

Pulmonary BALT Lymphoma Successfully Treated with Eight Cycles Weekly Rituximab: Report of First Case and F-18 FDG PET/CT Images

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Extra marginal-zone lymphomas of the lung is a very rare tumor and it originates from bronchial-associated lymphoid tissue. A 68-yr-old woman presented with productive cough and dyspnea. A thorax computed tomography scan showed a 9 × 10 cm in size mass in the left lung and pleural effusion in the lower lobe of left lung. Positron emission tomography/computed tomography (PET/CT) revealed intense uptake foci at the upper and middle sites of left lung and slight uptake foci at the mediastinal lymph nodes which showed malignant involvement. After bronchoscopic biopsy, the diagnosis of pulmonary bronchial-associated lymphoid tissue (BALT) lymphoma was confirmed. At the end of the eight cycles weekly rituximab treatment, complete response was obtained by PET/CT findings. It is concluded that extended rituximab schedule is more effective and it would be beneficial to investigate the use of PET/CT in the diagnosis and evaluating of the treatment response of pulmonary BALT lymphoma.

Key Words: BALT lymphoma; Rituximab; Extended Schedule; Positron-Emission Tomography

INTRODUCTION

Marginal-zone lymphomas (MZLs) comprise the mucosa-associated lymphoid tissue (MALT) type (extranodal marginal-zone lymphoma [EMZL]), the nodal marginal-zone B-cell lymphoma and the splenic MZL. It is a distinct clinico-pathologic entity that usually follows an indolent course (1, 2). MALT lymphomas most commonly arise from gastrointestinal tract, however, they have been described in a wide variety of extranodal sites of the body including salivary glands, orbit and ocular adnexae, lung, skin, thyroid, breast, liver, kidney, bladder and prostate (3, 4). Pulmonary non-Hodgkin's lymphoma (NHL) is very rare tumor, comprise only 0.5% of all pulmonary malignancies, more than two-thirds of all NHL of the lung, moreover, it is a rare entity and accounts for less than 1% of all lymphomas (5). EMZL of the lungs originates from bronchial-associated lymphoid tissue (BALT), which is histologically different from true intrapulmonary lymph node (6). While there is recognised association with *helicobacter pylori* infection in gastric MALT lymphomas, no certain agents have been identified that related with pulmonary MALT lymphoma. Previously it showed that chronic antigenic stimulation from smoking and some autoimmune diseases could play a role as trigger for the pulmonary MALT lymphomas (5).

Recommended treatment options include complete surgical

excision, surgery followed by radiotherapy or chemotherapy alone but, the optimal therapy remains unclear (7-9). An alternative to cytotoxic chemotherapy is the use of rituximab because pulmonary MALT lymphoma cells typically expresses the CD 20 antigen. Recently, we reported that a case of BALT lymphoma successfully treated with six cycles single agent rituximab therapy (10). We describe here first case of pulmonary MALT lymphoma who had obtained complete response after extended, eight cycles rituximab treatment.

CASE DESCRIPTION

A 68-yr-old woman was admitted to our hospital in January 2009, with six month history of productive cough and dyspnea for six months in January 2009. She had a history of hypertension for 8 yr and was treated with amlodipine, 5 mg/day, p.o. She had never smoked. Her family history was non-contributory. On physical examination, lung auscultation revealed decreased breath sounds, coarse crepitations on the left lower lung site. There were no lymphadenomegaly and organomegaly.

Initial laboratory results were as follows: urea 20 mg/dL, creatinine 0.66 mg/dL, LDH 500 U/L (N:210-480), white blood cell (WBC) 6,500/μL, platelets 210,000/μL, hematocrit 41.7%, MCV 91.4 fL. Other laboratory values were within normal limits. Her

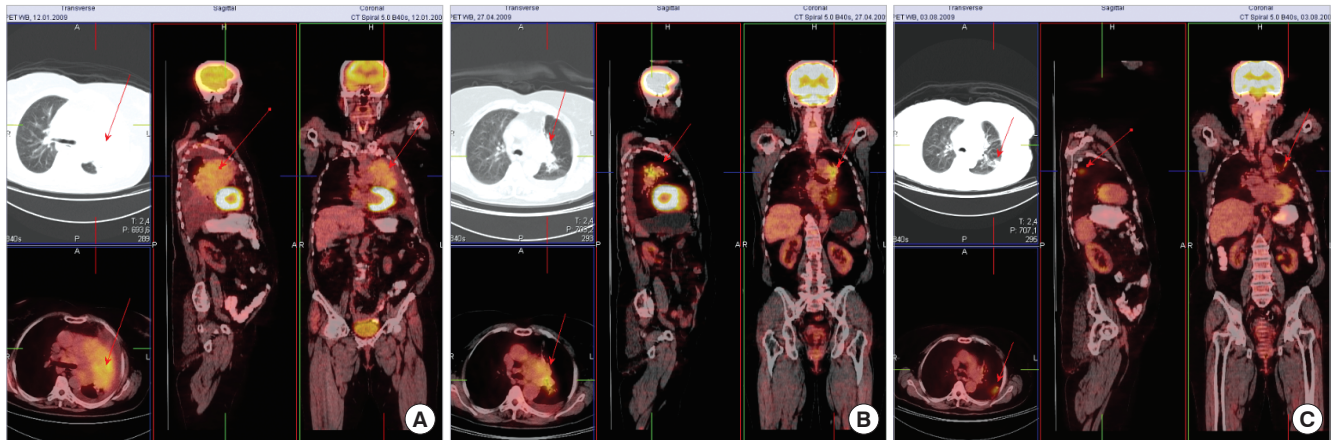


Fig. 1. Images by PET/CT scanning. (A) Diffuse hypermetabolic involvement (standard uptake value [SUV]:7.2) at the upper and middle site of the left lung and mild uptake foci at the mediastinal lymph nodes (SUV:3.4) which was compatible with malignancy. (B) Partial response after the sixth cycles rituximab. (C) Complete remission after eight cycles of rituximab medication.

