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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Multifocal Epstein-Barr Virus-Positive Mucocutaneous Ulcers in a Patient With Crohn's Disease

Lotus Alphonsus, BScN[1], Qi Zhang, MBBS, PhD[2], and Vipul Jairath, MBChB, PhD[3,4,5]

[1]*Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada*
[2]*Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University and London Health Sciences Centre, London, Ontario, Canada*
[3]*Division of Gastroenterology, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada*
[4]*Lawson Health Research Institute, Western University, London, Ontario, Canada*
[5]*Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada*

ABSTRACT

Epstein-Barr Virus-positive mucocutaneous ulcer (EBVMCU) is a rare and new category of mature B-cell neoplasms commonly linked to immunosuppression. It often has a benign course and regresses spontaneously after discontinuation or dose reduction of immunosuppressive agents. We report the case of a 48-year-old woman on long-term azathioprine therapy for rectosigmoid Crohn's disease. In contrast to the prevalent sites typically associated with EBVMCU, such as the oral mucosa and skin, this patient was found to have locations in the gastrointestinal tract and upper neck. These areas tested positive for histopathology consistent with EBVMCU and were excised due to bowel perforation and concern for malignancy.

KEYWORDS: Crohn's disease; EBVMCU; EBV-Positive Mucocutaneous Ulcer

INTRODUCTION

Epstein-Barr Virus-positive mucocutaneous ulcer (EBVMCU) is a relatively new clinicopathologic entity that was first described in the literature in 2010.[1] It was categorized as a mature B-cell neoplasm by the World Health Organization in 2016, and since then, there have been only 200 cases described worldwide.[2,3] Patients with inflammatory bowel disease (IBD) have an elevated susceptibility to lymphoproliferative diseases including lymphoma (both non-Hodgkin and Hodgkin types) and Epstein-Barr virus-associated lymphoproliferative disorders.[4] The disease process of IBD and its treatment contribute to the increased incidence of this rare complication described in the literature.[5–11] EBVMCU is associated with iatrogenic or age-related immunosuppression and typically has an indolent clinical course requiring conservative management.[1,12] We report a 48-year-old female patient with Crohn's disease treated with azathioprine who developed EBVMCU resulting in a rectosigmoid perforation requiring Hartmann procedure.

CASE REPORT

A 48-year-old woman with Crohn's colitis diagnosed in 1998 received 150 mg of azathioprine daily for over 18 years. Her Crohn's disease was well controlled with minimal steroid exposure. Between 2014 and 2017, she developed new tenesmus-type symptoms and endoscopic evaluation revealed an inflamed rectosigmoid stricture for which a shared care decision was made to proceed with regular dilatations. In the remainder of the colon, there was patchy inflammation and a normal ileum. Pathology reported classic granulomatous changes with chronic active inflammation involving the colon. By 2018, she experienced increased stool frequency, reduced oral intake, and subacute obstructive symptoms, with unintentional weight loss of 55 pounds over the year. On repeat endoscopic evaluation, the stricture did not allow passage of a colonoscope and cross-sectional imaging in the form of computed tomography (CT)-demonstrated progression of circumferential thickening in the upper rectum and lower sigmoid colon with mesenteric inflammation in the pelvis. No obstruction, perforation or concern for malignancy was reported. Adalimumab was added

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Correspondence: Vipul Jairath, MBChB, PhD (vipul.jairath@lhsc.on.ca).

to azathioprine to control inflammation, alongside supplemental enteral nutrition to improve nutritional status. In June 2018, she developed shingles on her face and neck, night sweats, and a new right-sided submandibular mass. Azathioprine was suspended, and workup of the submandibular mass was initiated.

In November 2018, she presented acutely with lower gastrointestinal (GI) bleeding requiring blood transfusion. Inpatient colonoscopy revealed progressive inflammatory changes in the rectosigmoid mucosa. The previously identified rectosigmoid stricture was now more ulcerated and inflamed and impassable to an adult colonoscope. Shortly after the procedure, she developed signs and symptoms consistent with perforation and underwent emergency surgery, resulting in sigmoid resection and Hartmann procedure. The histopathology specimen had a transmural defect and revealed an EBVMCU with proximal margins uninvolved. The hematology service completed a malignancy workup to assess for further involvement of lymphoma in other organs. A positron emission tomography scan completed in January 2019 reported a hypermetabolic upper neck lesion; this was completely excised and found to have atypical lymphoid infiltrates. A second opinion at National Institutes of Health reported a similar EBVMCU pathology for the neck lesion.

