Annals of Hematology (2018) 97:877–883
https://doi.org/10.1007/s00277-018-3241-9

ORIGINAL ARTICLE

Cecum ulcer is a reliable endoscopic finding in cytomegalovirus colitis concomitant with graft-versus-host disease after allogeneic hematopoietic stem cell transplantation

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Received: 3 October 2017 / Accepted: 5 January 2018 / Published online: 16 January 2018

Abstract

Although graft-versus-host disease (GVHD) is the major complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), cytomegalovirus (CMV) reactivation also occurs in patients after allo-HSCT and these conditions often clinically overlap. The aim of this study was to determine reliable endoscopic findings of CMV colitis in patients with gastrointestinal graft-versus-host-disease (GI-GVHD). Patients after allo-HSCT who were histologically confirmed to have GI-GVHD with or without CMV colitis and patients with an immunosuppressive condition were retrospectively analyzed. We divided the patients into three groups: GI-GVHD with CMV colitis (group A), GI-GVHD without CMV colitis (group B), and CMV colitis without undergoing allo-HSCT (group C). From medical records, the involved colorectal areas and endoscopic findings according to the groups were compared. A total of 70 patients were divided into three groups (group A: $n = 19$, group B: $n = 28$, group C: $n = 23$). Mucosal injuries in groups A and C frequently occurred in the cecum including ileocecal valves. On the other hand, there were no abnormal lesions on ileocecal valves in group B. Furthermore, ulcer lesions were more frequently observed in groups A and C than in group B ($p < 0.001$). The sensitivity and specificity of mucosal injuries in the cecum for prediction of CMV colitis were 89.5 and 76.5%, respectively, and mucosal injuries in the cecum were more reliable findings than CMV antigenemia. Ulcer lesions in the cecum are reliable endoscopic findings for CMV colitis in patients with GI-GVHD after allo-HSCT.

Keywords Cytomegalovirus · Infection · Graft-versus-host-disease · GVHD · CMV

Introduction

Graft-versus-host disease (GVHD) is one of the most common complications of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is also a cause of morbidity and mortality [1]. The gastrointestinal (GI) tract is a common target organ of GVHD [2]. On the other hand, cytomegalovirus (CMV) reactivation often occurs in immunocompromised patients including patients who have undergone allo-HSCT, and symptoms of CMV disease of the GI tract are similar to those of GI-GVHD such as diarrhea, nausea, and abdominal pain [3, 4]. It is difficult to distinguish GI-GVHD and CMV disease of the GI tract without histological confirmation, and these two conditions sometimes occur concomitantly in the GI tract [5].

Background

There have been some reports on endoscopic findings of GI-GVHD and those of CMV GI disease, and it was shown that

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the incidence rates of ulcers ranged from 66 to 72.5% in CMV enterocolitis and from 10 to 33.3% in GI-GVHD [2, 6–9]. However, the endoscopic characteristics of GI-GVHD concomitant with CMV disease have not been clarified [4]. Actually, histological diagnosis is a gold standard for both GVHD and CMV infection, but the time required for obtaining a histological diagnosis leads to a delay in treatment and serious consequences. Not only taking GI specimens for histological diagnosis but also endoscopic findings would be helpful for rapid treatment of CMV GI disease. In this study, we therefore compared endoscopic findings of GI-GVHD, CMV GI disease, and the two diseases occurring concomitantly to clarify endoscopic features according to each condition.

Patients and methods

Patients

Patients after allo-HSCT who were histologically confirmed to have GI-GVHD and/or CMV enterocolitis from a GI biopsy and patients with an immunosuppressive condition who were histologically confirmed to have CMV colitis during the period from January 2008 to December 2016 were enrolled in this study. From their medical records, the following parameters were analyzed: sex, age, underlying diseases, treatment, medication, and abdominal symptoms at the time of diagnosis; involved sites of colorectal regions; endoscopic findings; and histopathological grade of GVHD [10]. The clinical grade was determined by using the Glucksberg grading system with addition of the Keystone criteria (stage 1: presence of diarrhea > 30 ml/kg or 500 ml/day or persistent nausea and vomiting with positive GI-GVHD histological findings, stage 2: diarrhea > 60 ml/kg or > 1000 ml/day, stage 3: diarrhea > 90 ml/kg or > 1500 ml/day, stage 4: diarrhea > 90 ml/kg or > 2000 ml/day or the presence of severe abdominal pain with or without ileus) [11]. In addition to these criteria, the overall grading of acute GVHD also included the clinical criteria for liver and skin acute GVHD [11].

