Rituximab-induced Interstitial Pneumonitis in a Young Patient: A Case Report and Review of the Literature

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Side effects of rituximab are mild in most cases, but there have been a few cases of severe pulmonary toxicity reported in elderly patients. Here we report a case of interstitial pneumonitis following rituximab treatment in a young patient. A 35-year-old woman with diffuse large B-cell lymphoma was admitted complaining of dry cough and dyspnea without fever after the 3 treatments with rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy. Her chest CT with high-resolution CT scanning confirmed the presence of bilateral diffuse ground-glass opacities. The analysis of arterial blood gases indicated hypoxemia. The pulmonary function testing showed a restrictive pattern. There were no other findings suggesting an infection. The findings were compatible with a rituximab-induced interstitial pneumonitis. After the patient was treated with prednisolone, the symptoms resolved. Cases with rituximab-induced interstitial pneumonitis develop principally in elderly patients. However, the condition also can occur in young patients. ***(Korean J Hematol 2007;42:423-427.)***

Key Words: Rituximab, Interstitial pneumonitis, Young patient, Diffuse large B-cell lymphoma

INTRODUCTION

Rituximab is a monoclonal antibody against the CD20 B-cell antigen.[1] It is effective in relapsed or refractory indolent CD 20+ B-cell non-Hodgkin's lymphoma (NHL) and advanced stage chemoresistant or relapsed follicular lymphoma. It is also the first-line treatment for aggressive NHL, including diffuse large B-cell lymphoma in combination with CHOP.[2] An evaluation of the efficacy of this treatment in autoimmune disorders and other malignancies has been recently conducted.[3]

The most frequently observed type of non-Hodgkin's lymphoma is diffuse large B-cell lymphoma, and accounts for up to 40 percent of cases. In a large, prospective randomized multicenter trial for previously untreated patients with aggressive NHL, a combination of rituximab- cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) established a significantly more complete response (CR) (76% versus 63%, P=0,005), superior 2-year progression-free survival rates (PFS) (57% versus 38%, $P<0.001$) and overall survival (OS) rates (70% versus 57%, P=0.007), but no significant toxicity as compared to CHOP treatment alone.[4]

There are no known risk factors for ritux-

접수 : 2007년 9월 13일, 수정 : 2007년 11월 23일
승인 : 2007년 11월 26일
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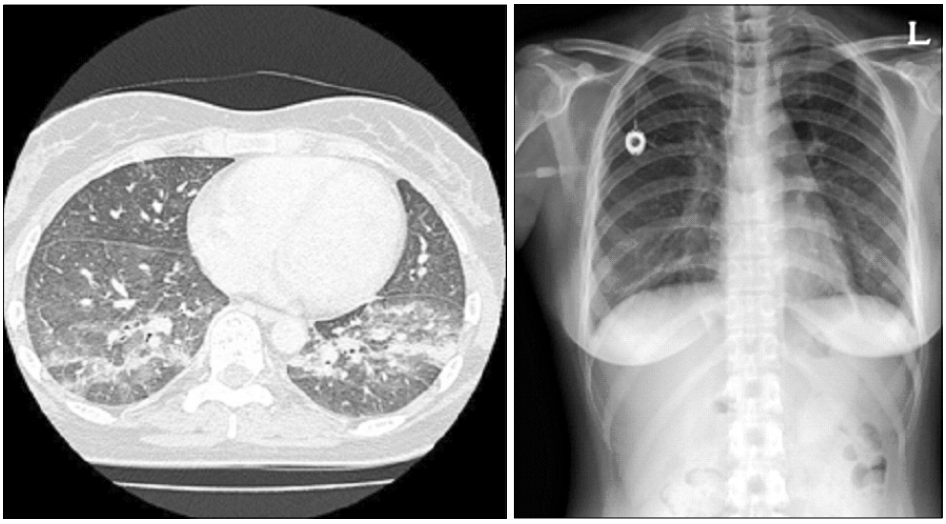

Fig. 1. Rituximab-induced interstitial pneumonitis in chest HRCT scan and radiography.

imab-induced interstitial pneumonitis, but advanced age is considered to be one of its significant risk factors.[5] Herein, we report an unusual young patient with diffuse large B-cell lymphoma who developed interstitial pneumonitis following R-CHOP chemotherapy.

CASE REPORT

A 35-year-old woman presenting with a tingling sensation in the lower extremities and radiating pain visited our hospital. The lumbar spine MRI imaging evidenced a mass around the presacral and spinal canal area at the Sacral 1, 2, 3 levels. The excisional biopsy of that mass was diagnosed as diffuse large B-cell lymphoma.

