

Case Report

Epstein-Barr infection of the colon in a patient with first attack of severe ulcerative colitis: A case report and review of the literature

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SUMMARY

Epstein-Barr virus infection is related to oral carcinoma, beta-lymphocytic lymphoma, oral leucoplacia and sarcoidosis. To the best of our knowledge there are no case reports describing concurrent appearance of severe ulcerative colitis and infection with Epstein-Barr virus. Aim: The aim of this study was to present a patient with severe first attack of total ulcerative colitis and concurrent infection of the inflamed bowel mucosa with Epstein-Barr virus. Case report: A man aged 34, was admitted to our department complaining of bloody diarrhoea, fever, abdominal pain and fatigue of one month duration. The diagnosis of total ulcerative colitis was based on the endoscopic and histological picture of the colon mucosa, as well as on the exclusion of other causes of colitis, mainly of infectious origin. The situation of the patient improved slowly over the next few days after application of prednisolone 1mg/KgBW per day, and metronidazole and ciprofloxacin for the first 5 days. However, clinical symptoms reappeared after 2 weeks while the patient was on reduced doses of prednisolone with the main clinical symptoms being bloody diarrhoea, abdominal pain, severe anaemia, and hypoalbuminemia. Both, serum antibodies against cytomegalovirus and polymerase chain reaction assay on the large bowel mucosa for CMV were negative. However, search for the presence of Epstein-Barr in the bowel mucosa (polymerase chain reaction) became positive. The patient improved con-

siderably with antivirus treatment while the administration of prednisolone was continued. The source of the infection was probably his wife, as she developed severe infectious mononucleosis some weeks before. In the follow-up period of two years another exacerbation of colitis of moderate severity appeared which was settled promptly. Conclusion: Infection with Epstein-Barr virus could complicate the course of patients with severe attack of ulcerative colitis. The exact role of this co-infection on the pathogenesis and course of ulcerative colitis remains obscure.

Key words: Inflammatory bowel disease, Epstein-Barr virus, ulcerative colitis

INTRODUCTION

Severe chronic active Epstein-Barr virus infection (EBV) is a rare, debilitating, nonneoplastic, inflammatory disorder. EBV infection has been linked to oral carcinoma, beta-lymphocytic lymphoma, oral leucoplacia and sarcoidosis.¹⁻³

There are some reports claiming that EBV infection is associated with acute exacerbations of chronic inflammatory bowel disease (IBD). In a relevant study, it was reported that in 5 children EBV infection was associated with acute flare-ups of ulcerative colitis (UC).⁴ Moreover, reactivation of latent herpes viruses was identified in children with active disease indicating that the converse relationship may also occur.⁴

On the other hand, increased numbers of EBV-infected B lymphocytes have been detected in intestinal mucosal samples affected by UC and, to a lesser extent, by Crohn's disease (CD).⁵

Finally, EBV may be detected in the neoplastic tissues of lymphomas of patients with CD treated with immunosuppressants and infliximab.⁶

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However, there are no so many studies related to the role of this virus in the pathogenesis and clinical course of patients with UC and descriptions of EBV infection in patients with severe first attack of UC have not been so far published.

The aim of this presentation is to describe a male patient with severe first attack of UC and documented concurrent infection of the inflamed bowel mucosa with EBV. The patient responded well to specific antiviral treatment.

CASE REPORT

A man aged 34, was admitted to our department complaining of bloody diarrhoea, fever, abdominal pain, loss of weight and fatigue of one month duration. Diagnosis of total UC was based on the compatible endoscopic and histological picture of the colon mucosa, as well as on the exclusion of other causes of colitis, mainly of infectious origin. The situation of the patient improved slowly over the next few days after administration of prednisolone intravenously at a dose of 1mg/Kg BD per day, and antibiotics (metronidazole and ciprofloxacin) for the first 5 days. However, clinical symptoms reappeared after 2 weeks while the patient was on reduced doses of prednisolone with main clinical symptoms being bloody diarrhoea, abdominal pain, anaemia, and hypoalbuminemia. Both, serum antibodies against cytomegalovirus and polymerase chain reaction applied on the large bowel mucosa, were negative. However, polymerase chain reaction assay on the diseased colonic mucosa revealed the presence of Epstein-Barr infection (Picture 1). Over the next days, the patient improved considerably with antiviral treatment (Gancyclovir IV) while the administration of prednisolone was continued. The source of the infection was probably his wife, as she some weeks before she developed severe infectious mononucleosis. In the follow-up period of two years he developed another exacerbation of colitis of moderate severity which was settled with specific treatment.

DISCUSSION

This report describes the case of a 34-year old man with severe attack of total UC complicated by EBV infection. Diagnosis of UC was based on the classical clinical, endoscopic and histological criteria, while diagnosis of EBV co-infection was documented by polymerase chain reaction in the inflamed bowel mucosa. The patient responded well to specific treatment for UC as well as to the concurrently administered of specific antiviral treatment.

