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CASE REPORTS

Epstein-Barr Virus-Related Diarrhea or Exacerbation of Inflammatory Bowel Disease: Diagnostic Dilemma▽

Ido Weinberg,[1]* Tzahi Neuman,[2] Maya Margalit,[1] Fadeela Ayman,[3] Dana G. Wolf,[3] and Arie Ben-Yehuda[1]

Division of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel[1]; Pathology department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel[2]; and Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, Jerusalem, Israel[3]

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While the presence of Epstein-Barr virus (EBV) in colonic specimens from patients with inflammatory bowel disease (IBD) has been documented, diarrhea secondary to gastrointestinal involvement by EBV in the context of primary EBV infection in patients with IBD has not been reported. We describe a patient with IBD who presented with diarrhea and primary EBV infection and propose a role for colonic involvement by EBV in the pathogenesis of his symptoms.

CASE REPORT

A 26-year-old male was admitted with fever and watery diarrhea of 2 days' duration. Past medical history was significant for indeterminate colitis and primary sclerosing cholangitis. Inflammatory bowel disease (IBD) was diagnosed 18 months earlier, when he presented with abdominal pain. At that time, colonoscopy revealed patchy inflammation throughout the rectum and colon. Biopsies revealed a mixed inflammatory infiltrate in the lamina propria, cryptitis, and crypt abscesses (Fig. 1A).

At the time of admission, the patient was receiving mesalamine (1 g once a day), azathioprine (50 mg once a day), and ursodeoxycholic acid (500 mg twice a day). He denied symptoms consistent with IBD in the months prior to the present episode. The patient's baseline white blood cell count under azathioprine treatment was 4.6×10^9/liter.

Physical examination was significant for fever (39°C), jaundice, and hepatosplenomegaly. The complete blood count revealed leukopenia (white blood cell count, 1.6×10^9/liter, 36.9% lymphocytes) and macrocytic anemia (hemoglobin, 7.7 g/dl, and mean corpuscular volume, 116.5 fl). The blood smear revealed atypical lymphocytes and multiple rouleaux formations. The serum C-reactive protein level was elevated (3.8 mg/dl [normal, <1 mg/dl]).

Serological tests for Epstein-Barr virus (EBV) infection disclosed immunoglobulin M (IgM) and IgG anti-viral capsid antigen antibodies and borderline levels of anti-EBV nuclear antigen antibodies. EBV antibodies were negative in serum samples collected 3 and 15 months before the current hospitalization. Serum PCR for EBV DNA was positive (4,650 copies/ml). PCR for cytomegalovirus DNA was negative. Stool culture and microscopy were negative for pathogens; stool enzyme-linked immunosorbent assay for *Clostridium difficile* toxin was negative.

Sigmoidoscopy revealed normal-appearing mucosa; random biopsies showed a reduced number of crypts, crypt distortion, cryptitis with numerous apoptotic bodies, and a mixed inflammatory infiltrate in the lamina propria with abundant eosinophils (Fig. 1B and C). PCR of DNA extracts from biopsies was positive for EBV DNA; in situ hybridization for EBV-encoded small RNA 1 (EBER-1) was positive in epithelial cell nuclei (Fig. 1D). Viral inclusion bodies were not observed; results of immunohistochemical staining for cytomegalovirus and EBV latent membrane protein-1 were negative.

On admission, empirical intravenous corticosteroid (CS) treatment was initiated for presumed IBD exacerbation. In view of the leukopenia, azathioprine was withheld. Upon clarification of the clinical picture, which was thought to be consistent with primary EBV infection with colonic involvement on a background of relatively quiescent IBD, CS treatment was stopped. Marked improvement of symptoms and abnormal lab results occurred within a week, without specific treatment.

Patients with IBD are occasionally hospitalized due to fever, abdominal pain, and diarrhea, which are commonly attributed to an exacerbation of their underlying disease. Cytomegalovirus infection may also cause these symptoms, especially in immunosuppressed patients (6). EBV infection is usually characterized by a self-limited, nonspecific illness or an infectious mononucleosis syndrome (7). While the presence of EBV in colonic specimens from patients with IBD has been documented (1, 5, 10–13), to our knowledge, the presence of diarrhea secondary to gastrointestinal involvement by EBV in patients with IBD and primary EBV infection has not been reported. We describe a patient with IBD who presented with primary EBV infection and diarrhea and propose a role for

* Corresponding author. Mailing address: Division of Medicine, Hadassah University Hospital, POB 12000, Jerusalem, Israel. Phone: 972-2-6777111. Fax: 972-2-6777740. E-mail: idow@hadassah.org.il.

