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Pneumocystis jirovecci pneumonia in connective tissue diseases: Comparison with other immunocompromised patients

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ABSTRACT

Introduction: *Pneumocystis jirovecci* pneumonia (PJP) is an opportunistic fungal infection occurring in immunocompromised patients, such as those with human immunodeficiency virus (HIV), organ transplantation, malignancies and connective tissue diseases (CTDs). Risk factors for PJP are not well characterised, leading to uncertainty regarding the indications for antimicrobial prophylaxis and monitoring. This study compared differences between patients with and without CTDs who developed PJP.

Methods: Retrospective data was collected for all subjects with a positive toludine blue O stain or a positive *P. jirovecci* PCR and a concurrent respiratory illness that was clinically consistent with PJP between 2002 and 2013 at the Royal Melbourne Hospital, Australia. Sub-groups were assigned according to the underlying disease. Peripheral blood results were retrieved from an in-house pathology database.

Results: Eleven of 90 subjects (12.2%) diagnosed with PJP had underlying CTDs. The CTDs group was more likely to have been exposed to corticosteroids (100% versus 35.2%, $p < 0.001$) and other iatrogenic immunosuppression (90.9% versus 24.6%, $p < 0.001$). After adjusting for age and gender, the CTDs group had greater lymphopaenia (0.17 versus 0.58 $\times$ 10^9/L; $p = 0.034$) and were older (69.6 versus 50.6 years; $p < 0.001$) than the non-CTD group. Excluding renal transplant recipients, people with CTDs also had lower eGFR than the non-CTD group (65 versus 80; $p = 0.015$).

Conclusions: CTDs contributed to a significant proportion of total PJP diagnoses. Clinicians treating CTDs must be vigilant for PJP, particularly in older patients with exposure to corticosteroids or other iatrogenic immunosuppression, lymphopaenia and renal impairment; factors which may lower the clinical threshold for initiating prophylaxis.

Introduction

Pneumocystis jirovecci (formerly *Pneumocystis carinii*) pneumonia (PJP) is an opportunistic fungal infection most commonly occurring in acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV). However, iatrogenic immunosuppression is now commonplace for organ transplantation, malignancy and systemic inflammatory illnesses, giving rise to another at-risk patient population. A potentially underappreciated group within the non-HIV-infected cohort is that of connective tissue diseases (CTDs), including patients with conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory muscle diseases and systemic vasculitides.

The incidence of PJP infection in the CTD population has been estimated at 1–2% [1,2], but with new detection methods such as polymerase chain reaction (PCR), the prevalence of PJP in CTDs populations may be even higher than previously considered [3]. Although PJP is relatively uncommon in CTDs patients, it is often fatal and mortality rates may be higher than in the HIV population [1].

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Unlike HIV, there are no evidence-based guidelines regarding the use of PJP prophylaxis in the CTDs population and recommendations have been extrapolated from studies in the non-CTDs setting [2,4]. Nevertheless, relative to other conditions, a higher rate of adverse events have been noted among people receiving PJP prophylaxis for CTDs [5], raising safety concerns for clinicians.

Lymphopaenia is prevalent in cohorts developing PJP, including those with haematological malignancies, renal transplants and HIV [6–8]. Lymphopaenia has also been associated with PJP infection in CTDs and may be associated with increased mortality [9–11]. However, it is unclear whether the degree of lymphopaenia or other laboratory parameters differ significantly between CTDs and other immunocompromised states. Determining such factors may help to inform recommendations for PJP prophylaxis. The aims of this study were therefore (i) to examine the contribution of CTDs to the total number of PJP diagnoses and (ii) to determine any between group differences in subject characteristics and basic laboratory parameters between people with non-CTDs and CTDs who had been diagnosed with PJP.

Methods

Data collection

This single-center Australian study was conducted at the Royal Melbourne Hospital (RMH), which is a public, university-affiliated tertiary referral adult teaching hospital. Retrospective data collection covered the period January 2002 to September 2013. Inclusion criteria comprised all patients who had a positive toludine blue O stain or a strongly positive (as judged by low polymerase chain reaction (PCR) cycle number, i.e., <32 cycles) PCR on sputum or bronchoalveolar lavage (BAL) specimens. Although toludine blue O stains were available from study inception in 2002, *P. jirovecci* PCR was only available at RMH from 2006 onwards.

All cases were reviewed to ensure the presence of a respiratory illness consistent with PJP, together with either a positive toludine blue O stain or a positive *P. jirovecci* PCR. Where a subject was found to have recurrent admissions for PJP ($n = 3$), only the initial episode was included in the study. Where a subject was found to have both a positive toludine blue O and *P. jirovecci* PCR, the first positive result was considered to be the time of PJP diagnosis.

