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ORIGINAL ARTICLE

Cytomegalovirus disease in nonimmunocompromised, human immunodeficiency virus-negative adults with chronic kidney disease

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Background/Purpose(s): To identify the clinical characteristics of cytomegalovirus (CMV) disease in chronic kidney disease (CKD) patients.
Methods: Patients from two sources were reviewed: (1) a retrospective study of hospitalized patients admitted between January 1990 and February 2009 was performed at a tertiary hospital in Taiwan; (2) the English literature from 1990 to 2009 was reviewed for additional cases, and adults with CKD and histopathologically documented cytomegalovirus disease were included.
Results: Seven CKD patients from our hospital and seven from the literature were included. Nine (64.3%) patients were males, and the mean age was 66 years. Histopathologically proven CMV disease was present in the gastrointestinal (GI) tract of 13 (92.9%) and in the skin of one (7.1%)

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patient. GI symptoms included bleeding (78.6%), abdominal pain (35.7%), and diarrhea (28.6%).The most common comorbidities were diabetes mellitus (7, 50%) and hypertension (8, 57.1%). Thirteen patients had CMV GI disease. The endoscopic gross features of the GI tract lesions included single or multiple ulcers and a large polypoid or uneven surface mass. Of the seven cases with available data, a low body mass index (22.3 ± 1.3 kg/m^2) and hypoalbuminemia (25 ± 7.0 g/L) were noted. Twelve patients had received ganciclovir or valganciclovir therapy. Five (35.7%) patients died, and the death of two patients was directly related to bowel perforation caused by CMV colitis.

Conclusion: CMV disease may occur in CKD patients without the presence of overt immunodeficiency. The gastrointestinal tract is the most common site of involvement. Clinicians should be aware of this possibility in CKD patients who have GI symptoms.

Introduction

Cytomegalovirus (CMV) infections are common and worldwide. The seroprevalence rate of cytomegalovirus infections in adults was approximately 40—100% of the general population.[1] In immunocompromised individuals, such as those with human immunodeficiency virus (HIV) infection or transplant recipients, CMV can cause a broad spectrum of diseases, including meningoencephalitis, pneumonitis, hepatitis, retinitis and gastrointestinal (GI) ulcerations, and is associated with significant morbidity and mortality.[2,3] Although CMV infection is common in immunocompetent adults, most infected adults show no symptoms or occasionally show self-limited infectious mononucleosis, which warrants no antiviral treatment.[4]

The prevalence of chronic kidney disease (CKD) in the general population has been increasing in recent years.[5,6] Data from the Department of Health in Taiwan indicates that the prevalence of end-stage renal disease was 384/million population in 1990 and increased to 1630/million population in 2003.[7] This prevalence and incidence of CKD in Taiwan is relatively high compared with other countries.[5,7] end-stage renal disease patients may have a higher risk of encountering CMV because of frequent blood transfusion and contaminated dialysis equipment when receiving hemodialysis.[8] Despite reports of high seroprevalence of CMV infection in CKD patients (66—84%), CMV disease in this population has rarely been reported.[9,10] The aim of the present study is to determine the clinical presentation, laboratory findings, and associated comorbidities of CMV disease in CKD patients.

Materials and methods

Study patients were obtained from two sources. First, a retrospective study was performed at the National Cheng-Kung University Hospital, a medical center in southern Taiwan. Using the keyword "cytomegalovirus", the discharge database of patients admitted between January 1990 and February 2009 was searched. The inclusion criteria were as follows: adults (minimum age 18 years) with CKD, defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 for at least 3 months, irrespective of the cause,[8] and clinical presentations that were compatible with active CMV disease, as evidenced by either large viral inclusion bodies or positive findings of CMV immunostaining on histological studies of the biopsied tissues or resected sites. Immunocompromised patients, including those with HIV infections, congenital or acquired immunodeficiency syndrome, histories of allogeneic transplantation, malignancy, or the receipt of immunosuppressive therapy, were excluded. The medical records of patients with CKD and CMV disease were reviewed for the demographic information, underlying diseases, laboratory data, image findings, clinical courses, and outcomes. The body mass index (BMI) is defined as the body weight divided by the height^2.

