Clinical Analysis of Chronic Active EBV Infection Involving Gastrointestinal Tract

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Abstract

Objective This study aimed to analyze the clinical manifestation, prognosis, and risk factors of pediatric chronic active Epstein-Barr virus infection (CAEBV) associated with gastrointestinal tract involvement.

Methods This retrospective case series study included pediatric CAEBV associated with gastrointestinal tract involvement treated at Beijing Children's Hospital, Capital Medical University from June 2017 to Jun 2021. The control group was consisted of Children with CAEBV without gastrointestinal involvement. The clinical manifestations, laboratory and ultrasound examinations, treatment and prognosis of the children were observed.

Results There were 15 children with CAEBV combined with gastrointestinal involvement, including 11 males and 4 females, accounting for 20.8% (15/72) of CAEBV patients in the same period, with an onset median age of 3.71 (0.64-14.47) years. The most common clinical manifestation at onset was diarrhea (13/15). Gastrointestinal ultrasound showed air accumulation accompanied by intestinal wall swelling and thickening, mild to moderate swelling of the surrounding mesentery and omentum, and enhanced echo. The endoscopic features were hyperemia, edema, and ulcers of variable morphological characteristics. Pathological examination showed lymphocyte infiltration with EBER (+), and the common involvement locations were the colon (n=6) and gastric antrum (n=3). The median follow-up time was 13.26 (0.31-51.89) months. Ten patients survived, and 5 patients died (including one patient who died of intestinal perforation due to necrotizing enterocolitis). Compared with the control group, the case group had higher levels of alanine aminotransferase, aspartate aminotransferase and whole blood EBV-DNA copies (P=0.038, 0.040 and < 0.001) and lower NK cell activity (P < 0.001). The 3-year overall survival rate of the case group was significantly lower than that of the control group (59.3% ±12.9% vs. 79.4%±4.9%, P=0.021).

Conclusion The incidence of CAEBV with gastrointestinal tract involvement was low. The most common involvement location was colon. CAEBV with gastrointestinal involvement had poor prognosis. Patients who had high whole blood EBV-DNA copy levels early in their illness were more likely to develop gastrointestinal involvement.

1 Introduction

Epstein-Barr virus (EBV) categorized under the human herpes virus family, is a double-stranded DNA virus. EBV infections are usually acquired during childhood or adolescence. The primary infection mainly invades B lymphocytes and can cause infectious mononucleosis (IM) and EBV-associated hemophagocytic lymphohistiocytosis (HLH). EBV is an oncogenic virus and occasionally causes a variety of lymphoproliferative diseases (LPDs)[1–2].

CAEBV is an intractable and progressive disease, the symptoms include persistent or recurrent inflammation, harboring EBV-infected clonally proliferating T- or NK-cells. The characterized of this disease including lymphadenopathy, fever, liver dysfunction, hepatosplenomegaly, and so on. However, CAEBV combined with gastrointestinal tract involvement has rarely been reported, and sometimes it may clinically mimic gastroenteritis or inflammatory bowel disease (IBD)[3]. The treatments for those diseases are completely different, and misdiagnosis may lead to poor prognosis. Herein, we report 15 cases of pediatric patients diagnosed with CAEBV with gastrointestinal tract involvement.

2 Patients And Methods

2.1 Patients

From June 2017 to June 2021, 15 patients suffering from CAEBV combined with gastrointestinal tract involvement were enrolled in this study. Data were retrospectively reviewed for basic information, clinical manifestations, laboratory findings, treatment, and prognosis. Children with CAEBV without gastrointestinal tract involvement (n=57) at the same period in the same hospital were selected as the control group.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University ([2021]-A-142-R). All patients' parents signed informed consent.

2.2 Diagnostic criteria

The inclusion criteria for diagnosing CAEBV in this study were as follows[4–5]: (1) persistent or recurrent IM-like symptoms for >3 months, such as fever, liver dysfunction, lymphadenopathy, hepatosplenomegaly, hydroa vacciniform, or hypersensitivity to mosquito bites; (2) EBV-encoded small RNA (EBER)-positive cells in tissues or EBV-DNA in plasma and whole blood >$10^{2.5}$ copies/ml; and (3) no identifiable underlying immunodeficiency disease, such as chronic granulomatous disease or X-linked SCID. Patients had to fulfill all three criteria.

The T cell or NK cell type of CAEBV was mainly determined by ProcartaPlex bead-linked immunoassay. The clonality of the EBV-infected cells was assessed by Southern blotting using EBV terminal repeats or T-cell receptor genes.

The diagnostic criteria for HLH were according to the HLH-04 criteria proposed by the International Histiocyte Society[6].

Gastrointestinal tract involvement was defined as CAEBV patients with typical clinical manifestations and imaging abnormalities of digestive tract involvement and/or EBER (+) in the digestive tract biopsy[7].

2.3 Therapeutic regimens

(1) The first step was to use the L-DEP regimen to reduce the number of EBV DNA copies and EBV-infected T and/or NK cells (ChiCTR1900020574)[8]. (2) In the second step, after 2 cycles of chemotherapy, patients were referred for allogeneic stem cell transplantation. The L-DEP regimen could be repeated in patients who did not receive allo-HSCT for various reasons, with a maximum of four courses.

