***Pneumocystis* Pneumonia in Patients Treated With Rituximab**

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Background: *Pneumocystis pneumonia* (PcP) is an opportunistic fungal infection. Although T-cell immunity is classically related to *Pneumocystis* defense, recent data support roles for B lymphocytes in the development of PcP in animals, and we have observed several cases of PcP in patients receiving rituximab. These observations prompted a systematic review of our experience to define the spectrum of clinical presentations in which PcP has occurred in the setting of rituximab therapy.

Methods: Using a computer-based search, we reviewed the records of patients who received rituximab and developed PcP at Mayo Clinic Rochester over the years 1998 to 2011 to establish the underlying conditions, clinical course, possible risk factors, and potential association between this drug and the development of PcP.

Results: Over this period, 30 patients developed PcP during treatment with rituximab. The underlying diseases included hematologic malignancies in 90% of cases. Glucocorticoids were used in 73% of these patients, under different chemotherapeutic regimens. Three patients (10%) developed PcP in the setting of rituximab without concomitant chemotherapy or significant glucocorticoid exposure. Of these 30 patients, 88% developed acute hypoxemic respiratory failure and 53% required ICU admission. The clinical course was fatal in 30%.

Conclusion: PcP can occur in association with rituximab, with the majority of cases having also received cytotoxic chemotherapy or significant doses of glucocorticoids. The clinical course of cases of PcP in patients treated with rituximab can be quite fulminant, with significant mortality. Primary prophylaxis should be considered in patients at risk, and secondary prophylaxis provided unless immune reconstitution is well assured.

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Abbreviations: G-CSF = granulocyte-colony stimulating factor; GPA = granulomatosis with polyangiitis (Wegener); PcP = *Pneumocystis pneumonia*; PCR = polymerase chain reaction; R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; TMP-SMX = trimethoprim-sulfamethoxazole

Pneumocystis pneumonia (PcP) remains a serious threat to immune-compromised patients. Host defenses against PcP have largely been attributed to CD4⁺ lymphocytes, which are defective in most diseases associated with PcP.¹ However, animal studies have also indicated a role for B lymphocytes and anti-

body defenses in this infection.² In addition, recent studies have suggested that the novel anti-B-lymphocyte agent rituximab may be associated with the development of PcP.^{3–11}

Rituximab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes. It has been used for both hematologic malignancies such as chronic lymphocytic leukemia and for non-Hodgkin's lymphoma. More recently, this agent has been used in inflammatory conditions and has been approved for the treatment of patients with rheumatoid arthritis and antineutrophil cytoplasmic antibodies-associated

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vasculitis.^{3-10,12} The possible mechanisms by which rituximab may be a risk factor for PcP are unclear, but the depletion of B lymphocytes may adversely alter the ability of T lymphocytes to clear *Pneumocystis*.² In addition, rituximab can also cause prolonged hypogammaglobulinemia and failure of naive B lymphocytes to differentiate into plasma cells.¹³⁻¹⁵ Accordingly, we sought to describe the characteristics of patients who received rituximab and subsequently developed PcP. We further analyzed concomitant immunosuppressive drug therapy to determine how often rituximab was the only immunosuppressive agent these patients with PcP had been exposed to. Finally, we studied the clinical course and determined whether anti-*Pneumocystis* prophylaxis was administered.

MATERIALS AND METHODS

Patient Population

Patients were identified by a computerized search of the epidemiologic database at Mayo Clinic, using the diagnosis “*Pneumocystis pneumonia*.” A subgroup of adult patients who developed PcP was further identified as also being treated with rituximab over the period of January 1998 through August 2011. This was accomplished by manual review of the medications of all patients with PcP, including rituximab administered at Mayo Clinic. These years were selected because they coincided with the period of widespread use of rituximab at our institution. Patients who had any evidence of HIV infection, or who were younger than 18 years of age, were excluded. All patients provided consent allowing the use of their records. Approval for this retrospective review was obtained from the Mayo Clinic Rochester institutional review board, under the number 09-008573 and the protocol name “*Pneumocystis* experience from the last 20 years.” The protocol was last reapproved on December 14, 2011.

