Case Report

A series of four cases on plasmablastic lymphoma: A rare Epstein–Barr virus-positive lymphoma in immunocompetent patients with varied presentation

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ABSTRACT

Plasmablastic lymphoma (PBL) is a rare and aggressive type of non-Hodgkin lymphoma (NHL) which is typically seen in the setting of an immunocompromised state, classically associated with human immunodeficiency virus infection. It is often also associated with Epstein–Barr virus infection. It has an immunophenotype of a terminally differentiated B lymphocyte. The diagnosis of PBL is challenging due to complex overlap with myeloma and other B-cell NHL having a plasmablastic morphology. In the past few years, there are an increasing number of cases being identified in patients with no known immunocompromised state. We hereby report a case series of four such cases in immunocompetent patients with different sites of involvement and varied presentation to add to the literature.

Key words: Epstein–Barr virus, Immunocompetent, Plasmablastic lymphoma

Plasmablastic lymphoma (PBL) was first described as a specific clinicopathologic entity by Delecluse and colleagues in 1997 as an aggressive B-cell lymphoma occurring in the oral cavity arising in the context of human immunodeficiency virus (HIV) infection [1]. Since the original description, it has become apparent that the clinical and morphological features of PBL are broader and these are thus reflected in the current 2008 World Health Organization classification [2]. In the past decade, <250 PBL cases, including case series, have been published worldwide [3]. Recently, cases involving the extraoral sites have also been reported in HIV seronegative individuals in the setting of solid organ transplants or in the elderly [3,4]. Some other cases were reported in other lymphoproliferative disorders and also in autoimmune disorders [4]. Still, occasional cases diagnosed as PBL had no known underlying immunocompromised condition [5]. Less than20 cases have been reported as PBL, following transplantation, in the literature [6]. We hereby report a case series of four such cases in immunocompetent patients at different sites of involvement and varied presentation to add to the literature.

CASE REPORT

Four cases diagnosed as PBL in the year 2016 were retrieved from the archives of the Department of Histopathology, National Reference Lab, Dr. Lal PathLabs. Their histopathological slides were accessed and reviewed by two histopathologists for their histopathological findings and the signed out diagnoses. Their clinical history forms were also accessed and reviewed. Any crucial input missing in the original clinical data was asked for and procured from the clinician and/or patient, such as the age of the patient, site of the lesion, and chief complaint with the duration of the illness. The clinical features of the patients are summarized in Table 1.

A comprehensive panel of immunohistochemistry (IHC) markers consisting of cluster of differentiation (CD) CD45, CD3, CD20, CD79a, Pax5, CD138, MUM1, EMA, CD 56, CD30, Bcl-2, Bcl-6, Alk-1, Ki-67, Epstein–Barr encoding region *in situ* hybridization (EBER-ISH), and human herpesvirus 8 (HHV 8) was performed on the paraffin blocks of biopsies from the patients. Hematoxylin-eosin (H and E) sections were reviewed, and morphological findings were noted. The final histological diagnosis was based on H and E staining and immunophenotyping results. Immunohistochemical studies were performed on formalin-fixed paraffin-embedded tissue using an automated immunostainer and a broad panel of antibodies, including leukocyte common antigen (LCA) (CD45), CD3, CD20, CD79a, PAX5, CD 56, CD10, Ki-67, HHV8, ALK-1, CD138, CD30, Bcl-2, Bcl-6, MUM-1, EMA, HHV8, and EBER-ISH. The IHC characteristics are summarized in Table 2.

Case 1

A 67-year-old female presented with a chief complaint of a lump in the neck for 15 days. There were no other

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Table 1: Clinical features of PBL cases

Clinical features	Case 1	Case 2	Case 3	Case 4
Age	67	20	74	75
Gender	Female	Male	Male	Male
Primary site(s)	Cervical lymph node	Skin over chest wall	Soft-tissue chest wall	Gastric mass
Lymph node involvement	Present	None	None	None
Other organs involved	None	None	Rib cartilage	None
B symptoms	None	Present	Present	None
HIV status	Negative	Negative	Negative	Negative
BM involvement	None	None	None	None
M protein	No	No	No	No

