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CASE REPORT

Acute gastritis caused by concurrent infection with Epstein–Barr virus and cytomegalovirus in an immunocompetent adult

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Abstract
Herein, we describe an extremely rare case of gastritis due to concurrent infection with Epstein–Barr virus (EBV) and cytomegalovirus (CMV) occurring in an immunocompetent adult. The patient was a 35-year-old man who presented with slight fever, nausea, anorexia, weight loss for 3 weeks, mild transaminitis, and leukocytosis with atypical lymphocytes in peripheral blood. The clinical presentation and elevated IgM titers to both EBV-VCA and CMV strongly suggested infectious mononucleosis syndrome caused by co-infection with EBV and CMV. A computed tomographic scan of the abdomen showed diffuse thickening of the gastric wall mimicking linitis plastica, and upper endoscopy revealed thickened and eroded mucosa throughout the stomach. Histologic examination of gastric biopsies showed a dense lymphoid and neutrophilic infiltrate in the lamina propria with erosion. In situ hybridization assay revealed many lymphocytes positive for EBV-encoded RNA. Moreover, immunohistochemistry using an anti-CMV monoclonal antibody identified some CMV-positive cells (i.e. foveolar epithelium and endothelium). We finally diagnosed this case as gastric involvement in infectious mononucleosis, and the patient recovered without the administration of antiviral drugs. To our knowledge, this is the first reported case of gastritis co-infected with EBV and CMV, as a manifestation of infectious mononucleosis in an immunocompetent adult.

Keywords Epstein–Barr virus · Cytomegalovirus · Gastritis · Mononucleosis

Introduction

Epstein–Barr virus (EBV) and cytomegalovirus (CMV), members of the herpesvirus family, are common viruses that infect at least 90 percent of the world's population and can persist in a latent form after primary infection [1]. The primary EBV infection usually occurs subclinically in childhood; however, some children or young adults manifest an acute viral syndrome known as infectious mononucleosis. Infectious mononucleosis, with typical symptoms of fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, and atypical lymphocytosis, is usually a self-limited clinical syndrome. Although EBV is the major cause of infectious mononucleosis, primary CMV infection is estimated to comprise 7% of all infectious mononucleosis syndromes [2]. Although both EBV and CMV can affect any organ system and be associated with diverse and severe clinical presentations, these manifestations usually occur under conditions of immunosuppression [1, 2]. In immunocompetent individuals, predominant gastrointestinal involvement as a manifestation of infectious mononucleosis, either caused by EBV or CMV, is very rare [3–7].

Co-infection with EBV and CMV occurs occasionally in children or immunocompromised hosts, but co-infection of these two viruses in the immunocompetent adult is also an extremely rare phenomenon [8–11]. Here, we describe the case of a previously healthy patient who presented with infectious mononucleosis and digestive symptoms, and findings of serological tests and histological examination of gastric biopsy specimens indicated the concurrent acute infection of these two etiological agents. To our knowledge, this is the first reported case of acute gastritis co-infected with EBV and CMV in the context of infectious mononucleosis.

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Case report

A 35-year-old Japanese man presented with complaints of slight fever, night sweats, nausea, anorexia, and a weight loss of 10 kg in the previous 3 weeks. He was a non-smoker and consumed alcohol occasionally, and had no significant medical history. He neither took medications such as non-steroidal anti-inflammatory drugs (NSAIDs) nor suffered from mental stress. He denied having coughs, runny nose, diarrhea, or constipation, and had no known specific exposures or recent travels.

