

Gastrointestinal Tract Infections With Human Cytomegalovirus And Mycobacterium Tuberculosis

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Abstract

Gastrointestinal (GI) diseases due to infectious agents *Mycobacterium tuberculosis* and *Human Cytomegalovirus* (HCMV) in immunocompetent patients are usually asymptomatic and are related to rare cases of GI complications. The present study reviews the most prevalent clinical findings and GI tract symptoms of CMV and TB cases for a better prognosis and therapeutic approaches. Epigastric pain or tenderness is the most reported symptom in patients with HCMV infection of the GI tract. Patients may develop a fever in some cases with antrum ulcers (~39°C). Edema is also reported in young adults and children, mainly depicted on the feet or face. Similarly, epigastric pain is the main symptom observed in patients with gastric TB. Weight loss due to decreased appetite, nausea, and vomiting in TB patients was also reported. The diagnosis of gastric CMV and TB could be symptomatic. Clinical findings, including positive anti-CMV IgM and endoscopic enlarged gastric folds and high liver enzymes with hypo (proteinemia) albuminemia, can be the indications of gastric CMV in immunocompetent patients. Additionally, a positive PCR of acid-fast bacilli and endoscopy of necrotic epithelial cells can be the signs of gastric TB. Gastric infection can lead to further complications and gastric cancer, which increases the disease's burden and cost and lengthens the period of treatment. The clinical findings and symptoms of gastritis caused by CMV and TB are reported in this paper. Understanding gastritis infections might improve the clinical outcome of the condition by allowing better prognosis and earlier therapeutic interventions.

Keywords: Gastritis; Gastrointestinal tract infection; *Human Cytomegalovirus*; *Mycobacterium tuberculosis*; Prognosis

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Introduction

Gastrointestinal (GI) diseases encompass complications ranging from the mouth to the anus. GI includes esophageal, stomach, intestine, liver, pancreas, gallbladder, and biliary tract ailments. Common manifestations of GI disorders include epigastric pains or tenderness and distention, gastrointestinal bleeding, intestinal obstruction, and malabsorption [1,2]. Infectious agents can also affect GI tract inflammation or gastritis [3]. *H. pylori*-associated gastritis is the most common cause of gastritis in the world. Several other *H. pylori*-negative gastritis is autoimmune gastritis [3], gastritis due to infectious agents *Mycobacterium*

tuberculosis (*M. tuberculosis*) [4], *Cytomegalovirus* (CMV) [3], *Herpes Simplex virus* (HSV) [6], radiation gastritis, collagenous gastritis, eosinophilic gastritis, Sarcoidosis-associated gastritis, lymphocytic gastritis, Ischemic gastritis, Crohn disease-associated gastritis, vasculitis-associated gastritis, and Ménétrier disease [7].

In particular, CMV infection occurs almost only in immunocompromised patients, especially in transplant recipients. CMV infection in immunocompetent patients is usually asymptomatic or, if symptomatic, most commonly causes a mononucleosis-like syndrome [8]. CMV can affect any organ in these patients, with the most common site of infection being the

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gastrointestinal tract. CMV disease of the GI tract is defined by infection and the presence of macroscopic pathological features or significant GI symptoms [9]. Endoscopic features associated with gastric CMV infection, including ulcers and erosions, were observed in most cases [10]. In the diagnosis of CMV-associated GI infection, it is crucial to detect the presence of the virus in the mucosa of the upper GI tract. In addition, CMV serology can help distinguish primary infection from CMV reactivation.

