

Case Report

Diffuse large B-cell lymphoma with initial symptoms of myelofibrosis treated with rituximab: a case report and literature review

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Received February 6, 2017; Accepted March 22, 2017; Epub June 1, 2017; Published June 15, 2017

Abstract: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma that develops from the B cells of the lymphatic system. The first symptom of DLBCL is usually painless swelling of lymph nodes in the neck, armpit, groin or abdomen. Patients may also experience fevers, night sweats and unexplained weight loss. Here, we reported a 73-year-old man with DLBCL. Specifically, initial myelofibrosis-related symptoms were considered at the time of onset. After 11 cycles of chemotherapy with rituximab, the patient achieved complete remission. This case suggests that elderly patients treated with rituximab could achieve significant effects, although myelofibrosis was their first symptom.

Keywords: DLBCL, myelofibrosis, initial symptom, rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma that develops from the B cells of the lymphatic system. It accounts for approximately 40-50% of new cases of lymphoma [1]. The first symptom of DLBCL is commonly painless swelling of lymph nodes in the neck, armpit, groin or abdomen. Patients may also experience fevers, night sweats and unexplained weight loss. Secondary myelofibrosis (SMF) is rare but can be caused by a variety of malignancies such as chronic myeloproliferative disorders, acute/chronic leukemia, multiple myeloma, and lymphomas. When lymphoma cells spread to the bone marrow, the disease may cause myelofibrosis. To the best of our knowledge, myelofibrosis as the initial symptom at the onset of DLBCL is a very rare event. Herein, we presented a unique case of DLBCL with myelofibrosis as the primary symptom and treatment with rituximab, which is widely used for the treatment of DLBCL.

Case presentation

A 73-year-old man was hospitalized because of a 3-month-history of fatigue, pallor, fever up to

38.5°C and emaciation. No lymph node swelling or palpable spleen was detected. Severe pancytopenia could be observed from his complete blood counts (white blood cell $1.74 \times 10^9/L$ (normal range: $4-10 \times 10^9/L$), hemoglobin 51.1 g/L (normal range: 120-160 g/L), and platelets $8.3 \times 10^9/L$ (normal range: $100-300 \times 10^9/L$)). The lactate dehydrogenase (LDH) level was increased (727 U/L, normal range: $104-245 \times 10^9/L$). An interstitial deletion of 7q31 was detected by fluorescence in situ hybridization (FISH). Both abnormal lymphocyte proliferation and prolymphocyte elevations (5.5%) could be observed in bone marrow cell (BMC) morphology (**Figure 1A**). We were surprised to find that the bone marrow biopsy demonstrated interstitial fibrosis. A significant reticular fiber network and collagen fibers could also be discovered via specific staining. Immunohistochemistry revealed that the bone marrow cells were positive for CD20 and CD79a and negative for CD3, CD30 and CD138 (**Figure 2A-C**). His swelling and thickening spleen was discovered by PET/CT scan (**Figure 3A, 3B**). After thorough examination, the patient was diagnosed with non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL, Ann Arbor stage IV, International Prognostic Index (IPI) score of 4), with secondary myelofibrosis.

