Clinical and Endoscopic Features for Alimentary Tract Cytomegalovirus Disease: Report of 20 Cases with Gastrointestinal Cytomegalovirus Disease

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- **Background:** The clinical presentations and endoscopic features of cytomegalovirus (CMV) infection in the gastrointestinal (GI) tract are diverse, and can mimic other inflammatory gastrointestinal diseases.
- **Methods:** From 1987 to 2003 at Chang-Gung Medical Center, 20 patients with CMV infections of the GI tract who were assessed using endoscopic examinations and diagnosed via pathologic studies were retrospectively reviewed.
- **Results:** Most of the patients were adults with immunocompromised conditions (10/20). GI tract bleeding was the most common clinical manifestation (11/20). Five patients presented with abdominal pain, and two patients presented with diarrhea. Fifteen patients suffered from fever. The endoscopic abnormalities could be classified into four main groups: inflammatory mucosa alone (3/20), ulceration alone (7/20), inflammatory mucosa associated with ulcer (9/20) and sub-mucosal tumor with ulcer (1/20). Of the 17 patients with ulcer lesions, ten had multiple ulcers and 12 had large ulcers exceeding 2 centimeters in diameter. Of the six patients followed up with colonoscopy, one was free of disease, one had a single ulcer, and four had colitis and were CMV positive on repeat biopsy. Two patients had colon strictures with persistent CMV colitis.
- **Conclusion:** Many patients with GI tract CMV infection are immunocompromised. Gastrointestinal bleeding is the most common initial presentation of gastrointestinal CMV disease. Fever is the most common associated toxic sign. Sigmoidoscopy cannot replace colonoscopy for detecting CMV colitis. The most common feature is multiple ulcers with at least one large ulcer. Endoscopic follow-up in patients with CMV colitis is recommended to investigate for possible persistent colitis and strictures. (*Chang Gung Med J 2005;28:476-84*)

Key words: cytomegalovirus (CMV), gastrointestinal (GI) tract, ulcer, colonic stricture.

Cytomegalovirus (CMV), a member of the herpes group of viruses, affects 40% to 100% of adults,

and like other herpes viruses, produces latent infection. Although CMV disease can occur in immuno-

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competent individuals, it is most frequent in persons with immune deficiencies, for example patients with acquired immunodeficiency syndrome (AIDS), organ transplant recipients, and patients receiving chemotherapy and steroid therapy.⁽¹⁻⁶⁾ Owing to the recent dramatic increase in the number of patients with immune deficiency, and because CMV is one of the most common infectious complications in these settings, the number of patients with alimentary tract CMV disease is also increasing. CMV infection in adults exhibits various clinical manifestations, such as mononucleosis, pneumonitis, hepatitis, and gastrointestinal disorder. Alimentary tract involvement is common in CMV infection and is generally well documented because of the frequency of complaints and the accessibility of the gastrointestinal (GI) tract to biopsy.^(7,8) GI tract involvement may vary in location, manifestation, extent and severity. This investigation reviewed the endoscopic findings and clinical data of 20 patients, and discussed the clinical settings in which they occurred, the type and location of GI tract lesions, and the subsequent endoscopic findings.

METHODS

The departmental files of the Department of Pathology, Chang-Gung Medical Center, were reviewed with computer assistance to retrieve records of patients diagnosed with CMV infection in the GI tract. Twenty patients with CMV infections of the alimentary tract diagnosed between 1987 and 2003 were identified. CMV infection was diagnosed based on the histological identification of CMV inclusion bodies^(7,9,10,11) in routine hematoxylin and eosin-stained sections of formalin-fixed, paraffinembedded materials (Fig. 1) and/or immunohistochemical (IHC) stain (Fig. 2). All specimens were obtained using biopsy forceps from areas of severe mucosal inflammation or ulcers. The locations of the lesions in the 20 patients included the esophagus (n =1), stomach (n = 8), and large intestine (n = 11). The following clinical parameters were recorded from the medical charts: gender, age, indications for endoscopic examination and underlying disease. The endoscopic abnormalities were photographed, and the location, size and appearance of the lesions were recorded. Inflammatory mucosa(12) was defined endoscopically as loss of the normal vascular pattern



Fig 1. Inclusion body (yellow arrow) in a colon endothelium cell (Hematoxylin and eosin, X200).



