Plasmablastic lymphoma presenting as proptosis and impending visual loss

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A 40-year-old Hispanic man with an unremarkable medical history presented to the emergency department with sudden onset swelling of and loss of vision in the left eye. His symptoms had initially developed 3 months before his presentation and were considered to have been the result of a possible infection of the orbital muscle and associated inflammation. He had symptomatic improvement after steroid treatment. However, he began to notice increasing left nasal congestion, double vision, and facial numbness after discontinuation of steroids. He had no previous exposure to chemicals such as nickel, copper, or wood dust and he denied any alcohol, nicotine, or other substance abuse. He had no previous sinus problems or known sinus polyps. His laboratory data, including complete blood count, showed a white blood count elevated at 14,700 cells/mm^3, with absolute neutrophils at 9,200 cells/mm^3, lymphocytes at 4,300 cells/mm^3, and monocytes at 1,200 cells/mm^3. His hemoglobin was normal at 15.2 g/dL as was his platelet count at 298,000 cells/mm^3. His comprehensive metabolic panel showed albumin, 3.6 g/dL; calcium, 9.2 mg/dL; and protein, 7.0 mmol/L. He had normal LDH (164 IU/L) and beta-2 microglobulin (1.75 mcg/mL) levels, and had no monoclonal spike on serum protein electrophoresis. His other laboratory data were also within normal limits, his HIV antibody test was nonreactive, and his hepatitis panel was negative. The Epstein-Barr virus panel showed evidence of past infection, with negative EBV polymerase chain reaction in the blood.

The patient was initially evaluated by an otolaryngologist for a mass in his left maxillary sinus. His physical examination showed that his vital signs were stable: weight, 160 lb; temperature, 98.6°F; pulse, 69 beats/min; respiration rate, 20 breaths/min; blood pressure, 128/90 mmHg. He was found to have injection of left bulbar conjunctiva with proptosis. His pupils were equally round and reactive to light. He had restricted left lateral ocular movements superiorly and inferiorly with double vision when tracking. There was no tenderness on palpation of his maxillary sinus. He had intermittent loss of sensation extending from his upper teeth on the left, up his cheek and above his eye with intact sensation on opposite side. Facial nerve function was intact bilaterally. Intraoral examination revealed no evidence of loose dentition or erosion through the palate. There was no palpable lymphadenopathy in the neck or the parotid.

A computed tomography scan of the face and sinuses revealed a large soft-tissue mass that originated from the left maxillary sinus or left nasal cavity. It extended superiorly with partial permeative destruction of the orbital floor with elevation and distortion of the globe. The inferior rectus was pushed medially, the optic nerve was slightly elevated, and there was associated proptosis. The mass occluded the left nasal cavity with partial involvement of the inferior turbinate. A magnetic resonance imaging of the brain and orbits showed a solid enhancing mass measuring 4 x 4.5 x 3 cm that filled the left maxillary sinus, abutting the optic nerve and eroding through the orbital floor into the left orbit, and causing orbital globe and inferior rectus muscle displacement; there was no evidence of intracranial tumor extension (Figures

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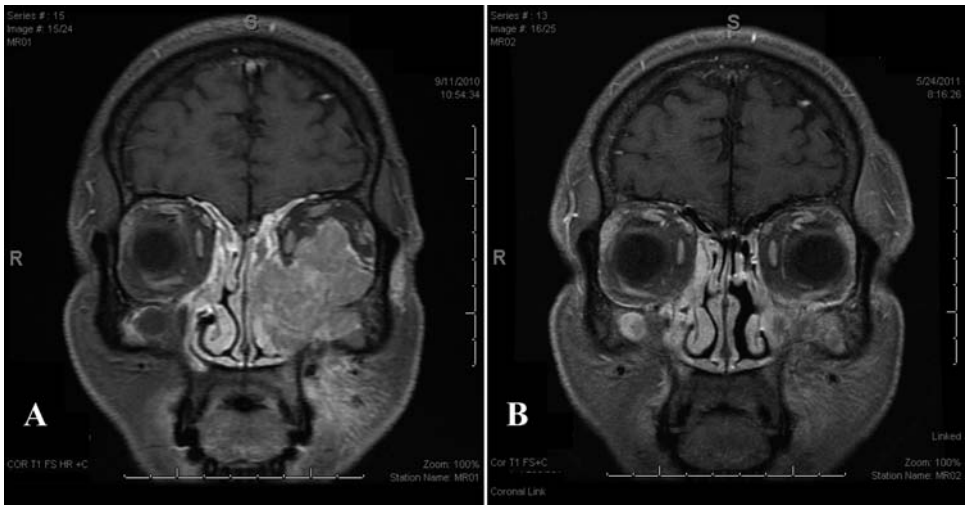

