Lymphoid neoplasms of the oral cavity with plasmablastic morphology—a case series and review of the literature

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Plasmablastic lymphoma (PBL) is a rare aggressive variant of large B-cell lymphoma defined as a proliferation of large neoplastic plasmablasts/immunoblasts. PBL was first described as a distinct entity in a group of 16 patients with lymphoma of the oral cavity. Most patients are HIV-positive men. The disease has also been reported in other patient groups, often in association with primary or other acquired immunodeficiency. PBL shows a predilection for the oral cavity, although extraoral involvement also occurs. Because of its rarity, unique clinical features, and overlapping morphologic/immunophenotypic features, care must be taken to distinguish PBL from diffuse large B-cell lymphoma and plasma cell neoplasms with plasmablastic features. We report 3 cases of neoplasms with plasmablastic histomorphology involving the oral cavity. The relevant clinical, morphologic, and immunophenotypic features and treatment are presented, along with a review of the literature. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:651–659)

It is well established that up to 25% of primary non-Hodgkin lymphoma (NHL) may present in extranodal sites. However, primary lymphomas of the oral cavity are rare and consist predominantly of NHL of mature B-cell origin; such cases are thought to represent 3% of all extranodal NHL.[1] Plasmablastic lymphoma (PBL) is a rare and aggressive subtype of mature B-cell lymphoma, with a peculiar predilection for the oral cavity.[2-9] Some studies have suggested that PBL may represent up to 66% of primary oral NHL occurring in the anterior oral cavity.[10] The morphologic and immunophenotypic features may overlap with other neoplasms, including diffuse large B-cell lymphoma (DLBCL) and plasma cell myeloma (PCM) with plasmablastic transformation. However, PBL has unique clinical and epidemiologic features, as well as an overwhelmingly poor prognosis and diminished survival time.[2-10] We report 3 cases of intraoral lymphoid neoplasms with predominantly plasmablastic morphology. For each case, we discuss the relevant clinical, histologic, and immunophenotypic features and review the literature concerning this uncommon entity.

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CASE SERIES

Case 1

A 56-year-old HIV-negative male was referred to an oral surgeon by his oncologist for evaluation of a painful growth on his mandibular alveolar ridge and vestibule, present for a long time. The patient's medical history was significant for immunoglobulin A (IgA)–lambda PCM (with gain of 1q and *BRAF* D594N mutation), initially diagnosed in 2009. The rest of the medical history was noncontributory. Clinical examination revealed an approximately 2.5-cm, painful, reddish growth on the right side of the mandible. The lesion also extended to the right maxillary and mandibular vestibules, as well as to the buccal and pharyngeal areas. The patient had undergone prior debulking of the lesion but, unfortunately, there was rapid recurrence, leading to fungating growth across the occlusal surface of his teeth and thus hindering dental apposition and mastication. Computed tomography imaging of the chest, abdomen, and pelvis revealed increased size of multiple soft tissue masses. Magnetic resonance imaging of the head showed diffuse myelomatous involvement of the skull, with multiple foci of calvarial enhancement and involvement and expansion of the right sphenoid bone surrounding the foramen ovale.

The patient underwent incisional biopsy of the mandibular lesion, and histologic examination showed sheets of plasma cells with vesicular chromatin and

Statement of Clinical Relevance

Plasmablastic lymphoma is a rare aggressive variant of large B-cell lymphoma with distinct clinical and prognostic implications, but it shows overlapping phenotypic characteristics with other lymphoid neoplasms. Relevant clinical, morphologic, and immunophenotypic features are presented, along with a review of the literature.

