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Case Report

Rituximab, Cyclophosphamide, Vincristine, and Prednisolone with High-Dose Methotrexate as an Effective Regimen in a Frail Patient with Intravascular Large B-cell Lymphoma

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare non-Hodgkin lymphoma characterized by the presence of lymphoma cells within the lumina of small vessels. Membranous CD20 is universally expressed on IVLBCL cells in immunohistochemical staining. The outcome of IVLBCL was dismal in the prerituximab era; however, rituximab in combination with chemotherapy has been proposed to be an effective treatment for IVLBCL. Herein, we report a 68-year-old female with "Asian variant" IVLBCL diagnosed from a pleural biopsy. We administered rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) with high-dose methotrexate as the initial treatment. The patient achieved a complete response after the treatment. Therefore, R-CVP with high-dose methotrexate can be considered as a treatment option for frail IVLBCL patients.

Keywords: Intravascular large B-cell lymphoma, rituximab, cyclophosphamide, vincristine, and prednisolone, rituximab

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare mature B-cell lymphoma. It is characterized by the presence of lymphoma cells in the lumina of small vessels with multiple organ involvement.[1,2] The clinical course of IVLBCL is mostly aggressive with a dismal outcome, especially in the prerituximab era. Rituximab in combination with anthracycline is considered to be the standard of care for IVLBCL patients who are fit.[3] However, the treatment for frail IVLBCL patients remains unclear. Herein, we report a frail 68-year-old female with IVLBCL and a fulminant disease course. Complete remission was successfully achieved with rituximab,

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cyclophosphamide, vincristine, and prednisolone (R-CVP) and high-dose methotrexate treatment.

Case Report

A 68-year-old female without any systemic diseases initially presented to a local hospital with exertional dyspnea with lower limb edema for 1 month. She reported that she had had intermittent fever and progressive abdominal fullness for 2 months. Chest computed tomography (CT) showed bilateral pleural effusion, ascites, and one left adnexal mass. A pleural effusion study disclosed exudates without a definitive etiology. She was then referred to our institute because of progressive shortness of breath and anasarca.

Physical examinations revealed a distended abdomen and generalized pitting edema. No lymphadenopathy was palpable over the neck and inguinal area. Laboratory tests disclosed thrombocytopenia (99,000/μL; normal range: 150,000–450,000/μL), elevated lactic dehydrogenase (1257 U/L; normal range: 120–240 U/L) and hyperuricemia (9.5 mg/dL; normal range: 2.4–7.2 mg/dL). Serologic tests for liver function, renal function, and electrolytes were all within the normal limits. Abdominal CT showed bilateral pleural effusion, ascites, hepatosplenomegaly [Figures 1 and 2], and a 4-cm mass over the left adnexal. A gynecologist performed sonography and favored a benign dermoid cyst. Repeated pleural effusion analysis at our institute still showed exudates, and a cytology examination showed no evidence of malignancy. A diagnostic pleural biopsy was performed, and the specimen was examined at our pathology department. The results showed fibroadipose tissue without overt inflammatory cell infiltration; however, abundant large atypical lymphocytes were found in the intravascular space. These large atypical lymphocytes were highly pleomorphic with a high nucleocytoplasmic ratio and bizarre nuclei. On immunohistochemical staining, the atypical lymphoid cells were positive for CD20, CD79a, CD5, BCL2, and MUM1, but negative for cyclin D1, CD34, and thyroid transcription factor 1 [Figure 3]. The Ki-67 proliferation index was 90%. A bone marrow biopsy was also performed, which showed a few large atypical B-cells in the marrow sinus. Taken together, these findings indicated the diagnosis of IVLBCL with bone marrow involvement.

