

Pneumocystis Pneumonia in a Patient With Colorectal Cancer Receiving Bevacizumab and mFOLFOX6 Therapy

MASATOSHI MAKI¹, RYO TAKADA¹, NAOYUKI NOMURA¹, YUKI CHIKO²,
SATORU SENOO³, YOKO TAKAHASHI¹, SEIJI SAITO⁴ and TERUTAKA HAMAOKA¹

¹Department of Hospital Pharmacy, NHO Fukuyama Medical Center, Hiroshima, Japan;

²Department of General Medicine, Okinawa Prefectural Yaeyama Hospital, Okinawa, Japan;

³Department of Respiratory Medicine, NHO Fukuyama Medical Center, Hiroshima, Japan;

⁴Department of Infection Control, NHO Fukuyama Medical Center, Hiroshima, Japan

Abstract

Background/Aim: *Pneumocystis* pneumonia (PCP) can be a life-threatening fungal infection for immunocompromised individuals. We report a case of PCP in a 75-year-old male with colorectal cancer receiving bevacizumab plus mFOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil) therapy.

Case Report: The patient, diagnosed with unresectable advanced colorectal cancer, developed fever and neutropenia during the 40th course of bevacizumab plus mFOLFOX6 therapy and was diagnosed with febrile neutropenia. Moreover, laboratory tests and imaging studies indicated PCP. Although initial treatment with corticosteroids and trimethoprim-sulfamethoxazole temporarily improved the patient's condition, the patient later developed acute respiratory distress syndrome and succumbed to the disease. Lymphocytopenia associated with the prolonged bevacizumab plus mFOLFOX6 therapy may have contributed to the onset of PCP.

Conclusion: This case reaffirms that advanced age, immunosuppression, and cumulative steroid exposure are critical risk factors for PCP. Early imaging and prophylactic TMP-SMX administration should be considered in high-risk patients. Early intervention is crucial to prevent PCP progression to ARDS in patients with solid tumors.

Keywords: Colorectal cancer, cancer chemotherapy, *pneumocystis* pneumonia, febrile neutropenia, dexamethasone.

Introduction

Pneumocystis jirovecii pneumonia, formerly known as *Pneumocystis carinii* pneumonia, is a fungal infection that can be life-threatening in immunocompromised individuals.

Although *Pneumocystis* pneumonia (PCP) is commonly observed in patients with hematologic malignancies, autoimmune diseases, or those undergoing bone marrow transplantation, its incidence in patients with solid tumors is relatively low (1). However, PCP in non-HIV-infected



Masatoshi Maki, Department of Hospital Pharmacy, NHO Fukuyama Medical Center, Hiroshima, Japan. E-mail: maki.masatoshi.zh@mail.hosp.go.jp