The patients were divided into the following three groups: GI-GVHD with CMV colitis (group A), GI-GVHD without CMV colitis (group B), and CMV colitis without any transplantation (group C). All patients provided written informed consent or opted out, and permission to study patient records was approved by the Hokkaido University Hospital Review Board (016-101, 016-103).

Endoscopic diagnosis

Within 7 days after symptoms such as diarrhea and abdominal pain appeared, total colonoscopy from the rectum to terminal ileum was performed using CF-H260, PCF-H260AZI, or PCF-H260AI (Olympus Medical Systems, Tokyo, Japan). In cases with strong pain, limitations of preparation, or difficulty in total colonoscopy, endoscopists decided to stop the procedures.

Concerning endoscopic findings, an ulcer was defined as a well-defined break in the colonic mucosa of more than 3 mm, and a punched-out ulcer was defined as a well-demarcated ulcer with a sharply defined wall and a smooth base [12]. Erosion was defined as a mucosal break of less than 3 mm. Erythema was defined as focal or spotted redness of the colonic mucosa without erosion. Edema was defined as an indistinct vascular pattern with mucosal thickening without redness (Fig. 1). We divided the colon into six parts: cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

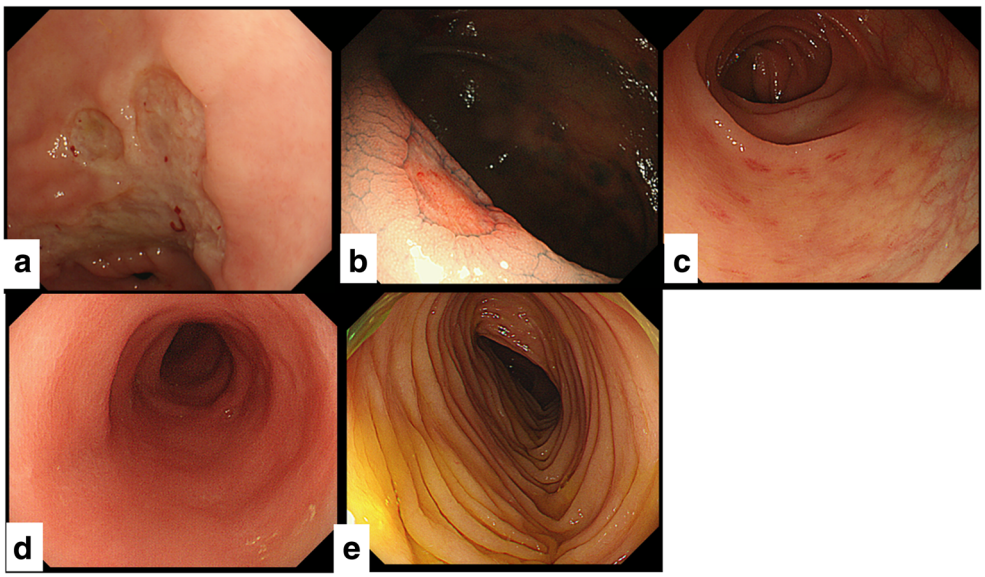

Fig. 1 Endoscopic findings. **a** Ulcer. Well-defined break in the colonic mucosa of more than 3 mm. **b** Punched-out ulcer. A well-demarcated ulcer with a sharply defined wall and a smooth base. **c** Erosion. Mucosal break of less than 3 mm. **d** Erythema. Focal or spotted redness of the colonic mucosa without erosion. **e** Edema. Indistinct vascular pattern with mucosal thickness without redness

Histological diagnosis of GI-GVHD and CMV colitis

Biopsy specimens were taken from severely involved areas. If there were no abnormal findings, biopsy specimens were randomly obtained from endoscopically normal-appearing areas.

