Endoscopic Manifestations and Clinical Characteristics of Cytomegalovirus Infection in the Upper Gastrointestinal Tract

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We retrospectively analyzed the cases of 14 patients (9 women, 5 men, mean age: 51.6 years) with cytomegalovirus (CMV) involvement in the esophagus, stomach, and/or duodenum diagnosed at a single center, to determine their endoscopic features and clinical backgrounds. Thirteen patients (92.9%) had hematologic disease; the other had rheumatoid arthritis. Of the former, 12 patients underwent allogeneic hematopoietic stem cell transplantation, and 9 of these patients had graft-versus-host disease (GVHD) before undergoing esophagogastroduodenoscopy (EGD). All 14 patients had been taking one or more immunosuppressive agents including cyclosporine (n = 10), corticosteroids (n = 9), mycophenolic acid (n = 6), tacrolimus (n = 3), and methotrexate (n = 1). Tests for CMV antigenemia were positive in 11 patients (78.6%). EGD examinations revealed esophageal (n = 3), gastric (n = 9), and duodenal involvement (n = 6). Macroscopically, esophageal lesions by CMV infection presented as redness (n = 1), erosions (n = 1), and ulcers (n = 1). Gastric lesions manifested as redness (n = 7), erosions (n = 3), exfoliated mucosa (n = 2), and verrucous erosions (n = 1). Mucosal appearances in the duodenum varied: redness (n = 2), ulcers (n = 2), multiple erosions (n = 2), single erosion (n = 1), edema (n = 1). CMV was detected even in the intact duodenal mucosa (n = 1). In conclusion, physicians must recall the relevance of CMV infection when any mucosal alterations exist in the upper gastrointestinal tract of immunosuppressed patients.

Key words: cytomegalovirus, duodenum, esophagogastroduodenoscopy, esophagus, stomach

Cytomegalovirus (CMV) belongs to the herpes virus family and remains latent within the human body. Symptomatic CMV disease rarely occurs in an immunocompetent host, whereas immunosuppressed patients are susceptible to developing CMV infections. CMV affects various organs, frequently causing retinitis, pneumonitis, gastroenteritis, hepatitis, and encephalitis. Among CMV infections involving the gastrointestinal tract, one of the most typical manifestations is colorectal ulcers in ulcerative colitis patients [1]. Conversely, the prevalence of upper gastrointestinal tract lesions is relatively low [2], and only a few articles have presented large series of patients with this disease [3-8]. In the present study, we retrospectively analyzed the endoscopic features and clinical background of 14 patients with CMV-related lesions in the upper gastrointestinal tract.
Materials and Methods

A database search of medical records at the Department of Pathology at Okayama University Hospital identified 14 patients with CMV infection in the upper gastrointestinal tract (esophagus, stomach, and duodenum) diagnosed between July 2003 and February 2015. The diagnosis of CMV infection was made histologically, based on the existence of intranuclear or cytoplasmic inclusion bodies and/or positive immunophenotypic staining for CMV on endoscopically biopsied specimens (Fig. 1). The presence of graft-versus-host disease (GVHD) was also histologically investigated in each biopsied sample. We reviewed the patients’ clinical records to collect data on the patients’ background and the endoscopic, radiologic, biologic, and pathologic examinations performed. One of the 14 patients examined was also the subject in our case report [9]. The Ethical Committee of the Okayama University Hospital approved this study (no. 1041), which also adhered to the Declaration of Helsinki.

Results

We summarize the patients’ backgrounds in Table 1. The cases included 9 women and 5 men, and their mean age was 51.6 years. All but one patient (i.e., 13 of the 14 patients) were diagnosed with a hematologic disease: acute myeloid leukemia (n = 6), extranodal NK/T cell lymphoma, nasal type (n = 2), chronic active Epstein-Barr virus infection (n = 1), aplastic anemia (n = 1), follicular lymphoma (n = 1), myelodysplastic syndrome (n = 1), and chronic lymphocytic leukemia (n = 1).

Seven of these 13 patients underwent allogeneic bone marrow transplantation, and 5 patients underwent umbilical cord blood transplantation for the treatment of hematologic diseases. All 12 of these patients were on immunosuppressant medicine for the prevention or treatment of GVHD. One patient (Case 14) had been taking cyclosporine for the treatment of cytopenia associated with chronic lymphocytic leukemia (10). The last patient was diagnosed with rheumatoid arthritis (Case 12) and was treated with methotrexate.

