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Note

Diagnosis and treatment of *Pneumocystis jirovecii* pneumonia in HIV-infected or non-HIV-infected patients—difficulties in diagnosis and adverse effects of trimethoprim-sulfamethoxazole☆

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ABSTRACT

The clinical characteristics of *Pneumocystis jirovecii* pneumonia (PCP) in patients with immunodeficiency virus (HIV) infection (HIV-PCP) differ from those in patients without HIV infection (non-HIV-PCP). We analyzed 31 adult HIV-PCP cases and 44 non-HIV-PCP cases between 2008 and 2018. The symptomatic period before the diagnosis was shorter in non-HIV-PCP (5 [3–8] days vs. 29 [14–55] days, $P < 0.001$) and the overall survival rate was lower in the non-HIV-PCP group ($P = 0.022$). Serum β-D glucan positivity (72.7% vs. 93.5%, $P = 0.034$) and Grocott stain positivity for *Pneumocystis jirovecii* in the bronchoalveolar lavage fluid (4.3% vs. 73.3%, $P < 0.001$) were significantly lower in the non-HIV-PCP group. This difficulty in laboratory diagnosis possibly resulted in the administration of concurrent antibiotics such as quinolones and macrolides (56.8% vs. 19.4% $P = 0.002$) in the non-HIV-PCP group. The adverse effects due to trimethoprim-sulfamethoxazole were more frequently observed in HIV-PCP (86.2% vs. 35.3%, $P < 0.001$). The duration of discontinuation of trimethoprim-sulfamethoxazole was 11 [8–14.5] days in HIV-PCP cases. Co-administration of adjunctive corticosteroid therapy did not mitigate hypersensitivity to trimethoprim-sulfamethoxazole. Our analysis indicated that the characteristics of PCP in patients with or without HIV was quite different. HIV-positive patients with PCP should be monitored closely to avoid adverse effects due to trimethoprim-sulfamethoxazole. Because positivity polymerase chain reaction test for *P. jirovecii* remained high (91.7%), it is suggested that bronchofiberscopy is warranted for diagnosis of PCP in HIV-negative patients.

Pneumocystis jirovecii pneumonia (PCP) is a severe respiratory infection that frequently develops in patients with strongly immunosuppressive conditions [1], such as human immunodeficiency virus (HIV) infection and its consecutive acquired immunodeficiency syndrome (AIDS) as well as other immunosuppressive conditions. PCP in HIV-negative patients was associated with immunosuppressive conditions such as hematological malignancy, solid cancer, inflammatory diseases, and transplantations, for which immunosuppressive treatment was administered [2]. The incidence of PCP in HIV-negative (non-HIV-PCP) patients has increased, whereas that in HIV-positive (HIV-PCP) patients is stable [3,4]. The characteristics of non-HIV PCP differ from those of HIV-PCP [5]. The difference is attributed to the amount of parasite, which is thought to be higher in HIV-PCP cases; however, the symptoms of HIV-PCP are less severe than those of non-HIV PCP [5,6]. Trimethoprim-sulfamethoxazole (TMP-SMX) had been considered as a standard antibiotic therapy for PCP, despite several associated adverse effects [7]. The incidence of skin eruptions as hypersensitivity to TMP/SMX were observed in 24%–45% HIV-PCP cases [8], which was much higher than that in non-HIV-PCP cases. The aim of our study was to analyze the difference between the HIV-PCP and non-HIV-PCP cases in the last decade.

Abbreviations: PCP, *Pneumocystis jirovecii* pneumonia; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; PCR, polymerase chain reaction; TMP-SMX, Trimethoprim-sulfamethoxazole.

