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Donor-derived Epstein-Barr Virus Mucocutaneous Ulceration: A Unique and Complex Case of Rectal Hemorrhage

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Epstein-Barr virus (EBV) is pervasive, with a significant proportion of humans being asymptomatic carriers. Latent infection risk is an issue in the immunosuppressed because of the exerted effects of expressed viral proteins on B-lymphocyte maturation and proliferation or because of T-lymphocyte reaction.[1,2] This interaction produces a spectrum of lymphoproliferative disorders that includes EBV-mucocutaneous ulcer (MCU), in which the most severe disease process on the spectrum is posttransplant lymphoproliferative disorder (PTLD).[3]

EBV-MCU is separate from PTLD, because of its indolent clinical course, without its progression to disseminated disease, and despite a significant degree of cytological atypia seen histologically.[4] Although it may not disseminate, it can be locally destructive and, in the case we discuss here, is the only EBV-MCU in the literature in the rectal mucosa to present with rectal hemorrhage. Hemorrhage in a young posttransplant patient is difficult to manage, given reluctance for multiple sensitizing blood transfusions, especially if, as in this case, they are reliant on anticoagulation.

CASE REPORT

A 25-y-old male with end-stage renal failure secondary to IgA nephropathy on hemodialysis attended for a deceased renal transplant from a donation after brainstem death donor in their 40s, mismatch 1-1-0. The recipient had no medical comorbidities and no family history of inflammatory bowel pathology. The viral status was cytomegalovirus (CMV) negative to negative and EBV positive to negative. The transplantation proceeded uneventfully, with discharge on postoperative day 5 with primary function and creatinine trough of 120 μmol/L and an estimated glomerular filtration rate of 72 mL/min/1.73 m^2. Alemtuzumab was an agent for the induction immunosuppression and 13 mg of Advagraf and 50 mg of azathioprine for postoperative immunosuppression. As per our standard postoperative care, the patient was seen weekly in our posttransplant follow-up clinic. The patient gave written consent.

Two months posttransplant, he was admitted in the clinic with general illness and significant graft injury (creatinine >700 μmol/L), requiring dialysis. His symptoms were 1 wk of cough, lethargy, fevers, and persistent diarrhea. His initial computerized tomography (CT) failed to find a septic source but incidentally found a right-sided femoral deep vein thrombosis and left lower lobe pulmonary embolism (PE) with a downstream pulmonary infarct. His EBV polymerase chain reaction was 7.09 log(10) copies/mL, a diagnosis of acute donor-derived EBV infection with incidental deep vein thrombosis and PE was made, dalteparin was commenced, and azathioprine was stopped, maintained now on tacrolimus and prednisolone. The etiology of the thromboembolism was thought to be a hypercoagulable state from prolonged diarrhea producing severe dehydration because of his EBV infection. A transplant biopsy performed because of the significant graft acute kidney injury showed only acute tubular necrosis, along with CT positron emission tomography revealing F-fluorodeoxyglucose avid lymphadenopathy above and below the diaphragm, and within the colon (maximum standardized uptake value 12.7), nonspecific findings were present in both primary EBV and PTLD. Troublesome diarrhea settled shortly after discharge following the 2-wk admission with an EBV DNA level of 6.36 log(10) copies/mL.

Following his discharge, he returned to his weekly clinic appointments and remained well; until 3 mo after discharge, he reported some abdominal pain in the clinic at which point his EBV DNA levels reduced to 4.42 log(10) copies/mL. Then 4 d after clinic, he presented as an emergency with significant rectal bleeding and sepsis, requiring 2 units of packed red blood cells (PRBCs) because of hemodynamic instability and intravenous antibiotics for a vancomycin-resistant enterococcus faecium group D–positive blood culture. A repeat CT positron emission tomography showed that the previously

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extensively avid lymphadenopathy had mostly resolved, but colonic avidity persisted. On flexible sigmoidoscopy, 3 rectal ulcers and 1 anal canal ulcer were seen, with further ulceration in the transverse colon. Initially, the biopsies, given the clinical picture, were reported as consistent with antimetabolite-related colitis. Immunohistochemistry results for CMV, herpes simplex virus, and adenovirus were negative. The pathologist warned of clinical concern for possible underlying lymphoproliferative disorder and rereviewed the slides. As reported, given the morphological features, a panel of immunostains (including CD20, CD79a, CD3, and light chains) demonstrated no evidence of any underlying lymphoproliferative disorder with in situ hybridization for EBV (EBV small RNAs), highlighting only scattered small cells. Blood EBV DNA level at this point was 4.36 log(10) copies/mL, continuing to fall from initial immunosuppression reduction.

