

Intraoral plasmablastic lymphoma as a primary oral manifestation: A case report and review of literature

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Abstract

Plasmablastic lymphoma (PBL) is an aggressive type of large B-cell lymphoma as stated in the WHO classification of 2008. It is a rare form of non-Hodgkin's lymphoma, generally seen in human immunodeficiency virus (HIV)-acquired immunodeficiency syndrome affected individuals. A case of a 42-year-old female patient is presented here. The patient complained of swelling in the lower right back tooth region and presented with a history of extraction of molars. The underlying HIV status was detected after the oral examination. The diagnosis of PBL was confirmed with immunohistochemical analysis.

Keywords: Acquired immunodeficiency syndrome, human immunodeficiency syndrome, human immunodeficiency virus, non-Hodgkin's lymphoma, plasmablastic lymphoma

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INTRODUCTION

Lymphomas originate as somatic mutations in lymphocyte progenitor cells (B-cells, T-cells, or both). They are commonly classified as Hodgkin's and non-Hodgkin's lymphomas (NHL). Plasmablastic lymphoma (PBL) is classified under the category of 'Mature B-cell neoplasms', according to the 2016 revised classification of lymphoid neoplasms by the WHO.^[1] The NHL classification given by the WHO in 2001 has divided the lymphomas: (1) according to the cells of origin B-cell origin and T-cell/NK cell origin and (2) according to the Type-Indolent lymphomas and aggressive lymphomas.^[2]

The NHL are characterized by diffuse or nodular sheets of lymphocytes or lymphoblasts without the presence of Reed–Sternberg cells,^[3] whereas the Hodgkin's lymphomas

are B–cell-derived neoplasms in which the Reed–Sternberg cells form its pathognomonic feature.

Plasmablastic or large B-cell lymphomas account for 30% of all the cases and are the most common type.^[4] They are diffused type of aggressive large B-cell lymphomas and have been reported in the human immunodeficiency virus (HIV)-positive and -negative patients, while the incidence of PBL is 2.6% of all the acquired immunodeficiency syndrome (AIDS) associated NHL, the prevalence of disease-related deaths was 59.6% in oral NHL and the average mean survival is 14 months, which indicates its aggressiveness.^[5,6] Furthermore, from 1997 to 2015, a total of 612 cases have been reported worldwide.^[7]

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The terminology “Plasmablastic Lymphoma” was given by Delecluse *et al.*, when they reported 16 cases of unusually presenting lymphomas, which were associated with HIV infection and which showed the various sites in the oral cavity as the primary tumor sites such as gingiva, floor of the mouth, palate and tonsil, which were with or without infiltration of the surrounding jaw bone.^[7] It often involves the head-and-neck area with other sites, including the nasal cavity, gastrointestinal tract, bone, skin, soft tissue and lungs.^[8,9] PBL is an uncommon B-cell tumor which is limited to the jaw and oral cavity at presentation but can spread to distant sites at later stages. Plasmablastic Lymphoma is categorised by WHO under the category of 'Mature B-cell Neoplasms'.^[10] It is reported to occur in a setting of multicentric Castleman’s disease with associated involvement of the lymph nodes and spleen.^[5,10,11]

CASE REPORT

This case of a 42-year-old female patient reported to the outpatient department with a chief complaint of swelling in the lower right back tooth region. The patient was of average built and normal gait. The patient had a habit of chewing tobacco 4–5-times a day for 20 years.

The right submandibular and submental lymph nodes were palpable (IB and II). The extraoral swelling extended from the right corner of the mouth to the lower border of the mandible, including the lower left third molar region. The swelling was approximately 5 cm by 5 cm in dimension [Figure 1]. The patient gave a history of extraction of molars and a subsequent increase in the swelling.

After blood investigations, the patient was advised advanced investigations which revealed that the patient was HIV (positive).