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Our institution has 672 beds and 31 departments including a hematology and rheumatology department that provides hematopoietic stem cell transplantation and a variety of immunosuppressive therapy or biologics. Our institution is also registered as a regional HIV/AIDS core center where approximately 250 HIV-infected patients regularly visit. In our study, we retrospectively collected consecutive adult PCP cases (age $\geq$ 18 years) between November 2008 and March 2018 from the medical records in our institution. The PCP diagnosis was defined by (1) clinical suspicion and presumptive treatment of PCP performed by physicians and (2) having met at least one laboratory test reflecting *P. jirovecii* infection – Grocott stain or polymerase chain reaction (PCR) test positive for *P. jirovecii* on bronchofiberscopy, or positive serum β-D glucan. The predisposing conditions and clinical status at the time of PCP diagnosis were obtained from the medical records. The presence of deoxygenation was defined as under 90% of arterial blood oxygen saturation or under pO_2 60 torr in atrial blood gas analysis. For patients who received a bronchofiberscopy, the results of a PCR test for *P. jirovecii* or Grocott stain for *P. jirovecii* were also analyzed. Serum β-D glucan titers were measured and positivity was judged using commercial laboratory tests (WAKO beta-glucan test, Wako Pure Chemical Industries, Ltd., Osaka, Japan) and was determined according to the manufacturers' instructions. As for comparing serum β-D glucan titers, values below the detection threshold for serum β-D glucan (value of <6.0 pg/mL) were assigned half the threshold value (3.0 pg/mL); those beyond the detection threshold (value of >600 pg/mL) were assigned 600.0 pg/mL. Continuous data are presented as means and 95% confidence intervals or medians and interquartile ranges (IQRs). Categorical data are presented as numbers and percentages. Data were analyzed using a two-tailed Mann–Whitney *U* test for comparisons of continuous variables among two or three groups and by Fisher's exact test for comparisons of categorical data. Kaplan–Meier analysis was used for survival analysis with or without HIV infection. Statistical analyses were performed with Prism 7 (GraphPad Software, San Diego, CA, USA). *P*-values <0.05 were considered statistically significant. This study was approved by the ethics committee at our institution (approval number B180800007).

A total of 75 PCP cases including 44 non-HIV-PCP cases and 31 HIV-PCP cases were analyzed (Table 1). The number of cases in each year included in this study was shown in Fig. 1. Most patients were male (96.8% vs 56.8%, $P < 0.001$). Patients were younger in the HIV-PCP group compared with the non-HIV-PCP group (41 [36–48] vs. 66 [53–69], $P < 0.001$). The underlying diseases in the non-HIV-PCP group were inflammatory diseases (n = 23, some patients had two or three underlying diseases), hematological malignancy (n = 12), solid cancer (n = 9) and critical organ failure such as renal failure or liver cirrhosis (n = 3). The proportions of current smokers, patients with diabetes, deoxygenation at the time of diagnosis, admission to the intensive care unit were not different between the two groups. Only two patients received chemoprophylaxis against PCP prior to the onset in the non-HIV-PCP cases, yet no chemoprophylaxis was administered for HIV-PCP cases. A longer duration of symptoms prior to diagnosis was observed in the HIV-PCP group compared with the non-HIV-PCP group (29 [14–55] vs. 5 [3–8] days, $P < 0.001$). There was no significant difference in serum LDH and peripheral lymphocyte count between the two groups. The average peripheral $CD4^+$ lymphocyte count in the HIV-PCP group was 43 [19–43]/μL. The serum β-D glucan positivity (93.5% vs. 72.7%, $P = 0.034$) and the mean titer of serum β-D glucan was higher in the HIV-PCP group compared with the non-HIV-PCP group (107.1 pg/mL vs 30.5 pg/mL, $P < 0.001$). Cytomegarovirus antigenemia was

Table 1
Characteristics and predisposing conditions of the study subjects.

	Total (N = 75)	Non-HIV PCP (N = 44)	HIV PCP (N = 31)	*P*-value
Male gender – no. (%)	55 (73.3)	25 (56.8)	30 (96.8)	<0.001[a]
Age (years), median [IQR]	53 [41–67]	66 [53–69]	41 [36–48]	<0.001[a]
Underlying conditions – no. (%)				
Current smoker	41 (54.7)	24 (54.5)	17 (54.8)	1.0
Diabetes	11 (14.7)	8 (18.2)	3 (9.7)	0.346
Received chemoprophylaxis for PCP	2 (2.7)	2 (4.5)	0 (0)	0.509
Deoxygenation	33 (44.0)	23 (52.3)	10 (32.3)	0.102
ICU admission	8 (10.7)	6 (13.6)	2 (6.5)	0.458
Length of symptoms (days), median [IQR]	8.5 [4–20]	5 [3–8]	29 [14–55]	<0.001[a]
Serum LDH titer (IU/mL), median [IQR]	338 [238–432]	335 [237–415]	338 [241–435]	0.862
Peripheral lymphocyte count (/μL), median [IQR]	676 [380–1027]	672 [346–959]	698 [492–1155]	0.441
Serum β-D glucan positive – no. (%)	61 (81.3)	32 (72.7)	29 (93.5)	0.034
Serum beta-D glucan titer (pg/mL), median [IQR]	56.7 [18.1–134.3]	30.5 [7.1–83.0]	107.1 [50.5–200]	<0.001[a]
CMV antigenemia – no. (%)	7 (9.3)	1 (3.1)	6 (21.4)	0.043[a]
Performed bronchofiberscopy – no. (%)	40 (53.3)	24 (54.5)	16 (51.6)	0.819
PCP-PCR positive – no. (%)	34 (94.4) [N = 36]	22 (91.7) [N = 24]	12 (100) [N = 12]	0.543
Grocott stain positive – no. (%)	12 (31.6) [N = 38]	1 (4.3) [N = 23]	11 (73.3) [N = 15]	<0.001[a]
Initiative treatment – no. (%)				
TMP-SMX	64 (85.3)	34 (77.3)	29 (93.5)	0.107
Atovaquone	9 (12.0)	8 (18.2)	1 (3.2)	0.072
Pentamidine	1 (1.3)	1 (2.3)	0 (0)	
No treatment	1 (1.3)	1 (2.3)	1 (3.2)	
Adjunctive corticosteroid therapy – no. (%)	47 (62.7)	33 (75.0)	14 (45.2)	0.015[a]
Concurrent antibiotics – no. (%)	31 (41.3)	25 (56.8)	6 (19.4)	0.002[a]
Discontinuation of TMP-SMX due to adverse effects – no. (%)	38 (60.3)	12 (35.3)	26 (89.7)	<0.001[a]
Hypersensitivity to TMP-SMX — no. (%)	19 (30.2) [N = 63]	6 (17.6) [N = 34]	13 (44.8) [N = 29]	0.027[a]