On physical examination, the patient was afebrile with appropriate vital signs. Superficial lymphadenopathy, exudative tonsillitis, skin rash, palpebral conjunctiva anemia, and bulbar conjunctiva jaundice were not detected on examination, and hepatosplenomegaly was not noticed upon palpation. Complete blood count revealed the following: white blood cell count 10,900/μL (segmented neutrophils 19%, lymphocytes 55%, atypical lymphocytes 10%), hemoglobin level 16.4 g/dL, hematocrit 47.0%, and platelet count 202,000/μL. Results of liver function tests were abnormal, including aspartate aminotransferase 83 IU/L (normal 13–33 IU/L), alanine aminotransferase 122 IU/L (normal 6–30 IU/L), lactate dehydrogenase 368 U/L (normal 120–230 U/L), alkaline phosphatase 374 U/L (normal 115–359 U/L), γ-glutamyl transpeptidase 118 U/L (normal 10–47 U/L), and albumin 3.4 g/dL (normal 4.0–5.0 g/dL). Other abnormal test results included elevated C-reactive protein (CRP) 5.15 mg/dL (normal less than 0.29 mg/dL). Serological tests did not indicate recent infection with hepatitis B virus or hepatitis C virus. Although the patient was not tested for human immunodeficiency virus (HIV), he was not a member of a group at high risk for HIV infection. Serological tests for anti-EBV antibodies produced demonstrated that IgM and IgG antibodies for EBV viral capsid antigen (EBV-VCA) and EBV nuclear antigen (EBNA) were all positive. Moreover, both IgM and IgG antibodies for CMV were positive. Thus, the patient was diagnosed with infectious mononucleosis caused by co-infection of EBV and CMV.

An abdominal computed tomographic scan revealed an enlarged spleen and a diffuse thickening of the gastric wall with regional lymphadenopathy (Fig. 1a), and subsequently, endoscopic examination was performed to evaluate for possible gastric malignancies. Endoscopic findings revealed hyperemic, thickened, and eroded mucosa extending from the upper body to the antrum of the stomach (Fig. 1b). The esophagus and duodenum were unremarkable. Gastric biopsies were obtained and submitted for pathological examination.

Histopathological specimens stained with hematoxylin and eosin (H&E) revealed a dense and diffuse lymphocytic and neutrophilic infiltrate in the lamina propria with surface erosions (Fig. 2a). Some dilated glands with attenuated lining epithelium and luminal debris were noted (Fig. 2b). Most of the infiltrating lymphoid cells were small or intermediate in size without nuclear atypia, and no lymphoid follicles were observed (Fig. 2c). These lymphocytes were composed of a mixture of B cells and T cells, immunoblasts, and plasma cells (Fig. 2c–e). Most of the infiltrating T cells were positive for CD8 (Fig. 2f), and only a small number of the cells showed positive staining for CD4. In the light of serologic data suggesting dual EBV and CMV infections,

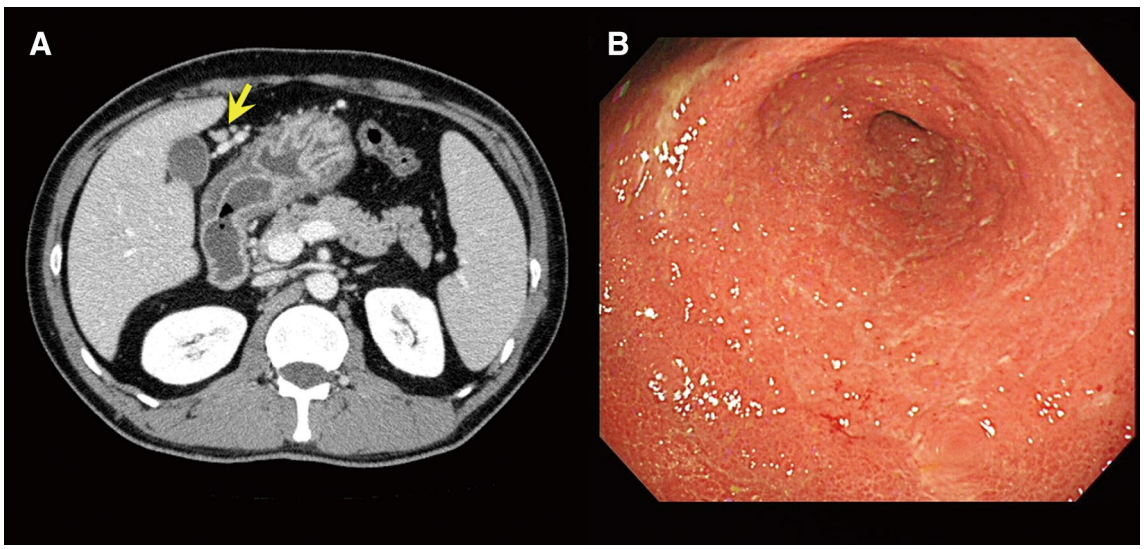


Fig. 1 **a** Diffuse wall thickening of the stomach and regional lymphadenopathy (arrow) detected by computed topographic scan, and **b** erythematous gastric mucosa with multiple irregular erosions observed by endoscopy

