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Risk Factors for *Pneumocystis jirovecii* Pneumonia in Patients with Rheumatic Disease

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Abstract

Background: *Pneumocystis Jirovecii* Pneumonia (PCP) remains a significant cause of pneumonia in non-HIV immunosuppressed patients. There are no established guidelines on PCP prophylaxis in patients with rheumatic diseases. This study aimed to identify the risk factors associated with PCP infection with the aim of guiding prophylaxis in patients with rheumatic disease.

Method: Patients with rheumatic diseases diagnosed with PCP in a single tertiary care center were included as cases. Control patients were selected from patients followed up by the Division of Rheumatology. The ratio of case to control was 1:3. Demographic characteristics, clinical and laboratory findings of patients, systemic involvement of rheumatic disease and recent treatment history were recorded.

Results: Seventeen patients were diagnosed with PCP during the study period. A total of 51 patients completed clinical data were included in the control group. Rheumatoid arthritis (33.8%) was the most common disease, followed by systemic lupus erythematosus. None of the patients received PCP prophylaxis. The recent treatment of all patients consisted of methylprednisolone, disease modifying anti-rheumatic drugs, other immunosuppressive drugs, and biological agents (55.9%, 35.3%, 19.1%, and 11.8% of the patients, respectively). None of the PCP patients had active arthritis, but 52.9% of the control group had. Regarding treatment, PCP patients more frequently used glucocorticoids at a dose of 16 mg or higher (58.8% *vs.* 11.8%, p<0.001). Similarly, PCP developed more frequently in patients who had received pulse treatment in the preceding six months (47.1% *vs.* 2%, p<0.001). None of the patients receiving biological agents developed PCP, all patient used biologic agent were in the control group (p=0.056)

Conclusion: PCP develops more frequently in patients with rheumatic diseases receiving moderate-to-high doses of glucocorticoids and/or who have received pulse immunosuppressive therapy in the last six months. These patients should be strongly considered for PCP prophylaxis.

Keywords: Rheumatic diseases • Prophylaxis • *Pneumoccytis jirovicii* • Immunosuppression • Pneumonia

Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; COPD: Chronic Obstructive Pulmonary Disease; F: Female; Hb: Hemoglobin; M: Male; WBC: White Blood Cells; PCP: *Pneumocystis jirovecii* Pneumonia

Introduction

Pneumocystis jirovecii causes Pneumonia (PCP) in patients with immunosuppression due to underlying malignancy, organ transplantation, AIDS, and other conditions [1] The development of high-activity anti-retroviral therapies and the use of prophylaxis lead to significant reduction in the incidence of PCP in AIDS patients [2]. However, there is an increase in the frequency of PCP in patients with cancer, organ transplantation and connective tissue diseases due to the growing use of new immunosuppressive and immunomodulatory therapies [3]. Additionally, PCP patients without HIV appear to have more serious disease in that they have longer hospital stays, more frequently require intensive care unit admission and mechanical ventilation than HIV(+) PCP patients [4-7]. Similarly, the mortality rate is higher (32-50%) in patients with rheumatic disease [8].

In recent years, the treatment and course of rheumatic diseases have changed with the use of disease modifying anti-rheumatic drugs like methotrexate at earlier disease stages and the development and use of new biological agents targeting specific molecules and pathways of the immune system [9,10]. The use of methotrexate, however, has been reported to be associated with an increased risk of PCP [11]. Besides, systemic steroids commonly used in the treatment of autoimmune diseases have been shown to be a major predisposing factor for the development of PCP [12]. Different immunosuppressive agents also appear to be associated with varying incidence of and mortality rates associated with PCP [13]. Additionally, the immune dysfunction related to rheumatic diseases may also contribute to the increased risk of infection [14].

