

Case Study

Sustained Remission after Rituximab-containing Chemotherapy for Intravascular Large B-cell Lymphoma

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Intravascular large B-cell lymphoma (IVL) is rare aggressive disseminated lymphoma associated with poor outcomes. Rituximab is a novel molecular agent that can reportedly improve outcomes for patients with diffuse large B-cell lymphoma. However, the safety and efficacy of rituximab in patients with IVL are unclear. A 76-year-old woman was hospitalized due to altered consciousness, fever and respiratory abnormalities. Definitive diagnosis of IVL was obtained following repeated biopsies of bone marrow. The patient received chemotherapy consisting of cyclophosphamide, vincristine, doxorubicin, prednisolone, and rituximab (R-CHOP), and achieved complete remission after 3 courses of treatment. She has remained in complete remission for over 3 years after diagnosis. This report suggests that rituximab-containing regimens could be safe and effective for elderly patients with IVL. [*J Clin Exp Hematopathol* 48(1): 25-28, 2008]

Keywords: intravascular large B-cell lymphoma, rituximab, combination chemotherapy

INTRODUCTION

Intravascular large B-cell lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL), as classified by the World Health Organization.¹ IVL is a rapidly aggressive disseminated disease, characterized by the presence of lymphoma cells only in the lumina of small vessels of the central nervous system, skin, lungs, kidneys, and bone marrow, without marked lymphadenopathy. The absence of IVL in traditional sites of lymphoma presentation makes accurate and timely diagnosis difficult. In previous reports, around half of patients have been diagnosed post mortem,² and repeated biopsies of skin, kidney, and bone marrow are often necessary for the diagnosis of this type of lymphoma.^{3,4}

Left untreated, IVL is uniformly fatal. Steroids generally

provided only transient improvement.² Most therapeutic regimens were ineffective, with a median survival of several months from the date of clinical presentation.^{4,5} Recently, anthracycline-containing chemotherapy has been reported to improve clinical outcomes of patients with IVL. Ferreri *et al.* reported an overall 3-year survival rate of 33% and a response rate of 59% in the patients who received anthracycline-containing chemotherapy.⁶ Murase *et al.* reported a median survival duration for IVL patients receiving anthracycline-based chemotherapy of 13 months.⁷ Considering that most IVL patients are categorized in the high-risk group according to the International Prognostic Index,⁷ the survival of IVL patients is probably comparable to that of patients with DLBCL.⁸ Thus anthracycline-containing chemotherapies appear to be useful, and that the poor prognosis of IVL⁹ might be attributable to delayed initiation of chemotherapy.

Rituximab is a novel monoclonal antibody against CD20 B-cell antigen. The addition of rituximab to the CHOP regimen has been found to improve treatment outcomes in patients with DLBCL.¹⁰ Recent reports suggest the efficacy of rituximab for the treatment of IVL,^{11,12} however, the scale of these studies was small and the long term outcomes remain unclear.

CASE REPORT

A 76-year-old woman with no past medical history of note was admitted to Ogaki Municipal Hospital in July 2003 with a one-week history of continuous malaise, headache, and leth-

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argy. After admission, she developed neurological signs including disorientation and unresponsiveness, in addition to a persistent fever. Blood examination revealed: white blood cell count, 6,280/ μ L; red blood cell count, 380 x 10⁴/ μ L; hemoglobin, 11.3 g/dL; and platelet count, 25.3 x 10⁴/ μ L. Laboratory studies showed: aspartate aminotransferase, 90 IU/L; alanine aminotransferase, 79 IU/L; C-reactive protein, 10.2 mg/dL; lactate dehydrogenase (LDH), 2249 IU/L (normal range: 130-450 IU/L); and ferritin, 846.5 ng/mL. Soluble IL-2 receptor (sIL-2R) was elevated to 7955 U/L. Physical examination showed no systemic lymphadenopathy, splenomegaly or focal neurological deficits. Arterial blood gas analysis demonstrated respiratory insufficiency with a partial pressure of arterial oxygen (PaO₂) of 48.5 mmHg without hypercapnia. Computed tomography (CT) of the abdomen revealed mild splenomegaly without lymphadenopathy or hepatomegaly. Transbronchial lung biopsy revealed no evidence of malignancy. CT of the brain showed no marked abnormalities. Bone marrow aspiration revealed hemophagocytic syndrome, but no evidence of malignancy.

In addition, skin and renal biopsies were negative. However, repeat bone marrow examination revealed CD20-positive lymphoma cells in the lumen of vessels (Fig. 1). These lymphoma cells were immunohistochemically negative for CD3, CD10, MUM-1, and Bcl-6. IVL was subsequently diagnosed on the basis of the CD20-positive intraluminal lymphoma cells in October 2003.

