Pneumocystis jirovecii pneumonia in non-Hodgkin's lymphoma after rituximab-based chemotherapy: a case series

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Background: The incidence of *Pneumocystis jirovecii* pneumonia (PCP) has been increasing in patients with hematologic malignancies due to the use of glucocorticoid therapy and immunosuppressive medication. The reports of PCP in non-Hodgkin's lymphoma (NHL) after rituximab-based chemotherapy are still rare. We reported a case series of PCP in NHL to show the clinical features and prognosis in those patients.
Methods: We conducted a retrospective review of 15 NHL patients who developed PCP after rituximab-based chemotherapy during June 30, 2014 to June 1, 2020. We analyzed the laboratory and radiographic findings for those patients through descriptive statistics analysis.
Results: The study revealed that PCP in NHL patients was complicated by chemotherapy after about 4 courses (range, 2 to 6 courses). Most patients had a standard lymphocyte count before treatment, and 14 of 15 patients (93.3%) had lymphopenia at the time of diagnosis of PCP. In addition to typical symptoms such as fever and dyspnea at the diagnosis of PCP, most patients had abnormal laboratory indexes such as marked elevations of C-reactive protein (CRP) and lactic dehydrogenase (LDH) both before and at the time of diagnosis. The (1,3)-β-D-glucan test was also revealed as a sensitive index for PCP. Bilateral ground-glass opacity was detected in 14 cases through computed tomography (CT) scans. Positive results of microbiological testing were observed in 7 cases; sputum culture was positive in 3 and next-generation sequencing (NGS) was positive in 3 of these 7 patients, and the other case was positive in both sputum culture and NGS. Patients received high-dose trimethoprim/sulfamethoxazole (TMP/SMZ), caspofungin, and steroids as the treatment for PCP. Ventilatory support was required by 3 patients, so they were admitted to the intensive care unit (ICU), and 1 patient died from PCP.
Conclusions: Dynamic monitoring of CRP, LDH, and (1,3)-β-D-glucan test during the treatment of NHL may have a predictive value for the diagnosis of PCP. Additionally, we should use NGS as a rapid and sensitive method for the early diagnosis of PCP. When patients are classified as 'probable PCP', early and effective treatment has obvious significance to improve the prognosis.

Keywords: *Pneumocystis jirovecii* pneumonia (PCP); non-Hodgkin's lymphoma (NHL); rituximab; case series

Introduction

Pneumocystis jirovecii pneumonia (PCP) is a common disease occurring in patients with acquired immunodeficiency syndrome (AIDS). As immunosuppressive medications become more widely used, the incidence of PCP has been increasing in patients without human immunodeficiency virus (HIV) infection due to the use of glucocorticoid therapy and immunosuppressive medications, solid organ transplantation, allogeneic hematopoietic stem cell transplantation, and congenital immunodeficiency syndromes (1).

Recently, several studies have reported that there is an increased risk of PCP in patients with non-Hodgkin's lymphoma (NHL) treated with rituximab-containing regimens (2-4). Lee's study estimated the incidence of and risk factors for PCP infection in diffuse large B-cell lymphoma (DLBCL) and showed the importance of PCP prophylaxis during R-CHOP treatment (2). Without PCP prophylaxis, the approximate incidence of PCP may be up to 15% in such patients (2,5). And the risk of PCP increased in patients received R-CHOP-14 (3). More importantly, the mortality of PCP can reach 29% in patients with hematologic malignancies (6), which is significantly higher than that of those with HIV (6–7%) (7,8). Only isolated cases of PCP in NHL have been reported in the literature, and information on clinical presentation, criteria for clinical diagnosis, and prognosis remains unclear.

The objective of this study was to review the clinical findings and outcomes of the instances of PCP in patients with NHL seen at our institution, in the hope of providing some guidance for the prevention and treatment of these patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1216/rc).

