EBV$^+$ mucocutaneous ulcers in the setting of pre-existing cutaneous T-cell lymphoproliferative disorders: A report of 2 cases

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INTRODUCTION

The diagnostic category of Epstein-Barr virus–positive (EBV$^+$) mucocutaneous ulcer is a relatively new one describing a localized, slowly growing, ulcerative EBV$^+$ lymphoproliferative disorder (LPD).[1-4] Here we present 2 cases of iatrogenic EBV$^+$ mucocutaneous ulcers presenting in patients with pre-existing cutaneous T-cell LPDs.

Abbreviations used:

EBER:	Epstein-Barr–encoded RNA
EBV:	Epstein-Barr virus
LMP:	latent membrane protein
LPD:	lymphoproliferative disorder
LyP:	lymphomatoid papulosis

CASE REPORTS

Case 1: Iatrogenic EBV$^+$ mucocutaneous ulcer associated with prednisone therapy for peripheral T-cell lymphoma

A 76-year-old woman was referred for cutaneous involvement of peripheral T-cell lymphoma, which had progressed over 3 years to involve the lungs, adrenal glands, and skin. On examination, an indurated, scaly, erythematous plaque was present on the left upper buttock (Fig 1, *A*). Biopsy found granulomatous peripheral T-cell lymphoma, with CD3$^+$ and CD4$^+$, weakly CD5$^+$ and CD8$^+$, Epstein-Barr–encoded RNA (EBER)$^-$, and rare CD20$^+$ cells, and clonal T-cell receptor β rearrangement by polymerase chain reaction.

The skin lesions near completely resolved after a 10-week prednisone taper (starting at 60 mg/d). One month after completing prednisone, the skin lesions recurred on her extremities. Prednisone was reinitiated (80 mg/d) and again led to improvement. However, after another 2 months of prednisone, the patient had 2 new, expanding ulcerations on the right lower leg (Fig 1, *B*). Biopsy found a dense infiltrate of atypical Hodgkinoid cells that were CD20$^+$, CD30$^+$, and EBER$^+$, but CD3$^-$, consistent with EBV$^+$ mucocutaneous ulcer.

The patient subsequently underwent radiotherapy (total of 36 cGy in 18 fractions) with continued prednisone (60 mg/d), which led to some improvement. However, within 2 months of completing radiation, a new ulceration appeared outside the radiated field on the right lower extremity. This proved to be an EBV$^+$ mucocutaneous ulcer on biopsy. A rapid prednisone taper with weekly doses of rituximab (375 mg/m^2 intravenously) for 1 month was initiated. She was then started on sirolimus (1 mg/d), which led to resolution of all cutaneous lesions of both the EBV$^+$ mucocutaneous ulcers and the peripheral T-cell lymphoma.

Case 2: Iatrogenic EBV$^+$ mucocutaneous ulcer associated with methotrexate therapy for rheumatoid arthritis and lymphomatoid papulosis

An 84-year-old woman with history of rheumatoid arthritis treated chronically with oral methotrexate

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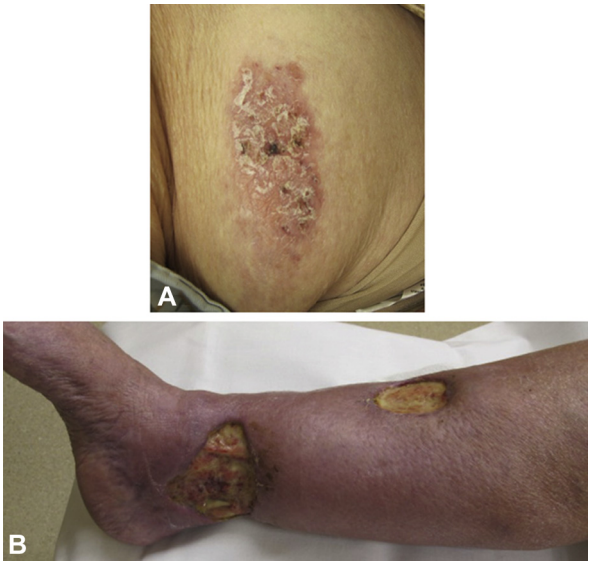

Fig 1. Two distinct lymphoproliferative processes in case 1. **A**, Biopsy-proven peripheral T-cell lymphoma involving the left buttock. **B**, Biopsy-proven EBV-associated CD30$^+$ B-cell LPD involving the right lower extremity.

