

# Jejunal diaphragm disease associated with cytomegalovirus infection



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## ABSTRACT

**Background and study aims** Diaphragm disease (DD) is a rare gastrointestinal disease featuring multiple thin, circumferential strictures in the intestine, related to prolonged intake of nonsteroidal anti-inflammatory drugs (NSAIDs). Here, we report a case of DD associated with cytomegalovirus (CMV) infection in a patient not taking NSAIDs. A 72-year-old man was referred to our hospital due to persistent epigastric pain. Push enteroscopy showed extensive mucosal detachment in the upper jejunum. Immunohistochemistry examination of biopsy specimens revealed CMV positivity. In addition, CMV antigenemia was positive. Antiviral treatment with ganciclovir improved his symptoms and the CMV antigenemia became negative. Wireless capsule enteroscopy performed 1 month after antiviral treatment showed regenerated mucosa and multiple diaphragm-like strictures in the jejunum, resulting in capsule retention. Balloon dilatation using double balloon enteroscopy (DBE) was performed and the capsule was retrieved endoscopically. DBE 6 months after antiviral therapy confirmed no recurrence of stenosis or inflammation. The patient had no history of long-term NSAID use. In a case of DD unassociated with NSAIDs, CMV infection should be considered in the differential diagnosis.

## Introduction

Cytomegalovirus (CMV) infection, usually associated with an immunosuppressed host, can cause symptomatic gastrointestinal disease in an immunocompetent patient. Although CMV can affect the entire gastrointestinal tract, the colon is most commonly involved, followed by the small bowel [1]. Clinical manifestations may range from mild anorexia to obvious gastrointestinal bleeding and perforation. Prototypical endoscopic findings are hyperemic edemas, longitudinal ulceration, and well-defined ulcerations with a punched-out appearance. There are few reports of diaphragm-like intestinal strictures caused by CMV infection [1, 2].

Diaphragm disease (DD) was first reported by Lang et al. in 1988 [3]. It is relatively rare and characterized by multiple thin, diaphragm-like strictures narrowing the intestinal lumen. DD sometimes causes obstruction of the small bowel requiring

surgery and it is difficult to diagnose both preoperatively and intraoperatively [4]. Although DD is generally related to long-term intake of nonsteroidal anti-inflammatory drugs (NSAIDs), pathogenesis is poorly understood, and it can occur in patients without long-term NSAID use [5].

We report a rare case of DD related to CMV infection in an immunocompetent patient who was not taking NSAIDs.

## Case report

A 72-year-old man presented to a nearby hospital with epigastric pain and vomiting lasting 4 weeks. He received antibiotic therapy and parenteral nutrition, as bacterial enteritis was suspected at first. Because his symptoms persisted despite treatment, he was referred to our hospital. He had a history of appendicitis and prostate cancer, both of which were cured by



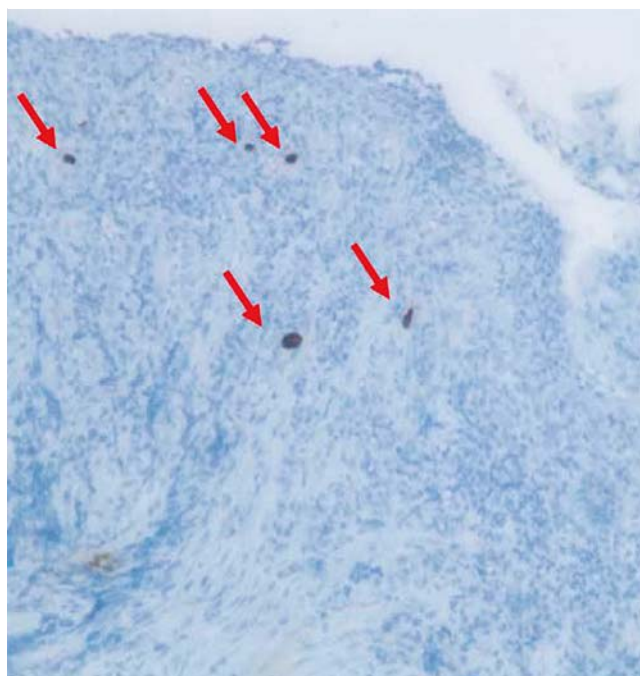
► **Fig. 1** Endoscopic images of push enteroscopy on admission to our hospital. Extensive mucosal detachment with small islands of residual epithelium was observed in the upper jejunum. **a** White light endoscopic image and **b** indigo carmine chromoendoscopic image are indicated.

surgery. He was on no medications including NSAIDs at transfer to our hospital.

