Gastrointestinal Tract Cytomegalovirus Disease in Southwestern Taiwan: A Clinical Study of 1950 Endoscopic Biopsies

Seng-Kee Chuah, MD; Chi-Sin Changchien, MD; Chung-Mou Kuo, MD; Keng-Liang Wu, MD; King-Wah Chiu, MD; Yi-Chun Chiu, MD; Jien-Wei Liu1, MD; Hock-Liew Eng2, MD; Shue-Shian Chiou, MD

Background: Gastrointestinal (GI) cytomegalovirus (CMV) disease occurs in adult patients with immune suppression. This study reviews and discusses the clinical settings, endoscopic features, and locations of GI CMV lesions.

Methods: In total, 1950 endoscopic biopsy reports for all GI tract lesions in Chang Gung Memorial Hospital, Kaohsiung were retrospectively reviewed for CMV disease from 1999 to 2002. Only those patients found to be positive for viral inclusion bodies in tissue specimens, with further confirmation by special immunohistochemical staining, were enrolled in this study.

Results: Our series showed that all 5 patients were immunosuppressed when attacked by the virus. The esophagus (n = 2) and colon (n = 2) were infected in 4 patients, while stomach was involved in one patient. Those patients with lesions of the esophagus and stomach followed a more-benign clinical course. Endoscopic examination showed 1 or more prominent ulcers in the distal esophagus and at the antrum of the stomach. Rare endoscopic findings of diffuse esophageal CMV disease and severe and extensive colitis were presented. The overall mortality rate was 20%, and all but 1 patient responded well to ganciclovir treatment.

Conclusions: We emphasize that GI CMV disease is still rare in Taiwan. A high degree of suspicion for CMV disease is important when diagnosing immunosuppressed patients suffering from GI symptoms. (Chang Gung Med J 2005;28:467-75)

Key words: GI tract cytomegalovirus disease, cytomegalic inclusion body.

All primary CMV infections usually resolve and enter a state of latency in healthy individuals. The GI tract is at risk for subsequent CMV disease, and may contain latent viruses which could lead to local disease with reactivation. This occurs particularly in adult patients with immune deficiencies, such as those suffering from acquired immunodeficiency syndrome (AIDS), organ transplant recipients, cancer patients undergoing chemotherapy, and those receiving steroid therapy. Although CMV...
may be present in the gastrointestinal tracts of 30%~43% of AIDS patients, only about 7.4% of these patients develop clinically apparent CMV disease. Therefore, the only reliable marker for CMV infection is typical viral inclusion bodies, thus making a diagnosis of GI tract CMV disease quite difficult. The number of reported AIDS cases is relatively low in Taiwan. However, with the rapid increase in the incidence of the human immunodeficiency virus (HIV) since 1988, and rapidly growing numbers of organ transplants, an increase in opportunistic infections such as cytomegalovirus should be expected in clinical practice. A few Asian reports about CMV disease over different sites of the GI tract have described individual case studies. One report from Cheung et al. studied CMV infections of the GI tract of non-AIDS patients 10 years ago. An important question is whether CMV is really still a rare disease in Asia. In this study, we attempted to locate patients who suffered from GI CMV disease, and compare and discuss their clinical and endoscopic features, with a view to continuing our work and helping such patients in the early stages of their illness.

**METHODS**

In total, 1950 endoscopic biopsy reports from the Gastroenterology Division, Chang Gung Memorial Hospital, Kaohsiung for all GI tract lesions were retrospectively reviewed for CMV disease from January 1999 to December 2002. We restricted our enrollment criteria to the gold standard of diagnosis for GI CMV disease, i.e., the presence of typical viral intranuclear inclusion bodies further confirmed by special immunohistochemical staining methods. At the same time, pathologists excluded other possible infections, such as fungi, other viruses, parasites, and bacteria before making a final diagnosis.

In total, 5 patients were enrolled (4 males and 1 female). The medical records of these 5 patients with GI CMV disease were also reviewed for their clinical background, laboratory data, treatment course, and clinical outcomes. The video recordings were reviewed, looking for any special characteristics of individual lesions and their locations and extents. All upper GI studies were performed by a free-hand technique using a forward-viewing electric endoscope (Olympus GIF-XQ230 or XQ200). Lower GI tract studies were carried out by colonoscope. After the patients were prepared by ingestion of an electrolyte lavage solution, an endoscopic examination was conducted using a CF200Z electronic videendoscope (Olympus, Tokyo, Japan). Tissue specimens were obtained in multiple sessions by endoscopic snare biopsy forceps from the bases of abnormal mucosal lesions. These multiple biopsies obtained by the snare forceps technique were necessary to obtain sufficient tissue specimens. The diagnosis was confirmed by pathologists using hematoxylin and eosin (H&E) staining, and immunohistochemical staining with anti-CMV monoclonal antibody (Fig. 1A, B).

