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Case Report

Life-threatening *Pneumocystis jiroveci* Pneumonia with Cytomegalovirus Coinfection in a Follicular Lymphoma Patient During Rituximab-based Chemotherapy

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Abstract

In the era of target therapy, we face the challenge of the risk of opportunistic infection in patients with B-cell lymphoma who receiving rituximab-based chemotherapy. Opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP) and Cytomegalovirus (CMV) pneumonia are life-threatening diseases. However, PJP with CMV coinfection is rare. Here, we report a follicular lymphoma patient who suffered from PJP with CMV coinfection after receiving three cycles of rituximab, cyclophosphamide, vincristine, and prednisone regimen and was successfully rescued after timely identification and treatment. We emphasize that physicians should be alert for the coinfection of PJP and CMV in lymphoma patients receiving rituximab-based chemotherapy and the timely recognition, and treatment that may avoid a deadly outcome.

Keywords: Coinfection, cytomegalovirus, follicular lymphoma, *Pneumocystis jiroveci* pneumonia, rituximab, cyclophosphamide, vincristine, and prednisone

Introduction

Rituximab, one of the biologic anti-CD20 monoclonal antibodies, is widely used in autoimmune disease and CD20-positive malignancies. However, rituximab has effects on immune function by depleting peripheral blood B-cells and modulating B- and T-cell interactions, resulting in impaired cellular immunity and may lead to serious infections.[1] A study in mice suggests that B-cells play an important role in generating protective effector and memory CD4+ T cells in defense against *Pneumocystis jiroveci* pneumonia (PJP) infection.[2] Although the incidence of PJP infection after

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rituximab-based chemotherapy in lymphoma patients seems to be low (<3%), it may lead to life-threatening condition if left unnoticed.[3] PJP-related mortality was approximately 27.2%.[4] On the other hand, cytomegalovirus (CMV) infection is also well-known opportunistic and life-threatening diseases. The incidence of CMV infection or reactivation in patients with hematologic malignancy receiving nontransplant therapy was approximately 5%.[5] The incidence of CMV coinfection in non-human immunodeficiency virus (HIV) patients with PJP who had received rituximab was approximately 1.4%.[6] Here, we report a rare case of PJP with CMV coinfection in a patient with follicular lymphoma after rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) therapy.

Case Report

A 68-year-old Taiwanese man with a history of hepatitis B infection (under tenofovir disoproxil fumarate) and hypertension was admitted due to shortness of breath, palpitation, and fever. The patient was diagnosed 3 months ago to have follicular lymphoma (Stage III Grade 1) with follicular lymphoma international prognostic index 3. He received the R-CVP regimen on 6/25–6/26/2021 (cycle 1), 7/22–7/23/2021 (cycle 2), and 8/13–8/14/2021 (cycle 3).

On admission for the third cycle of chemotherapy (08/11–08/14/2021), a cough with whitish sputum was noted. Oxygen (O_2) saturation was recorded at approximately 89%–92% under room air with no respiratory distress. Chest X-ray (CXR) showed no obvious pneumonia patch. Two-dimensional echocardiography showed a left ventricular ejection fraction of 81% without regional motion abnormality or valve problem. A pulmonary function test revealed normal result.

