Plasmablastic lymphoma in the ileum

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Plasmablastic lymphoma (PBL) is classified by the World Health Organization as a distinct type of diffuse large B-cell non-Hodgkin lymphoma, which is characterized by plasma cell differentiation and immunoblastic cell morphology.[1] PBL usually develops in middle-aged adults, with the age at onset in one large series ranging from 35 to 55 years with male predominance.[2-4] Although PBL has a strong affinity for the oral cavity, especially in HIV-positive patients, extraoral sites have also been reported.[5-10] In this report, we describe an unusual case of PBL presented as multiple masses mostly located at the ileum, which resulted in small bowel obstruction.

Case presentation

A 54-year-old man was admitted to the emergency department after he had experienced a week of intermittent nausea, vomiting, diarrhea, and abdominal pain. The patient, who was on hemodialysis, had a medical history significant for end-stage renal disease after kidney transplantation, which had been rejected and required removal of the transplanted kidney. Physical examination revealed peritonitis signs. Computed tomography of the abdomen and pelvis showed a probable distal small bowel obstruction (Figure 1). The patient was hypotensive and febrile. He was also diagnosed as having septic shock and started on aggressive intravenous fluids and broad-spectrum antibiotics.

In addition to undergoing the examination and tests, the patient was taken to the operating room for exploratory laparotomy. Intraoperatively, the surgeon found a large tumor and several small tumors that were adherent to the small bowels and mostly located at the ileum, which resulted in the bowel obstruction. Frozen section identified possible lymphoma rather than gastrointestinal stromal tumor from the resected mass. Microscopic examination (Figure 2; p 84) revealed proliferation of large lymphoid cells with irregular, eccentrically placed nuclei and immunoblastic features (abundant basophilic cytoplasm with occasional perinuclear hofs, vesicular chromatin, and prominent central nucleoli). Frequent mitoses, apoptosis, and focal necrosis were also seen, appearing as tingible body macrophages forming a "starry sky" appearance on low power.

Flow cytometry detected 2 distinct CD45-negative populations. It was also noted that 1 population was immunophenotypically positive for CD38 and CD138. Other tested markers were negative, including paired box gene-5 (PAX-5), lymphoid markers such as BCL-6, CD79A, CD2-4-5-7-8-10-20-34-56-57, and CD117. Staining for Epstein-Barr virus (EBV) by in situ hybridization (EBV-encoded RNA or EBER) was positive; human herpesvirus-8 (HHV-8) by immunohistochemistry was negative. The proliferation index by Ki-67 immunohistochemistry was close to 100%. The patient's serum beta-2 microglobulin level was highly elevated at 24.3 mcg/mL (normal, < 2.4 mcg/mL), with mild elevation of gamma globulin due to mild elevation of immunoglobulins (IgGs). The results of a serum protein electrophoresis test showed no M-spike, the HIV antibody test was negative, a and molecular gene rearrangement analysis by the polymerase chain reaction showed no T- or B-cell clonality. Kappa and lambda immunohistochemistry showed scattered polytypic plasma cells.

The patient was diagnosed with PBL on the basis of his clinical presentation, morphology, and immunophenotype. A bone marrow biopsy was performed for staging purposes and showed negative for monoclonality or aberrant antigenic expression by immunophenotypic flow cytometry. Blasts were not increased. Fluorescence in situ hybridization was also negative for myeloma.

Further staging work-up, which included computed tomography of the patient's neck and tho-

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rax, found mediastinal and right hilar lymphadenopathy. On the basis of this finding, the patient was staged as Ann Arbor IIIB (Table 1; p 85). (Although the Ann Arbor System was originally designed for Hodgkin lymphoma, it is also used for non-Hodgkin lymphomas.) B symptoms included fatigue, weight, and appetite loss.