Figure 1: Clinical presentation of the lesion (extraoral)

Intraoral clinical examination revealed a soft tissue growth on the right buccal mucosa, soft inconsistency. The lesion extended from the lower right canine to the lower right third molar and was accompanied by symptoms such as pain, bleeding, swelling and paresthesia of the right side of the lower lip. The swelling was present intraorally for 6 months according to the history given by the patient. The swelling was flat in appearance with no ulceration present on it, mixed in color and the approximate size of the lesion at the time of biopsy was <5 mm.

Radiographic examination was done including orthopantomogram (OPG) and computed tomography (CT) of the spine + brain + three-dimensional (3D) reconstruction. The OPG revealed an extraction socket with 46, 47, 48, compression of the inferior alveolar nerve canal, caries approaching the pulp with 17 and 18 along with resorption of the lower border of the mandible on the right side.

The CT-C spine + brain + 3D reconstruction showed lytic destruction in the body and ramus of right mandible, cortical erosion, enlarged soft-tissue mass on the right side and the overall picture was suggestive of malignancy of the mandible [Figure 2].

The gross examination of the specimen included multiple bits of soft tissues measuring 0.2 cm × 0.1 cm and

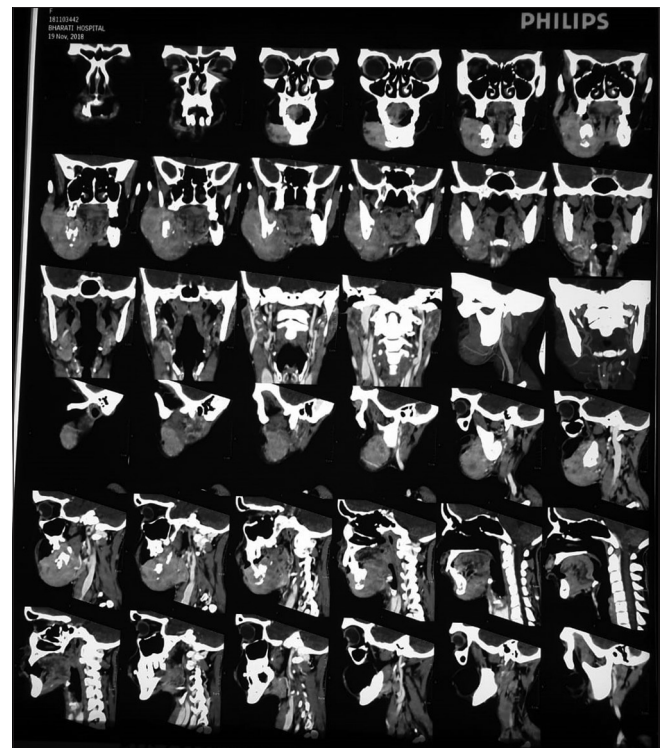


Figure 2: Computed tomography scan

0.5 cm × 0.3 cm in dimension, white in color, soft to firm in consistency with irregular surface and borders [Figure 3].

Histopathology [Figure 4] showed hyperplastic squamous mucosa and underlying connective tissue showing sheets of oval cells with eccentric nucleoli which were suggestive of plasmacytoid cells. These cells revealed a high mitotic activity and appeared pleomorphic, hyperchromatic with prominent round nucleoli surrounded by moderate cytoplasm and vesicular nuclei and moderate cytoplasm. As the overall histopathological picture was ambiguous, immunohistochemistry was advised since there was a definite involvement of the submental and submandibular lymph node.

A panel of immunohistochemical markers suggested were as follows: MiB1, CD3, CD138, leukocyte common antigen (LCA) and cytokeratin (CK).

Mib1 is a proliferative marker [Figure 5] and in this case showed increased mitosis, loss of pattern, prominent nucleoli and nuclear pleomorphism. This had taken up a brownish hue suggesting positivity.

CD3 is a T-cell antigen marker [Figure 6], and the brownish color indicated positivity for malignant plasma cells.

CD138 or syndecan is a marker [Figure 7] of plasmacytic differentiation and showed abundant plasma cells forming clusters, which was seen as a brownish color and hence marked increased expression.