Physical examination revealed tenderness of the epigastrium and abdomen. The patient's legs had pitting edema, probably due to hypoalbuminemia because his heart function was normal. Laboratory tests showed a white blood cell count of 9290/ $\mu$ L, hemoglobin of 7.3 g/dL, C-reactive protein of 13.6 mg/dL, and albumin of 1.1 g/dL. Human immunodeficiency virus antibody was negative. Stool culture was negative for pathogenic bacteria. Enhanced computed tomography revealed intestinal wall thickening and fluid collection in the jejunum.

Push enteroscopy showed extensive mucosal detachment with small islands of residual epithelium in the upper jejunum (► **Fig. 1**). Immunohistochemical staining of biopsy specimens showed CMV positivity (► **Fig. 2**). CMV antigenemia was also positive.

The patient was diagnosed with CMV enteritis and received ganciclovir intravenously for 14 days. At the end of treatment, his epigastric pain, vomiting and leg edema had improved. CMV antigenemia became negative and the patient's serum albumin levels improved to 2.8 g/dL. We performed wireless capsule endoscopy 1 month after the antiviral treatment to evaluate the entire small intestine. Although the detached mucosa of the jejunum was almost regenerated, multiple diaphragm-like strictures in the jejunum were observed (► **Fig. 3**). Because the capsule was retained, we performed anterograde double-balloon enteroscopy (DBE), which also revealed multiple thin stenoses with regenerative mucosa in the jejunum (► **Fig. 4**). The capsule was not able to pass through the most distal stricture of the middle jejunum. We dilated the stenosis with a balloon and removed the capsule with a basket-catheter. Histologic examination of biopsy specimens from the stenotic lesions revealed nonspecific inflammatory changes and immunohistochemical staining for CMV was negative. Thereafter, the patient's clinical course was unremarkable without recurrence of CMV infection. Follow-up anterograde DBE at 6 months after antiviral therapy showed almost normal jejunal mucosa without strictures.



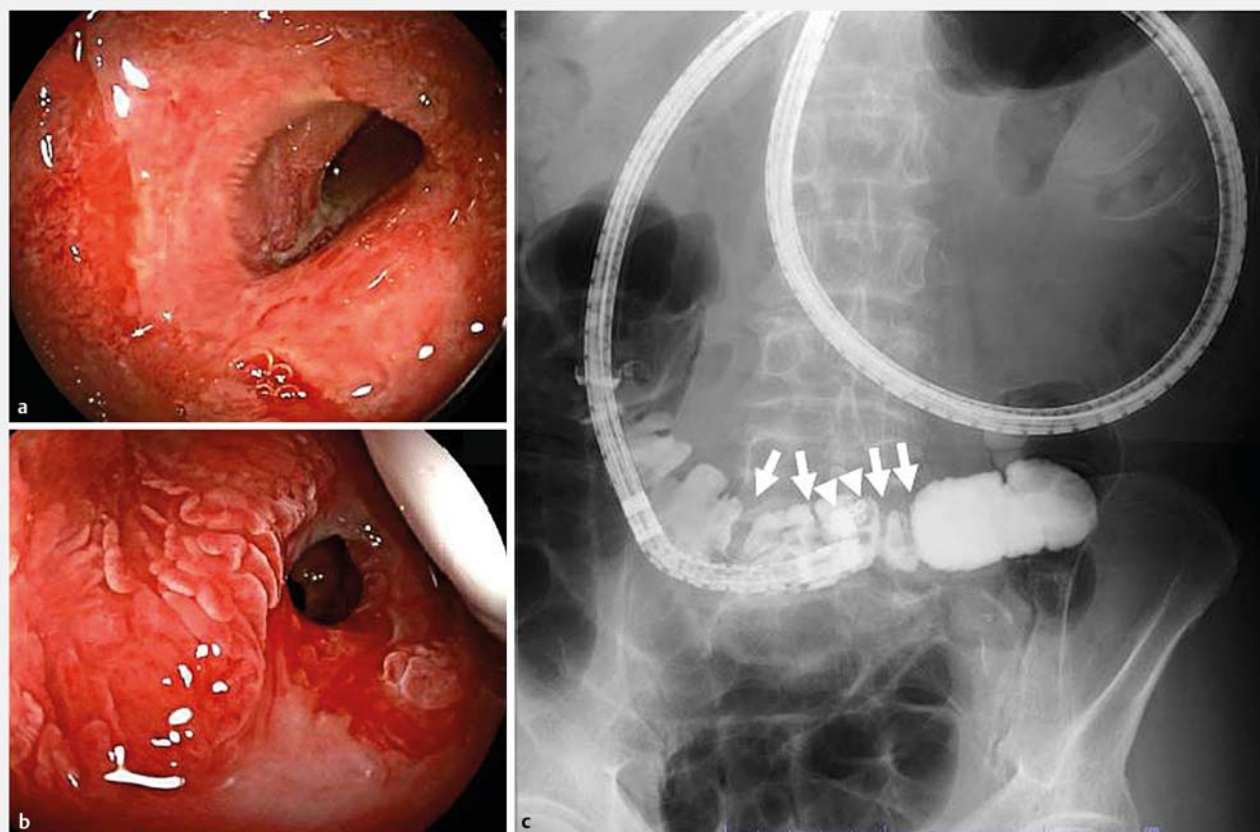
► **Fig. 2** Microscopic images of endoscopic biopsy specimens at push enteroscopy. Immunohistochemical staining for CMV was positive (arrows).