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Despite the facts that there is a growing number of immunosuppressed patients with rheumatic diseases and that PCP is a frequent infectious complication in such patients, there is no standard approach for PCP prophylaxis. In fact, a recent survey has shown that there is little consensus among infectious disease physicians about PCP prophylaxis in connective tissue diseases [15]. One rational approach could be to examine whether any high-risk subgroup(s) exists, to whom prophylactic treatment could be targeted. Therefore, the aim of this study was to determine the risk factors for the development of PCP in patients with rheumatic disease.

Materials and Methods

This was a case-control retrospective study of patients with rheumatic disease followed up at a single tertiary care center.

The case group, hereafter named "PCP group", was composed of all patients with rheumatic diseases who developed PCP and who were hospitalized in the Department of Pulmonary Diseases between March 2009 and January 2016. These patients were being followed up at the rheumatology outpatient clinic prior to their admission for PCP. The diagnosis of PCP was based on detecting *P. jirovecii* in respiratory samples using microscopy and molecular assays (real-time PCR) in the presence of consistent clinical and radiological findings. To detect *P. jirovecii*, microbiological examination was performed on various respiratory samples. The majority of the samples were Bronchoalveolar Lavage (BAL) and mini-BAL fluids. Sputum and endotracheal aspirate were used in two patients only. One of them was not intubated, and was able to provide a sputum sample, and a sufficient amount of endotracheal aspirate was obtained in the other. For microscopic investigation, Giemsa, and Gram Weigert stains were used [16-18]. For real-time PCR, DNA was extracted from raw respiratory samples (BAL, mini-BAL, tracheal aspiration material and sputum). The DNA isolation was performed using the QIAamp DNA mini kit according to the manufacturer's protocol (Qiagen) [19,20].

The control group included patients with rheumatic diseases followed up at the Rheumatology outpatient clinic of the Department of Internal Medicine. They were extracted from the clinic patient list to reach a case-to-control ratio of 1:3. Thus, the control group consisted of 51 patients who were selected from outpatients seen within the same months as the cases and who matched the PCP group in terms of age and underlying rheumatic disease.

The hospital records of all patients were retrospectively examined and the following parameters were recorded: demographic data, diagnoses at admission, underlying diseases and comorbidities, organ involvement of rheumatic diseases, laboratory findings including the blood cell count, renal and hepatic function tests, treatment for rheumatic diseases. To evaluate whether there was any association with the development of PCP, all treatments and pulse therapies administered for the rheumatic disease during the previous six months were recorded. The drugs were classified as glucocorticoids, biological agents, disease modifying anti-rheumatic drugs (sulfasalazine, methotrexate and leflunomide) and other immunosuppressive drugs (azathioprine, cyclophosphamide, and cyclosporine). For the glucocorticoid therapy, the effect of different previously reported dose thresholds was analyzed [8,21,22]. Pulse treatment was defined as the use of methylprednisolone, 500-1000 mg daily, for 3-5 days and/or of cyclophosphamide at a dose of 750 mg/m^2 per month.

The study was approved by the Institution's Ethical Committee (20-4.1T/33).

Statistical methods

SPSS version18 (SPSS, Chicago, IL, USA) was used for data recording and analysis. Descriptive analysis was performed for the demographic characteristics of the patients. The Mann-Whitney U test was used to compare the continuous variables with abnormal distribution and to analyze subgroups with small numbers of patients. Chi-square test or Fisher Exact test were used to compare categorical variables. We considered $p<0.05$ as statistically significant.

Results

A total of 68 patients with rheumatic diseases were included in the study. Seventeen patients with a definite diagnosis of PCP formed the PCP group. Besides, 51 other patients with rheumatic diseases matched for age, gender and underlying disease and who had no history of PCP were included as the control group. The median age of all patients was 54.5 (44-63) years and 51.5% were female. The most common rheumatic disease was rheumatoid arthritis (33.8%) followed by systemic lupus erythematosus (17.6%). Demographic and clinical features of the patients are shown in Table 1. None of the patients had previously received any prophylaxis for *P. jirovecii*. All patients with PCP diagnosis were hospitalized and received anti-PCP therapy (mainly trimethoprim-sulfamethoxazole) together with supportive care, including, when necessary, invasive mechanical ventilation. Of the 17 patients, 10 (58.8%) died.

