Epstein Barr virus - related diarrhea or exacerbation of inflammatory bowel disease: A diagnostic dilemma

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Abstract

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 (GI) 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.

Key Words: Epstein Barr virus, inflammatory bowel disease, exacerbation
Introduction

Patients with inflammatory bowel disease (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 [1]. Epstein Barr Virus (EBV) infection is usually characterized by a self limited, non specific illness or an infectious mononucleosis syndrome [2]. While the presence of EBV in colonic specimens from patients with IBD has been documented [3-8], to our knowledge, the presence of diarrhea secondary to GI 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 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 two days’ duration. Past medical history was significant for indeterminate colitis and primary sclerosing cholangitis. 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 (figure 1A).

At the time of admission, the patient was receiving mesalamine (1g x 1/d), azathioprine (50 mg x 1/d) and ursodeoxycholic acid (500 mg X 2/d). 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 4.6X10⁹/L.

Physical examination was significant for fever (39°C), jaundice and hepatosplenomegaly. The complete blood count revealed leukopenia (white blood cells 1.6X10⁹/L, 36.9% lymphocytes) and macrocytic anemia (Hb –7.7 g/dL, MCV – 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 EBV infection disclosed IgM and IgG anti VCA (viral capsid antigen) antibodies, and borderline levels of anti EBV nuclear antigen (EBNA)
antibodies. EBV antibodies were negative in serum samples collected 3 and 15 months before the current hospitalization. Serum PCR for EBV DNA was positive (4650 copies/ml). PCR for CMV DNA was negative. Stool culture and microscopy were negative for pathogens; stool ELISA 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 (Figures 1B and 1C). PCR of DNA extracts from biopsies was positive for EBV DNA; *in situ* hybridization for EBER-1 (EBV-encoded small RNAs - 1) was positive in epithelial cell nuclei (Figure 1D). Viral inclusion bodies were not observed; immunohistochemical stainings for CMV and EBV-LMP-1 (EBV-Latent Membrane Protein 1) were negative.

On admission, empirical intravenous corticosteroid 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, corticosteroid treatment was stopped. Marked improvement of symptoms and abnormal lab results occurred within a week, without specific treatment.
Discussion

To our knowledge, the presence of diarrhea secondary to GI 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 corticosteroid (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 inflammatory bowel disease 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 – VCA IgG and EBNA antibodies. In contrast to our patient, their patient's symptoms did not correlate with other clinical manifestations of EBV infection and abated only upon introduction of aggressive treatment for IBD [8].

The presence of EBV in gastrointestinal tissue from IBD patients, as determined by PCR [3, 7], immunohistochemistry or in situ hybridization, has also been reported in several small series in which colon biopsies were examined retrospectively [4-6]. 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 [4]. In another report, EBV RNA was present in lymphocytes in colonic biopsy samples of 7 of 17 patients (41%) with active ulcerative colitis [7]. 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 contrary
to these findings, Gehlert et al. documented EBV-infected lymphocytes in biopsy specimens with or without active inflammation in patients with either UC or CD [6].

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 UC than in CD. BZLF1 positivity was documented in only 2 of the specimens, both from patients with UC. 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 UC [5].

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 [9, 10]. Gastrointestinal involvement by EBV has been documented in the context of the post transplant lymphoproliferative disorder, for which primary exposure to EBV is an important risk factor [11]. To our knowledge, the incidence of gastrointestinal involvement by EBV in non-transplanted immunosuppressed patients has not been reported. Notably, EBV was reported by Clayton et. al. to cause gastrointestinal hemorrhage and ulceration in an immunocompetent host [12].

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 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.
**Figure 1**

A. Mixed inflammatory infiltrate in the lamina propria (H&E; x100).

B. Paucity of crypts, crypt distortion, cryptitis and abundant apoptotic bodies (H&E; x100)

C. High resolution image of apoptotic bodies (arrows); abundant eosinophils can also be observed (H&E; x300)

D. *In situ* hybridization for EBER; arrows point to positive signals in epithelial cell nuclei (x200)
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