IJKD KIDNEY DISEASES

Multifocal Cranial Plasmablastic Lymphoma as a Rare Manifestation of Posttransplant Lymphoproliferative Disorder

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We present an unusual case of a young woman who developed multiple cranial masses and unilateral facial palsy 10 years after a successful living-unrelated kidney transplant. She was diagnosed with diffuse large B-cell plasmablastic differentiated lymphoma, a rare form of posttransplant lymphoproliferative disorder. She responded to 5 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy with resolution of all cranial masses. However, her facial palsy did not resolve, and she died 6 months after diagnosis with pneumonia and sepsis.

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Case Report

INTRODUCTION

Posttransplant lymphoproliferative disorders (PTLDs) are a heterogeneous group of lymphoproliferative disorders ranging from reactive polyclonal hyperplasia to aggressive non-Hodgkin lymphoma that often originate from the recipients' lymphoid tissue.[1-4] The incidence of PTLD varies according to the transplanted organ, intensity of immunosuppressive regimen, and Epstein-Barr Virus (EBV) serological status of the recipient before transplantation. Posttransplant lymphoproliferative disorder occurs most frequently (> 80% of cases) within the 1st year of solid organ transplant, a median onset of 6 months,[5,6] as early as 1 week to as late as 17 years posttransplantation.[6,7]

Early PTLDs are caused by the outgrowth of EBV-infected B lymphocytes favored by the profound impairment of T lymphocytes.[2,3] The histology and molecular patterns range from polymorphic polyclonal hyperplasia to monomorphic monoclonal lymphomas in the early PTLD.[3,8,9] Late PTLDs are usually a monoclonal proliferation of B cells and are characterized by frequent lack of EBV genome in tumor cells, and sometimes, by detection of translocations or point mutations of oncogenes or tumor suppressor genes.[9,10] Studies show that early PTLD has a better prognosis with a mortality rate of 36% versus 70% in late PTLD.[11,12] Also, the risk of death increases significantly with multi-organ PTLD and increasing age.[11]

Among solid organ transplants, the highest incidence of PTLD has been reported with intestinal transplant at 19%,[13] followed by 2% to 10% in heart transplant, 5% to 9% in heart and lung transplant, 2% to 8% in liver transplant, and 2% in kidney transplant.[14,15] Despite the fact that in 53% of the

PTLD cases, multiple organs or sites are involved,[16] multifocal involvement of cranial vault has been rare. In the recent years, the spectrum of PTLD has been expanded to include extramedullary plasmacytoma-like PTLD[17] and plasmablastic lymphomas.[18]

We report a young patient who developed rapidly growing multiple cranial masses 10 years after a successful living-unrelated transplant, diagnosed as diffuse large B-cell plasmablastic differentiated lymphoma form of PTLD.

CASE REPORT

A 30-year-old woman with a history of end-stage renal disease of unknown etiology who had received a living-unrelated kidney transplant 10 years earlier was referred to Rasool-Akram Medical Center in Tehran with a 3-week history of right-sided auricular pain that was followed by progressive pre-auricular swelling and right-sided facial palsy (Figure1). She denied any fever, chills, weight loss, itching, or night sweats. She was on oral cyclosporine, 50 mg twice per day; mycophenolate mofetil, 500 mg twice per day (replacement of azathioprine 6 months earlier); prednisone, 5 mg per day; enalapril, 5 mg per day; and nifedipine, 10 mg three times per day.

During her admission, the patient was alert and oriented with a blood pressure of 100/60 mm Hg, heart rate of 84 beats/min, respiratory rate of 16/min, and oral temperature of 36.5°C. The patient was pale and had no peripheral lymphadenopathy. She had right-sided peripheral facial palsy with a tender, firm right pre-auricular mass (4 × 5 cm).