Methods

This was a single-center and retrospective cohort study of NHL patients diagnosed at the First Affiliated Hospital of Wenzhou Medical University between 30 June 2014 and 1 June 2020, who developed PCP. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board at the First Affiliated Hospital of Wenzhou Medical University (No. KY2022-R066). Individual consent for this retrospective analysis was waived. Patients who displayed clinical symptoms such as fever, cough, sputum,

or dyspnea, had radiological features including patch bilateral ground-glass opacity on chest radiography or chest computed tomography (CT), and received microbiological confirmation were classified as 'definite PCP'. Patients who had clinical and radiological features strongly suggestive of PCP but without microbiological examination or had a negative test result were classified as 'probable PCP'. A positive microbiological test was defined as clinical findings of pneumonia with identification of *Pjiroveci* organisms by smear, polymerase chain reaction (PCR), or next-generation sequencing (NGS) in sputum, bronchoalveolar lavage (BAL) fluid, or lung biopsy specimens. Their medical records were reviewed and the following data were abstracted: age at NHL diagnosis, gender, date at diagnosis of PCP, symptoms at PCP diagnosis, laboratory and radiographic findings at the time of PCP diagnosis, corticosteroid dose, any other immunosuppressive treatment or comorbidities, treatment of PCP, and outcome. Participants were followed up until death or 31 August 2021, whichever came first. As information bias may occur in description of clinical symptoms, the diagnosis of PCP should be comprehensively assessed by clinical symptoms, signs, and laboratory examination results. We recruited all consecutive patients with clinical and radiographic findings, so the number of cases in our center during the study period determined the sample size.

Statistical analysis

The data were analyzed using descriptive statistics and paired-samples *t*-test. A P value <0.05 was considered statistically significant. Statistical analyses were conducted with the software SPSS 21.0 (IBM Corp., Armonk, NY, USA).

Results

During the study period, we included a total of 15 patients who acquired PCP during the course of chemotherapy (*Table 1*). Of these 15, 7 were classified as 'definite PCP'; the other 8 were classified as 'probable PCP'. All patients were treated with chemotherapeutic regimens including rituximab such as R-CHOP (rituximab 375 mg/m² d0, cyclophosphamide 750 mg/m² d1, hydroxydaunorubicin 50 mg/m² d1, vincristine 1.4 mg/m² d1, prednisone 100 mg d1–5), R-DHAP (rituximab 375 mg/m² d0, cis-platinum 1,000 mg/m² d1, cytarabine 2 g/m² q12h d2, dexamethasone 40 mg d1–4), and R-CVP (rituximab 375 mg/m² d0, cyclophosphamide 750 mg/m² d1, vincristine 1.4 mg/m²