2.4 Statistical Analysis

The results of the statistical analysis are expressed as the median (range). Statistical analysis was performed by using IBM SPSS Statistics 24 software (IBM, USA). Skewed data are presented as the median (quartile). The independent-samples t-test was used to test for differences between quantitative variables. The Kolmogorov-Smirnov test was used to verify the overall survival rate, and the log-rank test was used to compare the survival rate between different groups. $P<0.05$ was considered a significant difference.

3 Results

3.1 General patient information

Fifteen patients with CAEBV combined with gastrointestinal tract involvement were enrolled in this study, accounting for 20.8% (15/72) of CAEBV cases in the same period, including 11 males and 4 females. The median age of disease onset was 3.71 (0.64-14.47) years (Table 1).

Table 1
General information

NO	Gender	Age(year)	Gastrointestinal tract			Treatment	Prognosis
			Symptom	Ultrasound abnormal	EBER(+)		
1	M	12.90	Y	Y	–	L-DEP+HSCT	Alive
2	M	1.34	Y	Y	Y	L-DEP	Dead
3	M	1.87	Y	Y	–	L-DEP	Alive
4	F	14.47	Y	Y	–	L-DEP	Alive
5	M	3.71	Y	Y	Y	Antiviral +Prednisone	Alive
6	M	8.20	Y	Y	–	L-DEP	Dead
7	M	1.52	Y	Y	–	L-DEP	Dead
8	M	13.29	Y	Y	–	L-DEP	Dead
9	M	0.76	Y	Y	Y	Antiviral +Prednisone	Alive
10	F	13.42	Y	Y	–	L-DEP+HSCT	Dead
11	F	4.90	Y	Y	Y	L-DEP+HSCT	Alive
12	M	6.64	N	Y	Y	L-DEP+HSCT	Alive
13	F	2.34	Y	Y	Y	Antiviral +Prednisone	Alive
14	M	1.28	Y	Y	Y	–	Alive
15	M	0.65	Y	Y	Y	–	Alive

Note: NO, Number Oder; M, Male; F, Female; Y, Yes; N, No.

3.2 Clinical manifestations and laboratory examination

In the early stages of the disease, 13 patients had fever, and the median duration of fever was 3 (0.4-24) months. Eleven patients presented with various degrees of hepatomegaly, 9 patients had different degrees of splenomegaly, and 7 patients developed skin rashes, which were mainly red papules or maculopapules without itching, occurring predominantly on the torso. Eight patients had lymphadenopathy, 7 of whom had cervical lymph node enlargement and 1 had bilateral axillary lymph node enlargement. At onset, 13 patients had diarrhea, 3 of whom had hematochezia, and the others had yellow/yellow-green mush or watery stools, without mucus, pus, or blood. The other clinical manifestations included hematemesis in 2 cases, abdominal distention with vomiting in 2 cases, and abdominal pain in 2 cases. One patient showed no gastrointestinal

symptoms. Three patients were admitted to the infectious department due to fever and diarrhea; two patients were admitted to the gastroenterology department due to hematochezia; and the other 10 patients were admitted to the hematology department due to fever or hepatosplenomegaly.

After admission, laboratory examinations showed that 12 patients had varying degrees of hemocytopenia. Two patients (cases 10 and 11) had high triglyceride levels (>3 mmol/L), 4 patients (cases 1, 4, 8 and 10) had high serum ferritin levels (>500 μg/L), 8 patients (cases 2, 4, 5, 7, 8, 11, 12 and 13) had low NK cell activity (<15.11%), 6 patients (cases 2, 4, 5, 7, 10 and 12) had high sCD25 levels (>6400 ng/L) and 3 patients (cases 4, 7 and 10) had hemophagocytosis in bone marrow smears. Routine stool examination showed that the fecal occult blood test was positive in 7 patients, 1 patient was positive for the fat globule test, and 1 patient could detect red and white blood cells in the stool. Serological and PCR tests for other pathogens (such as rotavirus, norovirus, herpes zoster virus, hepatitis B virus, cytomegalovirus, bacteria, and parasites) were negative. All exon genetic examinations and bone marrow cell flow cytometry evaluations were normal. The other laboratory examination results of the 15 patients are summarized in Table 2.