A rare case of myelofibrosis as the initial symptom of DLBCL

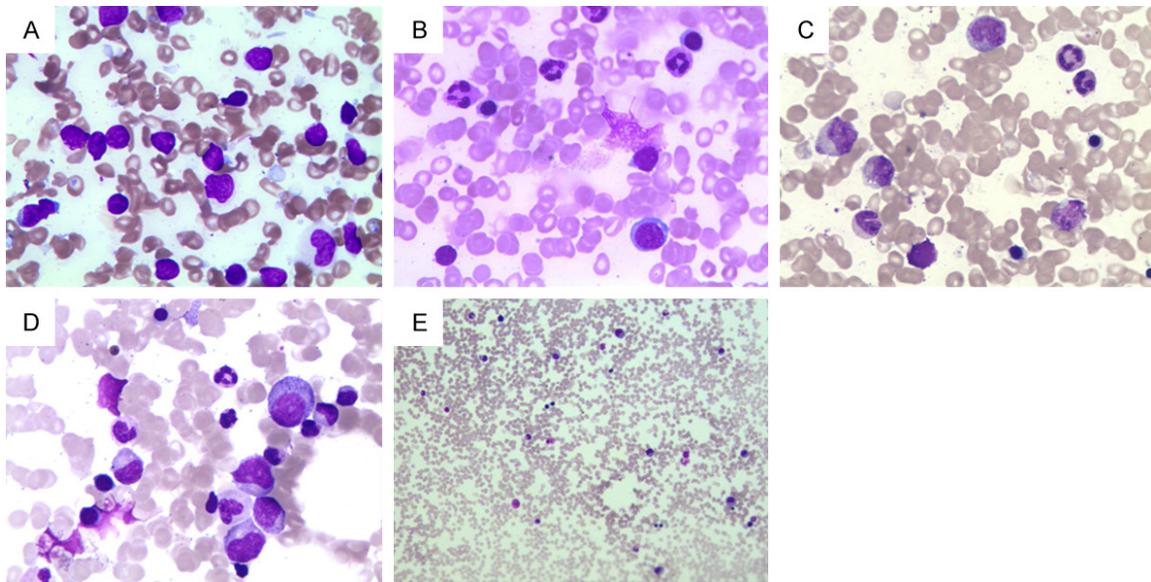


Figure 1. Bone marrow cell (BMC) morphology of the patient. A: BMC morphology at the initial visit (40 ×), showing abnormal lymphocyte proliferation, an elevated ratio (5.5%) of prolymphocytes and irregular cell deformation. Nucleoli of some cells could be seen. B: The second BMC morphology of the patient (40 ×), showing a decreased ratio of lymphocytes (41%) and prolymphocytes (2%). C: The third BMC morphology of the patient (40 ×), showing that there were almost no prolymphocytes. D: The fourth BMC morphology of the patient (40 ×), also showing that there were almost no prolymphocytes. E: The final BMC morphology of the patient (10 ×), which showed very few (1%) observable blast cells.