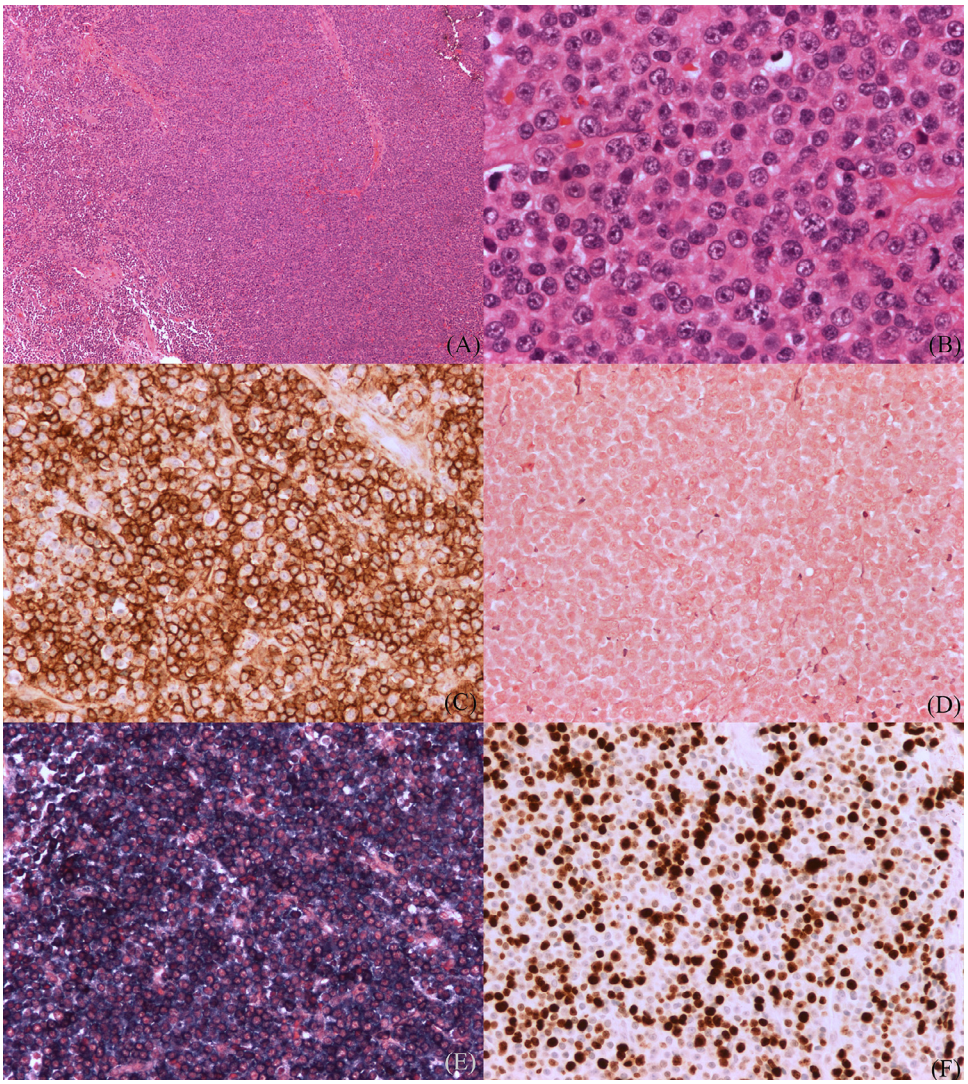

Fig. 1. Case 1. **A,** Hematoxylin and eosin (H&E) stain showing diffuse proliferation of large monomorphic cells (magnification × 40). **B,** H&E stain showing sheets of large cells with abundant eosinophilic cytoplasm, and large eccentric nuclei with prominent nucleoli (magnification × 400). **C,** Immunohistochemical stain for CD138, showing diffuse and strong membranous immunoreactivity (magnification × 200). **D,** Epstein-Barr virus (EBV)−encoded small RNA (EBER) by in situ hybridization (ISH) is negative (magnification × 200). **E,** ISH for lambda light chain showing lambda restriction (magnification × 200). **F,** Immunohistochemical stain for Ki-67, showing 60% to 70% proliferation index (magnification × 200).

prominent centrally located nucleoli (Figures 1A and 1B). Brisk mitotic activity was noted. Immunohistochemical staining revealed that the neoplastic cells were positive for CD138 (Figure 1C). In situ hybridization (ISH) revealed a kappa restricted phenotype. ISH for Epstein-Barr virus (EBV)−encoded small RNA (EBER), however, was negative (Figures 1D and 1E). The proliferation index was 70% to 80% by Ki-67 (Figure 1F). The final diagnosis was plasma cell neoplasm with plasmablastic morphology. The diagnostic comment was that the current plasmablastic features may portend a poor prognosis. Of note, biclonal plasma cell neoplasms (expression of both kappa and lambda light chains), although rare, have been reported. In some cases, the biclonal nature can be initially missed as one clone presents dominantly over a minor subclone.[11,12] The discrepant light chain expression is this case may suggest the possibility of isotype switch or, perhaps, expansion of a previously minor kappa-restricted subclone.

The patient had undergone multiple cycles of chemotherapy and radiotherapy, as well as autologous stem cell transplantation, throughout the course of his disease. Even with aggressive therapy, the patient did not achieve durable remission (maximum period of 13 months), and aggressive relapse occurred. The patient was eventually started on a clinical trial (UPCC39413) of an experimental bromodomain extra-terminal motif

inhibitor (CPI-0610). Despite treatment, the disease progressed, and the patient was lost to follow-up for a time. The patient has since died. See patient summary in Table I.

