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CASE REPORT | INFLAMMATORY BOWEL DISEASE

# Colonic Epstein-Barr Virus-Associated Mucocutaneous Ulcer Associated With Ulcerative Colitis

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## ABSTRACT

Epstein-Barr virus-associated mucocutaneous ulcer is a rare lymphoproliferative disorder that occurs in immunosuppressed states that can develop in the gastrointestinal tract and mimic inflammatory bowel disease or other malignancies. We present the case of a 61-year-old man who presented with concurrent acute severe ulcerative colitis and colonic Epstein-Barr virus-associated mucocutaneous ulcer requiring rituximab therapy and a subtotal colectomy.

## INTRODUCTION

Epstein Barr virus (EBV) or human herpes virus 4 establishes latency in the human body after primary infection which typically occurs before adulthood. A long-term reservoir is believed to develop through infected germinal center B cells which differentiate into memory B cells. Activation of these memory B cells triggers the EBV life cycle and production of EBV virions, upregulation of nuclear factor-κB, and suppression of apoptotic mechanisms. EBV is implicated in several B-cell-related lymphoproliferative disorders through inducing malignant transformation of infected B cells. Immunosuppressive disease states (such as human immunodeficiency virus) or iatrogenic cytomegalovirus immunosuppression accelerates this process by dampening T-cell-mediated immunosurveillance of the infected B-cell reservoir. The risk of lymphoproliferative disorders in patients with inflammatory bowel disease (IBD) has long been established, particularly with the use of thiopurines, as demonstrated in the CESAME study, which demonstrated a 5-fold increased risk.[1]

## CASE REPORT

A 61-year-old man presented with a 6-week history of bloody diarrhea (up to 15 times per day), abdominal pain, 5 kg of weight loss, and night sweats. On admission, his resting heart rate was 105 bpm and his C reactive protein was elevated at 82.9 mg/L. This occurred on a background of ulcerative colitis diagnosed 12 years prior. His disease since diagnosis has been limited to the rectum, requiring only intermittent aminosalicylate suppositories. His medical history included hyperlipidemia and a low-grade urothelial carcinoma under surveillance. There was no personal or family history of immunodeficiency. The patient was commenced on intravenous hydrocortisone for acute severe ulcerative colitis. An abdominal computed tomography demonstrated thickening, mucosal enhancement, and hyperemia of the rectum and sigmoid colon. There was no abdominal lymphadenopathy. Flexible sigmoidoscopy revealed severe inflammation (Mayo 3; UCEIS 8) confluent from the rectum to the distal sigmoid colon, a 5 mm perianal ulcer, and a large, ulcerated mass in the descending colon concerning for malignancy (Figure 1). Rectosigmoid biopsies demonstrated active chronic colitis with a single-cell positive for cytomegalovirus inclusion bodies on immunohistochemistry with an associated viral cytopathic effect. Biopsies from the descending colon mass were consistent with a diagnosis of EBV-associated

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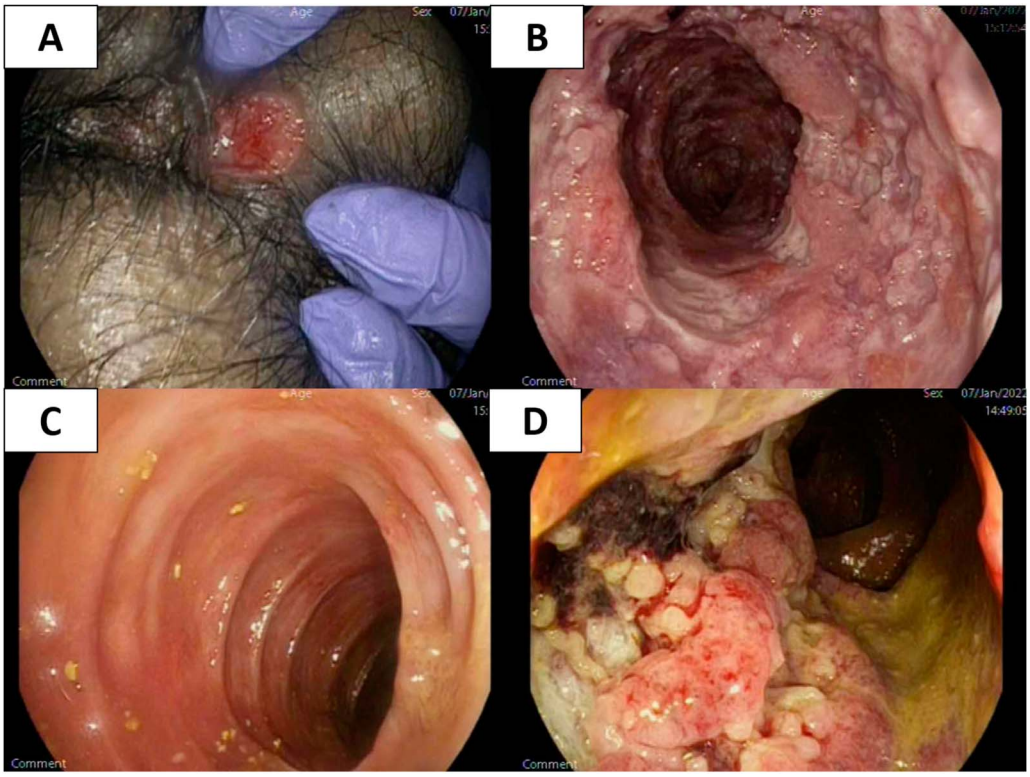