**RESULTS**

Our review discovered 5 documented cases of GI CMV disease, with a male to female ratio of 4: 1. The mean age was 59.2 ± 22.5 (range, 40~92) years. All 5 patients were immunocompromised at the time they were diagnosed with GI CMV disease. The mean serum albumin level was 1.68 ± 0.44 (range, 1.2~2.4) g/dl, while the mean serum hemoglobin level was 8.48 ± 1.91 (range, 6.1~10.1) g/dl. Three patients (60%) had positive urine or blood anti-CMV antibody assays (IgM).

Two male patients suffered from esophageal CMV disease (one had AIDS while the other had long been bedridden by a stroke and multiple organ failure). Only 1 instance of gastric CMV disease was observed in a male patient who had undergone long-term steroid treatment for systemic lupus erythematosus disease. Two CMV colitis patients, one suffering from prostate cancer with bone metastasis and the other multiple myeloma, were referred by a hematologist and an oncologist, respectively (Table 1).

Our youngest patient was a 40-year-old male AIDS patient receiving treatment at the Infectious Diseases Department. He had suffered from unrelied sensations of heartburn and lower chest pain for 6 months, even after being treated with high dosages of omeprazole. The delay in conducting an endoscopic study was due to the patient’s initial reluctance. The endoscopy picture showed prominent ulcers in the lower esophagus (Fig. 2A). The patient was treated with 250 mg ganciclovir administered intravenously every 12 h for 3 weeks, and was subse-
We also found a rare endoscopic presentation of esophageal CMV disease in a 75-year-old woman. She suffered from a stroke, diabetes mellitus, hypertension, and repeated infections of the urinary tract, and had been bedridden for many years. Endoscopy was performed due to the patient’s severe vomiting, bleeding, and intractable chest pain. Diffuse and severe esophagitis with small ulcers were found over almost the entire esophagus (Fig. 2B). Initially, she was diagnosed as having an esophageal fungal infection, but sufficient biopsy tissue specimens allowed the pathologist to make a correct diagnosis. She responded well to a 3-week course of 250 mg ganciclovir administered intravenously every 12 h.

The only gastric CMV disease in our series was a 54-year-old male systemic lupus erythematosus (SLE) patient with multiple myelomas. He was prescribed triple anti-HIV viral medications regularly since then, and has been symptom-free for more than 1 year.

Table 1. Patient Backgrounds and Outcomes of Treatment for Gastrointestinal Cytomegalovirus Disease

<table>
<thead>
<tr>
<th>Organ involved</th>
<th>Underlying disease</th>
<th>Treatment course</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus (n = 2)</td>
<td>(1) AIDS</td>
<td>Ganciclovir x 3 weeks</td>
<td>good 3 weeks</td>
</tr>
<tr>
<td></td>
<td>(2) Elderly stroke victim</td>
<td>Ganciclovir x 3 weeks</td>
<td>good 3 weeks</td>
</tr>
<tr>
<td>Stomach (n = 1)</td>
<td>(1) SLE</td>
<td>Ganciclovir x 3 weeks</td>
<td>good † weeks</td>
</tr>
<tr>
<td>Colon (n = 2)</td>
<td>(1) Prostate cancer</td>
<td>Ganciclovir x 3 weeks</td>
<td>good 3 weeks</td>
</tr>
<tr>
<td></td>
<td>(2) Multiple myelomas</td>
<td>Ganciclovir x 1 week</td>
<td>expired 1 week</td>
</tr>
</tbody>
</table>

Abbreviations: AIDS: acquired immunodeficiency syndrome; SLE: systemic lupus erythematosus.

† Death was caused by bacterial pneumonia 1 month after the gastric CMV was cured (the actual overall CMV-related mortality was 20%).
(SLE) patient with long-term steroid usage. He had suffered from epigastric pain for at least 2 months. We found 2 deep, round, ulcers, each about 1.0 cm in diameter at the antrum of the stomach (Fig. 2C, D). The patient was symptom-free after a 3-week course of intravenous ganciclovir treatment, but he died of pseudomonas-induced pneumonia 1.5 months later.

