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Contents

Monthly Volume 15 Number 3 March 27, 2023

MINIREVIEWS

- 307 Surgical management of acute pancreatitis: Historical perspectives, challenges, and current management approaches
Alzerwi N
- 323 Current trends in perioperative treatment of resectable gastric cancer
Yıldız İ, Özer L, Şenocak Taşçı E, Bayoglu İV, Aytac E
- 338 Vascular injury during laparoscopic cholecystectomy: An often-overlooked complication
Pesce A, Fabbri N, Feo CV

ORIGINAL ARTICLE

Basic Study

- 346 Differential expression and significance of 5-hydroxymethylcytosine modification in hepatitis B virus carriers and patients with liver cirrhosis and liver cancer
Li YC, Hu WY, Li CH, Zhang LL, Xu XW, Li J, Luo HX

Retrospective Cohort Study

- 362 Compliance with enhanced recovery after surgery predicts long-term outcome after hepatectomy for cholangiocarcinoma
Jongkatkorn C, Luvira V, Suwanprinya C, Piampatipan K, Leeratanakachorn N, Tipwaratorn T, Titapun A, Srisuk T, Theeragul S, Jarearnrat A, Thanasukarn V, Pughkem A, Khuntikeo N, Pairojkul C, Kamsa-Ard S, Bhudhisawasdi V
- 374 Pain management in patients with hepatocellular carcinoma after transcatheter arterial chemoembolisation: A retrospective study
Guan Y, Tian Y, Fan YW

Retrospective Study

- 387 Risk factors and prediction model for inpatient surgical site infection after elective abdominal surgery
Zhang J, Xue F, Liu SD, Liu D, Wu YH, Zhao D, Liu ZM, Ma WX, Han RL, Shan L, Duan XL
- 398 Percutaneous management in hepatic alveolar echinococcosis: A sum of single center experiences and a brief overview of the literature
Eren S, Aydın S, Kantarci M, Kızılgöz V, Levent A, Şenbil DC, Akhan O
- 408 Clinical features of acute esophageal mucosal lesions and reflux esophagitis Los Angeles classification grade D: A retrospective study
Ichita C, Sasaki A, Shimizu S
- 420 Positive correlation between latent Epstein-Barr virus infection and severity of illness in inflammatory bowel disease patients
Wei HT, Xue XW, Ling Q, Wang PY, Zhou WX

Clinical Trials Study

- 430** Efficacy and outcome of extensive intraoperative peritoneal lavage plus surgery *vs* surgery alone with advanced gastric cancer patients

Song ED, Xia HB, Zhang LX, Ma J, Luo PQ, Yang LZ, Xiang BH, Zhou BC, Chen L, Sheng H, Fang Y, Han WX, Wei ZJ, Xu AM

Randomized Controlled Trial

- 440** Endoscopic mucosal resection with double band ligation versus endoscopic submucosal dissection for small rectal neuroendocrine tumors

Huang JL, Gan RY, Chen ZH, Gao RY, Li DF, Wang LS, Yao J

SYSTEMATIC REVIEWS

- 450** Preoperative risk modelling for oesophagectomy: A systematic review

Grantham JP, Hii A, Shenfine J

META-ANALYSIS

- 471** Effect of music therapy on chemotherapy-induced nausea and vomiting in gastrointestinal cancer: A systematic review and meta-analysis

Zhong FP, Zhong J, Zhong MY

CASE REPORT

- 480** Immunotherapy in combination with chemotherapy for Peutz-Jeghers syndrome with advanced cervical cancer: A case report

Hu XC, Gan CX, Zheng HM, Wu XP, Pan WS

- 488** Xanthogranulomatous inflammation requiring small bowel anastomosis revision: A case report

Wang W, Korah M, Bessoff KE, Shen J, Forrester JD

ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Retrospective Study

Positive correlation between latent Epstein-Barr virus infection and severity of illness in inflammatory bowel disease patients

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Abstract

BACKGROUND

Emerging studies indicate the critical involvement of microorganisms, such as Epstein-Barr virus (EBV), in the pathogenesis of inflammatory bowel disease (IBD). Immunosuppressive therapies for IBD can reactivate latent EBV, complicating the clinical course of IBD. Moreover, the clinical significance of EBV expression in B lymphocytes derived from IBD patients' intestinal tissues has not been explored in detail.