For each episode, patient characteristics (age at diagnosis and gender) and blood results were retrieved from the hospital pathology database. The lowest peripheral blood cell counts, eGFR and albumin and the highest liver function test abnormalities and inflammatory markers, documented within a week either side of the microbiological diagnosis of PJP, were recorded. Mortality was attributed if the patient died within the admission where PJP was diagnosed. Medical histories were also examined to determine exposure to PJP prophylaxis, as well as exposure to corticosteroids or other immunosuppressive drugs (e.g., chemotherapy and anti-rejection medications) within the 3 months preceding PJP diagnosis.

The study was approved by the Royal Melbourne Hospital Human Research Ethics Committee.

Statistical analyses

Independent *t*-tests were used to compare unadjusted differences in the characteristics between subject groups. The CTD group was compared with the remainder of the cohort in its entirety and with the major non-CTD sub-groups of HIV, renal transplant, haematological malignancy and solid malignancy. To quantify the between group differences for blood parameters such as the lymphocyte count, general linear models were used and estimated marginal means calculated, adjusting for age and gender. Chi-squared analyses were used to compare between group differences with dichotomous outcomes (e.g., exposure to corticosteroids). A *p*-value of less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed using SPSS statistical package (standard version 21.1; SPSS, Chicago, IL, USA).

Results

A total of 90 subjects who fulfilled the diagnostic criteria of either a positive *P. jirovecii* PCR (64%) or toludine blue O stain (36%) with a concurrent respiratory illness were included in the study. Four other cases were excluded because no information regarding an underlying disease process or the presence of a concurrent respiratory illness could be determined. Of the 90 subjects, 39 (43.3%) had HIV/AIDS, 16 (17.8%) had haematological malignancies, 14 (15.6%) had solid malignancies, 11 (12.2%) had CTDs, 7 (7.8%) had renal transplants, 2 (2.2%) had inflammatory bowel disease and 1 (1.1%) had chronic airways disease. The characteristics of the 11 patients with CTDs are shown in Table 1. All CTD patients were exposed to corticosteroids in the 3 months prior to PJP diagnosis, and only subject 8 had not been taking any other biological or non-biological disease modifying anti-rheumatic drug (DMARD). The maximum dose of corticosteroids in the 3 months preceding PJP diagnosis for each participant is shown in Table 1. The mean dose of oral corticosteroids in the CTD group was 15.5 mg ($\pm$ 12.3 mg) (range: 5–37.5 mg). One CTD subject (subject 11) had been pulsed with intravenous methylprednisolone in the month prior to developing PJP. Three of the 11 patients had been exposed to cyclophosphamide, but in 2 of these patients, it was 3 years prior to the diagnosis of PJP. Patient 8 had been exposed to cyclophosphamide 3 months prior to the diagnosis of PJP. Although one CTD patient had PJP prophylaxis (Pentamidine), compliance with this therapy is unknown.

Clinical information was examined in 57 of the 79 non-CTDs patients where the medical record was available. Fewer patients in the non-CTDs group had been exposed to any corticosteroids in the 3 months preceding PJP diagnosis (35.1% versus 100%, $p < 0.001$). The mean corticosteroid dose tended to be greater in the CTD sub-group (15.5 mg versus 7.6 mg, $p = 0.11$). Moreover, the CTD group were more likely than the non-CTD group to have been exposed to other forms of iatrogenic immunosuppression in the 3 months preceding PJP diagnosis (90.1% versus 24.6%, $p < 0.001$). Exposure to corticosteroid and other immunosuppression was limited to the non-HIV patients. When the HIV sub-group was excluded, the CTD group still had a higher percentage of people exposed to corticosteroids (100% versus 40.5%, $p = 0.01$) and iatrogenic immunosuppression (100% versus 24.6%, $p < 0.001$). Two patients in the non-CTDs group had received PJP propyhlaxis (Trimethoprim-sulfamethoxazole). Five people died during the admission for PJP, 3 in the CTDs group and from the non-CTDs group (27.3% versus 2.5%, $p < 0.001$), both of whom had underlying haematological malignancies.

The laboratory and subject characteristics of the total PJP cohort, as well as the CTD and non-CTD sub-groups are shown in Table 2. On average, the total cohort was lymphopaenic ($0.53 \pm 0.56 \times 10^9$/L) but was not leukopaenic or neutropaenic and was mildly anaemic (108.5 $\pm$ 20.3 g/L) and hypoalbuminaemic (26.1 $\pm$ 5.9 g/L). Moreover, despite having raised inflammatory markers (CRP, 109.5 $\pm$ 95.7 mg/L; ESR, 83.7 $\pm$ 45.0 mm in an hour), the total cohort did not have a reactive thrombocytosis (platelet count: $240 \pm 133 \times 10^9$/L). The total cohort demonstrated renal impairment, with a mild reduction in the eGFR (74 $\pm$ 23).