Case 2

A 68-year-old HIV-negative male presented to an oral surgeon for evaluation of an exophytic, large, irregular, lobulated mass of the right maxillary vestibule and alveolar ridge, which extended from the canine to the second molar area and had been present for a considerably long time. Radiography revealed an irregular radiolucent lesion of right maxilla, involving caries in the molar and canine teeth. The patient's past medical history was significant for a genetic form of focal segmental glomerulosclerosis and had been on renal hemodialysis for chronic kidney disease since 2003.

Incisional biopsy of the maxillary lesion revealed sheets of monotonous, highly atypical, large cells with irregular nuclei, open chromatin, and prominent nucleoli (Figures 2A and 2B). Numerous mitotic figures were identified. Immunohistochemical staining revealed that the neoplastic cells were strongly positive for MUM1 (Figure 2D), subset positive for CD138 (Figure 2C), heterogeneously positive for CD45 and CD30, and weakly positive for CD79a. Pertinent negative makers included CD20, PAX5, CD10, BCL6, Cyclin D1, and ALK1, as well as epithelial and melanocytic markers. EBER-ISH yielded a positive result (Figure 2E). The proliferation index was estimated at 90% by Ki-67 (Figure 2F). The overall features were compatible with EBV-positive plasmablastic lymphoma.

The patient was referred to his oncologist with a recommendation for positron emission tomography/computed tomography and bone marrow biopsy for disease staging. Radiation therapy was also recommended for management of local disease. However, the patient refused further workup and treatment. The patient has since died, but the definitive cause of death was not established. See patient summary in Table I.

Case 3

A 50-year-old HIV-negative female presented to an oral surgeon for evaluation of a painless mass of unknown duration on her right posterior alveolar ridge. The patient's medical history was noncontributory. On physical examination, no other lesions were noted. The clinical impression for this gingival mass included pyogenic granuloma, and the patient underwent incisional biopsy for further evaluation.

Histologic examination revealed sheets of highly atypical plasma cells, multifocal necrosis, and mucosal ulceration (Figure 3A). The plasma cells exhibited varying morphology, ranging from intermediate-sized cells to polymorphic, large, irregular cells with large nuclei and prominent nucleoli (Figure 3B). Numerous mitotic figures were identified. Immunohistochemical staining revealed that the neoplastic cells were positive for CD138 (Figure 3C), and CD79a, but were negative for CD20, CD30, epithelial membrane antigen, and ALK1. CD20 identified few focal B cells, and CD3 highlighted scattered T cells. The plasma cells were lambda light chain restricted by ISH, and the EBER-ISH result was negative (Figure 3D). Immunohistochemical stain for MUM1 revealed strong diffuse immunoreactivity (Figure 3E). The proliferation index was estimated at 50% to 60% by Ki-67(Figure 3F). The final diagnosis was plasma cell neoplasm with plasmablastic morphology, and a recommendation was made to correlate the diagnosis with additional laboratory/radiologic workup, clinical findings, and the patient's prior history.

After further evaluation, the patient underwent bone marrow biopsy, and histologic examination revealed 5% involvement by lambda restricted plasma cells with prominent plasmablastic features. The diagnosis of plasma cell neoplasm compatible with PCM was

Table I. Summary of case features

	Case 1	*Case 2*	*Case 3*
Gender	Male	Male	Female
Age (years)	56	68	50
HIV status	Negative	Negative	Negative
Myeloma history	Yes	No	No
Tumor location	Mandible	Maxilla	Mandible
Other clinical information	Multiple lytic lesions of calvarium, soft tissue masses	History of genetic FSGS kidney disease	Bone marrow involvement by plasma cell neoplasm
EBER (ISH)	Negative	Positive	Negative
Treatment	BET inhibitor (CPI-0610)	Lost to follow-up	CyBorD, Revlimid
Clinical status	Dead	Dead	Alive
Final diagnosis	Plasma cell myeloma	Plasmablastic lymphoma (presumed)	Plasma cell myeloma

BET, bromodomain extra-terminal motif. *CyBorD,* cyclophosphamide, bortezomib, and dexamethasone *EBER,* Epstein-Barr virus (EBV)–encoded small RNA; *FSGS,* focal segmental glomerulosclerosis; *ISH,* in situ hybridization.