Two CMV colitis patients were diagnosed. A 93-year-old patient with prostate cancer was admitted to our oncology ward for a urinary tract infection. However, he began suffering from progressive bloody diarrhea 1 week after admission. A colonoscopy was planned, but the patient could only tolerate a sigmoidoscopic examination. Marked inflammatory mucosal changes, with ulcerations of the rectosigmoid colon were found (Fig. 3A, B). CMV colitis was confirmed, and ganciclovir treatment was initiated, curing his viral disease. A 72-year-old female patient with multiple myelomas who received chemotherapy had episodes of bloody stools in the latter stage of her hospital course. A colonoscopic examination was performed when she finally gave her consent. Severe infection involving almost the entire colon, except for the cecum and rectum, was discovered, and was proven to be CMV colitis by biopsies. The endoscopic morphology showed

Fig. 2 (A) Typical round ulcers of lower-esophagus cytomegalovirus (CMV) disease, each about 0.8 cm in size (arrow). (B). A rare feature of diffuse esophagitis with small CMV ulcers resembling lesions caused by herpetic and fungus infections. (C, D) Round and deep ulcers at the antrum of the infected stomach (arrow).
extensive nodular surfaces and ulcerations throughout the involved segments, resembling an exacerbation of ulcerative colitis, but with a rare presentation of pseudo-polyp formation at the hepatic flexure site (Fig. 3C, D). Mortality due to massive bleeding and sepsis occurred later, despite having received ganciclovir treatment.

**DISCUSSION**

The principal risk factor in the development of CMV disease in these patients is immunosuppression and the presence of other opportunistic infections.\(^{6,17,21}\) In Taiwan, HIV infection is becoming an increasingly more-serious public health problem. Data show that more than 60% of these infected patients are in a serious condition when they are first diagnosed; that is, with a CD4\(^+\) lymphocyte count below 50/mm\(^3\).\(^{21}\) This was true for our only HIV patient suffering from esophageal CMV disease (who had a CD4\(^+\) lymphocyte count of 34/mm\(^3\)). In Taiwan, there is also an increase in the number of recipients of solid organ and bone marrow transplants, and of cancer patients receiving chemotherapy.\(^{18}\) Therefore, it is very important to recognize the symptoms of opportunistic infectious diseases, such as oral and esophageal candidiasis, pneumocystic carinii pneumonia, tuberculosis, cytomegalovirus infection, and Kaposi sarcoma, and conduct careful histological reviews.

![Fig. 3](image.png)

Fig. 3 (A, B) Marked inflammatory changes with ulcerations over the infected sigmoid colon and rectum (arrow). (C, D) Colon severely infected with extensive nodular surfaces and ulcerations throughout the involved segments, resembling an exacerbation of ulcerative colitis, with rare presentations of pseudo-polyp formation at the hepatic flexure site (arrow).
CMV is a member of the herpes virus family.\(^1\)\(^-\)\(^3\) It may be a new infection or the consequence of superimposed infections in previously damaged tissue.\(^1\)\(^-\)\(^3\) CMV is highly prevalent in America, with seropositivity in the range of 53\%~79\% of adults.\(^22\)\(^,\)\(^23\) However, serological markers of active CMV infection often do not appear. The only reliable marker of CMV infection is typical viral inclusion bodies.\(^15\)\(^,\)\(^16\) The target organs of CMV disease in immunodeficient adults are the lungs, adrenal glands, liver, and less commonly, the GI tract.\(^16\) We also observed the rarity of GI tract CMV disease, with only 5 cases discovered for a 3-year period after reviewing 1950 endoscopic biopsies. GI tract CMV may be an under-diagnosed condition in immunocompromised populations. The main reason could be the difficulty in diagnosis due to inadequate biopsies which may account for the under-representation.

In our series, 4 of the 5 patients were senior citizens, with one 40-year-old male AIDS patient (with a low CD4\(^+\) lymphocyte count when discovered). All of them were immunocompromised in different ways, as determined by their clinical backgrounds, low serum albumin levels (mean value of 1.68 \(\pm\) 0.44 g/l), and anemia (mean serum hemoglobin level of 8.48 \(\pm\) 1.91 g/dl) when diagnosed with GI CMV disease. A poor host immune background is the most-important factor accounting for GI CMV disease.