Table 2
Laboratory data at diagnosis

Pt	WBC(x10^9/L)	Hb(g/L)	PLT(x10^9/L)	ALT(U/L)	AST(U/L)	CK (U/L)	IFN-γ (ng/L)	IL-6 (ng/L)	IL-10 (ng/L)	EBV-DNA(Whole blood) (Copies/L)	EBV-DNA(Plasma) (Copies/L)
1	0.28	86	26	48.2	55.8	27	116.01	22.87	2.44	1.65x10^6	1.30x10^3
2	11.15	76	521	37.2	32.4	35	333.97	109.83	14.09	4.56x10^6	9.59x10^2
3	4.27	83	647	22.5	14.9	62	2.89	15.01	4.65	6.63x10^6	5.00x10^2
4	8.01	140	27	227.7	199.4	14	716.83	210.52	324.15	2.25x107	7.05x10^4
5	4.78	60	131	24.5	8.9	50	0.5	40.06	12.34	5.70x104	7.50x10^2
6	7.61	123	380	113.2	215.6	33	1.65	7.97	4.4	5.61x10^6	6.37x10^2
7	1.43	88	234	34.6	18.4	13	140.28	78.3	47	1.31x10^6	1.26x10^4
8	14.41	115	108	213.6	208.7	33	16.32	460.44	12.79	1.32x10^7	5.30x10^3
9	8.78	127	383	40.4	19.5	52	1.63	4.01	5.18	1.25x104	5.68x10^2
10	1.70	83	54	60.6	15.8	12	20.91	7.48	90.2	6.89x10^6	2.63x10^5
11	3.66	96	138	79.8	27.6	96	58.98	20.33	3.99	6.24x10^6	8.82x10^3
12	6.07	99	309	28.3	17	32	9.22	14.9	5.9	2.42x10^6	5.90x10^2
13	9.87	68	382	41	18.6	17	91.81	165.5	41.2	1.02x10^6	5.00x10^2
14	21.53	106	554	19.9	6.3	22	20.16	4.10	16.71	2.35x107	6.50x10^2
15	16.39	120	326	36.3	14.3	41	20.75	45.2	16.45	1.64x104	5.00x10^2

Note: Pt, patients; WBC, White blood cell; Hb, hemoglobin; PLT, platelet; ALT, Alanine transaminase; AST, glutamic oxalacetic transaminase; CK, creatine kinase; IFN, Interferon; IL, interleukin.

3.3 Ultrasound and endoscopic features All patients underwent intestinal ultrasonography examination, which showed gas accumulation with swelling and thickening of the intestinal wall. Hypoecho could be seen near the intestinal wall. The mesentery surrounding the intestine had mild to moderate swelling, with hyperecho. There was no intestinal loop with abnormal effusion and dilation and no free ascites. Duodenal wall swelling (max 0.8-1.0 cm) could be seen in 2 patients, small intestinal wall swelling (max 0.2-0.5 cm) in 3 patients, ileum wall swelling (max 0.4-1.6 cm) in 5 patients, and jejunum wall swelling (max 0.3-1.0 cm) in 6 patients.

Enteroscopy was performed in 7 patients, and gastroscopy was performed in 4 patients. Those patients had biopsy by endoscopy. Under gastroscopy, the gastric mucosa showed hyperemia and edema as blotchy changed, and 1 patient was complicated with a superficial ulcer. The enteroscopy manifestations varied from normal to multiple deep ulcers, erosion, and bleeding. No cobblestone-like appearance was observed in any of the 15 patients (Fig. 1). Pathological examination showed inflammatory infiltration of lymphocytes, plasma cells and eosinophils infiltrated into the submucosa and muscular layer. All infiltrating lymphocytes exhibited polyclonal proliferation instead of monoclonal proliferation. No crypt abscesses or granulomas were found in any of the patients. No neural hypertrophy, thickened muscularis mucosae, or abscesses were observed in any of the samples. TB, HP and Giemsa stain were all negative. The results of in situ hybridization for EBER were all positive. The most frequently affected sites were the colon (n=6), followed by the gastric antrum (n=3). More detail information could be seen in Table 3.

