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CASE REPORT

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Clinical characteristics and literature review of chronic active Epstein–Barr virus-associated enteritis

Yajie Meng[1] | Rendong Li[2] | JieWen Ding[1] | Bo Xiang[1] | Qin Wang[1] | Min Wang[1] | KeJiang Tang[1]

[1]Department of Gastroenterology, The People's Hospital of Nanchuan, Chongqing, China

[2]The People's Hospital of Nanchuan, Chongqing, China

Correspondence
KeJiang Tang and Min Wang, Department of Gastroenterology, The People's Hospital of Nanchuan, No. 16 South Street, Nanchuan District, Chongqing 408400, China.
Email: tttkkj@163.com and wangmin_0815@163.com

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Key Clinical Message

Chronic active Epstein-Barr virus (EBV) infection-associated enteritis (CAEAE) in nonimmunodeficient individuals is rare. To report a case of CAEAE, relevant articles were searched through databases. The clinical manifestations, endoscopic findings, strategies of treatment, prognoses, and follow-up results of CAEAE patients were analyzed. Including this report, seven citations in the literature provide descriptions of 27 cases of CAEAE. There were 21 males and six females, with a mean age of 40 years. The main clinical manifestations were fever (25/27), abdominal pain (14/27), diarrhea (16/27), hematochezia or bloody stools (13/27), and decreased hemoglobin and red blood cell counts in routine blood tests (14/27). Elevations in inflammatory markers, white blood cell (WBC) counts, and C-reactive protein (CRP) were common. Coagulation was often abnormal. Histopathology confirmed EBV-encoded small nuclear RNA (EBER) in the affected tissue via in situ hybridization. The average serum EBV DNA load was 6.3 ×10^5 copies/mL. All patients had varying degrees of intestinal ulcers endoscopically, and the ulcers and pathology were uncharacterized and misdiagnosed mostly as inflammatory bowel disease (IBD). The course of the disease was progressive and later complicated by intestinal bleeding, intestinal perforation, septic shock, and a high rate of emergency surgery. However, the conditions of the patients often did not improve after surgery, and some patients soon died due to reperforation or massive hematochezia. Hormone and antiviral treatment had no obvious effect. There was a significant difference in surgical and nonsurgical survival ($p < 0.05$). The proportion of patients who died within 6 months was as high as 63.6% (7/11). CAEAE belongs to a group of rare, difficult conditions, has an insidious clinical course, has a high case fatality rate, and may later develop into EBV-positive lymphoproliferative disorder (EBV-LPD), which in turn leads to carcinogenesis. Clinicians should raise awareness that in patients with multiple ulcers in the intestine of unknown etiology, attention should be paid to EBV serology, and histology to make the diagnosis as early as possible.

Yajie Meng and Rendong Li are equal contributors.

KEYWORDS
chronic active Epstein–Barr virus infection-associated enteritis, Epstein–Barr virus, EBV-positive lymphoproliferative disorder, inflammatory bowel disease, misdiagnosis

1 | INTRODUCTION

Epstein–Barr virus (EBV) is a double-stranded γ-DNA herpesvirus of B lymphocytes.[1] In general, the younger population is more susceptible, as acute infection is common in children and adolescents and rare in adults.[1] The disease course is usually less than 1 month, and the clinical course is self-limited with a favorable prognosis.[1,2] However, the virus then targets B lymphocytes for its life cycle, and in immunocompetent individuals, EBV can reenter the lytic infection phase by latent infection.[3–5] Viruses can infect not only B lymphocytes but also T or natural killer (NK) cells.[1–5] Clinically, there are systemic symptoms such as chronic or recurrent fever, hepatosplenomegaly, and lymphadenopathy, as well as damage to different organs/tissues caused by active viral replication; this is referred to as chronic active Epstein–Barr virus (CAEBV) infection.[3–5] Some cases involve the intestine and exhibit intestinal symptoms, that is, CAEBV infection involving the intestine (with systemic symptoms), which, in the absence of a basis for malignant lymphoproliferative disease, may also be referred to as chronic active EBV infection-associated enteritis (CAEAE).[4,5] In recent years, CAEAE has gained increasing attention. We performed a literature report and analyzed and summarized the clinical features, differential diagnoses, prognoses, etc., to increase awareness and improve the diagnosis of this class of diseases among clinicians.

2 | PATIENT AND METHODS

2.1 | Study subject and informed consent

The family of the patient in this study agreed to publish the patient's medical records and signed informed consent was obtained.

