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CASE REPORT

Epstein–Barr virus and human immunodeficiency virus-negative oral plasmablastic lymphoma

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Plasmablastic lymphoma (PBL) is an unusual subtype of human immunodeficiency virus (HIV)-related diffuse large B-cell lymphoma that was first described in the oral cavity. HIV-related lymphomas are frequently associated with Epstein–Barr virus (EBV). Recently, dual infection with EBV and human herpesvirus 8 (HHV8) has been demonstrated in PBL. So far, a few cases of PBL occurring in an HIV-negative patient have been documented and all of them were associated with immunosuppression status and/or EBV infection. Here we report a EBV and HHV8-negative oral PBL occurring in an immunocompetent HIV-negative male, which would be the first case. *J Oral Pathol Med* (2006) **35**: 382–4

Keywords: Epstein–Barr virus; human herpesvirus 8; human immunodeficiency virus; oral cavity; plasmablastic lymphoma

A previously healthy 66-year-old male visited the emergency room at the Chungbuk National University Hospital with post-operative gingival bleeding. In the morning of the day, he underwent drainage procedure due to clinical impression of gingival abscess at the local dental clinic. He reported no weight loss, fever or night sweats. The patient had no prior history of habitual drug abuse or homosexuality. In the course of 2 weeks follow-up, gingival swelling on the distal area of the left first molar of the mandible was growing to be a gingival mass, measuring about 2 cm in diameter. The mass was covered by intact mucosa and was non-tender on palpation (Fig. 1a). Panoramic X-ray (Fig. 1b) and computed tomography scan for mandible showed a soft tissue mass with partial destruction of the alveolar bone of the mandible and external resorption of the distal root of the left lower first molar. The rest of the head and neck examination was normal. He had no peripheral lymphadenopathy, organomegaly, or other remarkable findings. Most of the laboratory tests were within normal limits except for hemoglobin, 10.7 g/dl (13–17 g/dl) and lactate dehydrogenase, 567 IU/l (180–460 IU/l).

An incisional biopsy of the gingival mass was performed, followed by histopathologic examination, immunohistochemistry, *in situ* hybridization and polymerase chain reaction. Microscopically, the tumor was composed of diffuse sheets of highly atypical large cells with the intact overlying mucosa (Fig. 2a). Tumor cells had round to irregular nuclei, one or more distinct nucleoli, and moderate to abundant amphophilic cytoplasm. Many of the tumor cells had a flankly blastic cell morphology with eccentrically placed nuclei (Fig. 2b). There were frequent mitoses with atypical forms.

Immunohistochemical staining was carried out using formalin-fixed and paraffin-embedded tissue. The atypical large cells showed strong positivity for CD138 (Fig. 2c) and vimentin, weak positivity for leukocyte common antigen (LCA, CD45) and CD79a, and negativity for CD3, CD10, CD13, CD19, CD20, CD34, CD56, CD68, ALK1, cytokeratin, epithelial membrane antigen, S100 and HMB45. The stain for Ki-67 demonstrated nuclear staining in approximately 90% of the atypical cells. Based on the blastic morphology and CD138 expression, this tumor was consistent with plasmablastic lymphoma (PBL). *In situ* hybridization for Epstein–Barr virus (EBV) using the EBER-1 probe showed no evidence of EBV-specific RNA, and polymerase chain reaction for human herpesvirus 8 (HHV8) was negative. Serology was also negative for syphilis, hepatitis B and C virus as well as human immunodeficiency virus (HIV). The serum protein electrophoresis revealed normal findings. Bone marrow biopsy was performed and no tumor involvement was observed.

Comments

Plasmablastic lymphoma is a lymphoproliferative disorder that is considered a morphologic variant of diffuse large B-cell lymphoma (DLBCL), which occurs almost exclusively in HIV-positive patients and the oral cavity (1). However, unusual sites of PBL including the lung,

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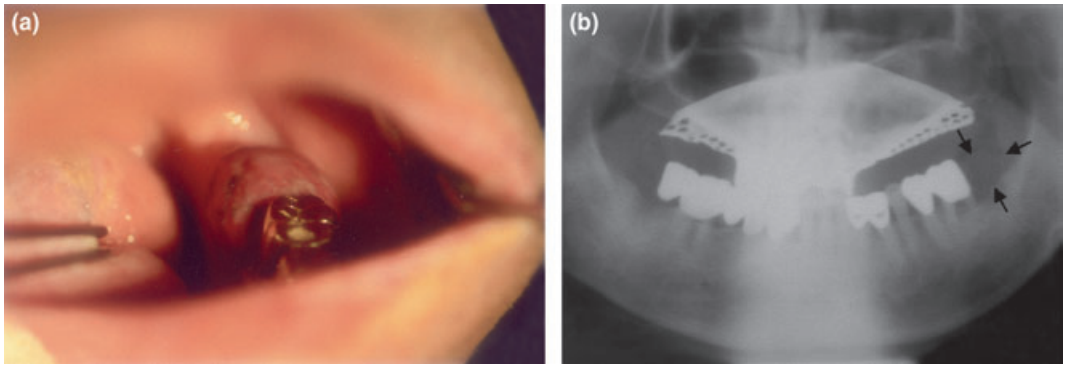

Figure 1 (a) A rapidly growing mass measuring about 2 cm in diameter is present in the left first lower molar area of the mandible. (b) A panoramic X-ray view reveals a relatively well-demarcated round osteolytic lesion.