It appeared that the 2 patients with lower GI tract involvement were more seriously affected, one of whom bled to death (Table 1). However, these 2 patients were 72 and 93 years old, and the number of cases studied was too small to form a hypothesis. Interestingly, we observed 2 rare morphologies of GI CMV disease. One infected the esophagus and the other involved almost the entire colon. We treated 2 cases of esophageal CMV disease. To our surprise, only 1 patient was HIV positive. A previous report identified these lesions as large, solitary, and situated in the distal esophagus but most lesions presented as multiple, well-circumscribed, shallow ulcerations larger than 1 cm located in the middle to distal section of the esophagus.\(^7\) Our AIDS patient had typical ulcers in the lower esophagus (Fig. 2A). This patient has had no relapse 1 year after a course of ganciclovir treatment, which may also be due to the effective control of his underlying disease with anti-HIV agents.\(^24\)

Ganciclovir is the treatment of choice for dealing with GI CMV disease, with a recommended 250 mg of ganciclovir administered intravenously every 12 h for at least 3 weeks.\(^27\)\(^-\)\(^30\) Prophylaxis with oral ganciclovir has been studied for use by HIV-infected adults who are CMV-seropositive with low CD4\(^+\) T lymphocyte count of < 50 cells/mm\(^3\).\(^21\) However, concerns about the side effects of neutropenia and anemia, conflicting reports of its efficacy, a lack of proven survival benefits, risks of experiencing ganciclovir-resistant CMV, and costs should be addressed.\(^21\) The other alternative is valacyclovir, but an unexplained increase in death rates has been reported with its use.\(^31\) CMV ulcers of the esophagus respond particularly well to foscarinet, a pyrophosphate derivative, with a rapid resolution of clinical symptoms and healing of the ulceration, and it could be an alternative medication if ganciclovir fails.\(^32\) However, foscarinet is virostatic, and reactivation of
CMV could be expected in an immunosuppressed host even after a complete course of therapy.

CMV disease is not considered cured regardless of whatever courses of available antiviral agents are used. Maintenance therapy is still recommended in cases of rapid relapse of CMV esophageal ulceration after the initial treatment. Discontinuing maintenance therapy should be done with care among HIV-infected patients unless sustained CD4+ T lymphocyte counts > 100–150 cells/mm³ in response to HAART are achieved.(33,34) However, reinitiation of secondary prophylaxis should be given when the CD4+ T lymphocyte count drops to < 100–150 cells/mm³.(33)

In conclusion, GI CMV disease is still rare, but an increase in the prevalence can be expected in the near future. Therefore, a high degree of suspicion is mandatory for any physician treating a patient from among these immunosuppressed populations who is suffering from GI disorders. Endoscopy and tissue biopsy confirmation of the specific inclusion body by a pathologist still comprise the gold standard of diagnosis.

REFERENCES

25. Rene E, Marche C, Chevalier T, Rouzioux C, Regnier B,
CMV infection of the gastrointestinal tract

南台灣巨細胞病毒引起的消化道疾病之臨床經驗：
1950 件腸胃道病灶之組織切片所見
蔡成枝 張簡吉幸 郭仲謀 吳耿良 趙景華 邱逸群 劉建衛 秦福柳 邱世賢

背 景：文獻報告中，巨細胞病毒引起的消化道疾病相當少見。但隨著免疫力低下的病患如愛滋病、癌症以及器官移植日益增加，巨細胞病毒感染的增加是可預期的，但少見的消化道感染是否也一樣呢？本研究乃討論這些病患的臨床表現，尤其是內視鏡所見，以及其治療之經驗。

方 法：1999 年一月至 2002 年十二月期間，我們配合有消化道疾病症狀的病患接受內視鏡檢查，發現腸胃道病灶之組織切片共 1950 件。臨床診斷必須在病理組織裡找到典型的巨大細胞聚合體 (cytomegalic inclusion body)，並經特殊免疫染色法確定且須排除其他感染的可能如其他病毒，黴菌，寄生蟲，或細菌感染。

結 果：我們只發現 5 例消化道受感染的病患，食道和大腸各 2 例，胃部 1 例。上消化道受感染的症狀在臨床表現似乎比大腸受感染病患輕。其中一例食道受感染的內視鏡所見相當罕見。一例幾乎整段大腸嚴重感染者因延誤而死亡，死亡率為 20%，其他四位病患皆對 ganciclovir 有很好的療效。

結 論：我們強調消化道之巨細胞病毒疾病仍然少見，因此，對於有消化道症狀的病患接受內視鏡檢查，尤其是免疫力低下的病患如愛滋病、癌症以及器官移植者，提高警覺並將針對腸胃道病灶做組織切片檢查是必要的。

(長庚醫誌 2005;28:467-75)

關鍵字：消化道巨細胞病毒疾病，巨大細胞聚合體。