FIGURE 1 A, MRI scan of the brain and orbits coronal plane showing a solid enhancing mass measuring 4 cm × 4.5 cm × 3 cm filling the left maxillary sinus, abutting the optic nerve and eroding through the orbital floor into the left orbit, causing orbital globe and inferior rectus muscle displacement. B, MRI scan 4 months after completion of therapy.

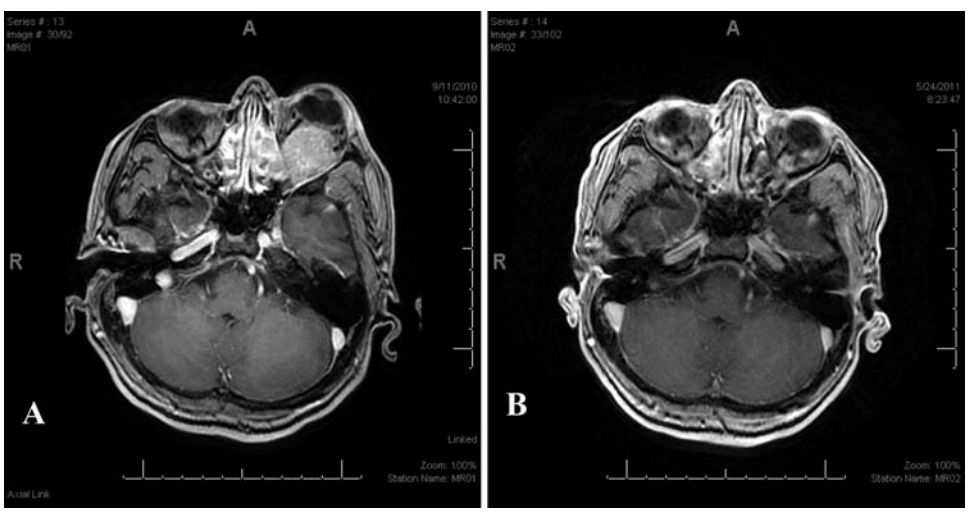

FIGURE 2 A, MRI scan showing a large soft tissue mass originating from the left maxillary sinus or left nasal cavity with extension and partial destruction of the orbital floor with elevation and distortion of the globe. B, MRI scan 4 months after completion of therapy.

1A and 2A). Subsequent computed tomography and positron emission tomography imaging of the chest, abdomen, and pelvis showed no evidence of distant metastatic involvement.

The results of a cerebrospinal fluid analysis and bone marrow biopsy were negative for malignancy. A fine-needle aspiration and core biopsy of the sinus mass was performed. The aspirate smears demonstrated a population of markedly atypical cells with increased nuclear-to-cytoplasmic ratios and slightly eccentric nuclei (Figure 3A). The core biopsy revealed a monomorphic population of large, atypical mononuclear cells with prominent nucleoli (Figure 3B). Lymphoglandular bodies were present on the touch preps of the core biopsy. No monoclonal B-cell or immunophenotypically aberrant T-cell population was identified in a flow cytometry analysis. Immunohistochemistry on the core biopsy revealed the following:

- CD138 (Figure 3C) and multiple myeloma oncogene 1 (MUM1) were diffusely, strongly positive (Figure 4B);
- CD2, CD3, CD20 (Figure 3D), CD30, CD43, CD45, CD56, cytokeratin AE1–AE3 (a mixture of 2 different clones of anticytokeratin monoclonal antibodies, AE1 and AE3, and a commonly used reagent in diagnostic immunohistochemistry), CAM 5.2 (low molecular weight cytokeratin), cytokeratin 5–6, synaptophysin, S-100 protein, kappa light chain, and lambda light chain were negative; and
- CD79a and chromogenic in situ hybridization for EBV-encoded RNA were positive (Figure 4A).

The results of the immunohistochemical and in situ hybridization analyses, in combination with the morphologic findings, supported a diagnosis of plasmablastic lymphoma (PBL).

