

CASE REPORT

Pneumocystis jiroveci pneumonia in patients with non-Hodgkin's lymphoma after Rituximab-containing regimen: two cases of report and literature review

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ABSTRACT

Rituximab, a monoclonal antibody against CD20+ antigen specific B cell, has been increasingly used in the treatment of non-Hodgkin's lymphoma and some other autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. It is noted that Rituximab could enhanced the efficacy of CHOP-based chemotherapy. Meanwhile it could increase the opportunity of lung infection. Pneumocystis jiroveci pneumonia (PCP), a rare opportunistic infection that was not reported in the large-scale clinical trials of Rituximab, was found recently in patients with non-Hodgkin's lymphoma treated with remedy containing Rituximab. We herein report two cases of PCP in lymphoma patients after Rituximab-containing chemotherapy. Both patients were successfully treated, with trimethoprim-sulfamethoxazole (TMP-SMX) in one case and Caspofungin alone in the other. We also reviewed the literature and concluded that PCP is an infrequent but potentially life-threatening infection in patients with non-Hodgkin's lymphoma subjected to Rituximab-containing regimen. Therefore, adequate prophylaxis, timely diagnosis and treatment are necessary.

KEY WORDS

Rituximab; non-Hodgkin's lymphoma; pneumocystis jiroveci pneumonia (PCP); Caspofungin

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Introduction

Pneumocystis jiroveci pneumonia (PCP), an opportunistic infection, is one of the major infectious complications in patients with human immunosuppressive virus (HIV) or in non-HIV immunocompromised patients subjected to chemotherapy. PCP is usually easy to be diagnosed but sometimes apt to be under-diagnosed for its atypical symptoms and signs. The occurrence of PCP is mainly due to the decrease of white blood cells especially CD4+ lymphocytes which influence the anti-infection ability of patient (1). Patients with low CD4+ lymphocyte counts usually have a higher risk of developing PCP (2).

Rituximab is a chimeric monoclonal antibody which targets

the B cell-specific antigen CD20. Rituximab can reduce the number of B cells and has been increasingly used and proved rather effective in combination with other chemo-drugs in the treatment of non-Hodgkin lymphoma. However, as B cells play a vital role in generation of CD4+ T cells for defending PCP infection in the lungs, reduction of B cells could lead to insufficient generation of CD4+ T cells and subsequently higher risk of pneumocystis jiroveci infection. PCP was not reported in large scale, multi-centered clinical trials of Rituximab involved over 3,000 patients, and infrequently reported in patients with lymphoma who were treated with Rituximab-containing therapy in recent years.

Herein, we present two cases of patients with non-Hodgkin lymphoma who developed PCP after Rituximab-containing chemotherapy. PCP was confirmed by Giemsa-staining and both patients were treated successfully, with oral trimethoprim-sulfamethoxazole (TMP-SMZ) and corticosteroid therapy in one case and Caspofungin alone in the other respectively. We also reviewed the literature to give an overview including cause, diagnosis, treatment, and prophylaxis for PCP in patients with non-Hodgkin lymphoma who received Rituximab-containing regimen.

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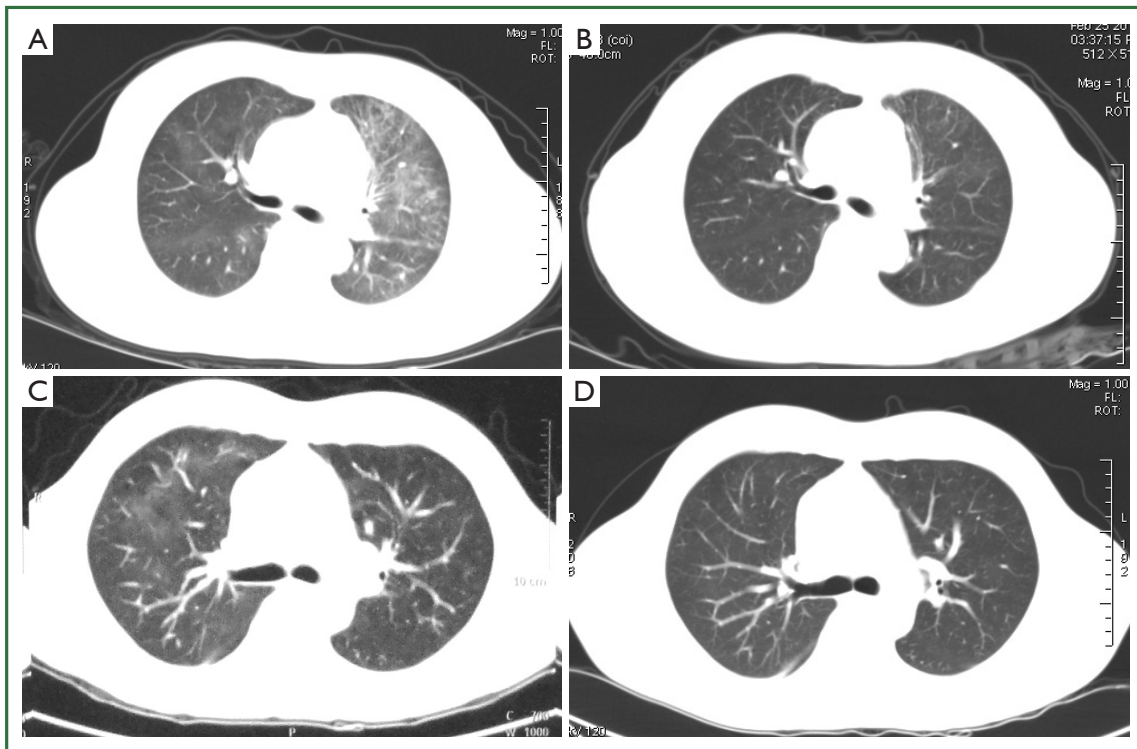