After admission, her renal function deteriorated and oliguria developed. Considering her frailty and renal function impairment, we administered immunochemotherapy with the combination of R-CVP. After the first cycle of R-CVP treatment, the symptoms of dyspnea, abdominal fullness, and profound edema greatly improved. However, Grade 4 neutropenia (absolute neutrophil count: 490/mm^3) developed. After recovering from neutropenia and acute kidney injury, we administered methotrexate (1 g/m^2) for central nervous system (CNS) prophylaxis. She subsequently recovered from the bedridden status and returned to independent daily activity after the treatment. She finally received six cycles of R-CVP and four cycles of high-dose methotrexate. Positron-emission tomography with fluorine-18-fluorodeoxyglucose after the treatment showed a complete metabolic response. She has currently been in complete remission for 6 months.

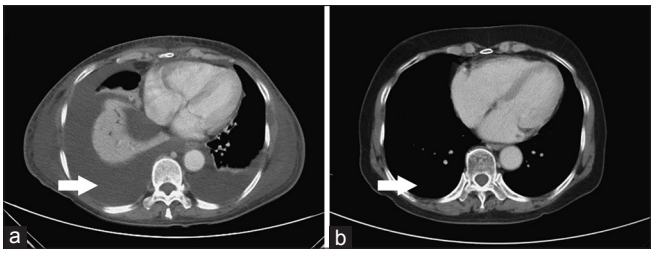

Figure 1: (a) Computed tomography scan showed massive pleural effusion (arrow) with anasarca at the time of diagnosis. (b) Six months after completing chemotherapy, computed tomography scan showed resolution of the pleural effusion (arrow)

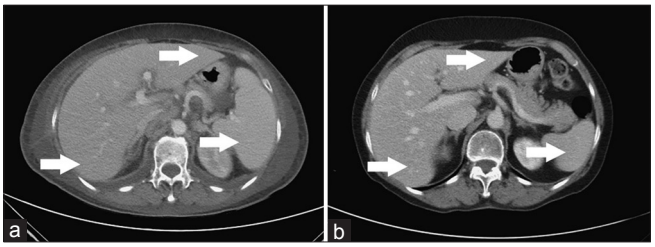

Figure 2: (a) Computed tomography scan showed hepatosplenomegaly (arrows) at the time of diagnosis. (b) Six months after completing chemotherapy, the computed tomography scan showed resolution of the hepatosplenomegaly (arrows)

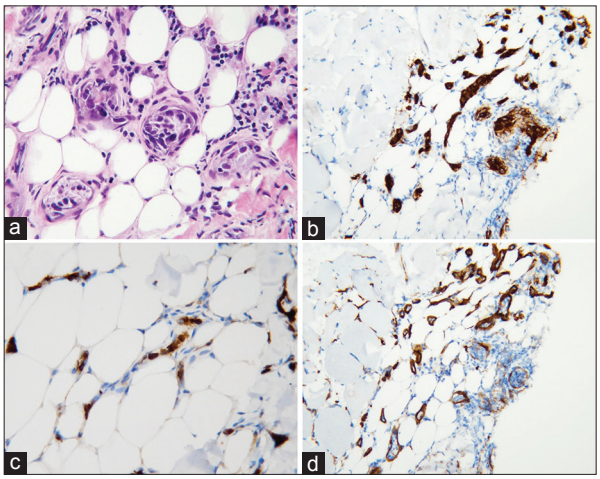

Figure 3: Histopathology of a pleural biopsy. (a) Hematoxylin and eosin. Large atypical lymphocytes were found in the intravascular space. (b) Immunohistochemistry staining of CD20. The large atypical lymphocytes were strongly positive for CD20. (c) Immunohistochemistry staining of MUM1. Tumor cells showed a strong nuclear expression which indicated an activated B-cell origin. (d) Immunohistochemistry staining for CD34. Endothelial marker showed tumor cells in intravascular spaces