2.2 | Patient report

In December 2017, a 49-year-old man was admitted to the Gastroenterology Department of the People's Hospital of Nanchuan Chongqing for intermittent lower abdominal pain, intermittent diarrhea and occasional mucous bloody stools. The first enteroscopy suggested multiple ulcers in the colon. Pathology suggested chronic inflammatory changes. Because ulcerative colitis (UC) could not be excluded, 5-aminosalicylic acid was given for 4 weeks, after which Clostridium butyricum supplemented with intestinal probiotics was intermittently administered. In 2018–2019, repeat enteroscopies still suggested multiple ulcers in the colon, and pathology suggested chronic inflammation. During the course of the disease, the patient had no fever or night sweats, consumed a high-fat food without diarrhea, and did not lose weight. The patient had no history of long-term heavy drinking and no personal or family history of immunodeficiency-related diseases. In May 2020, the patient was again hospitalized due to diarrhea and mucous and bloody stools.

The routine laboratory test results were as follows: CRP 38.67 mg/L, CA72-4 10.32 U/mL, UA 446 μmol/L. The fecal occult blood test was positive, and other autoantibodies, including immunoglobulin, IgA, IgG and IgM, were negative; TB-AB and T-SPOT were negative. Enhanced abdominal CT showed thickening of the ileocecal region, partial infiltration around the ascending colon, and a blurred surrounding fat space. Enteroscopy suggested a large ulcer in the ileocecal region, and the location of the ulcer was different from that on review in 2019. Giant ulcers showed a migratory appearance, as shown in Table 1 and (Figure S1). A satisfactory and accurate diagnosis could not be obtained by pathology at our hospital. Therefore, we seek help from Wechat at Zhongnan Hospital of Wuhan University, which has a well-known inflammatory bowel disease (IBD) research center and a digital telepathology consultation center.

The pathological results showed slight mucosal changes (crypt branching, twisting and elongation) from the ileocecal part to the descending colon, focal enhancement, inflammation, obvious crypt withering, ulcers in the ileocecal region, and prominent lymphocyte infiltration. Immunohistochemistry showed that the local CD3-positive T cells were dense, and the Ki-67-positive rate was 30%. In situ hybridization showed that EBV-encoded small nuclear RNA (EBER) + cells reached 30/HPF as well as the following: CD2 (T cells+), CD20 (B cells+), CD30 (−), CD5 (T cells+), CD56 (scattered cells+), granzyme B (scattered cells+), and CD21 (FDC Net +). No pylorus gland metaplasia or granuloma was found. A pathological image is shown in (Figure S2).

At this time, we performed an EBV serological examination, and the results showed the following: IgA negative

TABLE 1 Clinical and colonoscopic manifestations of the case.

	2017	2018	2019	2020
Clinical symptoms	Abdominal pain	Abdominal pain with diarrhea, mucopurulent and bloody stools	Abdominal pain, diarrhea, bloody stool	Abdominal pain, diarrhea, bloody stool, fever
Endoscopically confirmed site of involvement	Ascending colon, transverse colon, descending colon	Ascending colon, transverse colon, descending colon	Ileocecal region, ascending colon, transverse colon, descending colon	Ileocecal region, ascending colon, transverse colon, descending colon, small intestine
Intestinal stricture	No	No	Yes	Yes
Maximum ulcer diameter (cm)	0.5	0.5	Circumflex 3/4	5
Pathological biopsy	Acute and chronic inflammation of the colonic mucosa	Acute and chronic inflammation of the colonic mucosa	Acute and chronic inflammation of the colonic mucosa	Lymphocytes and inflammatory cells infiltrate the lamina propria, intraepithelial lymphocytes, cryptitis, and crypt abnormalities

(−), IgM negative (−), IgG positive (+), and peripheral blood EBV DNA concentration: 1.75×10^3 copies/mL. Combined with the clinical manifestations, pathology and serological results, the final diagnosis was CAEAE.

The treatment regimen was as follows: prednisone (55 mg QD for 4 weeks, then reduced to one tablet (20 mg) a week and then to one tablet every 2 weeks until discontinuation). One week after treatment, the liver and kidney function tests and electrolyte levels were normal. The patient was followed up every 2 weeks, and no abnormalities were found. After 4 weeks of hormone therapy, the patient developed right abdominal pain with high fever and immediately went to the emergency department. Abdominal CT was performed to consider cavity/organ perforation. Laparotomy was performed immediately. Ileocecal perforation was found during the operation, and right hemicolectomy was performed. Postoperative pathology showed intestinal perforation (right colon). A large number of acute and chronic inflammatory cells infiltrated the intestinal wall with necrosis. Mesenteric lymph nodes showed reactive hyperplasia (18 pieces). EBER was positive in the surgical and pathological specimens. After the operation, the patient's condition was unstable, with repeated high fever and occasional abdominal pain. Laboratory examinations showed a reduction in leukocytes, thrombocytopenia, and liver dysfunction. The patient died 32 days after the operation.