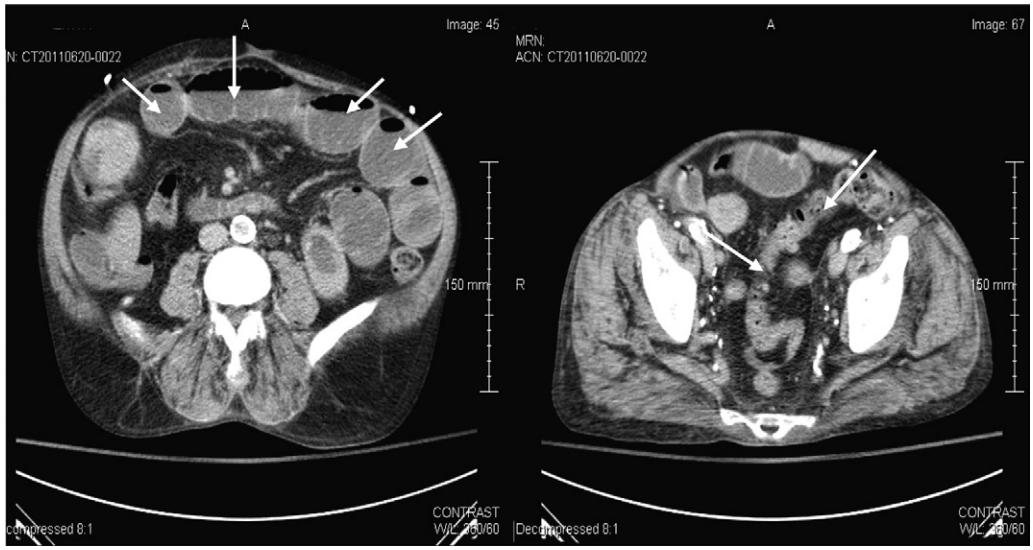

FIGURE 1 Dilated loops of small bowels in the upper- to midpelvis (a) and sigmoid diverticulosis (b).

The patient was started on the combination chemotherapy regimen cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP). After he had completed 3 cycles of chemotherapy, we repeated computed tomography of the thorax, abdomen, and pelvis, which showed a significant improvement of the hilar and mediastinal as well as pelvic and para-aortic lymphadenopathy. Finally, he was scheduled to receive 6 complete cycles of multiagent chemotherapy.

Discussion

PBL is classified by the World Health Organization as a distinct type of diffuse large B-cell non-Hodgkin lymphoma, which is characterized by plasma cell differentiation and immunoblastic cell morphology.[1] It was first described by Delecluse and colleagues as highly malignant diffuse large B-cell lymphoma with unique immunohistologic features.[11] PBL usually develops in middle-aged adults, with the age at onset in 1 large series ranging from 35 to 55 years[2] and is more prevalent among men,[2-4] although it can also occur in the pediatric age group.[12] Although PBL has a strong affinity for the oral cavity, especially in HIV-positive patients, extraoral sites including the stomach, lung, cervical lymph node, cecal, jejunal anorectal region, and paranasal sinuses have also been reported.[5-10] Indeed, several PBL cases in the oral cavity have been reported in HIV-seronegative patients.[13,14]

Some researchers have divided PBL into 3 categories.[15-17] The first type is PBL of oral mucosa. These lymphomas have a monomorphic group of plasmablasts with no or minimal plasmacytic differentiation. They are found mostly in the oral cavity but may also occur in other nodal or extranodal regions. The second type is PBL with plasmacytic differentiation. These lymphomas are extranodal and consist predominantly of plasmablasts but with more differentiation to mature plasma cells. The third type of PBL is that associated with Castleman disease (giant or angiofollicular lymph node hyperplasia, lymphoid hamartoma, angiofollicular lymph node hyperplasia) and is typically nodal or splenic.[18,19] This entity has also been described after renal and cardiac transplantation.[20,21]

As was the case with our patient, it has been established that there is an increased incidence of lymphoproliferative disorders in transplant recipients of solid organs, with frequent association with EBV. The overall incidence of posttransplant lymphoproliferative disorders (PTLDs) is 1.4%-1.7%. The incidence for kidney transplantation is 0.3%-3%.[3] With modern regimens in renal and heart transplantation, PTLDs develop at medians of 1.5-17 months.[22] As transplantation rates and successes increase, it is not surprising that more PTLDs are being seen, and that the spectrum of morphology is expanding.

