Characteristics and outcome according to underlying disease in non-AIDS patients with acute respiratory failure due to Pneumocystis pneumonia

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Abstract (196)

Purpose : In the non-AIDS group, several underlying conditions and immune defects could lead to different PCP presentations. This study compared PCP presentation and outcome according to the underlying disease.

Methods : Secondary analysis of a previous published prospective observational study including 544 PCP patients. Only non-AIDS patients were included. Underlying disease was defined as chronic lymphocytic leukemia (CLL), organ transplantation, solid cancer, allogenic hematopoietic stem cell transplant (AHSCT), other hematological diseases, and immunosuppressive treatment. Clinical characteristics and outcome were compared between groups. Multiple correspondent analyses compared clinical characteristics at diagnosis. Day 30 ~~(Day 30)~~ mortality was analyzed.

Results: Three hundred and twenty-one patients were included in the study. The underlying diseases were hematological malignancy (n = 75), ~~(~~AHSCT~~)~~ (n = 14), CLL (n = 19), solid organ transplant (n = 94), solid tumor (n = 39), and immunosuppressive treatment (n = 57). Compared with other underlying diseases, PCP related to CLL was closer to PCP related to AIDS presentation (long duration of symptoms before diagnosis, high level of dyspnea, and low oxygen saturation at diagnosis). Day 30 mortality was associated with underlying disease, oxygen flow, and shock at ICU admission.

Conclusion: PCP presentations may vary according to the underlying reason for immunosuppression. Response to treatment and adjuvant steroid therapy should be analyzed regarding this result.

Introduction

Pneumocystis jirovecii pneumonia (PCP) remains a life-threatening, opportunistic disease related to T cell suppression, macrophage defect, or other immunodeficiencies. New treatments and higher life expectancies in various oncologic or immune disease illustrate that PCP among non-AIDS patients is steadily increasing [1–6].

Several studies thus far have demonstrated significant differences between AIDS and non-AIDS patients in clinical pictures, physiopathology, and mortality related to PCP. In fact, non-AIDS patients experienced a shorter length of symptoms, a higher inflammation in the lungs, and a significantly higher severity and mortality despite a lower pulmonary burden of *Pneumocystis* [6–8].

However, immunosuppressive conditions leading to PCP onset remain different inside the subgroup of non-AIDS patients. Immune defects for solid organ transplant recipients may be different from those in chronic lymphoid leukemia (CLL) patients or solid tumor patients [9–11]. The clinical presentation and response to treatment may vary between all those underlying diseases, but those differences are not well established in the literature. Indeed, comparing patients inside the non-AIDS group may be of importance.

The aim of this study was to identify different clinical profiles and mortality-related factors among the different non-AIDS groups at risk for PCP.

Materials and methods

The study was a secondary analysis of an observational study. The study has already been described [6]. Briefly, between January 1, 2007, and December 31, 2010, all consecutive patients (AIDS infected or non-AIDS infected patients) with confirmed *Pneumocystis* pneumonia were included in the study. The study was conducted in accordance with French law for observational studies on retrospective data which did not require patient consent for this analysis. Confirmed *Pneumocystis* pneumonia was defined as having a positive result for *Pneumocystis jirovecii* by Gomori-Grocott or toluidine blue stain or positive immunofluorescence test results for a broncho-alveolar lavage (BAL) fluid or induced sputum specimen. Patients for whom only PCR results were positive were not included in the study.

All clinical, biological, and imaging data were prospectively reviewed based on patients hospitalization records. Clinical characteristics at admission included respiratory symptoms and extra-respiratory organ failure.

Diagnosis criteria were assessed, and outcome during ICU stay was recorded.

In this secondary study, only non-AIDS patients were analyzed. Underlying diseases were described as chronic lymphoid leukemia (CLL) diagnosis with or without treatment, AHSCT whatever the length from transplantation, other acute hematological malignancies, active solid tumor when patients had been treated within the past 5 years with chemotherapy, solid organ transplantation, immunosuppressive treatment for immune disease, or other reasons. Because of the high prevalence of PCP during CLL and the physiopathology assumed close to the one of PCP related to AIDS, patients with CLL was firstly described separately [12,13]. For CLL patients, high prevalence of PCP was usually associated T cell depletion related to fludarabine treatment [9] In the further analysis, all patients with

hematological malignancies were analyzed in the same group. In case of several underlying disease, hematological disease was first considered (for example, if patient had hematological disease after solid organ transplantation (SOT), he was considered as hematological patient), then the most recent underlying disease (for example if patient with SOT had a recent increase of immunosuppressive treatment, he was classified as drug related immune suppression).