GI-GVHD was defined as detection of an apoptotic body from the biopsy specimens by the pathologist [13]. Histopathological grades of GVHD were based on the following criteria: isolated apoptotic epithelial cells without crypt loss (grade 1), loss of isolated crypts without loss of contiguous crypts (grade 2), loss of two or more contiguous crypts (grade 3), and extensive crypt loss with mucosal denudation (grade 4) [10]. CMV enterocolitis was defined as evidence of CMV by immunohistochemical staining with a monoclonal antibody against CMV from biopsy specimens [14]. GI-GVHD concomitant with CMV enterocolitis was defined as evidence both of an apoptotic body and CMV in the patient.

CMV antigenemia

CMV reactivation was monitored by the CMV antigenemia assay using C7-HRP (Teijin Inc., Tokyo, Japan) [15]. One CMV antigen-positive cell/50,000 leukocytes was defined as positive for CMV infection.

Statistical analysis

IBM SPSS Statistics 24 (Japan IBM Inc., Tokyo, Japan) for Windows was used for data analysis. Summarized numerical data are expressed as medians with standard deviation. Categorical data were compared in the groups using Tukey's test, the Mann-Whitney test, and Fisher's exact test. A p value of < 0.05 in each analysis was considered statistically significant.

Results

Characteristics of patients

Among 338 patients who had received allo-HSCT during the study period, 47 patients were diagnosed with GI-GVHD and 19 patients were diagnosed with CMV enterocolitis concomitant with GI-GVHD (group A). Twenty-eight patients had no histopathological evidence of CMV infection (group B). Furthermore, 23 immunocompromised patients were diagnosed with CMV enterocolitis during the same period (group C). The total of 70 patients were divided into three groups (group A: $n = 19$, group B: $n = 28$, group C: $n = 23$). Clinical characteristics of the patients are shown in Table 1. Before colonoscopy, five patients in group A and four patients in group B received medication for CMV because of high levels of CMV antigenemia.

Table 2 shows abdominal symptoms and results for CMV antigenemia. Diarrhea and abdominal pain in groups A and B were more frequent than those in group C. On the other hand, hematochezia frequently occurred in patients with CMV enterocolitis (groups A and C). CMV antigenemia was positive in 63.2% of the patients in group A and in 17.9% of the patients in group B.

Comparison of severities of GI-GVHD with and without CMV colitis

Clinical and histological grades of severities of GI-GVHD with and without CMV enterocolitis are shown in Table 3. There were no significant differences in clinical and histological severity grades between group A and group B.

Table 1 Characteristics of patients. Average age in group C was higher than that in other groups. Except for age, there were no significant differences in the three groups

	Group A ($N = 19$)	Group B ($N = 28$)	Group C ($N = 23$)	p value
Age, years ± SD	48.4 ± 13.8	45.0 ± 13.9	61.7 ± 14.2	< 0.001
Gender, M/F	9/10	15/13	6/17	0.128
Underlying disease	Leukemia 9	Leukemia 15	Autoimmune disease 15	
	Lymphoma 2	Lymphoma 7	Blood disease 3	
	MDS 3	MDS 3	Others 5	
	Others 2	Others 3		
Stem cell sources	BMT 9	BMT 14	Not applicable	0.572
	PBSCT 8	PBSCT 5		
	CBSCT 2	CBSCT 9		
Use of drugs	Corticosteroids 13	Corticosteroids 4	Corticosteroids 16	
	FK 506 12	FK 506 16	FK 506 1	
¶	Others† 4	Others† 8	Others† 7	

MDS myelodysplastic syndrome, *BMT* bone marrow transplantation, *PBSCT* peripheral blood stem cell transplantation, | *CBSCT* cord blood stem cell transplantation

¶ Including methotrexate, cyclosporine, and mycophenolate mofetil

Table 2 Abdominal symptoms and cytomegalovirus antigenemia. Diarrhea was significantly more frequent in groups A and B, and hematochezia was significantly more frequent in groups A and C. The positive rates of CMV antigenemia in groups A and C were higher than that in group B