2.3 | Literature review

We did not limit the publication years and conducted a full-text literature search in the PubMed, Science ISI Web, Embase and Wanfang, Chinese National Knowledge Infrastructure (CNKI), and Weipu and databases. Search to identify all studies that may involve the following keywords: “EBV infection” or “chronic EBV infectious diseases” and “enteritis” or “gastrointestinal symptoms.” We retrieved documents and perused the reference lists that were eligible retroactively to avoid missing relevant literature.

A total of 13 English studies and five Chinese studies were retrieved. After a careful review of the full text, seven studies[6–12] (three Chinese and four English) and 26 case reports of CAEBV were included in the statistical analysis.

2.4 | Statistical methods

This was a descriptive study. If the measurement data conformed to a normal distribution, the average value is reported. Those that did not conform to a normal distribution are reported as the median. A p-value less than 0.05

was considered statistically significant. Statistical analysis was conducted with SPSS version 23.0.

3 | RESULTS

Together with our own case report, a total of 27 case reports[6–12] described CAEBV. A summary is shown in Tables 2 and 3.

1. Basic information: The age of onset was mostly concentrated in 20–40 year olds and 40–60 year olds. The average patient age was 40 years. The ratio of males to females was 4:1 (21 M:6 F). The disease course was less than half a year ($n=6$) and more than 1 year ($n=7$). The median disease course was 29.4 months (range 0.5–14 years).
2. Clinical manifestations: Fever (25/27), abdominal pain (14/27), diarrhea (16/27), and bloody stool (13/27) were the most common symptoms and the first symptoms. Combined with lymphadenopathy and hepatosplenomegaly. High fever (body temperature > 39°C), intestinal bleeding, intestinal perforation and septic shock occurred in the late stage of the disease. Other symptoms were not typical, such as loss of appetite, weight loss, nausea, and vomiting. There were no obvious extraintestinal manifestations, such as skin damage, joint swelling and pain, or ophthalmitis. All patients were in good health and had no history of immune deficiency, tumors, family history, or previous immunosuppressive drug treatment.
3. Laboratory examinations: In routine blood tests, decreases in hemoglobin and red blood cell counts (14/27) were common, as well as decreases in platelet and white blood cell (WBC) counts. Increases in WBC counts and C-reactive protein (CRP) were common. Coagulation function was abnormal. Immunological tests, such as TB-Ab, T-SPOT, hepatitis A and hepatitis C, were negative. All 27 cases were confirmed by histopathology, and EBER was positive based on in situ hybridization. The average DNA load of EBV in the serum was 6.3×10^5 copies/mL.
4. Endoscopic features: All patients had colonic and rectal ulcers of varying degrees, with ulcers that were deep, shallow, and of varying sizes accompanied by luminal narrowing and no apparent specificity for ulceration. The small and large intestines were mostly involved. CAEAE was often misdiagnosed as Crohn's disease (CD), UC, intestinal tuberculosis, etc. Pathological characteristics: Most patients had full-thickness chronic and acute Intestinal mucosal inflammation with the infiltration of lymphocytes and plasma cells without obvious structural changes in crypts and occasionally cryptitis and crypt abscesses. The pathological findings were not typical, and there were no definite pathological features, such as lymphoma, CD, and UC.
5. Nine patients were treated surgically, mostly with emergency surgery, and seven died postoperatively due to infection, rebleeding, perforation, and shock. The mortality rate was 77.7%, and three patients (3/7) died within 1 month of surgery. Twelve patients did not undergo surgery and were medically treated, four of whom died, seven of whom remained alive, and one of whom was lost to follow-up. The mortality rate was 33.3%. There were significant differences in surgical and nonsurgical survival ($p<0.05$). The proportion of deaths within 6 months was as high as 45.4%.
6. Twenty-one individuals were treated with medications, mainly glucocorticoids (prednisone, methylprednisolone), antiviral agents (ganciclovir), immunoglobulins for injection, immunosuppressive agents (methotrexate, azathioprine), antibiotics (cefoperazone sodium, sulbactam sodium, and vancomycin), mesalazine, infliximab, Chinese medicine, etc.

