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

Ya Jie Meng[1], Li Rendong[1], Ding Jiewen[1], Xiang Bo[1], Wang Qin[1], Wang Min[1], and Tang Kejiang[1]

[1]Chongqing yike daxue

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YaJie Meng[1+], RenDong Li[2+], JieWen Ding[1], Bo Xiang[1],Qin Wang[1],Min Wang[1] *and KeJiang Tang[1]*

*Correspondence:KeJiang Tang :tttkkj@163.com and Min Wang

[+]Equal contributors.

[1]Department of Gastroenterology, The People's Hospital of Nanchuan, No. 16

South Street, Nanchuan District, Chongqing 408400, China

[2]The People's Hospital of Nanchuan, No. 16 South Street, Nanchuan District, Chongqing 408400, China

Abstract

Background: Chronic active Epstein-Barr virus (EBV) infection-associated enteritis (CAEAE) in nonimmunodeficient individuals is rare.

Methods: 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 analysed. Including this report, 7 citations in the literature provide descriptions of 27 cases of CAEAE.

Results: There were 21 males and 6 females, with a mean age of 40 years. The main clinical manifestations were fever (25/27), abdominal pain (14/27), diarrhoea (16/27), haematochezia or bloody stools (13/27), and decreased haemoglobin 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 x 10 ˆ 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 haematochezia. 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).

Conclusions: 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 aetiology, attention should be paid to EBV serology and histology to make the diagnosis as early as possible.

Keywords:Chronic active Epstein-Barr virus infection-associated enteritis,Epstein-Barr virus,Inflammatory bowel disease,Misdiagnosis,EBV-positive lymphoproliferative disorder

Introduction

Epstein-Barr virus (EBV) v 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 favourable 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[3-6]. Viruses can infect not only B lymphocytes but also T or natural killer (NK) cells[1-6]. 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[3-6]. 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)[4,6]. In recent years, CAEAE has gained increasing attention. We performed a literature report and analysed and summarized the clinical features, differential diagnoses, prognoses, etc., to increase awareness and improve the diagnosis of this class of diseases among clinicians.

Patient and methods

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.

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 diarrhoea and occasional mucous bloody stools. The first enteroscopy suggested multiple ulcers in the colon. Pathology suggested chronic inflammatory changes. Because ulcerative colitis 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 diarrhoea, 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 diarrhoea 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 faecal 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 T**able 1 and Attachment 1(Figure1)** . A satisfactory and accurate diagnosis could not be obtained by pathology at our hospital. Therefore, we seeked help from Wechat at Zhongnan Hospital of Wuhan University, which has a well-known inflammatory bowel disease research centre and a digital telepathology consultation centre.

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 **Attachment 1(Figure2).**

At this time, we performed an EBV serological examination, and the results showed the following: IgA negative (-), IgM negative (-), IgG positive (+), and peripheral blood EBV DNA concentration: 1.75* 10 ˆ 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 four weeks, then reduced to one tablet (20 mg) a week and then to one tablet every two 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.

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: "Epstein-Barr virus infection" or "chronic Epstein-Barr virus 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 5 Chinese studies were retrieved. After a careful review of the full text, 7 studies[7-13] (3 Chinese and 4 English) and 26 case reports of CAEBV were included in the statistical analysis.

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.

Results

Together with our own case report, a total of 27 case reports[7-13] described CAEBV. A summary is shown in **Table 2 and Table 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 one 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), diarrhoea (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), 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, tumours, family history or previous immunosuppressive drug treatment.

3. Laboratory examinations: In routine blood tests, decreases in haemoglobin 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*10ˆ5 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), ulcerative colitis (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.

Discussion

CAEBV usually occurs in persons with congenital or acquired immunodeficiency[14]. 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[15]. 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[6]. Currently, the cases of CAEAE occurring in nonimmunodeficient individuals are very limited, and all have been case reports[7-13]. 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 inflammatory bowel disease (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, diarrhoea, and bloody stools accompanied by lymphadenopathy and hepatosplenomegaly. (3) Decreased haemoglobin, 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[16]. An elevated serum EBV DNA load was evident. (6) The disease is progressive, and severe complications, including massive lower gastrointestinal bleeding, haemorrhagic 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 haematochezia, resulting in a high rate of reoperations. Consistent with reported case characteristics[10,17]. (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 multicentre study to compare the clinical characteristics of 11 patients with CAEAE to those of 100 patients with IBD and found the following[10]: (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[16,18]. (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[10,16]. (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[10,16,19]. 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. Anti-herpesvirus 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[20]. Haematopoietic stem cell bone marrow transplantation is a curative procedure for CAEBV infection, but there is also an associated risk of transplantation complications[21]. Recently, Lingling Xu reported a case of CAEBV with intestinal[22], 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 as EBV + LPD[23]. EBV + LPD includes the CAEBV-b cell type, the CAEBV-T/NK cell type, lymphomatoid granulomatosis, and EBV + immunodeficiency-associated LPD[23]. 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[11]. Finally, lymphomas may develop as a result of enhanced cell tumorigenicity and inhibited apoptosis[11]. Yu Zhang reported a case of CAEAE diagnosed in an immunocompetent male who eventually developed LPD. In 2018, Yaxin Wang[24] 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[25-27]. From the EBV-infected intestine to the development of LPD, the disease features and prognosis are more severe than those of CAEAE[25-27].