Fig 2. Inclusion bodies (red arrow) in the ulcerative colonic mucosa and endothelium (Immunohistochemical stain, X200).

accompanied by subepithelial hemorrhage and mucosa friability (Fig. 3). Moreover, ulcer⁽¹³⁾ was defined endoscopically as a well-defined break in the gastro-intestinal mucosa covered with exudates and measuring at least 3 mm at its widest point, as assessed using open biopsy forceps or on the basis of clinical judgment (Fig. 4). Multiple ulcers were defined when the number of ulcers equaled three or more. A large ulcer referred to an ulcer 2 cm or larger in diameter. Eight patients received follow-up endoscopy. This investigation also reviewed the follow-up endoscopic findings and pathological results if biopsies were taken.



Fig. 3 Inflammatory mucosa in the sigmoid colon.

RESULTS

The sample included 15 male patients and five female patients. The patient ages ranged from 5 months to 87 years (mean age \pm standard deviation, 51.1 \pm 25.3 years).

Among the 20 patients with gastrointestinal cytomegalovirus disease, two had AIDS, four had autoimmune disease and were receiving steroid therapy, one had an organ transplant and was receiving cyclosporine therapy, three had malignancies and were under chemotherapy, four had sepsis, one had end-stage renal disease and was receiving regular hemodialysis, one had a recent stroke and four were immunocompetent individuals without significant disease.

All patients displayed GI symptoms, with GI bleeding being the most common presentation. The bleeding was from the upper GI tract in five patients and from the colon in six patients. Furthermore, five patients had persistent abdominal pain, two had persistent watery diarrhea and one complained of abdominal fullness. One patient felt odynophagia owing to ulceration of the esophagus. Fever (15/20; 75%) was the most common toxic sign in our patients.

IgM anti-CMV and IgG anti-CMV was checked in six patients. Three of them had positive IgM anti-CMV results. The others had negative results for IgM anti-CMV but positive IgG anti-CMV findings (Table 1).

All patients were examined via endoscopic stud-



Fig. 4 Single ulcer in the stomach.

ies, with nine patients examined by esophageal-gastro-doudenoscopy (EGD), five by sigmoidoscopy and six by colonoscopy. The lesions were located at the esophagus (n = 1), stomach (n = 8), and colon (n = 1)= 11). Of eight patients with gastric involvement, six had antrum involvement and four patients had Helicobacter pylori (H. pylori) co-infection detected by pathological examinations. The four patients with H. pylori co-infection all had ulcer lesions. The colon (n = 11) was the most common site of involvement. Of the five patients undergoing colonoscopy to the cecum, two (40%) had endoscopic evidence of disease limited to the colon proximal to the splenic flexure, while two (40%) only had involvement distal to the splenic flexure, and one (20%) had both proximal and distal colon involvement.

The mucosal changes in CMV disease could vary from mild erythematous changes to deep ulceration. This investigation modified the classification of CMV colitis in AIDS⁽¹⁴⁾ and classified macroscopic features into inflammatory mucosa alone (3/20; 15%) (Fig. 3), ulceration alone (7/20; 35%) (Fig. 4), inflammatory mucosa associated with ulcer (9/20; 45%) (Fig. 5) and sub-mucosal tumor with ulcer (1/20; 5%) (Fig. 6). A large ulcer referred to an ulcer 2 cm or larger. (Fig. 7). Twelve of the 17 patients had large ulcers, including one in the esophagus, four in the stomach and seven in the colon.

Follow-up endoscopy examinations were performed on eight patients (two by EGD, six by colonoscopy) (Table 2). One of the two patients with upper GI tract lesions had superficial gastritis and