Histologic features

Cellular proliferation of large lymphoid cells is distributed in a sheet-like growth pattern. In our patient, the sheets of tumor cells were interspersed by tingible body macrophages, resulting in a "starry-sky" appearance on low power examination. The tumor cells were evocative of immunoblasts and plasmablastic differentiation in the form of a round to oval shape with eccentrically placed nuclei and abundant basophilic cytoplasm. Mitotic index is usually very high (more than 4 mitotic figures per high-power field).

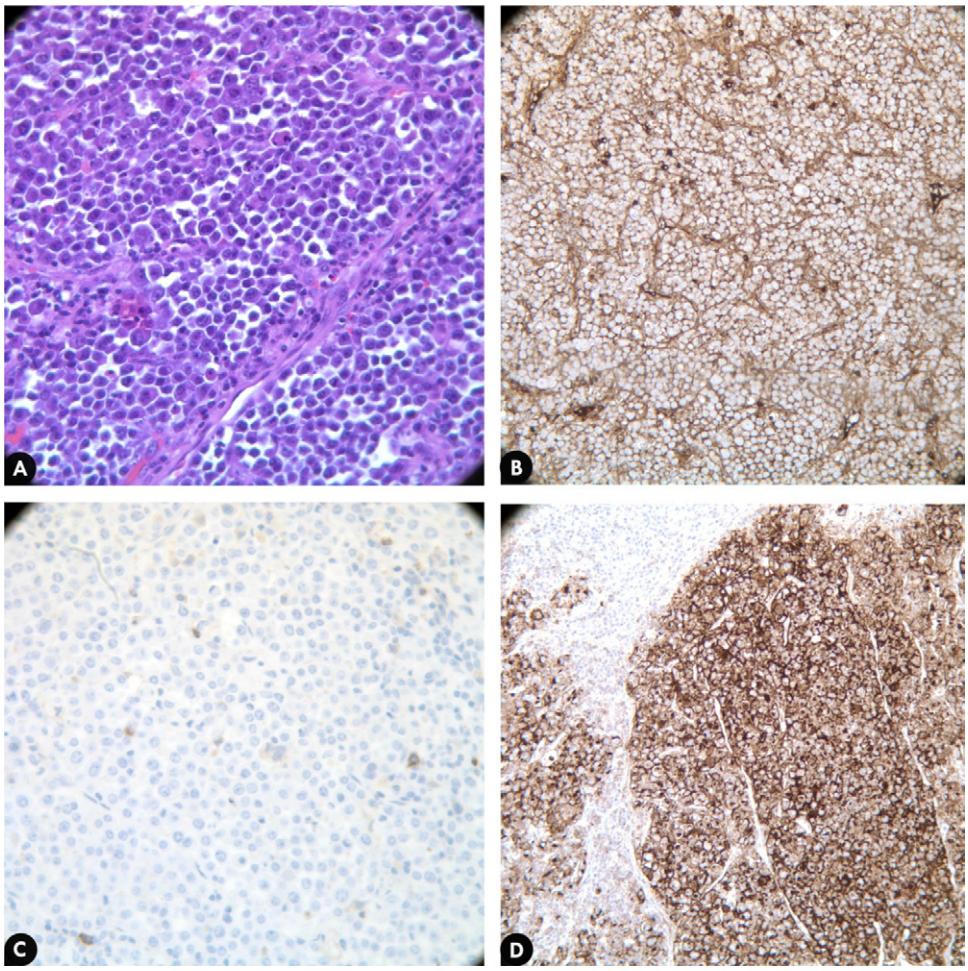

FIGURE 2 The histopathologic features of plasmablastic pymphoma: Hematoxilin-eosin section of the small bowel reveals a diffuse plasmablastic infiltrate with abundant cytoplasm, round nuclei, and occasionally central locating nucleoli (A; H&E stain, ×200), kappa immunohistochemical stain (B; ×100), lambda immunohistochemical stain (C; ×2000), CD138 immunohistochemical stain (D).