Table 1 Clinical features and outcomes in 15 DLBCL patients with PCP

Patient/gender	Age at PCP diagnosis (years)	Symptoms	Lymphoma type/stage	Number of cycles before PCP infection	Microbiological testing	ICU admission	Total lymphocyte count pretreatment [ref. range: (1,500–4,000)×10^6/mL]	Total lymphocyte count at time of PCP diagnosis	Outcome
1/M	49	Fever, cough, sputum, and dyspnea	DLBCL/IVA	3	Sputum culturing positive	N	1,590	1,010	Survived PCP, still alive
2/F	68	Fever, cough, sputum, and dyspnea	DLBCL/IIA	4	Negative	N	2,740	790	Survived PCP, still alive
3/M	75	Fever, cough, sputum, and dyspnea	DLBCL/IIA	3	Negative	N	810	400	Survived PCP, still alive
4/M	36	Fever and cough	DLBCL/IIA	6	Negative	N	1,730	380	Survived PCP, still alive
5/M	30	Fever and dyspnea	DLBCL/IIIA	4	Negative	N	1,350	750	Survived PCP, still alive
6/M	71	Fever and dyspnea	DLBCL/IIA	4	Sputum NGS positive	N	2,280	270	Survived PCP, still alive
7/M	55	Fever and dyspnea	DLBCL/IIIA	5	BAL NGS positive	N	1,850	520	Survived PCP, died from other disease
8/M	56	Fever and dyspnea	DLBCL/IIA	3	Negative	Y (7 days)	3,070	1,730	Survived PCP, still alive
9/M	66	Fever and dyspnea	DLBCL/IIA	2	Negative	N	2,450	660	Survived PCP, died from other disease
10/F	70	Fever	DLBCL/IIIA	4	BAL NGS positive	N	2,420	190	Survived PCP, still alive
11/F	59	Fever	DLBCL/IIA	5	Negative	Y (7 days)	1,290	1,210	Survived PCP, still alive
12/M	50	Fever and dyspnea	FL/IVA	5	Sputum culturing positive	N	1,910	200	Died from PCP
13/M	56	Fever, cough, and dyspnea	FL/IIIA	3	negative	N	1,570	480	Survived PCP, still alive
14/M	67	Fever, cough, sputum, and dyspnea	FL/IIIA	2	BAL NGS and sputum culturing positive	Y(17 days)	1,900	340	Survived PCP, still alive
15/M	61	Fever, cough, sputum, and dyspnea	MZL/IIA	4	BAL NGS positive	N	1,490	490	Survived PCP, still alive

DLBCL, diffuse large B cell lymphoma; PCP, *Pneumocystis jirovecii* pneumonia; FL, follicular cell lymphoma; MZL, marginal zone lymphoma; ICU, intensive care unit; BAL, bronchoalveolar lavage; NGS, next-generation sequencing.

Table 2 Laboratory/radiographic findings in 15 patients with NHL and PCP

Variable	Pre-treatment/7–10 days before diagnosis	At diagnosis	P value
Laboratory findings			
Total lymphocyte count, median (range)/mL	1,850 (810–3,070)	490 (190–1,730)	0.001
CRP, median (range) mg/L	24.8 (3.02–74.6)	79.3 (37.8–105)	0.001
Serum LDH, median (range) U/L	320 (179–683)	535 (235–841)	0.002
(1,3)-β-D-glucan test, median (range) mg/mL	–	224.7 (67.4–1,893.9)	–
Microbiological test			
Sputum culturing, n (%)	–	3 (20.0)	–
NGS, n (%)	–	5 (33.3)	–
Imaging findings			
Bilateral ground-glass opacity, n (%)	–	14 (93.3)	–
Cavitary mass, n (%)	–	1 (6.7)	–
Pleural effusion, n (%)	–	5 (33.3)	–

NHL, non-Hodgkin's lymphoma; PCP, *Pneumocystis jirovecii* pneumonia; CRP, C-reactive protein; NGS, next-generation sequencing; LDH, lactate dehydrogenase.

d1, prednisone 100 mg d1–5). Patients did not receive PCP prophylaxis during chemotherapy. All participants received combined therapy including high-dose trimethoprim/sulfamethoxazole (TMP/SMZ), caspofungin, steroids, and empiric broad-spectrum antibiotics (as bacterial infection could not be excluded initially). Ventilatory support was required by 3 participants, so they were admitted to the intensive care unit (ICU), and only 1 patient died from PCP.

The age of patients with PCP ranged from 30 to 75 years, and PCP was complicated by chemotherapy after about 4 courses (range, 2 to 6 courses). Most patients had a standard lymphocyte count pretreatment, and 14 of 15 patients (93.3%) had lymphopenia at the time of PCP infection, 6 of whom had absolute lymphocyte count ≤0.5×10⁹/L. All participants underwent etiology inspection tests during the course of PCP. A total of 7 patients had a positive result of microbiological testing: sputum culture was positive in 3 patients, NGS was positive in 3 patients, and 1 was positive result in both sputum culture and NGS. A total of 14 patients survived PCP, 2 of whom eventually died from other diseases; 12 patients are currently alive.

