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SHORT COMMUNICATION

Clinical and endoscopic complications of Epstein-Barr virus in inflammatory bowel disease: an illustrative case series

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Abstract

Background and aim Epstein-Barr virus (EBV) is a proposed trigger in the etiopathogenesis of inflammatory bowel disease (IBD) and is associated with lymphoproliferative diseases. Nevertheless, testing for EBV DNA in the intestinal mucosa and screening for EBV infection before initiation of a drug therapy are not routinely performed. The aim of this article is to increase awareness of the relevance of EBV infection in specific clinical situations.

Methods In this short communication, we describe the disease course of three IBD patients with EBV infection, varying from EBV reactivation during disease flare up to a trigger of EBV-related mucocutaneous ulcer (EBV-MCU) and haemophagocytic lymphohistiocytosis (HLH).

Results Our first patient was diagnosed with EBV reactivation-associated severe colitis and showed a rapid clinical improvement after induction therapy with infliximab and azathioprine. Without antiviral treatment, the patient remained in complete remission and no complications of EBV were seen. After diagnosing EBV-MCU in the second patient, immunosuppressive medication was discontinued and four infusions of rituximab resulted in a rapid clinical recovery and eventually complete response. After discontinuation of the immunosuppression in our last patient with haemophagocytic lymphohistiocytosis, treatment with a combination of corticosteroid and antiviral therapy resulted in a complete recovery over a time span of several weeks.

Conclusion EBV infection has a wide variety of potentially life-threatening clinical manifestations in IBD patients. Testing for EBV in case of a flare up and screening for EBV before the start of immunosuppressive therapy will create awareness for EBV-related symptoms or complications during follow-up.

Keywords Inflammatory bowel disease · Epstein Barr-virus · Haemophagocytic lymphohistiocytosis · EBV-associated mucocutaneous ulcer

Introduction

Epstein-Barr virus (EBV) has been proposed as a trigger in the complex multifactorial etiopathogenesis of inflammatory bowel disease (IBD) [1], as well as an aggravating agent during flares and for perpetuation of the inflammatory process. [2] In addition, EBV-associated lymphoproliferative disease in IBD is a feared complication, mostly attributed to immunosuppressive agents. [3] Nevertheless, indications for testing the presence of EBV in intestinal mucosa of IBD patients are unclear and serologic EBV screening before initiation of drug therapy is not routinely performed. To increase awareness of its relevance, we describe the disease course of three IBD patients with an EBV infection.

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Case 1

A 29-year-old male patient with ulcerative proctitis, Montreal classification E1S2, in complete remission for 4 years, presented with a 4-week history of bloody diarrhoea, low-grade fever and weight loss. Physical examination was unremarkable. Blood results showed CRP (C-reactive protein) 109 (< 10) mg/L, haemoglobin (Hb) 6.6 (8.6–10.5) mmol/L and

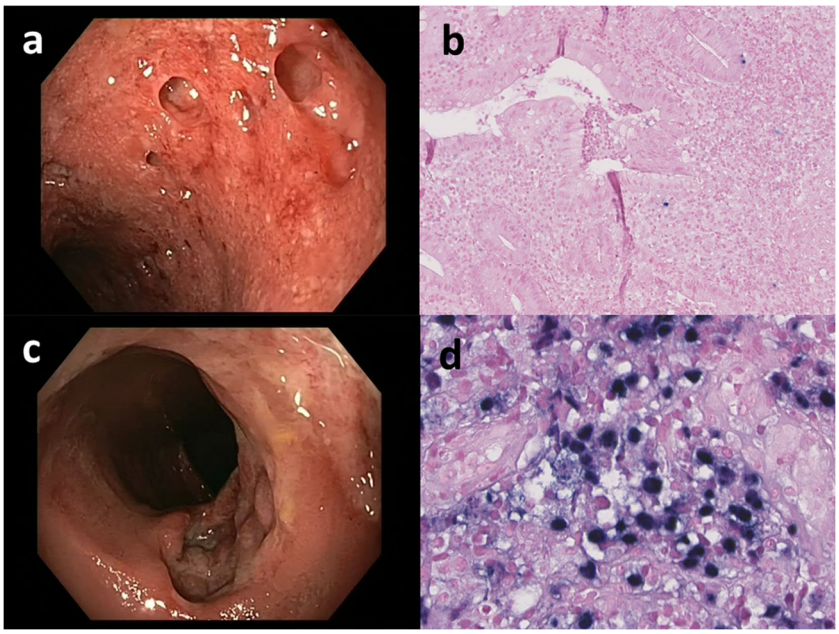

Fig. 1 **a** Punched-out ulcers as endoscopic findings of EBV-associated colitis in active ulcerative colitis, associated with reactivation of EBV infection. **b** Diffuse severe chronic and active inflammation, cryptitis and crypt abscesses. Few EBER-positive lymphocytes in the lamina propria in the colon-epithelium (EBER × 200). **c** Deep punched-out ulcer of 15 × 20 mm in the descending colon. **d** Chronic active ulcerative inflammation with EBV-positive immunoblasts (EBER, × 200)