PBL: Plasmablastic lymphoma; HIV: Human immunodeficiency virus; BM: Bone marrow

Table 2: The immunohistochemical characteristics of the PBL cases

Immunophenotype	Case 1	Case 2	Case 3	Case 4
CD3	–	–	–	–
CD10	–	–	–	–
CD20	–	–	–	–
CD30	–	–	–	–
CD45	–	–	+	–
CD56	–	–	–	–
CD79a	+	+	+	+
CD138	+	+	+	+
ALK1	–	–	–	–
Bcl2	–	–	–	–
Bcl6	–	–	–	–
EMA	+	+	+	+
HHV8	–	–	–	–
MUM1	+	+	+	+
EBER-ISH	+	+	+	+
KI67	High	High	High	High
PAX5	–	–	–	–

PBL: Plasmablastic lymphoma

constitutional symptoms including fever or pain to the site. The vitals were stable. On palpation, the lump was found to be a 1.5 × 1.2 × 1.0 cm lymph node which was firm, mobile, and non-tender. There were few other small subcentimeter bilateral cervical lymph nodes. She underwent chest X-ray and ultrasound abdomen along with the clinical examination and routine laboratory investigations. She was then subjective to fine-needle aspiration cytology (FNAC) of the largest lymph node. FNAC was reported as features suggestive of non-Hodgkin lymphoma (NHL). Subsequent lymph node biopsy supplemented by IHC confirmed the diagnosis of PBL. On histopathological examination (HPE), there was a diffuse proliferation of predominantly large cells with an eccentric nucleus, having clumped chromatin and a basophilic moderate amount of cytoplasm. These cells expressed immunophenotype of plasma cells, that is, positive for CD138, MUM1, CD79a, and EMA. EBER-ISH was also positive on IHC. Ki67 proliferative index was high (50–60%). These cells were negative for CD45, CD3, CD20, Pax5, CD 56, CD30, Bcl-2, Bcl-6, Alk-1, and HHV8 (Fig. 1a-i). Her HIV status was evaluated and she was found to be HIV seronegative. During further workup, the bone marrow was found to be negative for lymphoma involvement and serum electrophoresis did not show M-protein spike.

Case 2

A 20-year-old young male presented with a chief complaint of a skin lump over the chest wall for the past few weeks which was slightly tender and increasing in size. There was a history of on and off mild grade fever for the past 1 month. The skin had slight reddish discoloration, and on examination, these were found to be indurated. The area of ill-defined induration and thickening measured 2 × 1.5 × 1 cm and was fixed to the overlying skin. There were no palpable axillary or cervical lymph nodes. On subsequent clinical workup, he was found to be HIV seronegative with unremarkable bone marrow and no M-protein spike on serum electrophoresis. The skin lesion was subjected to biopsy. Histopathological slides showed diffuse proliferation of large atypical plasmacytoid cells infiltrating skin. IHC study showed these cells to be positive for CD138, MUM1, CD79a, EMA, and EBER-ISH. Ki67 proliferative index was high (45–50%). CD45, CD3, CD20, Pax5, CD 56, CD30, Bcl-2, Bcl-6, Alk-1, and HHV8 were negative in tumor cells (Fig. 2a-i).

Case 3

A 74-year-old elderly male had a soft-tissue lump over the chest wall. Furthermore, there was mild pain at the site of the lump. The patient gave a history of recent mild fever for 3–4 days which was not recorded. At the time of presentation, the patient was afebrile. No history of trauma was present. On examination, there was a 2.5 × 2.0 × 1.5 cm mildly tender, subcutaneous lump over the chest wall which was fixed to the underlying bone but the overlying skin was free and unremarkable. The X-ray showed a subcutaneous soft-tissue lesion abutting the underlying rib with erosion. The lesion was subjected to the first FNAC which was reported as atypical lymphoid proliferation requiring biopsy/HPE study. On

