【 CASE REPORT 】

A Rare Case of Ulcerative Colitis with Severe *Pneumocystis jirovecii* Pneumonia and Cytomegalovirus Colitis: A Case Report and Literature Review

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Abstract:

Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) colitis are opportunistic infections that occur during immunosuppressive treatments for ulcerative colitis (UC). The prognosis of PJP and CMV colitis is very poor. We herein report a rare case of a 74-year-old UC patient with PJP and CMV colitis that was successfully treated with intensive therapy. PJP progresses rapidly, so the timing and choice of treatment are critical. Furthermore, a literature review of similar cases suggested that prophylactic therapy for opportunistic infections might be important, especially in the elderly. This case will serve as a reference for successful treatment in future cases.

Key words: *Pneumocystis jirovecii* pneumonia, ulcerative colitis, cytomegalovirus colitis, immunosuppressive agent, prophylactic therapy

Introduction

In recent years, advances in medicine have led to an increase in the use of immunosuppressive agents; this enables better management of even the severe stages of ulcerative colitis (UC). However, immunosuppressive agents increase the risk of opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV) infection (1-3).

PJP occurs mainly in patients with human immunodeficiency virus (HIV); in addition, it occurs in patients with UC treated with immunosuppressive agents (4-14). The incidence of PJP is not high; however, the prognosis is very poor (15). CMV infection is often associated with CMV colitis in patients with UC, making UC treatment difficult (16-18).

We herein report a rare case of UC with PJP and CMV colitis that was successfully treated with intensive therapy. The increased use of immunosuppressive agents is expected to increase the number of opportunistic infections, and we believe this report will be valuable for future reference.

Case Report

A 74-year-old man with no history was admitted to a previous hospital because of diarrhea and bloody stool; he underwent total colonoscopy and was diagnosed with UC (Fig. 1A-C). He was treated with the oral administration of 5-aminosalicylic acid and prednisolone (40 mg/day, 0.5 mg/kg) for 2 weeks; however, the gastrointestinal symptoms did not improve. The dose of prednisolone was increased (80 mg/day, 1.0 mg/kg), and the diarrhea and bloody stool gradually alleviated with tapering at 5 mg/week. Two weeks later, he had abdominal pain and bloody stool again and underwent total colonoscopy, showing punched-out ulcers in the entire colon (Fig. 1D, E). In addition, he had a high fever and dyspnea.

Chest radiography and computed tomography showed wide-range consolidations in both lobes as well as ground-