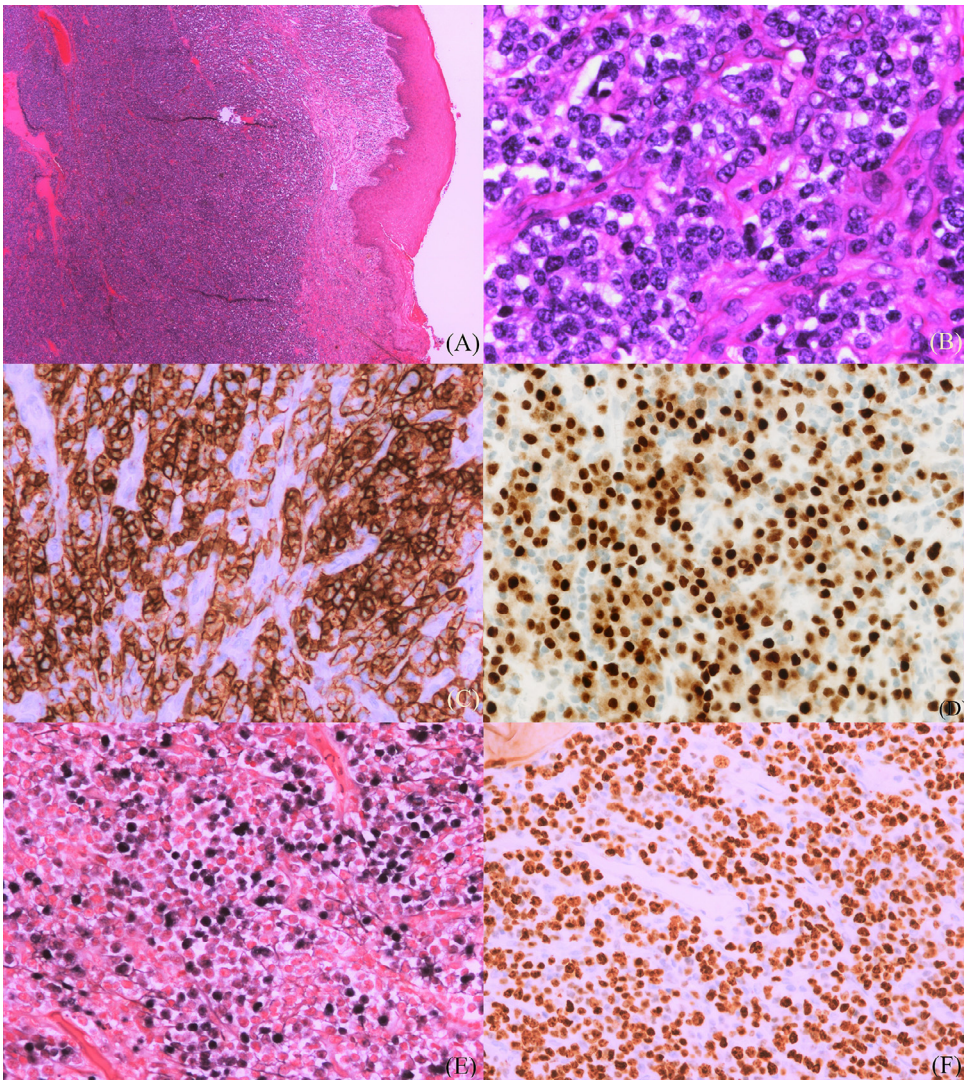

Fig. 2. Case 2. **A,** Hematoxylin and eosin (H&E) stain showing a submucosal diffuse proliferation of large monomorphic cells (magnification × 40). **B,** H&E stain showing sheets of large cells with abundant cytoplasm, and large eccentric nuclei with prominent nucleoli (magnification × 400). **C,** Immunohistochemical stain for CD138, showing diffuse and strong membranous immunoreactivity (magnification × 200). **D,** Immunohistochemical stain for MUM1, showing strong diffuse immunoreactivity (magnification × 200). **E,** Epstein-Barr virus (EBV)−encoded small RNA (EBER) by in situ hybridization (ISH) is positive (magnification × 200). **F,** Immunohistochemical stain for Ki-67, showing 90% proliferation index (magnification × 200).

rendered. The patient was treated with 3 cycles of CyBorD (cyclophosphamide, bortezomib, and dexamethasone), and achieved a partial response, with normal post-therapy serum protein electrophoresis, quantitative immunoglobulin, and free light chain assays. The patient remains on maintenance therapy with lenalidomide (Revlimid®) and is under the care of her oncologist. See patient summary in Table I.