in situ hybridization for EBV-encoded small RNA (EBER) and immunohistochemistry using an anti-CMV monoclonal antibody were performed on these gastric biopsies. Consequently, a number of lymphocytes were positive for EBER (Fig. 2g). Moreover, some foveolar epithelium and stromal cells (i.e. endothelial cells) were positive for CMV (Fig. 2h). In these gastric biopsy samples, no distinct viral inclusions were identified by the H&E staining. *Helicobacter pylori* was absent, and there was no evidence of malignancy in any of the biopsy specimens.

Treated with only supportive care, the patient's symptoms resolved within 1 month, and improvement of the mucosal lesion was shown by follow-up gastroscopy. Histological findings of gastritis had also improved, and neither EBER- nor CMV-positive cells were detected. The patient's liver function tests and white blood cell count were also completely normalized, serum IgM antibodies for both EBV-VCA and CMV turned to be negative, and the patient has remained healthy for 6 months.

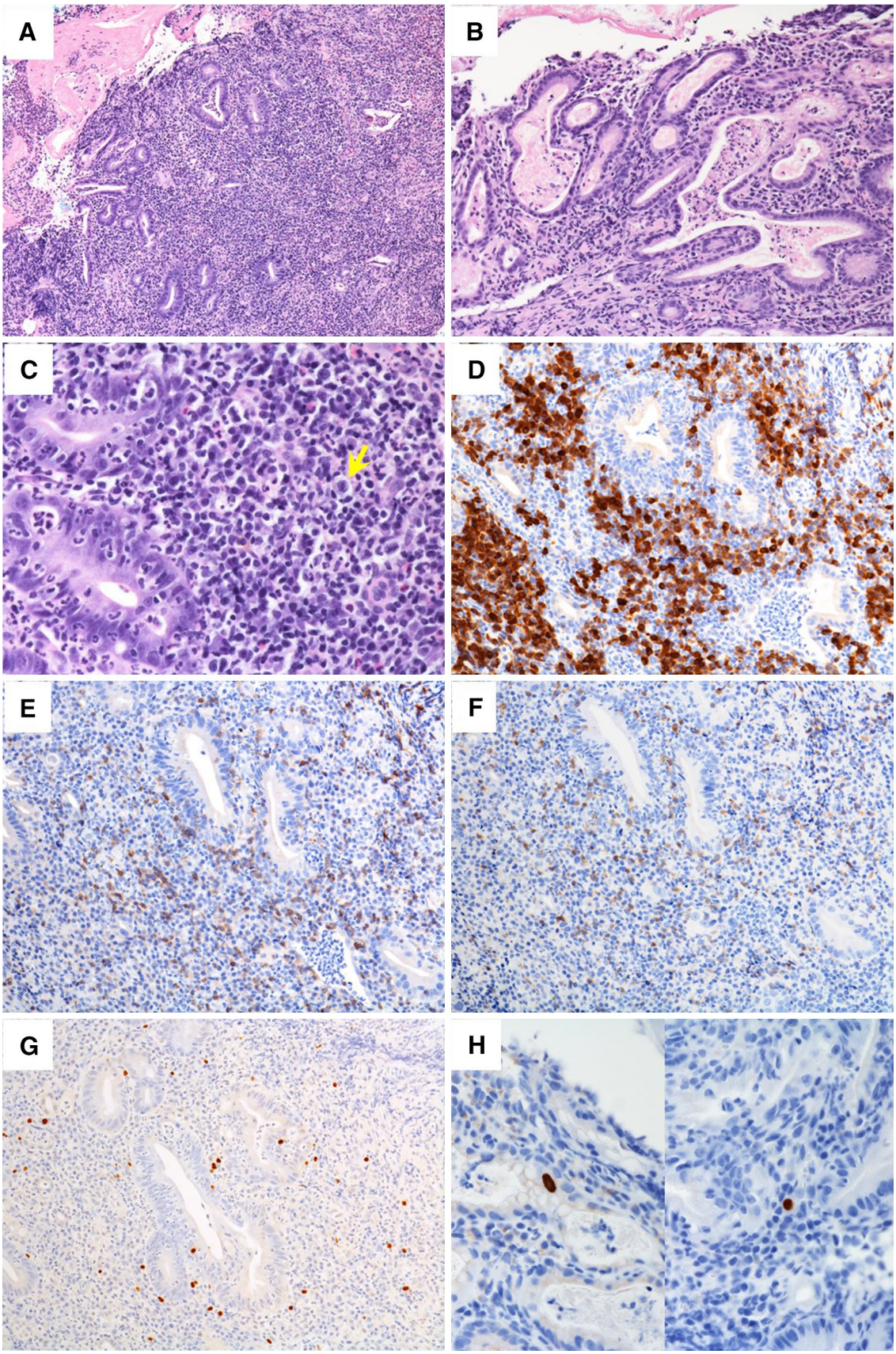
Discussion

The spectrum of clinical symptoms caused by primary infection of EBV and CMV is diverse, with the major manifestations being infectious mononucleosis. EBV is the most common cause of infectious mononucleosis, accounting for 90% of the total cases, and many of the remaining cases are attributed to primary CMV infection. CMV-induced mononucleosis will manifest symptoms almost indistinguishable from those of EBV-induced mononucleosis. In this report, we describe an extremely rare form of gastritis that developed in an immunocompetent adult as the major manifestation of infectious mononucleosis under the presence of dual infectious agents: EBV and CMV. The diagnosis was established by serologic tests that reflect acute EBV/CMV