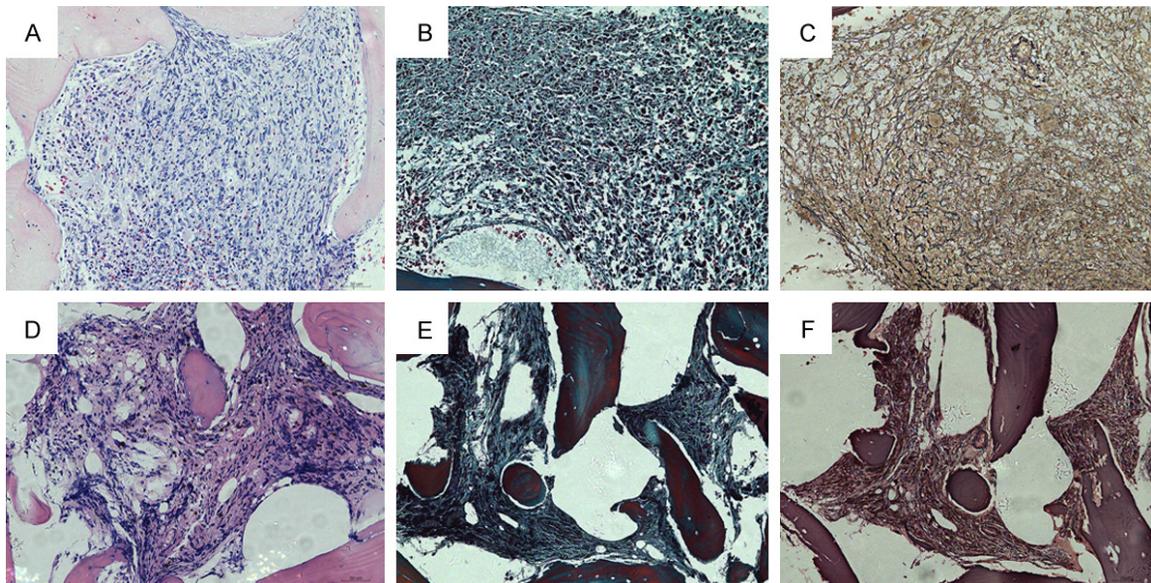


Figure 2. Bone marrow biopsy of the patient. A: HE staining of biopsy (20 ×) at the initial visit, showing interstitial fibrosis of the bone marrow, large irregular cells scattered in the distribution with reduced cytoplasm, thick stained nuclei and large eosinophilic nucleoli. Pathological mitotic figures could be seen. The immunohistochemistry supported a B cell source. B: Masson staining of biopsy (20 ×) at the initial visit, showing fibroblastic proliferation. C: Staining of reticular fibers at the initial visit, showing reticular fibers (+++). D: HE staining of the third biopsy, in which a small number of irregular medium-large cells could be observed locally. E: Masson staining of the third biopsy of the patient. F: Staining of reticular fibers of the third biopsy of the patient, showed proliferation of reticulum fibers, Ag (++++).

The patient was sequentially treated with Rituximab (500 mg), reduced-dose R-COP regimen
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(rituximab 0.5 g/d₁, cyclophosphamide 0.4 g/d₃, vincristine 0.2 g/d₃, and dexamethasone 10
Int J Clin Exp Pathol 2017;10(6):7093-7099