Immunohistochemical findings and main differential diagnoses

The strong and diffuse reactivity with CD38 and CD138 confirms that the tumor cells are of plasma cell differentiation. PBLs typically either fail to or only weakly express CD20 and CD45RB, and variably express CD79a and PAX5.[3] In our case, these tumor markers were negative. A possible explanation is that, with unusual differentiation pattern such as PBL, tumors may be maintained. The frequent expression of Bcl-6 in diffuse large B-cell lymphomas (DLBCLs) can also help differentiate tumors from PBL, which typically have faint or no staining for this antigen.[2]

Other B-cell markers such as PAX5 and CD20 may help differentiate between PBL and DLBCL. Findings from a study of 35 PBL cases and 111 conventional DLBCL cases showed that the use of a limited combination of immunohistochemical markers (PAX5 and CD20, or PRDM1/BLIMP1 and XBP1) may enable the differentiation between PBL and DLBCL. This panel has reflected different stages of the gradual terminal differentiation of B cells (Figure 3; p 86).[4]

Another differential diagnosis that should be considered is that of extramedullary plasmablastic myeloma (PBM). Although it is difficult to differentiate between PBL and PBM, it is important to do so because the treatment for each is significantly different.[16] The distinction between PBL and PBM often depends on the clinical presentation—PBM manifests in bone marrow, whereas PBL prefers the oral cavity in HIV-positive patients and extramedullary regions. Immunosuppression is more frequently associated with PBL (related to HIV, EBV, and HHV-8). The detection of paraproteinemia in the blood or excess light chains (Bence-Jones proteins) in the urine, and hypercalcemia favors the diagnosis of PBM over PBL. However, several tumor markers may be expressed in both entities, such as CD79a, which is an antibody to the B-cell antigen receptor component immunoglobulin alpha from the Mb-1 gene (negative in our case), the VS38c (a p63 protein homolog found in the rough endoplasmic reticulum), CD38, and CD138.

Conversely, both PBL and PBM are Bcl-6 negative. The expression of PAX-5, which is a B-cell specific transcription factor detectable at the pro-B-cell stage before the plasma cell stage, is generally absent in plasma cell malignancies and present in nearly all cases of DLBCL. However, in PBL, its expression may be negative or weak. Although CD56 (negative, in our case) is specific for plasma cell myelomas, Colomo and colleagues found it to be positive in 1 out of 18 cases of PBL.[15]

Recently, a new marker called peroxiredoxin I, which is expressed in the terminally differentiated plasma cells

TABLE 1 Ann Arbor Staging System

Stage I
I if involvement of a single lymph node region
IE if involvement of a single extralymphatic organ or site
Stage II
II if two or more lymph node regions on same side of diaphragm
IIE if localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm
Stage III
III if Involvement of lymph node regions on both sides of the diphragm
IIIS if spleen involved
IIIE if extralymphatic site involved
Stage IV
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement
Systemic Symptoms in 6 months preceding admission
Fever, night sweats, 10% weight loss
A = absent
B = present
Extranodal sites are also designated
M+ = marrow
L+ = lung
H+ = liver
P+ = pleura
O+ = bone
D+ = skin and subcutaneous tissue

but not in B-lymphocytes, has been identified as specific for plasma cell neoplasms. A study showed that all myeloma cases, including plasmablastic, were positive for peroxiredoxin I, compared with all the PBL cases that tested negative for this protein.[23]

Role of EBV

EBV may play a part in tumorgenesis in some PBL cases, though its role is unclear. It has been demonstrated that EBV is involved in the down-regulation of the B-cell identity program through different mechanisms such as PAX5 promoter hypermethylation.[24] In addition, this does not apply to all cases of PBL, as demonstrated in several reported cases of EBV-negative PBLs.[3,11,25,26]

EBV positivity is more frequently associated with immunosuppression-related lymphoma. Indeed, the EBV positivity of the PBL in our case further supported that the patient may have had a state of relative immunosuppression when he was the recipient of renal allograft before it failed.