Nevertheless, 10 days after the third cycle of the R-CVP, he suffered from shortness of breath and palpitation; thus, he came to our emergency department on August 26, 2021 [Figure 1]. Accompanying symptoms included cough with scant whitish sputum and fatigue for 2 weeks. At home, his heart rate was approximately 90–110 beats per min, O_2 saturation 84%, and body temperature was over 37°C but below 38°C. He denied having headaches, sore throat, muscle soreness, chest pain, vomiting, diarrhea, abdominal pain, joint pain, or an abnormal sense of smell. In the emergency department, a body temperature up to 38.2°C was noted. The laboratory results were shown as below: white blood cell: 3700/uL, band form 3.1%, neutrophil 46.4%, lymphocyte 22.7%, monocyte 15.5%, eosinophil 3.1%, basophil count 8.2%, a typical lymphocyte 1%, hemoglobin 15.2 g/dL, hematocrit: 44.8%, mean corpuscular volume: 85.5fL, platelet 221,000/uL, alanine transaminase 31 U/L, total bilirubin 0.52 mg/dL, albumin 3.7 g/dL, creatine 1.14 mg/dL, glucose 113 mg/dL, NT-pro B-type natriuretic peptide 22 pg/mL, C-reactive protein 2.56 mg/dL, D-dimer: 1,114.9 ng/mL, lactate dehydrogenase 202 IU/L, sodium 132 mmol/L, potassium 3.6 mmol/L, calcium 2.29 mmol/L, prothrombin time 9.9 s, lactate acid 1.9 mmol/L, O_2 partial pressure/fractional inspired O_2 150 (48/0.32), hs-troponin I 8.5 pg/mL, procalcitonin <0.05 ng/mL, and coronavirus disease 2019 using polymerase chain reaction (PCR) was negative. Electrocardiogram (ECG) showed sinus tachycardia with right bundle branch block (no obvious change compared with the previous ECG result). CXR on August 26, 2021 [Figure 2] shows cardiomegaly, and a clear bilateral costophrenic angle was noticed. Under the impression of fever of unknown origin, an empirical antibiotic with levofloxacin was administered, but a chest computed tomography (CT) scan showed diffuse ground-glass patches [Figure 2] mixed with subpleural nodularity at both lungs. Under the impression of CMV or PJP infection with hypoxemic dyspnea, ganciclovir and sevatrim (trimethoprim and sulfamethoxazole) were prescribed. PJP with CMV coinfection was confirmed later by sputum *P. jiroveci* PCR and serum CMV viral load (8000 IU/mL). HIV result using enzyme immunoassay showed nonreactive in the further workup. CXR on day 7 showed bilateral ground-glass opacity [Figure 2]. After 2 weeks of intravenous IV antibiotic and antivirus treatment, clinical symptoms improved, and he was discharged with oral morcasin (sulfamethoxazole and trimethoprim) and valganciclovir. In addition, although we did not obtain tissue biopsy to prove CMV pneumonitis, but according to CMV viremia with associated symptom and image finding, inferred probable CMV pneumonitis, and preemptive therapy was given. CMV plasma viral load decreased, and O_2 saturation was improved after antiviral treatment [Figure 3] CXR and CT were followed up in the outpatient department and showed significant improvement [Figure 2]. The patient finally successfully completed another three cycles of R-CVP and is going on rituximab maintenance therapy.

Discussion

Follicular lymphoma is relatively common non-Hodgkin's lymphoma, only second to diffuse large B-cell lymphoma. The incident rate of follicular lymphoma is increased in Taiwan.[7] The overall survival had improved in the era of rituximab-based therapy.[8] However, we have to face the challenge of the risk of opportunistic infection in patients receiving target therapy.[9] The median time to viral infection diagnosis was 5 months (1–20 months) after rituximab treatment.[10] Some risk factors may further increase the risk of infection for patients receiving rituximab, such as received rituximab maintenance, hypogammaglobulinemia, decrease of immunoglobulin M levels after administration of rituximab, short duration of rituximab therapy, administration of granulocyte colony-stimulating factor, older age, chronic lung disease, cardia insufficiency, steroid exposure, higher cumulative dose of cyclophosphamide, and concomitant chemotherapy.[11] The measurement of immunoglobulin levels before and during rituximab may be helpful to the identification of higher risk of infection cases and may provide us with prevention strategy reference. Further study may prove this point of view.