In postoperative management of her Crohn's disease, repeat colonoscopy in July 2022 found longitudinal ulcers in the descending colon for which vedolizumab was initiated. Repeat endoscopic evaluation in January 2023 revealed worsening and deep ulceration in addition to increased output stoma and therefore was switched to infliximab. Repeat biopsies of the ulcerated lesions were negative for lymphoproliferative disorder and showed only chronic colitis with mild-to-moderate activity and granulomas. This was supported by CT which did not indicate any evidence for recurrence of her lymphoproliferative disease.

In the present case, our patient had an 18-year history of azathioprine use for management of Crohn's colitis. Although most literature describes EBVMCU as a unifocal ulcer, our patient had 2 different sites in the GI tract and neck both demonstrating histopathology consistent with EBVMCU. Owing to the patient's clinical course, both areas were excised. The patient remains at risk for recurrence of EBVMCU due to continued immunosuppression, and thus, she continues to be closely monitored for recurrence of lymphoproliferative disease by GI and hematology services.

DISCUSSION

Epstein-Barr Virus-positive mucocutaneous ulcer (EBVMCU) is a rare proliferation of EBV-positive atypical B cells that most often occurs in the oropharyngeal mucosa, followed by the skin and GI tract.[3,13] While the exact pathogenesis is not fully understood, in the context of IBD, it likely involves the complex interplay of chronic mucosal inflammation, host immune dysregulation, and immunosuppressive therapies. EBVMCU is believed to be associated with decreased T-cell levels impairing their ability to fully target all EBV-associated antigens.[14] Exposure to additional site-specific immune-modulating factors such as thiopurines and anti-RNF agents may result in localized EBV-driven lymphoproliferation and result in ulcerating lesions.[14,15] There is no formalized diagnostic criteria for EBVMCU, and diagnosis relies on a combination of clinical, histopathological, and laboratory findings. Diagnostic challenges involve differentiating EBVMCU from related conditions such as classic Hodgkin lymphoma and EBV-positive diffuse large B-cell lymphoma.[14,16] Histopathologically, EBVMCU is a polymorphous infiltrate of atypical immunoblasts with Reed-Sternberg-like morphology and contains various inflammatory cells including lymphocytes, eosinophils, and histiocytes (Figure 1).[1,3,15–17] The atypical immunoblasts stain positive for CD-20, CD-30, EBER-1, MUM-1, OCT-2, and PAX-5 with variable positivity for BCL-6, CD15, CD45, and CD79a.[3,15–17] The lesions exhibit distinctive characteristics, appearing well defined and superficial, with many cases noting a prominent rim of small T lymphocytes at the base.[1,3,16]

EBVMCU generally has an indolent, self-limiting course, and treatment involves discontinuation or limiting immunosuppressive medications.[1,17] However, it is important to note that other cases indicate that EBVMCU can have more varied clinical trajectories requiring surgical resection, chemotherapy, or radiotherapy.[5,7–9,14,18] A systematic review of patients with iatrogenic immunosuppressant-associated EBVMCU found that 68% of patients underwent clinical remission with reduction of immunosuppression, while others required additional treatments.[12] Looking at the few cases available on EBVMCU in patients with IBD, some required the need to start rituximab or brentuximab to achieve a clinical response.[7–9] Chan et al and Juan et al describe eventual surgery even with these therapies to control patient symptoms.[5,7] Other cases have described relapse or progression to overt lymphoma months to years later, underscoring the potential need for regular surveillance based on risk factors.[11,19] Managing patients with concurrent active IBD and EBVMCU presents a therapeutic challenge as it restricts the available immunosuppressive treatment options. This case highlights the importance of considering this diagnosis in patients with IBD being treated with immunosuppressive agents.

DISCLOSURES

Author contributions: V. Jairath: study supervision. L. Alphonsus, Q. Zhang, and V. Jairath: acquisition, analysis, and interpretation of the data. L. Alphonsus, Q. Zhang, and V. Jairath: drafting of the manuscript. L. Alphonsus, Q. Zhang, and V. Jairath: critical revision of the manuscript for important intellectual content. V. Jairath is the article guarantor.