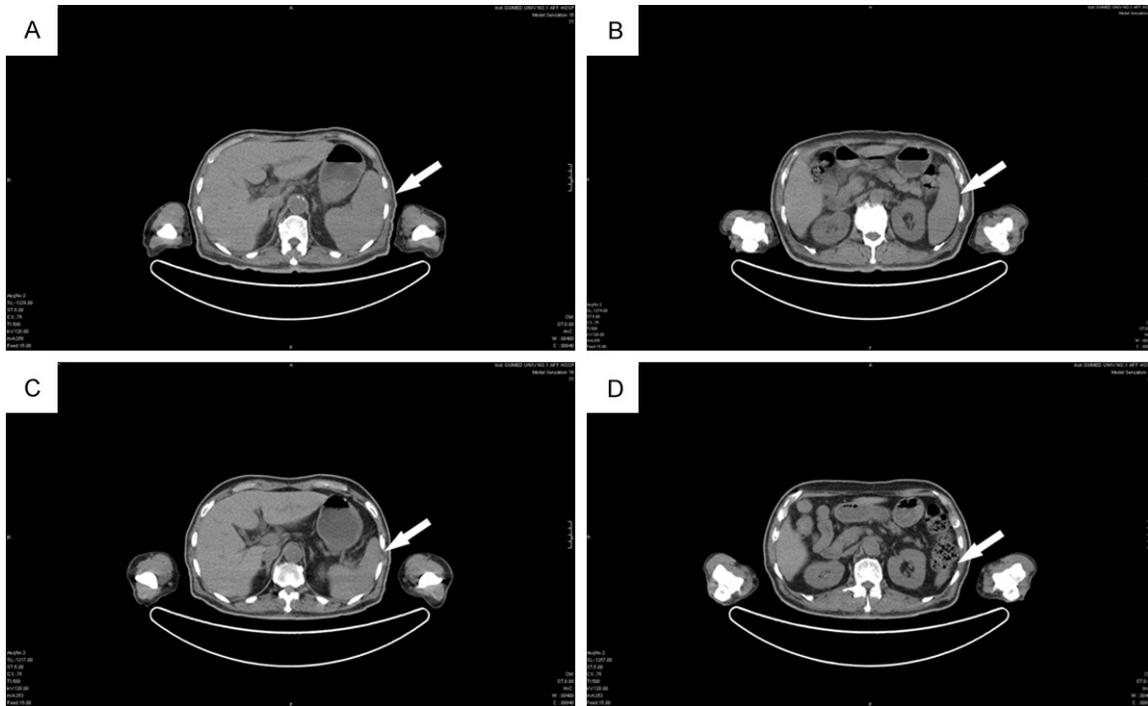


Figure 3. Changes in the spleen of the patient before and after chemotherapy in PET/CT imaging. A, B: The PET/CT before chemotherapy showed that the patient's spleen was swollen and thickened. C, D: The PET/CT after chemotherapy showed that the patient's spleen had returned to normal.

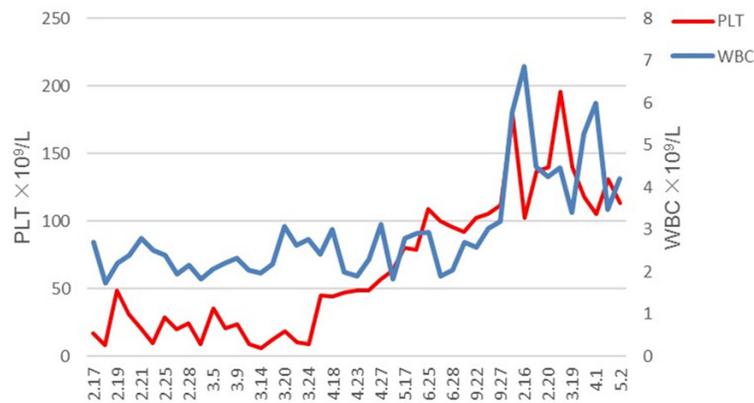


Figure 4. Leukocyte and platelet changes in the patient between February 2013 and May 2014.

mg/d₃₋₇) and reduced-dose R-CP regimen (rituximab 0.5 g/d₁, cyclophosphamide 0.4 g/d₃, and dexamethasone 10 mg/d₃₋₇) after diagnosis. After 4-months of treatment, both his white blood cell and hemoglobin were clearly increased (**Figure 4**). Then, the BMC morphology showed that the ratio of immature lymphocytes was 2% (**Figure 1B**). The reduction of lymphoma cells in the bone marrow indicated the effectiveness of the chemotherapy. No sign of myelofibrosis was demonstrated in the bone

marrow biopsy. Furthermore, immunohistochemistry revealed that there was no evidence of DLBCL via staining of CD20, CD79a, CD3 and Ki-67. The PET/CT also indicated that the size of his spleen had returned to normal (**Figure 3C, 3D**).

BMC morphology after 8 months without treatment showed there were no polymorphocytes in the bone marrow (**Figure 1C**). However, biopsy demonstrated that the bone marrow cells were positive for CD20, CD38, CD79a, PAX-5 and negative for CD30, CD138. Moreover, clear fibrosis was revealed by silver staining (Ag (++++)), **Figure 2D-F**. We also discovered enlarged lymph nodes in the right supraclavicular fossa, right hilum of the lung and mediastinum, as well as a recurrent lesion on the right posterior lobe of the liver discovered by PET/CT scan (**Figure 5**).

Accordingly, the patient was subsequently provided with a chemotherapy regimen of R-COP (rituximab 0.5 g/d₁, cyclophosphamide 0.4 g/