In the case of TB, the most common form of the disease is the pulmonary form, and involvement of other organs is less common. However, it is vital that in immunosuppressed patients, such as those infected with human immunodeficiency virus (HIV), the risk of coinfection CMV with TB in the gastrointestinal tract increases due to immune system defect [11,12]. Gastrointestinal tuberculosis can be caused by the entry of infected respiratory tract secretions into the abdomen and cause granulomatous inflammation. Diagnosing abdominal tuberculosis can be challenging because it can be confused with other abdominal diseases such as malignancy and inflammatory bowel disease. The most common symptoms include weight loss followed by abdominal pain, sweats, and fever. The most common site of involvement in the abdomen was the lymph nodes and then the peritoneum. TB can be activated in infected people under such circumstances that the immune system is disrupted, and coinfection CMV with TB can also lead to serious damages in infected people [13]. According to available data, patients with TB are more likely to become infected with CMV. Also, CMV can cause TB activity in infected individuals. In addition to lung involvement, tuberculosis can affect other body parts, especially when co-infected with CMV [14].

Developing a new model using the clinical findings and symptoms could be helpful for clinicians to predict rare cases of gastric CMV and TB infections. Therefore, this review summarizes the previous reports of GI infections with CMV and TB to discriminate against both infections.

GI infection of HCMV

Human *Cytomegalovirus* (HCMV) is a DNA virus belonging to the *Herpesviridae* family. CMV has been increasingly recognized as an important common pathogen in an immunocompromised state [15], including individuals with AIDS and organ transplant recipients [16,17]. An increased number of cases of gastrointestinal diseases caused by HCMV infection has been reported (18,19).

The colon and stomach are the most common sites of GI infection (20), and CMV infection of GI is rare, especially in those with normal immunity.

CMV might infect epithelial cells of the GI tract by infected body fluid through an unknown mechanism. Symptoms of CMV-associated gastric disease are varied. In the immunocompetent patients, diarrhea was reported as the most common symptom along with other common symptoms, including weight loss, fever, hematochezia, dysphagia, abdominal distension, and abdominal pain (8). Several case reports were investigated in this review to identify specific CMV-associated symptoms (Table 1). The findings show that epigastric pain or tenderness is the most reported symptom in patients with HCMV infection of the GI tract. It could also lead to weight loss and vomiting due to decreased appetite in patients with CMV-induced gastric ulcers, which, if remained untreated, might be accompanied by anorexia and nausea (Table 1).

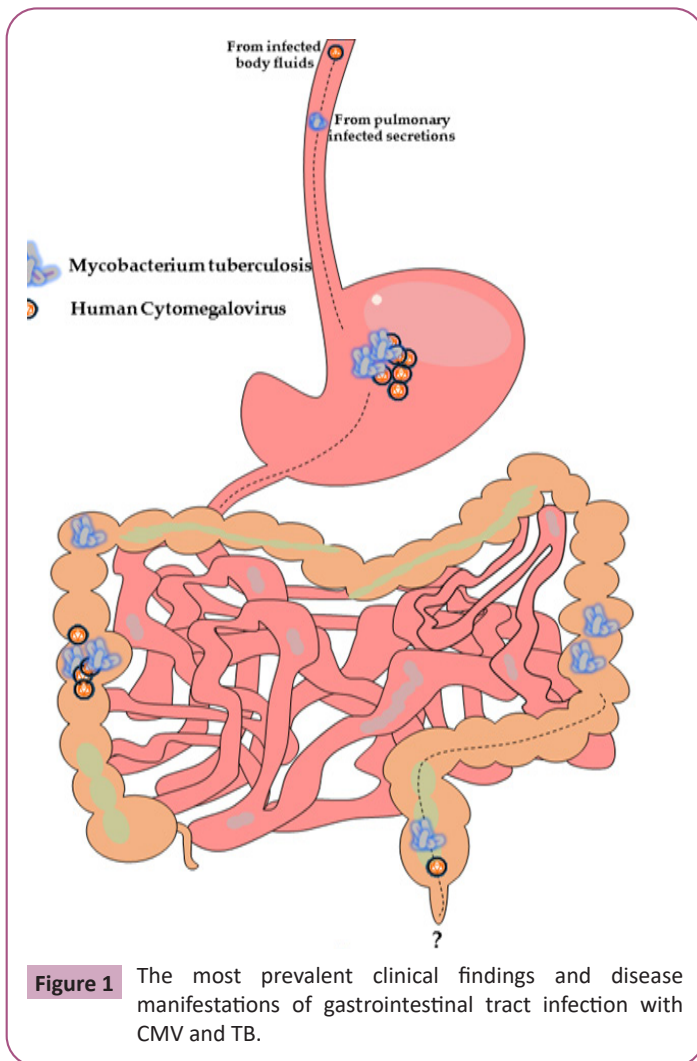
In some cases with antrum ulcers, patients may suffer from fever (~39 °C). One of the important symptoms in patients with CMV infection is decreased movement activity. Edema is also reported in younger adults and children, mainly represented on feet or face (Figure 1).