infection and by detecting EBER-positive and CMV-positive cells in gastric biopsy samples, and explained by the self-limiting nature of the symptoms. In this patient, essentially all of the abnormal laboratory results including leukocytosis with atypical lymphocytes and elevated transaminases could be attributed to mononucleosis.

Concurrent infection with CMV and EBV has been reported in children and immunocompromised adult patients who have undergone organ transplantation [8–11]; however, it is an extremely rare phenomenon in immunocompetent adults such as in the case described here. In the present case, serological evidence of dual acute EBV/CMV infection (i.e. elevated IgM titers to both EBV and CMV) suggests a simultaneous primary/acute infection with the two viral agents. However, it is noteworthy that acute CMV infection can cause EBV immunoreactivation, although the reverse (i.e. CMV immunoreactivation by EBV) has not been reported [12]. Therefore, our case may represent reactivation of the latent EBV by an acute CMV infection. This would be consistent with the serological profile of a positive VCA IgM and IgG together with EBNA–IgG antibodies. On the other hand, because VCA IgM may persist for several months after acute infection, EBNA-1 IgG as well as VCA IgG and IgM may also be simultaneously present in patients with primary EBV infection, which has been termed "recent infection" or "primary infection, transient phase, or convalescence" [13]. Although the serological tests have greater than 90% specificity, it has been shown that false-positive EBV detection can occur due to cross-reactivity with IgM against other viruses such as CMV [13]. However, this was unlikely in our case because, in the stomach biopsy specimens, EBER- and CMV-positive cells were not overlapping with each other.

