Methotrexate-induced CD30$^+$ T-cell lymphoproliferative disorder of the oral cavity

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INTRODUCTION

For more than 30 years, methotrexate (MTX) has been a mainstay in the treatment of various inflammatory disorders including rheumatoid arthritis (RA) and psoriasis.[1] Off-label use of MTX has expanded in recent years, as it is found to be effective in treating dermatoses such as atopic dermatitis, bullous pemphigoid, pemphigus vulgaris, and mycosis fungoides.[1] Because of its common use in dermatology, the oncogenic potential of MTX is of special significance for the clinician interested in prescribing this drug.[1] Although MTX has been implicated in squamous cell carcinoma in patients treated for psoriasis, its potential to induce lymphoma is controversial, as studies find either an increase or no clinically significant increase in malignant potential with chronic MTX use.[1] Herein, we report a case of a CD30$^+$ T-cell lymphoproliferative disorder (LPD) of the lip and oral cavity in a patient taking MTX for RA.

Abbreviations used:

EBER:	Epstein-Barr encoded RNA
EBV:	Epstein-Barr virus
LPD:	lymphoproliferative disorder
MTX:	methotrexate
RA:	rheumatoid arthritis

CASE REPORT

A 66-year-old white woman with a 20-year history of RA presented to our dermatology clinic with a 10-month history of a painful lesion on her lower lip. She was initially treated with topical desoximetasone and triamcinolone until July 2013 when it was discontinued because of treatment failure. Topical clobetasol ointment was then initiated and provided the patient some relief until she reported a burning sensation after administration. At the time of presentation in October 2013, the lip lesion had progressed to a deep ulceration of the lip, and she reported that the lesion spread onto her upper lip and the floor of her mouth, impeding her ability to eat and causing significant weight loss. Our patient had been taking MTX for RA for greater than 5 years.

Clinical examination of the vermillion border of the lower lip found a large, erythematous, atrophic area surrounded by soft nodules that extended to the mucosal surface of the lower lip (Fig 1, *A*). The right upper lip had a 1-cm atrophic defect without erosions or ulcerations. The anterior portion of the floor of her mouth was nodular and erythematous. No lymphadenopathy or hepatosplenomegaly was appreciated.

A 5-mm shave biopsy specimen from the lower lip was taken for pathologic examination. A small portion of the oral mucosa was ulcerated and infiltrated by an atypical mononuclear cell infiltrate (Fig 1, *B*). The epidermis was free of atypia and lacked viral cytopathic changes.

Immunoperoxidase stains found that the atypical infiltrate was negative for CD20, PAX-5, and CD79a, ruling out a B-cell lineage. Although the atypical cells were CD3$^-$, CD4$^-$, and CD7$^-$, they were CD2$^+$, CD5$^+$, and CD8$^+$, suggestive of a T-cell lineage. Strong CD30 expression was found, whereas ALK-1 staining was negative (Fig 1, *C*). These immunohistochemical studies suggested a histologic diagnosis of CD30$^+$ ALK-1$^-$ T-cell LPD with involvement of the oral mucosa. Other lymphomas, specifically

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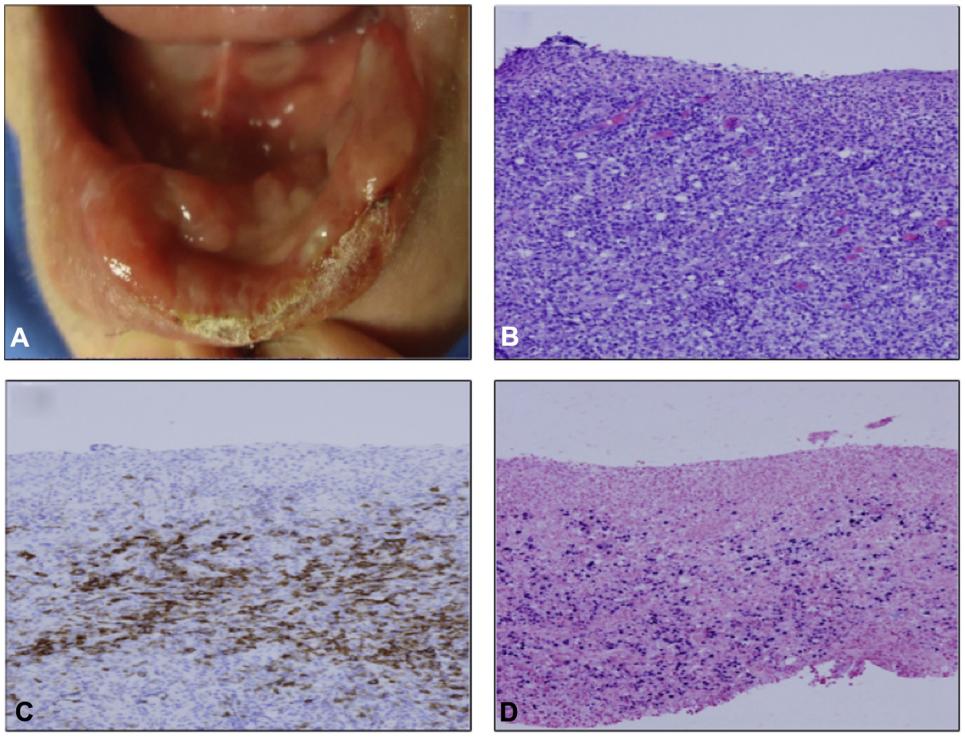