Thirty patients met the criteria for inclusion. The following clinical data were collected: sex; age; smoking status; diagnosis of lung, renal, rheumatologic, and hematologic diseases; concomitant use of immune suppressive drugs, particularly glucocorticoids and cytotoxic agents; and the number of cycles of rituximab and dates of administration relevant to the onset of PcP. In addition, the clinical course, laboratory data, radiologic findings, ICU admission, need for mechanical ventilation, treatment regimens, primary and secondary prophylaxis, and mortality were abstracted. Mortality was defined as death associated with the hospitalizations during which PcP was diagnosed and treated. Mortality was determined in an identical manner for patients with PcP associated with rituximab and for patients with PcP in a setting other than AIDS, reviewed in the institutional review board-approved cohort analysis noted previously. These cases have not been reported previously.

Diagnosis of PcP

The diagnosis of PcP was defined predominantly as positive microbiologic testing using either our single copy, real-time polymerase chain reaction (PCR) assay or smear for *Pneumocystis* performed on spontaneous sputum, induced sputum, or BAL. It should be noted that the nonnested PCR we use recognizes the single copy *PcCdc2* gene, providing added sensitivity for clinical diagnosis of PcP, but this assay is specifically designed to detect clinical pneumonia and does not detect colonization.¹⁶ In two cases, the clinical suspicion of PcP was extremely high, including

response to anti-*Pneumocystis* therapy, but the patients were unable to complete microbiologic testing. These two patients have been identified in Table 1. These two cases had highly suggestive clinical presentations and chest radiography, and other infectious agents were excluded by blood culture and culture of respiratory secretions.

Data Analysis

Data are expressed as the mean and SD for continuous normally distributed variables and as the median and range for non-Gaussian distributed data. Potential differences in variables were determined using χ^2 analyses and Fisher exact tests. Differences were considered significant if *P* values were < .05.

RESULTS

Patient Demographic Information

Between January 1998 and August 2011, a total of 30 patients treated with rituximab alone or in combination with another drug developed PcP. In our practice, which has large referral oncology and rheumatology patient bases, HIV-associated PcP represents about 10% of the total PcP cases. Rituximab administration was documented in 14.5% of our total non-HIV cases of PcP during this period. Twenty-two patients (73%) with PcP after receiving rituximab were men. The median age was 70 years (range, 27-88 years). Active smoking was reported in three patients (10%), 12 (40%) were former smokers, and two (7%) had been given a diagnosis of COPD. The remaining patients (50%) were never smokers.

Underlying Conditions

Most patients had underlying hematologic malignancies (Table 1). In 51%, rituximab was employed as part of the treatment of diffuse large B-cell lymphoma. Rituximab was also administered for chronic lymphocytic leukemia in 13%, mantle cell lymphoma in 10%, follicular lymphoma in 7%, non-Hodgkin's lymphoma in 7%, and Hodgkin's lymphoma in one patient. Rituximab was used in a few cases for non-malignant conditions, which included granulomatosis with polyangiitis (Wegener) (GPA) (one patient), idiopathic thrombocytopenic purpura (one patient), and rheumatoid arthritis with bronchiolitis obliterans (one patient). Interestingly, eight patients (27%) had chronic renal disease; seven of these had underlying hematologic malignancies and one had GPA. None of these patients were receiving chronic hemodialysis at the time they developed PcP. However, three patients (10%) did require a renal transplant.