Discussion

IVLBCL is a rare non-Hodgkin lymphoma. It was classified as an independent disease entity of mature B-cell neoplasms in the

revised 2016 World Health Organization classification.[4] IVLBCL is usually diagnosed in elderly patients, with a median age at diagnosis in the sixth to seventh decades of life. No significant gender predilection has been reported.[3] The clinical presentations are heterogeneous because IVLBCL cells can involve any organ. The symptoms often result from the occlusion of small vessels. Fever and constitutional symptoms are the most common initial presentation. IVLBCL is classified into two subtypes according to the clinical manifestations and geographic areas. In Western countries, IVLBCL often involves the CNS and skin,[5] whereas the so-called "Asian-variant" IVLBCL, which was initially reported in Japan, predominantly presents with fever, hepatosplenomegaly, bone marrow involvement, cytopenia, and hemophagocytic syndrome.[6] Laboratory tests in patients with IVLBCL disclose various abnormalities, of which high lactate dehydrogenase is the most common, accounting for 69%–98% of patients. Western and Asian studies have reported similar incidence rates of anemia of around 70%. However, Asian patients seem to have a higher incidence of thrombocytopenia, which could be related to the greater bone marrow involvement and hemophagocytosis.[1]

Since lymphadenopathies cannot be identified in the majority of patients, tissue proof from the involved organs is mandatory to confirm IVLBCL. Definite diagnoses of IVLBCL have been made with the liver, lung, skin, bone marrow, gastrointestinal tract, adrenal gland, brain, and lymph node biopsies.[5,7,8] Notably, IVLBCL is characterized by the presence of lymphoma cells within the lumina of small vessels. These lymphoma cells are large in size with prominent nucleoli and frequent mitotic figures. A Ki-67 index of >90% is very common. In terms of immunophenotyping, IVLBCL is positive for CD20, in addition to CD5 (38%), CD10 (13%), BCL6 (26%), MUM1 (95%), and BCL2 (91%).[2,6]

In our patient, fever, hepatosplenomegaly, cytopenia, and bone marrow involvement without skin lesions were consistent with the features of a typical "Asian variant" of IVLBCL. However, a definite diagnosis of IVLBCL was difficult because no lymphadenopathy could be identified. Finally, the diagnosis of IVLBCL was confirmed with a pleural biopsy. To the best of our knowledge, this is the first reported case of IVLBCL confirmed with a pleural biopsy.

Most cases of IVLBCL have a fulminant clinical course because of disseminated organ involvement. In the prerituximab era, the outcome of IVLBCL was dismal with a response rate of only around 60% with anthracycline-containing chemotherapy. The long-term survival, however, remains disappointing.[9] In 2008, a Japanese cohort reported a significant outcome improvement by adding rituximab to the chemotherapy. A retrospective analysis by Shimada *et al*. reported 2-year progression-free survival (PFS) and overall survival (OS) rates of 56% and 66%, respectively, in patients treated with rituximab-containing chemotherapy. In contrast, the 2-year PFS and OS were only 27% and 46%, respectively, in IVLBCL patients treated with chemotherapy only.[3] In Western IVLBCL patients, the complete remission rate can be as high as 90% in those receiving rituximab-containing chemotherapy.[10] CNS prophylaxis with high-dose methotrexate-based chemotherapy is recommended due to the high risk of CNS involvement in patients with IVLBCL.[11,12]

We chose R-CVP to treat our patients initially because she was frail at diagnosis. When the frailty improved after the R-CVP treatment, high-dose methotrexate was administered for CNS prophylaxis. After completing six cycles of R-CVP and four cycles of high-dose methotrexate, she has been disease free for more than 6 months without significant treatment-associated toxicity.

One of the major limitations in this case is the lack of brain imaging and cerebrospinal fluid studies at the initial diagnosis. Therefore, CNS lymphoma involvement at the diagnosis could not be confirmed.

Conclusion

A pleural biopsy can be a valuable diagnostic approach for patients who have pleural effusion with the suspicion of IVLBCL. R-CVP with high-dose methotrexate may be an effective alternative treatment to anthracycline-containing chemotherapy for frail IVLBCL patients.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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