We sought to determine whether there are any clinical and laboratory parameters that may be associated with a higher likelihood of PCP development. Univariate analysis showed that the groups were similar in terms of underlying rheumatologic disease types and organ/system involvements related to the disease, including the pulmonary involvement. However, 52.9% of the control group *vs.* none of the patients in the PCP group had signs of active arthritis. PCP patients, on the other hand, had a higher rate of other pulmonary comorbidities (35.3% *vs.* none $p<0.001$). Additionally, the patients diagnosed with PCP had lower hemoglobin levels, and higher neutrophil counts and aspartate aminotransferase levels, although none of these differences were clinically significant (Table 1).

Most of the patients were being treated with glucocorticoids at the time of assessment and the patients in the PCP group more frequently received methylprednisolone at doses equal to or higher than 16 mg (58.8% and 11.8%, $p<0.001$). Besides, 8 (47.1%) of the PCP patients *vs.* one of the control patients had received pulse treatment within the preceding six months ($p<0.001$). None of the patients in the PCP group had received any biologic agent, whereas 10 patients in the control group had been treated with one such agent during the six months prior to assessment (Table 2).

The most recent treatments of all patients consisted of glucocorticoids, disease modifying anti-rheumatic drugs, other immunosuppressive drugs and biological agents, which were used in 55.9%, 35.3%, 19.1%, and 11.8% of the patients, respectively.

We found that the development of PCP was associated with a history of pulse therapy within the preceding six months and the use of methylprednisolone at a daily dose of 16 mg or higher at the time of diagnosis.

Discussion

In this study we have shown that a history of pulse therapy within the preceding six months and the use of methylprednisolone at a daily dose of 16 mg or higher at the time of diagnosis were significant risk factors for development of PCP in patients receiving treatment for rheumatic diseases.

PCP, which may cause severe respiratory failure, carries a significant risk of morbidity and mortality. The PCP-related mortality and morbidity rates are higher in solid organ and hematological stem cell transplant recipients, patients treated with immunosuppressive drugs for rheumatic diseases or for interstitial lung diseases than in HIV-positive patients [3]. Not only the medical therapy but also the immune disorders associated with the underlying rheumatic diseases may increase the risk for PCP in these patients [14]. In spite of the relatively poor prognosis of this opportunistic infection, we found that prophylaxis was not given to any of the immunosuppressed patients who were followed up for rheumatological disease. Consistently with these observations, recent surveys of practicing rheumatologists and infectious disease physicians have shown that there is limited consensus about PCP prophylaxis in connective tissue diseases. 57.3% of infectious disease physician made recommendations for PCP prophylaxis, but there were unclear results when prophylaxis should be recommended and which factors

Table 1. Underlying diseases, organ involvement and laboratory findings of the two groups.