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 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, diarrhoea, 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.

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Table 1 Clinical and colonoscopic manifestations of the case

	2017	2018
Clinical symptoms	Abdominal pain	Abdominal pain wi
Endoscopically confirmed site of involvement	Ascending colon, transverse colon, descending colon	Ascending colon, tr
Intestinal stricture	NO	NO
Maximum ulcer diameter (cm)	0.5	0.5
Pathological biopsy	Acute and chronic inflammation of the colonic mucosa	Acute and chronic

Table 2 Review of the literature

Author/Year	Age/Sex	Symptoms
Our case	49/M	Abdominal pain
Yangxiao Zhou, 2020	50/M	Abdominal pain, diarrhoea, high fever, Weight loss
	51/M	High fever, diarrhoea, abdominal pain,Haematochezia
	24/M	Fever, rash, haematochezia
Bo Zhang, 2020	39/M	Abdominal pain, fever, adenopathy, diarrhoea, haematochezia
	28/M	Abdominal pain, fever, adenopathy, retrosternal pain, diarrhoea, splenomegal
	48/F	Abdominal pain, fever, adenopathy
Dong Xuyang, 2018	62/M	Abdominal pain, haematochezia, high fever, diarrhoea
	27/M	High fever, diarrhoea, haematochezia, abdominal pain
	28/M	High fever, haematochezia, abdominal pain, diarrhoea
	32/F	Abdominal pain, diarrhoea, high fever, haematochezia
	29/M	Abdominal pain, dyssynergistic defecation, high fever, haematochezia
	26/F	High fever, diarrhoea, abdominal pain, haematochezia
Rongbei Liu, 2018	72/M	Watery stool, intermittent fever (>39 °C)
	21/M	Watery stool, intermittent fever (>39 °C)
	50/F	Watery stool, intermittent fever (>39 °C)
	50/M	Bloody stool, intermittent fever (>39 °C)
	70/F	Intermittent fever
	40/M	Bloody stool, intermittent fever (>39 °C)
	57/M	Intermittent fever (>39 °C)
	30/M	Bloody stool, Intermittent fever (>39 °C)
	12/M	Intermittent fever (>39 °C

	12/M	Watery stool, Intermittent fever (>39 °C)
	34/F	Bloody stool, intermittent fever (>39 °C)
Yu Zhang, 2017	55/M	Abdominal pain, diarrhoea, high fever, bloody stool
Si Wei, 2016	55/M	Recurrent fever with diarrhoea
Antonio Cuadrado Lav í n, 2008	49/M	Worsening epigastric pain,

Abbreviations: EBV- LPD EBV associated lymphoproliferative disorder, PCR polymerase chain reaction, VCA-IgM Viral capsid antigen Immunoglobulin M, VCA-IgG Viral capsid antigen Immunoglobulin G, EA early antigen, EBNA Epstein-Barr virus nuclear antigen, EBER EBV-encoded early small ribonucleic acid, EBV Epstein–Barr virus, DNA Deoxyribose Nucleic Acid, F Female, IBD Inflammatory Bowel Disease, NT not tested, NA not assessed, UC ulcerative colitis, CD Crohn disease, TB tuberculosis,, + 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)
Diarrhoea	16 (59.2)
Haematochezia	13 (48.1)
Hepatosplenomegaly	4 (14.8)
Lymphadenopathy	4 (14.8)
Laboratory examination	
Increased WBC	15 (55.5)
Increased CRP	11 (40.7)
Decreased haemoglobin	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)

Supporting material supplementary note

Attachment Figure1:Endoscopic findings of our cases in the article ◦ Figure 2: Article pathologic findings of our cases.

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Authors' contributions

JieWen Ding BoXiang,Qin Wang and YaJie Meng diagnosed the case and prepared the manuscript; YaJie Meng and RengDong Li prepared the manuscript; KengJiang Tang and MinWang designed and proofread the manuscript. All authors reviewed the final version of the manuscript. The author(s) read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.