Figure 1. Thoracic computed tomography scanning revealed ground-glass opacities (GGO) in both upper lobes in Case 1 (A) and GGO vanished after treatment with SMZ/TMP (B). GGO were found in the right lung in Case 2 (C) and attenuated after treatment with Caspofungin alone (D).

Case reports

Case 1

A 46-year-old female was diagnosed with large-B-cell lymphoma, grade IIb, in December 2011 by pathological observations from left supraclavicular lymph node biopsy specimen. On Dec 15th, she was given chemotherapy with Rituximab-CHOP regimen, including cyclophosphamide 750 mg/m², day 1; doxorubicin 50 mg/m², day 1; vincristine 2 mg, day 1; prednisolone 100 mg/day for 5 days. Rituximab was given at a dose of 600 mg, day 1. The patient well tolerated the treatment and discharged on Dec 20th with a normal blood white cell count (WBC 8.95×10⁹/L), normal hepatic and renal functions. The chemotherapy was given in three cycles biweekly. Ten days after discharging, the patient presented with bone marrow suppression as peripheral blood WBC lowered to 1.59×10⁹/L. GSM-GF injection was given for continually three days and the WBC counts rose to 21.9×10⁹/L at day 3. On Jan 22nd, the patient presented with chest-tightness and dyspnea but no cough and fever. Chest CT scanning was performed and revealed obvious diffuse ground glass opacities (GGO) with interstitial thickening in both upper lungs (Figure 1A). A diagnostic bronchial-alveolar lavage (BAL) was immediately performed and bronchial-alveolar lavage fluid was collected. Under microscope foamy masses that highly suggestive

of pneumocystis jiroveci were observed and the diagnosis was finally established by Giemsa-staining. The patient was given oral TMP-SMZ (400/80 mg, at every eight hours) and corticosteroid (30 mg, daily) therapy. A chest CT scanning three weeks after the TMP-SMX therapy demonstrated a complete disappearance of pulmonary infiltrates (Figure 1B).

Case 2

A 46-years old male was admitted to our hospital for a mass on left jaw. After operation, pathological examination revealed a diffuse large-B cell lymphoma in salivary gland. Immunolabeling showed that CD20, CD79alpha, CD21, Ki-67, and bcl-2, 6 were all positive. The patient was wholly accessed and diagnosed as diffuse large-B-cell lymphoma, stage II A, IPI score 0, and given R-CHOP regimen (Rituximab 0.6, day 1, CTX 1.2, day 1, doxorubicin 100 mg, VCR 2 mg day 1, prednisone 100 mg, day 1-5). The patient well tolerated the chemotherapy and discharged on Dec 31st, 2011. The chemotherapy was repeated biweekly for 5 cycles. In March, 2012, he presented with cough, slight chest-tightness, and a fever of 37.5 degrees centigrade. He was admitted to hospital on April 2nd, 2012. Physical examination did not find any abnormal signs of the lung like rale. Peripheral blood cell count was normal (WBC 8.1×10⁹/L, Neutrophileocyte 64%). A chest CT scanning was

Table 1. Reported incidence of PCP in patients with non-Hodgkin's lymphoma received regimen containing Rituximab.