AIM

To explore the clinical significance of latent EBV infection in IBD patients.

METHODS

Latent EBV infection was determined by double staining for EBV encoded RNA and CD20 in colon specimens of 43 IBD patients who underwent bowel resection. Based on the staining results, the patients were divided into two groups, according to their latent EBV infection states - negative ($n = 33$) and positive ($n = 10$). Illness severity of IBD were assigned according to Crohn's disease activity index (ulcerative colitis) and Mayo staging system (Crohn's disease). The clinicopathological data were analyzed between the two different latent EBV groups and also between the mild-to-moderate and severe disease groups.

RESULTS

Systolic pressure ($P = 0.005$), variety of disease ($P = 0.005$), the severity of illness ($P = 0.002$), and pre-op corticosteroids ($P = 0.025$) were significantly different between the EBV-negative and EBV-positive groups. Systolic pressure ($P = 0.001$),

variety of disease ($P = 0.000$), pre-op corticosteroids ($P = 0.011$) and EBV infection ($P = 0.003$) were significantly different between the mild-to-moderate and severe disease groups.

CONCLUSION

IBD patients with latent EBV infection may manifest more severe illnesses. It is suggested that the role of EBV in IBD development should be further investigated, latent EBV infection in patients with serious IBD should be closely monitored, and therapeutic course should be optimized.

Key Words: Epstein-Barr virus; Epstein-Barr virus encoded RNA; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core Tip: Inflammatory bowel disease (IBD) patients with latent Epstein-Barr virus (EBV) infection may manifest more severe illnesses. It is suggested that the role of EBV in IBD development should be further investigated, latent EBV infection in patients with serious IBD should be closely monitored, and therapeutic course should be optimized.

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INTRODUCTION

Inflammatory bowel disease (IBD) collectively refers to the chronic inflammation of the intestinal lining due to the altered immune response of the gut microbiota. The cases of IBD are increasing globally at an alarming rate in the 21st century[1]. Two major types of IBD, namely Crohn's disease (CD) and ulcerative colitis (UC) are the most commonly occurring ones, seriously threatening global health burden. Therefore, understanding the pathogenesis of IBD plays an important role in the prevention and disease management. Emerging studies have indicated the critical involvement of microorganisms in the IBD pathogenesis and progression[2].

Epstein-Barr virus (EBV), also called human herpesvirus 4, infection accounts for one of the leading viral infections (approximately 90%) in humans. While most infections have been found to be involved in the oral route, other infection pathways like sexual transmission, transmission during blood transfusion, and organ transplantation have also been noted. EBV primarily targets resting B lymphocytes inducing their proliferation and polyclonal activities. Under this condition, adaptive immunity-associated cytotoxic T cells play important roles in regulating the EBV infection in the host. Notably, acutely infected individuals may present with infectious mononucleosis in a small cohort. Mostly, EBV integrates its DNA element into the memory B lymphocytes and establishes a lifelong latent infection status. While the virus can enter the lytic stage in individuals with compromised immune systems. In such cases, EBV may be reactivated, promoting the onset of virus-related malignancies, including Burkitt's lymphoma, Hodgkin's lymphoma, gastric cancer, and nasopharyngeal cancer subtypes[3]. In addition, EBV infection is associated with autoimmune diseases, such as multiple bone marrow fibrosis[4].

Moreover, the pathological connection between EBV and IBD has been receiving increasing attention in recent times[5,6]. Notably, immunosuppressive therapies, including anti-tumor necrosis factor alpha therapy, have been found to induce IBD pathogenesis and reactivate latent EBV[7], thereby increasing the susceptibility toward lymphocyte proliferation diseases. There is currently a lot of controversy regarding the direct involvement of EBV in inducing IBD and whether to include the EBV screening prior to IBD treatment initiation[8,9]. On the other hand, EBV co-infection may complicate the clinical course of IBD by aggravating the severity, chronicity, refraction to therapy, and increasing the recurrence rate of IBD[10]. However, most studies on EBV infection and IBD severity included a relatively small number of cases[6,11], and the clinical significance of EBV expression in B lymphocytes in the diseased intestinal tissue of IBD patients has not been discussed in detail.