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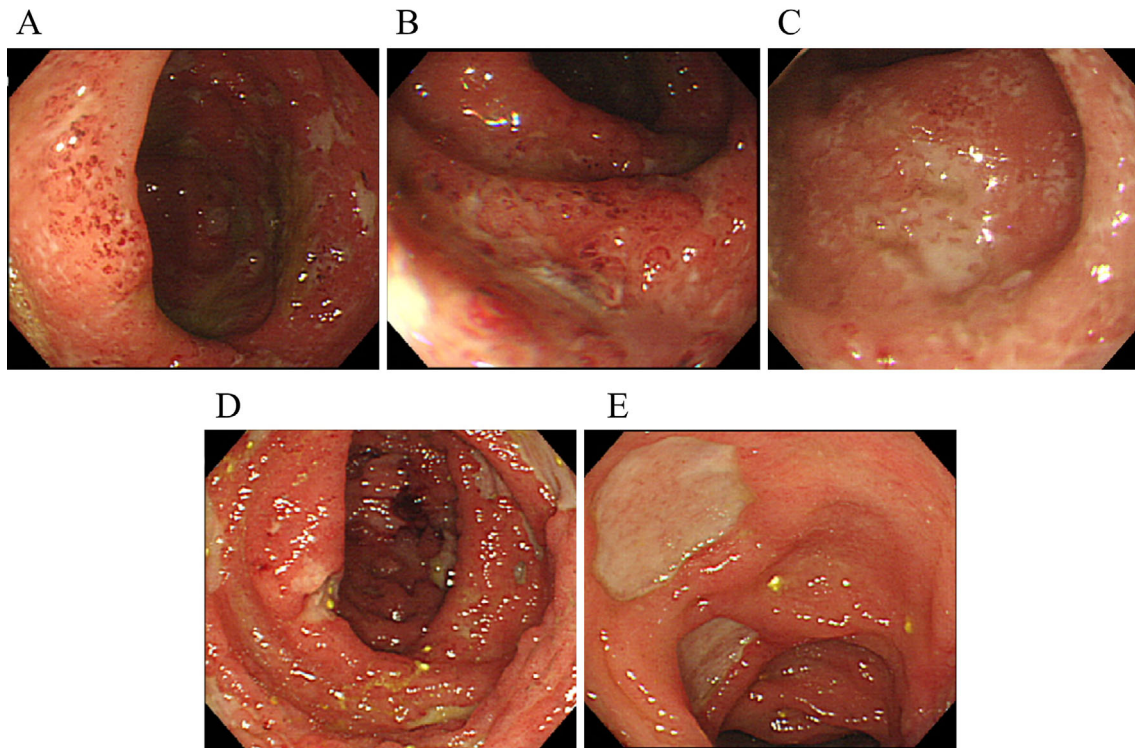
Figure 1. Total colonoscopy. Total colonoscopy was performed during the first and second procedure. (A) Ascending colon, (B) transverse colon, and (C) rectum, showing mucosal ulceration, mucosal erythema, and abscess, during the first colonoscopy. (D) Ascending colon and (E) rectum, showing punched-out ulcers, during the second colonoscopy.
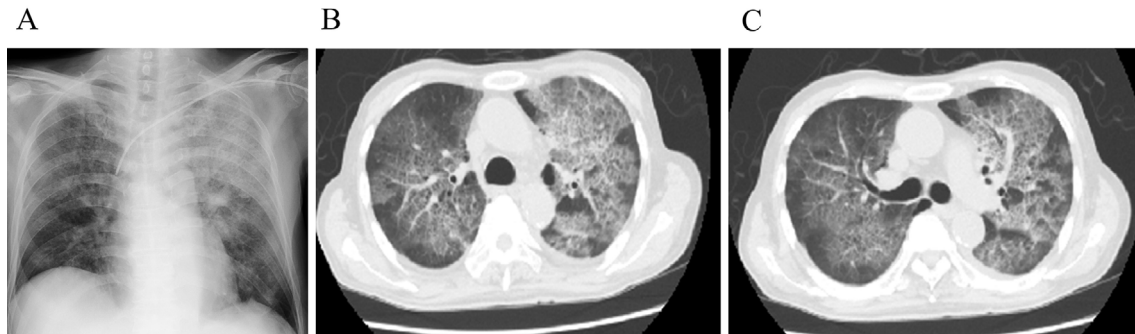

Figure 2. Chest X-ray and computed tomography. (A) Chest X-ray showing wide-range consolidations in both lobes. (B) and (C) Chest computed tomography showing ground-glass opacity in both lobes.

glass opacity (Fig. 2). He was transferred to our institution, because of severe dyspnea. The laboratory results on the day of admission are shown in Table 1. CMV was detected in the punched-out ulcers by pathology obtained from an endoscopic biopsy, and many inflammatory cells were found to have infiltrated the ulcer; in contrast, few inflammatory cells had infiltrated the intervening mucosa around the ulcer. The CMV antigenemia (CMV-Ag, C10/C11 method) in sera was 26 cells. Based on these findings he was diagnosed with CMV colitis rather than UC exacerbation.

The bronchoalveolar lavage fluid did not show *P. jirovecii*; however, based on the ground-glass opacity, high levels of β-D-glucan (β-D-glucan in sera was 1,690 pg/ml,

and β-D-glucan in bronchoalveolar lavage fluid was 5,760 pg/ml), absence of CMV-infected cells in the bronchoalveolar lavage fluid, absence of prophylactic trimethoprim/sulfamethoxazole (TMP-SMX), and sudden deterioration of his respiratory condition, he was diagnosed with PJP.

An arterial blood gas analysis indicated hypoxia (PaO_2= 55.2 mmHg, $PaCO_2$=34.9 mmHg, 10 L/min oxygen); therefore, mechanical ventilation was initiated. He was treated with TMP-SMX (9.0 g/day), ganciclovir (1,000 mg/day), and pulse steroid therapy (methylprednisolone 1,000 mg/day, for 3 days). Methylprednisolone was continued at the tapering dose following pulse therapy. Bacterial pneumonia could not be completely ruled out, so the antibiotic meropenem

Table 1.   Laboratory Results on the Day of Transfer to Our Institution.