The prognosis was poor for PJP and CMV pneumonia. The 30-day mortality rate can be as high as 78.6%.[12] Chest CT

	Last time admission	ER	hospital															OPD				
Day		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15					
Year	2021																					
Month	8							9													10	
Date	11-14	26	27	28	29	30	31	01	02	03	04	05	06	07	08	09	10	17	23	29	07	13
Body temperature °C	35.8-36.3	38.2	39.3	37.4	37.3	36.6	36.8	36.1	36.4	36.2	36.6	36.3	36.4	36.5	36.4	36.4	35.6					
SpO2%	89-92	85	85	85	86	87	87	89	88	89	91	94	93	94	95	95	95	95				
Cough	Since 8/13																					
Dyspnea		Since 8/23																				
O2 (A/M=aerosol mask)		Nasal 3L	A/M 8L 40%	A/M 10L 50%	A/M 15L 100%	A/M 12L 75%		Mask 8L 40%		Mask 6L 35%	Nasal 3L											
Sputum PJP PCR													8/31 (+)									10/6 (-)
Serum CMV viral load										8/28 (8000)				9/3 (4360)				9/10 (770)	9/17 (101)		9/29 (<35)	10/7 (<35)
CXR/CT		CXR	CT						CXR							CXR		CXR		CXR	CXR	CT
levofloxacin				Levofloxacin 750mgQD																		
Anti-PJP				IV Sulfamethoxazole 800mg and trimethoprime 160mg Q8H														Oral Q12H	Oral QD			
Anti-CMV				Ganciclovir 125mg Q12H														Valganciclovir 900mg QD				

Figure 1: Clinical course of the patient. Body temperatures, oxygenation saturation, symptoms, and oxygenation therapy usage according to day of illness and day of hospitalization, August 27 to September 10, 2021. Preemptive treatment using ganciclovir and sevatrim before definite diagnosis by cytomegalovirus viral load and sputum *Pneumocystis jiroveci* Pneumonia polymerase chain reaction. CXR: Chest X-Ray, PJP: *Pneumocystis jiroveci* Pneumonia, CMV: Cytomegalovirus, O_2: Oxygen, SpO2: Saturation of peripheral oxygen, ER: Emergency room, OPD: Outpatient department, A/M: Aerosol mask

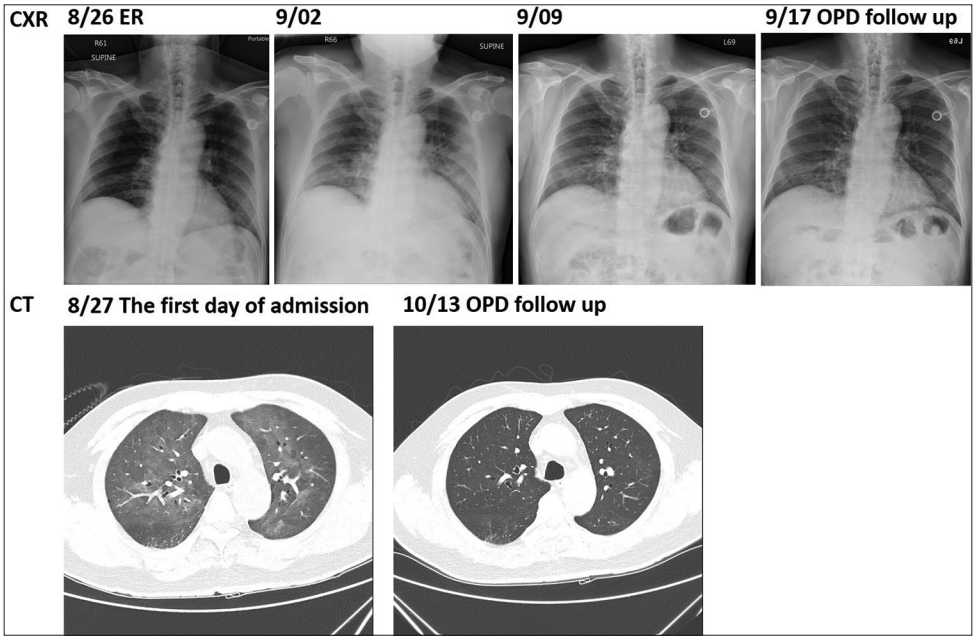

Figure 2: Images of chest X-ray (CXR) and Chest computed tomography (CT). CXR on 8/26 shows image finding out of proportion to clinical SYMPTOMS in the early disease course. CXR on 9/2 reveals bilateral ground-glass opacity (GGO) compared with the image on 8/26. CT scan upon admission show bilateral GGO, suggesting *Pneumocystis jiroveci* pneumonia or Cytomegalovirus infection. Another CT scan follow-up in the outpatient department show bilateral ground-glass opacity significant in regression. CXR: Chest x-ray, CT: computed tomography, OPD: Outpatient department