	Group A ($N = 19$)	Group B ($N = 28$)	Group C ($N = 23$)	p value
Symptoms (%)				
Diarrhea	100 (19/19)	92.3 (26/28)	39.1 (9/23)	< 0.001
Abdominal pain	47.4 (9/19)	34.6 (9/28)	17.4 (4/23)	0.117
Hematochezia	26.3 (5/19)	3.8 (1/28)	43.5 (10/23)	0.002
Antigenemia (%) (C7-HRP)				
Positive	63.2 (12/19)	17.9 (5/28)	39.1 (9/23)	< 0.001
Negative	36.8 (7/19)	82.1 (23/28)	26.1 (6/23)	
Not done	0.0 (0/19)	0.0 (0/28)	34.8 (8/23)	
Number of positive cells	6.5	1	16	
Median (range)/50,000	(1–50)	(1–3)	(1–47)	

Endoscopic findings of colonoscopy

Observation of the cecum was possible in 71.4% of the patients, and the terminal ileum was reached in 67.1% of the patients (intubation of the terminal ileum was not possible in three patients because of stenosis and strong pain). Endoscopic findings in each group are shown in Table 4. Ulcer lesions, especially punched-out lesions, were more frequently observed in the patients with CMV enterocolitis (groups A and C), and edema and erythema without mucosal defects were rare in group C.

Endoscopic findings according to location are shown in Table 5. Although ulcer and erosion were frequently observed in the cecum including ileocecal valves in patients in groups A and C, there were no abnormal lesions on ileocecal valves in patients in group B. Most of the mucosal injuries in group C were located in the cecum. On the other hand, mucosal injuries without mucosal defects were significant endoscopic findings in groups A and B. Furthermore, group A showed characteristic endoscopic findings of both groups B and C.

Table 3 Clinical and histological severities of graft-versus-host disease. There were no significant differences in clinical and histological GVHD grades between group A and group B

		Group A ($N = 19$)	Group B ($N = 28$)	p value
Clinical grade, *n*	1	0	0	0.186
	2	8	17	
	3	7	8	
	4	4	3	
GI-GVHD stage, *n*	1	10	16	0.542
	2	2	6	
	3	4	4	
	4	3	2	
Histopathological grade, *n*	1	5	7	0.648
	2	2	5	
	3	5	10	
	4	7	6	

GI-GVHD gastrointestinal graft-versus-host disease

Sensitivity and specificity of predictive factors of concomitant CMV enterocolitis

Predictive factors of concomitant CMV colitis in patients with GI-GVHD are shown in Table 6. The sensitivities of CMV antigenemia and cecum lesions for prediction of CMV colitis were 63.2 and 89.5%, respectively, and the specificities were 82.1 and 76.5%, respectively. Abnormal lesions on the ileocecal valve had high specificity.

Treatment

Antiviral therapy was performed in 19 patients in group A and in 18 patients in group C.

Discussion

GI-GVHD is a major complication of allo-HSCT, and CMV disease sometimes complicates the clinical course of those patients [5, 16]. If there is a suspicion of CMV disease, antiviral therapy should be started as soon as possible [17]. In fact, it was reported that the incidence of CMV organ disease was 15 to 25% in patients undergoing allo-HSCT [18]. Liu et al. reported that 9% of GI-GVHD patients also had CMV GI disease, and Bhutani et al. reported that 12.3% of GI-GHVD patients were complicated with GI-CMV [18]. Our data showed that 40.4% of patients with GI-GVHD were complicated with CMV enterocolitis, a higher incidence than those in previous reports. The reason for this difference might be the rates of total colonoscopy. In the previous study, total colonoscopy was performed in 56.4% of the patients, whereas it was performed in 71.4% of our patients [5]. Since CMV colitis often occurs in the right-side colon, diagnosis of CMV colitis might not be possible by uncompleted colonoscopy.