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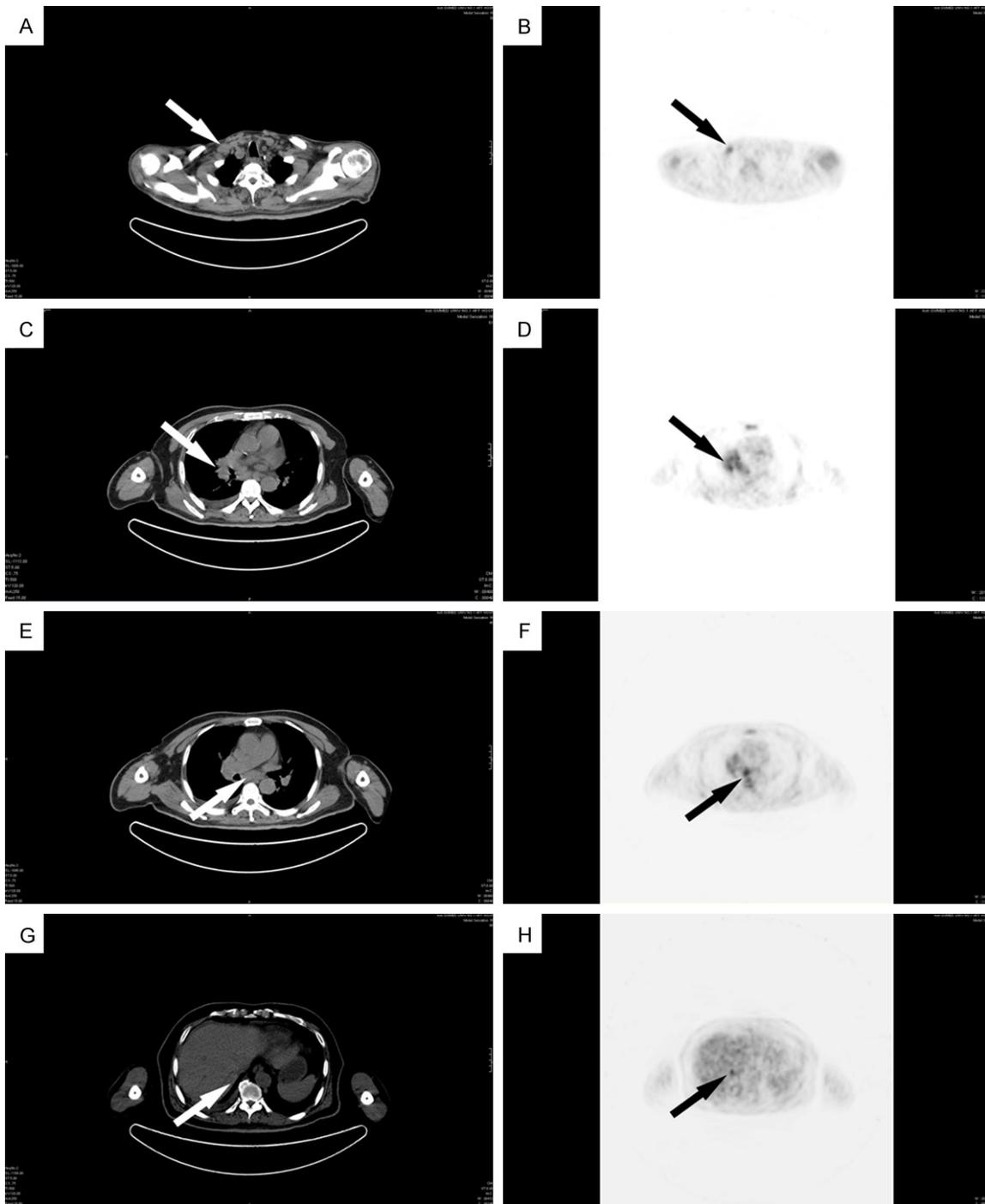


Figure 5. PET/CT imagery when the neoplasms relapsed. A, B: Abnormal lymph nodes of the right clavicle; C, D: Abnormal lymph nodes of the right hilum of the lung; E, F: Abnormal lymph nodes of the mediastinum; G, H: Recurrent lesion on the right posterior lobe of the liver.

