Associations with *Pneumocystis* Pneumonia in Solid Organ Transplant Recipients: Impact of Posttransplant Lymphoproliferative Disorder

Zachary A. Yetmar, MD[1]; Dustin Duffy, MS[2]; Byron H. Smith, PhD, MS[2]; Holenarasipur R. Vikram, MD[3]; Lisa Brumble, MD[4]; Andrew H. Limper, MD[5]; Elena Beam, MD[1]

[1]Division of Public Health, Infectious Diseases, and Occupational Medicine; [2]Division of Clinical Trails and Biostatistics; [5]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

[3]Division of Infectious Diseases, Mayo Clinic, Phoenix, AZ, USA; [4]Division of Infectious Diseases, Mayo Clinic, Jacksonville, FL, USA

ABSTRACT

BACKGROUND

Pneumocystis jirovecii pneumonia (PCP) is a potentially deadly infection afflicting the immunocompromised population, including solid organ transplant recipients. Several risk factors have been described, including acute rejection, lymphopenia, and cytomegalovirus (CMV) infection. However, little is known regarding the risk imparted by posttransplant lymphoproliferative disorder (PTLD).

METHODS

We performed a nested case-control study of solid organ transplant recipients diagnosed with PCP from 2000-2020. PCP was defined as positive smear or polymerase chain reaction testing with compatible clinical symptoms and radiographic findings. Two control were matched to each case by year of first transplant, first transplanted organ, and sex. Each control had at least as much follow-up from their transplant date to their matched case's PCP diagnosis date. Multivariable conditional logistic regression was performed to analyze theorized risk factors.

RESULTS

Sixty-seven cases met inclusion criteria and were matched to 134 controls (**Table 1**). Median age was 60.9 years, and the most common transplant type was kidney (52.2%). Fourteen patients had a history of PTLD, 12 of which developed PCP. All cases of PTLD were monomorphic, 6 were EBV-positive, 9 were receiving chemotherapy at the index date, and only 1 control patient was receiving PCP prophylaxis. The cases with PTLD developed PCP a median of 85 days after PTLD diagnosis, while the two controls were diagnosed more than 1 year earlier. After adjusting for age, acute rejection requiring treatment within the last 6 months, CMV infection within 6 months, current PCP prophylaxis, and lymphopenia (lymphocyte count < 0.5 x10^9/L) within 6 months, PTLD had a significant association with PCP (OR 14.0, 95% CI 1.7-114.5; p = .014). Lymphopenia was also associated with PCP (OR 8.2, 95% CI 3.2-20.7; p < .001), while the other factors were not.

CONCLUSIONS

Diagnosis of PTLD is independently associated with subsequent PCP after adjustment for recognized risk factors. This association is likely influenced by PTLD-directed chemotherapy, particularly regimens containing rituximab. PCP prophylaxis should be initiated in solid organ transplant recipients with PTLD, particularly those undergoing active therapy, and those with severe lymphopenia.

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BACKGROUND

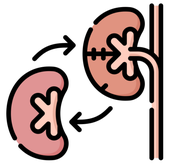
- Solid organ transplant recipients (SOTRs) are at risk for *Pneumocystis* pneumonia (PCP)
- Described risk factors for development of PCP include augmented immunosuppression for acute rejection, cytomegalovirus (CMV) infection, and use of rituximab.
- Posttransplant lymphoproliferative disorder (PTLD) is common early after transplantation and often requires alterations in maintenance immunosuppression or cytotoxic chemotherapy.
- Few data have evaluated the association between PTLD and PCP in SOTRs and timing of PCP after PTLD.
- We sought to evaluate a group of SOTRs with PCP and matched controls to evaluate an association with PTLD.

METHODS

- Nested case-control study of adult SOTRs with PCP and matched controls from 2000-2020.
- PCP defined as positive *Pneumocystis* smear or PCR with compatible signs, symptoms, and/or radiographic findings of PCP.
- Controls were matched 2:1 by year of first transplant, first transplanted organ, sex, and adequate follow-up from date of transplantation to date of their associated case's PCP diagnosis date.
- Associations were analyzed by multivariable conditional logistic regression and time-to-event data were analyzed by the Kaplan-Meier method.