Based on the findings from previous studies and the mode of EBV pathogenesis in relation to IBD, in this study, we examined 43 patients who underwent surgical resection, using EBV encoded RNA (EBER) and B lymphocyte (CD20) double staining technique to correlate the latent EBV infection and clinic-pathological data of IBD patients. Furthermore, we explored the clinical value of latent EBV

infection in predicting the severity of IBD.

MATERIALS AND METHODS

Sample collection

This study involved the retrospective review of 43 IBD patients' demographics and basic clinical information, including characteristics, medical history, clinical data, biochemical data, and pathological information. The enrolled patients underwent bowel resection surgery in the Department of Surgery at Peking Union Medical College Hospital between July 2010 and September 2013. These patients were diagnosed with either CD or UC by both pathological and clinical examinations. Exclusion criteria of the study included: (1) Extraintestinal chronic diseases, such as chronic renal insufficiency, heart failure, cirrhosis and severe chronic obstructive pulmonary disease, *etc.*; (2) Medical history of immunodeficiency diseases, such as chronic infections and/or history of inflammatory diseases, including vasculitis, systemic lupus erythematosus, and rheumatologic condition; and (3) History of synchronous malignancies.

Collection data included the following parameters, patient age at the time of surgery, gender, past medical history, variety and severity of disease, cause of surgery, surgery procedure, symptoms, signs, complications, accompanying diseases, treatment course, and biochemical data. Illness severity of CD and UC were assigned according to CD activity index and Mayo staging system.

Detection of EBV latent infection

EBV latent infection was diagnosed based on the results of double staining of EBER and CD20 (specific biomarker of B lymphocytes) markers. The double staining was performed following the pre-optimized staining protocol. Briefly, the IBD samples were fixed in 10% buffered formalin, dehydrated in alcohol, and embedded in paraffin. Paraffin blocks were sectioned at 4 μ m thickness. Routine hematoxylin and eosin staining was performed for histopathological examinations. For double staining with EBER and CD20, *in situ* hybridization (ISH) using 3,3'-diaminobenzidine (DAB) chromogen was first performed, followed by immunohistochemistry (IHC) for CD20 using Fast Red DAB chromogen. IHC was performed on an automated immunostainer (BOND-MAX, Leica Microsystems), according to the manufacturer's protocols (Bond Polymer Refine RNA ISH protocol and Bond Polymer Refine Red IHC protocol, Leica Microsystems).

For each test sample, a second section (consecutive section wherever possible) was hybridized with a mixture of sense (non-complimentary) EBER probe as the negative control. The number of EBER positive cells, which were stained in the cell nucleus, were manually counted in the high-power field (HPF) for each optical field. B-lymphocytes cytomembrane showed positive staining for CD20 expression in IHC analysis.

Statistical analysis

Based on the double staining results, patients from the EBV latent infection (EBER positive) and EBV non-latent infection (EBER negative) were compared in terms of demographics, clinical characteristics, and biochemical findings. The clinic-pathological results were also compared between the patients with mild-to-moderate and severe disease symptoms. To analyze categorical variables, the χ^2 test was used. Measurement data that met the normal distribution were compared using the *t*-test between the two groups, and measurement data that did not conform to the normal distribution were compared using the Mann-Whitney *U* test between the two groups. To perform statistical analyses, SPSS 25.0 (SPSS for Window, SPSS Inc, Chicago, IL) was adopted. A *P* < 0.05 indicated significant differences.