Table 3
Endoscopic manifestations of CAEBV patient

Pt	Gastroscopy	Enteroscopy	Pathology	Special staining and immunohistochemistry	Location of EBER(+)
2	Congestion and edema of gastric antrum mucosa, scattered coffee spots. No abnormalities in the rest.	No obvious abnormality in colorectal mucosa	(stomach and small intestine) infiltration of focal lymphocytes, plasma cells and eosinophils (0-30/HPF) in the lamina propria. (whole colon) infiltration of lymphocytes, plasma cells in the lamina propria, local lymphocyte aggregation, without obvious atypia. No crypt abscess and granuloma.	HP(-), CMV(-), CD3(+), CD20(occasional +), Ki-67(colon 5%+, gastric antrum 5%+, duodenum 10%+)	gastric antrum, duodenum, colon
5	–	The mucosal eminence, with irregular ulcer erosion, brittle mucosa, easy bleeding and blurred vascular network can be seen on the surface of the whole colon and rectum.	(ascending, descending, and sigmoid colon) mucosal edema and infiltration of focal lymphocytes, plasma cells and eosinophils (0-8/HPF) in the lamina propria. No crypt abscess and granuloma.	TB(-), Giemsa(-), HP(-), CMV(-)), EBNA(-)	ascending colon, descending colon, sigmoid colon
9	Gastric fundus, body and antrum mucosa rough, eroded, and multiple scattered superficial ulcers. The mucosa of duodenal bulb and descending part rough and granular changes. No abnormalities in the rest.	The mucosa of transverse, descending and sigmoid colon slightly swollen, with scattered granule-like eminence, no erosion and ulcer, brittle, and easy bleeding.	(esophagus, gastric body, antrum and duodenum) infiltration of focal lymphocytes, plasma cells and eosinophils (0-17/HPF) in the lamina propria.(transverse, descending, rectum, sigmoid)infiltration of focal lymphocytes, plasma cells and eosinophils (0-16/HPF) in the lamina propria. No crypt abscess and granuloma.	TB(-), Giemsa(-), HP(-), CMV(-)), EBNA(-)	gastric antrum, duodenum, gastric body
11	–	Scattered ulcers can be seen in ascending, descending, transverse, sigmoid colon, and rectum.	(ascending, transverse, sigmoid colon, and rectum) mucosal edema and infiltration of focal lymphocytes, plasma cells and eosinophils in the lamina propria. No crypt abscess and granuloma.	TB(-), Giemsa(-), HP(-), CMV(-)), EBNA(-), Ki-67(3%+)	ascending colon, transverse colon, sigmoid colon, rectum
12	–	Terminal ileal mucosa hyperemia, edema, multiple irregular deep ulcers, surface covered with white moss. Mucous membrane brittle, easy to bleed. Erosion and ulcer on the surface of ileocecal valve.	(ileocecal valve, transverse, descending and sigmoid colon)infiltration of focal lymphocytes, plasma cells and eosinophils in the lamina propria. No crypt abscess and granuloma.	CD3(+), CD20(+), CD56(+), Gram-B(occasional +), Ki-67(30%+), CD21(follicle +)	terminal ileum, ileocecal valve, transverse colon, descending colon, sigmoid flexure
13	–	No obvious abnormality in colorectal mucosa	(terminal ileum, sigmoid colon, rectum) infiltration of focal lymphocytes, plasma cells and eosinophils (1-8/HPF) in the lamina propria. No crypt abscess and granuloma.	TB(-), Giemsa(-), HP(-), CMV(-), EBNA(-)	terminal ileum, sigmoid flexure, rectum
14	Congestion and edema of gastric antrum mucosa, scattered coffee spots. No abnormalities in the rest.	Congestion, edema, and multiple deep ulcers of ileocecal, ascending, transverse, descending colon, and rectal mucosa.	(duodenum, gastric antrum, esophagus) infiltration of focal lymphocytes, plasma cells and eosinophils (0-3/HPF) in the lamina propria.(ileum, ascending, transverse, sigmoid colon)infiltration of focal lymphocytes, plasma cells and eosinophils (0-2/HPF) in the lamina propria. No crypt abscess and granuloma.	TB(-), Giemsa(-), HP(-), CMV(-), EBNA(-)	ascending colon
15	Congestion and edema of gastric antrum mucosa, scattered coffee spots. No abnormalities in the rest.	–	(duodenum, gastric antrum)infiltration of focal lymphocytes, plasma cells and eosinophils (0-5/HPF) in the lamina propria.	TB(-), Giemsa(-), HP(-), CMV(-), EBNA(-)	gastric antrum

Note: Pt, patient; TB, tuberculosis; HP, Helicobacter pylori; CMV, cytomegalovirus; EBNA, Epstein Barr Nuclear Antigen.

3.4 Diagnosis, treatment, and prognosis

All the patients met the diagnostic criteria for CAEBV, with 12 patients having T-cell type EBV infection and 3 patients having NK-cell EBV infection. Children with CAEBV developed the following complications: HLH (8 cases), coronary artery dilatation (2 cases), pancreatic damage (3 cases), and coagulation dysfunction (5 cases). Among the 15 patients, gastrointestinal involvement was diagnosed by pathology in 8 patients and by clinical manifestations and gastrointestinal ultrasound results in 7 patients. Of the 15 patients, 2 patients discontinued treatment due to financial reasons. The remaining 13 patients accepted treatment, including 11 patients who accepted the L-DEP protocol (Table 1). Related donor haploidentical stem cell transplantation was performed for 4 patients.

The last follow-up was September 1, 2021, and the median follow-up time was 13.26 (0.31-51.89) months. At the last follow-up, 10 patients survived. One patient died of intestinal perforation caused by necrotizing enterocolitis (case 7), 3 died of multiple organ failure caused by HLH outbreaks (cases 2, 6 and 8), and 1 died of complications after HSCT (case 10). After chemotherapy, the clinical manifestations of digestive tract involvement were improved in 5 patients, swelling of the digestive tract wall was absorbed, and gastrointestinal lesions returned to normal in 3 patients (including 2 patients after transplantation).

3.5 Comparison of CAEBV patients with and without gastrointestinal involvement

We compared the characteristics of CAEBV patients with and without CAD. ALT, AST and whole blood EBV-DNA copies in the case group were relatively higher than those in the control group (P=0.038, 0.040 and <0.001, respectively). NK cell activity levels in the case group were relatively lower than those in the control group (P0.001). The age at onset, sex, and other laboratory indices did not show significant differences between the case group and the control group. The 3-year overall survival (OS) rate in the case group was significantly lower than that in the control group. (59.3%±12.9% VS. 79.4%±4.9%, log-rank test, P = 0.021) (Fig. 4).

4 Discussion

CAEBV infection is a rare lymphoproliferative disease. It was defined as an EBV-positive T- or NK-lymphoproliferative disease (EBV-T/NK-LPD) in 2016[9–10]. The most common symptoms were fever, hepatosplenomegaly and lymphadenectasis. The main laboratory results were leukopenia, anemia, and high EBV-DNA copies[11–12].