In view of the patient's impending vision loss and proptosis, he received radiation therapy for a total dose of 600 cGy in 2 fractions, with an excellent response. He then completed 6 cycles of chemotherapy treatment with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH), along with intrathecal treatment with methotrexate, hydrocortisone, and cytarabine during each chemotherapy cycle. Postchemotherapy MRI scans showed a marked interval decrease in the size of the enhancing mass lesion except for a small region of residual intraorbital disease (Figures 1B, 2B). Given the aggressive nature of his disease with erosion through the bony orbit and the likelihood of recurrence, the patient received radiotherapy with a total dose of 3,960 cGy. He remains well without

clinical and radiological evidence of disease recurrence almost 2 years after his original diagnosis. Figure 5 shows positron emission tomography scans before therapy initiation (A) and almost 1 year after diagnosis (B).

Discussion

Recent evidence suggests that diffuse large B-cell lymphoma (DLBCL) with plasmablastic differentiation represents a clinically heterogeneous spectrum with different clinicopathologic characteristics representing distinct entities. Subtypes of DLBCL with plasmablastic features and terminal B-cell differentiation include:

- PBL of oral mucosa type;
- PBL with plasmacytic differentiation;
- Primary effusion lymphoma (PEL);
- Extracavitary PEL/human herpesvirus (HHV)-8–associated DLBCL; and
- Anaplastic lymphoma kinase-positive DLBCL.

In contrast, PBL that is associated with multicentric Castleman disease, DLBCL with secretory differentiation, and atypical Burkitt lymphoma with plasmacytoid differentiation have the morphologic appearance of plasma cell differentiation but maintain a mature B-cell (CD20-positive) phenotype.[1] Plasmablastic lymphoma is a distinctive B-cell neoplasm that shows diffuse proliferation of large neoplastic cells, most of which resemble B-immunoblasts and have immunophenotype of plasma cells and are CD20 negative.

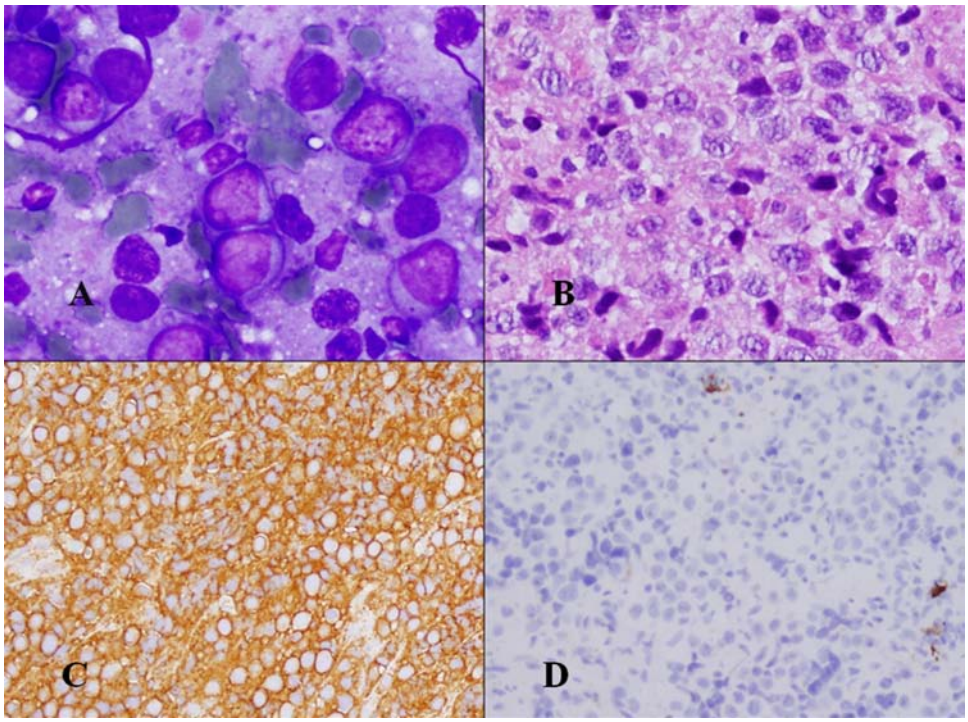

FIGURE 3 A, aspirate smear of the sinus mass with atypical intermediate to large lymphoid cells with plasmacytoid features (Wright-Giemsa stain). B, sinus mass core biopsy with numerous large atypical lymphoid cells with coarse chromatin and prominent nucleoli (hematoxylin and eosin stain). C, Core biopsy with strong CD138 expression in the lymphoma cells. D, The tumor cells are negative for CD20 (200×).

