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Pneumocystis jiroveci pneumonia in rheumatic disease: a 20-year single-centre experience

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ABSTRACT

Objective. *Pneumocystis jiroveci pneumonia (PJP) is an opportunistic infection with high mortality among patients with underlying rheumatologic conditions. Given the paucity of prospective data to guide treatment, clinical guidelines to initiate PJP prophylaxis are based on expert opinion and identify patients on ≥20 mg daily prednisone for ≥4 weeks duration for treatment. Herein we describe the PJP experience in rheumatic disease over a 20-year period at a single academic medical centre to investigate this 20 mg threshold and risk associated with lymphocyte counts, co-existing lung disease and immunosuppressive medications.*

Methods. *We conducted a retrospective review of all admitted patients who received a PJP or PCP ICD-9 code (136.3) from January 1996 through October 2015.*

Results. *Twenty-one cases of confirmed PJP (by immunofluorescence or polymerase chain reaction) were reviewed, averaging to one case/year. The most common underlying rheumatologic conditions were inflammatory myopathy, lupus, and granulomatosis with polyangiitis. None of these 21 patients was receiving PJP prophylaxis upon admission. Eighteen (86%) were receiving ≥20 mg prednisone daily at the time of PJP diagnosis. Of the 3 treated with <20 mg prednisone, all received concomitant immunosuppressive medications, 2 with cyclophosphamide. Overall, there was a 43% (9/21) mortality rate. Immunosuppressant medication use, interstitial lung disease, or lymphocyte count did not impact mortality risk.*

Conclusion. *PJP portends high mortality yet is a largely preventable complication of rheumatic disease treatment. Consideration to initiate prophylaxis should be made for patients exceeding the daily 20 mg prednisone threshold, and those receiving cyclophosphamide.*

Introduction

PJP is an opportunistic infection that is associated with high mortality in patients with underlying rheumatologic diseases. Despite being described in patients with rheumatic diseases since the 1960s (1), there still exists great heterogeneity in how physicians risk-stratify patients and prescribe PJP prophylaxis (2). This is in large part due to a lack of prospective studies that accurately assess medication dosage, duration, and underlying disease characteristics. Given the paucity of data in this area, clinical guidelines are based on expert opinion extrapolated from non-rheumatic disease patient populations (3-5). A commonly cited recommendation is to consider PJP prophylaxis in patients who are on ≥20 mg prednisone for ≥2 or 4 weeks duration which is largely based in retrospective studies on oncology and transplant patients (3, 4). However, these cut-offs have not been rigorously evaluated in the rheumatologic field, in patients who are often on combination immunosuppressant therapy. In addition, many studies emphasise lymphocyte count as a potential biomarker to determine risk for developing PJP and/or guiding prophylaxis decision-making (6-8, 12). Again, studies have not adequately investigated particular threshold values of lymphocyte counts (either absolute lymphocyte count or CD4 T cell count) to act upon when deciding whom to prescribe prophylaxis. Herein we describe our 20-year experience at a single academic tertiary care medical centre, in order to investigate the following compelling issues: the trend in PJP diagnosis over time, the threshold of 20 mg prednisone to inform prophylaxis decision-making, and examination of risk factors including specific immunosuppressant medications, interstitial lung disease, and lymphopenia.

Materials and methods

We conducted a retrospective review of all patients admitted to a single tertiary academic institution who were assigned an ICD-9 code for Pneumocystis jiroveci (PJP) or Pneumocystis carinii (PCP) (136.3) with an underlying rheumatologic disease from January 1st 1996 to September 30th 2015. These cut-off dates were based on the adoption of an electronic medical record at our institution (January 1996) and when ICD-10 coding went into effect (October 2015). Inclusion criteria were patients who had documented evidence of PJP (by im-

Table I. Demographic profile on 21 consecutive cases of PJP at Johns Hopkins Hospital, 1996-2015.