Initial chest radiography and chest computed tomography (CT) with high resolution computed tomography (HRCT) following excisional biopsy revealed nonspecific findings, with the exception of a slight pleural effusion, left lower. Pleural effusion was resolved on the follow-up chest radiography.

The patient was treated with R-CHOP chemotherapy every three weeks. After the second administration of R-CHOP chemotherapy, the patient developed a mild cough, but the chest radiography and physical examination were unremarkable.

Table 1. Analysis of arterial blood gases before and after prednisolone treatment

Parameter	Before treatment	After treatment
pH	7.449	7.427
pCO_2 (mmHg)	38.0	33.0
pO_2 (mmHg)	66.4	130.6
O_2 saturation (%)	94.0	98.7

After the third R-CHOP chemotherapy, she was admitted for dry cough and dyspnea. The physical examination showed reduced breath sounds in both lungs. Her chest radiography evidenced bilateral diffuse haziness and a chest CT with an HRCT scan verified the presence of bilateral diffuse ground-glass opacity with bilateral basilar consolidation and thickening along the bronchovascular bundle (Fig. 1). The arterial blood gas analysis demonstrated a PO_2 of 66 mmHg and an oxygen saturation of 94%. Pulmonary function tests revealed a restrictive pattern and the pulmonary diffusing lung capacity of carbon dioxide was reduced (Table 1, 2).

Other findings suggesting infection, including blood, urine, sputum culture, sputum culture, cytomegalovirus (CMV) IgM antibody, pneumocystis carinii PCR, mycoplasma antibody, antineutrophil cytoplasmic antibody (ANCA), and antinuclear antibody (ANA) tests were all negative.

These results were consistent with drug (rituxi-

Table 2. Pulmonary function tests before and after prednisolone treatment

Variable	Predicted value	Before treatment	After treatment
FVC (liters)	3.78	1.93 (51%)	3.21 (85%)
FEV_1 (liters)	2.98	1.52 (51%)	2.79 (94%)
FEV_1/FVC (%)	78	79	87
TLC (liters)	5.30	3.86 (73%)	4.41 (83%)
DLCO (mL/min/mmHg)	21.6	7.0 (33%)	14.1 (65%)

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; TLC, total lung capacity; DLCO, carbon monoxide diffusing capacity.

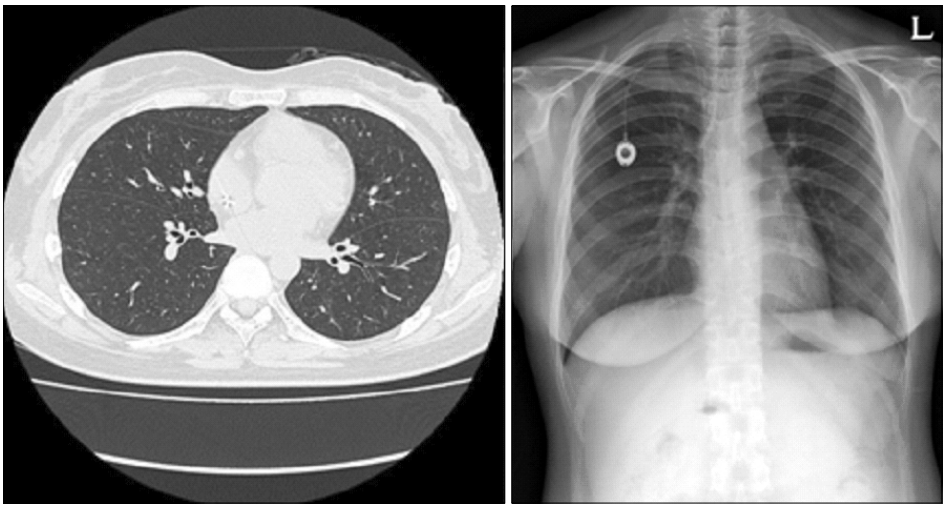

Fig. 2. After prednisolone treatment for 2 weeks, interstitial pneumonitis resolved in chest HRCT scan and radiography.

mab)-induced interstital pneumonitis with organizing pneumonia in both lower lobes.

She was prescribed 30mg of prednisolone daily. Her symptoms evidenced dramatic improvement.

The follow-up chest HRCT revealed nearly total resolution of drug-induced interstital pneumonitis in both lower lobes and bronchiolitis obliterans (Fig. 2). Repeated pulmonary function tests recovered to normal, and the pulmonary diffusing lung capacity of carbon dioxide was improved-by 65% of the predicted value. The analysis of arterial blood gases revealed a PO_2 of 130 mmHg and an oxygen saturation of 98.7% (Table 1, 2).

