Epidemiologic Trends and Clinical Features of *Pneumocystis jirovecii* Pneumonia in Non-HIV Patients in a Tertiary-Care Hospital in Korea over a 15-Year-Period

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SUMMARY: Subsequent to the increasing use of immunosuppressant therapy, *Pneumocystis jirovecii* pneumonia (PcP) has emerged as a life-threatening condition in human immunodeficiency virus (HIV)-negative patients. We investigated changes in epidemiological and clinical characteristics among PcP cases with and without HIV infections. Data of 424 patients diagnosed with PcP in a 2,700-bed Korean tertiary care hospital between February 2003 and April 2017 were retrospectively analyzed. The study included patients with compatible clinical findings in whom PcP was confirmed via direct immunofluorescence assay. The annual average number of cases increased from 12.2 (initial 5-year period) to 42.2 (recent 5-year period). In HIV-negative patients, hematologic malignancy (34.8%) and solid organ transplantation (32.9%) were the most frequent major underlying conditions, and immunosuppressive therapies including corticosteroids (342/362, 94.5%) and chemotherapy (122/362, 33.7%) were significantly associated with PcP infection ($p < 0.001$ for both). The incidence of PcP has continued to increase among non-HIV-infected immunocompromised patients in recent years.
Epidemiologic Trends of PcP Infection without HIV

For statistical analysis, categorical variables were analyzed using the chi-square test or Fisher’s exact test and continuous variables were analyzed using Student’s t-test or the Mann–Whitney U test as appropriate. All tests were two-tailed, and a p value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

The annual numbers of PcP cases admitted per year and the proportions of HIV-positive and HIV-negative patients are illustrated in Fig. 1. During the initial 5-year period of the present study (2003–2007), the average annual incidence of PcP was 12.2 cases; by contrast, this incidence increased to an average of 42.2 PcP cases per year during the most recent 5-year period (2012–2016) (Fig.1). Among all PcP cases, the ratio

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**Table 1. Comparison of the demographics, underlying diseases, and clinical characteristics of HIV-negative and HIV-positive patients with Pneumocystis pneumonia (PcP)**

| Characteristics                        | HIV-negative PcP (n = 362) | HIV-positive PcP (n = 62) | p-value |
|----------------------------------------|----------------------------|--------------------------|---------|
| **Age, yr**                            | 51.0 ± 16.5                | 41.6 ± 13.2              | < 0.001 |
| **Sex**                                |                            |                          |         |
| Male                                   | 211 (58.3%)                | 58 (93.5%)               | < 0.001 |
| Female                                 | 151 (41.7%)                | 4 (6.5%)                 |         |
| **Previous steroid treatment**         | 342 (94.5%)                | 49 (79.0%)               | < 0.001 |
| **Prophylaxis before diagnosis**       | 94 (26.0%)                 | 28 (45.2%)               | 0.002   |
| **Chemotherapy**                       | 122 (33.7%)                | 0 (0.0%)                 | < 0.001 |
| **Radiological findings**              | 301 (83.1%)                | 59 (95.2%)               | 0.015   |
| **Laboratory findings**                |                            |                          |         |
| Hemoglobin, g/dL                       | 9.8 ± 1.9                  | 11.1 ± 1.9               | < 0.001 |
| WBC, /μL                               | 8142.1 ± 7036.3            | 5695.2 ± 3319.2          | 0.008   |
| ANC, /μL                               | 6408.3 ± 4526.2 (n = 342)  | 4048.5 ± 2894.3 (n = 48) | < 0.001 |
| ALC, /μL                               | 788.5 ± 922.0              | 746.3 ± 541.5            | 0.727   |
| Total protein, g/dL                    | 5.4 ± 0.8 (n = 361)        | 6.7 ± 1.0 (n = 61)       | < 0.001 |
| Albumin, g/dL                          | 2.6 ± 0.6 (n = 361)        | 2.6 ± 0.6 (n = 61)       | 0.907   |
| LDH, IU/L                              | 525.9 ± 446.6 (n = 305)    | 463.3 ± 208.0 (n = 50)   | 0.331   |
| CRP, mg/dL                             | 12.1 ± 39.7 (n = 354)      | 7.6 ± 8.0 (n = 54)       | 0.411   |
| CD4, /μL                               | 303.4 ± 524.3 (n = 190)    | 45.5 ± 58.5 (n = 46)     | < 0.001 |
| CD4/CD8                                | 1.3 ± 1.6 (n = 187)        | 0.2 ± 0.1 (n = 3)        | 0.010   |
| **Mortality**                          | 118 (32.6%)                | 11 (17.7%)               | 0.019   |

Values are shown as means ± standard deviations or numbers (%). HIV, human immunodeficiency virus; IDL, interstitial lung disease; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein; LDH, lactate dehydrogenase.
of patients with and without HIV was 1:2.1 during the initial 5-year period but increased to 1:10.9 during the most recent 5-year period. The total number of cases of PCP increased during the study period, but no difference in seasonal frequency was observed (data not shown).