RESULTS

The clinico-pathological characteristics of patients

All clinic-pathological data are detailed in Table 1 and Table 2. Among the 43 IBD patients recruited to this study, there were 34 male- and 9 female patients. The age of the patients ranged from 13 to 70 years, and the mean age was 43.6 years. Among these patients, 20 patients had a history of smoking, and 17 patients had an alcohol drinking habit. Twenty-seven patients were diagnosed with CD and 16 patients with UC. The number of mild, moderate and severely affected patients were 10, 21, and 12, respectively. Three patients underwent surgery as they were seriously required, 9 patients were non-responsive to internal medicine therapy, and the other patients were medically required. Regarding the surgical procedures, 14 patients received laparoscopic partial enterectomy, and the other 29 patients had partial enterectomy through open surgery. The mean heart rate of these patients was 87.2 times/min, the median systolic pressure was 101 mmHg, and the mean diastolic pressure was 66.2 mmHg. At admission, 17 patients complained of fever, 42 patients reported abdominal pain, 29 patients had diarrhea, 20 patients had fecal occult blood, 15 patients had mucus or bloody purulent stool, 39 patients

Table 1 Basic information on patients (n = 43)

Variables	Data
Characteristics	
Sex (Male/female)	34/9
Age (yr), mean \pm SD	43.6 \pm 2.7
Smoking (No/Yes)	23/20
Drinking (No/Yes)	26/17
Clinical data	
Crohn's disease/ulcerative colitis	27/16
Location	
Crohn disease (L1/L2/L3/L4)	9/0/18/0
Ulcerative colitis (E1/E2/E3)	0/2/14
Severity of illness (Mild/moderate/severe)	10/21/12
Cause of surgery	
Patient required	3
Non-response to intern medicine therapy	9
Medical required	31
Intestinal obstruction	18
Fistula	5
Definite diagnosis requires	1
Gastrointestinal bleeding	3
Intestinal stenosis	1
Gastrointestinal perforation	2
Carcinogenesis	1
Pre-op aminosalicylic acid (No/Yes)	8/35
Pre-op corticosteroids (No/Yes)	24/19
Pre-op immunosuppressive therapy (No/Yes)	34/9
Surgical procedures (Laparoscopic/open surgery)	14/29
Course (d), mean \pm SD	73.6 \pm 11.7
Indicators to be explored	
Latent Epstein-Barr virus infection (Negative/positive)	33/10

had a history of losing weight, 14 patients had abdominal mass, 2 patients had toxic megacolon, 14 patients had a gastrointestinal hemorrhage, 24 patients had intestinal obstruction, 9 patients had intestinal perforation, 8 patients had a perianal disease, and 16 patients had extraintestinal manifestations. Before surgery, 35 patients received aminosalicylic acid, 19 patients had corticosteroids, and 9 patients undertook immunosuppressive therapy. The mean treatment course was 73.6 d.