Further chemotherapy was conducted via a CHOP regimen, with the exception of rituximab. The patient had no symptoms, including dyspnea, dry cough.

DISCUSSION

The diagnosis of interstitial pneumonitis is possible in cases in which typical symptoms and signs such as exertional dyspnea, dry cough, abnormal breathing sounds, and a restrictive pattern on pulmonary function testing are combined with radiological abnormalities including ground glass opacity and multiple infiltrations upon computed tomography (CT).[6] If these findings are equivocal, a lung biopsy can help to verify the diagnosis. Smoking, occupational exposure to dusts, advanced age, diabetes mellitus, hyperlipidemia, and obesity are known to be risk factors of interstitial pneumonitis.[5]

In this case, although other drugs-cyclophosphamide and vincristine also could be an etiology of drug-induced lung injury, but interstitial

pneumonitis did not occur when we treated with CHOP regimen. So, we described rituximab related interstitial lung disease.

The adverse events of rituximab are usually mild, and include infusion-related symptoms including fever, chill, and rigors. The use of rituximab has not been commonly associated with pulmonary toxicity. Drug-induced lung injury associated with rituximab has been reported in less than 0.03 percent of cases, but sometimes proved fatal.[7,8)]

The mechanism underlying rituximab-induced interstitial pneumonitis has remained unclear until now. However, several immune mechanisms could be related to the acute and chronic adverse effects of rituximab treatment, which results in the activation of complement, B-lymphocyte cytolysis, cytotoxic T-lymphocytes, and the release of cytokines (TNF-alfa, IL-6, INF-gamma).[9)]

Small numbers of cases of interstitial pneumonitis have been previously reported (Table 3).[7,10-14)] Rituximab-induced lung injury occurred after 2 or 3 cycles of treatment. They evidenced no history of interstitial lung disease and was well controlled with low or high doses of steroid treatment. Also, they did not observe these effects under continued treatment, except for rituximab treatment. In this case, a similar clinical course was observed. However, all of the patient who were previously diagnosed with rituximab-induced interstitial lung disease were elderly (range: 56～82 years).[7,10-14)] The patient described herein, however, was only 35 years old. Rituximab-induced interstitial lung disease usually develops only in elderly patients. However, in our case, it developed in a younger patient.

Normally, cautious monitoring for respiratory symptoms is done in cases of rituximab treatment in geriatric patients. However, we also must remain vigilant for the occurrence of rituximab-induced interstitial pneumonitis, even in young patients.

Table 3. Patients' characteristics of reported cases

Case	Year	Sex	Age	Diagnosis
Kanelli et al. (10)	2001	Male	56	MCL
Burton et al. (7)	2003	Male	69	NHL
Alexandrescu et al. (11)	2004	Male	65	DLBCL
Hiraga et al. (12)	2005	Male	80	DLBCL
Choi et al. (13)	2006	Female	67	DLBCL
Lee et al. (14)	2006	Male	73	DLBCL
		Male	66	DLBCL
This report	2007	Female	35	DLBCL

Abbreviations: MCL, mantle cell lymphoma; DLBCL, diffuse large B cell lymphoma; NHL, non-Hodgkin lymphoma.

요 약

대부분의 경우, 리툭시맙의 부작용은 경미하지만 고령의 환자에서 드물게 중대한 폐합병증이 보고되었다. 본 증례는 젊은 환자에서 리툭시맙의 치료 후 생긴 간질성 폐질환에 관해 보고하고자 한다. 미만성 대세포 B형 림프종 진단 후 리툭시맙-CHOP 치료를 3주기 시행 받았던 35세 여자 환자로 기침과 호흡곤란을 주소로 내원하였다. 환자는 컴퓨터 단층 촬영상 양측 폐에 미만성의 간유리 음영소견을 보였고 동맥혈 검사상 저산소증을 나타내었으며 폐기능 검사상 제한적 형태의 폐기능 소견을 보였다. 감염의 소견은 발견되지 않았다. 환자는 스테로이드를 사용 후 증상의 호전을 보였고 이후 치료에서는 리툭시맙을 제외한 CHOP 요법으로 치료하였으며 호흡곤란의 소견은 관찰되지 않았다. 이전 보고에서 리툭시맙과 관련된 폐병변의 경우 고령에서 보고되었으나 본 증례를 통해 젊은 환자에서도 발생할 수 있음을 유념해야 하겠다.

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