4 | DISCUSSION

CAEBV usually occurs in persons with congenital or acquired immunodeficiency.[13] The presence of CAEBV in nonimmunodeficient individuals has been reported relatively rarely. In addition to the manifestations of fever, hepatosplenomegaly, and lymphadenopathy, CAEBV often has multiorgan involvement. The liver, bone marrow, spleen, skin, and lymph nodes are the most frequently involved, and digestive tract involvement is very rare.[14] However, CAEAE is diagnosed when digestive symptoms and intestinal lesions combine on the basis of CAEBV and cannot be explained by other diseases and when a malignant lymphoproliferative disorder is lacking.[5] Currently, the cases of CAEAE occurring in nonimmunodeficient individuals are very limited, and all have been case reports.[6–12] We excluded patients who had a diagnosis of (1) EBV-positive lymphoproliferative disorder (EBV-LPD); (2) EBV recessive infection; (3) acute EBV infectious enteritis; (4) opportunistic infection with EBV in IBD; (5) intestinal EBV infection with haemophagocytic syndrome; and (6) intestinal EBV-associated malignancies. After we excluded the patients described above, a total of 27 patients diagnosed with CAEAE were included in the analysis. We summarized their clinical features to provide the most comprehensive currently available resource to help increase the awareness of such disorders to clinicians.

From the 27 patients with CAEAE, we found the following characteristics: (1) There were significantly more

males than females (77.7% were male), and most patients were young (mean age 40 years). The median age of disease onset was 12 years and ranged from 20 to 40 years. Early screening enteroscopy is recommended for individuals older than 20 years. (2) Clinical symptoms often start with fever, abdominal pain, diarrhea, and bloody stools accompanied by lymphadenopathy and hepatosplenomegaly. (3) Decreased hemoglobin, cytopenia, and elevated inflammatory indicators are often observed during the course of the disease. (4) Endoscopic findings are mostly multiple ulcers in the gastrointestinal tract, with ulcers of varying sizes that are not pathognomonic, which are difficult to differentiate from IBD and can easily be misdiagnosed as CD, UC, TB, etc. (5) All patients who underwent EBER testing had positive results, and EBER in situ hybridization is considered the gold standard for detecting EBV latent infection.[15] An elevated serum EBV DNA load was evident. (6) The disease is progressive, and severe complications, including massive lower gastrointestinal bleeding, hemorrhagic shock, and intestinal perforation, occur in all patients late in the course, resulting in a high rate of emergency surgery. However, the conditions of patients often do not improve after surgery, and some patients soon experience reperforation or massive hematochezia, resulting in a high rate of reoperations. Consistent with reported case characteristics.[9,16] (7) Multiple regimens, including antiviral therapy and chemotherapy, are ineffective. The proportion of patients who die within 6 months is as high as 51%, with rapid progression and an extremely poor prognosis. Combined with our findings, it is suggested that the case fatality rate of patients with this group of diseases is extremely high and very insidious.

In addition to the manifestations described above in 11 of 27 patients, Liu R, a Chinese scholar, conducted a multicenter study to compare the clinical characteristics of 11 patients with CAEAE to those of 100 patients with IBD and found the following[9]: (1) Patients with CAEAE had intermittent fevers, hepatomegaly, splenomegaly, and lymph node involvement, which were more common systemic manifestations than in patients with IBD, and the fevers in CAEAE patients were febrile (greater than 39°C). (2) The percentage of patients with positive EBV DNA (100%) and serum EBV DNA load (1.9 ×10^6) was higher than the percentage of patients with IBD (23%) and viral load (9.8 ×10^3). These differences were statistically significant, at $p < 0.01$. (3) CAEAE is more insidious than IBD and progress more rapidly in the late stages. Three patients underwent total colectomy, two of whom died of infection and intra-abdominal bleeding within 1 month of surgery. The 5-year survival rate was 100% (6/6) in the nonsurgery group and 40% (2/5) in the surgery group. Combined with the statistical findings of this study, the 1-year survival rate after surgery was 22.2% (2/9) in the surgery group and 58.3% (7/12) in the nonsurgery group, and there was a correlation between prognosis and surgery ($p < 0.05$). It can be seen that the conditions of patients do not significantly improve after surgery, and they are at an increased risk of death. However, the survival rate after total colectomy was smaller than after nonsurgical treatment, but a larger study is needed to further address the prognosis and association of total colectomy with survival.

Intestinal lesions are the main and prominent manifestation of CAEAE, but they are currently poorly recognized. CAEBV infection involving the intestine shares endoscopic and pathomorphological similarities with IBD and is difficult to differentiate from IBD. Through the analysis of 27 cases, the key points for the differential diagnosis, as summarized initially, were as follows: (1) Rare manifestations of UC, such as mucopurulent stools and tenesmus, are seen in CAEAE. In contrast to UC, its pathology often lacks diffuse cryptic architectural changes, and crypt abscesses are rare.[15,17] (2) Endoscopic lesions were more extensive and involved most of the small bowel and colon and rectum. The ulcers are shallow and variable in size and are uncharacteristic, and there are no common classic cobblestone-like ulcers, slit-like ulcers, or aphthous ulcers in other locations, such as genital ulcers and ocular lesions.[9,15] (3) Although CAEAE can also have transmural inflammation with occasional granuloma-like structures, it is easily confused with CD. However, CAEAE generally lacks typical chronic interstitial changes, such as granulomas, mucosal muscle hyperplasia, and nerve hypertrophy.[9,15,18] On the basis of our experience with this case, the pathological diagnosis could not be obtained to differentiate it from IBD, but cooperation can be sought from global healthcare institutions through internet systems, leading to a better diagnosis and treatment.