**Figure 1.** (A) Perianal ulcer, (B) severe ulcerative colitis of the rectum (left), (C) relative sparing of the sigmoid colon (right), and (D) ulcerated descending colon mass with spontaneous bleeding.

mucocutaneous ulcer (EBV-MCU). Large atypical lymphoid cells with vesicular nuclei and prominent nucleoli were seen, arranged in sheets (Figure 2). Immunoperoxidase staining demonstrated variable CD20 staining in the large, atypical cells. There was variable weak to moderate positivity for PAX-5. CD30, CD79, MUM1, and BCL2 were positive, whereas CD10, BCL6, and cyclin-D1 were negative. There were scattered EBV-positive cells seen on the Epstein-Barr-encoding region in situ hybridization (EBER-ISH) (Figure 2). His positive emission tomography scan demonstrated intense uptake in the rectum and sigmoid colon consistent with his ulcerative colitis. Short segments of intense metabolic activity were noted in the remainder of the colon, including the area of the descending colon mass. There were no other areas of abnormal uptake in the body.

After multidisciplinary discussion between the patient's hematologist, gastroenterologist, and colorectal surgeon, he was treated with a combination of intravenous ganciclovir, withdrawal of corticosteroid immunosuppression, and 3 doses of

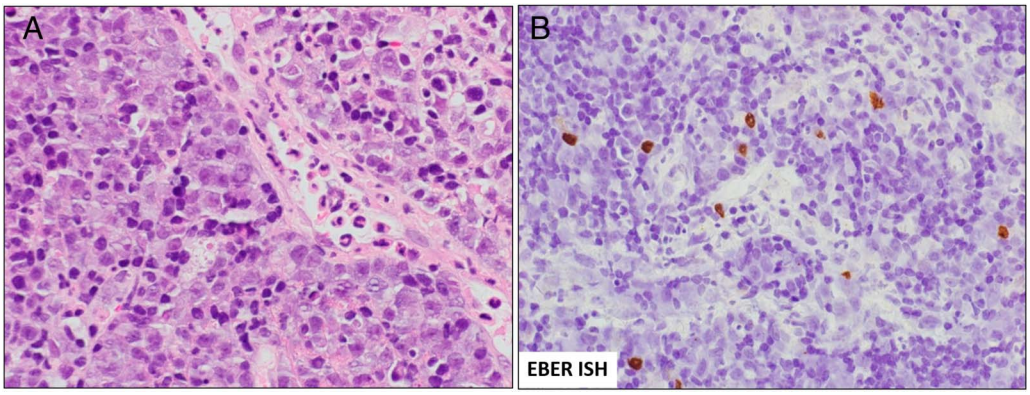


**Figure 2.** (A) Hematoxylin and eosin staining of the descending colon biopsy specimen (magnification ×40). Moderate amount of mixture of inflammatory cell infiltrate in the lamina propria with associated cryptitis consistent with active chronic colitis. Associated large monomorphic atypical cells with vesicular nuclei and prominent nucleoli arranged in sheets. (B) EBV-encoded small RNA in situ hybridization (EBER-ISH) probe identified EBV-positive cells (right). EBV, Epstein-Barr virus.