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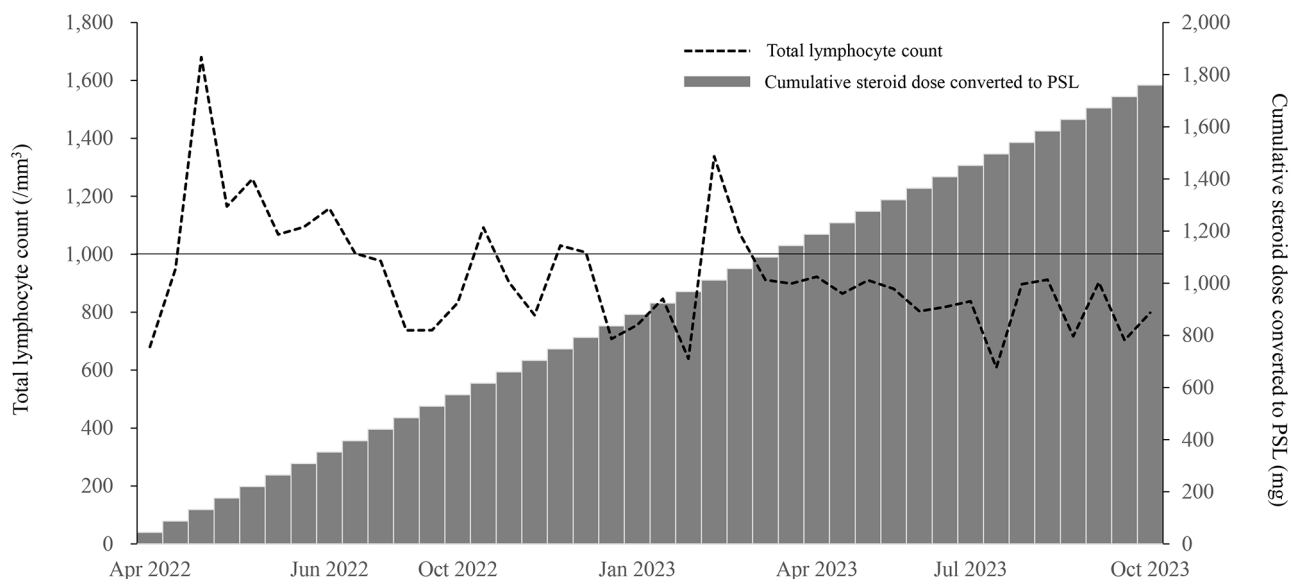


Figure 1. Changes in total lymphocyte count over time and cumulative steroid dose converted to prednisolone (PSL).

patients carries a high risk of severe disease progression, necessitating careful management. Here, we present a rare case of a patient with colorectal cancer undergoing chemotherapy who was diagnosed with PCP following the onset of febrile neutropenia (FN) and ultimately succumbed to the disease.

Case Report

Patient. A 75-year-old Japanese man with an Eastern Cooperative Oncology Group (ECOG) performance status of 1. This case report was approved by the Ethics Committee of Fukuyama Medical Center (Fukuyama City, Hiroshima Prefecture) (Approval No.: ERB2024026). Written informed consent for the publication of the patient's personal medical information, including clinical and imaging data, was obtained directly from the patient on the day of hospitalization.

Present illness. In April 2022 the patient was diagnosed with sigmoid colon cancer (cT4N1M1b, cStage IVb). Based on genetic analysis, the tumor was *KRAS* mutation-positive, *BRAF* mutation-negative, and *HER2*-negative

with microsatellite stability. First-line treatment with mFOLFOX6 and bevacizumab was initiated. The following chemotherapy regimen was administered every two weeks: dexamethasone (DEX, 6.6 mg), bevacizumab (5 mg/kg), oxaliplatin (85 mg/m²), leucovorin (200 mg/m²), 5-fluorouracil (5-FU) as a bolus infusion (400 mg/m²), and 5-FU as a continuous infusion over 46 h (2,400 mg/m²).

The patient underwent 40 treatment cycles over approximately 19 months until November 2023. The total dose of DEX administered was 264 mg, equivalent to 1,760 mg of prednisolone (PSL). Over the six months prior to hospitalization, the lymphocyte count remained below 1,000 cells/mm³ (Figure 1). In November 2023, three days prior to hospitalization, the patient developed generalized fatigue, which impaired mobility, and presented with a fever of 37.6°C. The patient was transported to our hospital *via* emergency services.

Patient history and current medications. The patient's past medical history included an old myocardial infarction, hypertension, hyperuricemia, and dyslipidemia. In addition, the patient had a 30-year history of smoking 20 cigarettes per day. No drug allergies were reported. The current

Table I. Laboratory findings on admission.