Histochemical double staining results of EBER and CD20 in IBD colon tissues

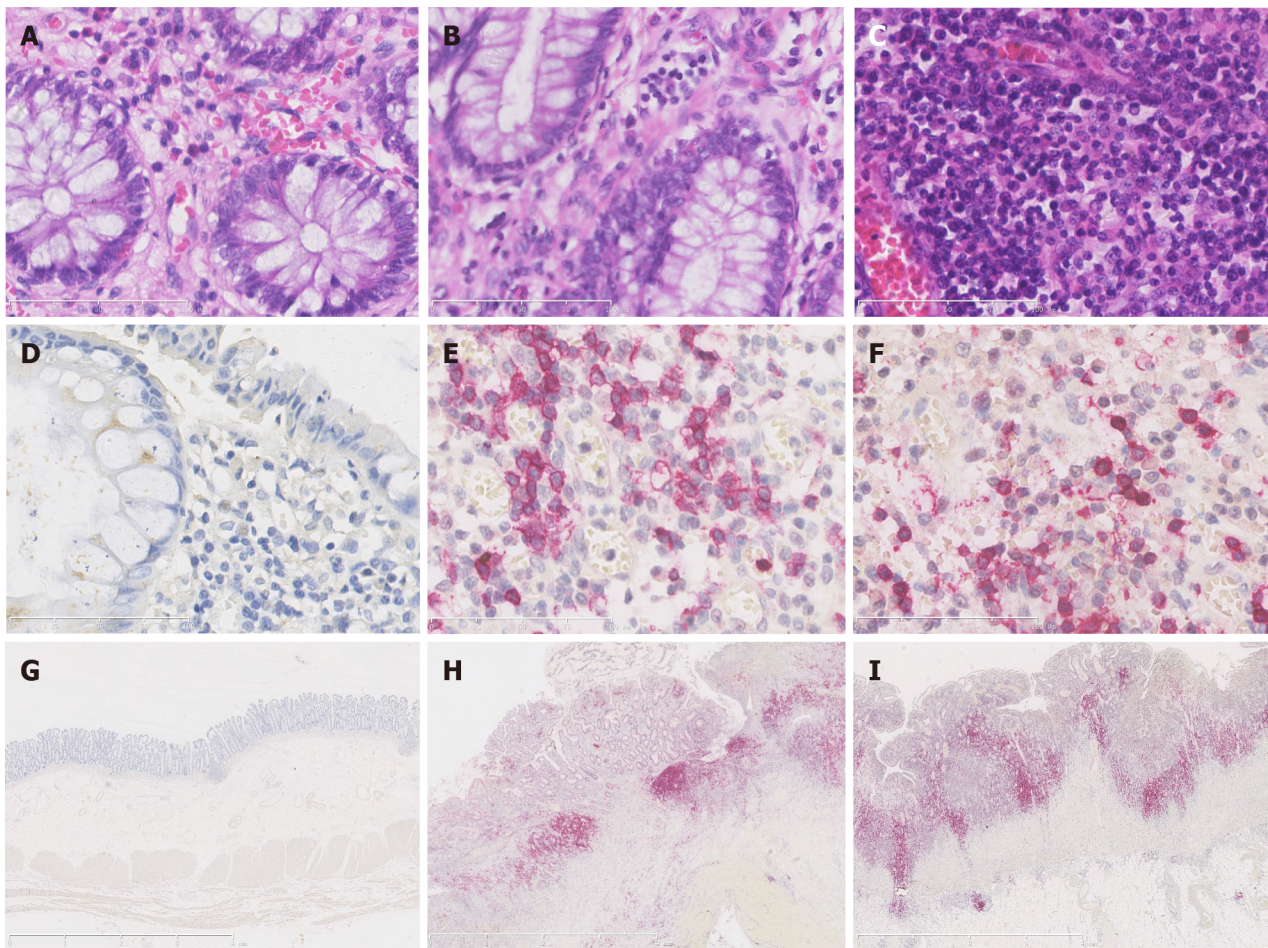
EBER positive staining, mainly distributed in the nucleus of B lymphocytes, suggested that the EBV latent infection status in the diagnosed patients. We found ten cases (23.3%) of IBD with EBV positive diagnosis, including 2 (7.4%) CD and 8 (50%) UC patients. **Figure 1A, D and G** show the normal control colon tissue.

In two cases of CD patients with EBV latent infection, numbers of EBER-positive B lymphocytes ranged from 8 to 15 cells per HPF, and the positively stained cells were scattered throughout the field, accounting for 80%-90% EBER-positive B lymphocytes. The CD pathology was manifested as the full-wall inflammation, but EBER-positive B lymphocytes were mainly concentrated in the mucosa and submucosa (**Figure 1B, E, and H**).

Table 2 Vital signs, clinical manifestations and biochemical data of the patients (n = 43)