All patients had fever before the diagnosis of PCP, and dyspnea was the second most common symptom. Laboratory and radiographic findings in patients with PCP are displayed in *Table 2* and *Figure 1*. Both CRP and LDH were routinely measured in follow-up examinations, and we recorded laboratory test results 7–10 days before diagnosis. In most cases, CRP and LDH had increased to varying degrees before the onset of clinical symptoms (*Figure 1*), and the difference was statistically significant (P=0.001, P=0.002, respectively). All patients had an abnormal elevation of CRP, the median was 79.3 mg/L (range: 37.8 to 105; reference range: 0 to 8). The median serum LDH of all participants was 535 U/L (range: 235 to 841; reference range: 0 to 247). The (1,3)-β-D-glucan test was shown to be another sensitive index for PCP. Abnormal results were observed in 13 of 15 patients in the (1,3)-β-D-glucan test, and the median was 224.7 mg/mL (range: 67.4 to 1,893.9; reference range: 0 to 100.5). Serum aspergillus galactomannan (GM) antigen was negative in all patients. A total of 14 patients had a typical finding in CT scan such as bilateral ground-glass opacity (*Figure 2*), and 5 of 15 patients had pleural effusion at the time of diagnosis.

Discussion

We have reported a case series of patients with PCP occurring in the context of treatment for NHL. The clinical features of this group of patients appear similar to those of other PCP patients without AIDS (6,7), although the mortality rate in our cohort was lower than that reported in
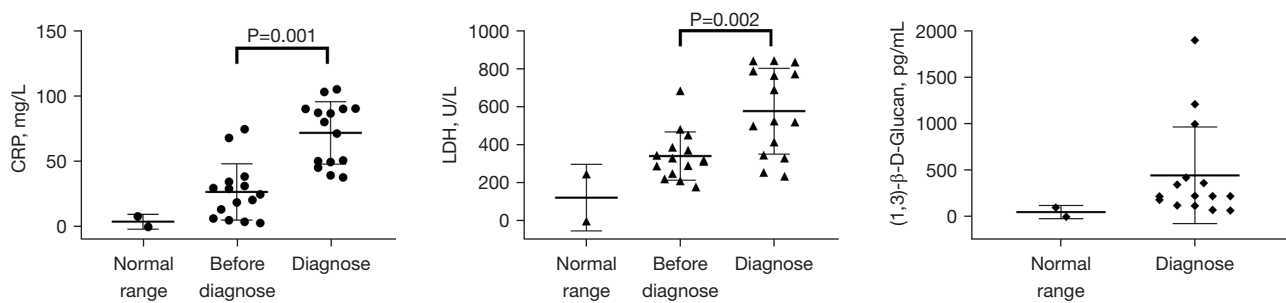
Figure 1 Laboratory findings before and at diagnose of PCP. PCP, *Pneumocystis jirovecii* pneumonia. CRP, C-reactive protein; LDH, lactic dehydrogenase.
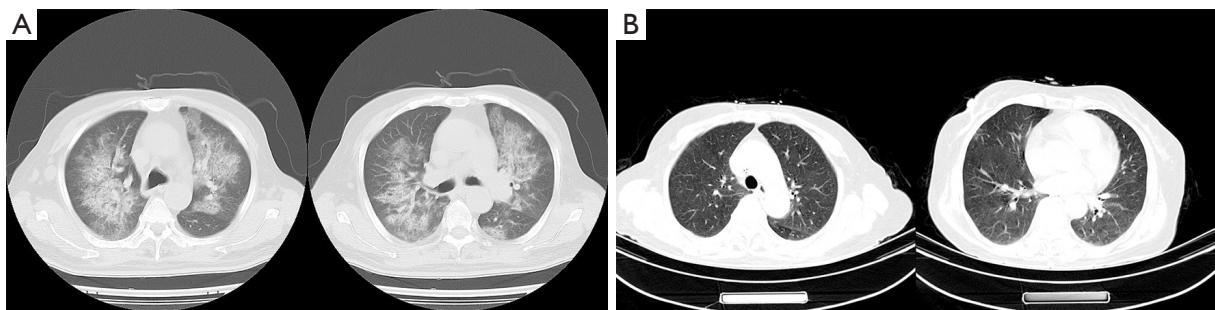