Treatment of CAEBV infection is more difficult. Antiherpesvirus drugs such as acyclovir and ganciclovir are not effective for active EBV infections. Drugs such as glucocorticoids, immunosuppressive agents, immunomodulatory agents, and cytotoxic chemotherapy can provide short-term relief for CAEAE, but there is no cure.[19] Hematopoietic stem cell bone marrow transplantation is a curative procedure for CAEBV infection, but there is also an associated risk of transplantation complications.[20] Recently, Lingling Xu reported a case of CAEBV with intestinal,[21] vascular, and neurological involvement. The patient had uncontrollable major digestive bleeding, and the patient's clinical symptoms improved after a new treatment regimen combining thalidomide and propranolol. This holds promise as a new and effective treatment but still requires further clinical validation.

In 2008, the International Conference on the classification of lymphoproliferative disorders of EBV held at the National Institutes of Health (NIH) designated CAEBV

TABLE 2 Review of the literature.

Author/Year	Age/Sex	Symptoms	Signs/laboratory examination	Disease course	Endoscopic findings
Our case	49/M	Abdominal pain	CRP 38.67 mg/L, CA72-4 10.32 U/mL, UA 446 μmol/L	3 years	Multiple ulcers in the colon
Yangxiao Zhou, 2020	50/M	Abdominal pain, diarrhea, high fever, Weight loss	WBC 13.4 × 109/L, neutrophil ratio 0.8, Hb 120.0 g/L, PLT 289.0 × 109/L; ESR 31 mm/1H, CRP 90.2 mg/L, calcitonin To 0.46 μg/L and ferritin >2000 μg/L	2 months	Multiple ulcers of colon, Ileal aphthous ulcer
	51/M	High fever, diarrhea, abdominal pain, Hematochezia	NA/procalcitonin 0.07 μg/L	1 months	Multiple deep ulcers of colon and rectum
	24/M	Fever, rash, hematochezia	Splenomegaly, Pelvic small lymph node shadow	3 years	Multiple jejunal ulcer
Bo Zhang, 2020	39/M	Abdominal pain, fever, adenopathy, diarrhea, hematochezia	Hb 12 g/L, inflammatory indicators increased, coagulation function altered		Numerous irregular ulcers in the colon
	28/M	Abdominal pain, fever, adenopathy, retrosternal pain, diarrhea, splenomegaly	Hb 92 g/L, inflammatory indicators increased, coagulation function altered		Numerous shallow and small ulcers in the colon
	48/F	Abdominal pain, fever, adenopathy	Hb 105 g/L, inflammatory indicators increased, coagulation function altered		Numerous irregular ulcers in the colon
Dong Xuyang, 2018	62/M	Abdominal pain, hematochezia, high fever, diarrhea	Hemoglobin decreased, RBC decreased, WBC decreased, thrombocytopenia, coagulation function altered	2 months	Multiple deep ulcers in the colon
	27/M	High fever, diarrhea, hematochezia, abdominal pain	Hemoglobin decreased, RBC decreased, WBC decreased, thrombocytopenia, coagulation function altered	2 months	Multiple deep ulcers in the colon
	28/M	High fever, hematochezia, abdominal pain, diarrhea	Hemoglobin decreased, RBC decreased, WBC decreased, thrombocytopenia, coagulation function altered	5 months	Multiple ulcers in the colon and ileum
	32/F	Abdominal pain, diarrhea, high fever, hematochezia	Hemoglobin decreased, RBC decreased, coagulation function altered	14 years	Multiple ulcers in the colon, duodenum and ileum
	29/M	Abdominal pain, dyssynergistic defecation, high fever, hematochezia	Hemoglobin decreased, RBC decreased, coagulation function altered	4 years	Multiple small intestinal ulcers