Author (ref)	Year	Pts. n.	C	C plus P	Incidence (%)
Kim (12)	2013	713	14	32	2.0-4.5
Kurokawa (13)	2010	114	2	5	1.7-4.4
Kamel (14)	2010	47	5	2	4.3-10.6
Hashimoto (2)	2010	176	6	6	3.4
Katusya (15)	2009	129	3	8	3.2
Venhuizen (16)	2008	30	3	3	10
Kolstad (10)	2007	46	6	6	14

"Pts", patients; "n", number; "C", confirmed; "P", probable.

performed and showed ground glass opacities and enhanced pulmonary infiltrates in right upper lobe of the lung which suggested lung infection (Figure 1C). He was given levofloxacin and cefoperaxone. However the symptoms were not satisfactorily relieved. For the relatively typical manifestations on CT scanning film, special pathogens were suspected and a diagnostic bronchial alveolar lavage was maneuvered. Smear of BAL fluid revealed foamy masses highly suggestive of *Pneumocystis jiroveci* and Giemsa-staining was further performed. PCP was confirmed by typical morphological features of *Pneumocystis jiroveci* under microscope and the diagnosis was finally established. Due to a history of allergic to sulfa drugs, he was given Caspofungin (50 mg daily with 70 mg at day 1) instead of TMP-SMZ beginning on April 7th. The symptoms were relieved remarkably within a week. A Chest CT scanning was performed on April 12th, and demonstrated that most of the patches were absorbed and the pulmonary infiltrations were reduced (Figure 1D). For the satisfactory result of anti-*Pneumocystis jiroveci* treatment and no contradiction of chemotherapy, the patient accepted further R-CHOP chemotherapies. The patient was given 7 cycles of R-CHOP regimen all together. PCP was not found during the later chemotherapies.

Discussion

Rituximab, a chimeric human/mouse monoclonal antibody, can bind to the CD20 antigen presented on the surface of B lymphocytes, suppress the growth of B-cells and even kill them. Rituximab has been widely used in treatment of B-cell neoplasm especially the CD20-positive non-Hodgkin lymphoma (NHL) and remarkably enhanced the efficacy of chemotherapy. It has also been applied in the treatment of some other disorders and situations as Wegener's Granulomatosis (3) systemic lupus erythematosus (SLE) (4), hematopoietic stem cell transplantation (5), rheumatoid arthritis (6), refractory nephrotic syndrome (7), and humoral renal transplant rejection (8).

With the increasing application of Rituximab, adverse

events induced by Rituximab were documented continually. Among them, the reactivation of hepatitis B virus was the most common event. Secondly, PCP was reported in patients treated with Rituximab or Rituximab-including regimen (9). In 2007, Ame Kolstad and his colleagues reported six cases of PCP in B-cell lymphoma patients treated with the Rituximab-CHOEP-14 regimen. They concluded that depletion of B cells caused by Rituximab monotherapy did not increase the risk of PCP infections. When used in combination with other agents like steroids, Rituximab can increase the opportunity of PCP infection since it can impair the cellular immune system (10). Since then, reports of PCP in patients with lymphoma subjected to Rituximab continually emerged (11). The incidences of PCP in patients with lymphoma treated with Rituximab-containing chemotherapy were different in every report (Table 1). Ennishi D. *et al.* (2008) reported that 13 of 90 (14%) patients developed interstitial pneumonia (IP) during R-CHOP therapy, compared with none of 105 patients treated with CHOP alone as a historical control. In five IP patients, two were confirmed positive for *Pneumocystis jirovecii* (17). Venhuizen A. C. *et al.* [2008] found three cases of PCP in thirty patients during first-line treatment with Rituximab in combination with CHOP-14 for aggressive B-cell non-Hodgkin's lymphoma (16). Katsuya H. *et al.* indicated 1 of 59 (1.7%) patients who received CHOP alone and 8 of 129 (6.2%) patients who were treated with R-CHOP experienced IP. Among the 8 patients who were diagnosed as IP during R-CHOP, three were confirmed having PCP (15). Kamel S. *et al.* even reported that among 47 consecutive patients treated with R-CHOP-14, five (11%) developed microbiologically proven PCP, with a further two (4%) having classical clinical and radiological features of PCP even though without microbiological confirmation (14).

The cause of increased incidence of PCP in those patients remains controversial. As corticosteroid was usually administrated in the same time, it is hard to conclude that the adverse events were induced by Rituximab alone. A history of Rituximab treatment might not be related to PCP (2). For the

B-cell suppressive effect of Rituximab and B-cells play a pivot rule in the activation of CD4 T cells, the addition of Rituximab to chemotherapy was identified as an independent risk factor for IP (18). It is reasonable to deduce that PCP was associated with the use of Rituximab at least in part.