The patient's respiratory failure and neurological manifestations resolved spontaneously following her first admission within 4 weeks. The patient was then discharged from the hospital without the definitive diagnosis of IVL. Three months later, she developed fever with elevated sIL-2R and

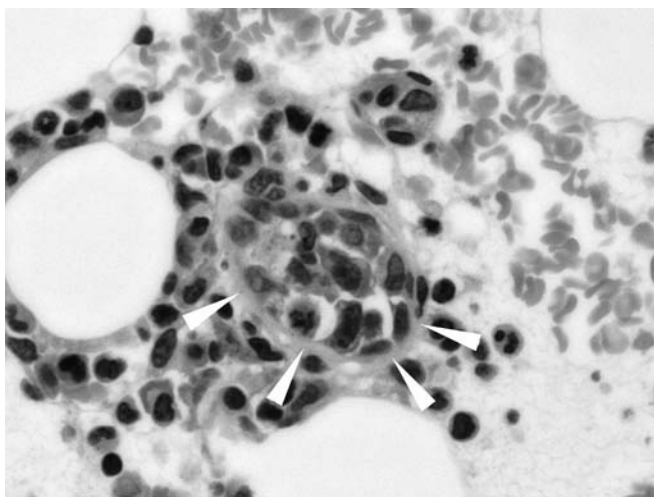


Fig. 1. Hematoxylin and eosin staining in bone marrow clot. The white arrows indicate tumor cells present in lumens of small vessels. These cells were highlighted by staining for CD20. Original magnification x400.

chemotherapy was initiated. Initially she was treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) alone as a first course. Subsequently, rituximab was added to CHOP regimen at the time of her second course of chemotherapy (R-CHOP). The patient received acetaminophen and diphenhydramine as premedication for rituximab. No infusion reaction occurred with any of the administrations. Her fever improved after starting chemotherapy, and sIL-2R and LDH levels normalized. The patient did not require any delay in administration or dose reduction and achieved complete remission after 3 cycles of R-CHOP with resolution of clinical symptoms, and normalization of clinical laboratory tests and bone marrow findings. As of the time of writing, the patient remains alive and in complete remission over 3 years after diagnosis.

DISCUSSION

The present report describes a sustained 3 year remission following a R-CHOP regimen for the treatment of IVL in an elderly patient. Our result is consistent with previous reports about rituximab therapy for IVL patients.^{11,12} These reports, in addition to ours, suggest that rituximab-containing regimens improve clinical outcomes for patients with IVL, as well as in patients with DLBCL.¹⁰

A recent report using cDNA microarrays has revealed that DLBCL can be divided into subgroups; germinal center B-cell (GCB) type and activated B-cell (ABC) type.¹³ Hans *et al.* found that these subtypes could be accurately identified according to immunohistochemical expression patterns of CD10, bcl-6, and MUM-1.¹⁴ In our patient, lymphoma cells were regarded as non-germinal center B-cell (non-GCB) type due to an immunexpression profile negative for CD10, bcl-6, and MUM-1 staining. Murase *et al.* revealed that most IVL cells belong to the non-GCB type.⁷ Recent reports indicate that non-GCB type DLBCL benefits from the addition of rituximab to CHOP, whereas the GCB type does not.^{15,16} Our experience suggests that this classification is useful for predicting treatment responses in IVL. However, further large-scale studies are warranted.

Patients possessing a high number of tumor cells in their peripheral blood have been reported to develop severe infusion reactions induced by rituximab.¹⁷ IVL patients with a high tumor burden in their vessels possibly are at risk for infusion reactions. In addition, respiratory distress syndrome following rituximab infusion has been reported.¹⁸ In our patient, respiratory insufficiency with a low PaO₂ was observed at the time of her first admission. Thus, we omitted the addition of rituximab over concern of infusion reaction in the first course of chemotherapy. Due to our therapeutic strategies against infusion reactions, no infusion reactions occurred in the clinical course of our patient. The addition of rituximab during second course or later of chemotherapy was

safe, without adverse events of rituximab.

Several reports have revealed long-term survival after autologous hematopoietic stem cell transplantation for IVL, not only in patients who achieved complete remission but also in patients with relapsed disease.¹⁹⁻²¹ However, transplantation is not a feasible option for most IVL patients of advanced age. Our patient was too elderly to receive autologous hematopoietic stem cell transplantation. Conversely, the R-CHOP regimen is reportedly feasible for elderly patients.¹⁰ Actually, the present patient completed 8 courses of R-CHOP regimen without any marked adverse effects. Considering the high median age for IVL (67 years), R-CHOP might be feasible for most IVL patients.⁶ The safety and efficacy of an R-CHOP regimen for elderly IVL patients should be investigated in further studies.

Several cases of central nervous system relapse were recently reported.^{22,23} Although our patient has maintained complete remission without intrathecal infusion, intrathecal chemotherapy as a precaution against central nervous system relapse may be worth investigating in future studies.

In summary, we report an elderly patient with IVL who achieved sustained remission after receiving R-CHOP without requiring steroids and antibiotics. Due to this atypical clinical course, further careful follow-up of this patient is needed.

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