Figure 2 Radiographic findings of patients with PCP. (A) Bilateral ground glass opacity on chest radiography; (B) CT in an NHL patient with PCP at early stage. PCP, *Pneumocystis jirovecii* pneumonia; CT, computed tomography; NHL, non-Hodgkin's lymphoma.

the existing literature (7).

Overall, PCP appears to be a rare infection in patients without AIDS. We identified only 15 cases of PCP despite the large volume of patients with NHL treated at our hospital. Reports of PCP in patients with NHL are scare in the literature and limited to isolated case reports (9-11). During the treatment of NHL, patients may occasionally develop PCP, but there have been no studies demonstrating benefit of PCP chemoprophylaxis for those patients (12). Also, there is no consensus on PCP prevention in the National Comprehensive Cancer Network (NCCN) guidelines.

Biotargeted therapies such as rituximab and corticosteroid treatment in chemotherapy are risks factors for PCP in non-HIV patients (13,14). In a study evaluating PCP in patients without AIDS, 90.5% of the patients had received systemic corticosteroids in the month prior to diagnosis (15). Compared with conventional chemotherapy, rituximab-based chemotherapy may increase the probability of PCP in patients with lymphoma (16,17).

At the early stage of PCP, chest radiography may appear normal in 5–10% patients (18,19). The pulmonary imaging changes on CT scan may be atypical infiltration, mostly located in the interstitium of the lung, and mainly manifested as lung texture thickening or reticular changes around the hilum of the lungs (20), shown as interstitial pneumonitis, alveolar-interstitial pneumonia, pulmonary fibrosis, and bronchiolitis obliterans organizing pneumonia (BOOP) (21), which is difficult to distinguish from rituximab-associated lung injury and viral pneumonia. In our study, 12 of 15 (80%) patients acquired PCP after 3–5 courses of treatment and all patients were excepted for the common viral pneumonia. According to our clinical experience, rituximab-associated lung injury usually occurs after 3 courses of biotargeted therapy (21), which is close to the time of PCP occurrence in most patients. The main clinical symptoms of PCP at the early stage were dry cough and fever, followed by chest pain, cyanosis, and dyspnea (1). However, it remains difficult to identify PCP patients at the early stage due to the atypical signs and symptoms. The gold standard for clinical diagnosis of PCP is etiology examination (20), but the positive rate of conventional sputum smear remains low. The LDH is an
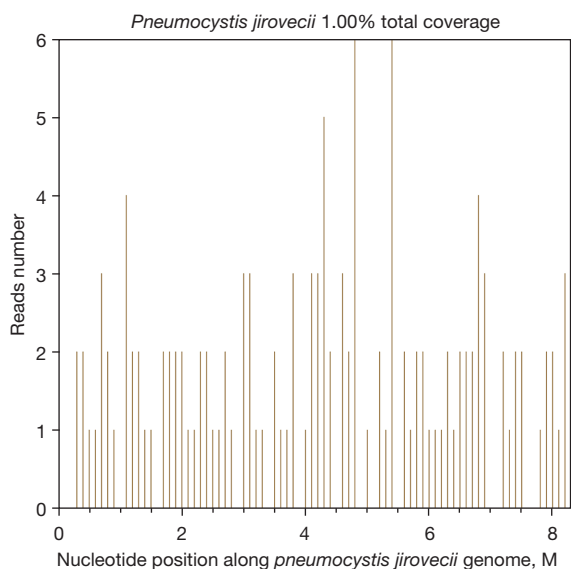
Figure 3 NGS for case 7. NGS, next-generation sequencing.