Patient characteristics	n=21 (%)
Age in years on admission	52±17
Sex (%)	13 (62) Female
Race	14 (67) Caucasian
	5 (24) African American
	1 (5) Asian
	1 (5) Other
Rheumatologic disease	4 (17) Myositis
	4 (17) SLE
	3 (14) GPA
	2 (7) RA
	2 (7) Sarcoid
	1 (4) PAN
	1 (4) SSc
	1 (4) Overlap
	3 Other
ILD*	6 (50)
Absolute lymphocyte count (cell/mm^3)	558±449
Average prednisone dose (on admission)	36 mg/day
Transfers from Outside Institutions (%)	8 (38)
Death (%)	9 (43)

SLE: systemic lupus erythematosus; GPA: granulomatosis with polyangiitis; RA: rheumatoid arthritis; PAN: polyarteritis nodosa; SSc: systemic sclerosis, ILD: interstitial lung disease.
*Records on ILD only available on 12 cases.

munofluorescence or polymerase chain reaction, PCR) as well as a canonical rheumatologic disease. Patients with HIV, underlying oncologic diagnoses or organ transplant history were excluded, as were diagnoses of PJP that were only presumptive. The initial query produced 290 records that were subsequently hand-searched to apply the aforementioned exclusion criteria, which yielded a total of 21 records. Records were abstracted for clinical information including demographic information, rheumatologic disease, presence of interstitial lung disease, immunosuppressive regimen, lymphocyte count on admission, and vital status at time of discharge. Information was extracted primarily from documents including the history of present illness, inpatient laboratory data, medication reconciliation, and discharge summaries. Interstitial lung disease was considered present if documented in past medical history and/or supported by previous pulmonary function studies or high resolution CT scan. Summary statistics were performed using Stata v.14 (College Station, TX). The Johns Hopkins School of Medicine Institutional Review Board approved of this study (no. IRB00062579).

Results

A total of 21 cases with confirmed PJP were identified, averaging to a rate of approximately one case per year. The cases were evenly distributed throughout the 20 year period; 10 Cases occurred between 1996-2006, and 11 cases occurred between 2007-2015. Demographic information for patients can be found in Table I.

The most common underlying rheumatologic conditions with PJP infection were inflammatory myopathy, systemic lupus erythematosus (SLE), and granulomatosis with polyangiitis (GPA). None of these 21 patients were receiving PJP prophylaxis upon admission. The average time from rheumatologic disease diagnosis to PJP diagnosis was 4.2±4.2 years. Data on duration of immunosuppressive therapy prior to diagnosis were unavailable. The average prednisone dose on admission was 36 mg/day with a range of 1-60 mg/day and the average absolute lymphocyte count was 558/mm^3 ± 449; range 0-1580; normal 1100-4800/mm^3). For those patients with available lung function data (pulmonary function testing and/or high-resolution CT imaging, n=12), half had ILD. Eight patients were transferred to our institution from an outside hospital. Overall, there was a 43% (9/21) mortality rate.

No single factor (cyclophosphamide exposure, presence of prior interstitial lung disease) was associated with an increased mortality. There was a substantial difference in ALC (615 cells/mm^3 in patients who survived *versus* 489 cells/mm^3 in patients who died) but this did not reach statistical significance (p-value=0.55). No patient died that was receiving less than 20 mg daily prednisone upon diagnosis of PJP.

Individual information regarding prednisone dose and other immunosuppressant medication can be found in Table II. Eighteen patients (86%) were receiving ≥20 mg prednisone dose at the time of PJP diagnosis. Of the 3 who were receiving <20 mg prednisone (patient numbers 6, 13, 14), all were prescribed concomitant immunosuppressive medications, including 2 who received cyclophosphamide. All but three patients were lymphopenic upon presentation (ALC<1100 cells/mm^3). The most common non-prednisone immunosuppressant medications were methotrexate (n=6, 29%) and cyclophosphamide (n=6, 29%). Among the patients in this series, none developed PJP on less than 20 mg daily prednisone monotherapy.

Discussion

Our study is consistent with prior literature that PJP is more often observed in patients with inflammatory myopathies, GPA, and SLE compared to other rheumatic diseases (10, 11). It remains uncertain as to what predisposes these diseases to a higher risk for developing PJP. Other authors have speculated that these conditions are more likely to be treated/managed with aggressive immunosuppression including high dose corticosteroids and cyclophosphamide, perhaps accounting for this increased risk. In our study, 3/7 (43%) of the patients with GPA/SLE received cyclophosphamide in addition to prednisone, but this was not seen in patients with inflammatory myopathy (0/4). In addition, the average prednisone dose of these three conditions, GPA, SLE, and inflammatory myopathy, was 32 mg/day, compared to 35 mg/day in patients with other rheumatologic diseases arguing against higher doses of corticosteroids being associated with these three diagnoses. Another proposed explanation for this increased risk is that other PJP risk factors such as lymphopenia and underlying lung disease are perhaps more prevalent in patients with DM and SLE compared to other rheumatic conditions (9). We speculate that it is likely a combination of these factors that are responsible for the increased risk of PJP in these specific rheumatic diseases.