There have been few reports on CAEBV with gastrointestinal tract involvement. A previous report found that gastrointestinal involvement accounted for only 8% of CAEBV patients and mainly manifested as diarrhea and abdominal pain[13]. Which was similar to IBD. In this study, patients with gastrointestinal involvement accounted for 20.8% of CAEBV patients in the same period. Among the 15 cases, the common gastrointestinal symptoms were diarrhea, abdominal distension, vomiting, hematemesis and hematochezia. These were consistent with previous reports. However, it is worth noting that 1 patient had no digestive tract symptoms, only abnormalities found on ultrasound examination, and was diagnosed by enteroscopy. This indicated that the clinical manifestations of gastrointestinal involvement of CAEBV were nonspecific and occult. Therefore, ultrasonography should be performed for CAEBV patients after admission to determine whether there were gastrointestinal symptoms. The main laboratory results of the enrolled patients were cytopenia, fecal occult blood and high levels of whole blood EBV-DNA copies.

To date, 28 cases of intestinal involvement of CAEBV have been reported in previous literature. Ulcer morphologies have generally been reported as small, shallow, irregularly shaped, and scattered, except for eight cases of large and profound ulcers. There was also a previous case in which the entire intestinal mucosa displayed lymphangiectasia [3,14–17]. In contrast to a previous report, our study found that the endoscopic findings of CAEBV with gastrointestinal tract complications were complicated. The major distortions were hyperemia, edema, erosion, and irregular ulcers. At the same time, we also reported 2 patients who had no abnormal findings under enteroscopy (only pathological EBER positive). This is probably because these patients were in the early stages of the disease. Therefore, biopsy and in situ hybridization (ISH) of EBER by pathological examination should be performed when gastrointestinal involvement is suspected by the clinician. This study reported gastroscopic findings of CAEBV involving the stomach, mainly hyperemia and edema, and plaque-like changes in the gastric mucosa, and only 1 patient had a superficial ulcer. Compared with previous studies, there were fewer ulcers under endoscopy in our study, and most of them showed hyperemia and edema. This study also reported the ultrasonographic findings of CAEBV involving the gastrointestinal tract, mainly gas accumulation with swelling and thickening of the intestinal wall, mild to moderate swelling of the surrounding mesentery and echo enhancement.

Histological features of chronic active Epstein–Barr virus infective enteritis showed increased mucosal lymphocytic, plasma cell and neutrophil infiltration and occasional eosinophil infiltration. The infiltrating lymphocytes were small without cytological atypia. No granulomas or crypt abscesses were identified in any cases. The above pathological manifestations were basically consistent with previous reports. Liu et al[7] found that in most patients, increased mucosal lymphocytic infiltration was seen, and lymphocytes occasionally infiltrated into the muscularis mucosae and submucosa. Intraepithelial lymphocytosis was observed in five cases. Mucosal plasma cell infiltration could be seen in all cases, but no basal plasmacytosis was observed. However, the difference was that in previous reports, they found cryptitis in 3 cases and occasional crypt abscesses

in 1 case[7]. These differences might be due to the small sample size or different samples, so the pathological manifestations of gastrointestinal tract involvement by CAEBV still need to be further expanded. The pathological findings of CAEBV with gastrointestinal involvement were similar to Crohn's disease, but the former lacks granulomas and chronic connective tissue changes such as neural hypertrophy and thickened muscularis mucosae[18]. According to the pathological results, the most common involvement locations were the colon (n=6) and gastric antrum (n=3). In a previous study, the most common diseased lesion was located in the colon (n=15), followed by the small intestine (n=6), ileocecal junction (n=2), stomach (n=1), and unknown location (n=2)[3,14–17]. The above results suggested that the gastrointestinal tract of CAEBV was mainly involved in the colon.

In adults, approximately 6% of CAEBV-related deaths originate from intestinal bleeding or perforation[19]. Xu et al[17] reported that all ten patients died within 5 years of disease onset. The average survival time was 21 months. In another article, the 5-year overall survival rate of 11 patients was 75%, and three patients died after total colectomy, but patients who did not accept surgery [all survived 7]. In this study, we found that the prognosis of gastrointestinal tract involvement of CAEBV was poor. Compared with CAEBV without gastrointestinal involvement, the 3-year OS decreased significantly. The main reason for the high mortality in our study was mainly related to serious disease conditions (8 cases complicated with HLH). Although 1 patient died of related complications after HSCT, at present, the only effective treatment strategy for eradicating EBV-infected T or NK cells was allo-HSCT[20]. Therefore, for CAEBV with gastrointestinal tract involvement, especially in patients with HLH, chemotherapy should be used as soon as possible and then followed by allo-HSCT to rescue the patients. During chemotherapy, attention should be given to strengthening gastrointestinal protection to avoid life-threatening conditions such as digestive tract perforation. In this study, 2 patients did not accept treatment, and 3 patients were given corticosteroid and antiviral therapy but survived. We consider that this might be due to the mild disease condition and low pathological grade (all grade I), and the follow-up time was relatively short. Chen[21] et al also pointed out that CAEBV patients with young age and low pathological grade had a better prognosis.