Hematology		ALP	675 IU/L	ABG	
WBC	15,640 /μL	LDH	324 IU/L	pH	7.517
neut	96.8 %	γ-GTP	223 IU/L	PaO_2	55.2 mmHg
lym	2.6 %	TP	4.5 g/dL	$PaCO_2$	34.9 mmHg
eosino	0.1 %	Alb	1.3 g/dL	BE	4.7 mmol/L
mono	0.4 %	T-bil	0.8 mg/dL	HCO_3	27.6 mmol/L
baso	0.1 %	D-bil	0.3 mg/dL		
RBC	372×10^4/μL	CRP	14.11 mg/dL	Immunology	
Hb	10.8 g/dL	BUN	9 mg/dL	CMV-Ag	26 cells
Hct	31.8 %	Cre	0.38 mg/dL	Candida-Ag	2 (negative)
Plt	36.8×10^4/μL	UA	1.7 mg/dL	Aspergillus-Ag	0.2 (negative)
		Na	137 mEq/L	β-D glucan	1,690 pg/mL
Biochemistry		K	3.8 mEq/L	HIV antibody	0.16 (negative)
AST	53 IU/L	Cl	99 mEq/L		
ALT	76 IU/L	PCT	0.21 ng/mL		

WBC: white blood cell, neut: neutrophil, lym: lymphocyte, eosino: eosinophil, mono: monocyte, baso: basophil, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, HIV: human immunodeficiency virus, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl-transpeptidase, TP: total protein, Alb: albumin, T-bil: total bilirubin, D-bil: direct bilirubin, CRP: C-reactive protein, BUN: blood urea nitrogen, Cre: creatinine, UA: uric acid, Na: sodium, K: potassium, Cl: chlorine, PCT: procalcitonin, ABG: arterial blood gas analysis, pH: potential of hydrogen, PaO_2: arterial partial pressure of oxygen, $PaCO_2$: arterial partial pressure of carbon dioxide, BE: base excess, HCO_3: hydrogencarbonate, CMV-Ag: cytomegalovirus antigenemia, Candida-Ag: *Candida* antigenemia, Aspergillus-Ag: *Aspergillus* antigenemia
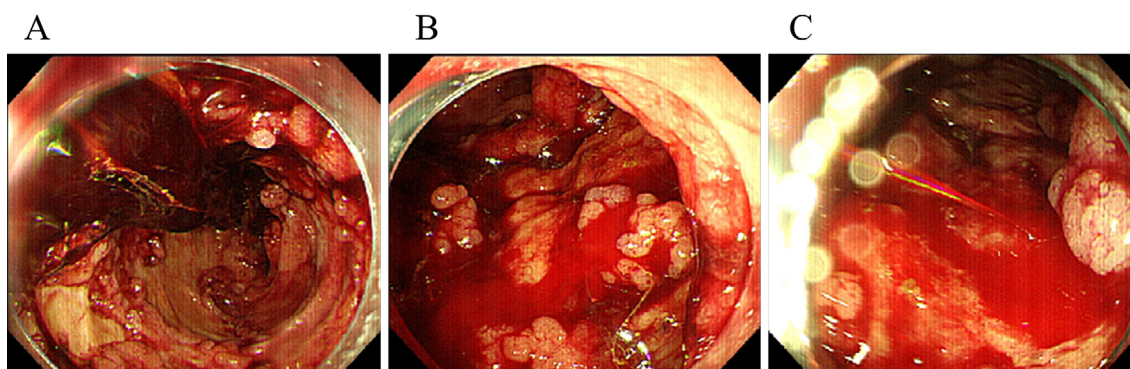

Figure 3.   Total colonoscopy during lower gastrointestinal bleeding. (A) and (B) Total colonoscopy at the first bleeding. (A) Ascending colon showing wide-range mucosal ulceration. (B) Transverse colon showing the bleeding spot. (C) Total colonoscopy during the second bleeding incident; ascending colon showing the bleeding spot.

(3.0 g/day) was administered.