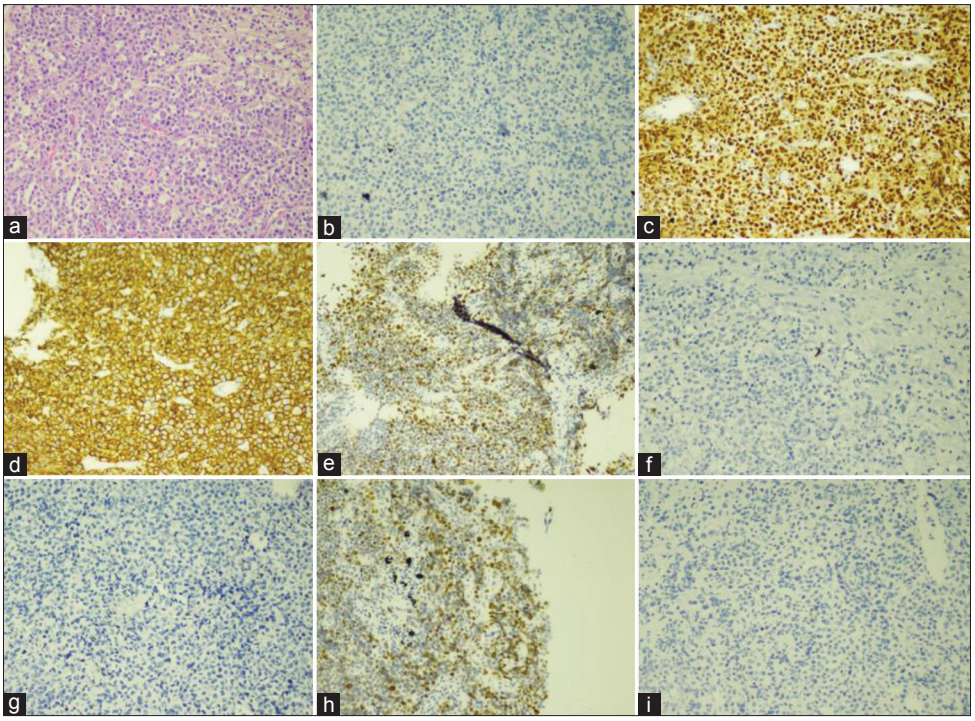

Figure 1: (a) Sheets of round to oval shaped tumor cells × 400-Hematoxylin and Eosin stain; (b) IHC for CD20 is negative in tumor cells × 400; (c) IHC for MUM1 is positive in tumor cells × 400; (d) IHC for CD138 is positive in tumor cells × 400; (e) IHC for EBER-ISH is positive in tumor cells x400; (f)IHC for CD56 is negative in tumor cells × 400; (g) IHC for ALK1 is negative in tumor cells × 400; (h) IHC for Ki67 shows high proliferative index in tumor cells x400; (i) IHC for HHV8 is negative in tumor cells × 400 (Case 1)

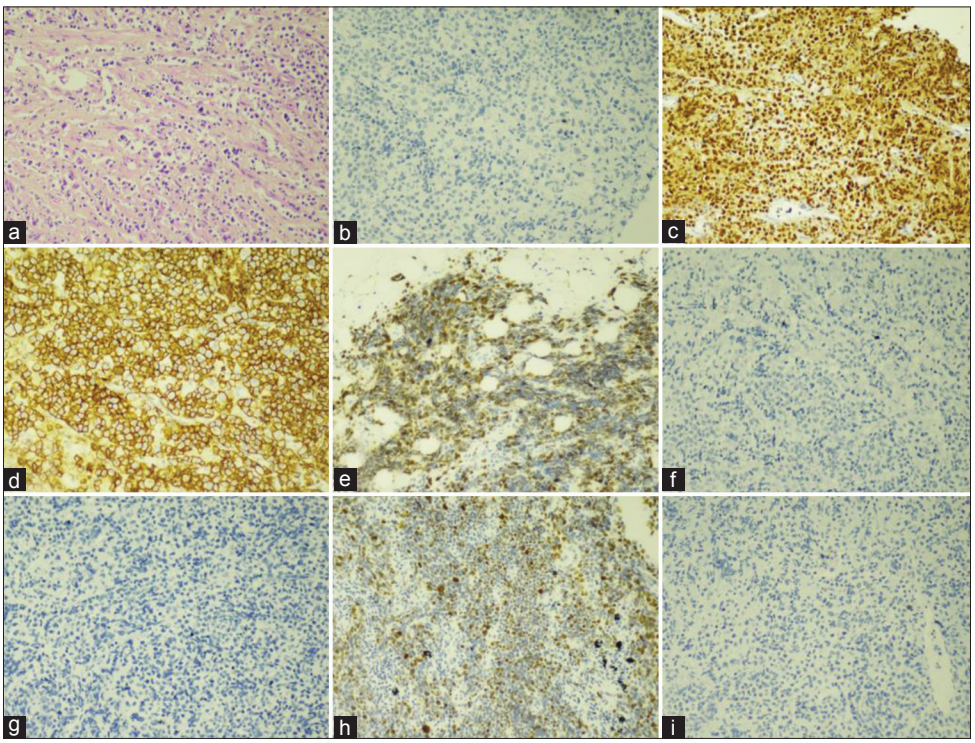

Figure 2: (a) Sheets of round to oval shaped tumor cells × 400-Hematoxylin and Eosin stain; (b) IHC for CD20 is negative in tumor cells × 400; (c) IHC for MUM1 is positive in tumor cells × 400; (d) IHC for CD138 is positive in tumor cells × 400; (e) IHC for EBER-ISH is positive in tumor cells × 400; (f) IHC for CD56 is negative in tumor cells × 400; (g) IHC for ALK1 is negative in tumor cells × 400; (h) IHC for Ki67 shows high proliferative index in tumor cells × 400; (i) IHC for HHV8 is negative in tumor cells × 400 (Case 2)