Hematology		Biochemistry		Urinalysis	
White blood cells	800/ μ l	AST	30 IU/l	pH	8.0
Neutrophils	15.0%	ALT	21 IU/l	White blood cells	(-)
Lymphocytes	63.0%	LDH	687 IU/l	Occult blood	(-)
Monocytes	20.0%	ALP	118 IU/l	Protein	1+
Eosinophils	1.0%	γ -GTP	62 IU/l	Glucose	(-)
Basophils	1.0%	T-bil	1.3 mg/dl	Ketone bodies	(-)
Hemoglobin	10.7 g/dl	D-bil	0.4 mg/dl	Nitrites	(-)
Platelets	8.3×10^4 / μ l	BUN	46 mg/dl	Bacteria	(-)
		Cre	0.97 mg/dl		
Blood coagulation tests		Alb	3.0 g/dl	Serology	
APTT	36.2 s	CRP	6.69 mg/dl	SARS-CoV-2 PCR	(-)
PT	14.1 s	Na	135 mEq/l	Influenza Antigen	(-)
PT-INR	1.14	K	5.9 mEq/l		
D-dimer	4.7 μ g/ml	Cl	102 mEq/l		
		Ca	8.5 mg/dl		

APTT: Activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; AST: aspartate aminotransaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ -GTP: gamma-glutamyl transferase; T-bil: total bilirubin; D-bil: direct bilirubin; BUN: blood urea nitrogen; Cre: creatinine; Alb: albumin; CRP: C-reactive protein.

medications and their daily doses were as follows: aspirin (100 mg), lansoprazole (15 mg), telmisartan (40 mg), amlodipine (5 mg), nicorandil (10 mg), ezetimibe (10 mg), rosuvastatin (2.5 mg), bisoprolol fumarate (1.25 mg), febuxostat (20 mg), ursodeoxycholic acid (300 mg), magnesium oxide (990 mg), and duloxetine (40 mg).

Findings on admission. On admission, the following findings were noted: height, 152.6 cm; weight, 49.6 kg; Glasgow Coma Scale, 14 (E3V5M6); temperature, 38.0°C; blood pressure, 106/82 mmHg; heart rate, 88 beats/min; respiratory rate, 24 breaths/min; SpO₂, 98% (room air). The heart sounds were regular without a murmur, and no abnormal lung sounds, or peripheral edema were observed. Laboratory findings on admission are presented in Table I.

Clinical course after admission. A chest computed tomography (CT) scan performed on admission showed no evidence of pneumonia (Figure 2A-a). The patient presented with grade 4 neutropenia and was diagnosed with FN. On hospital day (HD) 1, treatment with cefepime (CFPM, 4 g/day) and filgrastim (75 μ g/day) was initiated (Figure 3).

On HD 3, the patient's oxygen saturation (SpO₂) on room air decreased from 98% to 89%, necessitating supplemental oxygen (Figure 3). Chest radiography on HD 4 revealed mildly decreased translucency in the upper lung fields superimposed on emphysematous changes (Figure 2B-a). On the same day, tests for serum β -D-glucan (BDG) and cytomegalovirus (CMV) antigen (pp65 antigen, C10/11) were outsourced.

On HD 5, the patient developed grade 3 fatigue, classified according to the Common Terminology Criteria for Adverse Events, version 5.0. Despite an increase in the neutrophil count, the fever persisted, and respiratory distress showed no improvement. Treatment with tazobactam/piperacillin (TZP 18 g/day) was initiated instead of CFPM. However, SpO₂ remained unstable, and the oxygen supplementation was gradually increased to 12 l (Figure 3).

On HD 7, chest radiography revealed worsening pneumonia (Figure 2B-b). Hence, TZP was changed with meropenem (MEPM, 3 g/day) and vancomycin (VAN, dose adjusted *via* therapeutic drug monitoring). The outsourced tests showed a low CMV antigen count (10 positive cells across two slides) but an elevated BDG level of 120.1 pg/ml, raising the suspicion of fungal infection. Micafungin (MCFG,