Table 4 Endoscopic findings of mucosal injuries

	Group A ($N = 19$)	Group B ($N = 28$)	Group C ($N = 23$)	p value
Ulcer, % (n)	52.6 (10/19)	10.7 (3/28)	91.3 (21/23)	< 0.001†
Punched out, % (n)	36.8 (7/19)	0.0 (0/28)	34.8 (8/23)	
Erosion, % (n)	26.3 (5/19)	17.9 (5/28)	8.7 (2/23)	0.328
Aphtha, % (n)	5.3 (1/19)	10.7 (3/28)	13.0 (3/23)	0.705
Redness, % (n)	36.8 (7/19)	60.7 (17/28)	4.3 (1/23)	< 0.001‡
Edema, % (n)	52.6 (10/19)	57.1 (16/28)	8.7 (2/23)	< 0.001‡
Normal, % (n)	0.0 (0/19)	7.1 (2/28)	0.0 (0/23)	0.221

† Groups A and C vs group B

‡ Groups A and B vs group C

It has been reported that there are various symptoms related to CMV enterocolitis including abdominal pain, anorexia, nausea, vomiting, watery stool, hematochezia, and melena [5, 19–21]. Liu et al. reported that the rate of diarrhea in CMV colitis patients with acute GI-GVHD was higher than that in CMV colitis patients without acute GI-GVHD, whereas the rates of hematochezia and melena were similar in the two groups [5]. Our study showed that complication of CMV colitis with GI-GVHD tended to increase the rate of hematochezia. Some studies showed that ulcer lesions are induced by ischemia caused by CMV infection of vascular endothelial cells, and a CMV ulcer is therefore more likely to be a cause of hematochezia [22–24].

Our study showed that endoscopic findings in group A were similar to those in group C and that the rate of ulcers was higher than the rates of erythema and edema. On the other hand, the common endoscopic findings in group B were erythema and edema without ulcer lesions. Furthermore, the major involved site of mucosal injury in group A and group C was the cecum. CMV colitis frequently occurs in the cecum,

Table 5 Endoscopic findings according to the location

	Group A ($N = 19$)	Group B ($N = 28$)	Group C ($N = 23$)	p value
Terminal ileum, % (n)	41.1 (7/17)	50.0 (8/16)	28.6 (4/14)	0.507
Ulcer and erosion, % (n)	11.8 (2/17)	12.5 (2/16)	28.6 (4/14)	0.514
Others†, % (n)	29.4 (5/17)	37.5 (6/16)	0 (0/14)	0.037‡
Cecum, % (n)	89.5 (17/19)	23.5 (4/17)	78.6 (11/14)	< 0.001§
Ileocecal valve, % (n)	63.2 (12/19)	0.0 (0/17)	71.4 (10/14)	< 0.001§
Ulcer and erosion, % (n)	63.2 (12/19)	5.9 (1/17)	71.4(10/14)	< 0.001§
Others, % (n)	57.8 (11/19)	23.5 (4/17)	21.4 (3/14)	0.001‖
Ascending colon, % (n)	68.4 (13/19)	52.9 (9/17)	21.4 (3/14)	0.026‡
Ulcer and erosion, % (n)	31.6 (6/19)	5.9 (1/17)	14.3 (2/14)	0.015‖
Others, % (n)	63.2 (12/19)	47.1 (8/17)	14.3 (2/14)	0.002‡
Transverse colon, % (n)	68.4 (13/19)	60.0 (12/20)	43.8 (7/16)	0.343
Ulcer and erosion, % (n)	26.3 (5/19)	5.0 (1/20)	31.3 (5/16)	0.069
Others, % (n)	57.8 (11/19)	50.0 (10/20)	12.5 (2/16)	0.003‡
Descending colon, % (n)	63.2 (12/19)	59.1 (13/22)	22.2 (4/18)	0.021‡
Ulcer and erosion, % (n)	26.3 (5/19)	9.1 (2/22)	16.7 (3/18)	0.179
Others, % (n)	57.8 (11/19)	50.0 (11/22)	5.6 (1/18)	0.001‡
Sigmoid colon, % (n)	84.2 (16/19)	75.0 (21/28)	26.1 (6/23)	< 0.001‡
Ulcer and erosion, % (n)	36.8 (7/19)	14.3 (4/28)	26.1 (6/23)	0.203
Others, % (n)	68.4 (13/19)	67.9 (19/28)	0 (0/23)	< 0.001‡
Rectum, % (n)	68.4 (13/19)	60.7 (17/28)	39.1 (9/23)	0.133
Ulcer and erosion, % (n)	26.3 (5/19)	10.7 (3/28)	43.5 (10/23)	0.029§
Others, % (n)	52.6 (10/19)	53.6 (10/28)	8.7 (2/23)	0.002‡