HPE, there was a diffuse proliferation of large round tumor cells with plasmablastic to immunoblastic morphology. IHC showed tumor cells to be positive for CD138, MUM1, CD79a, EMA, and EBER-ISH. Ki67 proliferative index was high (50–60%). CD45 was found to be positive. However, CD3, CD20, Pax5, CD 56, CD30, Bcl-2, Bcl-6, Alk-1, and HHV8 were negative in tumor cells (Fig. 3a-i). A diagnosis of PBL was then rendered. Bone marrow aspiration done thereafter was unremarkable except for

microcytic hypochromic anemia. Serum electrophoresis was negative for the M-protein spike.

Case 4

A 75-year-old elderly male presented with complaints of dyspepsia and bloating. After routine workup, the patient was undertaken for upper gastrointestinal endoscopy where the gastric mass lesion was visualized and subjected to biopsy for HPE study. Scanty tumor tissue was reported as a round cell tumor consistent with NHL. On IHC, tumor cells were positive for CD138, MUM1, CD79a, EMA, and EBER-ISH. Ki67 proliferative index was high (60–65%). CD45, CD3, CD20, Pax5, CD 56, CD30, Bcl-2, Bcl-6, Alk-1, and HHV8 were negative in tumor cells (Fig. 4a-i). Overall morphological and IHC findings were consistent with PBL. The patient was HIV seronegative. He had no bone marrow involvement by lymphoma in subsequent study. M-protein was not found on serum electrophoresis.

DISCUSSION

PBL is a rare and aggressive type of B cell NHL with a complex list of differential diagnoses which needs quick and accurate diagnosis for subsequent management with customized treatment modalities. PBLs have traditionally been described in HIV patients typically occurring as oral/mucosal lesions. However, other immunocompromised states, including transplantation, have recently been shown to cause similar lymphomas [7].

Morphologically, PBL is characterized by a monomorphic proliferation of round to oval cells with abundant cytoplasm, eccentric nuclei, and prominent central nucleoli (resembling immunoblasts). A perinuclear hof is sometimes seen. The background infiltrate consists of small mature lymphocytes with apoptotic bodies, mitotic figures, and tingible body macrophages.

However, the immunophenotype of these cells is that of a plasmacyte. PBL is typically negative for CD45, CD20, CD79a, and PAX5 while VS38c, CD38, CD138, and MUM1 seem to be almost universally expressed. CD56 negativity along with EBER expression [8] helps to differentiate it from the blastic transformation of plasmacytoma (PCM). EBER is present almost universally in PBLs. In a study by Vega *et al*. [9], EBER expression was the only difference between PBL and plasmablastic PCM. Kane *et al*. [10] proposed minimal morphological and immunohistochemical criteria for the diagnosis of PBL, which includes CD20 negativity and positivity for CD138/CD38 and/or MUM1, along with a high proliferation rate based on Ki-67 >60% and positive EBER expression.

The role of Epstein–Barr virus (EBV) in PBL is well established. EBV preferentially infects B cells, where its genome can lie dormant as an episome. In healthy immunocompetent individuals, activated T cells control the proliferation of infected

