CASE REPORT

Thalidomide in the concurrent management of recurrent aphthous ulcerations and Kaposi sarcoma in HIV patients with severe immunosuppression

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Introduction

A 37 year old African-American presented to the medically complex patient clinic with recurrence of an oral ulceration on the right lateral border of his tongue (Fig. 1). Patient stated he was experiencing difficulty swallowing foods secondary to pain for the past month and had lost 15 pounds. His medical history was significant for human immunodeficiency virus, hepatitis B and chronic depression. Human immunodeficiency virus was diagnosed in 2000. He had a CD4 count of 145 with a viral load of 82,000. The patient had a history of recurrent aphthous ulceration and had been previously treated with intralesional injections of triamcinalone (5 mg/ml) combined with oral prednisone with limited success. The patient was not on any antiretroviral therapy and had stopped taking medication for the past two years against medical advice. A physical examination revealed mild bilateral cervical lymphadenopathy, no salivary gland enlargement, no thyromegaly, no conjunctivitis. Diffuse, reddish-blue, soft, macular lesions on the posterior left hard palate were observed, with ill-defined margins extending to and involving the soft palate (Fig. 2). There was no tenderness. Two other dark-red nodules were observed on his left

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arm with the same characteristics described for the oral lesions (Fig. 3). Patient did mention that he was diagnosed with Kaposi’s sarcoma a few years ago and was not concerned about the same. He did not report any eye, nasal, genital or rectal lesions.

The viral and fungal cultures for the oral lesion were negative and an incisional biopsy of the ulcer on the lateral border of tongue was consistent with major aphthous ulcer (Fig. 4). The punch biopsy of the palatal lesion was signed out as an endothelial cell lesion consistent with Kaposi’s sarcoma. Additionally, head and neck magnetic resonance imaging (MRI) with contrast solution were ordered for further assessment of respiratory and/or esophageal tract obstruction and did not show any major obstruction of upper airways.

The patient wanted to seek immediate intervention for the ulcerative lesion on the tongue. Given the failure of traditional therapies, a trial of thalidomide for four weeks was initiated. Patient was started on 200 mg of thalidomide once a day for four weeks. The patient reported significant improvement in his symptoms and had no adverse effect due to the drug. The patient reported improvement in his symptoms with an 80% resolution of the lesion after four weeks of therapy. Thalidomide therapy was continued for four additional weeks, which resulted in a nearly complete resolution of the lesions (Fig. 5).
Figure 3  A dark-red macular lesion on the left hand. (For interpretation of the references in colour in this figure legend, the reader is referred to the web version of this article.)

Figure 4  A medium power resolution of an H&E Stain showing a non-specific ulceration.

Figure 5  Significant improvement and resolution of the apthous ulceration eight weeks after institution of thalidomide.
Interestingly, we also noted a significant resolution and shrinkage of the Kaposi sarcoma lesions on his palate (Fig. 6). The patient had refused to start antiretroviral therapy during the eight week course of thalidomide.

Discussion

Thalidomide was first marketed in Germany under the trade name "Contergan" in 1956 then in England in 1958 under the name of "Distaval". With few apparent side effects and little toxicity in animal studies, thalidomide was subsequently marketed in a number of other countries. In 1960, reports of peripheral neuropathy with chronic use began to surface. Growing evidence of severe infant limb defects (phocomelia) and internal organ deformities associated with maternal use of thalidomide soon eclipsed this lesser concern. However, in 1961, McBride had noted an association between thalidomide use by pregnant women and congenital abnormalities. It was estimated that while thalidomide was available, 5000–6000 cases of fetal deformities occurred, with 4000 of these in Germany which were temporally related to thalidomide sales. Thalidomide was withdrawn from the European markets in 1961, while it was pending approval by the FDA.

In 1964, a physician in Israel was confronted with a patient with erythema nodosum leprosum (ENL), one of the many manifestations of leprosy. ENL is characterized by painful skin nodules and nerve damage. With few options, the doctor administered thalidomide, some of which remained in a local hospital pharmacy. Within days, the nodules vanished and did not return as long as the drug was continued.

The success of thalidomide as a therapeutic agent in the treatment of this autoimmune inflammatory condition led other investigators to study thalidomide as a treatment for a number of other indications thought to have an autoimmune or inflammatory basis. Thalidomide was approved by the FDA on July 16, 1998 for the treatment of the cutaneous lesions associated with leprosy. In addition to controlled clinical trials for treatment of leprosy and the mucosal lesions of RAU there are reports of the efficacy of PO thalidomide for other cutaneous lesions such as pyoderma gangrenosum, actinic prurigo, sarcoidosis, and systemic and discoid lupus, as well as for oral mucosal lesions of Behcet’s disease and erosive lichen planus.

The mechanism of action of thalidomide is not fully understood, and it may be related to immune modulation, cytokine inhibition, and/or angiogenesis. Importantly the drug is not mutagenic, cytostatic, or myelosuppressive. The most frequently cited mechanism is TNF-α inhibition. Thalidomide reduces TNF-α production by enhancing the degradation of TNF-α mRNA. In addition, thalidomide produces a variety of effects on the immune system, including downregulating surface adhesion molecules and major histocompatibility antigens on endothelial and epidermal cells, reducing circulating T-helper cells, increasing circulating T-suppressor cells, and modifying integrin receptors and other surface receptors.

In vivo data demonstrate antiangiogenic activity, leading current testing of thalidomide for the treatment of malignancies. Antiangiogenic properties may account for its effect on developing...
Thalidomide has been associated with neurotoxicity characterized as distal lower extremity painful paraesthesia, anesthesia and/or delayed motor weakness, which can be irreversible. The neuropathy results from axonal degeneration without demyelination in the sensory fibers of the lower and occasionally upper extremities. Risk of peripheral neuropathy appears to rise with patient age and cumulative dose of thalidomide, resulting in an incidence of approximately 25% in non-lepromatous patients on chronic thalidomide therapy. This toxicity initially presents as numbness of toes and feet then superficial sensory loss in feet and hands. If therapy is not discontinued, the paresthesias of feet and hands will become permanent and will progress proximally. Universally, sedation or drowsiness and constipation are known side effects of thalidomide, regardless of the application of the drug. Some patients are more sensitive to these effects than others. Other less common clinical side effects include allergic vasculitis, brittle fingernails, decreased libido, dizziness, exfoliative reaction, erythodermic reaction, face/limb edema, galactorrhea, increased appetite, menstruation abnormalities, mood changes, nausea, pruritis, red palms, thrombocytopenic purpura, and xerostomia.

We present an unusual case documenting the use of thalidomide in the concurrent management of recurrent aphthous ulceration and kaposi sarcoma in a patient with severe immunosuppression.

References


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