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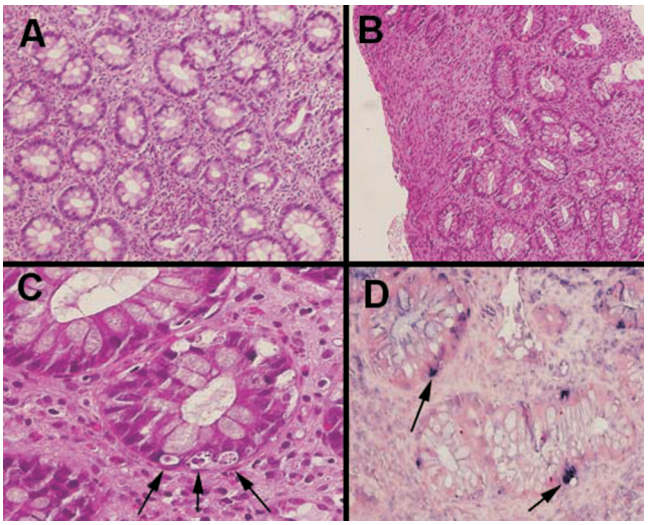

FIG. 1. (A) Mixed inflammatory infiltrate in the lamina propria (H&E; magnification, ×100). (B) Paucity of crypts, crypt distortion, cryptitis, and abundant apoptotic bodies (H&E; magnification, ×100). (C) High-resolution image of apoptotic bodies (arrows); abundant eosinophils can also be observed (H&E; magnification, ×300). (D) In situ hybridization for EBER; arrows point to positive signals in epithelial cell nuclei (magnification, ×200).

colonic involvement by EBV in the pathogenesis of his symptoms.

To our knowledge, the presence of diarrhea secondary to gastrointestinal involvement by EBV in the context of primary EBV infection in patients with IBD has not been reported. As diarrhea is not characteristic of primary EBV infection, this symptom was initially attributed to an exacerbation of the patient's underlying IBD, and high-dose CS treatment was initiated. Lack of clinical improvement despite CS treatment; the presence of EBV in colonic biopsies (particularly viral presence in epithelial cells); the eventual spontaneous improvement of gastrointestinal symptoms, which was temporally correlated with resolution of other symptoms; and lack of an alternative explanation led us to believe that EBV had a significant role in the pathogenesis of the patient's diarrhea.

Two possible predisposing conditions for gastrointestinal involvement by EBV in this patient are his underlying IBD and immunosuppression.

The presence of EBV in the gastrointestinal tract of IBD patients has been documented by others. Takeda et al. reported a patient with persistently active ulcerative colitis; EBV was found in biopsy specimens from the rectum and terminal ileum in both epithelial cells and lymphocytes. Although the presence of primary EBV infection could not be established, they noted elevated anti-EBV viral capsid antigen IgG and EBV nuclear antigen antibodies. In contrast to our patient, their patient's symptoms did not correlate with other clinical manifestations of EBV infection and abated only upon the introduction of aggressive treatment for IBD (11).

The presence of EBV in gastrointestinal tissue from IBD patients, as determined by PCR (1, 12), immunohistochemistry, or in situ hybridization, has also been reported in several small studies in which colon biopsies were examined retrospectively (5, 10, 13). Unfortunately, no clinical correlates were provided in these studies. In one study, in which the presence of EBV in colonic specimens from patients with and without IBD was established by in situ hybridization, EBV RNA was detected in B ($CD20^+$) lymphocytes in sites of IBD involvement (13). In another report, EBV RNA was present in lymphocytes in colonic biopsy samples of 7 of 17 patients (41%) with active ulcerative colitis (1). Serum PCR for EBV DNA, which was positive in these patients, was negative in controls, including patients with Crohn's disease and other types of colitis. In contrast to these findings, Gehlert et al. documented EBV-infected lymphocytes in biopsy specimens with or without active inflammation in patients with either ulcerative colitis or Crohn's disease (5). Speiker and Herbst used EBER (1 and 2) and BZLF1 as markers of latent or active EBV infection, respectively. EBER positivity was documented in 57 of 116 (49%) specimens from patients with IBD and was more frequent and prominent in specimens from patients with ulcerative colitis than from those with Crohn's disease. BZLF positivity was documented in only two of the specimens, both from patients with ulcerative colitis. The authors suggested that the presence of latent EBV markers may signify locally impaired antiviral immunity, which can affect the nature of the inflammatory reaction, particularly in ulcerative colitis (10).

Immunosuppression may also be expected to increase the susceptibility to gastrointestinal involvement by EBV in IBD patients. A predisposition to severe primary EBV infection and EBV-associated lymphoma has been reported in IBD patients treated with azathioprine (3, 8). Gastrointestinal involvement by EBV has been documented in the context of posttransplant lymphoproliferative disorder, for which primary exposure to EBV is an important risk factor (9). To our knowledge, the incidence of gastrointestinal involvement by EBV in nontransplanted immunosuppressed patients has not been reported. Notably, EBV was reported by Clayton et al. to cause gastrointestinal hemorrhage and ulceration in an immunocompetent host (2).

We suggest that in IBD patients who present with diarrhea and clinical manifestations of primary EBV infection, symptomatic colonic involvement by EBV should be actively sought by colonic biopsies and specific stains for EBV, as evidence of EBV infection is not readily apparent on standard hematoxylin and eosin (H&E)-stained specimens. This may be particularly relevant in younger patients with IBD, as primary EBV infection is common in this age group. Differentiation between EBV involvement of the gastrointestinal tract and IBD exacerbation has important therapeutic implications, as reduction rather than augmentation of immunosuppression may be warranted.

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