Epstein-Barr virus (EBV) is a ubiquitous oncogenic virus that has infected more than 90% of the world’s population. EBV is associated with multiple lymphoproliferative malignancies including Burkitt lymphoma, posttransplant lymphoproliferative disorder, and nasopharyngeal carcinoma. In 2008, the World Health Organization (WHO) listed EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly as a provisional entry. Subsequently, clinicians described multiple cases of EBV-positive DLBCL in younger patients.

Reflecting this, the WHO lymphoma working group updated their lymphoma classification in 2016 to include EBV-positive DLBCL, not otherwise specified. However, the definition of EBV-positive DLBCL remains unclear—thresholds for the degree of EBV positivity have ranged from 10% to 90% in the literature, making comparisons across studies difficult.

We have an incomplete picture of how EBV affects the natural history of DLBCL. There simply are not enough data. Most major DLBCL clinical trials have not routinely included or culled out patients with EBV-positive DLBCL from those who are EBV negative. Prior to the introduction of rituximab, older patients with EBV-positive DLBCL had inferior clinical outcomes compared with younger patients with EBV-negative DLBCL. In the rituximab era, EBV positivity does not appear to have prognostic significance in patients with DLBCL less than 45 years old and this may also be true in older patients. However, several studies still suggest that older patients with EBV-positive DLBCL have worse outcomes compared with EBV-negative patients treated with rituximab-based regimens. Furthermore, no clinical trials have compared rituximab with cyclophosphamide-doxorubicin-vincristine-prednisone (R-CHOP) against higher intensity regimens in patients with EBV-positive DLBCL. It is clinically uncertain whether EBV positivity alters the risk of central nervous system (CNS) lymphoma relapse.

Herein, we present the case of an older man with limited-stage EBV-positive DLBCL who received dose-adjusted infusional chemotherapy. His clinical course was characterized by a complete remission followed shortly thereafter by devastating and fulminant neurologic decline characterized by a locked-in syndrome.

Case Report

A 64-year-old white man presented with a painless mass in his right axilla. The mass had been growing for 6 weeks. He had...
Quantitative EBV levels were not obtained. His lactate dehydrogenase (LDH) was normal at 244 IU/L and β2 microglobulin was 3.06 μg/mL (normal <2.7 μg/mL). An initial positron emission tomography (PET)/computed tomographic (CT) scan showed increased uptake in the right supraclavicular, right axillary, mediastinal, right internal mammary, and right cardiophrenic angle lymph nodes. The dominant right axillary mass measured 4.1 cm × 3.4 cm and was associated with a maximum standardized uptake value (SUV) of 20.0. This right axillary mass extended from the axilla to involve the chest wall. No other abnormalities were identified (Figure 1).

The largest of the chest wall lesions was biopsied under ultrasound guidance and this revealed an EBV-positive DLBCL, which was positive for CD30, CD20, PAX5, CD79a, MUM-1, Bcl-2, and Bcl-6 and negative for CD3, CD10, CD15, and CD43 (Figures 2A to D). Fluorescent in situ hybridization studies were positive for BCL6 translocation and negative for MYC, BCL2, and IGH gene rearrangements. A bone marrow biopsy showed normal hematopoiesis and no lymphomatous marrow involvement. Neuroimaging and a lumbar spinal tap to assess for leptomeningeal involvement were not performed.

The patient was diagnosed with stage IIA EBV-positive DLBCL. His age-adjusted International Prognostic Index (IPI) was 2. He started treatment with infusional chemotherapy consisting of bolus rituximab on day 1 and cyclophosphamide on day 5, as well as a continuous infusion over 96 hours of etoposide, doxorubicin, and vincristine. He took oral prednisone daily for 5 consecutive days (DA-EPOCH-R). He received 6 treatment cycles repeated every 3 weeks.

His initial 3 chemotherapy cycles were uncomplicated. He continued to work full time as a lawyer and did not experience significant treatment-related side effects. His tumor shrank rapidly and after 2 cycles was no longer palpable. An interim PET/CT after 4 cycles showed significant reduction in the size of the chest wall mass and accompanying adenopathy and no residual fluorodeoxyglucose uptake in the right supraclavicular, right axillary, right internal mammary, right cardiophrenic angle, and mediastinal lymph nodes. There was mild residual activity (SUV: 1.8) in the right lateral chest wall mass, which was favored to represent inflammatory changes rather than active lymphoma. He continued to work full time during his final 2 cycles of DA-EPOCH-R; however, he became increasingly tired. There was no significant hematologic or neuropathic toxicity that required dose modifications.

