

Durable Remission of Intravascular Lymphoma With Central Nervous System Involvement Following Chemotherapy and Rituximab

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Intravascular lymphoma (IVL) is a rare form of non-Hodgkin lymphoma (NHL) and is most frequently diagnosed postmortem. IVL is also known as malignant angioendotheliomatosis or angiotropic large cell lymphoma.¹ IVL is a rare subtype of extranodal diffuse B-cell lymphoma. It is characterized by the presence of lymphoma cells in the lumina of small vessels, particularly in the capillaries.² Its clinical and biological properties are for the most part unknown. The varied clinical presentations and the lack of a diagnostic algorithm account for the fact that most cases are diagnosed postmortem. The course of this malignancy is rapidly progressive and is ultimately fatal.³

Case Report

A previously healthy 71-year-old woman presented in May 2002 with weakness, fatigue, and loss of appetite. She was found to have normocytic anemia and an elevated erythrocyte sedimentation rate. The initial bone marrow biopsy was nonspecific, showing polyclonal gammopathy, monocytosis, and reactive T cells and plasma cells. An abdominal computed tomography (CT) scan was unremarkable. She received no treatment at that time and spontaneously recovered from her symptoms. The following year the patient again presented with similar complaints and CT scan of the abdomen showed bilateral adrenal masses (Figure 1), biopsies of which were consistent with large B-cell lymphoma. She also had a bone marrow biopsy, which demonstrated small clusters of primitive cells consistent with lymphomatous infiltrates and intravascular B cells seen on immunohistochemistry compatible with IVL (Figures 2 and 3). Flow cytometry



Figure 1. Computed tomography image of the abdomen showing bilateral adrenal mass.

showed a monoclonal B-cell population with medium cells comprising 4% of the total, expressing 31% kappa and 8% lambda, and coexpressing 19% CD5 and CD19. The karyotype was normal. Subsequently, the patient was diagnosed with stage IVB NHL.

The patient's past medical history included hypothyroidism, vertigo, and fibroids. Past surgical history was significant for a total abdominal hysterectomy with bilateral salpingo-oophorectomy, and bilateral cataract surgery. She had been taking both hormone replacement therapy (estrogen [Premarin, Wyeth]) and levothyroxine (Synthroid, Abbott) for about 25 years. She denied any use of illicit drugs and did not note any allergies. Her mother died of breast cancer at the age of 77 and her maternal grandfather had been diagnosed with multiple myeloma.

On physical examination, she had a 1-cm palpable lymph node in the submandibular area. The remainder of

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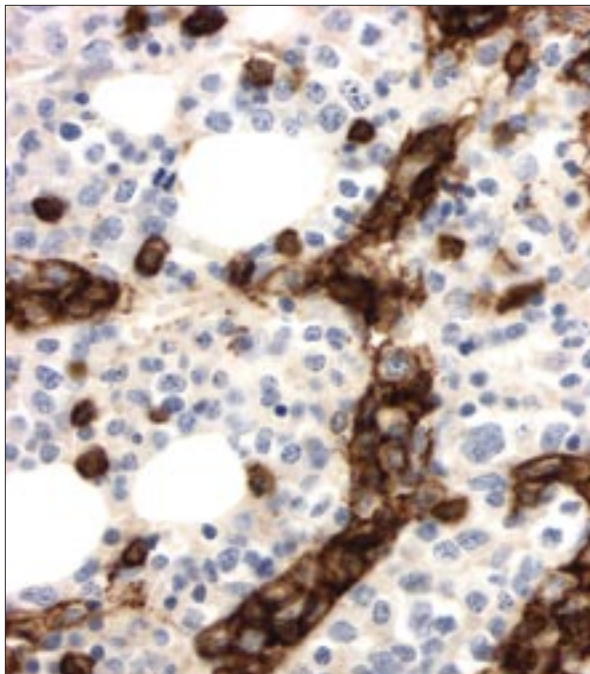


Figure 2. Immunohistochemical stain with antibody to CD20 shows the B-cell nature of the tumor cells and highlights their location within sinusoids. Original magnification 50 \times .