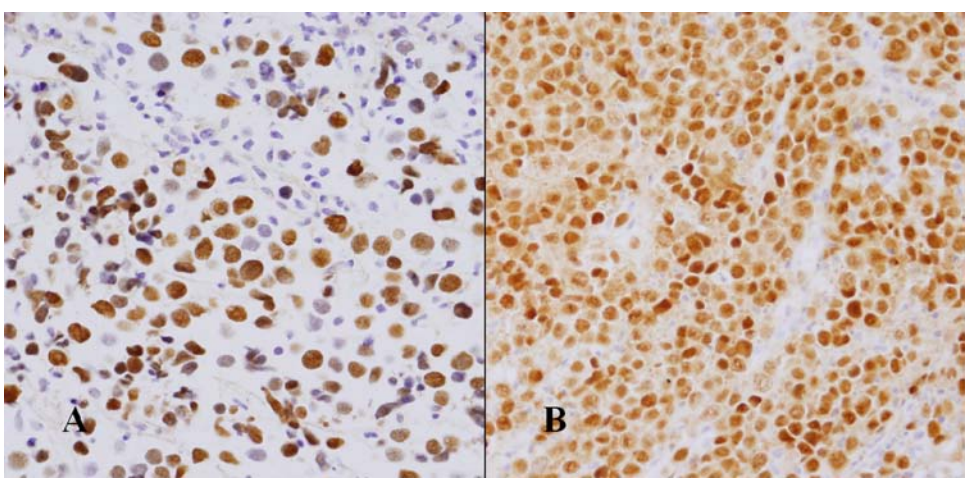

FIGURE 4 A, EBER by in situ hybridization is positive in the lymphoma cells. B, Strong expression of MUM1. EBER indicates EBV-encoded RNA; MUM1, multiple myeloma oncogene 1.

PBL was originally described as a rare variant of DLBCL that involved the oral cavity and occurred in the clinical setting of HIV and latent EBV infection. PBL accounts for 2.6% of all HIV-related non-Hodgkin lymphomas. It has been described, less commonly, in extraoral locations and immunocompetent settings.[2] Current evidence suggests that DLBCL with plasmablastic differentiation represents a clinically heterogeneous spectrum with different clinicopathologic characteristics that represent distinct entities. Important subtypes include PBL of oral mucosa type, PBL with plasmacytic differentiation, and extramedullary plasmablastic tumors secondary to plasmacytomas or myelomas. The morphologic

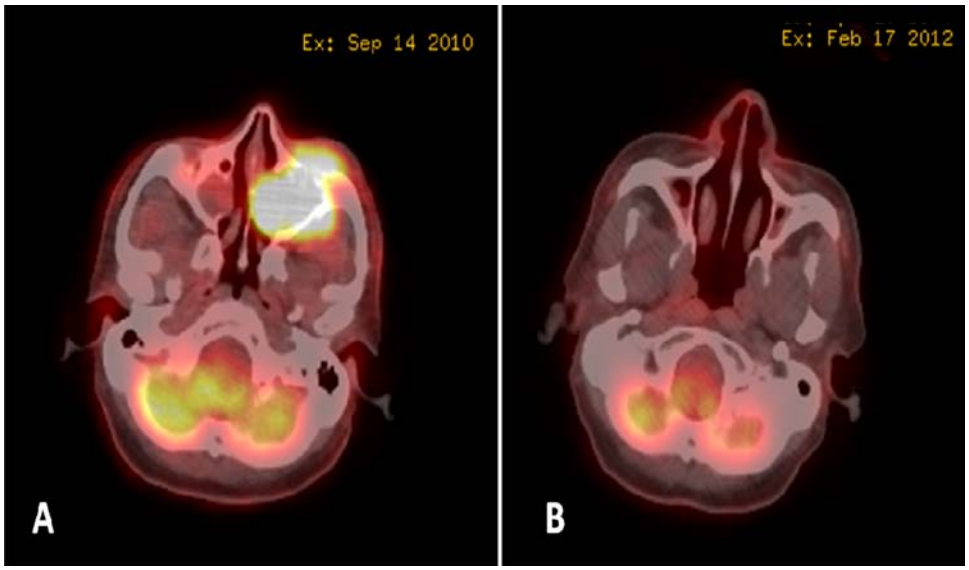

FIGURE 5 A, Computed tomography and positron emission tomography scans before initiation of chemotherapy and B, 17 months after diagnosis.