All 14 patients had been taking one or more immunosuppressive agents including cyclosporine (n = 10), steroids (n = 9), mycophenolic acid (n = 6), tacrolimus (n = 3), and methotrexate (n = 1). None of the patients were infected with the human immunodeficiency virus (HIV). Among the 12 patients who underwent allogeneic hematopoietic stem cell transplantation, esophagogastroduodenoscopy (EGD) was performed 29 to 221 days after transplantation. At the EGD examination, 9 patients had symptoms of acute GVHD, which manifested as skin eruption and/or diarrhea in 7 patients; the other 2 had symptoms of chronic GVHD, manifesting as skin eruption and elevated liver enzymes in 1 patient and histologically proven gastric GVHD in the other.

The chief complaints that prompted EGD examination were nausea (n = 6), diarrhea (n = 3), appetite loss (n = 3), vomiting (n = 2), throat irritation (n = 1),

![Fig. 1](image1.png) Pathological images of CMV infection in the stomach (Case 3). Intranuclear and cytoplasmic inclusion bodies are shown in hematoxylin and eosin staining (A, arrows). Immunophenotypic staining for CMV was also positive (B).
abdominal pain (n = 1), epigastric pain (n = 1), hematemesis (n = 1), precordial discomfort (n = 1), swallowing pain (n = 1), and fever (n = 1). All patients were tested for CMV antigenemia before the procedure, and the results were positive in 11 patients (78.6%) and negative in 3 patients. It is noteworthy that among the 3 patients for whom the CMV antigenemia assay was negative, the results turned out to be positive 4 days after EGD examination in 1 patient (Case 5) and 11 days after EGD examination in another (Case 2).

The EGD and biopsy examinations revealed the involvement of one or more sites. The esophagus was involved in 3 patients; 9 patients had gastric involvement and 6 had duodenal involvement (Table 2). Macroscopically, esophageal lesions by CMV infection presented as redness (n = 1), erosions (n = 1), and ulcers (n = 1) (Fig. 2). Gastric lesions were viewed as redness (n = 7), erosions (n = 3), exfoliated mucosa (n = 2), and verrucous erosions (n = 1) (Fig. 3). In the duodenum, CMV involvement was detected in the mucosa by redness (n = 2), ulcers (n = 2), multiple erosions (n = 2), single erosion (n = 1), edema (n = 1) (Fig. 4). Moreover, CMV involvement was detected even in intact duodenal mucosa.

In biopsied samples, GVHD was histologically confirmed in 2 cases (Cases 2 and 5) and suspected in 2 cases (Cases 7 and 8). This was in addition to histologic evidence of CMV infection. The endoscopic features of the 14 cases are summarized in Table 3.

Following the histologic diagnosis of CMV infection in the upper gastrointestinal tract or positive results of CMV antigenemia, antiviral drugs were administered

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying diseases</th>
<th>Symptoms</th>
<th>Immunosuppressive agents</th>
<th>CMV antigenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.4 F</td>
<td>CAEBV, post CBT (day 57)</td>
<td>Throat irritation, abdominal pain, diarrhea</td>
<td>Mycophenolic acid, cyclosporine, steroid</td>
<td>Positive (25 cells/50,000 cells)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>36.3 M</td>
<td>Acute myeloid leukemia, acute GVHD (skin), post UR-BMT (day 43)</td>
<td>Appetite loss, diarhea, fever</td>
<td>Cyclosporine, steroid</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.9 F</td>
<td>Extranodal NK/T cell lymphoma, nasal type, post UR-BMT (day 29)</td>
<td>Vomiting, epigastric pain</td>
<td>Tacrolimus, steroid</td>
<td>Positive (4 cells/2 slides)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>43.4 F</td>
<td>Aplastic anemia, chronic GVHD (gut), post UR-BMT (day 221)</td>
<td>Nausea, appetite loss</td>
<td>Mycophenolic acid, tacrolimus, steroid</td>
<td>Positive (7 cells/63,000 cells)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>51.2 F</td>
<td>Follicular lymphoma, acute GVHD (skin), post UR-BMT (day 34)</td>
<td>Nausea</td>
<td>Cyclosporine, steroid</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>53.4 M</td>
<td>Acute myeloid leukemia, post CBT (day 48)</td>
<td>Nausea, vomiting</td>
<td>Cyclosporine</td>
<td>Positive (11 cells/56,000 cells)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>55.8 F</td>
<td>Acute myeloid leukemia, acute GVHD (skin), post CBT (day 31)</td>
<td>Hematemesis</td>
<td>Mycophenolic acid, cyclosporine, steroid</td>
<td>Positive (57 cells/28,000 cells)</td>
<td></td>
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<tr>
<td>8</td>
<td>55.9 M</td>
<td>Acute myeloid leukemia, acute GVHD (skin, gut), post UR-BMT (day 47)</td>
<td>Nausea</td>
<td>Tacrolimus, steroid</td>
<td>Positive (2 cells/29,000 cells)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>56.2 M</td>
<td>Acute myeloid leukemia, acute GVHD (skin, gut), post UR-BMT (day 35)</td>
<td>Diarhea</td>
<td>Cyclosporine, steroid</td>
<td>Positive (115 cells/70,000 cells)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>57.6 M</td>
<td>Myelodysplastic syndrome, chronic GVHD (skin, liver), post UR-BMT (day 153)</td>
<td>Appetite loss</td>
<td>Mycophenolic acid, cyclosporine, steroid</td>
<td>Positive (7 cells/33,000 cells)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>59.9 F</td>
<td>Extranodal NK/T cell lymphoma, nasal type, acute GVHD (skin), post CBT (day 77)</td>
<td>Nausea</td>
<td>Mycophenolic acid, cyclosporine</td>
<td>Positive (13 cells/50,000 cells)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>60.2 M</td>
<td>Rheumatoid arthritis</td>
<td>Nausea</td>
<td>Methotrexate</td>
<td>Positive (20 cells/50,000 cells)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>61.3 F</td>
<td>Acute myeloid leukemia, acute GVHD (skin, gut), post CBT (day 29)</td>
<td>Precordial discomfort</td>
<td>Mycophenolic acid, cyclosporine</td>
<td>Positive (3 cells/52,000 cells)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>70.9 F</td>
<td>Chronic lymphocytic leukemia</td>
<td>Pain on Swallowing</td>
<td>Cyclosporine</td>
<td>Negative</td>
<td></td>
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</table>