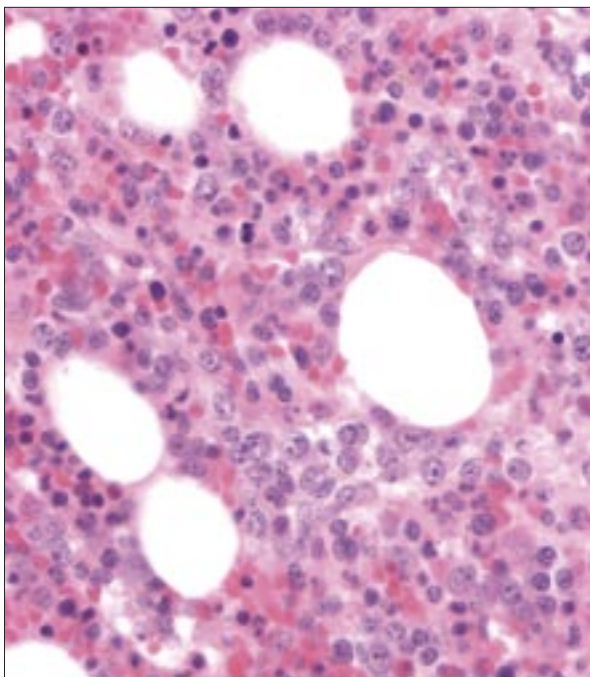


Figure 3. Section of bone marrow showing clusters of large tumor cells in sinusoids. Original magnification 50 \times .

the examination was normal. Initial laboratory findings included hemoglobin of 10.0 g/dL, hematocrit of 29.2%, normocytic anemia with mean corpuscular volume of 92 fl, mean corpuscular hemoglobin of 31.5 pg, mean corpuscular hemoglobin concentration of 34.3 g/dL and platelets of 279,000/mm³. Her iron level was at 78 mg/L, iron saturation was 20%, and total iron binding capacity and ferritin were both elevated at 399 μ g/dL and 350 ng/mL, respectively. The patient's chemistry panel was notable only for an elevated protein level of 8.5 g/dL and a low calcium level at 8.5 mg/dL. Her lactate dehydrogenase level was elevated at 908 u/L and her erythrocyte sedimentation rate was markedly high as well at 117 mm/h. She had a nondiagnostic autoimmune panel and a temporal artery biopsy was negative. Her β_2 -microglobulin level was 3.0 mg/L.

The patient was treated with eight cycles of CHOP (cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², doxorubicin 50 mg/m², and prednisone 100 mg) and rituximab (Rituxan, Genentech/Biogen Idec) 375 mg/m² (R-CHOP). On the fifth cycle the patient was started on subcutaneous injections of pegfilgrastim (Neulasta, Amgen). She tolerated the treatment well and was scheduled to return in 3 months for restaging of her lymphoma. She came in a month later with aphasia and right arm and leg weakness. Magnetic resonance imaging (MRI) of the brain showed a large temporal lobe lesion with necrosis and multiple lesions measuring less than 1 cm (Figure 4). A repeat CT scan of the chest/abdomen and pelvis was negative for new pulmonary nodules and enlarged lymph nodes. The adrenal lesions were also noted to be decreased in this study. A repeat bone marrow biopsy showed no morphologic or immunophenotypic evidence of lymphoma; however, a burr-hole biopsy done of the large intracranial lesion was consistent with lymphoma. The patient was then started on high-dose systemic methotrexate (MTX) 2.5 g/m², procarbazine 100 mg/m² per day, and vincristine 1.4 mg/m² every 2 weeks.⁴ She was able to tolerate only three cycles of the high-dose chemotherapeutic regimen and was not able to undergo radiotherapy or tolerate the high-dose cytarabine. An Ommaya reservoir was placed under the scalp and the patient was given intrathecal MTX 12 mg at 2-week intervals for a total of five cycles, the last of which she completed in December 2003. Twenty-eight months after diagnosis, repeat CT evaluation and positron emission tomography imaging revealed no evidence of recurrent disease and she was left with only mild residual neurological deficits.