d_3 , vincristine 0.2 g/ d_3 , and dexamethasone 10 mg/ d_{3-7}) and reduced-dose R-CHOP (rituximab 0.5 g/ d_1 , cyclophosphamide 600 mg/ d_3 , vincristine 2 mg/ d_3 , theprubicin 40 mg/ d_4 , and dexamethasone 10 mg/ d_{3-7}). After these thera-

pies for 4 months, the BMC morphology showed slight tumor cell invasion (**Figure 1D**). Bone marrow biopsy demonstrated that the myelofibrosis was improved using silver staining (Ag (+)). Immunohistochemistry revealed CD20 (-),

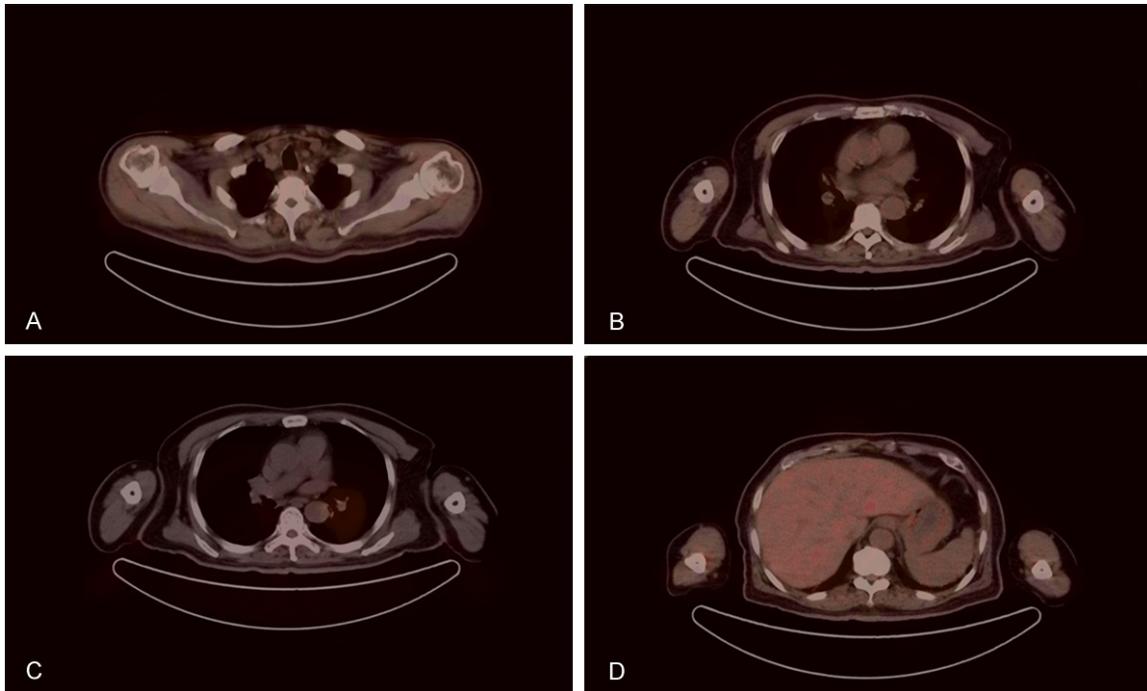


Figure 6. PET/CT imagery after consolidation therapy. Abnormal lymph nodes of the right supraclavicular fossa, right hilum of the lung and mediastinum. The recurrent lesion on the right posterior lobe of the liver had already reduced.

CD138 (-) and CD235a (+). PET/CT scanning showed that his lymph nodes had already returned to normal (**Figure 6**).

Four consolidation courses of a R-CHOP regimen were then performed (rituximab 0.5 g/d₁, cyclophosphamide 600 mg/d₃, vincristine 2 mg/d₃, theprubicin 40 mg/d₄, and dexamethasone 10 mg/d_{3,7}), along with one single Rituximab (500 mg) dose. After that, very rare (1%) blast cells were discovered in his BMC (**Figure 1E**). Bone marrow biopsy demonstrated that the myelofibrosis was cured as detected by silver staining (Ag (-)), and immunohistochemistry revealed no evidence of lymphoma involvement in CD10, CD20, CD79a, CD235a, CD3 or Ki-67. The examination confirmed that the patient was in complete remission (CR). At present, the patient remains asymptomatic and clinically stable.