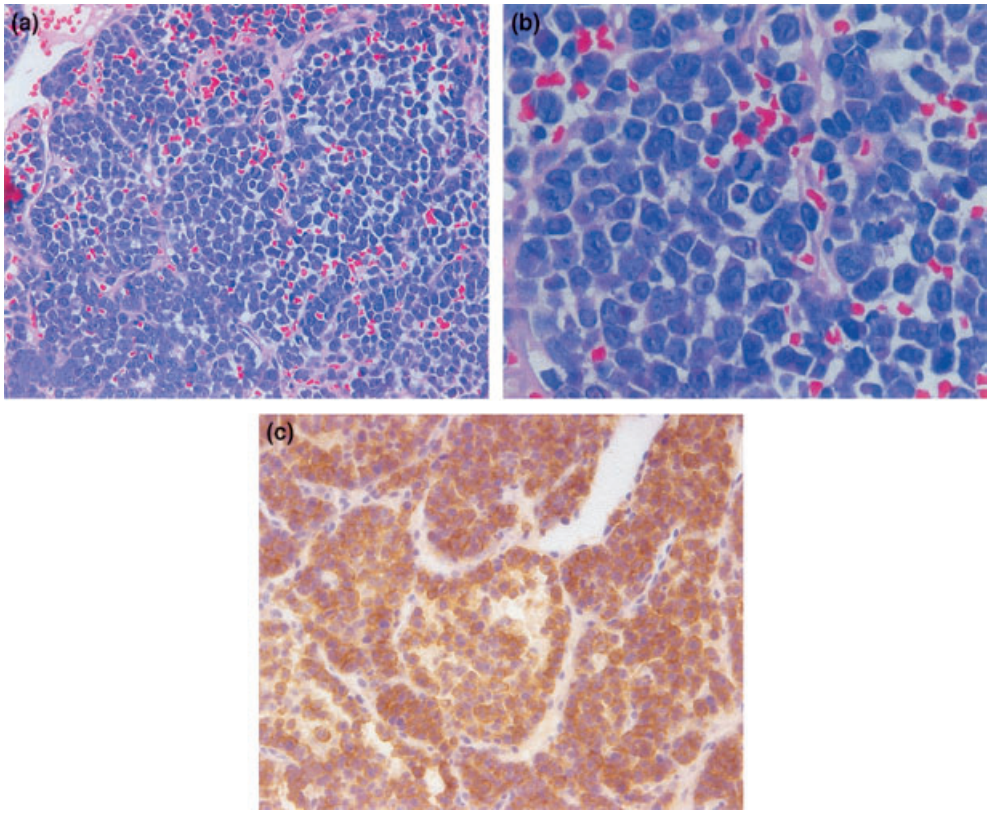

Figure 2 (a) The tumor is composed of diffuse sheets of highly atypical large cells (HE 200×). (b) The tumor cells have round to irregular and eccentrically placed nuclei, one or more distinct nucleoli and moderate to abundant amphophilic cytoplasm (HE 400×). (c) By immunohistochemistry, the tumor cells are strongly positive for CD138 (200×).

nasal cavity, stomach, skin and within sacrococcygeal cysts have been reported (2). PBL is characterized by diffused growth of large tumor cells with blastic morphology and numerous mitoses and expression of plasma cell-related antigen, CD38 and CD138.

Several tumor entities such as plasmacytoma, DLBCL of the immunoblastic type with plasmacytoid differentiation, Burkitt's lymphoma, metastatic undifferentiated carcinoma and metastatic melanoma should be considered in the diagnosis of PBL. The patient showed neither serum monoclonal protein nor bone marrow involvement. In addition, the blastic morphology with high rate of proliferation index as well as frequent mitotic figures would be unusual for plasmacytoma. Negative immunoreactivity of CD19 and CD20 and strong reactivity of the tumor cells with CD138 allowed to exclude the possibility of DLBCL and Burkitt's lymphoma. Moreover, no expression of epithelial and melanoma markers could lead to the diagnosis of PBL.

Because HIV-related lymphomas are frequently associated with EBV infection, it has been considered that EBV-specific RNAs in the neoplastic cells of some of PBL cases, in the frame of the immune deficiency, may play a role in the development of these tumors.

Recently, dual infection with EBV and HHV8 was reported in the tumor cells of PBL. It suggests that EBV and HHV8 expressions are cofactors in the development of PBL (2, 3). Till date, eight cases of PBL occurring in an HIV-negative individual have been documented and all of them were associated with immunosuppression status and/or EBV expression (2, 4).

In contrast to the previously reported cases, this case has unique features. First, it occurred in an HIV-negative individual. Second, the patient was not immunocompromised and had no antecedent medical illness with the exception of a history of hypertension. Third, there was no evidence of EBV and HHV8 infection. In this case, virus was not an etiologic agent, and it suggests that unknown causative factors other than EBV and HIV or immunosuppression also play a role in the tumorigenesis of PBL.

Therefore, this would be the first report of EBV and HHV8-negative oral PBL in an immunocompetent HIV-negative patient. The clinical course of this case was aggressive. The patient received five cycles of combination chemotherapy and radiotherapy. He died of the disease in 8 months after initial diagnosis. In HIV, EBV and HHV8 negative case, awareness and careful attention to the plasma-/immunoblastic morphology as well as expression of plasma cell-related antigens are needed to make a diagnosis of PBL.

References

1. 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**: 1413–20.
2. Verma S, Nuovo GJ, Porcu P, Baiocchi RA, Crowson AN, Magro CM. Epstein–Barr virus- and human herpesvirus 8-associated primary cutaneous plasmablastic lymphoma in the setting of renal transplantation. *J Cutan Pathol* 2005; **32**: 35–9.
3. Cioc AM, Allen C, Kalmar JR, Suster S, Baiocchi R, Nuovo GJ. Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. *Am J Surg Pathol* 2004; **28**: 41–6.
4. Scheper MA, Nikitakis NG, Fernandes R, Gocke CD, Ord RA, Sauk JJ. Oral plasmablastic lymphoma in an HIV-negative patient: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 198–206.