

Oral mycosis fungoides with CD30⁺ large cell transformation successfully treated with brentuximab vedotin



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INTRODUCTION

Mycosis fungoides (MF) is the most common subtype of primary cutaneous T cell lymphoma, accounting for about 50% of cases.¹ MF typically has 3 clinical stages: (1) patch, (2) plaque, and (3) tumor.¹ The patch and plaque stages of MF are slowly progressive and tend to overlap.² However, the tumor stage is often rapid in both onset and progression.² Oral involvement in MF is rare and usually indicates a poor prognosis.² The mortality rate is about 50% at 1 year, with most patients dying within 3 years.² Large cell transformation of MF also signifies a poor prognosis, with a mean 5-year survival rate of less than 20%.³

Historically, the treatment of oral MF has primarily involved radiation therapy.⁴ Prior cases of oral large cell transformed MF (LCT-MF) have also been predominantly treated with radiation therapy (Table I).^{2,5-7} However, this therapeutic approach is not ideal, as it can lead to significant adverse effects, including salivary gland dysfunction, severe mucositis, and osteoradionecrosis.⁸ We describe a new case of oral mycosis fungoides with CD30⁺ large cell transformation that demonstrated a complete response to 2 doses of brentuximab vedotin without significant side effects.

CASE

A 65-year-old white man with a medical history of Hodgkin lymphoma (diagnosed in 1987, treated with chemotherapy and radiation) and mycosis fungoides

Abbreviations used:

LCT:	large cell transformation
LCT-MF:	large cell transformed mycosis fungoides
MF:	mycosis fungoides

(diagnosed in 1990s, patient declined psoralen ultraviolet light A) presented with worsening skin lesions.

Physical examination found well-circumscribed erythematous patches with fine scale and a few scattered plaques involving approximately 15% of the total body surface area. The patient had several nodules on the upper extremities and trunk, which qualified as small tumors. However, the dominant lesional morphology consisted of plaques and patches. The facial skin was hyperlinear with alopecia affecting the eyebrows and eyelashes and ectropion present bilaterally.

The patient was found to have stage IIB cutaneous T cell lymphoma (T2, N1, M0, B1) and was started on narrow-band ultraviolet B therapy 3 times a week. Although the patient's facial findings of hyperlinearity and ectropion were suggestive of B2 involvement/Sézary syndrome, his blood work results showed a relatively low burden of circulating MF cells.

Several weeks later, the patient had multiple painful, eroded plaques and tumors on the tongue (Fig 1). Biopsy found tumor stage mycosis fungoides, with CD30⁺ large cell transformation

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Table 1. Previously reported cases of oral MF with large cell transformation in chronological order

Case	Author (Year)	Sex	Age at MF Dx	Age at oral lesion Dx	Location of oral lesion(s)	Immunophenotype	Tx of oral lesion	Prognosis
1	Kunishige et al ⁵ (2006)	Male	70	72	Tongue	CD3 ⁺ , CD20 ⁺ , rare CD30 ⁺	Local radiation therapy	Not provided
2	Kunishige et al ⁵ (2006)	Female	55	56	Tongue	CD3 ⁺ , CD20 ⁺ , CD25 ⁺ , CD30 ⁺	Boost radiation	Died 15 years after initial cutaneous symptoms and 4 months after appearance of tongue lesion
3	Bittencourt et al ⁷ (2015)	Male	48	48	Not specified	CD30 ⁺	Local radiotherapy and IFN	Alive with disease as of 2015
4	Bassuner et al ⁶ (2016)	Male	63	67	Tongue	CD3 ⁺ , CD4 ⁺ , CD30 ⁺ , ~90% of neoplastic cells expressed Ki-67	22Gy of electron beam radiation, bexarotene (maintenance)	Alive and disease free 7 years after oral lesion onset
5	Sultan et al ² (2017)	Male	Not provided	68	Tongue, buccal mucosa, hard palate	CD3 ⁺ , CD4 ⁺ , CD5 ⁺ , CD7 ⁺ , CD8 ⁺ , CD20 ⁺ , 60% dimly positive for CD30, S-100 ⁺ , HMB45 ⁺ , 50% of neoplastic cells expressed Ki-67	Excisional biopsy, PUVA photo-chemotherapy	Alive with disease as of 2017
6	Current case (2018)	Male	40	65	Tongue	CD15 ⁺ , CD30 ⁺	Brentuximab vedotin	Complete resolution of oral lesions, significant improvement in skin lesions