On day 12 of admission, he was weaned from mechanical ventilation because of improvement in his hypoxia. The CMV-Ag decreased to 1 cell; however, on day 15 of admission, he had bloody stool again. On the same day, total colonoscopy was performed, and bleeding was stopped by a coagulation procedure (Fig. 3A, B). On day 16 of admission, the patient experienced a second bout of lower gastrointestinal bleeding, and the bleeding was again arrested using a coagulation procedure (Fig. 3C). On day 17 of admission, he experienced lower gastrointestinal bleeding a third time, and his general condition deteriorated. On the same day, to control bleeding, a surgical procedure was performed. The ulcers were localized only in the colon, so sub-

total colectomy was performed. The ascending, transverse, descending, and sigmoid colon were resected, and a stoma of ileum was constructed. Considering his general condition, rectal resection was avoided after confirming that there was no bleeding from the rectum. On day 26 of admission, he was weaned from mechanical ventilation again. On day 161 of admission, the patient was discharged to continue his daily activities as before admission.

Discussion

PJP is an opportunistic infection caused by *P. jirovecii* (19). PJP can be classified as that associated with HIV infection (HIV-PJP) or non-HIV-PJP, depending on the

Table 2. Summary of 15 Cases of Ulcerative Colitis Patients with Pneumocystis Jirovecii Pneumonia.

No.	Reference number	Age	Gender	Prognosis	Immunosupressive agent	Prophylactic TMP-SMX	Treatment for PJP	Other infection
1	4	32	male	dead	hydrocortisone and cyclosporine	no	n/a	none
2	5	68	male	dead	steroid and 6-MP	no	TMP-SMX	none
3	6	63	male	dead	steroid and cyclosporine	no	Ampicillin and erythromycin	none
4	7	43	male	dead	steroid and 6-MP	no	TMP-SMX	none
5	8	32	male	alive	steroid	no	TMP-SMX and pulse steroid therapy	none
6	9	n/a	n/a	dead	steroid, thiopurine, and cyclosporine	no	n/a	CMV colitis
7	10	26	female	alive	steroid and thiopurine	no	TMP-SMX	none
8	10	68	female	alive	steroid	no	TMP-SMX	none
9	10	29	male	alive	steroid and thiopurine	no	TMP-SMX	none
10	11	32	male	dead	steroid, thiopurine, and cyclosporine	no	n/a	none
11	12	21	male	alive	steroid and thiopurine	no	TMP-SMX	none
12	13	72	male	dead	steroid and tacrolimus	no	TMP-SMX	none
13	13	74	male	dead	steroid, 6-MP, and tacrolimus	no	TMP-SMX	none
14	14	53	female	alive	steroid and filgotinib	no	TMP-SMX and steroid	varicella zoster virus infection
15	our case	74	male	alive	steroid	no	TMP-SMX and pulse steroid therapy	CMV colitis

CMV: cytomegalovirus, n/a: not applicable, PJP: *Pneumocystis jirovecii* pneumonia, TMP-SMX: trimethoprim/sulfamethoxazole, 6-MP: 6-mercaptopurine

association with HIV. The progression of HIV-PJP is relatively slow, with a mortality rate of approximately 10% (20). Causes of non-HIV-PJP include hematological disorders, malignancies, collagen disease, and immunosuppressive agents (21, 22). In contrast to HIV-PJP, non-HIV-PJP progresses rapidly, is often severe, and has a poor prognosis (21-24). To diagnose PJP, it is necessary to prove the presence of *P. jirovecii* in sputum or bronchoalveolar lavage fluid; however, the bacterial proof rate is lower in cases of non-HIV-PJP than in HIV-PJP, so it is difficult to diagnose non-HIV-PJP. The diagnosis is often based on the clinical course, β-D-glucan value, and computed tomography findings of the lungs (25, 26).

The rapid progression and difficulty making a diagnosis are two reasons for the poor prognosis of non-HIV-PJP, so making an early diagnosis and administering prompt treatment are very important (27, 28). TMP-SMX is the main treatment for PJP, and steroid or pulse steroid therapy is recommended as adjunctive therapy. The combination of TMP-SMX and steroid therapy shortens the admission period and improves the prognosis (29-31). Prophylactic administration of TMP-SMX is recommended (32, 33). This case was one of non-HIV-PJP associated with immunosuppressive agents. A definitive diagnosis could not be made based on the clinical course, high levels of β-D-glucan, and computed tomography findings; however, he was ultimately diagnosed

with PJP and started on TMP-SMX and pulse steroid therapy to save his life. The prognosis of non-HIV-PJP is poor; however, early treatment enabled a survival outcome in this patient. Therefore, in cases where patients treated with immunosuppressive agents present with a fever and severe hypoxia, it is important to actively suspect PJP and initiate early treatment and appropriate intensive therapy.