Characteristics at diagnosis and outcome were analyzed. Prophylaxis was defined as an antifungal therapy before PCP onset (sulfamethoxazole/trimethoprim or atovaquone or pentamidine). Shock was defined with the need of vasopressors. Only day 30 mortality was analyzed.

Statistical Analysis

Data from clinical or biological presentation and outcome were described according to underlying disease. Quantitative variables are presented as median (interquartile range) and were compared between disease groups using Kruskal-Wallis tests; categorical variables are presented as count (percent) and were compared between groups using χ^2 tests.

Multiple correspondence analysis (MCA) was performed to identify profiles of clinical presentation in non-AIDS *Pneumocystis* patients, possibly related to the underlying diseases. For the MCA, missing data were handled by imputation using a correspondence analysis procedure, with the missMDA package on R statistical platform. We report figures illustrating the first two components describing variability in observations based on clinical presentation signs. In figure 1, underlying diseases have been added on the plot to illustrate the link between clinical variables and underlying disease. Figure 2 represents the corresponding individuals factor map according to the underlying disease.

Factors associated with Day 30 mortality were evaluated with univariate analysis using a logistic regression model estimating odds ratios and their 95% confidence intervals. in the sample with available follow-up data (n=280). Variables that were significant at the 5% level in univariate analysis were candidates for multivariate analysis. A multivariate model was selected using a backward stepwise selection procedure based on p-values (threshold = 0.05). The main analysis was performed using multiple imputations by chained equations to handle missing data (50 imputations with 20 iterations). Estimates for the effect of variables on mortality from imputed data were computed using Rubin's rules. A sensitivity analysis was performed using a complete-cases approach, yielding consistent results

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All tests were two-sided, and a p-value lower than 0.05 was considered as indicating a significant association. Analyses were performed on the R statistical platform, version 3.2.2 with the FactoMineR, missMDA, and mice packages.

Results

During the study period, 321 non-AIDS immunosuppressed patients were included in the study. Median age was 59 [IQR 46–68] years, and 193 (62%) patients were male. Underlying immunosuppression was related to hematological malignancy (n = 75, 23%), chronic lymphoid leukemia (n = 19; 6%), AHSCT (n = 14; 4%), solid tumor (n = 39; 12%), SOT (n = 94; 29%) or immunosuppressive treatment for other reasons (n = 57; 18%), and other immunosuppressive reasons (n = 23; 7%).Hematological diseases were mostly non Hodgkin or Hodgkin disease (n=46, including 6 autologous HSCT), multiple myeloma (n=10) or acute myeloid leukemia (n=9). Solid organ transplantations were mostly kidney transplantation (77/94). Immunosuppressive treatment for underlying disease as connective tissue disease or systemic vasculitis was steroid (n=27), chemotherapy +/- steroids (n=21), anti CD20 +/- steroids (n=4), other (n=5). Other immunosuppressive conditions were pulmonary or cutaneous underlying diseases resulting in intermittent steroids treatment (n=14), underlying connective tissue disease without treatment (n=6), unknown reason of immunosuppression in the database (n=3). At the time of diagnosis, most of the patients did not receive anti-*Pneumocystis* prophylaxis or had recently withdrawn prophylaxis (n = 266; 83%).

The delay between respiratory symptoms and diagnosis was 5 [1–15] days, and below 7 days for 135(42%) patients.

Clinical presentations included fever over 38°C (n = 181; 83%), cough (n = 109; 54%), and dyspnea (n = 151; 73%). Oxygen flow required at diagnosis was 0 [IQR 0–6] l/min. Half of the patients were admitted to the ICU (n = 134; 50%). Noninvasive mechanical ventilation was required for 50 (15.6%) patients, among whom 46 (92%) needed secondary invasive

mechanical ventilation (iMV). One-third of the patients (n = 98; 30.5%) needed iMV. Shock occurred at diagnosis in 22 (6.8%) patients.

Pulmonary co-infections were frequent with bacteria (n = 48; 17%) or virus (n = 26; 9%). Viral coinfection included 16 CMV infections and 8 herpes simplex virus infections. Bacterial co-infections were mostly related to *Pseudomonas* (n=9), *Streptococcus pneumonia* (n=9), *Escherichia Coli* (n=4), *Staphylococcus or enterococcus* (n=12).

The lung CT scans of 165 (51.4%) patients were analyzed. Ground-glass opacity was the most frequent lesion (n = 110; 67%) but was associated with alveolar lesion in 36 (22%) patients. For 3 patients (2%), the lung CT scans was normal.

The delay from hospital admission to treatment was 2 [0–6] days. Adjuvant steroid therapy was prescribed in 106 (43%) patients.