Role of HHV-8

Evidence supporting a pathogenic role for HHV-8 in promoting lymphoma cell growth has been described almost exclusively in HIV-related cases of PBL.[18,27] In these cases, an interaction between HIV and HHV-8 has been suggested, whereby viral interleukin-6 may provide a mitogenic stimulus that result in enhanced proliferation of HIV in patients co-infected with both viruses. In addition, the stimulus supports the survival of infected lymphocytes, thus predisposing them to transforming events.[28,29] Of note, primary effusion lymphoma (PEL) is another type of non-Hodgkin lymphoma primarily found in the distal digestive tract and pleural cavity. It also has immunophenotypic and morphological characteristics similar to PBL, but is consistently HHV-8 positive.[27] Our HIV-negative, EBV-positive patient had no evidence of infection by HHV-8.

Chemotherapy and prognosis

Current guidelines for the treatment of lymphoma in early stage include CHOP or similar chemotherapy regimens, with or without local radiation therapy. In case studies of HIV-negative patients with PBL, all, including our patient, received CHOP. Despite our patient's advanced disease stage at presentation, he initially responded well to the lymphoma-specific combination chemotherapy and was still alive 6 months after the initial diagnosis. However, published data has indicated that these tumors are aggressive, are often resistant to therapy, and can be rapidly fatal.[30] Other data have shown that PBL carries a poor prognosis, with a median survival of about 12 months in HIV-negative patients.[11,21,31] The biological explanation for the poor response of PBLs to current immunochemotherapies with monoclonal antibodies against CD20 such as rituximab, might be related to the partial or complete loss of surface B-cell markers.[32]

It has been shown that outcomes in HIV-positive patients with PBL who were on antiviral therapy while receiving chemotherapy are better than outcomes in HIV-negative patients with PBL.[21,31] Developers of future therapies for PBL should consider the infection of lymphoma cells with EBV and possibly HHV-8 and the similarities of those cells to plasma cells, and should target new therapies to act on those specific features.

Conclusion

We report a case of a patient with PBL, an aggressive type of non-Hodgkin lymphoma that is usually associated with significant and documented immunosuppression. This type of suppression can occur in immunocompetent individuals, most commonly in the gastrointestinal tract.