DISCUSSION

Clinical presentation

Lymphoma of the oral cavity represents around 5% of all oral malignancies.[1] NHL accounts for the vast majority of oral lymphomas and often arises from the lymphoid tissues of the Waldeyer ring. DLBCL is, by far, the most common intraoral lymphoma, followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue lymphoma, follicular lymphoma, and mantle cell lymphoma. However, lymphoma may also arise in the gingiva, buccal mucosa, or hard palate. Unlike the posterior oropharynx (including the Waldeyer ring), lymphoma is relatively rare in the anterior oral cavity; however, PBL appears to be disproportionately overrepresented in this location and accounts for up to 66% of lymphomas involving the anterior oral cavity.[1-10,13] It is important to include plasma cell neoplasm in the differential

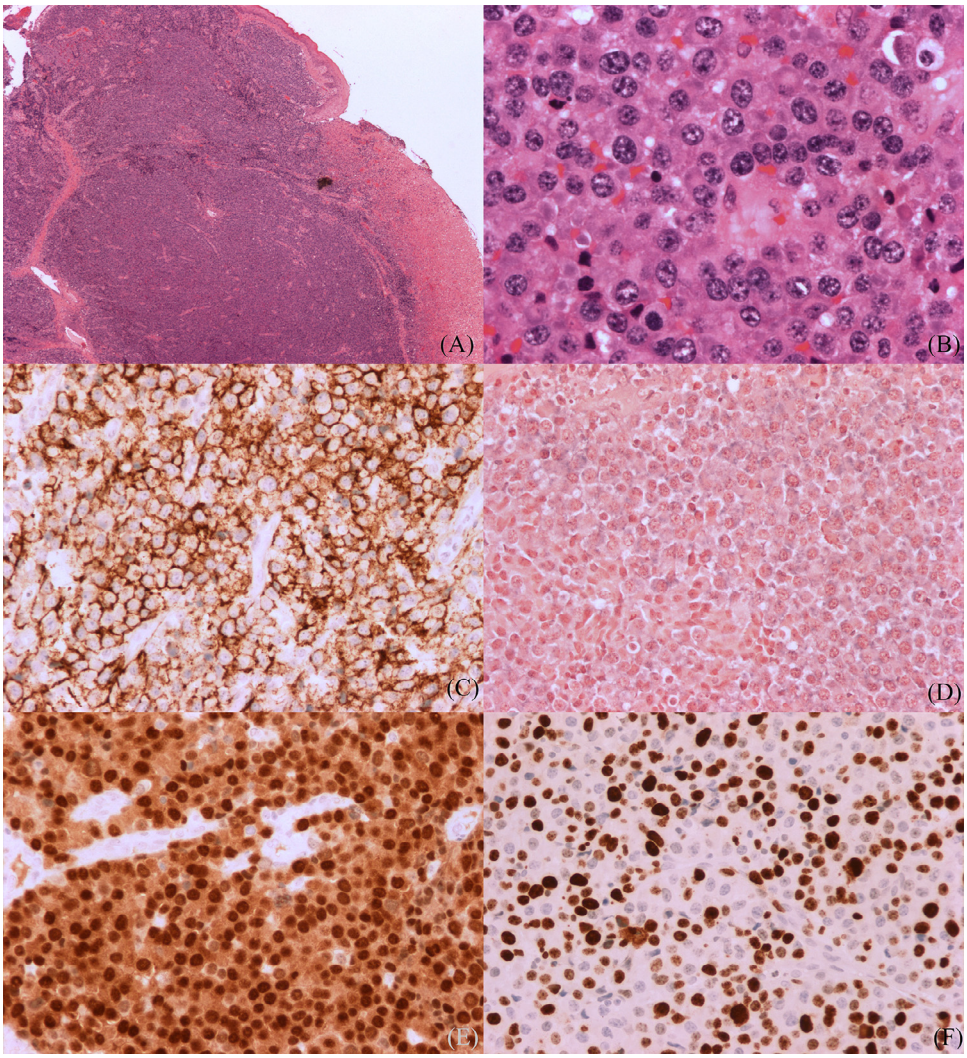

Fig. 3. Case 3. **A,** Hematoxylin and eosin (H&E) stain showing diffuse submucosal proliferation of large monomorphic cells (magnification × 40). **B,** H&E stain showing sheets of large cells with abundant eosinophilic cytoplasm, and large eccentric nuclei with prominent nucleoli (magnification × 400). **C,** Immunohistochemical stain for CD138, showing diffuse and strong membranous immunoreactivity (magnification × 200). **D,** Epstein-Barr virus (EBV)−encoded small RNA (EBER) by in situ hybridization (ISH) is negative (magnification × 200). **E,** Immunohistochemical stain for MUM1, showing strong diffuse immunoreactivity (magnification × 200). **F,** Immunohistochemical stain for Ki-67, showing 60% to 70% proliferation index (magnification × 200).