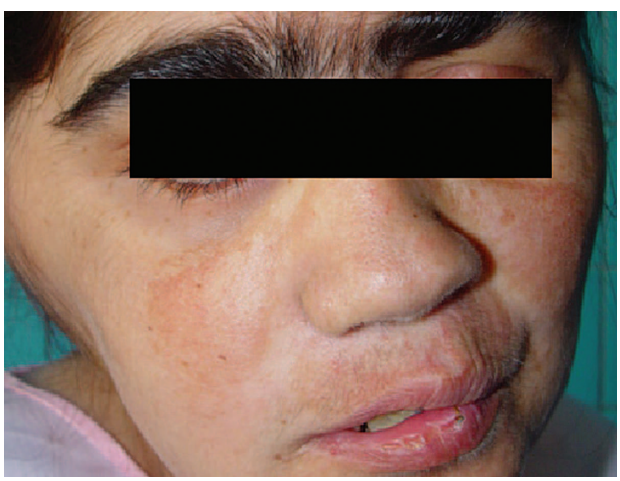

Figure 1. Right-sided periauricular 4 × 5-cm mass with right-sided peripheral facial palsy.

During this hospitalization, she developed 2 large nontender firm subcutaneous scalp masses in her left parietal region. Examination of the abdomen, pelvis, and extremities was unremarkable. Her serum creatinine on admission was 1.7 mg/dL (baseline serum creatinine had been between 1.5 mg/dL and 1.8 mg/dL in the past 4 years). Hematocrit was 27%. Blood EBV-polymerase chain reaction assay was negative, anti-EBV immunoglobulin G (IgG) titer was greater than 200 (negative, < 8), anti-EBV IgM antibody titer was 15 (negative, < 8) with no rise in titer during the hospital course. Serum protein immuno-electrophoresis revealed IgG of 855 mg/dL, IgA of 206 mg/dL, and IgM of 204 mg/dL, and no monoclonal band was present.

Skull radiography showed multiple lytic lesions (Figure 2). Computed tomography (CT) scans of the chest and abdomen revealed no lymphadenopathy or organomegaly. Temporal bone CT scan revealed a large destructive lesion arising from the right skull base, mostly from the sphenoid and petrous bones (Figure 3). Magnetic resonance imaging of the brain with gadolinium enhancement revealed a large lobular lesion arising from right skull base, mostly from sphenoid and petrous bones

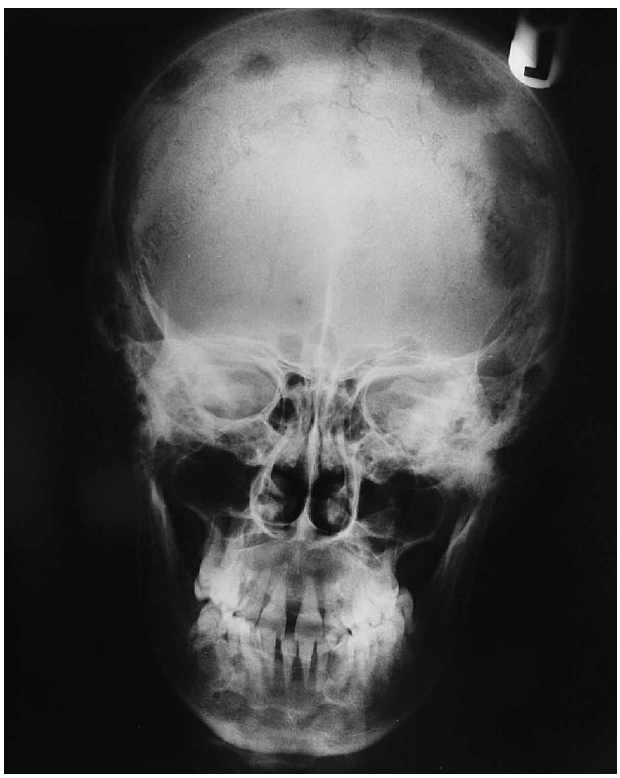

Figure 2. Skull radiography image showed multiple lytic skull lesions.