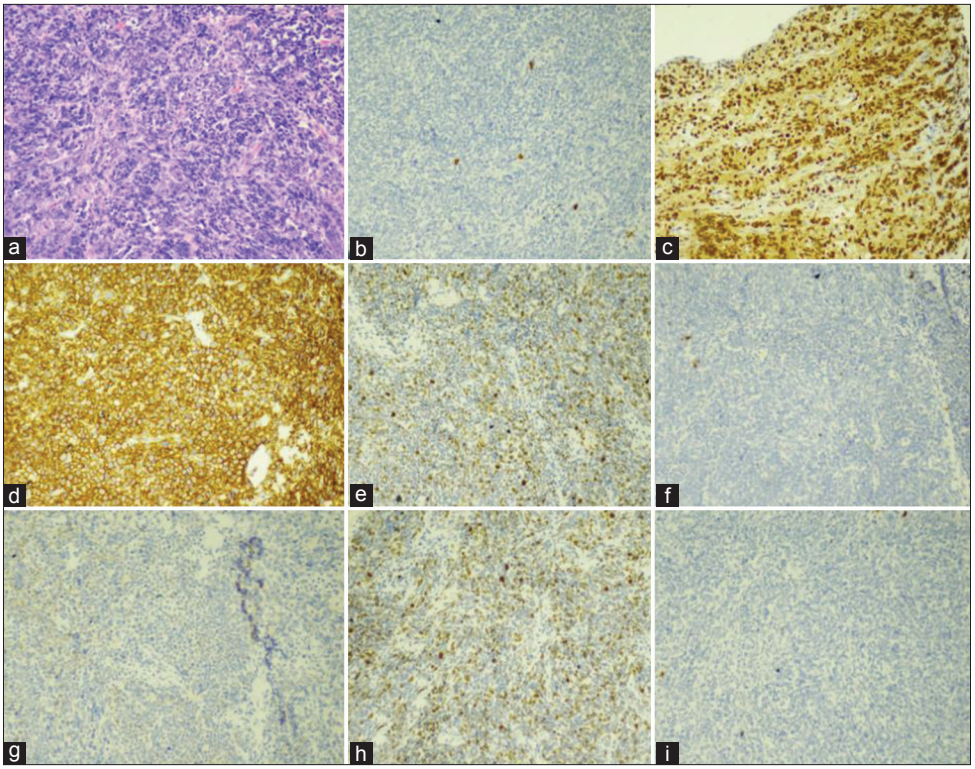

Figure 3: Figure 3: (a) Sheets of round to oval shaped tumor cells × 400-Hematoxylin and Eosin stain; (b) IHC for CD20 is negative in tumor cells × 400; (c) IHC for MUM1 is positive in tumor cells × 400; (d) IHC for CD138 is positive in tumor cells × 400; (e) IHC for EBER-ISH is positive in tumor cells × 400; (f) IHC for CD56 is negative in tumor cells × 400; (g) IHC for ALK1 is negative in tumor cells × 400; (h) IHC for Ki67 shows high proliferative index in tumor cells × 400; (i) IHC for HHV8 is negative in tumor cells × 400 (Case 3)