white blood cell count (WBC) 12.1 (3.5–10) × 10^9/L. Renal function and liver tests were normal. Sigmoidoscopy revealed a diffuse, erythematous, thickened mucosa with erosions and fibrin. Scattered throughout the mucosa, there were numerous typical small cavities, measuring 2 to 5 mm (Fig. 1a). Pathology examination demonstrated chronic active inflammation with ulceration, cryptitis, crypt abscesses and several EBV-encoded RNA (EBER)-positive lymphocytes (non-blasts) (Fig. 1b). Polymerase chain reaction (PCR) on biopsy specimens tested positive for EBV and negative for HSV1 and HSV2 and CMV. Serology was positive for immunoglobulin G (IgG) EBV viral capsid antigen (VCA), Epstein-Barr nucleid acid (EBNA) and early antigen (EA) antibodies and negative for immunoglobulin M (IgM) EBV VCA. A severe exacerbation of ulcerative colitis complicated by reactivation of EBV was diagnosed. Patient started induction therapy with infliximab and azathioprine and showed a rapid clinical improvement. No complications of EBV were seen, and patient remained in long-term clinical, biochemical and endoscopic remission.

Case 2

A 34-year-old male patient with ulcerative colitis, Montreal classification E2S2, with long-term clinical remission with mesalamine and 6-mercaptopurine (6-MP) presented with abdominal pain, night sweats haematochezia and severe anal pain. Sigmoidoscopy revealed a deep ulcer measuring 15 × 20 mm in the descending colon, several smaller ulcers in the sigmoid colon and a large circumferential rectal ulcer measuring 10 cm, localised above the anal ring (Fig. 1c). Colon biopsies showed a large area of chronic active, necrotic ulceration with a polymorphous infiltrate of lymphocytes and medium- and large-sized immunoblasts. The immunoblasts were especially EBV-encoded RNA (EBER) immunohistochemistry positive (Fig. 1d). Clonality was proven with immunoglobulin gene rearrangement analysis. Blood tests showed CRP 43 (< 10) mg/L, Hb 7.4 (8.6–10.5) mmol/L, WBC 4.6 (3.5–10) × 10^9/L and lactate dehydrogenase (LDH) 153 (< 248) U/L. Renal and liver function were unremarkable. PCR for EBV-DNA on the biopsies was positive.

As EBV-related mucocutaneous ulcer (EBV-MCU) and diffuse large B cell lymphoma were considered, 6-MP was stopped, patient was referred to the haematologist and a positron emission tomography (PET) scan was performed. The PET scan showed only local FDG avidity in the descending colon and rectum with two enlarged perirectal lymph nodes. EBV-MCU was the most likely diagnosis. After 4 weeks, the ulcer slightly decreased in size, but colonic biopsies showed persistent necrotic ulceration with EBV-positive immunoblasts. Treatment with four infusions of rituximab was prescribed and a rapid clinical recovery occurred. During 1-year follow-up, gradual improvement of the ulcer was seen, without signs of lymphoma in the colon biopsies. Patient remained in clinical remission with mesalamine monotherapy.

Case 3

A 17-year-old female patient, presented with a 2-week history of fever, night sweats and painless cervical lymphadenopathy. She had been treated with azathioprine for 1 year for Crohn's disease (CD), Montreal classification A1L1B1. EBV status was unknown prior