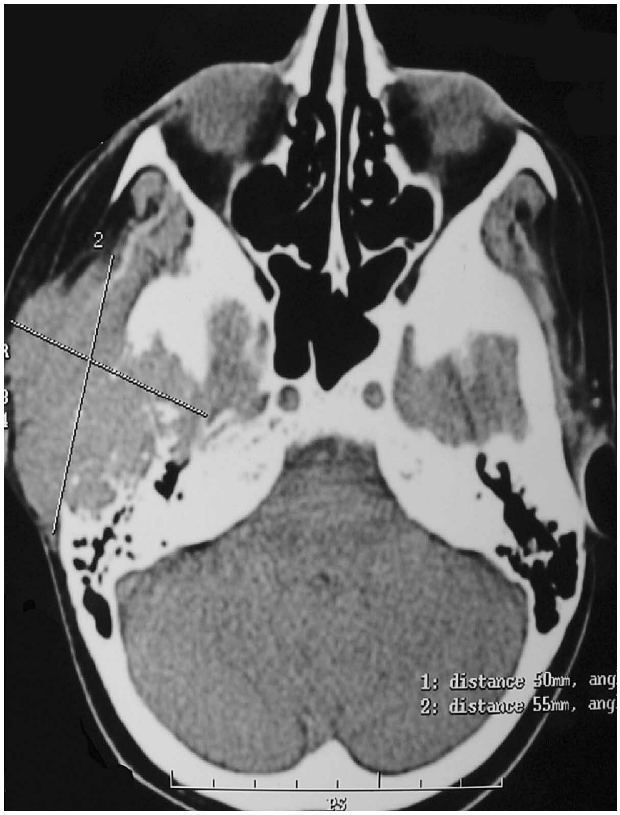

Figure 3. Computed tomography scan of temporal bone revealed a large destructive lesion arising from the skull base on the right side, mostly from the sphenoid and petrous bones.

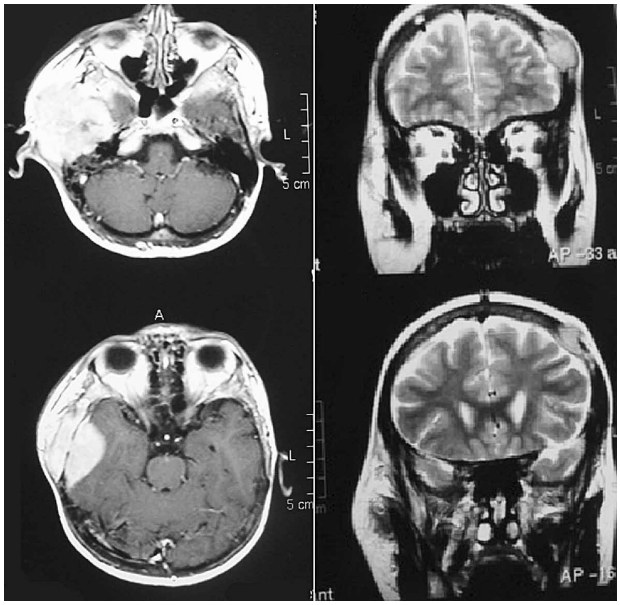

Figure 4. Magnetic resonance imaging with gadolinium enhancement revealed a right-sided large lobular lesion arising from the skull base mostly from the sphenoid and petrous bones. Similar lesions were also found in the left parietal bone.