Abbreviation: HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; LDH, lactate dehydrogenase; ICU, intensive care unit; CMV, cytomegarovirus; TMP-SMX, trimethoprim-sulfamethoxazole.
[a] Statistically significant.

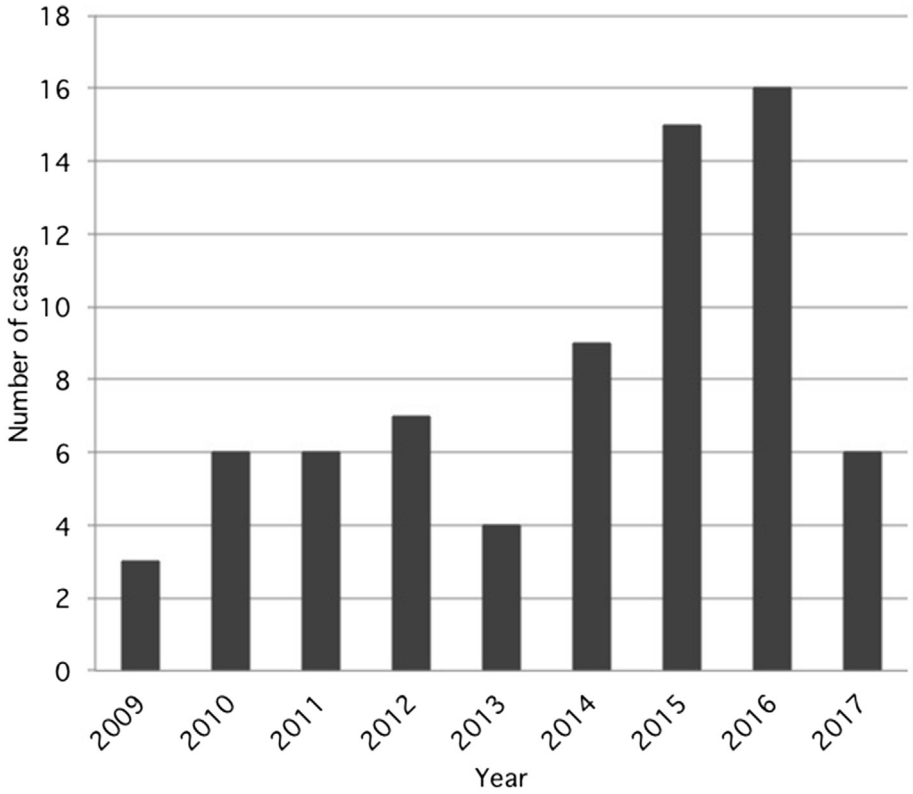

Fig. 1. Number of *Pneumocystis jirovecii* pneumonia cases in each year.

observed in six patients (21.4%) in the HIV-PCP group and one patient (3.1%) in the non-HIV-PCP group ($P = 0.034$). As for diagnosis, brochofiberscopy was performed in 24 non-HIV-PCP cases and in 16 HIV-PCP cases. Among them, positivity of PCR test for *P. jirovecii* in the bronchoalveolar lavage fluid (BALF) was 91.7% in the non-HIV-PCP group and 100% in the HIV-PCP group ($P = 0.543$). However, the Grocott stain for *P. jirovecii* in BALF was positive in only one case in the non-HIV-PCP group compared with the HIV-PCP group (4.3% vs. 73.3%, $P < 0.001$).