diagnosis because extraosseous plasmacytomas frequently occur in the head and neck region and disseminated myeloma may affect any extraosseous location. The presence of bony lesions strongly favors the diagnosis of a plasma cell neoplasm over PBL.[9] Although a measurable serum monoclonal protein is frequently reported with primary plasma cell neoplasms, it is exceedingly rare in PBL.[9,14]

PBL was first described in a case series[10] as a variant of large B-cell lymphoma, with morphologic and immunohistochemical features demonstrating plasmacytic differentiation. In this series, in all cases, the lesions originated in the oral cavity, with 15 of 16 patients reported to be HIV-positive.[2-10] Further case series have confirmed that PBL occurs most commonly in the anterior oral cavity, representing the presenting site of disease in about 58% of cases in HIV-positive patients; the gingiva appears to be the most common site of disease, representing approximately 40% of these cases, followed thereafter by lesions of the hard palate, floor of mouth, and buccal mucosa.[15-17] Some studies have reported a correlation with PBL of the gingival−buccal complex and oral tobacco consumption.[17] PBL is exceedingly rare in the oropharynx, and most primary lymphomas of this region, instead, are DLBCL, not otherwise specified, originating in the lymphoid tissues of the Waldeyer ring. The predilection for the oral cavity appears to be highest in the immunocompromised, with approximately 90% of intraoral PBLs occurring in patients

with HIV.[2-10,15-17] However, extraoral presentation is not uncommon, and the most frequent extraoral sites include the gastrointestinal tract or the sinonasal mucosa. Less common sites of disease include the lungs, skin, and soft tissue.[17-25] Primary nodal involvement is uncommon but has been reported much more frequently in patients who are HIV negative.[9,26] Secondary bone marrow involvement is uncommon, and raises the differential diagnosis of plasma cell neoplasm with plasmablastic features.[13,14,16-21,26]

The literature shows that PBL occurs across a very wide age range (7−75 years). However, PBL is rare in pediatric patients, with only a few cases reported.[9] The median age of presentation is in the 4th decade.[17-21] PBL is most commonly seen among adult males with HIV infection. The marked male predominance (male-to-female ratio 7:1) could partly be a result of the epidemiology of HIV infection. It is well established that HIV/AIDS markedly increases the risk for NHL. AIDS-associated lymphomas are generally high grade NHLs and include DLBCL, Burkitt lymphoma, PBL, and primary effusion lymphoma. Although PBL represents 2.6% of all AIDS-associated lymphomas, the majority of patients with PBL (up to 69%) are HIV positive.[9,10,15-21] In general, patients who are HIV negative tend to be older, with mean age at presentation being 58 years. PBL has also been reported in other immunosuppressed clinical groups; up to one-third of HIV-negative patients have evidence of secondary immunodeficiency, most often as a result of transplantation-related immunosuppression. A minority of patients are apparently immunocompetent, without known risk factors.[13,14,27-33]

PBL usually presents as an isolated and rapidly enlarging soft tissue mass in the anterior oral cavity, most often on the gingiva. Bony infiltration is typical, and pain is a frequent symptom. Grossly, the lesions often raise the clinical impression of Kaposi sarcoma, particularly in patients who are known to be HIV positive. Typical systemic manifestations of lymphoma, including fever, night sweats, and weight loss, may be present but are not specific to PBL; somewhat paradoxically, "B" symptoms are more likely to be present at diagnosis in immunocompetent patients.[28-30] PBL generally presents with advanced stage disease in both HIV-positive and HIV-negative patients (Ann Arbor stage 3/4). Interestingly, HIV-positive patients have a bimodal distribution of stage at presentation, with 32% presenting with stage 1 disease and 49% with stage 4 disease.[10,16-19]