This study also compared CAEBV patients without gastrointestinal involvement in the same period. It was found that CAEBV patients with gastrointestinal involvement were more likely to be complicated with liver function damage (ALT and AST increased). At the same time, the copy number of whole blood EBV-DNA copies was higher and the activity of NK cells was lower. Liver function damage and decreased activity of NK cells might be related to EBV activity and proliferation. Previous studies also found that EBV-DNA in CAEBV infective enteritis was higher than that in IBD[7]. However, the research sample size was still small, and further research is needed.

5 Conclusion

Clinical manifestations of gastrointestinal involvement of CAEBV were nonspecific and occult. The endoscopic findings were mainly hyperemia, edema, and ulcer. Histological features showed increased mucosal lymphocytic, plasma cell and neutrophil infiltration, without granulomas and crypt abscesses. The prognosis of these patients was poor, and chemotherapy should be used as soon as possible, followed by allo-HSCT.

Abbreviations

EBV Epstein-Barr virus;IM infectious mononucleosis; HLH hemophagocytic lymphohistiocytosis; CAEBV chronic active Epstein–Barr virus infection;EBER Epstein-Barr virus-encoded small RNA; IBD inflammatory bowel disease; L-DEP PEG-Aspegaspargase, doxorubicin, etoposide, and methylprednisolone; IL interleukin; HSCT hematopoietic stem cell transplantation; NK natural killer; sCD25 serum CD25.

Declarations

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Code availability: Yes

Authors' contributions:

AW, HM Writing - original draft; LZ, ZL, YZ Writing - review & editing; JZ, LH, QZ, SC Data curation; HL, DW Formal analysis; TW, WL, RZ Project administration.

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University ([2021]-A-142-R).

Consent to participate: All parents signed informed consent forms and approved the final manuscript.

Consent for publication: All authors have read and approved the final manuscript.

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Figures

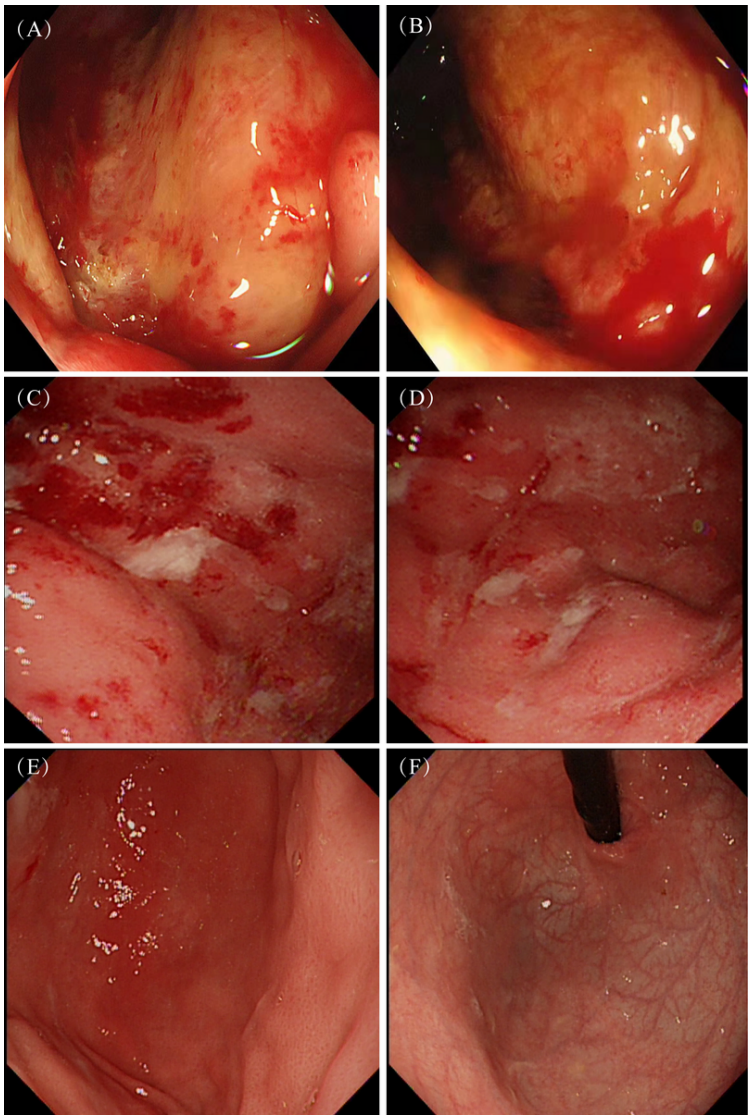

Figure 1

Endoscopic findings of CAEBV patients. (A-B) Enteroscopy showed scattered ulcers, deep bottom of some lesions, loss of mucous membrane, and diffuse blood osmosis in the local lesions (Case 11). (C-D) Gastroscopy showed that the mucosa of the gastric fundus, body and antrum were rough and eroded, with multiple scattered superficial ulcers (Case 9). (E-F) Gastroscopy showed that gastric involvement disappeared after 2 courses of L-DEP chemotherapy.