important assessment for lymphoma after treatment, which may rise when lymphoma progresses. It has been shown that a high level of LDH is associated with severe PCP and higher 90-day mortality (13). We found that the rise of LDH can occur before all of the clinical symptoms such as fever and cough. In the case of lymphoma monitoring, LDH may be a sensitive index for the early diagnosis of PCP. In our cohort, 12 of 15 cases had a rise of LDH during clinical follow-up and began to exhibit clinical symptoms such as fever and cough after several days, and were finally diagnosed as PCP. Both CRP and (1,3)-β-D-glucan testing are routine monitoring assessments in patients with NHL (13,22), which can be positive in the early stage of PCP, even in the presence of clinical symptoms. In case 4 and case 7, we monitored CRP, LDH, arterial blood gas analysis, and CT scan during follow-up. We found that hypoxemia appeared earlier than radiographic imaging features. So, we have identified that blood gas analysis should be performed promptly when the rise of LDH and CRP are monitored as abnormal elevations in patients with NHL as it was a reliable and sensitive index for 'probable PCP'.

Patients who are eligible to receive bronchoscopy and NGS for BAL are encouraged to undergo those examinations at the early stage. In case 7, we found a total of 129 reads mapped to *Pneumocystis jirovecii* in the reference database. The coverage of referenced *Pneumocystis jirovecii* genome was 1% (*Figure 3*). In solid organ transplantation, antimicrobial prophylaxis has been found to be a successful method in preventing PCP in patients with immunosuppression, while the standard prevention program in NHL remains unclear (23). Early prevention and treatment are important measures for patients with PCP to achieve prolonged survival.

In our study, 2 of the 15 patients needed ventilator-assisted ventilation treatment, and 14 patients experienced improved hypothermia and dyspnea after treatment and their lung performance was significantly improved on the CT scans. In all, 7 of 15 patients received a positive result from microbiological testing, 5 of whom had nucleic acid sequences indicating infection of *Pneumocystis carinii* through NGS. Studies have found that the mortality rate of PCP in non-HIV-infected patients is higher than that of HIV-infected patients (6-8). In addition, the in-hospital mortality rate of PCP in patients with autoimmune diseases is as high as 46% (24). However, there are few reports on the prognosis of NHL patients with PCP after treatment. The effectiveness of TMP/SMZ for PCP is limited with adverse events. Studies have shown that combination therapy with caspofungin and TMP/SMZ is an effective and promising, as the associated adverse events are comparable to those of TMP/SMZ monotherapy (25,26). Only 1 patient died from PCP, the mortality in our cohort was 6.7%, which is significantly lower than that reported in previous literature. In our report, patients received both TMP/SMZ and caspofungin as the therapy for PCP. We assume that early diagnosis and combination therapy with caspofungin and TMP/SMZ of PCP can significantly improve the prognosis of patients.

This study had the following disadvantages. Firstly, it was a retrospective study. Although 3/5 of the participants were suspected to be diagnosed with PCP, with typical lung changes and good treatment effect, no clear etiological basis was found. Secondly, most patients in our study received empiric broad-spectrum antibiotics treatment, although we could not confirm whether the patient was complicated with other fungal, bacterial, and viral infections. Thirdly, this was a single-center and retrospective study, thus selection bias was difficult to avoid.

In summary, this study demonstrates that dynamic monitoring of CRP, LDH and (1,3)-β-D-glucan test in patients with NHL is very significant for the early detection and diagnosis of PCP. Additionally, NGS is a rapid and sensitive method for the diagnosis of PCP. Bronchoscopy and NGS for BAL are extremely significant for diagnosis of PCP. When patients are classified as 'probable PCP', early and effective treatment has obvious significance to improve

their prognosis.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1216/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1216/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1216/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board at the First Affiliated Hospital of Wenzhou Medical University (No. KY2022-R066). Individual consent for this retrospective analysis was waived.

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