The second source of patients we reviewed was from a literature search (1990—2009, computerized PubMed database). The keywords used were "cytomegalovirus" and "renal failure", "renal insufficiency", or "chronic kidney disease". The inclusion and exclusion criteria were the same as those described in the case selection from our hospital. The clinical information of the case reports and detailed descriptions were extracted from the publications.

Results

Overall, 166 adults were clinically diagnosed as having CMV infections at the study hospital between January 1990 and February 2009. A total of 110 immunocompromised patients were excluded, including 74 patients with organ transplantation and immunosuppressive therapy, 30 with HIV infection, and six with malignancy and chemotherapy within the past month. Of the 56 immunocompetent patients with CMV infection, only 11 had histologically documented CMV disease. Seven of these 11 patients had CKD and were included in the study. An additional seven patients with nonimmunocompromised CKD and active CMV disease were identified in the English literature and eligible for this analysis (Table 1).[9—13]

The clinical characteristics of the 14 patients with CKD and active CMV infection are summarized in Tables 1 and 2. Nine (64.3%) patients were males. The mean $\pm$ standard deviation age was 66.1 ± 9.9 years, with 8 (57.1%) patients older than 70 years. Nine (64.3%) patients had been receiving regular hemodialysis. Other than CKD, the common comorbidities were hypertension (8, 57.1%) and diabetes mellitus (7, 50.0%). Complete blood cell counts were available for 10 patients who presented with CMV disease. Mild leukocytosis (mean 11.56×10^9 cells/L) and anemia (mean hemoglobin concentration 92 g/L) were noted.

Table 1 Clinical characteristics of 14 chronic kidney disease patients with cytomegalovirus disease

Number	Age (y)	Sex	Transfusion	Involved site	Chief complaints	Gross presentation	Albumin, g/L	Antiviral therapy	Outcome	Reference
1	74	Male	ND	Esophagus	Dysphagia	Upper GI endoscopy: several yellow patches with surrounding ulcer over the lower third of the esophagus	30	Yes	Survived	
2	76	Male	ND	Duodenum	GI bleeding	Surgical finding: large, deep invading duodenal ulcer, 20 × 20 mm in size, with perforation	20	Yes	Died	
3	54	Male	ND	Ileum	GI bleeding	Laparotomy: edematous ileum with congested, dusty serosa and creeping mesenteric fat	ND	Yes	Survived	12
4	75	Female	Yes	Colon	GI bleeding	Colonoscopy: uneven surface tumor with bleeding	25	Yes	Survived	
5	75	Male	Yes	Colon	GI bleeding	Colonoscopy: multiple shallow ulcers	25	Yes	Survived	
6	66	Female	No	Colon	GI bleeding	Colonoscopy: broad base ulcers with edematous surrounding folds	20	Yes	Survived	
7	77	Male	No	Colon	GI bleeding	Right hemicolectomy: uneven surface	21	Yes	Died	
8	74	Male	Yes	Colon	GI bleeding	Colonoscopy: diffuse and superficial ulcerations in the colonic mucosa, with poor inflammatory reactions	36	Yes	Survived	11
9	74	Female	ND	Colon	Abdominal pain, GI bleeding	Colonoscopy: pancolitis	ND	Yes	Died	13
10	71	Female	ND	Colon	Diarrhea	Colonoscopy: multiple colonic ulcers	ND	Yes	Survived	13
11	59	Female	Yes	Colon	GI bleeding	Colonoscopy: severely inflamed mucosa with multiple ulcerations	33.5	ND	Survived	11
12	57	Male	ND	Colon	GI bleeding	Colonoscopy: a large polypoid mass	ND	Yes	Survived	9
13	47	Male	ND	Anus	Anal pain, GI bleeding	Surgical finding: necrotic area over the anus	15	Yes	Died	
14	58	Male	Yes	Skin	Skin rash	Scaly erythematous macules and papules over the buttocks and lower limbs	ND	No	Died	10

GI = gastrointestinal; ND = no data.