A comparison of the basic demographics, clinical history, and laboratory findings between HIV-positive and HIV-negative patients is shown in Table 1. From February 2003 to April 2017, 424 patients with PCP were identified. Among them, 362 patients (85.4%) were HIV-negative and 62 patients (14.6%) were HIV-positive. HIV-negative patients with PCP had a mean age of 51.0 years and no predominance of either sex, whereas HIV-positive patients had a mean age of 41.6 years and were predominantly male. In most HIV-negative patients, the use of immunosuppressive therapies such as corticosteroids (342/362, 94.5%) and a history of chemotherapy (123/362, 34.0%) were associated with PCP infection. HIV-positive patients were significantly more likely to have received prophylaxis before a diagnosis of PCP than HIV-negative patients \( (p = 0.002) \). The difference in the rate of PCP infection-related mortality between HIV-negative (118/362, 32.6%) and HIV-positive (11/62, 17.7%) patients was statistically significant \( (p = 0.019) \).

The distribution of underlying diseases at the time of PCP diagnosis in HIV-negative patients is shown in Table 2. Among the 362 HIV-negative patients with PCP, hematological malignancy was the most frequent underlying condition \( (34.8\%) \), followed by solid organ transplantation \( (32.9\%) \), inflammatory and autoimmune diseases \( (14.6\%) \), and various organ tumors \( (11.6\%) \). Among the hematologic malignancies, lymphoma and leukemia were the most frequent \( (19.9\% \) and \( 13.0\% \), respectively). The majority of the solid organ transplantations \( (19.1\%) \) were kidney transplantation. The death rates according to underlying diseases ranged from 21.6% for solid organ transplantation to 51.1% for inflammatory and autoimmune diseases.

Our retrospective study of 424 confirmed cases of PCP yielded several important findings. First, the number of cases of PCP has increased among HIV-negative patients but decreased among HIV-positive patients during the last 15 years; however, PCP remains a significant problem in both HIV-positive and HIV-negative patients. Second, although the clinical outcome of PCP was more unfavorable in HIV-negative patients than in HIV-positive patients, only 26.0% of HIV-negative patients received prophylaxis. Third, our data show that HIV-negative patients harbor a diverse spectrum of underlying diseases of which hematological malignancy (including lymphoma and leukemia) is the most frequent.

PCP remains an unresolved opportunistic fungal infection in HIV-positive as well as HIV-negative patients who are severely immunocompromised as a consequence of the increased use of immunosuppressive drugs \( (8) \). Since the 2000s, several studies indicated an increase in the number of patients with PCP without HIV, but only a few studies conducted in France and China have compared the clinical features in HIV-positive and HIV-negative patients with PCP infection \( (9–11) \). Those studies emphasized the importance of primary prophylaxis for at-risk patients without HIV infection considering the high mortality rates, which ranged from 30% up to 60%, yet only 3.7% to 5.8% of the patients received prophylaxis \( (12,13) \). Comparatively, the PCP-related mortality rate and the PCP prophylaxis rate in HIV-negative patients based on our data were 32.6% and 26.0%, respectively. Both the previous and our studies showed that the mortality rate of HIV-negative patients with PCP was significantly higher, suggesting that early identification of patients at risk is necessary to implement prophylaxis before disease progression.

In conclusion, this study provides the current trend of PCP incidence and significant differences in clinical aspects between HIV-negative and HIV-positive patients with PCP. Our data indicate that immunocompromised patients at risk of PCP infection might need early identification and appropriate prophylaxis in a timely manner.

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Conflict of interest None to declare.

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Table 2. Underlying diseases at the time of Pneumocystis jirovecii pneumonia diagnosis in HIV-negative patients \( (n = 362) \)

| Hematologic malignancies | 126 (34.8%) |
|--------------------------|-------------|
| Lymphoma                 | 72 (19.9%)  |
| Leukemia                 | 47 (13.0%)  |
| Myeloma                  | 2 (0.6%)    |
| Hodgkin’s lymphoma       | 1 (0.3%)    |
| Myelodysplastic syndromes| 4 (1.1%)    |
| Transplant               | 119 (32.9%) |
| Kidney                   | 69 (19.1%)  |
| Liver                    | 30 (8.3%)   |
| Heart                    | 8 (2.2%)    |
| Pancreas                 | 12 (3.3%)   |
| Inflammatory and autoimmune disorders | 53 (14.6%) |
| Interstitial lung disease| 22 (6.1%)   |
| Ulcerative colitis       | 6 (1.7%)    |
| Dermatomyositis          | 6 (1.7%)    |
| Systemic lupus erythematosus | 5 (1.4%) |
| Behçet diseases          | 2 (0.6%)    |
| Autoimmune hepatitis     | 2 (0.6%)    |
| Rheumatoid polyarthritis | 1 (0.3%)    |
| Sarcoidosis              | 1 (0.3%)    |
| Wegener’s granulomatosis | 1 (0.3%)    |
| Sjögren’s syndrome       | 1 (0.3%)    |
| Solid tumor              | 42 (11.6%)  |
| Others\(^\text{1}\)       | 22 (6.1%)   |

\(^\text{1}\): End-stage renal disease, alcoholic liver cirrhosis, Sézary disease, asthma, Stevens-Johnson syndrome, pulmonary embolism, Takayasu’s arteritis, Still’s disease, immune thrombocytopenic purpura, acute kidney injury, and drug addiction.
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