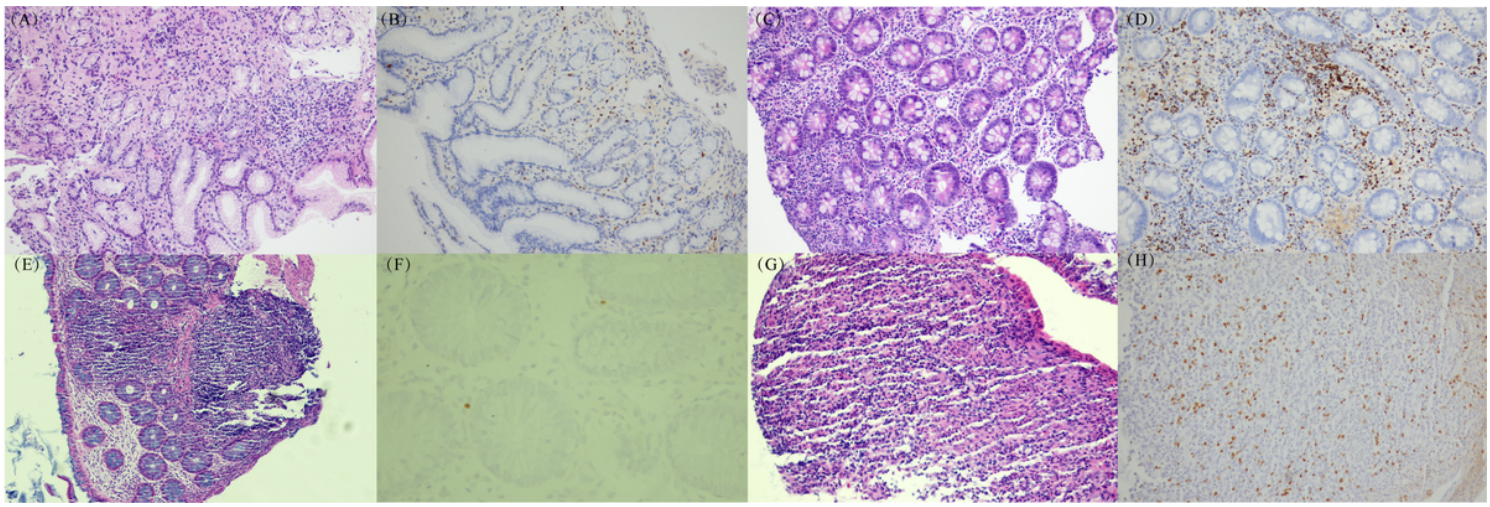

Figure 2

Histopathological findings of CAEBV patient. (A) Antrum (HE 200X), (C) duodenum (HE 200X), (E) sigmoid colon (HE 100X), (G) terminal ileum (HE 200X), infiltration of lymphocytes, plasma cells in the lamina propria, local lymphocyte aggregation, without obvious atypia. Special staining: EBER (+), gastric antrum (B), duodenum (D), sigmoid colon (F), terminal ileum (H).