Clinical findings can give a good prognosis for CMV infection in patients referred with GI tract complications. CMV in immunocompetent patients is rare, and its differentiation requires a quick and comprehensive intervention, like endoscopic, immunohistochemical, serological, and biochemical processes. The endoscopy address the involvement of GI tract infection, including enlarged gastric fold, ulcers (mainly in antrum and furus), and surface mucosal erosions. Thickness or enlarged gastric folds was the main endoscopic finding in CMV positive GI tract infection patients. Additionally, there are several ways to detect CMV infection based on the stage of the disease. Serological methods are used in cases in which an increased titer of IgM antibodies indicates active infection. In the case of CMV infection, especially in immunosuppressed patients, IgM seroconversion can indicate CMV reactivation that is accompanied by IgG seropositivity. Serologically, however, anti-CMV IgG or IgM or both could be observed in immunocompetent patients.

Further methods of HCMV detection are *Cytomegalovirus* antigenemia for diagnosing the infection in its early stages and histology and observing an intranuclear cytomegalic Owl's eye inclusion bodies. Further findings of CMV infection of the GI tract

Table 1. Case reports of CMV gastritis

Author	Year	Study	Country	Case	Coinfections	Ref.
Kim et al.	2020	Case report	South Korea	A 43-year-old woman presented with stage iii malignant melanoma	-	-21
Tard et al.	2019	Case report	France	A 7-year-old girl & a five-and-a-half years old girl	-	-22
Xiong et al.	2018	Case report	China	A 44-year-old man	-	-23
Yamamoto et al.	2018	Case report	Japan	A 35-year-old man	EBV	-24
Liu et al.	2017	Case report	Taiwan	A 77-year-old woman	-	-25
Ueno et al.	2017	Case report	Japan	An 80-year-old woman	<i>H. pylori</i>	-26
Wang et al.	2016	Case report	China	A 26-year-old man	<i>H. pylori</i>	-27
Gökçe et al.	2016	Case report	Turkey	An 11-year-old boy, a 3-month-old boy, & a 2-month-old boy	-	-28
Crespo et al.	2015	Case report	Portugal	A 31-year-old man	-	-29
Baek et al.	2015	Case report	South Korea	An 8-year-old girl	-	-30
Keskar et al.	2015	Case report	India	A 42-year-old woman & a 32-year-old man	-	-31
Peixoto et al.	2013	Case report	Portugal	A 71 years-old man	HSV-1 and EBV	-32



are Hypoalbuminemia and hypoproteinemia, which can be observed in both or one of each. Furthermore, in some cases, increased liver enzymes ALT and AST have been observed.

The majority of cases of GI tract HCMV infection patients are asymptomatic. In those cases with the symptoms mentioned above and clinical findings, therapeutic interventions should be started. Acyclovir, Gancyclovir, or Valgancyclovir have been shown to significantly reduce the symptoms of the disease in two or three months, and the recurrence of the disease is not reported.

Mycobacterium tuberculosis infection of GI tract

Tuberculosis (TB) is one of the oldest known human diseases caused by the *Mycobacterium tuberculosis* (*M. tuberculosis*) complex (MTBC). Despite a long history of understanding and treating TB, it remains the most important infectious pathogen globally and one of the ten leading causes of death worldwide. It is reported that *M. tuberculosis* is responsible for 15% of extrapulmonary infections, which may or may not be associated with pulmonary symptoms. Extrapulmonary infections are cervical lymphadenitis, pleural involvement, central nervous system (CNS) infection, and GI infection. GI is the sixth most common site of extrapulmonary TB, and it is mainly associated

with pulmonary TB or immune deficiencies. Furthermore, GI infection with TB is also reported in rare cases without evidence of pulmonary involvement.