► **Fig. 3** An image of wireless capsule enteroscopy. Multiple thin stenoses with regenerative mucosa in the jejunum were observed.

## Discussion

DD is defined by presence of multiple thin, diaphragm-like strictures narrowing the intestinal lumen to a pinhole. These lesions are histologically characterized by submucosal fibrosis with normal overlying epithelium and submucosal ulcers not



► **Fig. 4** **a, b** Endoscopic and **c** fluoroscopic images of peroral DBE 1 month after antiviral treatment. **a, b, c** Multiple diaphragm-like stenoses with ulceration (arrows) and **b, c** a retained capsule (arrowheads) were observed in the middle jejunum.

extending to the muscularis propria. Many symptoms of DD are reported, including iron deficiency anemia, hypoalbuminemia, and gastrointestinal bleeding. DD sometimes results in obstructive symptoms presenting as a surgical emergency. Almost all cases of DD are related to long-standing NSAID intake; 96% of patients with DD had taken NSAIDs for more than a year [4].

In our case, the patient did not take NSAIDs before symptom onset. Although the existence of CMV in the stricture lesions was not confirmed, CMV was detected by immunohistochemistry in biopsy specimens from the jejunal ulcer and both symptoms and endoscopic findings improved after ganciclovir treatment, strongly suggesting that the multiple thin strictures of the jejunum were induced by CMV infection. There are a few reports of colonic and ileal strictures like DD that occurred secondary to CMV infection in infants [6] and adults [7]. To our knowledge, this is the first report of jejunal DD related to CMV infection.

DD occurs mostly in the ileum (34.6%), followed by the right colon (27.7%), whereas it is uncommon in the jejunum (8.8%) [8], where multiple strictures were observed in our case. CMV enteritis can affect both the jejunum and ileum, without a significant difference in frequency. Because of the rarity of DD associated with CMV enteritis, it is unknown whether the site

of stenosis differs between DD related to NSAIDs and DD related to CMV infection. Further studies are necessary to reveal the specific clinical findings of DD caused by CMV infection.

The pathogenesis of DD remains poorly understood. It is hypothesized that NSAIDs cause microvascular injury leading to reduced villous circulation and mucosal damage. This leads to inflammation and ulceration, followed by reparative fibrosis and stricture formation [8]. Pathogenesis of CMV enteritis is also presumed to relate to its infection of vascular endothelial cells, which causes ischemic mucosal injury [1]. In our case, intestinal ischemia associated with CMV infection may have been involved in formation of multiple thin stenoses.

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) [9] and chronic enteropathy associated with *SLCO2A1* (CEAS) [10] are important differential diagnoses for DD. These two entities and DD have similar macroscopic findings of multiple thin ulcers in a linear or circumferential configuration and concentric strictures [9,10]. On the other hand, CMUSE and CEAS share common clinicopathologic features that differ from those in our case: age of onset (adolescence to middle age), chronic and recurrent clinical course, and normal laboratory findings of inflammatory reactants [9,10]. The etiologies of CMUSE and CEAS are not elucidated completely. Some reports suggested that CMUSE may be associated with mutations in the

PLA2G4A gene encoding cytoplasmic phospholipase A2- $\alpha$  [9], and CEAS with mutations in the SLCO2A1 gene encoding a prostaglandin transporter [10]. Both PLA2G4A and SLCO2A1 are presumed to play an important role in the physiology of prostaglandins, which could explain the similarity between these two chronic enteritis and DD.

Before the development of endoscopic techniques, resection of the involved intestine was the only available treatment for DD. Endoscopic balloon dilation (EBD) has been performed successfully in patients with DD, as in our case [5]. EBD is less-invasive therapy and can be repeated with each recurrence. Discontinuation of NSAIDs is essential for preventing recurrence of DD associated with NSAIDs. In our case, neither CMV infection nor intestinal stenosis had recurred at the last follow-up. The long-term prognosis of DD with CMV infection remains to be elucidated.

## Conclusion

We reported on a case of DD related to CMV. CMV infection should be considered in the differential diagnosis of DD, especially in patients not taking NSAIDs.

## Competing interests

None

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