Fig 1. MTX-induced CD30$^+$ LPD. **A**, Region of lower lip ulceration. **B**, Hematoxylin-eosin stain. **C**, Strong CD30$^+$ stain of the malignant cell population. **D**, EBER$^+$ staining of the malignant cells.

Hodgkin's and natural killer T-cell lymphoma, were not considered after a negative bone marrow biopsy result and a positron emission tomography scan that showed bandlike focal fluorodeoxyglucose uptake in the soft tissues anterior to the mandible without other evidence of lymphoma. Subsequent Epstein-Barr–encoded RNA (EBER) staining of the histologic specimen, however, showed abundant positive cells in small-, medium-, and large-sized lymphocytes. This finding suggested that her LPD was associated with Epstein-Barr virus (EBV) infection (Fig 1, *D*). Based on the positive EBER studies and the patient's history of MTX use, the case was reclassified as an immunodeficiency-related CD30$^+$ T-cell LPD. We discontinued MTX and initiated conservative treatment with twice daily clobetasol ointment. Within 2 months of treatment, the patient reported complete resolution of the lip lesions and denied any new or changing lesions, suggesting her lesion was related to MTX use. At 1-year follow-up, the patient remained disease free.

DISCUSSION

The World Health Organization in 2008 defined a broad category of "posttransplantation and iatrogenic" LPDs that recognizes iatrogenic immunosuppression as a pathogenic factor, with MTX included as an etiologic agent of iatrogenic immunodeficiency-associated LPDs.[2-4] The proposed mechanism by which this occurs is via MTX-induced suppression of EBV-specific cytotoxic T cells, which promotes the reactivation of EBV-specific B cells that proliferate.[4] Although MTX-induced LPDs in RA patients have been discussed in previous case reports, lesions presenting on the skin and oral cavity were rarely reported in the literature.[5,6] Furthermore, a literature search found that most EBV-related cases have B-cell involvement, unlike the T-cell involvement seen in our patient.[7] We report a rare case of a MTX-induced CD30$^+$ T-cell LPD presenting with an isolated primary lesion on the lip.

Our case highlights the importance of clinical-pathologic correlation with regard to challenging diagnoses. With larger numbers of patients on immunosuppressive therapies, a greater awareness of immunosuppression-related LPDs is necessary for early diagnosis and treatment. Despite a location similar to the B-cell LPD described by Jaffe et al[3] on the lip, our tumor showed clear features of a T-cell LPD despite the absence of CD3. Additional use of EBER testing because of known immunosuppressant use helped us arrive at the correct diagnosis, namely, a LPD related to immunosuppression. Thus, EBER

testing should be considered on all suspected lesions in patients presenting with unusual cutaneous findings in the context of iatrogenic immunosuppression with MTX or other immunosuppressive agents. Finally, this case shows that it is increasingly important that relevant clinical information is provided to the pathologist upon submission of a tissue specimen to help determine which immunohistologic tests are applied to the biopsy specimen.

In many cases of lymphoproliferative conditions induced by iatrogenic immunosuppression, resolution of the tumor occurs with withdrawal of the medication.[6-9] It is not clear that topical steroids were necessary in our patient, but we did observe rapid and complete resolution of the tumor after withdrawal of MTX and use of topical clobetasol. It is critical for dermatologists to monitor patients closely for any new or unusual mucocutaneous lesions in patients taking MTX and to consider MTX as a risk factor for any new neoplastic processes.

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