Discussion

We present the case history of a woman diagnosed with IVL with central nervous system (CNS) involvement who

responded well to treatment with R-CHOP and high-dose MTX. IVL is usually an aggressive and disseminated disease at presentation, primarily because of the delay in diagnosis (Ann Arbor stage IV in 68% of the cases). In most patients, the survival time is less than 1 year. The most common clinical features include fever of unknown origin, mental status changes and a rash. About two thirds of patients present with neurological signs such as diffuse and focal cerebral signs and dementia. Hepatosplenic and bone marrow involvement are also commonly seen. IVL usually affects elderly patients (median age 70 years) and has a male:female ratio of 0.9. Patients with the cutaneous variant of IVL have longer survival times, particularly those with single lesions. Our patient had initially presented with nonspecific symptoms and was diagnosed one year later with involvement of the adrenal glands, bone marrow, and CNS. She had many of the characteristic features of IVL but, unlike most long-term survivors, our patient did not present with skin lesions.^{2,5}

The standard treatment for IVL is anthracycline-based chemotherapy such as CHOP. In a cohort of 38 patients—the largest reported series of patients with IVL treated with anthracycline chemotherapy—the overall response rate was 59%. Less than half had complete remission (CR), 13% had a partial response and 32% had progressive disease. Among the population in study, 6 had CNS involvement; of these, 5 died within 4 months of diagnosis. Only 1 patient was alive with a disease-free interval for 19 months. The patient was a 52-year-old woman who was treated with doxorubicin, cyclophosphamide, vincristine, MTX, bleomycin, and prednisolone, followed by high-dose chemotherapy supported by autologous stem cell transplantation. The median time to treatment failure for patients who had been treated with primary chemotherapy was 8 months with an event-free survival of 27%.

Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody. This agent induces a rapid depletion of normal CD20-positive B cells and lymphoma cells. Recent studies have shown that the addition of rituximab to CHOP (R-CHOP) increases CR rates and event-free survival in elderly patients with diffuse large B-cell lymphoma (DLBCL), without a significant increase in toxicity.⁷ There was no mention of the IVL subtype in that particular study. Most studies of treatment of IVL have focused on the use of CHOP. There has been one report of IVL presenting as cauda equina syndrome that was treated initially with CHOP for two cycles, which had to be stopped due to a decreased left ventricular ejection fraction. This was followed by six cycles of cyclophosphamide, etoposide, and prednisone, then six doses of rituximab, with improvement of symptoms and CR for 8 months.⁸ Our patient was initially treated with R-CHOP for eight cycles. This

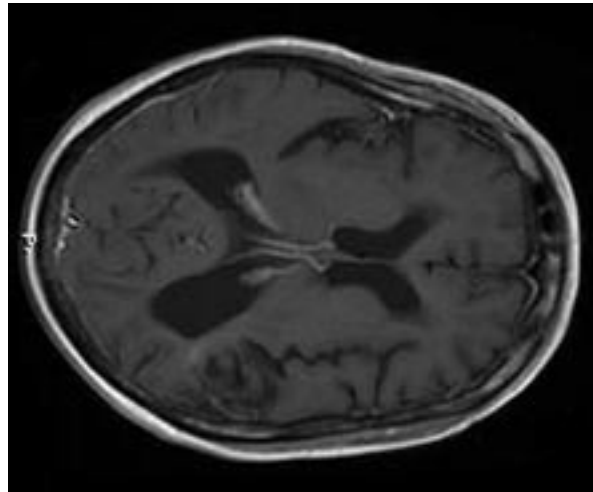


Figure 4. Magnetic resonance image showing a large temporal lobe lesion.

was followed by three cycles of systemic high-dose MTX, vincristine, and procarbazine followed by five cycles of intrathecal MTX, which has a higher bioavailability in the CNS.

This case report adds to the limited body of evidence showing excellent response with CR and prolonged event-free survival following a combination of chemotherapy and monoclonal antibody treatment. The treatment regimen includes CHOP with rituximab, with high-dose MTX if there is CNS involvement. Due to the rarity of IVL, it is unlikely that a prospective randomized trial will be conducted to evaluate the role of monoclonal antibodies in this disease.

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Review

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The clinical case study by Go and colleagues¹ illustrates some of the diagnostic and therapeutic challenges facing an oncologist with a suspected case of IVL and provides further evidence to an emerging body of case reports that support the use of the monoclonal anti-CD20 antibody rituximab in this disease. IVL is a rare subtype of DLBCL characterized by neoplastic lymphocytes packing the vascular lumina with a relative sparing of surrounding parenchymal tissues, and often presents with some combination of neurologic deficits, cutaneous involvement, and fever of unknown origin. Adenopathy and hepatosplenomegaly are relatively uncommon.² Interestingly, adrenal involvement is not uncommon in IVL and eight cases in the literature have had adrenal presentations often—as in this case—adrenal enlargement. As discussed in the case report, the standard therapy for IVL is multi-agent cytotoxic chemotherapy, usually CHOP. Only a few cases suggest a role for rituximab but the circumstantial evidence for its use is strong.