Initial TMP-SMX treatment was selected for 34 cases (77.3%) in the non-HIV-PCP group and 29 (93.5%) in the HIV-PCP group ($P = 0.107$). Adjunctive corticosteroid was administered for 33 patients (75.0%) in the non-HIV-PCP group and 14 (45.2%) in the HIV-PCP group ($P = 0.015$). Kaplan–Meier analysis of survival indicated that the overall survival rate was higher for the HIV-PCP group compared with the non-HIV-PCP group ($P = 0.022$) (Fig. 2). Concurrent antibiotics were co-administered with treatment for PCP in 56.8% of the non-HIV-PCP group and 19.4% of the HIV-PCP group ($P = 0.002$). Of the 63 patients who were initially treated with TMP-SMX, 37 patients (58.7%) experienced adverse effects of TMP-SMX requiring discontinuation. The major reasons were drug eruption (36.8%), drug fever (21.1%), serum creatinine elevation, and electrolysis abnormality (18.4%). Although only 12 patients (35.3%) experienced discontinuation in the non-HIV-PCP group, 26 out of 29 (89.7%) required discontinuation in the HIV-PCP group ($P < 0.001$). The mean duration from starting TMP-SMX to changing to other drugs were 10 [7–13.5] days (7.5 [4.5–12] in the non-HIV-PCP group and 11 [8–14.5] days in the HIV-PCP group). Six patients

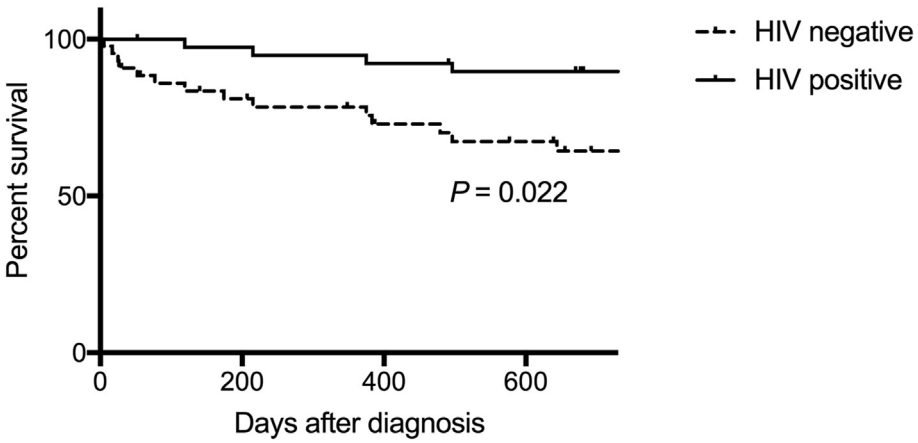

Fig. 2. Kaplan–Meier analysis for overall survival in the HIV-negative or HIV-positive patients with *Pneumocystis jirovecii* pneumonia.

(17.6%) in the non-HIV-PCP group and 13 patients (44.8%) developed assumed hypersensitivity to TMP-SMX (drug eruption and/or drug fever). Adjunctive corticosteroid was prescribed for 47.4% patients who developed hypersensitivity to TMP-SMX and for 52.3% patients who did not develop hypersensitivity ($P = 0.788$).