Concomitant Immune Suppressive Treatment Regimens

The majority of patients (27 of 30) had been exposed to either cytotoxic chemotherapy or glucocorticoid

Table 1—Concomitant Immune Suppressive Diseases and Therapies

Principal Underlying Disease	Age, y	Smoker	Principal Immunosuppressant Regimen	Glucocorticoids	Additional Agents	Renal Disease	GCSF	WBC	LYMPH	B Cells	CD4	CD8	PaO ₂ /Fio ₂	Diagnosis	PeP-Related Death	2° Prophylaxis
DLBCL	44	Former	R-CHOP-21	With chemotherapy	Methotrexate	Yes	Yes	7,700	630	...	...	...	361	BAL smear	No	Yes
DLBCL	47	Current	R-fludarabine-cyclophosphamide	Chronic glucocorticoids	Azathioprine	Yes	Yes	10,000	850	...	...	...	376	BAL PCR	No	Yes
DLBCL	82	Former	R-CHOP-21	With chemotherapy	No	No	Yes	4,200	580	...	...	...	>300	BAL PCR	No	No
HL	27	Never	R-ABVD	With chemotherapy	No	No	Yes	6,000	200	...	...	...	91	BAL smear	No	No
Mantle cell lymphoma	67	Smoker	R-cladabine	No	No	No	Yes	2,800	160	0	20	73	190	BAL smear	No	Yes
Mantle cell lymphoma	77	Never	R-cladabine-temsirolimus	No	No	No	Yes	2,700	70	...	...	...	>300	Induced sputum PCR	No	Yes
DLBCL	71	Never	R-CHOP-21	With chemotherapy	No	No	Yes	10,800	290	...	...	...	157	BAL smear	No	No
NHL	81	Never	R + R-CHOP	With chemotherapy	No	No	Yes	18,000	100	...	...	...	52	BAL smear	Yes	Pt expired
DLBCL	64	Never	R-CHOP-21	With chemotherapy	No	No	Yes	8,100	240	0	12	80	99	BAL smear	No	No
Follicular lymphoma	45	Former	Rituximab	With chemotherapy + chronic glucocorticoids	No	No	Yes	9,800	2,880	...	...	...	193	Sputum PCR	No	Yes
DLBCL ^a	75	Former	R-CHOP-21	With chemotherapy + chronic glucocorticoids	Hydroxychloroquine	No	Yes	16,100	1,310	...	...	...	>300	Clinical suspicion	No	No
CLL	64	Never	R-fludarabine	No	Darbepoetin α	No	Yes	2,100	60	0	35	14	191	Induced sputum PCR	No	Yes
DLBCL	78	Former	R-CHOP-21	With chemotherapy	No	No	Yes	14,700	670	...	30	100	74	Sputum PCR + BAL smear	Yes	Pt expired
DLBCL	79	Never	R-CHOP-21	With chemotherapy	No	No	Yes	10,500	170	...	...	...	73	BAL PCR	No	Yes
CLL ^b	82	Former	Rituximab	No	Darbepoetin α	Yes	Yes	5,200	520	234	282	279	279	Induced sputum PCR	No	Yes
DLBCL	59	Never	R-CHOP-21	With chemotherapy	Methotrexate	No	Yes	16,700	360	1	77	52	73	BAL smear	Yes	Pt expired

(Continued)