	All Patients (n=68)	PCP (n=17)	Control (n=51)	p value
Age, (year)*	54.5 (44-63)	55 (47.5-63.5)	54 (43-63)	0.55
Gender (M/F)	33/35	9/8	24/27	0.78
Underling rheumatic disease,n(%)				
Rheumatoid arthritis	23 (33.8)	5 (29.4)	18 (35.3)	0.77
Systemic lupus erythematosus	12 (17.6)	2 (11.8)	10 (19.6)	0.71
Behcet 's disease	6 (8.8)	1 (5.9)	5 (9.8)	1
Psoriatic arthritis	6 (8.8)	2 (11.8)	4 (7.8)	0.63
Microscopic polyangiitis	6 (8.8)	1 (5.9)	5 (9.8)	1
Ankylosing spondylitis	5 (7.4)	1 (5.9)	4 (7.8)	1
Dermatomyositis	5 (7.4)	2 (11.8)	3 (5.9)	0.59
Polymyositis	2 (2.9)	2 (11.8)	0	0.06
Takayasu arteritis	2 (2.9)	1 (5.9)	1 (2.0)	0.44
Granulomatous polyangiitis	1 (1.4)	0	1 (2.0)	1
Vasculitis, n (%)	15 (22.1)	3 (17.6)	12 (23.5)	0.74
Organ Involvement, n (%)				
Active arthritis	27 (39.7)	0	27 (52.9)	<0.001
Skin	25 (36.8)	4 (23.5)	21 (41.2)	0.37
Eye	7 (10.3)	1 (5.8)	6 (11.8)	1
Lungs	7 (10.3)	4 (23.5)	3 (5.9)	0.05
Kidney	4 (5.6)	1 (5.8)	3 (5.9)	1
Hematologic	1 (1.5)	1 (5.8)	0	0.24
Mononeuritis multiplex	1 (1.5)	0	1 (2.0)	1
Central nervous system	1 (1.5)	1 (5.8)	0	0.24
History of previous pneumonia, n (%)	4 (5.8)	1 (5.8)	3 (5.8)	1
Presence of pulmonary comorbidity, n (%)	6 (8.8)	6 (35.2)	0	<0.001
COPD	2 (2.9)	2 (11.7)	0	
Pulmonary Embolism	2 (2.9)	2 (11.7)	0	
Asthma	1 (1.5)	1 (5.8)	0	
Lung metastasis	1 (1.5)	1 (5.8)	0	
Lung involvement of rheumatic disease, n (%)	7 (10.2)	4 (23.5)	3 (5.9)	0.05
Laboratory parameters*				
Hb (gr/dL)	12.9 (11.5-14.2)	11.6 (10.2-13.3)	13.3 (12.1-14.2)	0.03
WBC count (103/µL)	7.8 (6.4-9.5)	8.1 (6.8-12.3)	7.6 (6.1-9.2)	0.26
Lymphocyte count (103/µL)	2.0 (1.2-2.6)	1.3 (0.6-2.5)	2.0 (1.3-2.7)	0.13
Neutrophil count (103/µL)	4.6 (3.1-6.3)	5.4 (4.6-8.8)	3.7 (2.9-5.3)	0.013
AST (U/L)	20 (17-28)	26 (20-47)	18 (15-26)	0.006
ALT (U/L)	21 (15-35)	29 (15-53)	20 (15-31)	0.19

*: median (p25-p75)

may effect on decision. In fact, 96% of these physicians were unaware of presence of guideline about PCP prophylaxis in patients with rheumatic disease [15]. In other studies, in which rheumatologists were assessed, the rates of prescription of prophylactic antibiotics were detected as 50.3% and 69.5% for these special group [22,23]. The results pointed that patient' characteristics who use prophylaxis were much widely.

The incidence of PCP may vary according to the underlying autoimmune or inflammatory diseases. The highest incidence rates have been reported in granulomatosis with polyangiitis (8-12%), followed by polyarteritis nodosa (6.5%) and polymyositis/dermatomyositis (2.7%). The lowest incidence rates have been observed in patients with rheumatoid arthritis (0.1-0.3%) [24-27]. In this series, although the number of patients was small, the distribution of the diseases in the two groups appeared similar.

The use of high-dose glucocorticoids has also been shown to be associated with a higher likelihood of developing PCP [28]. In another study, the patients with autoimmune diseases treated with high doses of glucocorticoids were found to have a 19-fold higher risk for PCP than patients receiving lower doses [8]. Similarly, the use of prednisolone at doses of 15 mg per day or higher, for a period longer than three months has been found to be associated with a significantly increased risk of PCP [12]. In accordance with the latter study, we have also found that ongoing treatment with methylprednisolone at a daily dose of 16 mg or higher was associated with an increased risk for the development of PCP.

Pulse therapies have previously been reported as a risk factor for PCP in HIV-negative immunocompromised patients [29]. This study also showed that patients diagnosed with PCP more frequently had a history of pulse treatment with glucocorticoids and/or cyclophosphamide during the preceding six months.