Histopathologic findings	Misdiagnosis	PCR/VCA-IgM/VCA-IgG/EA/EBV DNA/EBER	Serum EBV DNA (copies/mL)	Medication/surgery	Follow-up and prognosis
Slight mucosal changes (crypt branching, twisting and elongation) from the ileocecal part to the descending colon, focal enhancement, inflammation, obvious crypt withering and ulcers in the ileocecal region, prominent lymphocyte infiltration.	UC	+/−/+/NT/NT/+/T	1.75×10^3	Hormone plus gamma globulin/Emergency right hemicolectomy exploratory laparotomy	Died 1 month after exploratory laparotomy
Acute and chronic inflammation with lymphoproliferation in the ileocecal mucosa, which was dominated by T lymphoproliferation and ulcerated	IBD	NT/NT/NT/NT/NT/+	1.29×10^6	Intravenous methylprednisolone, glucocorticoids/NA	3 months, died of haemorrhagic shock, Gastrointestinal
Full thickness light moderate chronic inflammation of colonic mucosa	IBD	NT/NT/NT/NT/NT/+	4.63×10^4	Intravenous methylprednisolone, glucocorticoids/NA	Continuous follow-up
Moderate chronic inflammation of mucosa with lymphangiectasia	IBD	NT/NT/NT/NT/NT/+	4.34×10^6	Intravenous methylprednisolone, glucocorticoids/NA	Loss to follow-up
Lymphatic follicles in the lamina propria, crypt abscess in some glands, aggregation of atypical lymphoid cells	UC	NT/NT/NT/NT/NT/+	<5×10^3	-	-
Tissue granulation, atypical lymphocyte infiltration	IBD	NT/NT/NT/NT/NT/+	3.8×10^4	-	-
Granulomatous tissue and lymphoid tissue hyperplasia, atypical lymphocyte infiltration	CD	NT/NT/NT/NT/NT/+	NA	-	-
Acute and chronic inflammation	IBD	−/−/+/+/−/+	3.8×10^3	Ganciclovir, glucocorticoid, imipenem, cilastatin, vancomycin/NA	2 weeks, septic shock, death
Multiple ulcerations of the colon with lymphocytic and plasmacytic infiltration	CD	−/−/+/+/+/+	9×10^4	Glucocorticoid, intravenous immunoglobulin/emergency right hemicolectomy	2 weeks, haemorrhagic shock, death
Acute and chronic inflammation	CD	−/−/+/+/+/+	5×10^5	Ganciclovir, glucocorticoids/NA	6 months, perforation, death
Acute and chronic inflammation, focal lymphocyte accumulation, focal crypt architectural irregularity	UC	−/−/+/+/−/+	8.9×10^4	Glucocorticoid/NA	2.5 months, death
Severe stenosis of the small intestine with perforation, mucosal ulceration with bleeding and fibrosis, necrosis and granulation tissue seen on the serosal surface, abscess formation in the mesentery, and chronic inflammation of lymph nodes	CD	−/−/+/±/−/+	2.5×10^5	Intravenous immunoglobulin, methotrexate, CHOEP regimen for 3 months/partial resection of the small intestine	13 months, died of haemorrhagic shock

(Continues)

TABLE 2 (Continued)

Author/Year	Age/Sex	Symptoms	Signs/laboratory examination	Disease course	Endoscopic findings
	26/F	High fever, diarrhea, abdominal pain, hematochezia	Hemoglobin decreased, RBC decreased, coagulation function altered	2 years	Multiple ulcers in the small intestine, duodenum and ileum
Rongbei Liu, 2018	72/M	Watery stool, intermittent fever (>39°C)	Hepatomegaly, splenomegaly, lymphadenopathy/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous shallow and small ulcers in the colon
	21/M	Watery stool, intermittent fever (>39°C)	Hepatomegaly, splenomegaly/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous irregular ulcers in the colon
	50/F	Watery stool, intermittent fever (>39°C)	Hepatomegaly, splenomegaly/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous ulcers in the small intestine
	50/M	Bloody stool, intermittent fever (>39°C)	Splenomegaly/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous small ulcers in the colon and small intestine
	70/F	Intermittent fever	Splenomegaly/increased WBC, PLT, CRP and ESR, OB(+)	-	NA
	40/M	Bloody stool, intermittent fever (>39°C)	Splenomegaly, lymphadenopathy/ increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous irregular ulcers in the colon
	57/M	Intermittent fever (>39°C)	Splenomegaly, lymphadenopathy/ increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous irregular ulcers in the colon
	30/M	Bloody stool, Intermittent fever (>39°C)	Lymphadenopathy/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous irregular ulcers in the colon
	12/M	Intermittent fever (>39°C	Lymphadenopathy/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous irregular ulcers in the colon, a huge irregular ulcer in the ileocecal junction
	12/M	Watery stool, Intermittent fever (>39°C)	Lymphadenopathy/increased WBC, PLT, CRP and ESR, OB(+)	-	Huge irregular ulcer in the ileocecal junction
	34/F	Bloody stool, intermittent fever (>39°C)	Lymphadenopathy/increased WBC, PLT, CRP and ESR, OB(+)	-	Numerous ulcers in the colon
Yu Zhang, 2017	55/M	Abdominal pain, diarrhea, high fever, bloody stool	Mild splenomegaly/increased WBC, CRP, OB(+)	3 years	Multiple superficial polymorphic ulcers covered with pus Moss all over the terminal ileum and colon, resulted in partial luminal stenosis