Table 2 Summary of the clinical characteristics of 14 chronic kidney disease patients with cytomegalovirus disease

Characteristics	Mean ± standard deviation or *n* (%)
Male sex	9 (64.3)
Age, y	66.1 ± 9.9
Hemodialysis	9 (64.3)
Comorbidity	
Hypertension	8 (57.1)
Diabetes mellitus	7 (50.0)
Cerebrovascular accident	2 (14.3)
Liver cirrhosis	1 (7.1)
Chronic obstructive pulmonary disease	1 (7.1)
Congestive heart failure	1 (7.1)
Clinical presentations	
Fever	5 (35.7)
Gastrointestinal discomfort	14 (100.0)
Gastrointestinal bleeding	11 (78.6)
Abdominal pain	5 (35.7)
Diarrhea	4 (28.6)
Skin rash	1 (7.1)
Organ involvement	
Gastrointestinal tract	13 (92.9)
Skin	1 (7.1)
Ganciclovir or valganciclovir therapy	12 (85.7)
Mortality	5 (35.7)

The average body weight of the seven patients in the study hospital was 60.4 ± 9.5 kg, with a mean BMI of 22.3 ± 1.3 kg/m^2. The mean serum albumin was 25 ± 7.0 g/L. Cytomegalovirus antigenemia was assessed in five patients and found in one (8 cells/2 × 10^5 leukocytes). Serum CMV IgM was detected in one patient.

All but one patient had GI involvement that was caused by CMV infection. The involved sites ranged from the upper GI tract, including the esophagus and duodenum, to the lower GI tract, including the ileum, colon and anus. The gross features of the upper tract lesions were mainly single or multiple ulcers that could be easily mistaken for esophageal candidiasis (Fig. 1A). Colon involvement included multiple ulcers and large polypoid or irregular mass (Fig. 1B and C). All of the patients with CMV GI disease had GI symptoms, including bleeding (11, 78.6%), abdominal pain (5, 35.7%), and diarrhea (4, 28.6%).

The comorbidity of other organ systems with the GI tract manifestations, including Henoch–Schonlein purpura (in 1 case), was identified in a limited number of patients.[12] The affected patients seldom had fever. The only case of CMV disease involving a body site other than the GI tract was a patient with cutaneous CMV disease.[10] However, the patient died of upper GI bleeding.

Twelve patients had received intravenous ganciclovir or oral valganciclovir therapy for an average of 23 ± 14 days (range, 7–42 days); one patient did not receive any antiviral therapy, and one had no available data. Of five (35.7%) fatal cases, four patients had received antiviral therapy, and one had experienced recurrent CMV colitis after 3 weeks of ganciclovir therapy. Two of the five fatalities died of bowel perforations that were related to CMV colitis.

Discussion

With the increased prevalence of CKD,[6] clinicians should be familiar with the clinical manifestations of CMV infection in these patients. Although there is a high seroprevalence of CMV infection in CKD patients, there have been only case reports regarding CMV disease in these patients.[9–13] In a meta-analysis of CMV colitis in immunocompetent hosts, the most common concomitant condition was renal failure.[14] The pathogenesis underlying the association between CKD and CMV GI disease is unknown.

The sites of CMV disease in the digestive systems of CKD patients ranged from the esophagus to the anus. A clinical clue of CMV GI disease is GI bleeding, but the affected patients may have other manifestations, such as diarrhea or abdominal pain. In contrast to other immunocompetent patients, fever or constitutional symptoms were occasionally noted in the CKD patients with CMV GI disease.[4] The most common endoscopic finding of CMV GI disease was multiple ulcers. However, the variable patterns of CMV GI disease may be mistaken for candidiasis, polyps, or even malignancy. Therefore, the final diagnosis relied on the histological findings, including the presence of CMV inclusion bodies and the immunohistochemistry or hybridization results. Other diagnostic tests, such as CMV antigenemia or serum CMV IgM, may not be useful. Quantifying human CMV DNA is a novel method