intravenous rituximab (375 mg/m$^2$). Owing to ongoing bloody diarrhea from active ulcerative proctosigmoiditis, 3 doses of infliximab (5, 10, and 10 mg/kg) were prescribed on days 13, 15, and 23 of admission, respectively. His symptoms temporarily improved but relapsed on day 26. Given the lack of improvement with maximal medical therapy, the decision was made to proceed to a subtotal colectomy and end ileostomy formation. The patient's postoperative course was uncomplicated, and he was discharged 1 week later. Three months after his operation, he remains well with no evidence of relapse.

The colectomy specimen was compared with the original biopsies and revealed a more sparse population of lymphocytes with no significant large transformed lymphoid cells present. Most were CD3-positive T cells. IHC showed that most of the lymphocytes were CD3-positive T cells. EBER-ISH highlighted a focal vaguely aggregated collection of lymphoid cells with slightly enlarged nuclei. This suggested complete treatment response of descending colon EBV-MCU lymphoproliferative disorder. A follow-up positive emission tomography scan 1 month after colectomy demonstrated residual metabolic activity in the rectal stump consistent with colitis and no other sites of fluorodeoxyglucose avidity to suggest active lymphoma.

## DISCUSSION

EBV-MCU is a relatively new pathological entity that was added to the 2016 revision of the World Health Organization classification of lymphoid neoplasms. It was distinguished from EBV-related diffuse large B-cell lymphoma because of its differing prognosis and management. The predominant risk factor that has been identified is immunosuppression, either iatrogenic or age-related immunosenescence. In our patient, his ulcerative colitis never required treatment beyond rectal aminosalicylate therapy, and thus, age was his only risk factor.

To date, 6 cases of gastrointestinal EBV-MCU have been reported in patients with IBD, with this report being the seventh case.[2–8] Most cases (including this one) occurred within the rectum with 3 extending into the sigmoid colon. No cases occurred in the esophagus, stomach, or small bowel, which have been reported in the setting of rheumatoid arthritis and transplantation.[9] Hujoel et al reported isolated palatal involvement in a patient on azathioprine.[8] Two cases occurred with no immunosuppression (aminosalicylate monotherapy), 2 with immunomodulator monotherapy, 2 with combination immunomodulator and anti-tumor necrosis factor (TNF) therapy, and 1 with ustekinumab monotherapy (prior azathioprine and anti-TNF therapy). Although EBV-MCU is commonly described in the literature as a benign entity that resolves with withdrawal of immunosuppression alone, only 2 cases improved spontaneously or with cessation of immunosuppression alone. Two cases required rituximab to achieve clinical remission, 1 case described the successful use of brentuximab, and 2 cases (including this case) progressed to surgery. In the second case requiring surgery described by Moran et al, colonic EBV-MCU was confirmed in a 53-year-old patient with Crohn's disease in the setting of combination of immunosuppression with azathioprine and anti-TNF therapy. There was persistence, despite withdrawal of immunosuppression with subsequent progression to Hodgkin lymphoma requiring chemotherapy.[6]

Matnani et al described a patient with perianal Crohn's disease with a perianal ulcer that persisted despite the surgical management of perianal disease. Biopsies and EBER-ISH confirmed EBV-MCU, and the patient was managed successfully with withdrawal of azathioprine therapy.[10] In our patient, biopsies of the perianal ulcer revealed inflammatory slough only and no evidence of EBV-MCU. The operative specimen demonstrated a near complete response indicating success with rituximab therapy. The decision to proceed to surgery was driven by refractory hematochezia despite rescue therapy with infliximab for his ulcerative colitis.

In conclusion, EBV-MCU is a recently described entity that is driven by immunosuppression, a common issue in patients with IBD. It can present as both shallow ulcerations and a mass resembling colorectal carcinoma and should be considered in the differential diagnosis of patients with IBD.

## DISCLOSURES

Author contributions: PPY Chan: drafting and compilation of the manuscript. M. Farzin, P. Acharya, N. Viiala, A. Gilmore, H. Crane, C. Henderson, W. Ng, and A. Williams: assisted in editing and contributing to the final manuscript. SJ Connor: finalization and compilation of the manuscript. PPY Chan is the article guarantor.

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