spectrum ranges from the large immature tumor cells (immunoblasts, plasmablasts) to cells with a mature plasmacytic differentiation present in a variable and somewhat overlapping maturity range. The malignant plasmablastic cells have been described as having a squared-off appearance with either centrally or eccentrically placed nuclei. From an immunophenotypical perspective, the strong expression of CD38, CD138, VS38 (p63), and multiple myeloma oncogene-1 (MUM1), as well as a weak or absent expression of CD20 and CD79a, is considered a criterion for this group of neoplasms. Because PBL does not express the more common lymphoid and/or B-cell markers, it could be mistaken for a poorly differentiated carcinoma. It is clinically important and critical to differentiate between PBL and plasmablastic plasma cell myeloma. Some investigators have shown that positivity for the monoclonal antibody, Ki-67, which is associated with cell proliferation, is lower in plasmablastic myelomas (5%) than it is in PBLs (60%). Moreover, both diseases show similar tumor suppressor gene expression profiles, with frequent loss of expression of p16 and p27, and positive staining for p53.

Similar to other types of AIDS-related lymphomas, there is evidence that EBV and HHV-8 may have a role in the pathogenesis of PBL in HIV-positive patients. PBL patients have been treated heterogeneously, with a combination of chemotherapy, radiotherapy, and/or surgery, and their prognosis is usually poor, with a death rate of about 60% at 1 year in HIV-positive patients.[3,4] PBL patients are positive for EBV-encoded RNA but generally lack the HHV-8 latent nuclear antigen. PBL is often associated with *MYC*-IgH rearrangements and that finding may portend an aggressive clinical course, which suggests that cytogenetic studies should be routinely applied in cases of PBL.[5]

Although PBLs are commonly described as having a predilection for the oral cavity in HIV-positive individuals, extraoral lesions involving sinus, oral gastrointestinal, and lung manifestation have been noted.[6] There have been only a few cases involving the ocular adnexa. Rare EBV-encoded RNA-positive plasmablastic plasma cell tumors exist in immunocompetent patients. These tumors may have been driven by EBV to gain the plasmablastic cytomorphologic features and high proliferation fraction.[7] EBV has been detected in 74% of HIV-associated PBLs, and in 50%–60% of PBLs in HIV-negative individuals.[8] The overexpression of tissue inhibitor of metalloproteinase-1 (TIMP-1) correlates with aggressive clinical behavior as well as incomplete plasmacytic differentiation without altering cell proliferation despite *MYC* deregulation, which indicates an arrested plasmacytic or plasmablastic stage of differentiation.[9] The etiological role for EBV seems likely, but the association with HHV-8 is questionable. Plasmablastic lymphoma was initially described as a variant of diffuse large B-cell lymphoma (DLBCL) involving the oral cavity of HIV-positive patients and was characterized by immunoblastic morphology and a plasma cell phenotype. DLBCLs with plasmablastic differentiation, in contrast, are a heterogeneous group of neoplasms with different clinicopathological characteristics that may correspond to different entities.[10] Although the clinical and pathologic characteristics of these tumors have been defined; the genetic alterations involved in their pathogenesis are not well known. PBL are genetically characterized by frequent *MYC*-IgH translocations and gains in multiple chromosomal loci. The oncogenic activation of *MYC* in these lymphomas may be an important pathogenetic element associated with EBV infection. No survival differences based on *MYC* oncogene activation have been observed, but investigators have reported that patients with the longest survival (> 50 months) had

no or a low number of gains (< 3) of *MYC* oncogene.[11] The dysregulation of *MYC* may be a common genetic mechanism that imparts plasmablastic morphology and aggressive clinical course to B-cell neoplasms at a later stage of differentiation.[12]

Two distinct subtypes of PBL are classified as oral and extraoral PBL. The oral PBLs are strongly associated with HIV infection and commonly have plasmablastic morphologic features without plasmacytic differentiation. Extraoral PBLs tend to occur in patients with underlying non−HIV-related immunosuppression and universally demonstrates plasmacytic differentiation. Patients with oral PBL have better overall survival compared with patients with extraoral PBL ($P = .02$). PBLs with oral and extraoral manifestations represents 2 distinct clinicopathological entities.[13] A subset of PBL of the oral cavity carries the molecular clues of germinal center (GC) transit and originates from post-GC B-cells. Conversely, another portion of these lymphomas are devoid of somatic IgVH mutations and appear to originate from naive B-cells that have undergone preterminal differentiation independent of GC transit.[14]