Table 1—Continued

Principal Underlying Disease	Age, y	Smoker	Principal Immunosuppressant Regimen	Glucocorticoids	Additional Agents	Renal Disease	GCSF	WBC	LYMPH	B Cells	CD4	CD8	Pao ₂ /Fio ₂	Diagnosis	Death	2° Prophylaxis
DLBCL	88	Former	R-CHOP-21	With chemotherapy + chronic glucocorticoids	No	Yes	Yes	1,400	150	...	...	...	276	Sputum PCR	No	Yes
CLL	73	Former	R-fludarabine-cyclophosphamide	No	No	No	No	8,100	200	0	15	31	128	BAL PCR	Yes	Pt expired
DLBCL	64	Never	R + everolimus	No	No	No	No	700	280	...	...	...	266	BAL PCR	No	Yes
ITP	85	Former	Rituximab	With chemotherapy + chronic glucocorticoids	No	No	No	7,200	150	...	...	...	221	Induced sputum PCR + BAL	No	Yes
DLBCL	69	Never	R-CHOP-14	With chemotherapy + chronic glucocorticoids	Tacrolimus	Yes (transplant)	No	8,200	120	0	21	28	170	Induced sputum PCR + BAL	Yes	Pt expired
DLBCL	68	Never	R-CHOP	With chemotherapy + chronic glucocorticoids	BCVVP	No	No	2,850	360	0	9	87	80	BAL smear	Yes	Pt expired
GPA ^b	79	Former	Rituximab	No	No	Yes	No	10,200	1,200	...	...	...	115	BAL PCR	Yes	Pt expired
Follicular lymphoma	74	Never	R-CHOP-21	With chemotherapy + chronic glucocorticoids	No	No	No	4,800	500	...	...	...	186	BAL smear	No	Yes
Mantle cell lymphoma ^a	54	Smoker	Rituximab	High doses pulse glucocorticoids	No	Yes	No	8,100	390	...	...	...	680	Clinically suspected	No	No
CLL	68	Smoker	Rituximab	With chemotherapy + chronic glucocorticoids	No	Yes	No	600	410	...	...	...	> 300	Sputum PCR	No	Yes
NHL	59	Never	R-CHOP-14	With chemotherapy + chronic glucocorticoids	Tacrolimus	Yes (transplant)	No	7,200	790	4	363	260	238	BAL PCR	No	Yes
DLBCL	70	Former	R-CHOP	With chemotherapy + chronic glucocorticoids	Methotrexate (intrathecal)	No	No	7,200	420	...	...	...	198	BAL smear	Yes	Pt expired
DLBCL ^b	86	Former	Rituximab	No	No	Yes	No	18,500	1,150	...	...	...	90	Sputum PCR	Yes	Pt expired
RA/Sjögren/BO	40	Never	Rituximab	Chronic glucocorticoids	Azathioprine	No	No	13,000	600	...	...	...	383	BAL PCR	No	Yes

ABVD = adriamycin, bleomycin, vincristine, dacarbazine; BCVVP = bleomycin, vincristine, vinblastine, prednisone; BO = bronchiolitis obliterans; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; GCSF = granulocyte-colony stimulating factor; GPA = granulomatosis with polyangiitis (Wegener); HL = Hodgkin's lymphoma; ITP = idiopathic thrombocytopenic purpura; LYMPH = total lymphocyte count; NHL = non-Hodgkin's lymphoma; PCP = *Pneumocystis pneumonia*; PCR = polymerase chain reaction; Pt = patient; RA = rheumatoid arthritis; R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone.

^aClinically suspected PCP.

^bCase receiving rituximab alone.

therapy in addition to rituximab therapy within the 2 months preceding PcP. However, in three patients who developed PcP, rituximab was the only administered immunosuppressive agent. Thus, the significant majority had multiple treatment-related risk factors for the development of PcP, in addition to rituximab ($P < .001$, χ^2 and Fisher exact tests, comparing the number of patients with PcP after receiving only rituximab [three of 30] with the number of patients with PcP after receiving rituximab in combination with systemic corticosteroids or chemotherapeutic agents [27 of 30]). Rituximab was generally provided at the dosage of 375 mg/m² at 1- to 2-week intervals, either alone or in combination with other agents. The median number of cycles of rituximab prior to PcP was four. However, PcP occurred following as little as one course of rituximab in two patients.

The additional chemotherapeutic and immune suppressive regimens are shown in Table 1. This case series involved patients with multiple different underlying diseases treated with a wide variety of treatment regimens, including rituximab in association with chemotherapy regimens, in cyclical, interrupted, and suspended treatment regimens, many with cytotoxic chemotherapy. In addition to rituximab, 10 patients (33%) received glucocorticoids as part of their chemotherapy regimens. Two patients (7%) used chronic glucocorticoids over the course of their chemotherapy. An additional nine patients (30%) received chronic glucocorticoids in addition to higher IV glucocorticoid pulses during chemotherapy. Finally, six patients (20%) received chemotherapeutic agents with variable use of supplementary glucocorticoids. The mean total cumulative dose of prednisone was 9,455 mg. Patients receiving chemotherapy generally had received chemotherapy within 60 days of the diagnosis of PcP.