Histopathology

The typical histologic profile of PBL shows a diffuse and often monomorphic proliferation of large cells with abundant variably amphophilic cytoplasm and a large eccentrically localized nucleus. Nuclei typically have a smooth contour, vesicular to fine chromatin distribution, and a very prominent centrally located eosinophilic nucleolus, resembling a prototypical plasmablast. The background often shows small mature lymphocytes, abundant apoptotic debris and tingible-body macrophages, reminiscent of a "starry sky" pattern. The mitotic rate is typically high, and necrosis may be seen. As with plasma cell neoplasms, a perinuclear "hof" may occasionally be seen. However, immunoglobulin inclusions (Dutcher and Russell bodies) are not a typical feature in PBL.[9,10,15-21,34] Cases of PBL may also exhibit a more polymorphous pattern, with a mixture of plasmablasts, immunoblasts, and less commonly mature plasma cells.[17-21,34]

Histogenesis and immunohistochemistry

The current consensus is that the neoplastic cells in PBL are derived from the postgerminal center; but that, preterminally, differentiated B cells in transition between immunoblasts and mature plasma cells, with maturation arrest at the plasmablastic stage. This is supported by consistently weak or absent expression of CD45 (leukocyte common antigen) and B-cell markers, as well as usually strong expression of CD138. Cytoplasmic light chain restriction is frequently seen, with lambda predominance.[19-21] One immunohistochemical study by Montes-Moreno et al. revealed 2 immunophenotypic variations of the neoplastic plasmablasts in PBL. The full plasmablastic immunophenotype is characterized by consistent expression of MUM1, PRDM1/BLIMP1 (positive regulatory domain), XBP1 (X-box binding protein 1), and CD138, with absent expression of CD20 and PAX5. The variant plasmablastic immunophenotype, however, is characterized by the absence of XBP1 expression despite positivity for MUM1, BLIMP1, and CD138; CD20 and PAX5 are consistently expressed but weak.[35] Other frequently positive markers of plasmablastic differentiation include VS38c and frequently CD38. Expression of CD30 and epithelial membrane antigen are frequently reported but are uncommon in plasma cell myeloma. Expression of CD79a is variable. CD56 expression may be seen in some cases, in addition to stronger CD20 expression, a feature more often seen in patients with HIV. However, PBL does not show any expression of cyclin D1 (BCL1) or ALK1, all of which suggest other entities.[9,34,35] As with other AIDS-associated lymphomas, there is a strong association between PBL and EBV infection; up to 74% of cases show EBER by (ISH), with a higher frequency noted among HIV-positive patients.[19-21,27]

Molecular and cytogenetic characteristics

Because they are derived from the postgerminal center, preterminally differentiated B cells, the neoplastic cells of PBL, have, by definition, undergone both class switching and somatic hypermutation. Of note, a subset of PBL cases show *MYC* rearrangements (up to 49%), most

commonly t(8;14)(*MYC*/*IGH*). This is interesting because most other *MYC* rearranged lymphomas, including Burkitt lymphoma and DLBCL with *MYC* translocation, are of germinal-center origin. *MYC* rearrangement also appears to be more common in EBV-positive cases.[36-38] Genomic profiling of PBL by Chang et al. shows frequent segmental gains, particularly in chromosomes 1, 7, 11, and 22 (1p36.11-1p36.33, 1p34.1-1p36.13, 1q21.1-1q23.1, 7q11.2-7q11.23, 11q12n-11q13.2 and 22q12.2-22q13.3); this profile is frequently identified in PBL, irrespective of HIV status.[39] These changes are very similar in profile to those seen in DLBCL, supporting classification of PBL as a variant of DLBCL. Additionally, gain of 16p13.3 appears fairly specific to PBL and DLBCL but is not seen in PCM.[39] Rearrangements of cyclin D1 and ALK are not identified in PBL.[20,21]

Treatment and prognosis

PBL is an aggressive disease, with a generally poor outcome. Treatment guidelines suggest more intensive multidrug chemotherapeutic regimens (i.e., EPOCH, HyperCVAD, or CODOX-M/IVAC) instead of CHOP, although this does not appear to confer a survival advantage. Radiotherapy may be helpful, particularly for gingival disease. Initial response to chemotherapy is favorable (overall response rate of 77%), with up to 46% achieving initial complete therapeutic response. The prognosis is dismal for patients who do not receive chemotherapy, with a median survival of 3 months. Interestingly, HIV-positive patients show improved chemotherapeutic response compared with HIV-negative patients, particularly when chemotherapy is combined with highly active antiretroviral therapy. However, despite the initially positive chemotherapeutic response, median survival of patients is approximately 11 to 14 months, with a 5-year overall survival of approximately 31%.[17-21] The most significant predictors of poor prognosis are advanced stage at presentation as well as lack of aggressive chemotherapy. As CD20 is not consistently expressed, rituximab therapy is not common but may be considered in cases with weak expression of CD20.[16-19]