† Including redness, edema, and aphtha

‡ Groups A and B vs group C

§ Groups A and C vs group B

‖ Group A vs groups B and C

Table 6 Diagnostic accuracy of clinical and endoscopic findings

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Mucosal injury of cecum	89.5 (75.3–96.6)	76.5 (60.6–84.5)	81.0 (68.1–87.4)	86.7 (68.7–95.7)
Ileocecal valve	63.2 (50.9–63.2)	100 (86.3–100)	100 (80.6–100)	70.8 (61.1–70.8)
Ulcer	52.6 (37.1–62.3)	89.3 (78.7–95.9)	76.9 (54.2–91.1)	73.5 (64.8–79.0)
Positive for CMV antigenemia	63.2 (46.5–75.5)	82.1 (70.9–90.5)	70.6 (52.0–84.4)	76.7 (66.1–84.5)
Hematochezia	26.3 (14.6–30.6)	96.4 (88.5–99.3)	83.3 (46.2–97.0)	65.9 (60.4–67.8)

PPV positive predictive value, *NPV* negative predictive value, *CMV* cytomegalovirus

especially in the ileocecal valves [25]. Liu et al. found in their retrospective study that diagnostic sensitivity using colonic biopsy for CMV infection was highest from the cecum [5]. In our study, ulcers on ileocecal valves were observed in 63.2% of the patients in group A and in 71.4% of the patients in group C, but there were no ulcers in patients in group B. These results suggest that an ulcer in the cecum, especially on the ileocecal valve, is a specific endoscopic finding of CMV colitis in patients with GVHD.

Although the CMV antigenemia assay is noninvasive and useful for diagnosis of CMV disease, its low sensitivity for CMV GI disease is a problem [13, 26, 27]. In the patients with GI-GVHD in our study, sensitivity and specificity of CMV antigenemia were 63.2 and 82.1%, respectively, and they were similar to those in previous studies [13, 26, 27]. Since severe CMV infection is a cause of morbidity and mortality, treatment should be started early as soon as possible [17]. Although total colonoscopy is a slightly invasive procedure, our data showed that ulcers in the cecum were more reliable findings than CMV antigenemia. Many studies have shown that pp65 antigenemia is inferior to PCR in terms of sensitivity [28].

For diagnosis of GVHD, Ip et al. [29] and Ross et al. [30] reported a high diagnostic accuracy of biopsies in the left colon. On the other hand, Kreisel et al. reported that approximately 20% of GVHD patients showed an abnormality only in the terminal ileum [31]. Our results showed that mucosal injuries in patients with GVHD tended to be present continuously across several areas, and the ratios of patients of having an abnormality across more than 3 regions were 63.2% in group A, 54.4% in group B, and 11.1% in group C. Thus, typical GI-GVHD often occurs diffusely.

There are often differences between endoscopic diagnosis and histological diagnosis of GVHD [31]. Only three of six patients who were histological grade 4 had ulcers, and severe diffuse redness and edema with easy bleeding indicating denudation of the mucosa were observed in the other patients. Unfortunately, total colonoscopy could not be performed in any of the patients because of severe pain.

Our study has several limitations. The study was a retrospective study with a small sample size and lacked a defined protocol for the timing of endoscopic examination and biopsy. Furthermore, other infectious diseases of the GI tract were not excluded.

In conclusion, an ulcer lesion in the cecum is the most reliable endoscopic finding for CMV colitis in patients with GI-GVHD after allo-HSCT. Therefore, total colonoscopy and biopsy are recommended for early intervention for CMV enterocolitis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Hokkaido University Hospital Review Board (016-101, 016-103).

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