Following the initial sigmoidoscopy, the bleeding continued, necessitating 4 further units of PRBCs. A second emergency sigmoidoscopy was performed, demonstrating deep ulceration in the low rectum as the likely source of significant bleeding although not active at the time; however, there appeared to be complete mucosal loss and visible submucosa. The septic picture on admission was theorized to be from translocation of gut flora because of the breach in the mucosa of the large deep low rectal ulcer.

Biopsies showed large intestinal mucosa with a well-circumscribed ulcer and underlying inflamed granulation tissue; numerous withered crypts, cryptitis, and crypt abscess formation; and markedly edematous tissue appearance. The inflammatory infiltrate was polymorphous and consisted of lymphocytes, histiocytes, eosinophils, immunoblasts, Hodgkin-like cells, Reed-Sternberg–like cells, and apoptotic bodies. Furthermore, immunohistochemistry results for HSV and CMV were negative, but EBER showed scanty positive staining in lymphocytes, in keeping with previous or current EBV infection (see Figure 1).

During that time, a further 4 units of PRBCs was to be transfused before an inferior vena cava filter was placed to

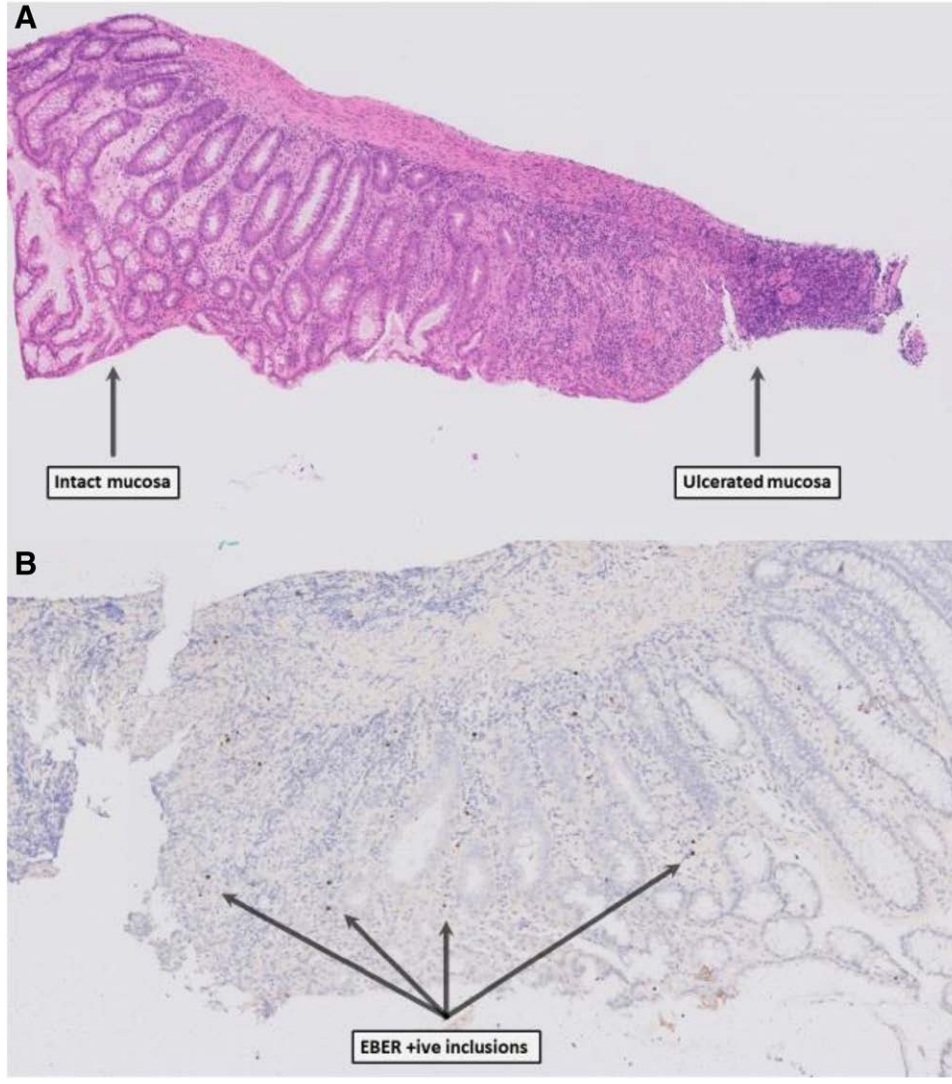

FIGURE 1. Rectal biopsies obtained from second sigmoidoscopy. A, Hematoxylin and eosin–stained large intestinal mucosa showing ulceration surrounded by areas with preserved crypt architecture. At the site of ulceration, inflamed granulation tissue is present. In the vicinity of granulation tissue, numerous withered crypts, cryptitis, and crypt abscess formation are seen. B, Immunohistochemistry results from large intestinal mucosa, herpes simplex virus, and cytomegalovirus tests are negative. EBER shows numerous positive staining in lymphocytes, consistent with Epstein-Barr virus infection. EBER, Epstein-Barr virus small RNAs.

facilitate the cessation of anticoagulation started 4 mo previously. In response to EBV viremia the following week, rituximab (1g IV) was given, and systemic immunosuppression reduced. Three weeks later, the rectal bleeding stopped, the patient stabilized on anticoagulation, and the inferior vena cava filter was removed; blood EBV DNA by that point was undetectable. Unfortunately, during that time, he required a further 7 units of PRBCs (17 in total); however, 1 mo after discharge, he returned to the clinic with stable graft function of creatinine <200 and no further gastrointestinal symptoms.

DISCUSSION

Rectal involvement of EBV-MCU is rare, with only a few cases recorded in the literature and none causing rectal hemorrhage. Dojocinov et al[1] first described EBV-MCU and highlighted its rarity, finding only 26 cases of EBV-MCU from 200 EBV-positive B-cell lymphoproliferative disorder patients during a 15-y period, only 2 of whom had rectal mucosal involvement.[1]