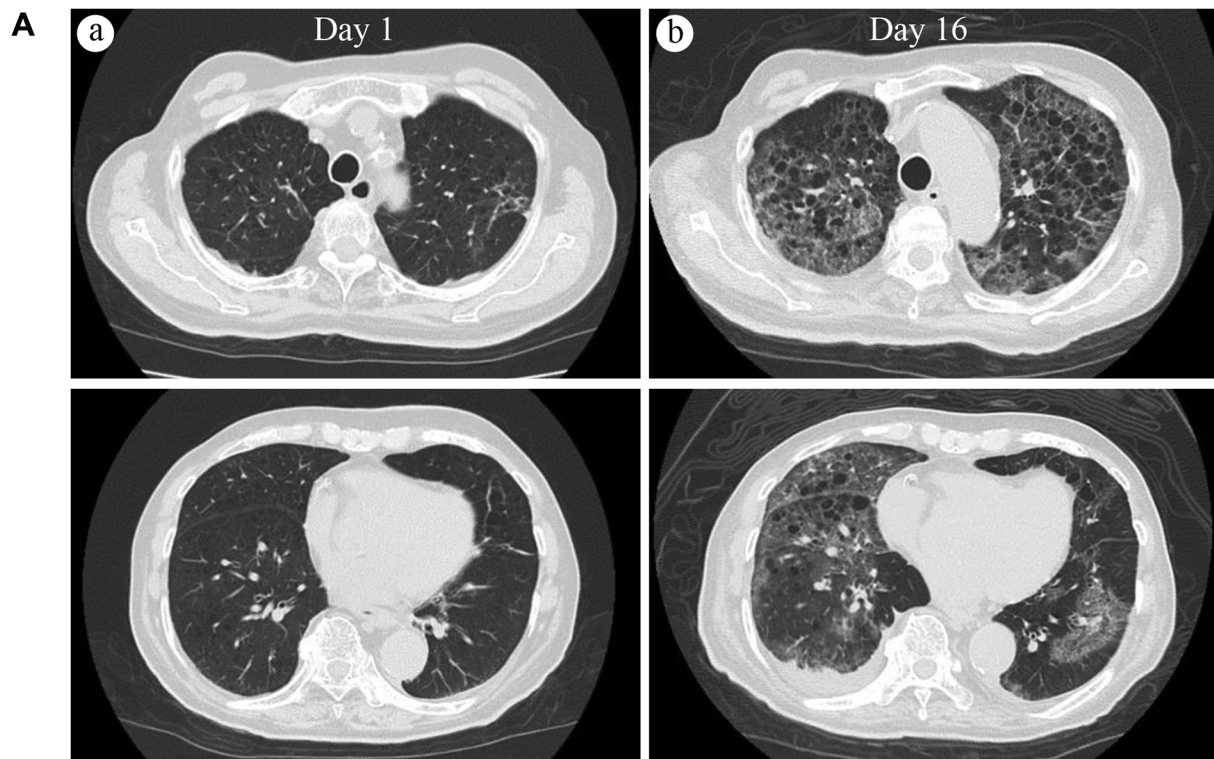


Figure 2. *Continued*

150 mg/day) was added to the treatment regimen. BDG levels were measured using the Fungitec G test ES “NISSUI” via a colorimetric method. Elevated lactate dehydrogenase (LDH) (1,226 U/l) and C-reactive protein (CRP) (35.28 mg/dl) levels were noted (Figure 3).

Given the possibility of PCP, consultation with the respiratory medicine department was sought. Owing to the patient’s age and clinical condition, bronchoscopy with bronchoalveolar lavage (BAL) was not performed. Based on the elevated BDG and LDH levels and rapid deterioration of respiratory status, trimethoprim-sulfamethoxazole (TMP-SMX, 6 g/day) and prednisolone [PSL, 1 mg/kg/day (50 mg/day)] were initiated for the treatment of PCP.

On HD 9, high-flow nasal cannula (HFNC) oxygen therapy was administered (Figure 3). Gradual improvement in oxygenation was observed, and chest radiography on HD 14 showed improvement in the bilateral upper lung field opacities (Figure 2B-c). The patient was weaned off HFNC on HD 15, prompting the

discontinuation of MEPM, while continuing TMP-SMX and MCFG. The PSL dosage was also tapered (Figure 3).