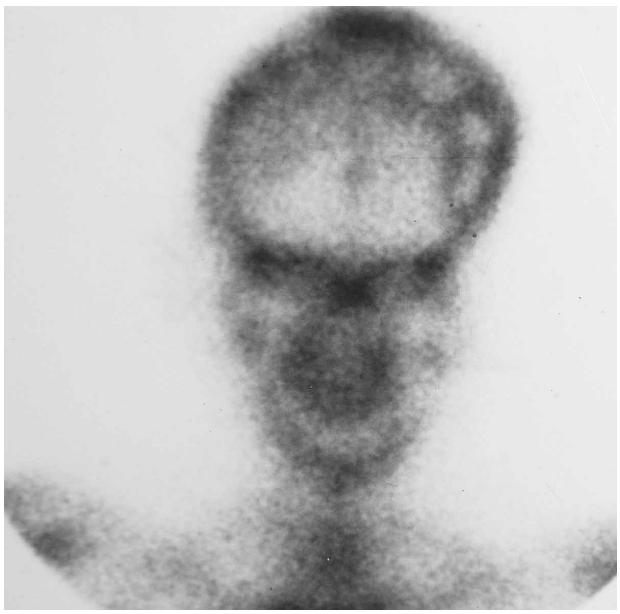

Figure 5. Cranial bone scan revealed increased tracer uptake with central septated photopenic areas in left parietal and temporal bones.

(Figure 4). Similar lesions were found in the left parietal bones. Whole body bone scan was only positive in the skull showing increased uptake with central septated photopenic areas in the left parietal and temporal bones (Figure 5).

Excision Biopsy of the right pre-auricular mass showed malignant neoplastic tissue composed of large cells with vesicular nuclei, small to indistinct nucleoli, and abundant amphophilic to eosinophilic cytoplasm (Figure 6). Scattered cells resembling immunoblasts with large eosinophilic nucleoli were also noticed. There were numerous mitotic figures and some apoptotic bodies. The inflammatory infiltrate was also composed of lymphocytes, plasma cells, and polymorphonuclear leukocytes. Immunohistochemical studies showed positive staining for vimentin, focally positive staining for epithelial membrane antigen in tumor cells, and positive staining for CD38, CD79a, and CD138 (Figure 6). Immunohistochemical studies were negative for leucocyte common antigen, CD3, CD20, CD30, CD99, cytokeratin, and kappa and lambda light chains. The histology and immunohistochemical studies were consistent with diffuse large B-cell plasmablastic differentiated lymphoma form of PTLD. Bone marrow studies were normal.

Cyclosporine and mycophenolate were discontinued and the patient received 5 courses of CHOP (cyclophosphamide, doxorubicin, vincristine,