is the key to timely diagnosis and preemptive treatment for CMV or PJP pneumonia. On the other hand, reporting time for sputum PJP PCR and CMV viral load takes some time. Initial presentation of our case was dyspnea and fever. These symptoms can appear in PJP, CMV, or other infections. In addition, desaturation was found in our case. However, the CXR on August 26, 2021 shows image finding out of proportion to clinical symptoms in the early disease course. Chest CT scan is a better tool to early identification of PJP compared to CXR.[13] However, the early CT findings cannot differentiate PJP and CMV pneumonitis. In our case, chest CT was arranged for assisting the differential diagnosis and showed a bilateral ground-glass pattern, which increased our confidence of using ganciclovir and

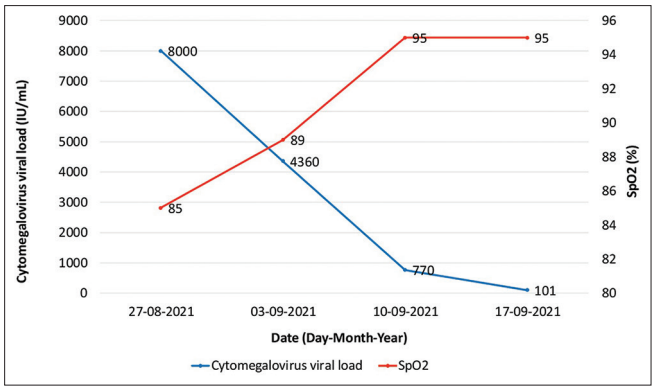

Figure 3: Relationship between cytomegalovirus (CMV) viral load and oxygen (O_2) saturation. CMV plasma viral load decreased, and O_2 saturation was improved after antiviral treatment. SpO2: Saturation of peripheral oxygen

sevatrim as a preemptive treatments in the dyspenic patient with hypoxemia in the presence of normal CXR before definite diagnosis by CMV viral load and sputum PJP PCR. A large dataset cohort study also shows that delay in the first antibiotic administration was associated with increased in-hospital mortality.[14]

To the best of our knowledge, there is lack of randomized control trial for prophylaxis for PJP in patients receiving rituximab base chemotherapy. Nevertheless, due to high mortality rate, prophylaxis treatment for opportunistic infection was discussed widely. A meta-analysis, based on data of cohort trial, demonstrates that PJP prophylaxis is effective in decreasing the incidence of PJP in lymphoma patients receiving rituximab-based chemotherapy.[15] A retrospective study conducted in a tertiary referral center in South Korea show the benefit of primary prophylaxis for PJP in patients receiving rituximab treatment is outweigh the potential risk of the prophylaxis.[4] In our case, primary prophylaxis of trimethoprim and sulfamethoxazole may be helpful. Further randomized control studies are still needed to confirm the benefit of prophylaxis treatment in lymphoma patients receiving rituximab-containing regimen.

Furthermore, although the identification of CMV inclusions or positive CMV-specific immunohistochemistry staining on histopathology is the gold standard for diagnosing CMV tissue invasive disease, like CMV pneumonia, the absence of CMV inclusions on histopathology does not exclude CMV disease, and sometimes, it is difficult to obtain tissue biopsy in clinical practice. On the other hand, CMV viremia is not representative of CMV disease, but CMV viral load has been utilized to guide preemptive therapy for patients receiving transplantation.[16,17]

In conclusion, in the era of targeted therapy, PJP with CMV coinfection could occur in a patient with follicular lymphoma who receives the R-CVP regimen. Therefore, we emphasize that physicians should be alert for the coinfection of PJP and CMV in lymphoma patients receiving rituximab-based chemotherapy and the timely recognition, and treatment that may avoid a deadly outcome.

Ethical approval

The Institutional Review Board (IRB) of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation has approving this study (Protocol No.: 11-CR-016).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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