Approximately 3 weeks after completing what was to be his last cycle of chemotherapy, the patient described profound fatigue coupled with progressive lower extremity weakness. An MRI of the brain, intracranial magnetic resonance (MR) angiogram, and contrast-enhanced MR angiogram of the neck showed nonspecific, patchy, increased T2 signal throughout the white matter of both cerebral hemispheres (Figures 3A to C), which was attributed to small vessel ischemic disease. Notably,

not experienced fevers, night sweats, or weight loss. He was previously in good health, save for a transient ischemic attack manifested by difficulty with word finding 6 months earlier. By the time that he had arrived at the local emergency room, his neurologic deficits had resolved and a brain magnetic resonance imaging (MRI) was unremarkable. In addition, he had been diagnosed with stage T2a prostate adenocarcinoma, Gleason 6 (3 + 3) for which he had been under active surveillance for the preceding 2 years without evidence of progression by serial prostate-specific antigen testing.

His physical examination was unremarkable, except for a palpable 5 cm × 7 cm right chest wall mass that spread to the right axilla. There was no hepatosplenomegaly and no additional lymphadenopathy. Imaging studies included a right chest wall MRI, which showed a lobulated ill-defined enhancing soft tissue mass in the inferior right axillary region that corresponded to the palpable lump. This structure did not appear to be arising from within the muscle; however, it was contiguous from the lateral margin of the pectoralis major muscle and the superficial fascia of the chest wall musculature. It measured approximately 4.2 cm × 3.0 cm × 4.9 cm in size. A breast mammogram showed that the right breast was almost entirely fat (less than 25% fibroglandular). A partially visualized, palpable irregular mass with spiculated margins was present in the axillary tail/lateral chest wall region. Axillary adenopathy was also present.

Laboratory studies included a white blood cell count of 3.7 × 10^9/L, hematocrit of 38%, and platelet count of 200 × 10^9/L. Chemistry and liver tests were in the broad range of normal and serology for hepatitis B and C viruses and for human immunodeficiency virus (HIV) were nonreactive. Quantitative EBV levels were not obtained. His lactate

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Figure 2. Representative photos of the patient’s chest wall mass biopsy. (A) Large atypical lymphoid cells; immunohistochemical studies for (B) CD20, (C) PAX5, and (D) CD30 (hematoxylin-eosin). Epstein-Barr virus (EBV) EBER1 messenger RNA in situ hybridization was positive (not shown as the original slides were too degraded at the time of this case report). The diagnosis of an EBV-positive diffuse large B-cell lymphoma was rendered. All photos were taken at 400x magnification.

Figure 3. (A-C) A brain MRI showed mild, nonspecific, patchy, and increased FLAIR signal throughout the white matter of both cerebral hemispheres. (D-F) A repeat brain MRI 8 days later showed extensive areas of signal abnormality in the midbrain (cerebral peduncles), centrum semiovale, corpus callosum, and basal ganglia bilaterally. These areas showed marked contrast enhancement (not shown). FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.
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A follow-up PET/CT showed no evidence of persistent DLBCL. His weakness was initially attributed to sarcopenia related to his chemotherapy. Over the following 2 weeks, the patient became increasingly weak. On 2 occasions, he presented to the emergency department complaining of fatigue. Initially, he was hospitalized for a short period and received intravenous fluids before being allowed to return home. A week later, he was readmitted after he developed difficulties with word finding and trouble managing his affairs. Over the course of the next week, he became increasingly debilitated and lethargic; he was no longer able to move his extremities or verbalize his wishes. He became bed-bound and was only able to communicate, similar to other patients with locked-in syndrome, through blinking his eyes. A repeat brain MRI showed extensive areas of signal abnormality and diffuse confluent enhancement of the centrum semiovale, corpus callosum, basal ganglia, and cerebral peduncles bilaterally (Figures 3D to F). In retrospect, the nonspecific MRI findings of several weeks earlier may have been initial manifestations of CNS parenchymal involvement by lymphoma. Prior to starting chemotherapy, our patient had indicated that if he developed a life-limiting process, he would not wish to pursue additional medical interventions. In light of this, no additional diagnostic measures were pursued and he died from a respiratory arrest while receiving inpatient hospice. His family agreed to a limited autopsy restricted to the brain. This revealed extensive lymphoma throughout the brain, particularly in the deep basal nuclei, midbrain, pons, centrum semiovale, and corpus callosum (Figure 4).