Patients with PCP had lower hemoglobin levels and higher neutrophil counts, possibly associated with more active rheumatic disease and, consequently, more frequent use of glucocorticoids. The PCP group also had numerically, but not significantly, lower lymphocyte counts than the control group. Lymphopenia and low CD4+ count have previously been found as other risk factors for PCP in immunosuppressed patients with autoimmune inflammatory disorders [12]. The lymphocyte counts in patients with PCP ranged between 88 and 1,053/µL in previous reports [3].

Biological anti-rheumatic drugs are relatively new and effective treatment options that are increasingly accepted in rheumatology practice. Although recent surveillance reports in Japan indicate a high incidence of PCP in patients with rheumatoid arthritis receiving tumor necrosis factor α inhibitors [30-32], there are contradictory reports on this association [33,34]. It appears that the incidence of PCP may differ according to the biological agents [3]. In

Table 2. Comparison of the two groups with regards to their treatments at the time of or prior to PCP diagnosis.

Treatments	PCP (n=17)	Control (n=51)	p value
Drugs used for pulse treatment, n (%)	8 (47.1)	1 (2.0)	<0.001
Methylprednisolone	4	0	
Methylprednisolone+Cyclophosphamide	4	1	
Biological agent in the preceding 6 months, n (%)	0	10 (19.6)	0.056
Methylprednisolone treatment, n (%)	14 (82.4)	24 (47.1)	0.013
>30 mg/day	5 (29.4)	3 (5.9)	0.016
>20 mg/day	7 (41.1)	3 (5.9)	0.001
≥16 mg/day	10 (58.8)	6 (11.8)	<0.001
<16 mg/day	7 (41.2)	45 (88.2)	
Azathioprine, n (%)	3 (17.6)	6 (11.8)	0.43
Methotrexate, n (%)	2 (11.8)	16 (31.4)	0.2
Leflunomide, n (%)	1 (5.9)	6 (11.8)	0.67
Sulfasalazine, n (%)	0	2	1

our study, none of the patients with PCP had been treated with these agents during the preceding six months; in other words, patients treated with biologic agents did not seem to have an increased risk for PCP. This may be due to the fact that biological agents allow better control of the disease and help avoid the use of high doses of glucocorticoids. Further observations are needed to more precisely determine the individual effect of these therapies on the development of PCP.

This study has some limitations. First, this was a single center study and had a relatively small sample size. Thus, although our initial aim was to perform multivariate logistic regression analysis to determine independent risk factors and to prevent the effect of confounding variables, we were not able to construct a model, as there was only one control patient who had received pulse treatment and no patient with PCP who had been treated with biologic agents. Second, it was a retrospective analysis. On the other hand, we were able to collect all the relevant data from the patients' hospital records and, as the incidence of PCP is low, a prospective study would take several years. Third, the control group did not have identical features to the study group, but we made every effort to find control patients from the same time periods as the cases who were matched for age, gender and underlying rheumatic disease. Although it may be argued that the control group consisted of outpatients, the patients who were diagnosed with PCP had also been followed up as outpatients prior to their admission for PCP. Despite these limitations, we were able to identify two subgroups of patients who may be targeted for prophylaxis.

Conclusion

We have shown that in patients with rheumatic diseases, treatment with pulse immunosuppressive drugs during the preceding six months and/or receiving high dose glucocorticoids are associated with an increased risk for development of PCP. As PCP is associated with a high mortality rate, these patients must strongly be considered for PCP prophylaxis.

Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki and informed consent was obtained from subjects. The study was approved by the Ethical Committee of Ege University (20-4.1T/33).

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Author Contributions

Study concept and design: AS. Acquisition, analysis, or interpretation of data: PKE, IN and FYZ. Drafting of the manuscript: IN, PKE, AS and FZY. Critical revision of the manuscript for important intellectual content: PKE, AS and FZY. Statistical analysis: PKE. Administrative, technical, or material support: AYG, ST and NT. Study supervision: AS.

Conflict of Interest

None.

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