Patient Number	Age/ Gender	Underlying disease	Indication for endoscopy	Endoscopy	Location	Endoscopic features					
						Mucosa Infl.	Ulcer		IgM	IgG	H. pylori
							Number	Size	anti-CMV	anti-CMV	co-intection
1	34/M	C/T	Odynophagia	EGD	Esophagus	Ν	Multiple	> 6 cm	NA	NA	NA
2	41/M	C/T	Hematemesis	EGD	Antrum, stomach	Ν	Multiple	1~2 cm	NA	NA	Ν
3	60/M	Ν	Abd. pain	EGD	Body, stomach	Р	1	4 cm	NA	NA	Р
4	41/M	Ν	Hematemesis	EGD	Antrum, stomach	Ν	Multiple	> 3 cm	NA	NA	Ν
5	41/M	AIDS	Abd. fullness	EGD	Antrum, stomach	Р	1	1 cm	NA	NA	Р
6	77/M	C/T	Black stool	EGD	Antrum, stomach	Ν	Multiple	5 cm	NA	NA	Ν
7	5m/F	Ν	Hematemesis	EGD	Antrum, stomach	Р	Ν	-	NA	NA	Ν
8	29/M	Steroid	Abd. pain	EGD	Body, stomach	Р	1	>4 cm	Р	Ν	Р
9	1.5/M	Steroid	Black stool	EGD	Antrum, stomach	Р	1	1 cm	Р	Р	Р
10	77/M	Sepsis	Bloody stool	Sigmoidoscopy	Sigmoid/rectum	Р	1	2 cm	NA	NA	NA
11	72/F	Steroid	Bloody stool	Sigmoidoscopy	Sigmoid/rectum	Р	Ν	-	NA	NA	NA
12	41/F	Sepsis	Bloody stool	Colonoscopy	Sigmoid/rectum	Ν	Multiple	> 3 cm	NA	NA	NA
13	82/M	Sepsis	Diarrhea	Sigmoidoscopy	Rectum	Р	2	> 3 cm	Р	Ν	NA
14	87/M	Sepsis	Bloody stool	Sigmoidoscopy	Sigmoid/rectum	Р	Multiple	> 3 cm	Ν	Р	NA
15	44/M	AIDS	Abd. pain	Colonoscopy	T-colon	Ν	1	3 cm	NA	NA	NA
16	37/M	Organ trans	Bloody stool	Colonoscopy	A to T colon	Р	Multiple	1 cm	NA	NA	NA
17	85/F	ESRD	Bloody stool	Colonoscopy	Pan colonic	Р	Multiple	1	NA	NA	NA
18	49/F	CVA	Abd. pain	Sigmoidoscopy	Sigmoid/rectum	Р	Multiple	> 3 cm	Ν	Р	NA
19	71/M	Steroid	Diarrhea	Sigmoidoscopy	Sigmoid/rectum	Р	Multiple	> 3 cm	NA	NA	NA
20	52/M	Ν	Abd. pain	Colonoscopy	Sigmoid/rectum	Р	Ν		Ν	Р	NA

Table 1. Clinical Data and Endoscopic Patterns of the Study Group

Abbreviations: F: female; M: male; N: negative; P: positive; NA: not available; C/T: chemotherapy; AIDS: acquired immuno-deficiency syndrome; Trans.: transplantation; ESRD: end stage renal disease; CVA: cerebral vascular accident; Abd.: abdomen; EGD: esophageal-gastro-duodenoscopy; A-colon: ascending colon; T-colon: transverse colon; Inf.: inflammation.



Fig. 5 Inflammatory mucosa with ulcers in the stomach.

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Fig. 6 Submucosal tumor with ulcer in the stomach.

one had ulcer scar formation. No evidence of CMV infection was identified through follow-up biopsy from inflammatory mucosa and ulcer scarring. Six patients with colonic CMV infection underwent colonoscopy six weeks to two months after the first

endoscopy. The pathology study showed that one patient was free of disease with negative CMV infection; one patient had a single ulcer in the ascending colon without evidence of CMV infection, while the other four patients had colitis with CMV infection.

	• /		Follow-up	Follow-up e	Pathology		
Patient	Age/	Location			Ule	For CMV	
number	gender		time	Mucosa inflammation	Number	Size	infecton
3	60/M	Body, stomach	8 weeks	Erythema	Ν	-	Ν
8	29/M	Body, stomach	32 week	Erythema	1	3 cm	Ν
13	82/M	Rectum	4 weeks	Erythema	1	3 cm	Р
14	87/M	Sigmoid/rectum	6 weeks	Erythema	Ν	-	Р
15	44/M	A-colon	5 weeks	Ν	1	3 cm	Р
18	49/F	Sigmoid/rectum	6 weeks	Erythema	Multiple	> 3 cm	Р
19	71/M	Sigmoid/rectum	8 weeks	Erythema	Multiple	> 3 cm	Р
20	52/M	Sigmoid/rectum	7 weeks	Edema	Ν		Ν

 Table 2. Follow-up Endoscopic Characteristics of the Study Group

Abbreviations: F: female; M: male; N: negative; P: positive; A-colon: ascending colon.

Two of the four patients with persistent CMV colitis had colon strictures too severe to allow passage of the scope. The strictures were in the distal sigmoid colon where large, deep ulcers had been located (Fig. 8).