chest radiography showed non-homogen increased density on the left lower site. A thorax CT scan revealed a 9×10 cm in size mass in the left lung and consolidation including air bronchogram and pleural effusion in the lower lobe of left lung. Fluorodeoxyglucose (FDG) PET/CT revealed intense uptake foci at the upper and middle sites of left lung and slight uptake foci at the mediastinal lymph nodes which showed malignant involvement (Fig. 1A). Thereafter, transbronchial biopsy was performed. Histopathological examination of biopsy specimen revealed a diffuse dense lymphocytic infiltrate composed of small mature lymphocytes with irregular nuclei. There was no evidence of large cell lymphoma. Immunohistochemical analysis showed that CD 20 (+), CD 43 focal (+), bcl 2 (+), CD 3 (-), CD 5 (-), CD 10 (-), bcl 6 (-). The diagnosis of EMZL (pulmonary) of MALT was made by these findings. HIV and hepatitis C serology were negative and she had no underlying autoimmune disease. No pathological findings were detected in bone marrow biopsy.

After the informed written consent was obtained, she was treated with the anti-CD 20 antibody rituximab, weekly intravenous infusions of a dose of 375 mg/m^2 with diagnosed clinical stage IE pulmonary MALT lymphoma. After six courses of rituximab, the mass localized in the left lung was partially regressed (Fig. 1B). Complete response was achieved after completion of eight cycles of chemotherapy (Fig. 1C). No side effect was observed associated with rituximab. She had no specific symptom and was remained in the remission, during a follow-up of 21 months.

DISCUSSION

Primary non-Hodgkin's lymphoma of the lung is a rare entity and although the prognosis of BALT lymphomas is favorable with 5-yr survival rates of over 85% and median survival of over 10 yr in the largest reported series, clinical features, prognostic factors, and patient management have not been clearly defined

(11). Treatment options of BALT lymphoma range from observation only to surgical resection alone or in combination with chemotherapy and radiotherapy but, the optimal therapy remains controversial in the absence of any prospective studies (7-9). Watchful waiting for asymptomatic patients with surgically unresectable disease, or single-agent chemotherapy are reasonable options. In addition, combination chemotherapy may be considered in symptomatic patients with bulky or disseminated disease. Various chemotherapeutic regimens without surgical resection have been used and reported with different outcome. Patients with unifocal disease may be often undergo surgery at the first diagnosis, whereas in patients with multifocal disease there are two choices: watchful waiting strategy or chemotherapy \pm antibody treatment (1).

Rituximab is a chimeric human/mouse anti-CD 20 monoclonal antibody that has emerged in recent years as an effective therapy for NHL and other B-cell malignancies. It has been approved for use in combination with CHOP chemotherapy regimen for the treatment of aggressive NHL (12). In the lack of prospectively collected data, the therapeutic role of rituximab is unclear. Nevertheless, as BALT lymphoma cells express CD 20 antigen, therefore, its use may be considered, alone or in combination with other therapy.

In a study performed by Conconi et al. (13), they reported first phase-II study of rituximab in 34 patients with extranodal MALT lymphomas. Four patients with lung MALT lymphomas have included in this study, but the clinical response to rituximab for these patients has not been clearly reported in this paper. The authors indicated that the overall response rate (ORR) was 73% with median response duration 10.5 months. There was the high relapse rate (36%) in Conconi's series and it showed that the 4-weekly-cycles regimen used may not represent the best schedule for administering rituximab in MALT lymphoma. However, previous studies reported that increasing evidence has already been provided in other lymphoma subtypes that higher

doses, maintenance treatment, and combination with conventional chemotherapy may all be of benefit (14, 15).

The efficacy of rituximab in BALT lymphomas has been reported (10, 16-19). In the English Medical literature, eight patients with BALOMA who received single agent rituximab therapy have been previously reported. In two of seven patients, it reported that CR was achieved with 4 and six cycles of rituximab, respectively (10, 18). Seker et al. (10) reported first case with BALT lymphoma treated with six cycles, weekly rituximab who had obtained CR, while all cases received four cycles of weekly rituximab. In our case, partial response was obtained after four and six cycles weekly rituximab chemotherapy. Therefore, two additional cycles were administered and pulmonary mass was regressed completely. In previous reports if additional two or four cycles rituximab could be administered in patients with PR, CR might be achieved as our patient. To our knowledge, extended treatment with weekly doses rituximab is more better effective and safety as previous reports (15, 20).

This report constitutes the first case of BALT lymphoma successfully treated with eight cycles, weekly rituximab in the literature. Also our case is noteworthy because of pre and after treatment PET/CT images. We demonstrated that extended rituximab schedules may result in increased efficacy in BALT lymphoma. On the other hand, the place and the duration of treatment or schedules of rituximab need to be investigated by prospective studies including a large sample size in the future.

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