Importantly, three patients developed PcP after receiving only rituximab. These patients are indicated in Table 1. The first individual received rituximab as a single immunosuppressant agent for the treatment of GPA. At the time of PcP, this patient did not exhibit lymphopenia, with a total lymphocyte count of 1,200/ μ L (normal, 900-2,900/ μ L). Unfortunately, information on CD4⁺, CD8⁺, and CD20⁺ lymphocytes was not available. This case was published recently as part of a report on the use of rituximab in chronically relapsing GPA, and this infection has been mentioned.¹⁷ The second individual received rituximab alone for diffuse large B-cell lymphoma. Again, at presentation with PcP, this patient had a normal total lymphocyte count of 1,500/ μ L, but information was unavailable on CD4⁺, CD8⁺, and CD20⁺ lymphocytes. Finally, a third patient was treated with rituximab for chronic lymphocytic leukemia and developed PcP with only darbepoetin α as additional therapy.

Diagnosis of PcP

The diagnosis of PcP was microbiologically confirmed in 28 of 30 patients (93%) with various techniques applied to respiratory samples: 10 patients (30%) using calcofluor white staining of BAL, eight patients (27%) by single-copy PCR applied to BAL, four patients (13%) by PCR applied to induced sputum, three patients (10%) by PCR applied to spontaneously provided sputum samples, and three patients (10%) by PCR applied to both sputum and BAL. The performance characteristics of this nonnested single PCR assay targeting the single copy *Pccdc2* gene has recently been shown to detect an additional 7% of cases with *Pneumocystis jirovecii* infection when added to direct visualization methods, while yielding minimal false-positive results in patients without PcP, thereby greatly reducing the detection of colonization.¹⁶

During the course of this study, patients who underwent BAL (21 individuals) were further studied with a comprehensive standardized laboratory approach to processing lavage, which included general comprehensive bacterial, mycobacterial, fungal, and viral detection assays, including culture-, antigen-, and PCR-based assays. An additional lung pathogen was detected by BAL in only two patients, namely cytomegalovirus in one individual and *Chlamydia pneumoniae* in another. Sputum examinations also did not yield bacterial pathogens. Five cases were found to also have bacteremia during the course of hospitalization, including bloodstream infections with *Staphylococcus aureus*, coagulase negative *Staphylococcus*, and *Escherichia coli*.

Clinical Course: The mean number of days from last administration of rituximab to development of PcP was 76.8 ± 21.6 days. The clinical presentation included nonproductive cough, low-grade fever, malaise, and chest tightness in 60% of patients. In 40%, the presentation was more acute, with high fever, chills, and rapidly progressive dyspnea with respiratory distress.

The median lymphocyte count at onset of PcP was 375/ μ L, ranging from 60 to 2,880/ μ L (normal, 900-2,900/ μ L). Retrievable data on CD4⁺ and CD8⁺ lymphocytes were present in 10 patients, with a median CD4⁺ cell count of 25.5 cells/ μ L and a range of 9 to 363/ μ L (normal, 430-1,513/ μ L) and a median CD8⁺ count of 76.5 cells/ μ L with a range of 14 to 282/ μ L (normal, 101-839/ μ L). In eight patients with measured B lymphocytes at the time of PcP, the counts were undetectable, as expected (normal, 74-441/ μ L).

The radiologic findings (chest radiograph or CT scanning) were variable. A predominance of diffuse interstitial infiltrates was observed in 36%, and a predominant diffuse alveolar infiltration pattern was seen in 18% of these patients. Patchy scattered infiltrates were

observed in 21%. However, more atypical presentations were also observed, such as nodular consolidations (in one) or pleural effusion (in one). The remainder of these patients had mixed alveolar or ground-glass infiltrates in combination with interstitial changes.