CAEBV, chronic active Epstein-Barr virus infection; CBT, umbilical cord blood stem cell transplantation; GVHD, graft versus host disease; UR-BMT, unrelated donor-bone marrow transplantation; CMV, cytomegalovirus.

* C7-HRP tests, except for Case 3 where C10/C11 test was performed.

"Turned to be positive (1 cell/25,000 cells) 11 days after esophagogastroduodenoscopy"
(i.e., ganciclovir, foscarnet, and valganciclovir). The upper gastrointestinal tract was re-evaluated in 9 patients. CMV-related upper gastrointestinal lesions improved after antiviral treatment in 5 patients, improved partially in 2 patients, and did not improve in 2 patients.

**Discussion**

Our retrospective analysis of the patients with CMV...
Endoscopic images of CMV involvement in the stomach. Gastric lesions are shown as verrucous erosions (A, Case 3), exfoliated mucosa (B, Case 10), and redness (C, D, Case 1), in addition to erosions. In Case 1, longitudinal, slightly depressed lesions were visualized after indigo carmine spraying (D).

Endoscopic images of CMV involvement in the duodenum. Duodenal lesions are seen as ulcers (A, Case 5; B, Case 8), redness (C, Case 1), multiple erosions, single erosion, edema, even in the intact mucosa (D, Case 6).
infection in the upper gastrointestinal tract who were diagnosed at a single institution in Japan during a roughly 12-year period revealed CMV involvement in the esophagus (n = 3), stomach (n = 9), and duodenum (n = 6). In the esophagus, we observed mucosal alterations such as redness, erosions, and ulcers. Wang et al. reported the apparently largest series of patients with regard to CMV esophagitis [8]. They found 16 patients with histologically proven CMV infection in the esophagus and noted the following endoscopic features: multiple ulcers in 14 patients (87.5%), friable mucosa in 10 patients (62.5%), and polypoid, nodular surface in 1 patient (6.25%). Another report by Bonetti et al. included 9 patients with esophageal CMV lesions, and the authors reported ulcers in 7 (77.8%), erosions in three (33.3%), and thickened mucosal fold in one patient (11.1%) [2].

Representative features of CMV esophagitis have been known to be discrete, superficial ulcers of ovoid, elongated, or diamond-shaped configuration [10,11]. The intervening mucosa between ulcers generally appears to be intact and lacks obvious inflammation or edema. In our study, only Case 14 showed such typical morphology (Fig. 2C, D). The differential diagnoses of esophageal discrete ulcers include HIV infection, herpes simplex virus infection, and drug-induced esophagitis.

In our patient series, the gastroduodenal lesions showed various morphologic types, redness, edema, erosions, exfoliated mucosa, and even visually intact mucosa (Figs. 3, 4). An earlier report noted that gastroduodenal involvement in CMV infection has non-specific manifestations [2]. Endoscopic features of CMV infection in the stomach that have been reported range from patchy erythema to thickened mucosa, hypertrophy of the gastric folds, exudates, erosions, and ulcers [2,12]. The morphologies of reported CMV-related duodenal lesions include mucosal depigmentation [13], erosion [9], ulcers with or without fresh bleeding [14,15], and pseudotumor formations [16].

