

Vascular leak syndrome with pleural effusions following treatment with denileukin diftitox for mycosis fungoides

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Citation

K Motaparathi, M Duvic. *Vascular leak syndrome with pleural effusions following treatment with denileukin diftitox for mycosis fungoides*. The Internet Journal of Dermatology. 2006 Volume 6 Number 1.

Abstract

Vascular leak syndrome (VLS) is characterized by hypotension, peripheral edema, and hypoalbuminemia. VLS is usually a mild and easily recognized complication of treatment with denileukin diftitox (DD), a recombinant fusion protein used in the treatment of patients with advanced or recurrent cutaneous T-cell lymphoma (CTCL). We report a case of VLS with pleural effusions in conjunction with congestive heart failure.

INTRODUCTION

Denileukin diftitox (DAB389-IL-2, Ontak[®]) is an FDA-approved treatment for patients with advanced or recurrent CTCL [1]. Denileukin diftitox (DD) is a recombinant fusion protein consisting of diphtheria toxin fragment A (DTA) and human interleukin 2 (IL-2) [2]. CD25 is the β -subunit in the heterotrimeric IL-2 receptor [3]. IL-2 receptors are expressed on malignant lymphocytes in 60% of patients with CTCL [4]. Following internalization, DD is enzymatically cleaved, and DTA is liberated into the cytosol [2]. DTA catalyzes the adenine diphosphate ribosylation of elongation factor 2, inhibiting protein synthesis and leading to cell death [2].

In the pivotal phase III trial, an overall response rate to DD of 30% was observed in patients with mycosis fungoides (MF) or Sézary syndrome refractory to 3 or more treatments or with stage IVa CTCL who failed at least 1 therapy [1]. Talpur et al. demonstrated that 79% of patients with CTCL and high CD25 expression ($\geq 20\%$ of lesional T-cells) had partial clinical responses to DD, while only 20% of patients with low to intermediate CD25 expression ($\leq 20\%$ of lesional T-cells) exhibited partial responses [5].

VLS (or capillary leak syndrome) occurred in 27% of patients treated with DD in the phase I and phase III trials [1,4]. VLS is defined retrospectively by at least 2 of the following 3 signs: hypotension, peripheral edema, and hypoalbuminemia (≤ 2.8 g/dl) [1]. We report a case of VLS with pleural effusions in a patient treated with DD for MF.

CASE REPORT

A 69 year-old Caucasian male with a 20-year history of pruritic skin rashes was diagnosed with stage IIB MF (T3N0B0M0) in 2004. Lesional skin biopsy demonstrated granulomatous MF with CD4⁺ lymphocytes and a clonal T-cell receptor- β gene rearrangement. He received systemic steroids, oral methotrexate, azathioprine, and psoralen plus ultraviolet A (PUVA) with almost complete response but relapsed with tumors. Skin cultures grew methicillin-resistant *Staphylococcus aureus*, treated with antibiotics, and scrapings showed tinea corporis, treated with terbinafine and topicals.

In 2004-2005, he received combined modality therapy [6] consisting of oral isotretinoin 1mg/kg and β -interferon 3 million units three times weekly for four months. He received 3600 Gy of total skin electron beam therapy. A facial tumor with histologic large-cell transformation was treated with local radiation. He was maintained with less than 10% body surface area (BSA) involvement on intermittent topical nitrogen mustard and oral bexarotene, limited to 75-150 mg daily due to uncontrollable hypertriglyceridemia, for the next year.

By February 2007, he had relapsed in the skin. Lesional biopsy revealed 35% CD25 expression. In April 2007, he received DD at a dose of 18 μ g/kg/day for 5 days. At baseline evaluation, BSA involvement was 43% (36% patch and 7% plaque), skin-weighted assessment tool (SWAT; patch x 1, plaque x 2, tumor x 3) was 50%. Serum albumin was 4.5 g/dl (normal: 3.4-5.4 g/dl), and weight was 88.7 kg.

