ABSTRACT

Immunosuppressive medications, frequently used to treat inflammatory bowel disease, have been linked to the development of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (LPD). We describe a case of an EBV-positive mucocutaneous ulcer involving the palate in an elderly woman with inactive Crohn’s disease. This patient had been on high-dose azathioprine for a decade. Following diagnosis of her LPD and discontinuation of azathioprine, her oral ulcers resolved completely.

INTRODUCTION

Lymphoproliferative disorders (LPDs) are a broad class of conditions involving abnormal lymphocytic proliferation. The 2016 revisions to the World Health Organization classifications describe a new entity in the LPD spectrum, Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCU). First identified in 2010, these are characterized by isolated cutaneous and mucosal ulcerations associated with old age and immunosuppression. EBVMCU present with highly atypical cells and were initially notable for their indolent course, although more recent cases highlight a heterogeneous prognosis.

CASE REPORT

A 75-year-old woman presented with a 2-month history of necrotic ulcerative lesions of the palate. Her medical history was significant for prior nicotine use and long-standing Crohn’s disease involving the terminal ileum. The diagnosis of ileal Crohn’s disease was made 10 years prior, and since then it had been consistently maintained on azathioprine monotherapy, 175 mg daily (weight 51.6 kg; 3.4 mg/kg dose). She had no history of perianal disease, extra-gastrointestinal (GI) manifestations, or surgical resections. She struggled with anemia attributed to azathioprine. Computed tomography (CT) enterography 3 years after diagnosis demonstrated quiescent disease. Two subsequent colonoscopies, most recently 5 months prior, confirmed inactive disease both endoscopically and histologically.

Two months prior to presentation, she was seen by a maxillofacial surgeon for weight loss and a painful expanding sore on her hard palate (Figure 1). She had no history of oral ulcerations. Due to concern for poorly fitting dentures, she was referred to otorhinolaryngology. Otorhinolaryngology was concerned for squamous cell carcinoma and therefore ordered a CT, which showed a plaque-like mucosal enhancement along the left medial aspect of the
alveolar reach. A tissue biopsy was consistent with EBVMCU, and she was prescribed topical triamcinolone (Figure 2). In follow-up 1 month later, new ulcers were noted, and she was referred to gastroenterology at our facility.

At her visit, she reported significant odynophagia. Her oral intake was diminished, and she had lost approximately 9 kg over the prior 2 months. She denied fevers, night sweats, pruritus, arthralgias, or adenopathy. Her bowel movements were at baseline. She continued on azathioprine. Physical exam identified necrotic ulcerations involving the hard and soft palate. Laboratory studies showed macrocytic anemia with hemoglobin 11 g/dL and mean corpuscular volume 106.7 fL in the setting of recently diagnosed vitamin B12 deficiency. There was mild thrombocytosis (587 × 10^9/L) and normal electrolytes. 6-TGN and 6-MMP levels were not checked.

Due to concern that the EBVMCU was secondary to azathioprine, she was advised to stop the medication completely. She was not started on another medication for her Crohn’s disease due to the absence of disease activity. She was seen 12 weeks after discontinuation of azathioprine, and although she remained anemic, her ulcers had completely resolved and she had no symptoms suggesting active Crohn’s disease.

DISCUSSION

This is a case of EBVMCU secondary to a decade of monotherapy high-dose azathioprine for Crohn’s disease. Since the identification of EBVMCU in 2010, roughly 52 cases have been reported, with 4 occurring in patients with inflammatory bowel disease (IBD). Iatrogenic immunosuppression and age are significant risk factors. Over half of reported cases were in the setting of immunosuppression, specifically cyclosporine, mycophenolate, tacrolimus, azathioprine, anti-tissue necrotic factor (TNF) agents, and mycophenolate. Azathioprine has been associated with a 4-fold increased risk for LPDs, and of the 5 cases of EBVMCU in patients with IBD (including ours), 3 were on azathioprine, and 1 of these 3 patients was on azathioprine in combination with an anti-TNF. While the risk for LPDs increases with duration, the relationship with dosage is unknown, although dose reduction often leads to remission. Of the 6 prior cases of EBVMCU in the setting of azathioprine use, 2 cases reported standard dosing and 4 cases either did not report dose or did not provide enough information to determine if the dose was standard or high. Age-related immunosenescence alone was associated with 40% of reported cases, and in individuals on immunosuppression, the median age was 63 years. Of the 5 IBD cases, median age was 63 years (range 26-78 years).

Characteristic ulcerations are typically solitary (83%), shallow, and circumscribed, and they can occur in the oropharynx (52%), skin (29%), and GI tract (19%; 40% colon, 30% esophagus, 20% rectum, and 10% terminal ileum). Of the 4 IBD cases (3 with Crohn’s disease and 1 with ulcerative colitis), the ulcer location was in the colon and rectum, perianal skin, anorectum, and rectum. To our knowledge, our case is the first...
with an ulcer in the oropharynx of an individual with IBD. While ulcers are a rare presentation of oral Crohn’s disease, they are a frequent presentation of oral lymphomas. 

Although EBV plays a pivotal role in the development of EBVMCU, EBV viremia has only been documented in 1 case. EBVMCU classically have an indolent course. While no guidelines exist, management is conservative and includes withdrawal or decrease of immunosuppressant dose. Nearly two thirds of immunosuppressive-associated cases went into complete clinical remission with reduction alone, and median time to lesion resolution has been reported to be 4 weeks (range 2–12 weeks). Of the 5 cases of patients with IBD, all were treated with immunosuppression cessation, and 3 had complete resolution (60%), one had no improvement (20%), and one progressed to Hodgkin’s lymphoma (20%). This was the only documented case of progression to lymphoma in an IBD case, which is congruent with increasing reports of more aggressive EBVMCU. We propose that clinicians faced with an oral ulcer of unclear etiology in someone on immunosuppressives have a low threshold to biopsy, particularly in elderly patients. Lack of response to reduction or withdrawal of immunosuppressives within 3 months should prompt re-evaluation of the diagnosis of EBVMCU.

Diagnosing EBVMCU and distinguishing them from other causes of ulcers, such as Hodgkin’s lymphoma, can prove challenging. The lack of lymph node, bone marrow, liver, and spleen involvement can help identify EBVMCU, and bone marrow biopsy and imaging may be needed to confirm the diagnosis. This case, and the delay in diagnosis and associated morbidity, highlights the importance of clinician awareness of EBVMCU when evaluating ulcers in a patient with IBD on immunosuppression.

**DISCLOSURES**

Author contributions: IA Hujoel wrote and edited the manuscript. A. Rubio-Tapia, LN Dao, LF Porrata, and SV Kane edited the manuscript. LD Dao provided the histologic images. A. Rubio-Tapia is the article guarantor.

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