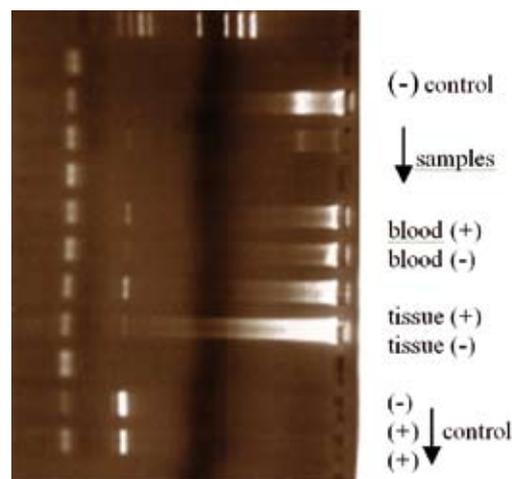


Figure 1. Epstein-Barr virus detection in blood and tissue specimens of a patient with severe ulcerative colitis

To the best of our knowledge, there are no such descriptions in the relevant literature concerning adult patients. However, in paediatric patients severe chronic active EBV infection could initially be presented with clinical and histopathologic features consistent with IBD, although subsequent investigation led to the diagnosis of concurrent EBV infection⁷. The consequences of co-infection with EBV in patients with IBD could probably be a more severe course sometimes making the colectomy unavoidable. We suggest the search for EBV and cytomegalovirus infection in all cases of UC with severe clinical course. Detection of EBV may help to discriminate between active UC and other inflammatory bowel diseases. Colon mucosa is a potential site of EBV replication and may be relevant for EBV transmission⁸. B lymphocytes predominate as the site of latent EBV infection in the colon and are most numerous in UC. In active UC, EBV-positive lymphocytes accumulated under and within the epithelium. It is expected that administration of the specific antiviral treatment would facilitate the appearance of clinical remission.

However, the importance of the concurrent appearance of UC and EBV infection lies in the possible etiological relationship between them. Although the pathogenesis of IBD remains unclear, several studies have suggested that the onset and development of IBD require the interaction between genetic susceptibility, stimulation by luminal bacterial antigens, and episodic environmental triggers which break the mucosal barrier.

In treatment-refractory and fulminant cases of UC infectious causes have to be kept in mind. Numerous viral and bacterial agents have been associated with complicated or treatment-refractory course of UC especially in

immunocompromised patients. In a relevant study it was found that EBV and adenovirus infection was associated with acute exacerbations of IBD in 5 out of 72 children with chronic IBD.⁹ In the same study it was noticed that reactivation of latent herpes viruses was identified in 4 children with active disease indicating that the converse relationship may also occur.

In an attempt to clarify the relationship between EBV infection and UC, Bertalot et al¹⁰ tried analyzed biopsies obtained from total colectomies for UC for the expression of EBV-proteins and RNAs. They found that 6 biopsies and 4 colectomies from 7 UC patients showed scattered lymphocytes expressing nuclear EBV-encoded small RNA1-2 (EBER 1-2) and harbouring polymerase chain reaction-amplifiable EBV-DNA. In some cases, linear viral DNA (typical of lytic EBV infection) was also found. They stated that the existence of EBV infection in the mucosal inflammatory cells of some UC patients suggests a possible role of this virus in the chronicity of UC.

Yanai et al¹¹ also tested the presence of EBV in the colon of IBD patients using highly sensitive in situ hybridization for EBV EBER-1. EBER-1 was detected in 63.6% of CD patients and 60% of UC patients, but not at all in noninflammatory controls and appendicitis cases. EBER-1-positive cells were very rare in the noninflammatory areas of colonic specimens from IBD patients. Moreover, EBER-1-positive cells were nonepithelial cells, located in erosive or ulcerative areas of the colonic specimens. Again these authors suggest that the presence of EBV-infected cells in the diseased areas of IBD colonic specimens could be in favour of the assumption that EBV infection may truly be related to IBD.

Gehlert et al¹² found larger numbers of EBV-infected cells in areas of active inflammation of UC patients and CD as compared to areas of inactive inflammation. They also found increased numbers of EBV-induced gene 3-expressing cells in areas of active inflammation of UC and CD although there was no statistically significant difference between the two diseases. The authors suggest that increased numbers of EBV-infected cells in areas of active IBD are secondary to influx or local proliferation of inflammatory cells.

The importance of EBV infection becomes greater if one takes into account the relationship between EBV and lymphoma development. Wong et al¹³ detected the presence of EBV in IBD patients who developed lymphomas but not in IBD patients who developed adenocarcinoma. It is widely accepted that treatment of IBD with immunosuppressants appears to be associated with a small increased

risk of EBV-positive lymphoma.¹⁴ It has been proposed that EBV-DNA in plasma or in faeces may be a candidate tumour marker in IBD patients at risk of developing lymphoma.¹⁵ Infliximab infusion does not seem to increase significantly EBV-viral load in the short-term.¹⁶ However, some patients with CD have transient, very high EBV-viral load values that are compatible with an increased risk of NHL in the transplant setting.

In conclusion, infection with EBV could complicate first attack of severe UC. Despite the plethora of information, the exact role of this co-infection on the pathogenesis of UC remains obscure. Further studies are needed in order to clarify the role of this infection in the course of UC and the appearance of lymphoma in some patients.

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