Table 1 described the clinical presentation and outcome according to the underlying disease. In this table, some characteristics must be highlighted. First, the duration of symptoms before diagnosis was longer for CLL and AHSCT (respectively 15 [10–26] and 26 [12–30] days), close to the duration in AIDS patients. Prophylaxis guidelines were different according to the underlying disease, and PCP occurred mostly during prophylaxis vacancy. Steroid before PCP onset was differentially prescribed depending on the underlying disease ($p < 0.001$); the highest frequency of steroid prescription was observed in patients with solid organ transplant or immunosuppressive treatment consistent with the usual treatment regimen for those underlying diseases. Although symptoms were similar for all underlying diseases, cough prevalence was different according to the underlying disease ($p<0.001$); it was mostly observed in hematological diseases, including CLL and AHSCT patients.

Age at diagnosis was different, reflecting the underlying age onset for each disease group.

Multiple correspondence analyses (Figs. 1 and 2) highlight those clinical differences according to the underlying disease. Overall, clinical presentation variables could be summarized in two main components explaining respectively 25.7% and 22.6% of observations variability. The presence of a coinfection was the main characteristic discriminating 2 clinical profiles.

Day 30 mortality was 23% (n = 64/280). Table 2 described the univariate analysis of factors associated with Day 30 mortality. Table 3 described the multivariate analysis of factors associated with Day 30 mortality. Higher oxygen flow at admission (OR = 1.16 per 1L/min increment [1.08–1.24], p < 0.001) and shock at ICU admission (OR = 7.67 [2.63–22.37], p = 0.0002) were associated with higher mortality. On the contrary, solid organ transplant (OR = 0.19 [0.07–0.53], p = 0.001) was associated with lower mortality rate compared to patients with immune diseases or solid tumors. The sensitivity analysis on the complete-case dataset was consistent with these results and is reported in table 1 suppl.

Discussion

This study is the first to compare several immunosuppressive conditions for PCP onset. Although the study was mostly an exploratory analysis several points should be highlighted. The study included a high number of patients with PCP. Although prevalence of PCP outside the group of AIDS patients, has been increasing, the number of cases has remained low, and this study included all the patients in 17 French hospitals within a three-year period [6,14,15]. We found that several immune conditions lead to variable clinical presentations.

First, PCP occurred in patients without prophylaxis, and the incidence of prophylaxis varied inside the non-AIDS group. Although prophylaxis remains recommended in CLL patients with treatment or in solid organ transplant patients during more than 6 months (depending on the organ) after transplant [20], there are no guidelines regarding the patients with solid tumor or receiving immunosuppressive treatment. However, this study confirmed that prophylactic treatment should be discussed for patients with immunosuppressive treatment, particularly for those who need steroid boli for rejection treatment in solid organ transplant or graft-vs.-host disease [4]. Also, prophylaxis may be discussed for some kinds of solid tumors for patients who receive steroids [3].

Second, clinical presentation seems different between underlying diseases. Presentation of PCP related to CLL or AHSCT were closer to that occurring in AIDS patients than other underlying diseases with a long duration of symptoms before diagnosis, high level of dyspnea, and low oxygen saturation at diagnosis. Furthermore, physiopathology of immunosuppression is different for those diseases. The use of fludarabine during the course of treatment for CLL or before AHSCT leads to a profound T cell depletion as in severe AIDS infection [9]. T cells are known to be involved in *Pneumocystis* clearance and also the CD4/CD8 ratio could regulate lung inflammation. Therefore, the duration of

symptoms for LLC and AHSCT could be related to T cell depletion after fludarabine. Secondarily after fludarabine treatment, T cell recovery has been associated with a shift toward Th1 cytokine secretion and could be associated with higher lung inflammation [9].

On the contrary, immunosuppressive treatment for immune disease or solid organ transplant, mostly steroid therapy, have been associated with altered macrophage function. Macrophages are highly involved in *Pneumocystis* pathogenicity. Indeed, a recent study demonstrated the double role of macrophages in anti-*Pneumocystis* defense [16]. This cell may recognize *Pneumocystis* and clear it from the lungs via an inflammatory response leading to TNFα, IL6, IL1β secretion. Also, macrophage could balance inflammatory response via IL10 secretion. Steroids may modify the balance between inflammatory and antifungal function by modifying macrophage response [10].

The pathogenicity of *Pneumocystis* could then be different according to the underlying disease or treatment. Our study brings some arguments to explore the different type of *Pneumocystis* disease. Thus, response to adjuvant therapy may be variable according to the underlying disease [17,18].