Although PBL has been described as a variant of DLBCL, it constitutes a distinct, rare entity that is composed with morphological resemblance to B-immunoblasts but it has a plasma cell immunophenotype with weak expression for B-cell antigens and a strong reactivity for plasma cells antigens such as CD138, CD38, and MUM1. The tumor cell proliferation index for Ki-67/MIB-1 usually approaches 100%. MUM1 protein may play a key role in the terminal phases of B-cell differentiation toward the plasma cell with a morphologic spectrum ranges from that of centrocyte to that of a plasmablast or plasma cell, and it displays a phenotype (MUM1 positive and Bcl-6 negative) different from that of most GC B cells and mantle B cells. These cells may represent surviving centrocytes and their progeny committed to exit GC (post-GC) and differentiate into plasma cells. Unlike normal GC B-cells, in which the expression of MUM1 and Bcl-6 were mutually exclusive, tumor cells in half of the cases of MUM1-positive B-cell lymphomas express MUM1 and Bcl-6, which suggests the deregulation of expression of these proteins.[15]

The histogenesis of the lymphoid neoplasms with plasmablastic differentiation has been further refined in studies of biological markers that identify distinct subsets of mature cells. In fact, tumor cells express CD138, a proteoglycan associated with post-GC terminal B-cell differentiation and MUM1 or interferon regulatory factor 4 (MUM1 or IRF4), a lymphocyte-specific transcription factor that identifies the transition from post-GC B-cells to immunoblasts and plasma cells. MUM1 positivity in plasmablastic tumors corroborates the notion that tumor cells reflect a post-GC phenotype. Of note is that HIV-associated lymphoma cases that belong to the immunoblastic (IB subtype with plasmacytoid differentiation express the EBV-encoded latent membrane protein 1 (LMP1) and display the Bcl-6 and CD1381 phenotype, thus reflecting post-GC B-cells.[9] The possible contribution of LMP1 to the loss of Bcl-6 expression seems plausible given that LMP1 can downregulate many B-cell specific genes.[11] Loss of B-cell identity occurs during the normal differentiation of a post-GC B-cell into plasma cells or memory B-cells. CD138 and MUM1, which are markers of post-GC, terminal B-cell, or plasmacytic differentiation, are useful in identifying the B-cell origin of these tumors that show variable or negative expression of CD20 and CD79a.[16]

Plasmablastic lymphomas share many cytomorphologic and immunophenotypic features with plasmablastic plasma cell myeloma. However, PBL is listed in the World Health Organization classification as a variant of DLBCL. Both PBL and plasmablastic plasma cell myeloma are positive for MUM1 or IRF4, CD138, and CD38, and negative for CD20, corresponding to a plasma cell immunophenotype. PAX-5 and Bcl-6 are negative in plasmablastic plasma cell myelomas. A high Ki-67 proliferation index, overexpression of p53, and loss of expression of p16 and p27 are present in both tumors. HHV-8 infection is usually not detected in either neoplasm. The only significant difference between PBL and plasma cell myeloma is the presence of EBV-encoded RNA, which is positive in PBL and negative in plasma cell myelomas. Most cases of AIDS-related PBL have an immunophenotype and tumor suppressor gene expression profile that are virtually identical to plasmablastic plasma cell myeloma and that do not support PBL as a variant of diffuse large B-cell lymphoma.[17] PBL survival is limited because of its highly aggressive local and metastatic behavior and poor response to treatment.[14,18] The treatment guidelines for PBL are not well defined, and patients with PBL have been treated heterogeneously with chemo and/or radiotherapy. Disease that is diagnosed at an early clinical stage and a patient's complete response to chemotherapy are associated with longer survival. Patients with HIV-associated PBL have a poor prognosis. Prognosis is strongly associated with achieving a complete clinical response to CHOP or CHOP-like chemotherapy. The role of more intensive regimens is not clear at this stage. Although patients with this malignancy may have an initial good response to therapy, there is typically a high rate of relapse, with resistance to intensive therapies and short survival.[19,20] Further research is needed to improve responses using novel therapeutic agents and strategies in HIV-positive and -negative patients.

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