DISCUSSION

CMV is a common human viral infection and can affect numerous organs, including the lung, retina, liver and GI tract. The course of infection is often not clinically apparent. Alimentary tract CMV disease is an increasingly widely recognized clinical problem because of the growing prevalence of AIDS and the increasing use of immunosuppression agents. Most patients in our study and previous studies were



Fig. 7 Large ulcer in the sigmoid colon.

immunocompromised.⁽¹⁻⁶⁾ Four of our patients (20%) had sepsis with CMV infection of the GI tract. Immunocompetent patients can also be infected by CMV in the GI tract. The study group had four immunocompetent patients (20%), all of whom suffered only mild gastrointestinal symptoms and recovered with only symptomatic treatment.

The clinical presentation of GI tract CMV disease is diverse, with symptoms such as odynophagia, hematemesis, dyspepsia-like symptoms, diarrhea, rectal bleeding and even intestinal perforation, depending on the site of the affected lesion.⁽¹⁵⁻²¹⁾ In AIDS-related cytomegalovirus gastrointestinal disease, odynophagia and diarrhea are the most common symptoms because the esophagus and colon are the most common sites of CMV infection in



Fig. 8 Previous ulcer (black arrow) with benign stricture in the sigmoid colon (follow- up 2 months after first endosopy).

AIDS.^(17,20) One study showed that diarrhea was the most common symptom in immunocompetent hosts with CMV GI tract infection.⁽¹⁸⁾ However, GI bleeding was the most common presentation in this series, in accordance with some reports.^(15,16) The most common associated toxic sign was fever (15/20; 75%) in our study. This was also reported in a previous study.⁽¹⁸⁾

In immunocompromised patients, the colon was the site most frequently affected by CMV infection,^(7,16) whereas in non-AIDS patients, the upper GI tract was preferentially involved.⁽⁷⁾ This investigation showed that the most common site of CMV infection in the GI tract was the colon (55%), while the stomach was involved in 40% of cases. Only one patient had esophageal involvement, and the clinical presentation was odynophagia. The antrum (25%) was the most common site of upper GI tract CMV infection while the sigmoid colon and rectum (35%) were the most common sites in lower GI tract involvement. However, two of five patients who underwent colonoscopy to the cecum had CMV infections limited to the colon proximal to the splenic flexure which were undetectable by sigmoidoscopy. Colonoscopy is recommended for patients suspected of having CMV infection with colon involvement.

Various macroscopic lesions caused by CMV infection of the GI tract were reported in previous studies. The macroscopic lesions could be mucosal ervthematous changes, mucosa erosion, ulceration, pseudotumor formation and even perforation.(22-26) This investigation analyzed the endoscopic features, adjusted the classification of CMV colitis in AIDS⁽¹⁴⁾ and classified the macroscopic lesions into four clinical pictures: inflammatory mucosa alone, ulceration alone, inflammatory mucosa with ulcer and submucosal tumor with ulcer. We found only three patients with inflammatory mucosa without ulceration. Moreover, 17 patients had ulceration with or without inflammatory mucosa. This finding is compatible with previous studies^(1,7,15,22) in which ulceration was the most common finding of CMV infection in the GI tract. Of the 17 patients with ulcer lesions, ten (58.8%) had multiple ulcers, 12 (70.6%) had one large ulcer and seven (41.2%) had multiple ulcers with at least one large ulcer.

Half of the patients (4/8) with gastric CMV infection had co-infection with H. pylori in our study. H. pylori-associated gastric ulcers often devel-

op in the antrocorporeal transitional zone in the area of the angular notch. The background mucosa usually reveals pangastritis, with a degree of atrophy. The inflammatory reaction is characterized by focal epithelial cell damage with inflammatory infiltrates such as polymorphonuclear leukocytes, eosinophils, and mononuclear cells in the lamina propria.^(27,28) In CMV infection of the stomach, the location tends to be in the gastric corpus/fundus area. The infection may cause hyperrugosity, ulceration, hemorrhage and even perforation. The histology shows deep mucosa inflammation, and cytomegalic inclusion bodies in epithelial and endothelial cells, and in the base of ulcerations.^(10,29) In AIDS patients, a lower prevalence of H. pylori but a higher prevalence of CMV-associated peptic ulcer disease has been found. The low prevalence of H. pylori infection in AIDS patients suggests a different role of H. pylori infection in peptic ulcers or even a different mechanism of peptic ulcerogenesis in HIV-positive subjects.⁽³⁰⁾ In our data, ulcer with inflammatory mucosa (4/4; 100%) was the main presentation in patients who had H. pylori and CMV co-infection. However, the relationship between H. pylori and CMV co-infection remains unclear and needs more further studies.