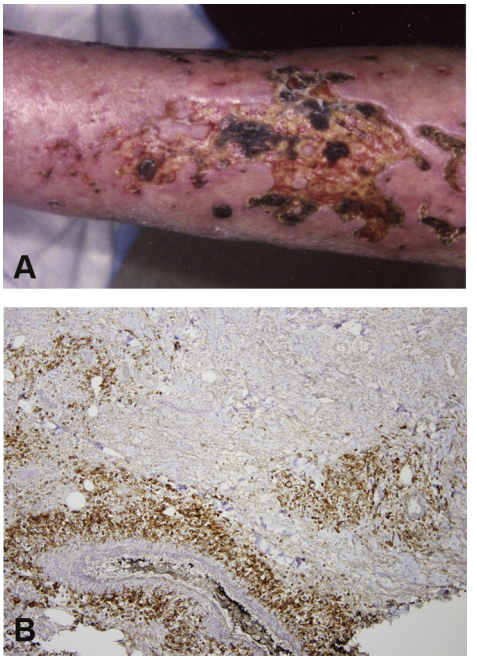

Fig 2. MTX-induced EBV-associated CD30$^+$ LPD in case 2. **A**, Confluent ulceration of medial right calf. **B**, CD30 stain.

(15 mg/wk) and prednisone (4 mg/d) was referred for a 6-month history of biopsy-proven lymphomatoid papulosis (LyP) of the bilateral lower extremities. Examination found several crusted erythematous macules of the left lower extremity and a regressing erythematous maculopapule on the right lower extremity.

Lesions worsened over the next several months despite continued methotrexate and prednisone at the same doses, ultimately with development of a large confluent area of crusted ulcers on the right medial calf (Fig 2, *A*). This clinical behavior prompted biopsy that found a mixed inflammatory infiltrate, with large atypical lymphoid cells with high nuclear/cytoplasmic ratio present in an angiocentric distribution, positive for CD20, CD30, EBV latent membrane protein (LMP), and EBER (Fig 2, *B*). Methotrexate was discontinued. Over the following 9 months, the lesions gradually resolved with regular wound care and occasional antibiotics as needed for superimposed infections.

DISCUSSION

EBV$^+$ mucocutaneous ulcer is a relatively new diagnostic category. Previously falling under the 2008 World Health Organization classification of EBV$^+$ diffuse large B cell lymphoma of the elderly, the 2016 World Health Organization split these lesions into the categories of (1) EBV$^+$ diffuse large B cell lymphoma, not otherwise specified and (2) EBV$^+$ mucocutaneous ulcer. The category of EBV$^+$ mucocutaneous ulcer was introduced as a provisional entity to highlight its self-limited growth potential and response to conservative management.[5]

Previously described EBV$^+$ mucocutaneous ulcers have occurred in the setting of age-related senescence and iatrogenic immunosuppression.[1-3] The pathogenesis is related to the limited repertoire of B and T cells in these settings, which increases the risk of EBV transformation of B and T cells, thus leading to LPD. Localized lesions of EBV$^+$ mucocutaneous ulcer typically present as slowly developing indurated ulcers, most commonly in the oropharynx, less commonly along the gastrointestinal tract or on the skin.[1] Clinically, these lesions may resemble EBV-associated genital ulcers seen in the setting of acute EBV infection in young patients. Histologically, there is well circumscribed, surface ulceration with a polymorphous lymphoid infiltrate that includes Hodgkin-like atypical immunoblasts, prominent apoptosis, and a discrete rim of small, reactive T lymphocytes at the base.[1,3,6] The large, atypical Hodgkin/Reed-Sternberg–like B cells have strong CD20, CD30, and EBER positivity.[1,3] The lesions tend to be indolent and resolve spontaneously with conservative management or with reduction of iatrogenic immunosuppression; however, lesions may recur with fluctuation of the effectiveness of EBV-associated immune responses.[6] Conversely, lesions associated with systemic EBV$^+$ LPDs tend to do very poorly. Table I summarizes