The characteristics of PCP that develop in HIV-infected or non-HIV-infected patients are known to differ [5]. The reason for this difference was attributed to the immune status and amount of parasite [9]. The immune response to the *P. jirovecii* was considered to be more suppressed in HIV-infected patients, therefore, the symptoms were less severe in the HIV-infected patients than in non-HIV PCP patients [9]. Our study focused on the difficulty in the diagnosis of non-HIV PCP and frequent discontinuation of TMP-SMX owing to adverse effects associated with the treatment of HIV-PCP. The average value of serum β-D glucan was significantly higher in HIV-PCP cases. HIV-PCP cases also had higher Grocott stain positivity for *P. jirovecii* in BALF, possibly reflecting the amount of *P. jirovecii* in BALF [6]. This caused difficulty in diagnosing PCP. Consequently, 25 (56.8%) non-HIV-infected patients with PCP were treated with anti-PCP drugs with other antibiotics compared with HIV-PCP patients (19.4%). Beta-lactam agents (n = 13), macrolides (n = 7), and respiratory quinolones (n = 6) were co-administered for the non-HIV-PCP cases. Differentiating PCP from other atypical pneumonia presenting bilateral ground-grass opacities is challenging based on the lung CT scan findings [1]. Owing to a possible impaired immune status, the severity of PCP was lower in the HIV-PCP group [4,10]. In our study, the symptomatic period prior to diagnosis of non-HIV PCP was shorter than that of HIV-PCP (5 days vs 29 days), as previously reported [5]. Overall mortality was higher in the non-HIV-PCP cases than the HIV-PCP cases. In our study, the positivity of the PCR test for *P. jirovecii* remained high (91.7%) in the non-HIV-PCP group. However, only half of the patients underwent bronchofiberscopy. It was warranted to perform bronchofiberscopy and obtain BALF for PCR to confirm the diagnosis of PCP especially in patients without HIV infection. Prompt diagnosis may also facilitate appropriate antibiotic selection. In our study, half of the non-HIV-PCP patients (n = 20) were diagnosed without the use of bronchofiberscopy. Among them, PCR tests were performed for nine patients using their sputum specimens. The positivity for *P. jirovecii* of sputum specimens was 77.8%. We suggest the PCR test using sputum specimens secure the diagnosis in the patients who do not receive bronchofiberscopy. The number of PCP cases included in this study each year had increased (Fig. 1). This was possibly because of several reasons. First, the PCR test had come to be widely performed for PCP diagnosis. The average number of PCR tests conducted each year for *P. jirovecii* was 19.6 tests in 2013–2017 compared with 9.0 tests in 2009–2012 in our institution. It was also considered that a variety of immunosuppressive therapies contributed to the prevalence of PCP.

Adverse effects possibly caused by TMP-SMX were highly observed in the HIV-PCP cases. Notably, of 30 HIV-PCP cases, TMP-SMX was discontinued in 26 cases (86.7%). The major reasons were drug eruption (30.8%), considered as a hypersensitivity to TMP-SMX. Conventionally in-hospital patients prescribed TMP-SMX experience gastrointestinal symptoms (3.9%) and hypersensitivity symptoms (3.3%) [11]. The incidence of skin eruption due to TMP-SMX increased to 40–80% in patients with HIV infection from 2 to 5% in subjects without HIV infection [12]. Veenstra et al. reported that the strongly immunosuppressive patients were more likely to develop hypersensitivity due to TMP-SMX [13]. However, Carr et al. reported an opposite result that the hypersensitivity was frequently observed in subjects with high $CD4^+$ lymphocyte counts [14]. In our study, the peripheral lymphocyte counts were 1208 (590–1809) and 625 (478–923) ($P = 0.153$) and $CD4^+$ lymphocyte counts were 80 (20–105) and 33 (21–61) ($P = 0.149$) in HIV-positive patients who developed drug eruption and those who did not develop drug eruption, respectively. Our result support the hypothesis that subjects who had more lymphocytes or $CD4^+$ lymphocytes were more likely to develop hypersensitivity to TMP-SMX, although this result was not statistically significant. The reasons of high frequency of adverse effects due to TMP-SMX in HIV-positive patients were not clearly explained. A hypothesis that co-infection with cytomegalovirus or Ebstein-Barr virus and altered immune status arouse the hypersensitivity due to TMP-SMX was proposed [12]. In our study, skin eruptions due to TMP-SMX developed within 10 days after administration as previously reported [15]. It is suggested that close monitoring of HIV-positive patients receiving TMP-SMX is required. Co-administration of adjunctive corticosteroid therapy did not mitigate the hypersensitivity to TMP-SMX.

There were several limitations in our study. This study was performed in a retrospective manner. The total number of participating patients was limited to 75, because PCP is a rare disease. Although we tried to recruit all cases of PCP in our institution within 10 years searching by medical records thoroughly, some cases were possibly missed. Our analysis indicated that the characteristics of PCP in patients with or without HIV infection were quite different. The adverse effects due to TMP-SMX were frequently observed in HIV-positive patients with PCP, requiring close monitoring and switching treatment. The diagnosis of PCP was challenging in the HIV-negative patients, therefore we suggest the bronchofiberscopy and PCR tests for *P. jirovecii* are warranted for the diagnosis of PCP.

Conflicts of interest

Hideaki Kato received grants from Shionogi & Company, Limited, and Merck & Co., Inc. Other co-authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical standards

This study was approved by the ethics committee at each participating institution.

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