Discussion

The peculiarity of the present case lies in myelofibrosis as the initial symptom of DLBCL resulting from neoplastic cells affecting the bone marrow. Finally, CR was achieved only after reduced-dose rituximab regimens. Rituximab had significant efficacy on DLBCL, thus improving the myelofibrosis symptoms. Conse-

quently, this case could play an instructional role for clinical treatment.

However, the pathogenesis of SMF has not yet been revealed. Some growth factors such as platelet-derived growth factor (PDGF), megakaryocyte-derived growth factor (MKDGF), epidermal growth factor (EGF), transforming growth factor- β (TGF- β) may promote the proliferation of fibroblasts in megakaryocytes, which may induce myelofibrosis [2]. A PDGR receptor-like gene, whose sequence is similar to the ligand-binding domain of PDGF receptor β is located on chromosome 8, and several cases of myelofibrosis have been reported as chromosome +8 abnormalities [3-6]. The case we reported was a confirmed chromosome deletion of 7q31 by FISH analysis, which suggested that the long arm of chromosome 7 of the patient had a deletion. Furthermore, the PDGF α polypeptide gene localized to band 7p22 in humans was reported as a mutation of chromosome 7 that might also cause bone marrow fibrosis [7]. Nonetheless, the relationship between myelofibrosis and the mutation of chromosome 7 remains to be further studied.

This is the first report of a rare DLBCL with the primary symptom of myelofibrosis in an elderly patient. Intriguingly, the patient achieved CR

with rituximab. Very few of cases of B-cell neoplasm with SMF have been reported, but none of them had a favorable outcome. A patient with splenic marginal zone lymphoma presenting with bone marrow and spleen fibrosis was reported. After splenectomy and chemotherapy with FC regimen (fludarabine and cyclophosphamide), the patient's bone marrow biopsy demonstrated an improvement of fibrosis. However, she finally died from interstitial pneumonitis, which demonstrated that the FC regimen had limited efficacy for prognosis [8]. Hatta Y et al. reported a case of pure red cell aplasia and myelofibrosis in B-cell Neoplasm that was treated with cyclosporine and prednisone. However, the patient rapidly deteriorated and died. Thus, the therapeutic effect on B-cell lymphoma with bone marrow fibrosis was not obvious [9]. Meckenstock G et al. once described a case of lymphoid myelofibrosis associated with high-grade B-cell lymphoma of the liver. They treated the patient with methylprednisolone. However, the patient died two weeks later due to aspergillus fumigatus. This also indicated that hormone therapy was not effective for the treatment of lymphoma with bone marrow fibrosis [10]. Furthermore, the neoplasm would not be effectively controlled if the patient with DLBCL and SMF was given chemotherapy with CHOP alone [11]. Rituximab was not used in the above cases, and all of the patients had a poor prognosis. This poor efficacy may have occurred because rituximab had not been popularized by that time.

Rituximab is a chimeric anti-CD20 monoclonal antibody that is effective when given as a single agent for the treatment of relapsed or refractory indolent lymphomas and DLBCL. CD20 is a cell surface protein that is present in mature B cells. Rituximab can directly act on the surface of B cells and kill B-cell neoplasms by binding to CD20 antigen [12]. Consequently, the rituximab has good efficacy in the treatment of B-cell lymphomas that are positive for CD20.

In this case, we gave chemotherapy drugs with a reduced dose to deliver effective treatment. An individualized therapeutic protocol for lymphoma is an essential step for treating the disease and improving the prognosis. With the widespread application of rituximab, the efficiency and prognosis of B-cell lymphomas can be improved either as monotherapy or in combination with other drugs. As research contin-

ues, we look forward to more treatment options in the future for patients with advanced lymphoma and multiple complications.

Disclosure of conflict of interest

None.

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