RESULTS 1

- 67 cases were matched to 134 controls (**Table 1**).
- Median time from first transplant to PCP diagnosis was 4.4 years (interquartile range [IQR] 2.1-9.0).
- Transplanted organs
  - Kidney 47.8%
  - Liver 17.9%
  - Heart 19.4%
  - Pancreas 3.0%
  - Lung 1.5%
  - Multiorgan 10.4%



RESULTS 2

- 14 patients (12 cases, 2 controls) had a history of PTLD prior to their index date
- 9 case patients with PTLD were currently receiving chemotherapy at the time of diagnosis.
- After adjusting for lymphopenia, CMV infection, age, recent acute rejection, and PCP prophylaxis, diagnosis of PTLD was significantly associated with PCP (**OR 14.02, 95% CI 1.72-114.51; *p* = .014**)
- Of the adjusted factors, lymphopenia (**OR 8.16, 95% CI 3.21-20.71; *p* <.001**) and CMV infection (**OR 9.21, 95% CI 1.0-84.69; *p* = .05**) were associated with PCP.
- Median time from PTLD diagnosis to PCP diagnosis was 85 days (IQR 47.5-104.5; **Figure 1**).
- Patients with PTLD who had not started chemotherapy had a range of 7-15 days to PCP diagnosis.
- Most patients who started chemotherapy received rituximab as a component (8/9)
- No discrete cutoff for absolute lymphocyte count was found; risk appears to continue to increase as lymphocyte count decreases (**Figure 2**).

Table 1: Patient characteristics

	Control (N=134)	Case (N=67)	Total (N=201)
Age, years	60.7 (48.3, 69.4)	61.7 (55.4, 68.5)	60.9 (50.9, 69.4)
Male sex	80 (59.7)	40 (59.7)	120 (59.7)
Subsequent transplant	11 (8.2)	8 (11.9)	19 (9.5)
Acute rejection	7 (5.2)	5 (7.5)	12 (6.0)
CMV infection	1 (0.7)	10 (14.9)	11 (5.5)
Charlson comorbidity index	2.0 (1.0, 4.0)	4.0 (2.0, 4.0)	2.0 (2.0, 4.0)
PTLD	2 (1.5)	12 (17.9)	14 (7.0)
Prior rituximab administration	3 (2.2)	14 (20.9)	17 (8.5)
Pneumocystis prophylaxis	12 (9.0)	4 (6.0)	16 (8.0)
Maintenance IS			
- Tacrolimus	95 (70.9)	49 (73.1)	144 (71.6)
- Cyclosporine	22 (16.4)	6 (9.0)	28 (13.9)
- Sirolimus	18 (13.4)	15 (22.4)	33 (16.4)
- Everolimus	1 (0.7)	2 (3.0)	3 (1.5)
- Mycophenolate	88 (65.7)	25 (37.3)	113 (56.2)
- Azathioprine	16 (11.9)	11 (16.4)	27 (13.4)
- Prednisone	83 (61.9)	47 (70.1)	130 (64.7)
Lymphopenia	24 (17.9)	46 (68.7)	70 (34.8)
ALC, x10^9/L, median (IQR)	1.2 (0.8, 1.8)	0.5 (0.3, 0.7)	0.9 (0.5, 1.6)

Figure 1: Time-to-PCP from PTLD diagnosis

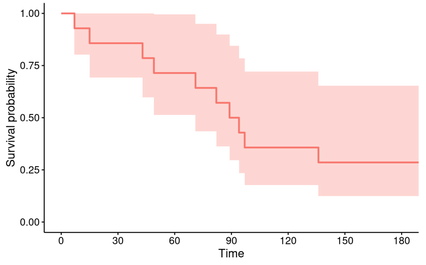
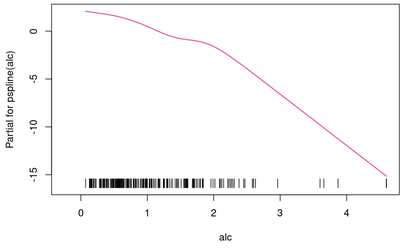


Figure 2: Depth of lymphopenia and PCP risk



DISCUSSION

- PTLD was associated with development of PCP.
- Most PTLD-associated cases of PCP are diagnosed within 90 days of PTLD diagnosis.
- The risk of PCP may be associated more so with chemotherapy associated with PTLD; however, cases do occur prior to chemotherapy initiation.
- Lymphopenia was likewise significantly associated with PCP; however, the risk appears to increase as lymphocyte count decreases without an optimal cutpoint.

CONCLUSIONS

- PTLD is a significant association with PCP in SOTRs.
- It remains unclear how much of this risk is associated with chemotherapy, though cases did occur in the absence of therapy initiation.
- PCP prophylaxis may be considered in SOTRs recently diagnosed with PTLD.
- The duration of prophylaxis is incompletely defined, though at least 90 days may be a reasonable duration.
- Lymphopenia and CMV infection were also associated with PCP and may be useful markers to decide on prophylaxis initiation.

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