Contrast-enhanced CT on HD 16 revealed findings consistent with PCP (Figure 2A-b). Together with the elevated serum BDG levels and clinical progression, these findings led to a diagnosis of PCP.

On HD 18, the oxygenation worsened, requiring the reintroduction of HFNC. Given the possible PCP exacerbation, TMP-SMX dosage was increased to 9 g/day, and steroid pulse therapy (1,000 mg/day methylprednisolone for three days) was initiated. In addition, MEPM (3 g/day) was reintroduced to address possible bacterial coinfection. On HD 22, the outsourced CMV antigen testing of samples submitted on HD 18 revealed 16 positive cells across two slides. Ganciclovir (GCV, 5 mg/kg/day q12h) was initiated, and MCFG was discontinued (Figure 3).

Despite these efforts, the oxygen demand increased, and subcutaneous morphine was administered on HD 23 to alleviate dyspnea. On HD 24, the oxygen demand further

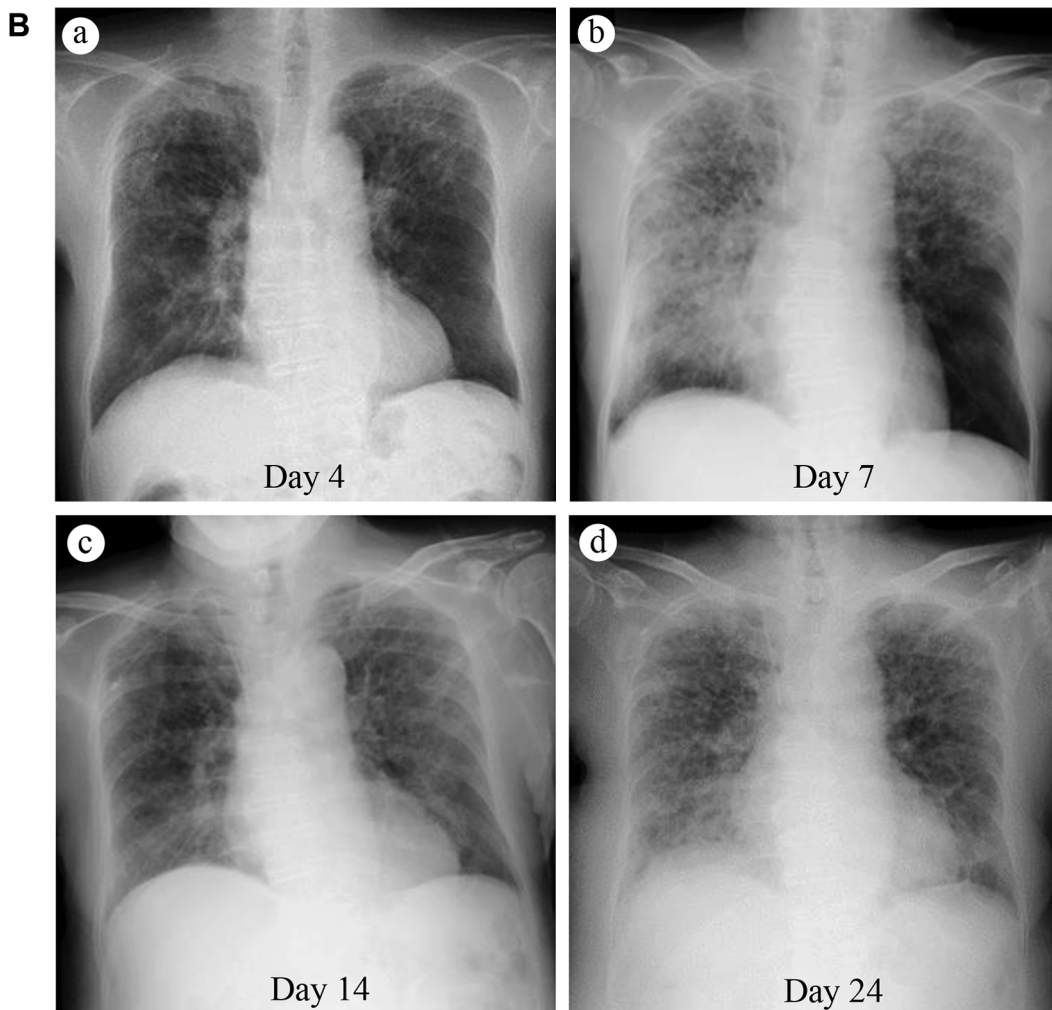


Figure 2. Changes over time in Chest computed tomography (CT) and chest radiography. A) (a) Chest CT on admission. (b) Chest CT on Day 16. Diffuse frosted shadows can be seen against a background of emphysematous changes. Some of the shadows are distributed in a well-defined and mottled pattern like a world map. B) (a) Chest radiography on Day 4. Mildly reduced permeability can be seen in both upper lung fields against a background of emphysematous changes. (b) Chest radiography on Day 7. Consolidation consistent with decreased permeability is visible throughout the right lung field, in addition to increased shadowing in the left upper lung field. (c) Chest radiography on Day 14. Compared to Day 7, the radiograph shows an improvement in the right lung field and left upper lung field, but increased shadowing can be seen in the left lower lung field. (d) Chest X-rays on Day 24. Diffuse increased shadows throughout both lung fields are visible.

increased, and worsening chest radiography findings (Figure 2B-d) prompted the initiation of continuous sedation with midazolam for refractory symptoms.

The patient's condition continued to deteriorate, and he died on HD 25. Blood cultures from HD 1, HD 5, and HD 18 were all negative. Sputum culture from HD 3 showed normal flora.

Discussion

This report describes a rare case of PCP following FN induced by BV+mFOLFOX6 in a patient with colorectal cancer. To the best of our knowledge, no previous reports have documented the incidence of PCP after FN during chemotherapy for colorectal cancer, making this case report