The etiology of EBV-MCU varies from iatrogenic immunosuppression, immune deficiency diseases, and age-related immunosenescence. Hart et al, in a study of 7 patients with EBV-MCU (4 within oral mucosa and 3 within gastrointestinal tract), found consistent immunohistochemical staining with the profile of CD 45, 20, and 30 in their studied lesions. They found ulcers were undermined by variable infiltrate with either polymorphic proliferation or a prominent large cell lymphoproliferation with a less polymorphous background and some with the presence of Reed-Sternberg–like cells.[3] Of these, only CD 20 was present in our patient's pathology specimen, and interestingly, in their series, none of their patients had measurable peripheral blood EBV DNA levels, in contrast to the prolonged raised levels in our case. Perhaps the measurable level correlates with the persistence of an active EBV infection resulting in the severity of the ulcer. The ulcers in our patient's case showed predominately T-cell expression making T-lymphocyte reaction the likely mechanism in these ulcers.

The management reported in the literature is variable and broadly based on PTLD management. In a review of the management of 45 published cases, 10 had no treatment, 19 only needed reduction in immunosuppression, 6 had rituximab, 3 rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone, 2 had resection, and 5 had radiotherapy (1 with rituximab and 1 with rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone). In the series, only 2 had rectal MCU, 1 had rituximab, and 1 had reduced immunosuppression.[5] Our patient had a rapid response with rituximab and concomitant reduction in immunosuppression. Although it is possible the EBV could have been community acquired, the temporal relationship with the EBV-positive transplant suggests that our patient had a primary donor-derived EBV with subsequent EBV-MCU.

Our unique case highlights the complex balancing act often needed in transplant recipient management, where multiple pathologies can arise and aggregate to generate worse problems. Here, we describe venous thromboembolism complicated by transfusion-dependent rectal bleeding and secondary sepsis from donor-derived primary EBV infection. This opportunistic infection occurred because of the significant immunosuppression required in the early transplant period for graft survival that led to a prolonged hospital admission and a large volume of sensitizing transfusions. As a result of this case, we have altered our practice around EBV-naive patients. Although the status of EBV donor and recipient was always checked and patients counseled about the relevant risks, our immune suppression protocol was unaltered. For under 70s, our standard induction protocol is alemtuzumab; however, we now, in the case of EBV-positive donor to a naive recipient, alter this to basiliximab.

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