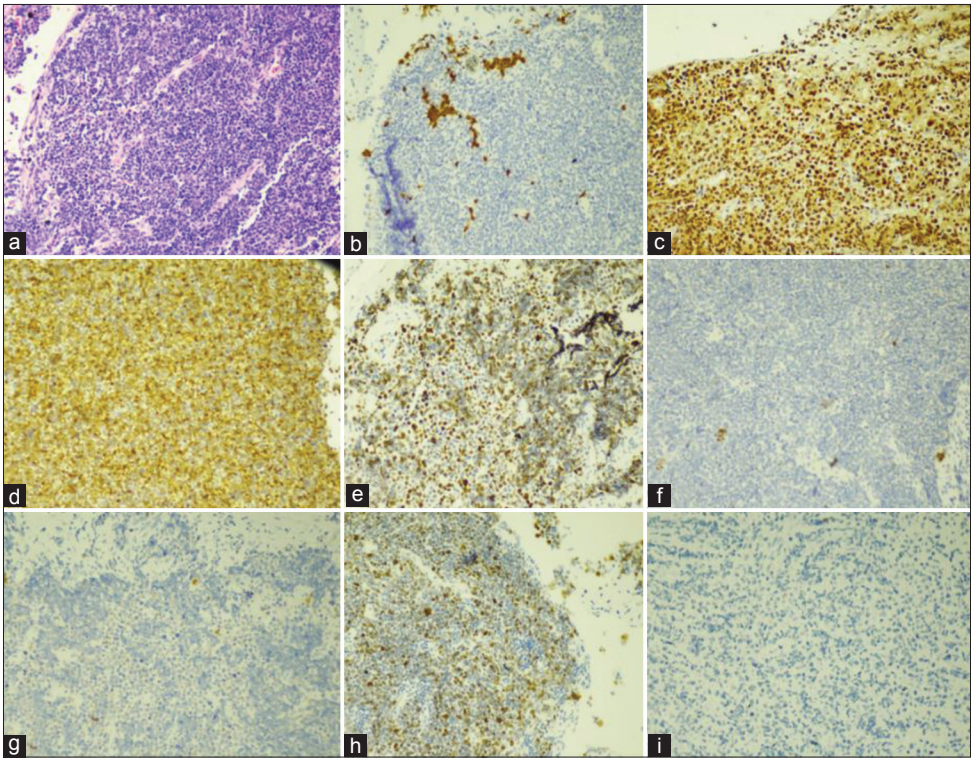

Figure 4: (a) Sheets of round to oval shaped tumor cells × 400-Hematoxylin and Eosin stain; (b) IHC for CD20 is negative in tumor cells × 400; (c) IHC for MUM1 is positive in tumor cells × 400; (d) IHC for CD138 is positive in tumor cells × 400; (e) IHC for EBER-ISH is positive in tumor cells × 400; (f) IHC for CD56 is negative in tumor cells × 400; (g) IHC for ALK1 is negative in tumor cells × 400; (h) IHC for Ki67 shows high proliferative index in tumor cells × 400; (i) IHC for HHV8 is negative in tumor cells × 400 (Case 4)

B cells and eliminate them. However, immunocompromised patients are at risk of uncontrolled proliferation of infected B cells. These patients need customized treatment modalities including reduced immunosuppression as well as chemotherapy (CHOP)-based CHOP with or without rituximab.

PBL remains a diagnostic challenge because of overlapping with the close differentials of PCM and other B cell NHL having plasma cell morphology. Rendering the correct diagnosis can be quite difficult in the absence of an exhaustive integration of clinical, morphological, phenotypic, and molecular features. The diagnosis of such neoplasms can be even more challenging in the setting of extraoral localizations and in immunocompetent patients. Immunoblastic diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma can be excluded on the basis of the characteristic CD20 and LCA positivity in combination with negative plasma cell markers such as CD138.

PBL is distinguished from anaplastic lymphoma kinase (ALK)-positive DLBCL by its lack of expression of the ALK protein, and the absence of HHV8 coinfection distinguishes PBL from primary effusion lymphoma (PEL) which usually manifests as pleural or pericardial effusion and is rarely associated with lymphadenopathy or mass lesions.

Similar to previously reported studies, the main differential diagnosis in our study was extramedullary plasmablastic PCM. PCM rarely presents *de novo* as high-grade lesions and the association with EBV and HIV, although previously reported, remains quite rare. Further CD56 negativity in our cases reinforces the diagnosis of PBL over PCM.

CONCLUSION

PBL has a predilection for immunocompromised individuals based on its prevalence in both HIV-positive patients and in those undergoing solid organ transplantation. PBL is best classified as a form of DLBCL. However, based on immunohistochemical data, PBL is more similar to an extramedullary PCM. PBL is a therapeutic challenge with a clinical course characterized by a high rate of relapse and death. Overall, PBL is associated with early dissemination, poor response to therapy, and limited survival. Therefore, early and accurate diagnosis is all the more critical in ensuring targeted therapy to the patients.

REFERENCES

1. Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, *et al*. Plasmablastic lymphomas of the oral cavity: A new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413-20.
2. Swerdlow SH, Harris NL. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008. p. 441.
3. Tsao L, Hsi ED. The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. Arch Pathol Lab Med 2007;131:1209-18.
4. Nicol I, Boye T, Carsuzaa F, Feier L, Villette AM, Xerri L, *et al*. Post-transplant plasmablastic lymphoma of the skin. Br J Dermatol 2003;149:889-91.
5. van Vrancken MJ, Keglovits L, Krause J. Plasmablastic lymphoma following transplantation. Proc (Bayl Univ Med Cent) 2013;26:152-5.
6. Hartmann C, Schuchmann M, Zimmermann T. Posttransplant lymphoproliferative disease in liver transplant patients. Curr Infect Dis Rep

2011;13:53-9.
7. Colomo L, Loong F, Rives S, Pittaluga S, Martinez A, Loopen-Guillermo A, *et al*. Diffue large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 2004;28:736-47.
8. Johnson LR, Nalesnik MA, Swerdlow SH. Impact of Epstein-Barr virus in monomorphic B-cell posttransplant lymphoproliferative disorders: A histogenetic study. Am J Surg Pathol 2006;30:1604-12.
9. Vega F, Chang CC, Medeiros LJ, Udden MM, Cho-Vega JH, Lau CC. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol 2005;18:806-15.
10. Kane S, Khurana A, Parulkar G, Shet T, Prabhash K, Nair R, *et al*. Minimum diagnostic criteria for plasmablastic lymphoma of oral/sinonasal region encountered in a tertiary cancer hospital of a developing country. J Oral Pathol Med 2009;38:138-44.

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