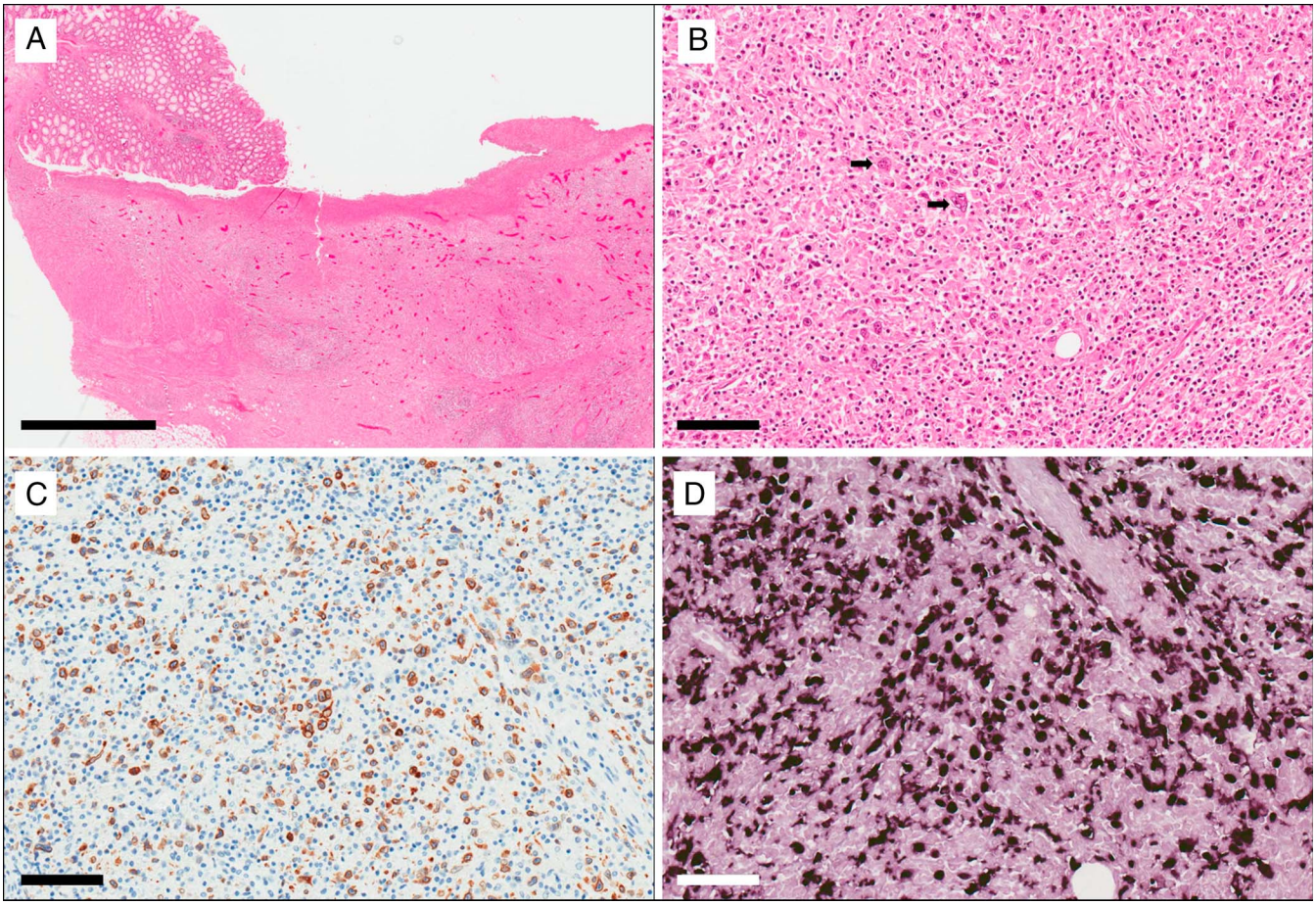

Figure 1. Pathology. (A and B) Hematoxylin and eosin staining reveals segment of large bowel with ulcer. There is a large cell lymphoproliferative neoplasm present. The tumor cells are pleomorphic with moderate amount of cytoplasm. The nuclei are highly atypical, with angulated nuclear contour, vesicular chromatin, and prominent nucleoli. Binucleation and multinucleation are commonly seen. Some of the tumor cells resemble Hodgkin and Reed-Sternberg cells (arrows in B). The neoplastic cells are extending through the muscularis propria into the pericolonic adipose tissue. (C) The tumor cells are immunopositive for CD 79. (D) Tumor cells are strongly positive for EBER (in situ hybridization). Scale bars: 2 mm in A; 100 μm in B–D.

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