In addition to the dual viral infections, the patient in this report showed severe acute gastritis, a rare complication of infectious mononucleosis. Specifically, EBV has been documented as one of the potential causes of acute gastritis, although only a limited number of cases have been reported [5–7]. In the present case, we needed to distinguish the gastric lesion from the lesions caused by advanced gastric cancer in view of the diffuse thickening of the gastric wall and perigastric lymphadenopathy visible on the computed tomography. Similar to our case, previously reported cases of both EBV- and CMV-associated gastritis also showed diffuse thickening of the gastric wall with or without regional lymphadenopathy on imaging studies [4–6]. In our case, endoscopic findings were nonspecific, with diffuse edematous mucosa and multiple erosive lesions, and those were also compatible with the findings in previous reports [4–7]. In terms of histopathological aspects, as shown in our case, CMV or EBV infection in the stomach commonly manifests as lesions that are morphologically difficult to differentiate from other types of gastritis such as *Helicobacter* gastritis and NSAID-related gastritis [4–7]. However, it should be noted that in EBV-associated gastritis, atypical lymphocytic proliferation may reach a degree where it is hard to differentiate from malignant lymphoma based solely on routine H&E staining of sections [14].

Because of the limited number of cases reported, the diagnostic criteria for gastritis caused by EBV have not been established. A majority of humans show a latent infection and, therefore, the mere presence of EBER-positive cells would not confirm its etiologic role in the development of gastritis. Namely, it is important to distinguish between "normal" background levels of circulating EBV-infected lymphocytes and an abnormally high level indicating its pathogenicity. In our case, EBER-positive lymphocytes in the gastric mucosa were many in number and in contrast to the occasional detection of rare EBV-positive cells in gastric mucosa of individuals with latent EBV infections [15]. Moreover, our immunohistochemical analysis revealed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◂**Fig. 2** Histopathology of the gastric mucosa. **a** Erosive mucosa with a dense inflammatory cell infiltrate (H&E, ×100 original magnification). **b** Dilated glands with attenuated lining and luminal cell debris (H&E, ×200 original magnification). **c** The inflammatory infiltrate was composed of a mixture of small- to intermediate-sized lymphocytes, neutrophils, plasma cells, and scattered immunoblast-like cells (arrow) (H&E, ×400 original magnification). The lymphocytic infiltrate consisted of a mixed population of CD79a-positive B cells (**d**) and CD3-positive T cells (**e**), and the majority of the infiltrating T cells were also positive for CD8 (**f**) (×200 original magnification for each). **g** In situ hybridization showed an Epstein–Barr virus-encoded small RNA expression in the nuclei of the lymphocytes (×200 original magnification). **h** Immunohistochemistry using an anti-CMV monoclonal antibody also confirmed the presence of CMV antigen in the foveolar epithelium (left) and the stromal cell (right) (×400 original magnification for each)

abundant infiltration of CD8-positive T cells with an abnormally low CD4+/CD8+ ratio, which is generally thought to cause the symptoms of mononucleosis, probably reflecting a cell-mediated host immune response against virally infected cells. Consequently, the stomach biopsy performed 1 month later showed healing of the mucosal lesions, and contained neither EBER- nor CMV-positive cells.

Because infectious mononucleosis is a self-limiting disease, antiviral treatment is not usually required in immunocompetent patients. The use of corticosteroids is reserved for mononucleosis-related airway obstruction, severe hemolytic anemia, or thrombocytopenia [1]. Although several case reports have documented successful therapy of previously healthy patients with severe manifestations of CMV infection [3, 4], it is important to note that most of the reported patients with EBV- or CMV-associated gastritis who were immunocompetent individuals did not require antiviral treatment [4–7]. In our case, the patient was completely recovered with only supportive care, which was consistent with previous reports [4–7].

In summary, we encountered an immunocompetent adult with infectious mononucleosis syndrome who had a dual infection of EBV and CMV, and this is the first reported case of gastritis caused by co-infection of EBV and CMV. Although it is presently unclear what role the dual viral infection could play in the development of gastritis, this case highlights that gastric symptoms are rarely the predominant clinical manifestation of infectious mononucleosis. Then, if endoscopic examination reveals diffuse erosive lesions of unknown etiology, EBV- and/or CMV-gastritis should be considered as a differential diagnosis not only by clinicians but also by pathologists. In general, the disease follows a benign self-limited clinical course lasting several weeks.

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Compliance with ethical standards

Conflict of interest The authors indicated no potential conflicts of interest.

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