Concurrent therapy included bexarotene 75 mg daily and hydrocortisone 2.5% applied twice daily. On day 14, he developed fever (100.4 °F), chills, hypotension (116/48), cough, 3+ pitting peripheral edema, and weight had increased to 93.9 kg. Hypoalbuminemia (2.2 g/dl) was treated with intravenous albumin 25 g every 6 hours, and he had an elevated brain natriuretic peptide (BNP, 787 pg/mL, normal: 0-99 pg/mL) consistent with congestive heart failure. Intravenous antibiotics were empirically given but were discontinued when cultures were negative. Two days later, he noted increased wheezing. CT scan showed bilateral pleural effusions occupying one-third of the hemithorax by volume, and he underwent thoracentesis, which yielded a transudate with negative cultures. Echocardiography demonstrated a normal ejection fraction (EF) of 60-65%. The likely etiology of the pleural effusions was judged to be VLS in conjunction with congestive heart failure.

He was diuresed with intravenous furosemide throughout hospitalization, returning to a euvolemic state by day 21. At discharge, the patient's skin involvement diminished to BSA of 24.6% and SWAT of 25.3%, his serum albumin level increased to 4.4 mg/dl, and his weight decreased to 87.4 kg. He was subsequently changed to an alternate dosing schedule of weekly DD and received two additional doses. VLS did not recur, but he developed a morbilliform rash, presumably a hypersensitivity reaction to DD. His BSA involvement improved to 8-9% after he received oral prednisone.

DISCUSSION

This is only the second case in which a pleural effusion was observed with DD-associated VLS. In 2000, Railan et al. reported the case of an 80-year-old man with stage IB MF who developed VLS including bilateral pleural effusions due to DD [7].

In the phase I and phase III studies of DD, the most commonly reported adverse effects overall were flu-like symptoms (91%), hypoalbuminemia (83%), elevated hepatic transaminase levels (61%), acute hypersensitivity-type reactions (69%), asthenia (66%), nausea/vomiting (64%), hypotension, and infections (48%) [1,4]. Less common side effects included back pain (28%), vasodilation (28%), dyspnea (28%), VLS (27%), rash (25%), angina (24%), elevated creatinine levels (14%), tachycardia (12%), dysphagia (5%), syncope (3%), and anaphylaxis (1%) [1,4]. Elevations in creatinine were mild and reversible [1,4]. No significant myelotoxicity occurred, although lymphocyte

counts fluctuated [1]. Recently, cases of vision loss following treatment with DD have been reported [8,9]. The side effects described in the phase III trial were most severe in the first two treatment cycles [1]. While 21% of patients were hospitalized due to adverse effects, only 5% of these events were life-threatening [10].

The delayed onset of VLS in this patient is typical: VLS develops within the first 14 days of a treatment course, usually on days 6-10 of the first cycle [2]. DD may cause renal damage leading to proteinuria and hypoalbuminemia; thus, pre-existing hypoalbuminemia is thought to predispose patients to VLS and is a contraindication to treatment with DD [11]. The severity and incidence of VLS may be prevented by enhancing renal elimination of DD by administering up to 1 L of saline after drug infusion [12]. Although the initial clinical trials prohibited the use of corticosteroid pretreatment, [1,4] premedication with intravenous dexamethasone or prednisone resulted in a lower rate of VLS (13%) [10]. This patient had all three features of VLS, but he had an elevated BNP with a normal EF. He did not receive post-DD intravenous fluids or pretreatment with corticosteroids.

The pathogenesis of VLS due to DD is not known precisely, but may involve nitric oxide, cytokines, tumor necrosis factor α , or a direct drug effect [7]. As patients with VLS often respond to therapy, as in this case, this adverse effect may be due to the destruction of malignant cells located near blood vessels [12]. During later treatment courses, the patient in this report did not experience VLS again, and recurrence of VLS is rare in general [12]. Given the response of VLS to conservative measures and the low likelihood of recurrence, this adverse effect should not warrant discontinuation of treatment with DD. Instead, prompt diagnosis of VLS, facilitated through patient education and close monitoring of weight and blood pressure, is recommended.

ACKNOWLEDGEMENTS

This case report was supported by the Sherry L. Anderson CTCL patient research fund.

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