The use of rituximab in IVL is a logical extrapolation from the data provided by the GELA (Groupe d'Étude de Lymphomes de l'Adulte) study, in which the addition of rituximab to standard CHOP in elderly patients led to increased CR and event-free and overall survival rates.³ The 5-year follow-up to this study showed a sustained survival benefit, with 58% of patients in the R-CHOP arm alive at 5 years compared with 45% of patients in the CHOP-alone arm.⁴ Median overall survival has not yet been reached in the R-CHOP arm compared to 3.1 years in the CHOP arm. Similar evidence from the weighted reanalysis of the Eastern Cooperative Oncology Group 4494 trial and the Mabthera international trial support the use of rituximab in all untreated DLBCL patients greater than 60 years of age and in patients aged 18–60 with International Prognostic Index (IPI) 0 or 1. This rationale

for the use of rituximab in patients of all ages with DLBCL can presumably be extended to the IVL subtype. Go and colleagues are correct to point out that the use of CHOP alone in the largest series of IVL patients yielded response rates and median survival that were much worse than for standard DLBCL, even accounting for advanced stage and IPI.⁵ Although the use of rituximab may improve overall outcomes in IVL when added to anthracycline-based chemotherapy, a retrospective analysis of 399 patients in the GELA study showed that rituximab had no effect on preventing relapse within the CNS.⁶ As a monoclonal antibody, rituximab has very little penetration through an intact blood-brain barrier and this likely accounts for its inability to influence relapse within the CNS. In addition, roughly 10% of IVL cases demonstrate a T-cell phenotype and these patients would not be expected to respond to anti-CD20 therapy.

The case report also makes an important management point. The appearance of a new neurological deficit is characteristic of IVL; however, brain MRI typically reveals multiple metachronous lesions that are hyperintense on T-2 weighting and that resemble vasculitis or demyelination, rather than distinct mass lesions, as seen in this case. It is important to establish a definitive tissue diagnosis as Go and colleagues¹ did, as one cannot reliably differentiate relapsed lymphoma from potential infectious causes or even small strokes by radiology alone. It would be interesting to know if the brain biopsy of the MRI abnormalities showed restriction of neoplastic B lymphocytes to the vascular space or whether there was mass-occupying parenchymal involvement. Although IVL by definition does not present with mass lesions, relapsed disease can present with a DLBCL-like space-occupying lesion. IVL that involves the CNS should be treated similarly to primary or secondary CNS lymphoma.

Given the predilection of IVL for CNS involvement, we routinely provide CNS prophylaxis with high-dose intravenous MTX. We view the risk as equivalent to that seen in primary sites such as testicular or breast extranodal DLBCL and to the risk of CNS relapse seen in nodal DLBCL with bone marrow involvement.

Lastly, this case illustrates that the treatment of any primary or secondary CNS lymphoma, IVL or otherwise, often includes the use of high-dose systemic MTX and/or intrathecal MTX or cytarabine. Go and colleagues¹ based their chemotherapy regimen on the RTOG 93-10 study in which MTX is combined with procarbazine and vincristine. Procarbazine is known to have relatively good penetration into the cerebrospinal fluid and vincristine

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may be able to penetrate areas of bulky tumors where the blood-brain barrier has broken down, as may have been the case in this patient's necrotic brain mass. At Massachusetts General Hospital, the practice of the neuro-oncology group is to use high-dose MTX as 8 g/m² intravenously over 4 hours with leucovorin rescue. This regimen is given on an every-other-week basis until a CR is achieved or up to eight total cycles. Radiation therapy is routinely deferred to avoid the long-term neurocognitive side effects of combined-modality therapy.

This case presentation by Go and colleagues¹ is a welcome addition to the growing literature of the successful use of rituximab in the treatment of IVL. It also serves as a reminder of the limitations of rituximab in treating CNS disease and the necessity of incorporating intrathecal and/or high-dose MTX into the treatment program for certain high-risk categories of DLBCL and for any primary or secondary CNS lymphoma.

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