Pneumocystis pneumonia in non-AIDS patients remains associated with high mortality, up to 50%, according to the underlying disease [14]. Although this infectious disease was associated with severe hypoxemia, shock remained rare. Consistently, in our study, only 8% of patients had shock during the course of *Pneumocystis* pneumonia. Only Day 30 mortality was analyzed to reduce the bias for the mortality related to the underlying disease. However, mortality remained higher in hematological diseases patients than in patients with solid organ transplant or immunosuppressive treatment. The severity of the underlying disease and the possibility of treatment after *Pneumocystis* pneumonia recovery may influence mortality and clinical decisions.

Our study had several limitations. First, this was a retrospective study, with missed data. However, we used a multiple imputation approach for the analysis and performed a sensitivity analysis on complete cases which did not modify results on factors associated with Day 30 mortality.

Second, data were recorded more than 10 years ago and medical care would be modified within this period. However, the primary objective of the study was to discriminate PCP presentation between several underlying diseases. Although, treatments and ICU procedures have been improving within the last 10 years which could have modified mortality, PCP presentation at admission may remained stable according to the underlying immunosuppression.

We also had no information about the functional status of each patient and their nutritional status, or comorbidities, which are also known factors associated with the outcome of these patients in the ICU and in the hospital [19]. Comorbidity scores, body mass index, and functional status were probably not the same in different patient groups, all of which could influence mortality.

Moreover we had no information about the decrease of dose or the suspension of immunosuppressive treatments in each group, which may also had an impact on the final outcome.

Finally, we separated patients in six groups according to the underlying disease, resulting in a limited number of patients in each group.

Conclusion

To conclude, our study shows different presentations and prognoses of *Pneumocystis* pneumonia according to the underlying disease. These differences may be explained with the different types of alterations of the immune system. All those data should be confirmed with further study. Our study added hypothesis concerning presentation and response to

292 treatment according the underlying diseases. For example, analyzing response to
293 adjunctive steroids for non-AIDS patients with PCP may include underlying disease in the
294 further study. Likewise, mortality is associated with the severity of the patients at the time
295 of diagnosis, determined by the presence of shock and higher need of oxygen.
296

Ethical approval: The appropriate ethics committee approved the first study

Consent to participate : non applicable

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Authors contributions :

GB, LB, EA, VL design the study, performed analysis and wrote the manuscript

AR, SV, FRG, SH, DM, AD, SLG, FD, ML, DT, CP, APB, JB, AB, XI, IDJ, DM, DP, CH, EM, included patients, reviewed and approved the manuscript

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Competing Interest: Antoine Roux, MD,; Sandrine Valade, MD; Florence Gangneux-Robert, PharmD, PhD; Samia Hamane, MD; Daniele Maubon, MD, PhD; Anne Debourgogne, PhD, MPH; Solène Le Gal, DVM, PhD; Frederic Dalle, PharmD, PhD; Marion Leterrier, PharmD; Dominique Toubas, MD, PhD; Christelle Pomares, MD, PhD; Anne Pauline Bellanger, PharmD, PhD; Julie Bonhomme, MD, PhD; Xavier Iriart, PhD; Isabelle Durand-Joly, PhD; Denis Magne, PhD; Denis Pons, Pharmacien Biologiste; and Eric Maury, MD, PhD, have disclosed no relevant financial relationships. Christophe Hennequin, MD, PhD, has disclosed the following relevant financial relationships: served as an advisor or consultant for Gilead Sciences, Inc., Merck Sharp & Dohme Corp; Pfizer Inc. Elie Azoulay, MD, PhD, has disclosed the following relevant financial relationships: Gilead Sciences, Pfizer, Astellas, Alexion, Fisher-Paykel. Dr Lemiale has disclosed being memeber of a research group which received grant from Pfizer, Fisher-Paykel, gilead, Alexion , Astellas.

Availability of data and materials : data are avalaible on reasonnable request. required because of observational study.

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386
387 Tables and figures legend

388 **Table 1**: Characteristics at diagnosis according to the underlying disease

389

390 * Missing values: gender (n = 11), age (n = 8), prophylaxis (n = 42), duration of respiratory
391 symptoms (n = 91), temperature (n = 102), cough (n = 119), dyspnea (n = 113), Sa02 (n =
392 184), oxygen flow (n = 144), ICU admission (n = 52), time from admission to treatment (n =
393 115), and day 30 mortality (n = 41)

394

395 **Table 2**: Univariate analysis of risk factors associated with DAY 30 mortality

396 IS: immunosuppressive treatment. CLL: chronic lymphoid leukemia

397

398 **Table 3**: Multivariate analysis of factors associated with DAY 30 mortality

399

400 **Figure 1**: Multiple correspondence analysis of clinical symptoms in non-AIDS
401 Pneumocystis patients according to the underlying disease

402 First two components could explain variability in observations up to 22.6 and 25.7%.

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404

405 **Figure 2**: Multiple correspondence analysis of patients according to the underlying
406 disease.