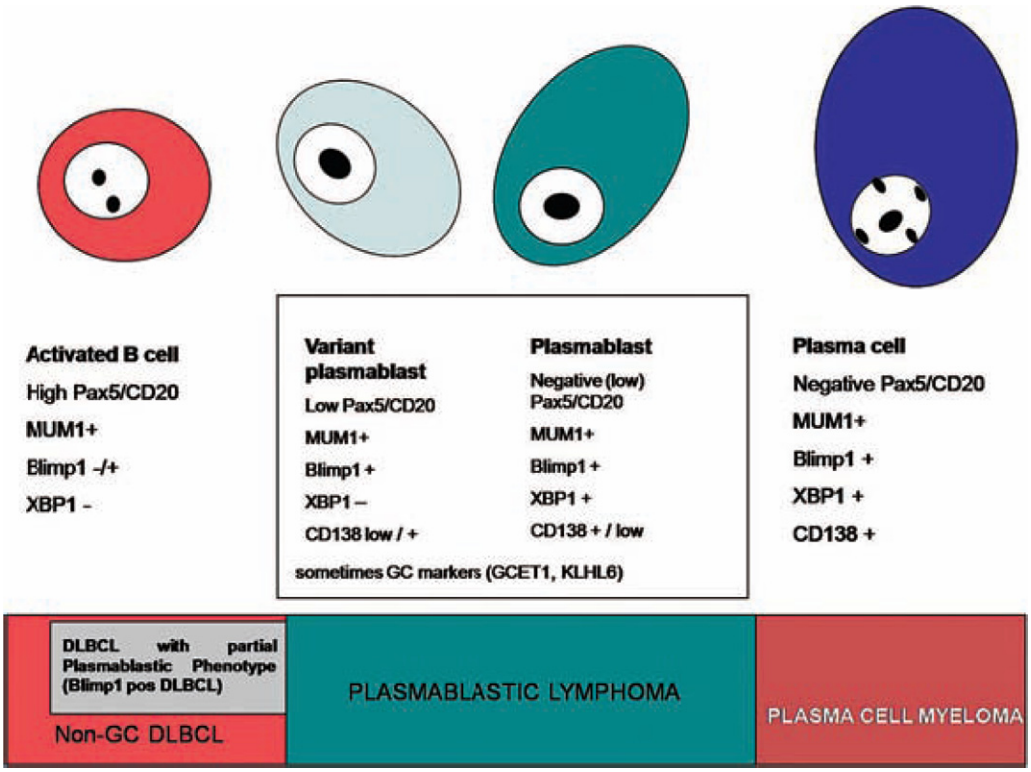

FIGURE 3 Use of a panel including PAX5&CD20, PRDM1/BLIMP1 and XBP1s allows a definition of a plasmablastic immunophenotype, which is variably expressed in PBL cases. The varying extent of this differentiation defines a spectrum of lesions that ranges from conventional DLBCL to plasmablastic lymphoma and identifies a group of aggressive large B-cell lymphoma tumors with immunophenotypic features intermediate between those of DLBCL and plasmablastic lymphoma.

Biopsy results that show diffuse infiltrative growth, brisk mitotic rate, and necrosis are consistent with the classification of PBL as a high-grade malignant lymphoma. Because PBL does not express the more common lymphoid and/or B-cell markers, it is understandable they may be mistaken for other B-cell tumors or poorly differentiated carcinoma. Acknowledgement of this entity by the pathologist and clinician is essential in establishing the correct diagnosis and treatment of the patient.

References

1. Sabattini E, Bacci F, Sagramoso C, Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. *Pathologica*. 2010;102(3):83-87.
2. Folk GS, Abbondanzo SL, Childers EL, Foss RD. Plasmablastic lymphoma: a clinicopathologic correlation. *Ann Diagn Pathol*. 2006;10(1):8-12.
3. Borenstein J, Pezzella F, Gatter KC. Plasmablastic lymphomas may occur as post-transplant lymphoproliferative disorders. *Histopathology*. 2007;51(6):774-777.
4. Montes-Moreno S, Gonzalez-Medina AR, Rodriguez-Pinilla SM, et al. Aggressive large B-cell lymphoma with plasma cell differentiation: immunohistochemical characterization of plasmablastic lymphoma and diffuse large B-cell lymphoma with partial plasmablastic phenotype. *Haematologica*. 2010;95(8):1342-1349.
5. Brahmania M, Sylwesterowic T, Leitch H. Plasmablastic lymphoma in the ano-rectal junction presenting in an immunocompetent man: a case report. *J Med Case Reports*. 2011;5:168.
6. Mihaljevic BS, Todorovic MR, Andjelic BM, Antic DA, Perunicic Jovanovic MD. Unusual presentation of gastric plasmablastic lymphoma in HIV-negative patient. *Med Oncol*. 2012;29(2):1186-1189.
7. Sun J, Medeiros LJ, Lin P, Lu G, Bueso-Ramos CE, You MJ. Plasmablastic lymphoma involving the penis: a previously unreported location of a case with aberrant CD3 expression. *Pathology*. 2011;43(1):54-57.
8. Hatanaka K, Nakamura N, Kishimoto K, Sugino K, Uekusa T. Plasmablastic lymphoma of the cecum: report of a case with cytologic findings. *Diagn Cytopathol*. 2011;39(4):297-300.
9. Cha JM, Lee JI, Joo KR, et al. A case report with plasmablastic lymphoma of the jejunum. *J Korean Med Sci*. 2010;25(3):496-500.
10. Lim JH, Lee MH, Lee MJ, et al. Plasmablastic lymphoma in the anal canal. *Cancer Res Treat*. 2009;41(3):182-185.
11. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*. 1997;89(4):1413-1420.
12. Radhakrishnan R, Suhas S, Kumar RV, et al. Plasmablastic lymphoma of the oral cavity in an HIV-positive child. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100(6):725-31.
13. Guan, B, Zhang X, Hu W, et al. Plasmablastic lymphoma of the oral cavity in an HIV-negative patient. *Ann Diagn Pathol*. 2011;15(6):436-440.