Gastric TB can be caused by the entry of infected respiratory tract secretions into the abdomen and cause granulomatous inflammation. Diagnosing abdominal tuberculosis can be challenging because it can be confused with other abdominal diseases such as malignancy and inflammatory bowel disease. Symptoms of gastric TB include cough, with or without fever, diarrhea, weight loss, vomiting, and hematemesis. Here, we have classified the disease symptoms of GI tract infection with TB according to their prevalences in several case reports (Table 2). As shown in Figure 1, epigastric pains are the main symptoms observed in patients with GI tract infection of TB. It also leads to weight loss due to decreased appetite, nausea, and vomiting in patients with TB-induced gastric ulcers, which, if remained untreated, might be accompanied by anorexia and constipation. The inflamed site of infection may also cause fever in some cases. The clinical findings of TB infection of the GI tract are also varying. (Table 2).

Endoscopically gastric TB presents frequently as a non-healing chronic ulcer gastric perforation, and erosions or lesions mimicking malignancy. In addition, Nodular hypertrophic lesions sensing the pylorus have been reported. As shown in Figure 1, caseating granulomatous with necrosis and gastric epithelial ulcers and inflammation of the involved tissue are more prevalent clinical findings.

The diagnosis of gastric TB can be made on histopathological examination, which shows caseating epithelioid cell granulomas, the bacteriologic study of the biopsies based on acid-fast bacilli staining or cultures to detect *M. tuberculosis*, and fast and accurate polymerase chain reaction (PCR). Almost all cases of GI tract TB infection reported positive PCR. This implicates a sensitive PCR as a good prognosis for TB infection in the cases of GI tract complications in immunocompetent with unknown etiology and history. It can also be suggested that acid-fast staining along with PCR can be a better prognosis of GI tract infection of TB than each alone.

Treatment of abdominal tuberculosis consists of two courses of treatment; in the first period, the patient uses four drugs of rifampin, isoniazid, pyrazinamide, ethambutol for two months,

Table 2. Case reports of TB gastritis.

Author	Year	Study	Country	Case	Coinfections	Ref.
Ma et al.	2019	Case report	China	A 26-year-old female	-	-45
Espinoza-Ríos	2017	Case report	Peru	A 30-year-old female	HIV	-44
Nayyar et al.	2016	Case report	USA	A 49-year-old female	HIV	-46
Ecka et al.	2013	Case report	India	A 31-year-old male	-	-42
Kang et al.	2012	Case report	Korea	A 54-year-old female	-	-47
Moghadam et al.	2012	Case report	Iran	A 43-year-old male	-	-48
Khan et al.	2008	Case report	Qatar	A 29-year-old man	-	-43

and in the second-period patient uses two drugs of rifampin, isoniazid for four months.

Discussion

Health care costs and burden of GI diseases are more than other prevalent ailments rising further. Among common causes of GI tract diseases, some opportunistic pathogens are associated with rare cases of GI complications. Accurate diagnosis and identification of such pathogens help to improve disease symptoms. HCMV and *M. tuberculosis* are reported in several immunocompetent patients with GI complications. In the present study, the most prevalent clinical findings and disease symptoms of both CMV and TB cases of GI tract infection are reviewed for better diagnosis and therapeutic interventions.

Epigastric tenderness or pain is the most common symptom in immunocompetent patients with CMV gastritis. Accordingly, the most common sites of gastrointestinal CMV infection are the colon and stomach. Enlarged gastric folds and ulcers are also the most common macroscopic manifestations of Cytomegalovirus infection in antrum or furus. Gastritis with CMV infection can be diagnosed in abdominal pains, weight loss, and vomiting cases. Children may also present superficial edema on their feet or face, which is self-limiting. This might be due to congenital CMV infections, acquired from parents with active CMV infection, or reactive infection due to immunotherapy or some illness like Menetrier disease. However, the latter needs to investigate in the future. As endoscopic findings like gastrointestinal ulcers are difficult to find, differentiation tests could benefit from a seropositive IgM with or without IgG. Furthermore, increased levels of liver enzymes along with hypo (proteinemia) albuminemia could be the prognosis factors of gastric CMV infection. Furthermore, the fecal-oral transmission of CMV in patients with positive gastric infection remains unidentified (Figure 2).