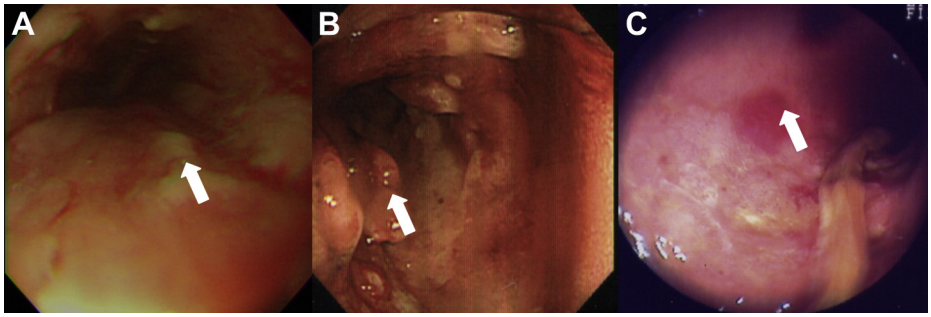

Figure 1. Gross presentations of the gastrointestinal tract in three patients from the study hospital; patients had histopathologically proven cytomegalovirus disease. (A) Upper endoscopy showed several yellow patches (arrow) with surrounding ulcers over the lower third of the esophagus (Case 1). Colonoscopy showed (B) uneven surface tumors (arrows) with bleeding (Case 3) or (C) broad base ulcers with edematous surrounding folds (Case 7).

of monitoring immunocompromised patients to identify those who require preemptive therapy.[15,16] However, assigning the relevant GI symptoms/signs to CMV infection remains a challenge. Therefore, diagnostic endoscopy and the biopsy of suspicious intestinal lesions are warranted.

The most common organ that was affected by CMV infection in our CKD patients was the digestive system. This result was different from the preferred organs in immunocompromised populations, such as HIV patients or transplant recipients, in whom CMV infection often causes a broad spectrum of diseases, such as meningoencephalitis, pneumonitis, hepatitis, and retinitis.[2,3] This difference is potentially related to a selection bias in our study because the clinical manifestations in organ systems other than the GI tract affected by CMV infection might be obscured or nonspecific, and the infected tissues are not easily available for histopathological or virological studies.

In our study, the most common comorbidities were diabetes mellitus and hypertension, which were also major comorbidities of CKD in the general population.[5] CKD patients with CMV infection tended to be older (age >70 years) and male sex compared with the general population of CKD patients.[5,6] In a meta-analysis of the outcome of CMV colitis in immunocompetent hosts, there was a higher mortality rate among males over age 55 and in patients with renal failure or diabetes mellitus,[14] which agrees with our study result that more than one-third of CKD cases with concomitant CMV infection were fatal.

Because our CKD patients with CMV infection had a low BMI and serum albumin levels, a cohort of 24 malnourished hemodialysis patients[17] with a low mean BMI (21.1 kg/m^2) and serum albumin levels (mean 36 g/L) was selected for comparison. The common underlying illness was similar in both groups (i.e., diabetes mellitus and hypertension). However, the average age of the malnourished group was younger than that of our CKD patients with CMV disease (mean, 60.6 vs. 66.1 years, respectively), which was in accordance with previous studies that showed that older CKD patients may be more vulnerable to CMV disease.[18,19]

There were several limitations in our study. First, the diagnosis of CMV infection in our study relied on the histology from biopsies or surgical resections. There may be some selection bias because enteroscopy is the most readily available and safe biopsy tool. Second, severe cases may prompt attending physicians to investigate the causes and report the results. Therefore, the morbidity and mortality may be overestimated. Third, this is a retrospective study with a limited number of cases; therefore, it is difficult to estimate the impact of CMV disease in the CKD patients. However, our results should bring CMV to the attention of clinicians, who should perform early diagnostic and therapeutic interventions.

In conclusion, CMV disease may occur in CKD patients without the presence of overt immunodeficiency. The GI tract is the most common site of involvement. Clinicians should be aware of this possibility in CKD patients who have GI symptoms.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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