Table I. Differential diagnosis of EBV$^+$ mucocutaneous ulcers

Diagnosis	Key clinical features	Key pathologic features
EBV$^+$ mucocutaneous ulcers	Ulcers in an elderly immunosuppressed patient; can involve skin and/or mucosa; improves with reversal of immunosuppression	Atypical B-cell infiltrate mixed with T cells; B-cells positive for EBER and CD30
Non-EBV infectious ulcers	One or more ulcers; sometimes with systemic symptoms	Neutrophilic, granulomatous or lymphocytic infiltrate; culture or special stains positive for specific bacterium, fungus or virus
Cutaneous B-cell lymphomas	Papules, plaques and/or tumors; usually w/o ulcers except in advanced tumor-stage disease	Atypical B-cell infiltrate; usually negative for EBER and CD30
Cutaneous T-cell lymphomas	Patches, plaques and/or tumors; usually w/o ulcers except for advanced tumor-stage cases and rare cytotoxic T-cell variants	Atypical T-cell infiltrate; usually CD30$^-$ except for anaplastic large T-cell lymphoma; usually EBER$^-$ except for nasal-type NK/T-cell lymphoma
Lymphomatoid papulosis	Spontaneously regressing papulonodules often w/o ulceration	Atypical T-cell infiltrate; EBER$^-$; CD30$^+$ large atypical T cells
Febrile ulceronecrotic Mucha-Habermann disease	Ulcerated papulonodules with fever and other systemic symptoms	Variably atypical T-cell infiltrate; negative for EBER and CD30
Leukocytoclastic vasculitis	Palpable purpura often w/o ulceration	Neutrophilic infiltrate with leukocytoclasis; negative for EBER and CD30

key differential diagnostic features of other cutaneous ulcerations that may arise in elderly or immunosuppressed patients and that often contain atypical lymphoid infiltrates.

We describe 2 cases of iatrogenic EBV$^+$ mucocutaneous ulcers in the setting of pre-existing cutaneous T-cell LPDs. Two similar case reports involve elderly men with mycosis fungoides treated with methotrexate.[7,8] Our first case is an example of EBV$^+$ mucocutaneous ulcer developing in the setting of peripheral T-cell lymphoma. The coexistence of 2 LPDs presented a particular challenge for management in this patient, as treatment of the peripheral T-cell lymphoma with prednisone resulted in exacerbation of the EBV-induced B-cell LPD. Ultimately, replacement of prednisone with sirolimus led to resolution of both LPDs without the need for chemotherapy. Of note, mechanistic target of rapamycin (mTOR) inhibitors have shown efficacy against EBV-driven B-cell and T-cell lymphoproliferative disorders.[9,10] In the second case, the patient had an EBV$^+$ mucocutaneous ulcer in the setting of LyP while taking methotrexate and prednisone for management of rheumatoid arthritis. Again, the coexistence of 2 LPDs presented a challenge in this patient, as the large atypical CD30$^+$ cells in the EBV$^+$ mucocutaneous ulcer could have been misinterpreted as worsening LyP. Subsequently, the patient might have had methotrexate increased with resultant exacerbation of EBV$^+$ lesions, rather than discontinued as required for resolution of the EBV$^+$ mucocutaneous ulcers.

It is clear from the literature that advanced age and use of methotrexate, azathioprine, and cyclosporin A are associated with EBV$^+$ mucocutaneous ulcers.[3,11,12] The isolated risks of rheumatoid arthritis or prednisone for inducing EBV$^+$ mucocutaneous ulcers are difficult to assess because they are often confounded by concomitant methotrexate.[2,11,12] Cessation of methotrexate in 8 cases resulted in complete (6 cases) or partial (2 cases) regression of ulcers.[2,7,8] Similar results were observed in 6 additional cases in which immunosuppressive drugs were discontinued.[3] Our cases and the literature show that iatrogenically immunosuppressed patients with EBV$^+$ mucocutaneous ulcers may benefit from a trial of immunosuppressant withdrawal before consideration of more aggressive interventions.

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