Histopathologic findings	Misdiagnosis	PCR/VCA-IgM/VCA-IgG/EA/EBV DNA/EBER	Serum EBV DNA (copies/mL)	Medication/surgery	Follow-up and prognosis
Extensive ulceration, disorganized crypt architecture, chronic inflammatory cell infiltration of the intestinal wall, chronic inflammation of periintestinal lymph nodes	IBD	−/+/+/−/−/+	4.5×10^4	Glucocorticoids, cefoperazone sodium sulbactam sodium, vancomycin/duodenectomy and partial jejunectomy	2 weeks, died of haemorrhagic shock
Dense lymphocytic infiltrate in the lamina propria, transmural inflammation, aggregation of lymphocytes		NT/−/+/NT/NT/+	2.30×10^4	Steroids and antibiotics/YES	Died
Dense lymphocytic infiltrate in the lamina propria, intraepithelial lymphocytosis, fissuring ulcers, crypt abnormalities		NT/−/+/NT/NT/+	8.84×10^6	Steroids, mesalazine, and antibiotics/YES	Died
Intraepithelial lymphocytosis, crypt abnormalities, intraepithelial lymphocytosis		NT/−/+/NT/NT/+	2.55×10^6	Mesalazine and antibiotics/YES	Died
Dense lymphocytic infiltrate in the lamina, transmural inflammation, fissuring ulcers		NT/−/+/NT/NT/+	3.01×10^4	Mesalazine and steroids/YES	Survived
Dense lymphocytic infiltrate in the lamina, crypt abnormalities, transmural inflammation, fissuring ulcers		NT/−/+/NT/NT/+	NA	Mesalazine and antibiotics/YES	Survived
Crypt abnormalities		NT/−/+/NT/NT/+	4.40×10^4	Mesalazine, steroids, and antibiotics/NO	Survived
Dense lymphocytic infiltrate in the lamina, intraepithelial lymphocytosis, crypt abnormalities		NT/−/+/NT/NT/+	8.17×10^3	Mesalazine and steroids/NO	Survived
Intraepithelial lymphocytosis		NT/−/+/NT/NT/+	7.06×10^6	Mesalazine, steroids, and antibiotics/NO	Survived
Dense lymphocytic infiltrate in the lamina		NT/−/+/NT/NT/+	4.11×10^4	Mesalazine, steroids, and antibiotics/NO	Survived
Dense lymphocytic infiltrate in the lamina		NT/−/+/NT/NT/+	NA	Mesalazine, steroids, antibiotics, and traditional Chinese medicine/NO	Survived
Intraepithelial lymphocytosis		NT/−/+/NT/NT/+	5.71×10^5	Mesalazine, steroids, and antibiotics/NO	Survived
Chronic active inflammation with a large amount of neutrophils and lymphocytes infiltrated with a normal tissue structure, partial cryptitis	IBD	+/NT/NT/NT/NT/+	NA	_	_

(Continues)

TABLE 2 (Continued)

Author/Year	Age/Sex	Symptoms	Signs/laboratory examination	Disease course	Endoscopic findings
Si Wei, 2016	55/M	Recurrent fever with diarrhea	Increased WBC	11 years	Diffuse patchy ulceration of the mucosa of the transverse, descending and sigmoid colons
Antonio Cuadrado Lav í n, 2008	49/M	Worsening epigastric pain	Decreased hemoglobin	16 days	Multiple ulcerated lesions and white-yellow pseudomembranes in the second duodenal portion

Abbreviations: CD, Crohn disease; DNA, deoxyribose nucleic acid; EA, early antigen; EBV-LPD, EBV associated lymphoproliferative disorder; EBNA Epstein–Barr virus nuclear antigen, EBER EBV-encoded early small ribonucleic acid, EBV, Epstein–Barr virus; F, Female; IBD, Inflammatory Bowel Disease; NT, not tested; NA, not assessed; PCR, polymerase chain reaction; TB, tuberculosis; UC, ulcerative colitis; VCA-IgM, Viral capsid antigen Immunoglobulin M; VCA-IgG, Viral capsid antigen Immunoglobulin G; + positive test; − negative.