This study expands our current understanding of PJP in rheumatic disease in multiple ways. Notably, none of the patients who developed PJP did so on less than 20 mg of prednisone monotherapy. This may be reflective of the low number of PJP cases, or, alternatively suggesting a threshold effect that 20 mg prednisone monotherapy portends.

Table II. Year of diagnosis, demographic, clinical, and immunosuppressive regimen among 21 cases of PJP at Johns Hopkins Hospital, 1996-2015.

Patient number	Year of Dx	Age	Disease	Absolute lymphocyte Count	Prednisone (mg/day)	Other Immunosuppressant	Death
1	2015	51	Inflammatory myopathy	820	40	MTX (22.5 mg q week), Rituximab	-
2	2010	56	Inflammatory myopathy	730	20	None	Yes
3	2006	20	Inflammatory myopathy	420	NR	MMF	Yes
4	1997	32	Inflammatory myopathy	500	60	None	Yes
5	2007	43	SLE	640	20	HCQ	-
6	2004	31	SLE	720	10	CYC	-
7	2000	37	SLE	568	50	None	-
8	1997	66	SLE	231	60	CYC (50 mg TID)	-
9	2000	64	GPA	612	NR	CYC	Yes
10	2012	75	GPA	NR	NR	Rituximab	-
11	2012	20	GPA	100	30	Rituximab	Yes
12	2008	63	RA	274	50	MTX	-
13	2006	64	RA	1520	1	TNFi, MTX	-
14	2011	49	SSc	220	5	CYC, MTX	-
15	2003	49	Sarcoid	517	55	CYC (25 mg daily)	-
16	2010	64	Sarcoid	173	30	None	Yes
17	2014	61	Sarcoid *vs*. GCA	40	35	MTX (15 mg q week)	Yes
18	2009	46	Other arthritis	130	35	None	Yes
19	2009	74	RA *vs*. GCA	1580	60	MTX (20 mg q week), HCQ	Yes
20	1998	79	PAN	156	27.5	CYC (50 mg daily)	Yes
21	1998	62	Overlap	1216	60	None	-

SLE: Systemic lupus erythematosus; GPA: granulomatosis with polyangiitis; RA: rheumatoid arthritis; SSc: systemic sclerosis; GCA: giant cell arteritis; PAN: polyarteritis nodosa; MMF: mycophenolate mofetil; CYC: cyclophosphamide; MTX: methotrexate; HCQ: hydroxychloroquine; TNFi: tumour necrosis factor inhibitor.

In addition, we explore the small but informative subpopulation of patients who developed PJP on less than 20 mg prednisone. Three of the patients developed PJP while on 1, 5, and 10 mg of daily prednisone in addition to other immunosuppressant medications. This group of patients who develop PJP while on less than 20 mg of prednisone presents a challenge for clinicians when developing guidelines regarding whom to prescribe prophylaxis.

In addition, while our study supports other work that has shown that individuals with rheumatologic diseases who develop PJP frequently have low lymphocyte counts (8, 12); three patients had normal lymphocyte counts.

Strengths of our study include the long study window of 20 years, focus on prednisone as a binary treatment (less than/greater than 20 mg), and confirmed documentation of every PJP case in a single institution. Limitations of our study include its retrospective nature. In addition, the total number of cases was small, particularly when examining results for specific rheumatic diseases. Furthermore, we were not able to detect any factor that was significantly associated with mortality, possibly due to small size of our study. However, our case series of 21 patients is one of the largest in the last 50 years from a single centre.

PJP is a largely preventable complication of rheumatic disease treatment with a high mortality, and often occurs years after the initial rheumatologic disease is diagnosed. No patient developed PJP while on less than 20 mg prednisone monotherapy; however, lower doses were noted in those who developed PJP while on concomitant cyclophosphamide. While expert guidelines recommend PJP prophylaxis with patients on ≥20 mg prednisone for ≥4 weeks, consideration should be made for patients receiving any dose of prednisone who are also receiving cyclophosphamide, regardless of the underlying rheumatic disease.

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