Two of the six patients who received follow-up colonoscopy (33.4%) displayed persistent CMV colitis, while two (33.4%) exhibited CMV colitis with severe colon stricture. The pathologic findings at stricture sites were acute and chronic inflammation with granulation tissue formation and inclusion bodies. The previous endoscopic features of these two patients were colitis with multiple ulcers with one large deep ulcer involving the sigmoid colon. It seems that persistent inflammation and fibrotic changes following large, deep ulcers in the colon result in lumen stricture.

In our study, three patients died during hospitalization. Two of them received anti-viral therapy. Some studies in organ transplant recipients and AIDS patients report clinical improvement in symptoms of enteric CMV infections after ganciclovir therapy.^(31,32) However, in the absence of immune reconstruction, recurrence of disease is common after short courses of therapy.⁽³³⁾ In immunocompetent hosts, the benefit of anti-viral therapy is unknown.⁽³⁴⁾

In conclusion, CMV infections of the GI tract occur mainly in immunocompromised and septic hosts, although occasionally immunocompetent patients may be affected. GI tract bleeding is the most common clinical finding in CMV infection of the GI tract and the antrum and distal colon are the most frequent sites of involvement. The most common endoscopic features of CMV GI tract infection are multiple ulcers with at least one large ulcer.

Colonoscopy is the preferred method of detection of colon CMV disease. Follow-up colonoscopy is recommended for all patients with CMV colitis, particularly for patients with colitis and multiple ulcers with at least one large ulcer.

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胃腸道巨大細胞病毒疾病的臨床與內視鏡診斷之特徵: 二十個病例研究

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- **背 景**: 巨大細胞病毒是人類常見的病毒感染,但是臨床上卻很少造成嚴重胃腸道疾病。此 研究目的在探討胃腸道巨大細胞病毒疾病之臨床表現,内視鏡下的病變型態,病患 預後及追蹤內視鏡之發現。
- 方法:從民國 76 年至民國 92 年,回溯性於一林口長庚醫學中心收集到 20 例胃腸道巨大細胞病毒疾病病例。這些病例皆接受上消化道或下消化道内視鏡檢查與黏膜生檢,經由病理切片發現巨大細胞併細胞核内包涵體與/或免疫組織化學染色確定巨大細胞病毒疾病。
- 結果:這20例胃腸道巨大細胞病毒疾病患者,男性15例,女性5例,平均年龄51.1±25.3 歲(範圍 5 個月大至87 歲)。患者中有免疫功能缺失或使用免疫抑制劑 7例(35%),癌症接受化學治療3例(15%),敗血症4例(20%),其他6例。9例接受胃鏡檢查,6例接受乙狀結腸鏡檢查,5例接受全大腸鏡檢查。接受內視鏡檢查原因爲消化道出血11例(55%),腹痛5例(25%),腹瀉2例(10%),腹脹1例(5%),吞嚥疼痛1例(5%)。病變部位食道1例,胃8例,大腸11例;其中胃以胃竇部最常見(75%;6/8),而大腸以乙狀結腸與直腸最常見(63.6%;7/11)。病變型態可分爲黏膜發炎型3例(15%),潰瘍型9例(45%),黏膜發炎併潰瘍型7例(35%),與黏膜下腫瘤併潰瘍型1例(5%)。在17 名有潰瘍病變的患者中,有10例有多發的(潰瘍數大於2個)潰瘍病變,有大潰瘍(潰瘍直徑大於2公分)12例,有7例合併有多發的大潰瘍。6例有大腸巨大潰瘍病變患者於下消化道內視鏡追蹤檢查時,有2例併發嚴重腸腔狹窄。
- 結論:嚴重胃腸道巨大細胞病毒疾病患者常有免疫功能缺失或敗血症,臨床症狀以出血最常見。病變部位以乙狀結腸,直腸與胃竇部最常見,病變型態以潰瘍型與黏膜發炎 併潰瘍型為主,常有大潰瘍病變。對於下消化道巨大細胞病毒感染的診斷能力,乙 狀結腸鏡不如大腸鏡。有遠端大腸大潰瘍病變可能併發嚴重腸腔狹窄。有巨大細胞 病毒腸炎的病患建議追蹤大腸鏡檢查。 (長庚醫誌 2005;28:476-84)
- 關鍵字:巨大細胞病毒,腸胃道,潰瘍,腸道狹窄。

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