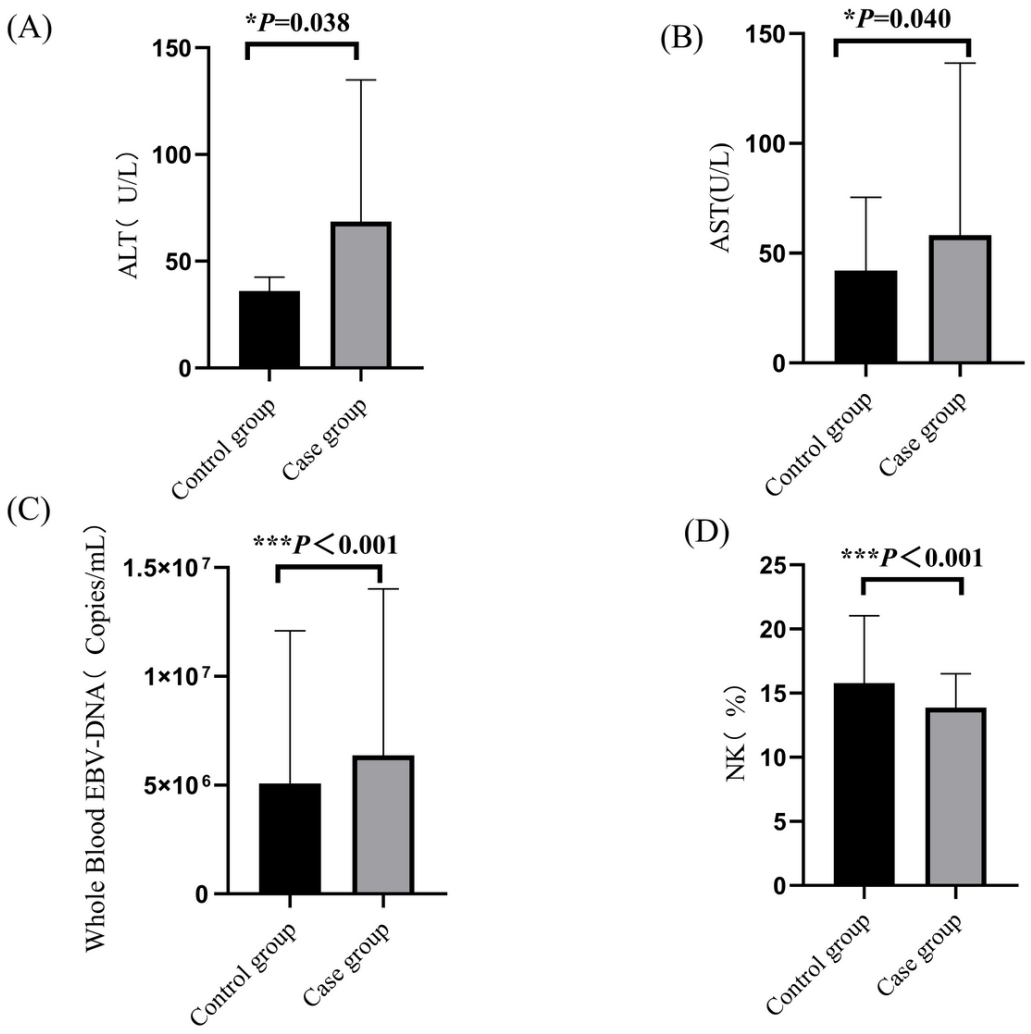

Figure 3

Prognostic factor analysis. ALT, AST and whole blood EBV-DNA copy levels were relatively higher in the case group than in the control group (P=0.038, 0.040 and <0.001, respectively). NK cell activity levels were relatively lower in patients in the case group than in those in the control group (P□0.001).

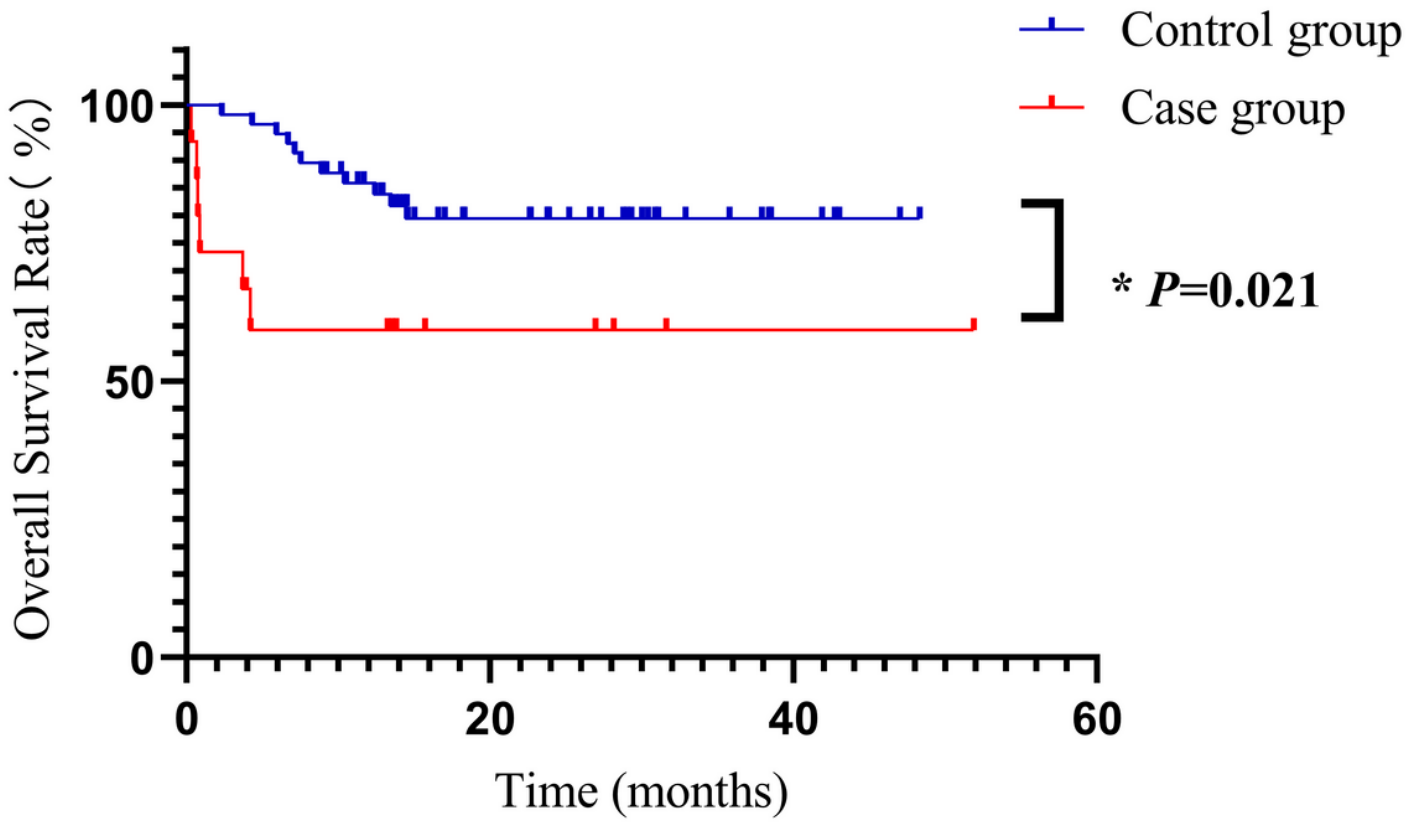

Figure 4

The 3-year overall survival rate in the case group was significantly lower than that in the control group (59.3%±12.9% vs. 79.4%±4.9%, log-rank test, P = 0.021).