**Discussion**

Our patient with limited-stage EBV-positive DLBCL suffered a tragic neurologic decline due to relapsed DLBCL isolated to the CNS. The decision to forgo evaluation for CNS disease at diagnosis was supported by his CNS-IPI score of 2. The CNS-IPI score was developed to address whether patients with DLBCL should be evaluated upfront for CNS involvement and receive prophylactic intrathecal chemotherapy to minimize the risk of CNS relapse. This scoring system uses the same scoring system used to calculate the age-adjusted IPI score (age >60 years, LDH higher than normal, ECOG (Eastern Cooperative Oncology Group) performance status >1, Ann Arbor stages III or IV, and more than 1 extranodal disease site) and allot additional points for kidney or adrenal involvement. It was derived from a multivariate analysis of risk for CNS relapse of 2164 patients with newly diagnosed aggressive B-cell lymphoma (80% of which had DLBCL) who received rituximab and CHOP or CHOP-like chemotherapy through International and German High-Grade Non-Hodgkin

![Figure 4. The patient’s autopsy brain showing perivascular and parenchymal involvement by lymphoma (hematoxylin-eosin, original magnification (A) ×200 and (B) ×400). Immunohistochemical studies for CD20 at (C) ×200 and (D) ×400. The brain was extensively and diffusely involved by lymphoma, particularly the deep basal nuclei, midbrain, pons centrum semiovale, and corpus callosum.](image)
Lymphoma Study Group (DSHNHL) studies. An independent validation was performed with a data set of 1597 patients with DLBCL from the British Columbia Cancer Agency (BCCA) database. Patients with 1 to 2 CNS-IPI risk factors were considered low risk and had a 2-year rate of CNS relapse of 0.6% (95% confidence interval [CI]: 0%-1.2%), intermediate-risk patients (2-3 risk factors by CNS-IPI) had a 2-year rate of relapse of 3.4% (95% CI: 2.2%-4.4%), and high-risk patients (4-6 points by CNS-IPI) had a 2-year rate of CNS relapse of 10.2% (95% CI: 6.3%-14.1%). Based on a CNS relapse risk of less than 5% for the low- and intermediate-risk groups, the authors proposed reserving CNS evaluation for patients with 4 or more CNS risk factors and/or testicular, renal, or adrenal involvement. Epstein-Barr virus positivity was not evaluated in the CNS-IPI model so it is unclear whether EBV altered our patient’s risk for CNS relapse.

In the rituximab era, secondary CNS involvement is an uncommon complication, with a 2-year rate of 2.8% to 4.8%. As proved true for our patient, most of the CNS relapses occur within the first 6 to 9 months after diagnosis; with the use of rituximab, there is no difference in the incidence of CNS relapses with the inclusion of etoposide. However, with the use of rituximab, there is no difference in the incidence of CNS relapse with the inclusion of etoposide.

There are no randomized trials to guide which chemotherapeutic regimen should be used in EBV-positive DLBCL. Our patient received DA-EPOCH-R; however, it is unknown whether DA-EPOCH-R is superior to R-CHOP in patients with EBV-positive DLBCL. A recent randomized control trial compared DA-EPOCH-R with R-CHOP in 524 patients with stage II or higher stage newly diagnosed DLBCL. This trial showed no difference in event-free survival at a median follow-up of 4.9 years with a hazard ratio of 1.02 (P = .89). The overall survival was also equivocal between the DA-EPOCH-R and the R-CHOP groups with a hazard ratio of 1.19 (P = .40). Patients who received DA-EPOCH-R had increased side effects and were less likely to complete all 6 planned treatment cycles, although there was no difference in grade 5 toxicities. Patients with EBV-associated DLBCL were not specifically included in the trial but this data suggest that R-CHOP may be a reasonable regimen for patients with EBV-positive DLBCL. Still, some caution in generalizing this trial to rare DLBCL variants is in order. Final subgroup analyses have yet to be released from this trial, and it remains unclear whether more toxic and cumbersome chemotherapy regimens affect favorably high-risk DLBCL subtypes such as double-hit and triple-hit lymphomas or mediastinal B-cell lymphoma. A single institution series of 129 patients and a US multicenter study of 311 patients showed a significantly improved event-free survival for those patients who were treated with DA-EPOCH-R compared with those who received R-CHOP.

In summary, this case illustrates an unusual presentation of CNS relapse in a patient with EBV-positive DLBCL and highlights the uncertainties underlying the management of this rare subtype. Prior to his autopsy, it was unclear what was driving our patient’s neurologic demise. Central nervous system relapse rarely presents as locked-in syndrome. Our patient could not communicate, but this condition has been vividly expressed by the French writer, Jean-Dominique Bauby, who had locked-in syndrome after a massive stroke. He managed to compose a book describing his experience using only eye movements. Bauby compared his disease to a diving bell, writing, “My diving bell becomes less oppressive, and my mind takes flight like a butterfly.”

Author Contributions
JNP and DMA wrote the manuscript. RD performed the pathology review and DMA was the primary oncologist for this case.

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