to presentation. At physical examination, an enlarged submandibular lymph node was noted. Blood tests showed CRP 45 (< 10) mg/L, Hb 5.6 (7.5–9.5) mmol/L, WBC 1.6 (3.5–10) × 10^9/L (lymphocytes 24.2% neutrophils 1.17 (1.5–7.5) × 10^9/L), bilirubin 109 (0–16) μmol/L, ALAT 193 (< 34) U/L, ferritin 1798 (10–140) μg/L, fibrinogen 3.5 (1.5–3.6) g/L, triglycerides 1.58 (0.4–1.6) mmol/L and soluble IL-2 receptor 67,200 (0–2500) pg/mL. A primary EBV infection was concluded after measuring high levels of EBV IgM antibodies and EBV viral load of 112.000 IU/mL using PCR. Computed tomography (CT) scan showed diffuse lymphadenopathy and hepatosplenomegaly. Lymph node aspiration showed architectural distortion with small T cell and B cell lymphocytes, some of which are EBER positive, compatible with a primary EBV infection. Bone marrow aspirate revealed increased numbers of macrophages and haemophagocytosis, after which haemophagocytic lymphohistiocytosis (HLH) was diagnosed. Treatment with azathioprine was stopped and oral dexamethasone and acyclovir were started. Shortly thereafter, a rapid fall of the EBV viral load was measured. Ferritin rose to a maximum of 4978 μg/L and total bilirubin and ALAT to a maximum of 201 μmol/L and 768 U/L, respectively. Acyclovir was discontinued after 10 days; dexamethasone was tapered in 30 days.

Three months later, the EBV viral load had decreased to a minimal value and hepatosplenomegaly had disappeared. Without immunosuppressive medication, she remained in long-term remission.

Discussion

These cases illustrate the spectrum of clinical and endoscopic complications of EBV infection in IBD patients. Several studies have reported on the presence of EBV in the intestinal mucosa of IBD patients with active inflammation and observed prevalences are as high as 64% using PCR assays of the EBV genome in inflamed colonic mucosa. [1, 4] However, it remains unclear whether the virus is involved in the pathogenesis or is an innocent bystander. The first case of this series is in line with previous observations that presence of EBV in inflamed colonic mucosa and increased proliferation are associated with severe mucosal inflammation. [5] Active inflammation with intramucosal expansion of EBV-infected B-lymphocytes might cause local impairment of viral immunity and subsequently self-perpetuation of the disease process. [2, 5] Mucosal immunity may be impaired because of the IBD itself, or may result from immunosuppressive medication. The immunomodulatory effects of EBV could delay the resolution of the IBD-associated inflammation, thus contributing to disease progression.

The colonic mucosal cavities seen in case 1 are similar to the punched-out ulcers that have been described in CMV-associated colitis. [6] To our knowledge, this is the first case in which this type of endoscopic findings is attributed to an associated solitary EBV infection. In CMV-associated colitis, antiviral treatment has the potential to shorten duration of severe exacerbations. [7] Although our patient responded rapidly to immunosuppressive therapy only, antiviral treatment may be valuable in patients with refractory disease showing signs of EBV-related disease. [8]

EBV-positive mucocutaneous ulcer (EBV-MCU), as described in case 2, is a rare B cell lymphoproliferative disorder that can affect the oropharynx, gastrointestinal tract and skin. [9] Main risk factors for the development of EBV-MCU are immunosuppression and age-related immunosenescence. [9] Principle treatment consists of cessation of immunosuppressive medication; however, in some patients, more intensive therapy is necessary. [9] Lymphoproliferative disorders occur more often in IBD, particularly in patients on thiopurines, and are frequently associated with EBV infection. [3] Thiopurines may be responsible for decreased immunosurveillance of EBV-infected B cells. Since the absolute lymphoma risk is still very low, it remains unclear whether this association justifies restrictive use of thiopurines for IBD. [3]

The European Crohn's and Colitis Organisation guideline recommends to consider screening for EBV infection before initiation of thiopurines. [7] Consideration implies this is not routinely performed in clinical practice. Case 3 illustrates a rare complication of an EBV infection in a young IBD patient treated with azathioprine. HLH is a potentially fatal lymphoproliferative disorder in which macrophages are overstimulated resulting in phagocytosis of all bone marrow-derived cells. [10] Although a primary EBV infection is considered the main initiator of this severe complication, other infections have been identified as triggers too. [11] Screening for EBV before start of thiopurines can identify high-risk individuals and lead to more restrictive use of thiopurines or more intensive surveillance. However, since the vast majority of adults will be seropositive and thiopurines remain a valuable option also in a negative serostatus, screening strategies are an issue of debate. [12]

In conclusion, EBV infection is associated with a variety of clinical manifestations in IBD patients, which is illustrated albeit not restricted to the described cases in this manuscript. Awareness of EBV infection in IBD patients should be increased, and biopsies should be assessed for the presence of EBV in patients with specific endoscopic findings of mucosal cavities, ulcerative tumours or large ulcerative punched-out lesions. In addition, screening for EBV infection prior to initiation of immunosuppressive medication may be useful to create alertness for EBV-related complications during

follow-up, and to carefully weigh the risks and benefits of the immunosuppressive treatment, especially in children and adolescents.

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