Differential diagnosis

The clinical and radiologic differential diagnosis for mass lesions of the anterior oral cavity is broad and includes pyogenic granuloma, squamous cell carcinoma, lymphomas, salivary gland neoplasms, and various infectious or inflammatory lesions, thus underscoring the need for a multidisciplinary approach with clinical, radiologic, and pathologic examination.[40] Plasmablastic features may be seen in a wide spectrum of neoplasms, and the differential diagnosis for intraoral PBL includes not only lymphoid neoplasms but also poorly differentiated carcinoma or melanoma. However, these latter entities are often easily differentiated by the presence of epithelial markers (i.e., cytokeratins) or melanocytic markers (i.e., S100, HMB-45 and Melan-A), respectively.[9,16-21] Epithelial membrane antigen is frequently reported on PBL as well as on other hematolymphoid tumors (i.e., anaplastic large cell lymphoma) and should not be used as a distinguishing marker of epithelial origin. Of note, CD138 expression is commonly seen in a subset of epithelial neoplasms, including squamous cell carcinoma, urothelial carcinoma (plasmacytoid variant), and breast carcinomas among others, and these should be excluded with a thorough immunohistochemical panel. The most important differential diagnoses include other lymphoid neoplasms, particularly DLBCL and PCM with plasmablastic morphology. Although weak CD20 expression may be seen in PBL, strong expression is unlikely. Strong uniform immunoreactivity for CD20, especially when CD45 is also positive, would be expected in DLBCLs or other mature B-cell lymphomas and virtually rules out a diagnosis of PBL. Rare cases of DLBCL may show partial plasmablastic immunophenotype, often with 25% or fewer such tumor cells. These cases show decreased survival compared with DLBCL but are still expected to show strong CD20 and CD45, in contrast to PBL.[34,35] Differentiating PBL from PCM, particularly in those with poorly differentiated, plasmablastic, or anaplastic morphology, can be difficult because the morphologic and immunophenotypic features of both entities show considerable overlap. The presence of multinucleation, immunoglobulin inclusions, and low proliferative index could suggest a diagnosis of PCM. Cyclin D1 rearrangement, if present, would also support a diagnosis of PCM. Genomic profiling (i.e., array comparative genomic hybridization) may be of utility but is often costly, and a small biopsy specimen may not be sufficient for extensive genomic analysis. Often, the most helpful tool in differentiating the two is a good clinical history and a thorough workup. A prior diagnosis of PCM, the presence of lytic bone lesions, systemic manifestations of myeloma, and bone marrow involvement, all strongly support PCM. However, caution should be exercised because an isolated intraoral lesion may represent a solitary plasmacytoma. This difficulty is compounded by the marked difference in prognosis between the two entities, with PCM frequently showing a chronic and more protracted clinical course even when there are marked plasmablastic or anaplastic features.[9,34]

Other important diagnoses to exclude in the differential diagnosis of PBL are ALK-positive large B-cell lymphoma (ALK+LBL), large B-cell lymphoma arising in human herpesvirus 8 (HHV-8)−associated multicentric Castleman disease, and extracavitary (solid) variant of primary effusion lymphoma. All these entities show

marked immunotypic or morphologic similarities to PBL. ALK+LBL is differentiated primality by the presence of a characteristic ALK rearrangement, typically t(2;17) (p23;q23); strong ALK1 expression by immunohistochemistry is usually sufficient for establishing this entity. The plasmablasts of LBL associated with HHV-8−associated multicentric Castleman disease, unlike those of PBL, are usually positive for CD20, but negative for CD138 and EBER-ISH; additionally, the presence of HHV-8 viral genome is expected. Finally, primary effusion lymphoma usually shows strong expression of CD45 and CD30, in contrast to PBL, as well as the presence of HHV-8 viral genome.[2,34]

CONCLUSIONS

PBL is a variant of large B-cell lymphoma with a strong association with HIV infection and has a particular predilection for the anterior oral cavity. Differentiating PBL from other entities, particularly conventional DLBCL or PCM with plasmablastic transformation, is important because these entities may share overlapping morphologic and immunophenotypic features. The virtually uniformly poor prognosis of PBL underscores the importance of this differential diagnosis. This case series and review illustrate the importance of good clinical history in conjunction with morphologic, immunohistochemical, and (if needed) molecular studies in the accurate diagnosis of this rare entity.

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