Most patients presented with hypoxemia, having a mean PaO_2 of 59.5 mm Hg (range, 39-97 mm Hg). Sixteen patients (53%) developed ARDS requiring ICU admission. The range of oxygenation, expressed as the $\text{PaO}_2/\text{FIO}_2$ ratio, is detailed in Figure 1. Indeed, 88.5% presented with $\text{PaO}_2/\text{FIO}_2 < 300$, indicative of acute lung injury. Overall, 11 of the 16 patients admitted to the ICU were intubated and mechanically ventilated. Six patients were managed with non-invasive mechanical ventilation. The median ICU length of stay was 5.8 days (range, 1-51 days).

Prophylaxis and Treatment

Most patients (29) had not received prophylaxis before the first episode of PcP while being B-cell depleted after receiving rituximab. In contrast, only one patient had received *Pneumocystis* prophylaxis with inhaled pentamidine prior to his first episode of PcP that followed treatment with rituximab. This patient had a prior episode of PcP, believed related to his chemotherapy and underlying lymphoma, prior to starting rituximab.

After diagnosis of PcP, all patients were treated with trimethoprim-sulfamethoxazole (TMP-SMX), except for one who was treated with atovaquone for milder disease. The median hospital stay was 9 days (range, 4-76 days). Among patients who were discharged, prophylaxis was prescribed in 16 of 21 (76%), with various regimens of TMP-SMX. Interestingly, two patients (12.5%) who had received secondary prophylaxis

were readmitted for a new episode of microbiologically documented PcP. Among the five who did not receive secondary prophylaxis because they were believed to be immune competent, one was readmitted for a new episode of documented PcP. Review of this patient revealed that ongoing immune suppression was likely related to his diffuse large B-cell lymphoma and ongoing treatment with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (R-CHOP) therapy, resulting in a reduced total WBC count of $1,400/\mu\text{L}$ (normal, $3,500\text{-}10,500/\mu\text{L}$).

Mortality: The overall mortality of these episodes of PcP was 30% (nine of 30). In comparison, the mortality related to PcP in patients not infected with HIV who did not receive rituximab was 28.6%. Thus, the PcP-associated mortality in this cohort was not different from the mortality observed for other cases of non-HIV-associated PcP ($P > .05$, not significantly different by either χ^2 or Fisher exact test).

DISCUSSION

Pneumocystis species comprise a genus of fungal pathogens. *Pneumocystis jirovecii* is the species responsible for infection in humans.¹ Most of our understanding of host defense against *Pneumocystis* has focused on T lymphocytes. Most notably, during the HIV/AIDS epidemic, PcP became a devastating opportunistic pneumonia in these patients, whose immunologic hallmark was severe suppression of CD4^+ lymphocytes. The widespread use of antimicrobial prophylaxis and the introduction of highly active antiretroviral therapy have resulted in a steady decline in the incidence of PcP among patients with HIV.^{1,18} In contrast, the broad use of glucocorticoids and newer potent immunosuppressive drugs have led to a resurgence of this important opportunistic infection in other patient groups. The mortality in patients without HIV with PcP is often higher than in patients with HIV.¹⁹ Immunosuppressed patients with PcP in settings other than AIDS exhibit more atypical presentations, a more fulminant course, and higher mortality and are more difficult to determine a diagnosis for because of the lower number of microorganisms present.²⁰ Fortunately, recent advances in molecular techniques and heightened awareness have improved the diagnosis of this infection.

Disparate views exist about the overall risks associated with many of the newer immune suppressants, particularly the risk of developing PcP in the setting of rituximab. Basic laboratory studies have emphasized the participation of B-lymphocyte immunity in host defense against *Pneumocystis*.²¹ However, no cases of PcP following rituximab therapy were noted in initial trials conducted with rituximab in

FIGURE 1. Gas exchange at diagnosis of *Pneumocystis* pneumonia.

rheumatoid arthritis.^{22,23} Furthermore, Coiffier et al²⁴ found no cases of PcP in patients with lymphoma treated with either cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone or R-CHOP.