Gastric TB is even more uncommon due to high acidity and lack of gastric mucosal lymphoid tissue but is usually associated with an immunodeficient state, particularly with HIV infection. The most common sites of TB lesions are in the antrum and prepyloric regions. Ileocecal and jejunal regions usually include more than 60% of gastric TB cases. The clinical manifestations of gastric tuberculosis are nonspecific. It can be seen as a fever of unknown origin, and it must be differentiated from Crohn's disease, sarcoidosis, syphilis, mycotic lesions, and exposure to beryllium, silicates, or reserpine. A positive PCR for acid-fast bacilli can be the diagnostic tool for patients admitted with epigastric pains, weight loss, or decreased activity, with or without fever. Acid-fast staining can sometimes show false negatives, PCR can diagnose. A coinfection of TB and CMV has also been reported by Stockdale et al.,. The results of this case-control study on persons with undiagnosed TB showed that a positive anti-CMV IgG indicates a higher risk of TB infection. This suggests that CMV infection may vulnerable patients for future infections with opportunistic pathogens.

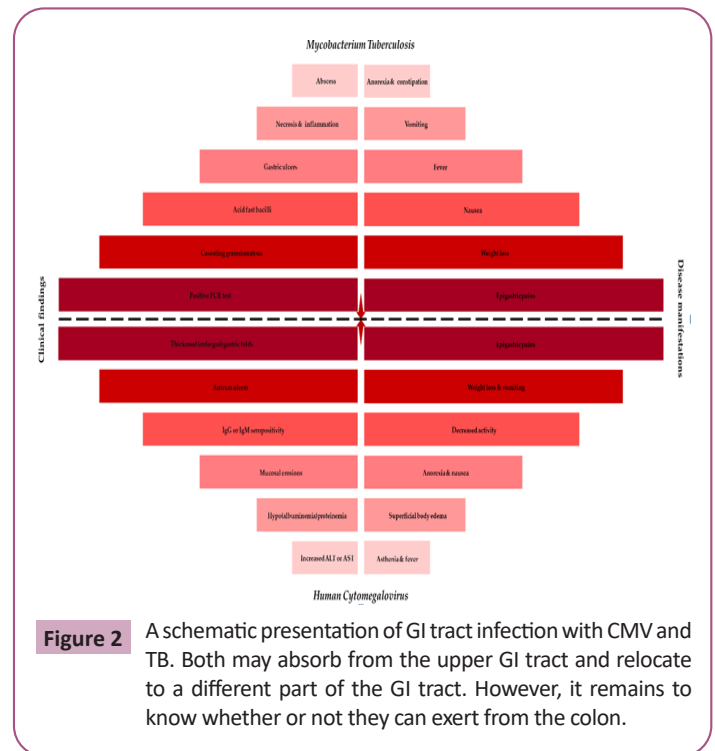


Figure 2 A schematic presentation of GI tract infection with CMV and TB. Both may absorb from the upper GI tract and relocate to a different part of the GI tract. However, it remains to know whether or not they can exert from the colon.

Conclusion

Gastrointestinal ulcers and lesions may induce anemia or, in a worse scenario, gastric cancer, increase the burden and cost of the disease, and in the case of infectious agents, it may also extend the duration of treatment. This study summarizes the clinical findings and symptoms of gastritis with CMV and TB. Understanding gastritis infections would enhance the clinical outcome of disease by faster interventions and therapy. Further studies can expand our knowledge on the molecular basis of GI tract infection with CMV and TB.

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Conflicts of Interest

No conflicts of interest exist.

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