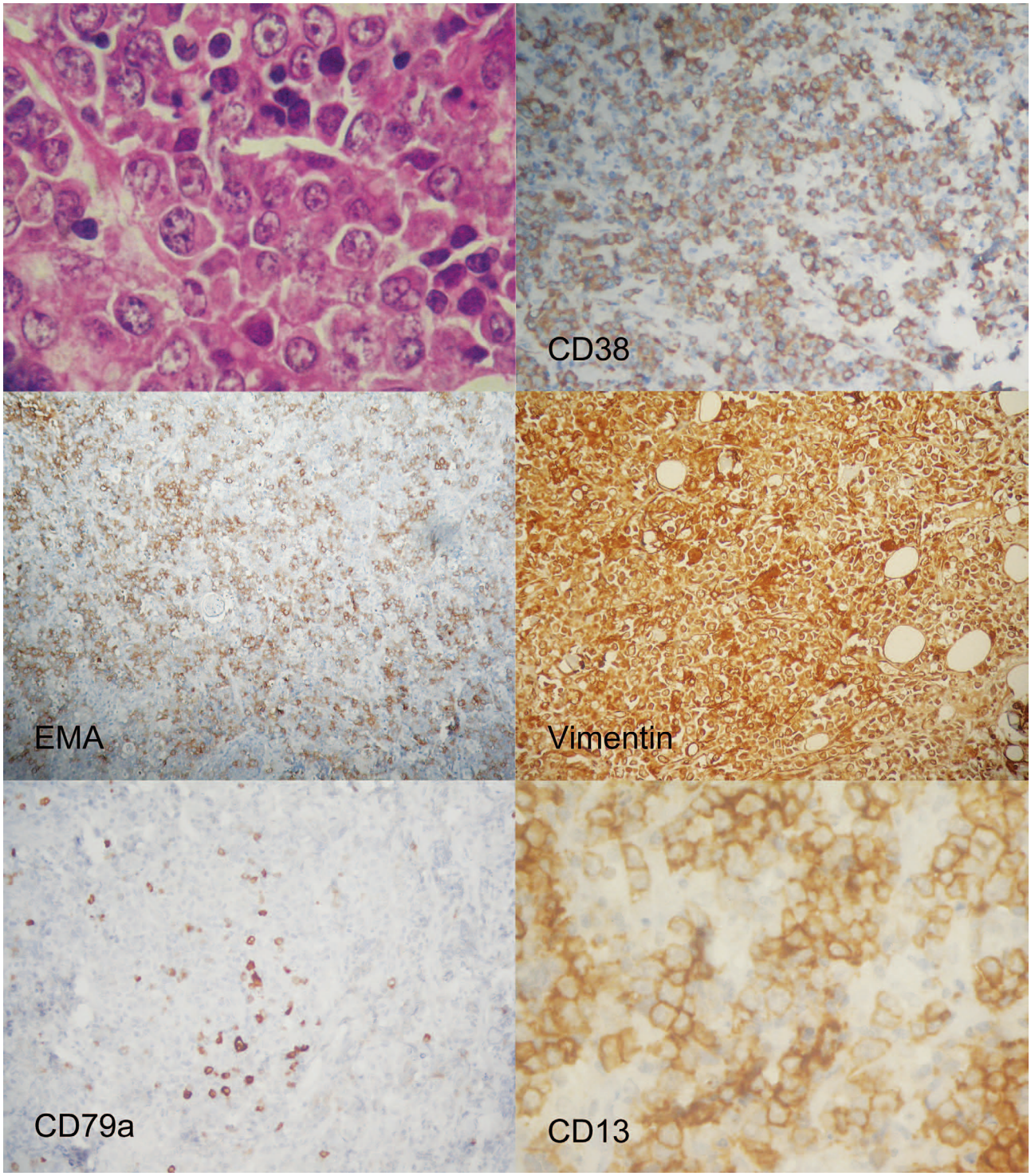

Figure 6. Biopsy shows malignant neoplastic tissue composed of large cells with vesicular nuclei, small to indistinct nucleoli, and abundant amphophilic to eosinophilic cytoplasm. Scattered cells resembling immunoblasts with large eosinophilic nuclei were also noticed. Immunohistochemical staining was positive for epithelial membrane antigen (EMA), vimentin, CD79a, CD138, and CD38.

and prednisone) chemotherapy. A follow-up magnetic resonance imaging of the brain after 1 month revealed significant shrinkage of the right skull base mass and disappearance of all other cranial lesions. The patient's serum creatinine was 1.5 mg/dL to 1.6 mg/dL at 2 months' follow-up. However, despite regression of the pre-auricular and the other cranial masses her facial palsy did

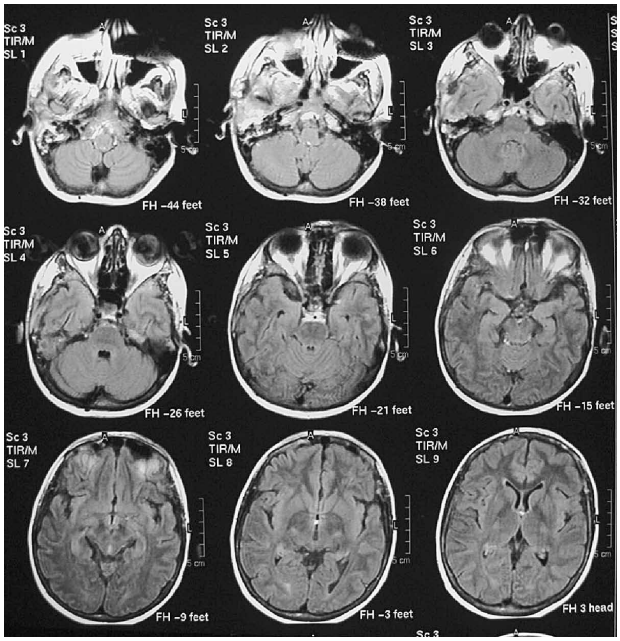

Figure 7. Repeated magnetic resonance imaging 1 month after beginning chemotherapy revealed a significant shrinkage of the right base mass lesion and disappearance of all other cranial masses.