It is noteworthy that in our present investigation, the numbers of patients with CMV involvement in the stomach (9/14, 64.3%) and the duodenum (6/14, 42.9%) were greater than the number of patients with CMV involvement in the esophagus (3/14, 21.4%). This finding of a higher prevalence of gastric involvement (19/30, 63.3%) compared to the esophagus (9/30, 30.0%) was also noted by Bonetti et al. [2]. Consequently, we consider that for the precise evaluation of the gastroduodenal mucosa to detect CMV infection in at-risk patients, it is essential to perform an endoscopic examination and biopsy sampling from gastroduodenal lesions with any mucosal alterations or even intact gastroduodenal mucosa.

In this study, all patients had been taking one or more immunosuppressive agents such as cyclosporine, steroids, mycophenolic acid, tacrolimus, or methotrexate. In addition, 13 of the 14 patients had hematologic diseases and 12 underwent stem cell transplantation. Our present findings are in agreement with the well-known finding that the reactivation of CMV occurs more frequently in immunocompromised patients [17,18]. Other risk factors for gastrointestinal CMV infection are HIV infection, solid organ transplantation, malignant diseases, and chemotherapy. Nevertheless, physicians should keep in mind that CMV infection in the gastrointestinal tract also occurs in immunocompetent individuals [19].

CMV antigenemia testing is a rapid, quantifiable assay to detect CMV pp65 lower matrix phosphoprotein in peripheral blood polymorphonuclear leucocytes [20]. Generally, an antigenemia assay has a lower sensitivity in patients with localized CMV infection than in patients with systemic CMV infection. For example, the sensitivity of CMV antigenemia testing for diagnosing CMV viremia is reportedly 93.5% [21], while it ranges from 50% to 54% for gastrointestinal CMV involvement [3,22]. In the present study, 11 of the 14 patients (78.6%) were positive for CMV antigenemia testing before undergoing EGD. Of the remaining 3 patients, the test was positive in 2 patients at 4 days and 11 days after their EGD examination, respectively. In those 3 patients, CMV was undetectable by CMV antigenemia testing before EGD, probably because the CMV viral load within blood was small at that time.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Summary of the endoscopic features</th>
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<tbody>
<tr>
<td></td>
<td>Esophagus</td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Redness</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
</tr>
<tr>
<td>Erosion</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Exfoliated mucosa</td>
<td>0</td>
</tr>
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</table>

*One case was presented as verrucous erosions.
despite positive gastrointestinal CMV involvement. It is likely that the changes in the 2 patients’ CMV antigenemia testing to positive reflected an increase of the viral load within blood after their EGD examinations.

The relatively higher sensitivity (78.6%) for diagnosing gastrointestinal CMV disease shown in our study may have been obtained because the subjects of this study included 12 patients who underwent stem cell transplantation and had periodic CMV antigenemia testing. In addition, the hematologic diseases and/or the immunosuppressive treatments after stem cell transplantation might have predisposed the patients to CMV viremia. Finally, in this study, the false-negative rate of the CMV antigenemia assay before EGD was 21.4%. These results indicate that an EGD examination is still required to detect a CMV infection in the upper gastrointestinal tract, even in patients with a negative CMV antigenemia test result.

Several limitations of this study should be noted. First, not all patients with mucosal alterations in the upper gastrointestinal tract underwent biopsy examinations and immunostaining for CMV, and several patients with CMV infection might thus have been overlooked. Second, GVHD may affect the macroscopic appearance of the upper gastrointestinal tract. It was reported that various mucosal changes occur in patients with GVHD, such as redness, erosions, ulcers, and lusters [23]. The gastric exfoliated mucosa observed in Case 4 and Case 10 (Fig 3B) is one of the representative findings of GVHD, rather than CMV infection, although both of these patients showed no evidence of GVHD in a histological evaluation of biopsied samples. Physicians must therefore carefully differentiate CMV infection from GVHD and consider the possibility of the concurrence of both diseases.

In conclusion, we reviewed endoscopic and clinical features of 14 patients with CMV infection in the upper gastrointestinal tract. More than 90% of the patients had undergone stem cell transplantation. The CMV antigenemia assay before EGD was positive in less than 80% of the cases, suggesting that the examination cannot sufficiently exclude CMV infection in the upper gastrointestinal tract. Macroscopic features were not specific or even visually intact. Physicians must consider CMV infection when any mucosal alterations exist in the upper gastrointestinal tract of immunosuppressed patients.

References