14. Rao DD, Aggarwal N, Anehosur V, Doddihal H, Shiraganvi M, Gopalkrishnan K. Plasmablastic lymphoma of the oral cavity in immunocompetent patients: report of two cases. *Int J Oral Maxillofac Surg*. 2010;39(10):1036-1039.
15. Colomo L, Loong F, Rives S, et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. *Am J Surg Pathol*. 2004;28(6):736-747.
16. Teruya-Feldstein J. Diffuse large B-cell lymphomas with plasmablastic differentiation. *Curr Oncol Rep*. 2005;7(5):357-363.
17. Tavora F, Gonzalez-Cuyar LF, Sun CC, Burke A, Zhao XF. Extra-oral plasmablastic lymphoma: report of a case and review of literature. *Hum Pathol*. 2006;37(9):1233-1236.
18. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000;95(4):1406-1412.
19. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood*. 2002;99(7):2331–2236.
20. Nicol I, Boye T, Carsuzaa F, et al. Post-transplant plasmablastic lymphoma of the skin. *Br J Dermatol*. 2003;149(4):889-891.
21. Teruya-Feldstein J, Chiao E, Filippa DA, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIV-positive and -negative patients. *Ann Oncol*. 2004;15(11):1673-1679.
22. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. *Br J Haematol*. 2010;149(5):675-692.
23. Demasi P, Magalhães MH, Furuse C, Araújo NS, Junqueira JL, Araújo VC. Peroxiredoxin I is differentially expressed in multiple myelomas and in plasmablastic lymphomas. *Oral Dis*. 2008;14(8):741-746.
24. Tierney RJ, Kirby HE, Nagra JK, Desmond J, Bell AI, Rickinson AB. Methylation of transcription factor binding sites in the Epstein-Barr virus latent cycle promoter Wp coincides with promoter down-regulation during virus-induced B-cell transformation. *J Virol*. 2000;74(22):10468-10479.
25. Porter SR, Diz Dios P, Kumar N, Stock C, Barrett AW, Scully C. Oral plasmablastic lymphoma in previously undiagnosed HIV disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999;87(6):730-734.
26. Gaidano G, Cerri M, Capello D, et al. Molecular histogenesis of plasmablastic lymphoma of the oral cavity. *Br J Haematol*. 2002;119(3):622-628.
27. Boulanger E, Agbalika F, Maarek O, et al. A clinical, molecular and cytogenetic study of 12 cases of human herpesvirus 8 associated primary effusion lymphoma in HIV-infected patients. *Hematol J*. 2001;2(3):172-179.
28. Song J, Ohkura T, Sugimoto M, et al. Human interleukin-6 induces human herpesvirus-8 replication in a body cavity-based lymphoma cell line. *J Med Virol*. 2002;68(3):404-411.
29. Gage JR, Breen EC, Echeverri A, et al. Human herpesvirus 8-encoded interleukin 6 activates HIV-1 in the U1 monocytic cell line. *AIDS*. 1999;13(14):1851-1855.
30. Li CF, Ye H, Liu H, Du MQ, Chuang SS. Fatal HHV-8-associated hemophagocytic syndrome in an HIV-negative immunocompetent patient with plasmablastic variant of multicentric Castleman disease (plasmablastic microlymphoma). *Am J Surg Pathol*. 2006;30(1):123-127.
31. Flaitz CM, Nichols CM, Walling DM, Hicks MJ. Plasmablastic lymphoma: an HIV-associated entity with primary oral manifestations. *Oral Oncol*. 2002;38(1):96-102.
32. Johnson NA, Boyle M, Bashashati A, et al. Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. *Blood*. 2009;113(16):3773-3780.