Dx, Diagnosis; IFN, interferon; PUVA, psoralen ultraviolet light-A; Tx, treatment.

(Figs 2 and 3). The patient was started on brentuximab, 1.8 mg/kg intravenously (with a max dose of 180 mg) once every 3 weeks. He had an excellent response to brentuximab therapy, with complete resolution of his oral lesions and an improvement in his skin lesions after just 1 dose. After the second dose of brentuximab, the patient's skin lesions were approximately 60% improved (physician's global assessment), and his oral lesions remained clear at 8-month follow up. To date, the patient has experienced no medication side effects and no evidence of neuropathy.

DISCUSSION

Only 5 cases of oral LCT-MF have been reported.^{2,5-7} Most of these cases were treated with

local radiation therapy, with variable responses (Table 1).^{2,5-7} It is well documented that radiation therapy to the oral cavity can lead to severe mucositis, candidiasis, dysgeusia, osteoradionecrosis, and soft tissue necrosis, among other side effects.⁸ The salivary glands are particularly sensitive to radiotherapy, resulting in decreased salivary flow and changes in salivary composition.⁸ The resultant salivary gland dysfunction leads to xerostomia, which increases the risk for oral infections and dental caries.⁸

Here we describe a new case of oral LCT-MF that was successfully treated with brentuximab vedotin. Brentuximab vedotin is an anti-CD30 antibody conjugated to monomethyl auristatin E by a protease-cleavable linker.⁹ It was initially developed for the



Fig 1. Eroded plaque on the tip of the dorsal tongue extending onto the ventral tongue. Biopsy found CD30⁺ large cell transformation of mycosis fungoides.

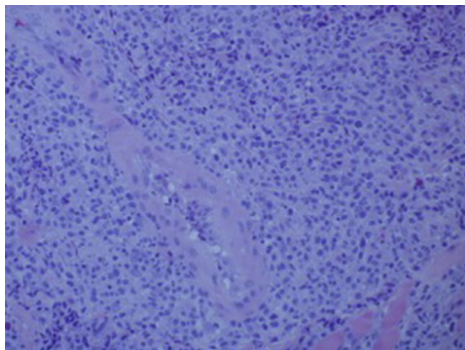


Fig 2. High-power view of oral ulcer.

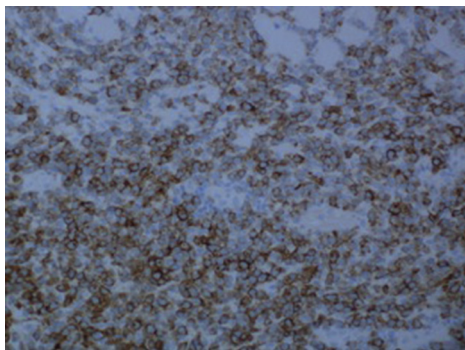


Fig 3. Positive CD30 staining.

treatment of systemic large cell anaplastic lymphoma and Hodgkin lymphoma.⁹ Recently, brentuximab was approved by the US Food and Drug Administration for CD30⁺ cutaneous MF in patients who have previously received systemic therapy. Interestingly, studies have found that brentuximab can successfully treat cutaneous MF regardless of CD30 expressivity.⁹ Despite the growing body of literature on the use of brentuximab vedotin in the

treatment of cutaneous MF, to date there are no reports on the use of brentuximab in the treatment of oral LCT-MF.