In contrast, with more intensive treatment regimens, in which patients were given R-CHOP at 2-week intervals, seven cases of interstitial pneumonitis and three episodes of PcP were documented among 50 patients.²⁵ Furthermore, Kolstad et al¹⁰ evaluated the incidence of PcP in patients treated for non-Hodgkin's lymphoma. The R-CHOEP-14 (including etoposide) regimen had the highest PcP incidence (six of 46 patients, 13%).¹⁰ The incidence was 4% for CHOEP-14 and 6% for R-CHOP-14 in their study. An additional report described PcP after rituximab therapy in solid transplant recipients receiving this agent for the treatment of humoral allograft rejection.⁸

We identified 30 patients with PcP after receiving rituximab, the largest cohort of such patients. The current study holds several important advantages over prior studies. First, it is a comprehensive review of patients with PcP related to rituximab therapy in a large general tertiary referral practice. Specifically, this study includes patients representing multiple susceptible populations, including individuals with lymphoma and hematologic malignancies, as well as individuals receiving rituximab for rheumatologic and autoimmune conditions. Accordingly, the study is more reflective of the variety of patients encountered in general medical settings, as opposed to those series based on focused practices such as in lymphoma clinics. Of note, many such patients with PcP have received multiple immunosuppressive chemotherapeutic agents with or without prednisone in addition to rituximab. However, the current study describes three patients in whom rituximab was the only immunosuppressive agent present in the setting of PcP, strongly supporting the theory that B-cell suppression is a risk factor for the development of PcP.

Many of our findings are similar to those of earlier reports. For instance, we observed a high frequency of acute respiratory failure (40%) with an associated mortality of 30%. Suppressed lymphocyte counts have been reported in several studies.^{9,10,26} Of interest, approximately 60% were concomitantly receiving granulocyte-colony stimulating factor (G-CSF). Whether there is a pathogenic connection between G-CSF and PcP is conjectural. However, it can be postulated that the induction of inflammatory cells by G-CSF may heighten the clinical presentation and severity of lung injury during infection.^{21,27,28}

The majority of these patients (29 of 30) had not received prophylaxis prior to the onset of pneumonia. Moreover, three patients discharged following PcP were readmitted for an additional episode of laboratory-documented PcP. Interestingly, two were

receiving TMP-SMX, and one was not receiving any prophylaxis for recurrent PcP. Green et al²⁹ performed a meta-analysis of PcP prophylaxis in non-HIV-infected patients and concluded that prophylaxis is warranted for PcP for recipients of solid organ transplants or allogeneic bone marrow transplants for 6 months after transplant, and with continued immunosuppression, in GPA, and in acute lymphoblastic leukemia.

Unfortunately, firm guidelines for prophylaxis against PcP in non-HIV-infected patients are lacking. However, we believe that rituximab may represent an additive immunosuppressive that enhances the risk of PcP. It is noteworthy that we described three cases in which rituximab was the only immunosuppressant agent being administered prior to the development of PcP. Thus, prophylaxis should be considered for patients receiving this treatment, either alone or as a component of a multiagent immunosuppressive regimen.

CONCLUSIONS

In conclusion, PcP can occur in association with rituximab alone, but most cases have also received either chemotherapy or significant doses of glucocorticoids. The clinical course and mortality of PcP in patients who have received rituximab can be quite fulminant. Primary prophylaxis should be considered in rituximab-treated patients. Importantly, secondary prophylaxis against recurrent PcP should be provided unless immune reconstitution is assured.

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Dr Martin-Garrido: contributed to the abstraction of the case materials, data analysis, and initial drafts of the manuscript.

Dr Carmona: contributed to the assembly of the initial PcP database, revision of the manuscript, and provision of additional data input.

Dr Specks: contributed to the initial study concept, provision of clinical information, and revision of the final manuscript.

Dr Limper: contributed to the study concept, provision of statistical analysis, and revision of the final draft of the manuscript.

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