The number of white blood cells seems to be an important risk factor in the occurrence of PCP. Few researchers reported that CD4+ lymphocyte counts were normal in PCP patients (3). But most others demonstrated the opposite (11,12,19). For example, patients with CD4+ lymphocyte counts $\leq 200/\text{mm}^3$ before chemotherapy had a higher risk of developing PCP (2). Among the patients treated by R-CHOP, 3 of 32 (9%) patients whose lymphocyte counts were $< 1,000/\text{microL}$ before chemotherapy developed PCP, while 70 patients whose lymphocyte counts were $> 1,000/\text{microL}$ did not (15). In a retrospective study including 529 patients, PCP was diagnosed in six patients whose absolute lymphocyte count was less than $1 \times 10^9/\text{L}$ at diagnosis (18) and the reporter concluded that low lymphocyte count was an independent risk factor for PCP. Because of this conclusion, prophylaxis was highly recommended for patients with low CD4+ cell counts (10). In our report, both patients developed PCP during normal lymphocyte count period, which did not support that conclusion. But, one patient had a history of neutropenic period before the diagnosis of PCP. It is obvious that to estimate how long had the patient been infected by pneumocystis jiroveci before the diagnosis of PCP is difficult. Therefore, more data are needed to come to a more convincing conclusion.

The use of corticosteroid was also considered a risk factor for PCP (14,20,21). In a large consecutive series, systemic corticosteroid therapy, even in moderate doses, was administered to most patients during the month before the onset of PCP (22). The continuous use of steroids for conditions other than lymphoma could also significantly increase the risk of pulmonary infection including PCP (23).

The diagnosis of PCP is usually based on the symptoms, manifestations of chest-X-ray or CT scanning, and laboratory examinations. Most patients have fever, cough and dyspnea. But it is not always the case. Some patients were asymptomatic (7,24). The symptoms can be atypical either. For example, case one in our report did not have cough and fever at all except dyspnea. On chest film, typical ground-glass opacities (GGO) can often be found. But these manifestations were not exclusive and often confused with other lung infection like viral pneumonia. In some cases, single or even multiple persistent granulomatous pulmonary nodules were presented (19,24). In laboratory technology, there are many methods including Giemsa-stain, Gomoris Methenamine silver nitrate stain, and PCR that are being used to confirm the existence of pneumocystis jiroveci (7,10,17). Up to date, the most sensitive method remains to be Giemsa-stain in which pneumocystis jiroveci appears to be

“ping-pong”-like pink coccus under microscope. In our report, both cases were confirmed by Giemsa-staining.

The treatment and prophylaxis of PCP are relatively not difficult. In most reports, patients were treated successfully with TMP/SMX (11,13,17,25). In our report, case one was also successfully treated with TMP/SMX. TMP/SMX was also effective in preventing patient from suffering from PCP. In one study, none of patients who had SMZ developed PCP, while 6 of 176 (3.4%) patients who had no prophylaxis developed PCP (2). A 91% reduction in the occurrence of PCP was observed in another study (26). In another study, none of 121 patients who received PCP prophylaxis with TMP/SMX during chemotherapy developed PCP, while among 176 patients who had no prophylaxis, six (3.4%) developed PCP after starting chemotherapy, which demonstrated that TMP/SMX was effective for prophylaxis (2). Prophylaxis with TMP/SMX was found to be highly efficient and recommended for patients receiving the R-CHOP-14 regimen (25).

Caspofungin (brand name Cancidas) is a lipopeptide antifungal drug which is a member of a new class of antifungals termed the echinocandins. It can inhibit the enzyme β (1,3)-D-Glucan synthase and thereby disturb the integrity of the fungal cell wall. Laboratory research showed that Caspofungin had anti-pneumocystis activity (27). Caspofungin has been used with TMP/SMX for treatment of PCP (28,29), and recommended as a salvage treatment in PCP (30). The patient in case two in our report was treated with Caspofungin but not combined with TMP/SMX because he was oversensitive to TMP/SMX. He was also cured successfully, which suggested that Caspofungin alone could be also effective for treatment of PCP.

In conclusion, based on the literatures and data of cases we reported above, PCP is an opportunistic infection that can occur in patients with lymphoma treated with Rituximab-included regimen. On CT scanning film, granulomatous pulmonary nodules can also be seen instead of the typical ground glass opacities. TMP/SMX is effective in treatment and prophylaxis in most cases, and Caspofungin could be an effective alternative.

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