Given the significant CD30 positivity (75%) of our patient's transformed tongue lesions coupled with the barriers to skin-directed therapy in the oral cavity, single-agent systemic brentuximab was selected. After just 1 dose, the patient's oral lesions completely resolved, and he had significant improvement in his patches, plaques, and isolated small tumors. After the second dose of brentuximab, the patient's oral lesions remained absent, and his cutaneous lesions improved by roughly 60% from pretreatment baseline.

The most prominent side effect of brentuximab is peripheral sensory neuropathy.^{9,10} In a phase II trial by Corbin et al,¹⁰ 25 of 36 patients (69%) who received brentuximab for the treatment of MF/Sézary syndrome went on to have peripheral neuropathy. Of these 25 patients, 18 had clinically significant peripheral neuropathy that was grade 2 or higher according to the Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0.¹⁰ For every increase in brentuximab vedotin dose by 100 mg, the likelihood of having clinically significant peripheral neuropathy increased by 23%.¹⁰ Fortunately, brentuximab-associated peripheral neuropathy is not necessarily permanent. Corbin et al¹⁰ reported that 13 of the 25 patients (52%) who had peripheral neuropathy had resolution or improvement of their symptoms by the end of the follow-up period. The prevalence of peripheral neuropathy after treatment with brentuximab vedotin appears to be a dose-dependent, inevitable side effect that typically resolves or improves over time.¹⁰ Our patient has not experienced any side effects, perhaps because of his very limited, 2-dose course.

Although brentuximab vedotin is not without adverse effects, its side-effect profile is arguably superior to that of radiation therapy in the oral cavity. In addition, systemic brentuximab offers the benefit of treating oral and cutaneous lesions simultaneously. This case provides evidence that brentuximab vedotin can successfully treat oral CD30⁺ LCT-MF. Further studies are needed to determine if our treatment success may be generalized to other patients with oral MF with CD30⁺ large cell transformation.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
2. Sultan AS, Mostoufi B, Papadimitriou JC, Koka R, Basile J, Younis RH. Large cell transformation of oral mycosis fungoides. *Head Neck Pathol*. 2018;12(2):247-251.

3. Pulitzer M, Myskowski PL, Horwitz SM, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. *Pathology*. 2014;46(7):610-616.
4. Feldman AM, Sevak P, McHargue C, Lim HW, Siddiqui F. Mycosis fungoides involving head and neck mucosal sites: review of the literature. *Appl Radiat Oncol*. 2017;6(2):11-19.
5. Kunishige J, Harriott Fisher A, Holsinger F, Feasel A, Duvic M. Mycosis fungoides of the tongue. *Internet J Dermatol*. 2006; 5(1):1-4.
6. Bassuner J, Miranda RN, Emge DA, DiCicco BA, Lewis DJ, Duvic M. Mycosis fungoides of the oral cavity: fungating tumor successfully treated with electron beam radiation and maintenance bexarotene. *Case Rep Dermatol Med*. 2016;2016: 5857935.
7. Bittencourt AL, Oliveira PD, Carvalho-Andrade A, Araujo I. Correlations between clinical and pathological features in 17 cases of mycosis fungoides before and after transformation. *Int J Dermatol*. 2015;54(9):e327-e331.
8. Tolentino E de S, Centurion BS, Ferreira LHC, de Souza AP, Damanthe JH, Rubira-Bullen IRF. Oral adverse effects of head and neck radiotherapy: literature review and suggestion of a clinical oral care guideline for irradiated patients. *J Appl Oral Sci*. 2011;19(5):448-454.
9. Kim YH, Tavallae M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J Clin Oncol*. 2015;33(32):3750-3758.
10. Corbin ZA, Nguyen-Lin A, Li S, et al. Characterization of the peripheral neuropathy associated with brentuximab vedotin treatment of mycosis fungoides and Sézary syndrome. *J Neurooncol*. 2017;132(3):439-446.