Variables	Data
Vital signs	
Heart rate (time/min), mean \pm SD	87.2 \pm 3.1
Systolic pressure (mmHg), median (Q1, Q3)	101.0 (94.5, 113.0)
Diastolic pressure (mmHg), mean \pm SD	66.2 \pm 1.7
Clinical manifestations	
Fever (No/Yes)	26/17
Abdominal pain (No/Yes)	1/42
Diarrhea (No/Yes)	14/29
Fecal occult blood (No/Yes)	23/20
Mucus or bloody purulent stool (No/Yes)	28/15
Lose weight (≥ 5 kg) (No/Yes)	4/39
Abdominal mass (No/Yes)	29/14
Toxic megacolon (No/Yes)	41/2
Gastrointestinal hemorrhage (No/Yes)	29/14
Intestinal obstruction (No/Yes)	19/24
Intestinal perforation (No/Yes)	34/9
Perianal disease (No/Yes)	35/8
Extraintestinal manifestations (No/Yes)	27/16
Oral ulcer (Yes)	13
Pyoderma gangrenosum (Yes)	1
Peripheral spondyloarthritis (Yes)	6
Others (Yes)	2
Biochemical data	
White blood cell ($\times 10^9/L$), mean \pm SD	6.7 \pm 0.6
Neutrophil count ($\times 10^9/L$), mean \pm SD	4.6 \pm 0.5
Hemoglobin (g/L), mean \pm SD	103.6 \pm 4.5
Platelets ($\times 10^9/L$), mean \pm SD	343.2 \pm 25.7
Alanine aminotransferase (U/L), median (Q1, Q3)	11.0 (8.0, 14.0)
Aspartate aminotransferase (U/L), median (Q1, Q3)	14.0 (10.3, 18.8)
Albumin (g/L), mean \pm SD	30.6 \pm 1.5
Lactate dehydrogenase (U/L), median (Q1, Q3)	127.0 (102.0, 140.0)
Creatinine ($\mu\text{mol/L}$), mean \pm SD	60.7 \pm 3.0
Potassium (mmol/L), mean \pm SD	3.8 \pm 0.1
Prothrombin time (s), mean \pm SD	12.2 \pm 0.2
Activated partial thromboplastin time (s), median (Q1, Q3)	29.3 (26.5, 32.9)
C-reactive protein (g/L), median (Q1, Q3)	26.3 (16.3, 71.4)

In cases of 8 UC patients with EBV latent infection, numbers of EBER-positive B lymphocytes ranged from 13 to 60 cells/HPF, and with a random distribution of the EBER-positive cells, accounting for 30%-70% cells per HPF. Like CD patients, EBER-positive B lymphocytes in UC patients were also concentrated in the mucosa and submucosa (Figure 1C, F, and I). Importantly, all cases of UC with EBV latent infection showed a full colon type pathology.



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Figure 1 Normal control colon tissue and latent Epstein-Barr virus infection in Crohn's disease and ulcerative colitis-affected colon tissues. A, D, G: Normal control colon tissue; B, E, H: Colon tissue in Crohn's disease patients; C, F, I: Colon tissue in ulcerative colitis patients. A-C: Hematoxylin and eosin staining, $\times 400$; D-F: CD20 and Epstein-Barr virus-encoded RNA (EBER) double staining, $\times 400$; G-I: CD20 and EBER double staining, $\times 12.5$.

Correlation between latent EBV infection and clinic-pathological features

Clinico-pathological data of all patients were compared between the EBER-positive and EBER-negative expressions in B lymphocyte groups, according to the IHC results, as demonstrated in [Table 3](#). Systolic pressure ($P = 0.005$), variety of disease ($P = 0.005$), the severity of illness ($P = 0.002$), and pre-op corticosteroids ($P = 0.025$) were significantly different between the two groups. While no significant difference was found between the two groups in terms of other characteristics, clinical and biochemical data.

Correlation between severity of disease and basic medical information

Clinico-pathological data of all patients were also compared between the mild-to-moderate and severe patient groups, as demonstrated in [Table 4](#). Systolic pressure ($P = 0.001$), variety of disease ($P = 0.000$), pre-op corticosteroids ($P = 0.011$) and latent EBV infection ($P = 0.003$) were significantly different between the two groups, and no significant difference was found between the two groups in terms of other categories of characteristics, clinical and biochemical data.

DISCUSSION

After excluding some confounding factors, our results showed that the latent EBV infection detected in colon tissue of IBD patients was positively related to the severity of the disease, and patients with latent EBV infection in their colon tissues were severely ill. Studies have confirmed that EBV can cause immune disorders, and IBD is one of the autoimmune diseases. Therefore, we hypothesized that EBV infection could aggravate the severity of IBD through complex immune mechanisms. In addition, advanced stage IBD patients with altered immune response and immunosuppressive therapy could also show increased susceptibility to EBV. Eventually, the immune imbalance following EBV infection and the resulting deterioration of the IBD stage are most likely to be mutually causal, leading to a vicious