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Table 1

Variables	Hematological malignancy (n = 75)	Chronic lymphoid leukemia (n = 19)	Allogeneic stem cell transplant (n = 14)	Solid tumor (n = 39)	Solid organ transplant (n = 94)	Immunosuppressive treatment (n = 57)	Other immunosuppressive condition	p
Age (year) *	61 [52–73]	67 [62–76]	43 [32–57]	59 [49–64]	54 [44–61]	64 {53–74]	60 [43-68]	<0.001
Male gender*	47 (67)	12 (63)	8 (62)	21 (54)	59 (65)	30 (55)	16 (70)	0.67
No prophylaxis or recently withdrawn prophylaxis*	64 (85)	15 (79)	8 (57)	38 (97)	76 (80)	52 (96)	13 (100)	<0.001
Steroids prior to PCP	26 (35)	4 (21)	8 (57)	17 (44)	75 (80)	51 (89)	2 (9)	<0.001
Duration of respiratory symptoms (days)*	5 [0–15]	15 [10–26]	26 [12–30]	4 [0–7]	7 [0–15]	4 [0–12]	6 [4-14]	0.004
Dyspnea*	37 (79)	11 (85)	8 (89)	13 (54)	43 (68)	30 (73)	9 (82)	0.22
Cough*	29 (62)	12 (86)	5 (71)	7 (30)	34 (58)	18 (44)	4 (36)	0.013
T°>38°C*	48 (91)	13 (93)	8 (100)	15 (65)	53 (83)	35 (78)	9 (75)	0.085
SaO2 at admission (%)*	90 [87–94]	93 [87–96]	83 [74–96]	90 [86–96]	92 [90–96]	95 [89–98]	72 [64-85]	0.13
Oxygen flow at admission (L/min)*	0 [0–4]	0 [0–1]	0 [0–6]	2 [0–14]	0 [0–2]	6 [0–14]	0 [0-4]	0.069
ICU admission*	26 (42)	4 (25)	9 (69)	18 (53)	37 (47)	33 (65)	7 (47)	0.055
Time from hospital admission to treatment (days)*	2 [1–6]	2 [0–3]	0 [0–1]	2 [1–8]	2 [1–6]	2 [0–4]	7 (1-10)	0.081
D30 Mortality*	15 (22)	3 (17)	6 (50)	14 (40)	6 (8)	17 (33)	3 (17)	<0.001

Table2

Variables	OR [CI95%]	p
Age (> or < 65 years)	2.37 [1.35–4.18]	0.003
Gender (female)	0.92 [0.52–1.64]	0.77
Underlying conditions		
Solid tumor and IS* treatment	1	
Solid organ transplantation	0.18 [0.07–0.44]	0.0002
Hematological malignancy or chronic lymphoid leukemia	0.56 [0.29–1.08]	0.083
Allogeneic stem cell transplantation	2.45 [0.77–7.83]	0.13
Prophylaxis		
None	1	
Continuous	0.25 [0.09–0.70]	0.009
Duration of respiratory symptoms		
<7 days	1	
7–21 days	0.58 [0.27–1.25]	0.17
>21 days	0.74 [0.26–2.13]	0.58
T>38°C	1.47 [0.59–3.64]	0.40
Cough	0.54 [0.27–1.09]	0.083
Dyspnea	1.32 [0.59–2.93]	0.49
SaO2 at diagnosis	0.96 [0.93–1.00]	0.029
Oxygen flow at diagnostic	1.15 [1.08–1.22]	<0.0001
Shock at admission	4.95 [2.03–12.1]	0.0005
Hospital acquired or coinfection	1.72 [0.95–3.13]	0.075
Adjuvant Steroid therapy	1.58 [0.86–2.93]	0.14

Table 3

Variables	OR [CI95%]	p
Underlying conditions		
Solid tumor and Is treatment	1	
Solid organ transplantation	0.19 [0.07–0.53]	0.001
Hematological malignancy or chronic lymphoid leukemia	0.75 [0.34–1.63]	0.47
Allogeneic stem cell transplantation	3.60 [0.93–13.9]	0.06
Oxygen flow at diagnostic	1.16 [1.08–1.24]	<0.0001
Shock at admission	7.67 [2.63–22.37]	0.0002