not resolve. After 6 months of chemotherapy she developed severe pneumonia and died with sepsis.

DISCUSSION

In a recent retrospective multicenter cohort study of 9917 kidney transplant recipients (between 1984 and 2008) from Iran, 0.5% of the patients developed PTLD, which represented 24% of all posttransplant malignancies.[19] The pattern of posttransplant malignancies was different in Iran as compared with the Western countries, in that Kaposi sarcoma was reported to be the most common malignancy (34.5% of all posttransplant malignancies) followed by PTLD (24% of all posttransplant malignancies).[19-22] Non-Hodgkin lymphoma was the most common variant, accounting for more than 92% of the cases, and was predominantly extranodal presenting in the gastrointestinal tract or in the central nervous system.[19]

In the recent years, the spectrum of PTLD has been expanded to include extramedullary plasmacytoma-like PTLD and plasmablastic lymphomas.[17,18] Extramedullary plasmacytoma-like PTLDs are an uncommon form of monomorphic PTLD. Richendollar and coworkers recently reported the 1st case series of 4 patients (6% incidence) from Cleveland Clinic case files and reviewed 15 prior single case reports that arose following kidney, heart, or liver transplantation.[17] They typically occur late after transplantation (mean, 7.0 years), show variable association with EBV, and demonstrate histologic and phenotypic findings that overlap with immunocompetent extramedullary plasma cell neoplasms.[17] On the other hand, plasmablastic lymphoma was originally described in patients with human immunodeficiency virus (HIV), presenting with oral cavity involvement.[23] It is considered a morphological variant of diffuse large B-cell non-Hodgkin lymphoma with plasmablastic differentiation characterized by acquisition of the transcriptional profile of plasma cells in concert with extinction of the B-cell differentiation markers and abundant proliferating immunoblasts, and almost always associated with an aggressive clinical behavior.[24,25] The plasmablastic lymphomas have been documented in extra-oral sites in HIV-positive and HIV-negative individuals and following organ transplantation.[18] Borenstein and colleagues recently reported 4 new cases of plasmablastic lymphoma following 2 renal, 1 heart, and 1 bone marrow transplantation. Their cases showed blastic non-Hodgkin lymphoma morphology and plasma cell-like immunophenotypic features: minimal or absent expression of leucocyte common antigen, absent CD20, variable CD79a and CD 138, and strong VS38 positivity, with a high proliferation index in all cases.[18] Monoclonal light chain restriction was also detected. The tumors involved the skin, lymph node, palate and prostate. In a MEDLINE search through June 2010, a total of 76 cases of HIV-negative plasmablastic lymphoma were identified; 74% were associated with immunosuppression, 18% had a concurrent lymphoproliferative or autoimmune disorder, and 9% had occurred after solid organ transplant.[26] Chemotherapy with CHOP-like regimens were used in 43% of the patients, which had resulted in a 2-year overall survival rate of 10%, and a median survival of 9 months.[26] A subsequent report on a series of 9 patients suggested that aggressive induction chemotherapy and consolidation followed by autologous hematopoietic stem cell transplant could result in a better intermediate and possibly long-term patient survival.[27] The present case and the recent reports in the literature show that plasmablastic lymphoma, which was originally reported in the oral cavity of HIV-positive patients,

can occur in other immunocompromized patients, and has a poor prognosis; this expands the spectrum of PTLDs.

CONFLICT OF INTEREST

None declared.

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