Table 3 Summary of factors related to latent Epstein-Barr virus infection

Variables	Epstein-Barr virus-negative (n = 33)	Epstein-Barr virus-positive (n = 10)	Statistical value (t/χ^2)	P value
Systolic pressure (mmHg), mean \pm SD	106.56 \pm 11.51	94.33 \pm 7.71	2.991 (t)	0.005 ¹
Variety of disease			7.965 (Adjusted)	0.005 ¹
Crohn disease	25	2		
Ulcerative colitis	8	8		
Severity of illness			12.293 (Likelihood ratio)	0.002 ¹
Mild	8	2		
Moderate	20	1		
Severe	5	7		
Pre-op corticosteroids			5.017 (Adjusted)	0.025 ¹
No	22	2		
Yes	11	8		

¹Significant differences.**Table 4 Data comparison between patients with mild/moderate or severe inflammatory bowel disease**

Variables	Mild/moderate (n = 31)	Severe (n = 12)	Statistical value (t/χ^2)	P value
Systolic pressure (mmHg), mean \pm SD	107.33 \pm 11.698	94.45 \pm 7.71	3.482 (t)	0.001 ¹
Variety of disease			12.542 (Adjusted)	0.000 ¹
Crohn disease	25	2		
Ulcerative colitis	6	10		
Pre-op corticosteroids			6.408	0.011 ¹
No	21	3		
Yes	10	9		
Latent Epstein-Barr virus infection			8.911 (Adjusted)	0.003 ¹
Negative	28	5		
Positive	3	7		

¹Significant differences.

cycle of disease aggressiveness and poor prognosis. However, unlike the effect of EBV on multiple myeloma, we observed that not all the patients with severe IBD had EBV-positive diagnosis, which led us to postulate that EBV infection could be one of the critical factors in inducing severe IBD symptoms, but was not an indispensable etiological factor. In addition to the involvement of EBV, the severity of IBD must have involved other complex pathophysiological mechanisms. Based on our findings, we suggest that patients with latent EBV infection should be closely monitored, and the effect of EBV infection on the IBD patients should be given attention, and the pathogenesis between them should be clearly defined.

The clinic-pathological relationship between EBV and IBD has always attracted the attention of researchers and clinicians. For example, Dimitroulia *et al*[12], and Li *et al*[13], have shown that the prevalence of EBV in the intestinal tissue of patients with IBD is significantly higher than that in the control group. Moreover, patients with a high prevalence of EBV infection exhibit worsening disease symptoms, as compared to non-EBV infected patients who present remission incidences, suggesting that the severity of IBD may be related to the EBV infection[12,13]. In addition, it has also been found that the positive expression of EBV in IBD patients is higher in refractory patients than in the control group. Further, the higher EBV positive expression has been linked to the mucous damage and high clinical indexes of activity[6,11,14]. Our results were consistent with these findings, suggesting that the positive expression of EBV in latent infection might be related to the severity of IBD. However, most of the above

studies used specimens from patients' serum or colonoscopy biopsies, while the specimens used in our study were specimens removed from bowel surgery. Relative to the determination of EBV in serum, EBV in bowel resection specimens can better reflect the direct role of EBV in the IBD pathology. In addition, compared to the EBV determination in colonoscopy biopsy specimens, the EBV of the bowel resection specimens can better reflect the EBV infiltration of the entire layer of the bowel wall. Therefore, our results based on the bowel resection specimens were more reliable and precise. We also obtained morphological data of EBV by IHC analysis of the colon wall of IBD patients to determine the exact location of EBV in the B lymphocytes of intestinal tissue, which was also the verification and supplementary to the previous studies.

In our study, we found that latent EBV infection rates were related to the pre-op corticosteroid administration. Crosstalk between EBV-positivity and corticosteroid administration has also been found in another study[14]. We thought two aspects should be considered to explain these reasons. Firstly, latent EBV infection might be related to the severity of the disease, and the disease severity was directly proportional to the increasing dose of corticosteroids, indicating EBV infection was related to corticosteroids. Secondly, following the corticosteroid therapy, the immunosuppressive condition of patients might have increased their susceptibility toward EBV infection. However, the exact reason is needed to be confirmed by cohort research in the future.

