximate 10-fold higher risk than the general population. Factors associated with increased risk of DVT in HIV-positive patients are low CD4 count, hypercoagulable state (protein C and S deficiency, antiphospholipid syndrome, and antithrombin deficiency), opportunistic infections, malignancy, and autoimmune hemolytic anemia. Thus, HIV-infected patients receiving thalidomide may have multiple factors that predispose them to thrombotic events. In the case presented here, the Naranjo probability scale indicates a possible adverse drug reaction.

Thalidomide remains one of the few viable treatment options for the management of severe aphthous stomatitis in the setting of HIV, particularly in those who fail corticosteroids. It is unclear whether patients with HIV who receive thalidomide therapy for RAS are at increased risk of DVT beyond the risk associated with HIV itself. The majority of data available on the thrombotic complications of thalidomide therapy comes from experience with patients with MM. There are several reasons this data may not be directly applicable to HIV-
infected patients. First, thalidomide use alone is not associated with a significant increase in thromboembolic events in patients with MM. Concurrent chemotherapy or steroid use among HIV-positive patients being treated for RAS is infrequent. Second, patients receiving thalidomide for MM treatment typically receive larger doses (400 mg) than patients receiving thalidomide for the treatment of aphthous ulcers (100-200 mg). Finally, the duration of therapy for the treatment of MM is generally longer than the duration of therapy for aphthous disease.

Based on the available data, there is insufficient evidence to recommend routine therapeutic or prophylactic anticoagulation of HIV-positive patients receiving thalidomide for the management of aphthous disease. However, all patients with HIV receiving thalidomide should be educated of the possible thromboembolic complications and should be closely monitored for symptoms of DVT/PE. All HIV providers should be aware of thromboembolism as a potential complication in any patient receiving thalidomide therapy.

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