Most patients are latently infected with CMV. CMV proliferates in hematopoietic cells and spreads to various organs via the vascular endothelium under immunocompromised conditions (34). The diagnosis of CMV colitis is based on gastrointestinal symptoms, the presence of gastrointestinal erosions or ulcers during endoscopy, and tissue or serological proof of the virus (35). Erosions and ulcers associated with CMV colitis often have a punched-out or longitudinal ulceration, and most of them occur in the terminal ileum, cecum, and transverse colon (36). CMV colitis is treated with anti-viral agents, such as ganciclovir; however, CMV colitis associated with UC tends to be severe and difficult to treat. CMV infection is the exacerbating factor of UC (16, 17), and CMV infection also associate with resistance for steroid therapy (37). Furthermore, bleeding from ulcers associated with CMV colitis often occur, leading to a poor prognosis (35, 38). Therefore, surgical resection for colitis control is considered useful for treatment (15, 16, 37). In the present case, a high level of CMV-Ag, multiple

punched-out ulcers in the colon, and proof of pathological CMV were consistent with a diagnosis of CMV colitis with UC. Based on the endoscopic features, it was strongly suspected that the patient's repeated lower gastrointestinal bleeding was due to CMV colitis, in addition to the UC component. The CMV-Ag tended to decrease following treatment with ganciclovir. However, his general condition worsened because of the uncontrolled gastrointestinal bleeding. Invasive therapy via subtotal colectomy was performed for this patient at the appropriate timing, which might have helped save his life.

A literature search using the terms "ulcerative colitis" and "pneumocystis (jirovecii) pneumonia" in PubMed showed that only 15 cases (including this case) of UC with PJP have been reported to date, and the available information is summarized in Table 2 (4-14). Previous patients include 11 men and 3 women (1 case unknown), with ages ranging from 21 to 74 (median age: 43) years old. The etiology was non-HIV-PJP in all cases. The survival outcome was 46.7% (7 out of 15 cases), confirming that non-HIV-PJP has a poor prognosis. The median age of the survival group was 32 years old, while that of the death group was 63 years old. PJP occurred in these 15 cases while under treatment with a single or multiple immunosuppressive agents without prophylactic administration of TMP-SMX. These cases were mainly treated with TMP-SMX for PJP, and three cases were successfully treated with a combination of steroid or pulse steroid therapy and TMP-SMX. This is consistent with the effect of steroids on PJP (29-31). In addition, aside from the present case, there was only one other case of PJP and CMV colitis with UC; however, the patient was not successfully treated because of the disease severity.

For patients undergoing immunosuppressive treatment, prophylactic administration of TMP-SMX is recommended (32, 33, 39, 40); however, TMP-SMX has severe side effects, including myelosuppression and liver damage (29, 41). Therefore, the prophylactic administration of TMP-SMX to all patients with immunosuppressive treatment is not recommended. However, there have been several patients who developed severe PJP, as in this case, and the prognosis was very poor. The prophylactic administration of TMP-SMX should thus be limited to patients with a high possibility of developing PJP. Previous studies reported that the possibility of PJP occurrence is higher in patients receiving over 20 mg/day of prednisolone treatment for 4 weeks (42, 43), those over 60 years old (15, 44), and those with a low lymphocyte count (<600/μl) (45, 46). Based on these criteria, the present patient had a high possibility of developing PJP and should have been administered prophylactic TMP-SMX.

In summary, elderly patients with UC, who undergo immunosuppressive therapy and have a high possibility of developing PJP, may be suitable for prophylactic treatment with TMP-SMX, where possible. Once non-HIV-PJP occurs, the mortality rate is high; however, adjunctive steroid treatment in addition to TMP-SMX may improve the prognosis.

The occurrence of PJP and CMV colitis with UC is a rare condition, and the present case was the only one to be treated successfully. Further analyses in a large number of cases are needed to understand the features and underlying mechanisms of PJP and CMV colitis with UC.

Conclusion

This case report describes an extremely rare case of UC with PJP and CMV colitis that was successfully treated with intensive therapy. While treatment with immunosuppressive agents for UC is useful, it can lead to opportunistic infections that can be fatal. The present case, in conjunction with the previously reported cases, suggests that prophylactic therapy for PJP might be particularly important in elderly patients. This case report and literature review will serve as a useful reference for the successful treatment of future cases.

The authors state that they have no Conflict of Interest (COI).

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