Interestingly, we also found that the proportion of latent EBV infection in UC patients was higher than that in CD patients. In addition, all UC patients with latent EBV infection exhibited full colon type pathology. The reason for the difference in the proportion of EBV latent infection in the UC and CD patients and the relationship between latent EBV infection and subtypes in UC patients are worthy of further research and discussion.

So far, there is no consensus on whether all IBD patients mandatorily require EBV infection testing at the early stage. At present, the detection of EBV infection in IBD patients is mainly focused on patients who require azathioprine treatment, which may increase the activation of EBV and the incidence of related lymphatic system proliferative diseases. Studies suggest that before starting to use azathioprine, detection of EBV serology should be performed first, following the counting of natural killer cells during treatment to determine whether the patient has the risk of developing an abnormally serious primary EBV infection and EBV-related malignancies[5,8,15-17]. But other studies have also shown that the activation of EBV has no direct connection with the impact of immunosuppressive therapy[13,18]. Notably, the exposure to EBV in adulthood is almost universal, and the incidences of hematological malignancies in IBD are rare. In the cost-benefit analysis, it seems that the value of EBV detection before the IBD patient starts treatment is limited[9,19-21]. Our results suggest that it is important not only to consider the activation of EBV by immunosuppressive drugs that can lead to related malignant tumors but also to understand the relationship between EBV infection and the severity of IBD. With regard to the question of whether to carry out EBV testing first in IBD patients, we suggest that determination should be made after the role of EBV infection on IBD progression rate and deterioration are clarified, or it can be used in high-risk patient populations (such as patients with full colon UC or those who require corticosteroid therapy for the disease).

In addition to the aforementioned obstacles, there are still several unsolved questions about the relation of EBV infection with IBD severity. For example, whether IBD patients with latent EBV infection should be treated for EBV. And recent studies have shown that different EBV strains have inconsistent pathogenic effects on nasopharyngeal carcinoma[22]. However, the exact causal relationship between different EBV strains and the progression of IBD is not clear yet.

Small sample size and one-center study were also considerable drawbacks of this retrospective study. A large sample size and multi-center studies to explain the serious relationship between latent EBV infection and the condition of IBD patients are needed for detailed investigation in the future.

CONCLUSION

In conclusion, our findings indicated that IBD patients with latent EBV infection might manifest severe symptoms. We suggest that the role of EBV in IBD development should be further investigated, and latent EBV infection in patients with serious IBD should be closely monitored and optimized treatment.

ARTICLE HIGHLIGHTS

Research background

Emerging studies indicate the critical involvement of microorganisms, such as Epstein-Barr virus (EBV), in the pathogenesis of inflammatory bowel disease (IBD). Immunosuppressive therapies for IBD can reactivate latent EBV, complicating the clinical course of IBD.

Research motivation

This study explored the clinical significance of EBV expression in B lymphocytes derived from IBD patients' intestinal tissues in detail.

Research objectives

This study aimed to explore the clinical significance of latent EBV infection in IBD patients.

Research methods

Double staining for EBV encoded RNA and CD20 to determine latent EBV infection. The clinic-pathological data were analyzed between the two different latent EBV groups and also between the mild-to-moderate and severe disease groups.

Research results

Systolic pressure, variety of disease, the severity of illness, and pre-op corticosteroids were significantly different between the EBV-negative and EBV-positive groups. Systolic pressure, variety of disease, pre-op corticosteroids and EBV infection were significantly different between the mild-to-moderate and severe disease groups.

Research conclusions

Latent EBV infection is positively related to severity of IBD illness.

Research perspectives

The role of EBV in IBD development should be further investigated; latent EBV infection in patients with serious IBD should be closely monitored.

FOOTNOTES

Author contributions: Wei HT made a major contribution to the study design, data analysis, and manuscript writing; Xue XW and Zhou WX had the same contribution to the manuscript by providing advice for the study design and giving suggestions to improve the manuscript writing; Ling Q and Wang PY collected and reviewed the experimental data; and all authors read and approved the final version of the manuscript.

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