TABLE 3 Clinical symptoms, signs, laboratory tests, and prognoses of patients with chronic active Epstein–Barr virus infectious enteritis (CAEAE).

Subject	Number of cases (%)
Sex	
Male	21 (77.7)
Female	6 (22.3)
Age	
<20	2 (7.4)
20–40	12 (44.5)
40–60	10 (37)
>60	3 (11.1)
Clinical manifestation	
Fever	25 (92.5)
Abdominal pain	14 (51.8)
Diarrhea	16 (59.2)
Hematochezia	13 (48.1)
Hepatosplenomegaly	4 (14.8)
Lymphadenopathy	4 (14.8)
Laboratory examination	
Increased WBC	15 (55.5)
Increased CRP	11 (40.7)
Decreased hemoglobin	14 (51.8)
Coagulation function altered	10 (37)
EBER	27 (100)
Prognosis	
Operation	9 (60)
Postoperative death/survival	7 (77.7)/2 (22.3)
Medicine	21 (100)/
After medication Death/survival	7 (33.3)/13 (61.9)

as EBV + LPD.[22] EBV + LPD includes the CAEBV-b cell type, the CAEBV-T/NK cell type, lymphomatoid granulomatosis, and EBV + immunodeficiency-associated LPD.[22] Therefore, CAEBV is not a single infectious disease and is essentially a group of lymphoproliferative disorders ranging from proliferative to borderline to neoplastic. It can be said that LPD is a precancerous lesion. Enteric EBV infection can lead to recurrent infections in immunocompetent individuals and develop into EBV-associated enteritis, which eventually develops into LPD. A possible reason is that EBV infects lymphocytes, possibly giving them an enhanced ability to activate and proliferate, leading to the development of lymphoproliferative disorders.[10] Finally, lymphomas may develop as a result of enhanced cell tumorigenicity and inhibited apoptosis.[10] Yu Zhang reported a case of CAEAE diagnosed in an immunocompetent male who eventually developed LPD. In 2018, Yaxin Wang[23] similarly reported a case of an immunocompetent middle-aged woman who developed IBD-like manifestations after EBV infection and was ultimately diagnosed with adult EBV + T-LPD (II: borderline). We believe that EBV latent infection develops into CAEBV during the development of CAEAE and then to lymphoid value-added disease. CAEAE is just an intermediate state, and eventually, CAEAE will develop into LPD and ultimately to malignant lymphoma. Many similar studies could demonstrate.[24–26] From the EBV-infected intestine to the development of LPD, the disease features and prognosis are more severe than those of CAEAE.[24–26]

In summary, it is difficult to differentiate IBD at the early stage from CAEAE, and the advanced stage is associated with rapid disease progression, a high case fatality rate, and carcinogenesis. Therefore, early identification is

Histopathologic findings	Misdiagnosis	PCR/VCA-IgM/VCA-IgG/EA/EBV DNA/EBER	Serum EBV DNA (copies/mL)	Medication/surgery	Follow-up and prognosis
Oedema of the colorectal mucosa, lymphocyte and plasma cell infiltration, crypt architectural changes were not evident, cryptitis and crypt abscesses occasionally seen, ulcer formation	IBD	NA/+	NA	_	_
Ulcerated lesions with ulcerated lesions with a lymphocytic and polymorphonuclear inflammatory infiltrate		+/−/+/NT/+/+	NA		

required, and early administration of the corresponding treatment becomes particularly critical. However, because CAEAE is relatively rare, in clinical work, patients with recurrent fever accompanied by abdominal pain, diarrhea, bloody stools, and multiple ulcers in the intestine whose pathological diagnosis of IBD is again not very supportive, should be considered for the diagnosis of CAEAE. Screening for EBV DNA, along with endoscopic biopsy, is recommended for EBER testing. Combined with the clinical features and discriminating points summarized in this article, the diagnosis of CAEAE should be made as early as possible, and it should be treated early to improve the survival rate of patients. Moreover, early screening enteroscopy is recommended in patients over 20 years of age with intestinal symptoms.

AUTHOR CONTRIBUTIONS

Yajie Meng: Data curation; formal analysis; writing – original draft; writing – review and editing. **Rendong Li:** Data curation; formal analysis; resources; writing – original draft; writing – review and editing. **JieWen Ding:** Data curation; investigation; resources. **Bo Xiang:** Resources. **Qin Wang:** Formal analysis; resources. **Min Wang:** Formal analysis; resources; supervision; writing – review and editing. **KeJiang Tang:** Data curation; resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All relevant data are within the manuscript and its Additional files.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal'spatient consent policy.

ORCID

Yajie Meng https://orcid.org/0000-0001-6673-2966

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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