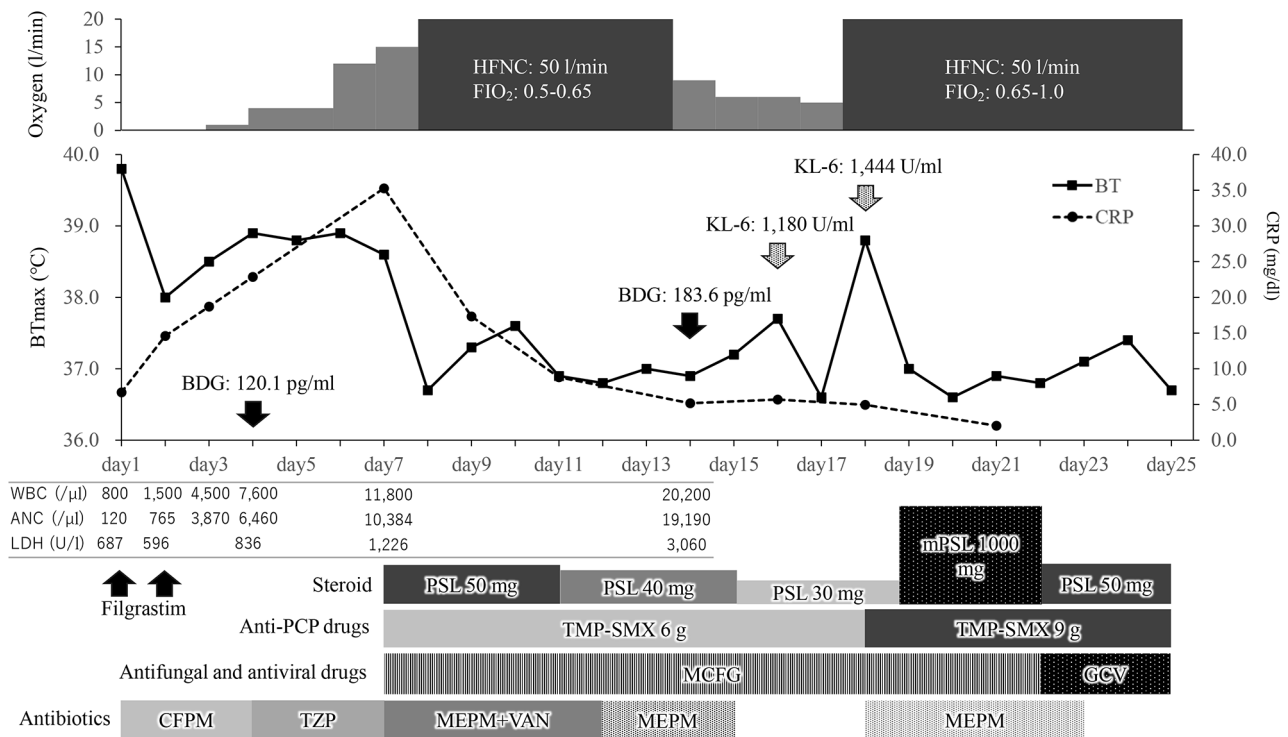


Figure 3. Treatment course and changes in temperature and C-reactive protein (CRP) levels during hospitalization. ANC: Absolute neutrophil count; BDG: β -D-glucan; BTmax: maximum body temperature; FIO₂: fraction of inspired oxygen; GCV: ganciclovir; HFNC: high-flow nasal cannula; KL-6: krebs von den lungen-6; LDH: lactate dehydrogenase; MEPM: meropenem; mPSL: methylprednisolone; PCP: pneumocystis pneumonia; PSL: prednisolone; TMP-SMX: trimethoprim-sulfamethoxazole; TZP: tazobactam/piperacillin; VAN: vancomycin; WBC: white blood cell.

a novel contribution to the literature. Advances in cancer chemotherapy have extended treatment durations; however, prolonged treatment durations pose a significant risk of infection due to cumulative immunosuppression. The critical takeaway from this case report is the necessity of considering prophylactic TMP-SMX administration in patients at high risk for PCP. This report also emphasizes the importance of early diagnosis and preemptive treatment when infection is suspected. These measures are expected to improve treatment outcomes and patient prognosis.

Definitive diagnosis of PCP requires the detection of *P. jirovecii* in respiratory specimens, either by microscopic examination or PCR. However, PCR is not covered by insurance in Japan and presents challenges such as low specificity. However, in our case, BAL, which is typically required for sample collection, was not performed owing to the patient's frailty, risk of post-procedure infection

during neutropenia, and potential respiratory deterioration. Instead, noninvasive serological markers were used for supplementary diagnosis. In this case, BDG (120.1 pg/ml), LDH (836 U/l), and KL-6 (1,180 U/ml) levels exceeded the reference ranges significantly, consistent with reports indicating elevated serological markers in patients positive for PCP (2). The highly positive predictive value of BDG, with a cutoff of 33.5 pg/ml (3), and the CT findings (4) supported the diagnosis of PCP in this case. Although invasive pulmonary aspergillosis is another frequent opportunistic fungal infection associated with elevated BDG levels in patients with neutropenia, radiological findings suggested it was unlikely.

Patients with solid tumors such as primary or metastatic brain tumors, lung cancer, and breast cancer are at a higher risk for PCP; however, PCP occurrence in patients with colorectal cancer is exceptionally rare (5).

Conversely, corticosteroid use is a recognized risk factor for PCP in patients not infected with HIV (6); however, the daily dose of PSL in our case did not exceed ≥ 20 mg. Therefore, the relationship between chemotherapy, corticosteroids, and the risk of PCP in patients with solid tumors warrants further investigation. Reports on other cancers have indicated that high-dose chemotherapy increases the risk of PCP (7). In this case, the 40 cycles of chemotherapy every two weeks and prolonged intermittent use of steroids may have caused lymphopenia, which may have contributed to the subsequent occurrence of PCP. Over approximately 18 months of anticancer treatment, the cumulative steroid dose reached 1,760 mg (PSL equivalent), far exceeding the 700 mg threshold associated with an increased risk of infection (8). Furthermore, the lymphocyte counts below $1,000/\text{mm}^3$ for over six months (Figure 1) likely heightened the patient's susceptibility to PCP (9). Hence, multiple factors, including chemotherapy, intermittent corticosteroid use, and lymphocytopenia, likely contributed to the development of PCP in this patient. Although no definitive guidelines exist for TMP-SMX prophylaxis during cancer treatment, this case, among others, emphasizes the importance of proactive prevention in high-risk individuals.

On admission, the patient presented with a high fever and elevated CRP and LDH levels, with BDG level elevation noted on Day 4, suggesting a prior *P. jirovecii* infection. However, treatment initiation was delayed by seven days. Contributing factors include the lack of clear CT abnormalities on admission, possibly due to an early infection stage or neutropenia obscuring radiological findings, and the focus on FN management compounded by delays in BDG test results due to external processing. These factors delayed the diagnosis of PCP and TMP-SMX initiation.

In our patient, TMP-SMX was initially administered at a low dose (10 mg/kg/day), as recommended for elderly patients (10), which was well-tolerated without interruption. However, respiratory deterioration recurred on Day 18, prompting a dose increase to 15 mg/kg/day, which did not result in an improvement. Acute respiratory distress syndrome (ARDS), known to complicate severe PCP (11), may have occurred in this case. Delayed

treatment initiation in patients with non-HIV PCP has been associated with poor outcomes (12), suggesting that treatment delay might have influenced our patient's clinical trajectory. The LDH level on admission (687 U/l) exceeded the threshold of 500 U/l, which is a known mortality risk factor in patients with PCP (13).

Differential diagnoses included CMV pneumonia, which is frequently observed in immunocompromised patients, with CT findings often indistinguishable from PCP. In this case, CMV pp65 antigenemia was low (2 slides, 10 cells in total) on Day 4, which did not require intervention. However, by Day 18, the antigenemia had increased (16 cells in total), necessitating GCV initiation. Our institution employs the C10/C11 method, with retrospective analyses from Japan indicating that preemptive therapy thresholds of 20 cells (equivalent to 10 cells by HRP-C7) do not increase the incidence of CMV infection (14). Given the potential of GCV for causing bone marrow suppression, the timing of GCV initiation was deemed appropriate.

Study limitations. The first is not testing for the organisms necessary to definitively diagnose PCP. Although these organisms can be detected in the induced sputum of patients with HIV, BAL is often required to test for these organisms in patients without HIV. BAL is burdensome to patients and carries risks, especially given the rapid progression of respiratory failure that frequently occurs in patients with PCP without HIV. In the present case, the patient's advanced age and deteriorating clinical condition made BAL difficult to perform. Second, an autopsy was necessary to more accurately determine the cause of death; however, it could not be performed due to ethical and family consent issues. This limited our ability to diagnose and interpret the data.

Conclusion

This case report presents the challenges in managing FN and PCP in a patient with colorectal cancer undergoing chemotherapy. Difficulties in early diagnosis and treatment initiation likely influenced the outcome of this

patient, underscoring the need for rapid, noninvasive diagnostic tools. This case reaffirms that advanced age, immunosuppression, and cumulative steroid exposure are critical risk factors for PCP. Therefore, early imaging and prophylactic TMP-SMX administration should be considered in high-risk patients. This report highlights the importance of early intervention to prevent the progression of PCP to ARDS in patients with solid tumors.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this report.

Authors' Contributions

M.M. wrote the manuscript. R.T, N.N., Y.C., S.S., Y.T, S.S., and T.H. provided critical feedback and reviewed the data. All the Authors have read and approved the final version of the manuscript.

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