LCA and CK negativity [Figure 8a and b] in the connective tissue ruled out the hematogenous and epithelial origin, respectively, of the malignancy.

The immunohistochemical panel showed

1. 90%–95% positivity in tumor cells with Mib-1
2. CD3-positive in reactive T-lymphocytes and negative in tumor cells
3. CD138-positive in tumor cells
4. LCA- and CK-negative in tumor cells.

Based on these findings, the confirmatory diagnosis of PBL was given.

DISCUSSION

Among the spleen and the lymph nodes, plasma cells are found in the reticular sinusoidal cells in the red pulp and medullary cords. Later, these cells interact with the reticular

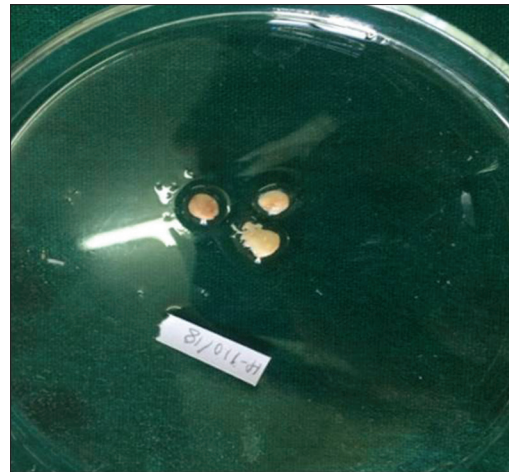


Figure 3: Grossing

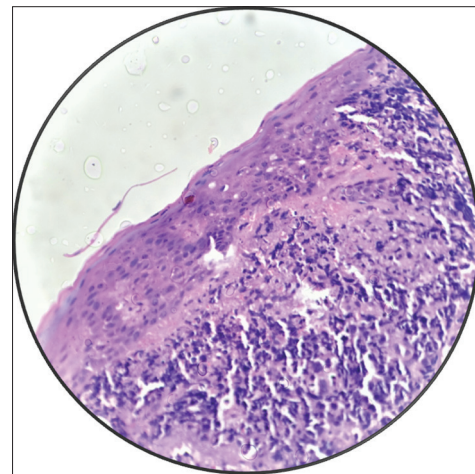


Figure 4: H & E stained section (x40)

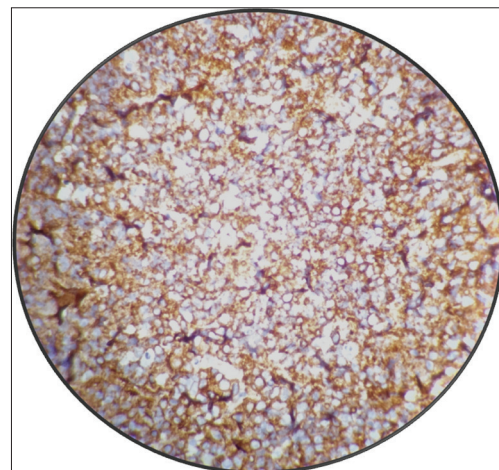


Figure 5: Immunohistochemical marker-MiB1

stromal cells and thus facilitate the antibody secretion directly into the bloodstream. They are not commonly found in the circulation, but they reside in the organs, for example, bone marrow.

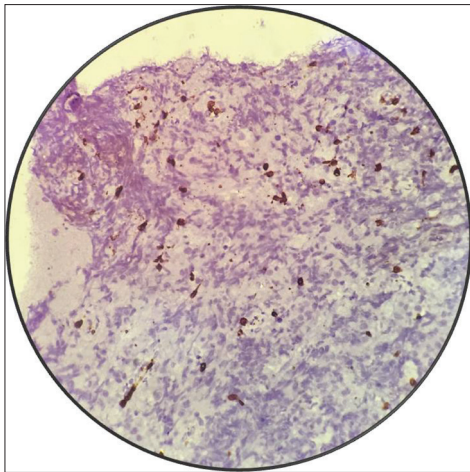


Figure 6: CD3 marker

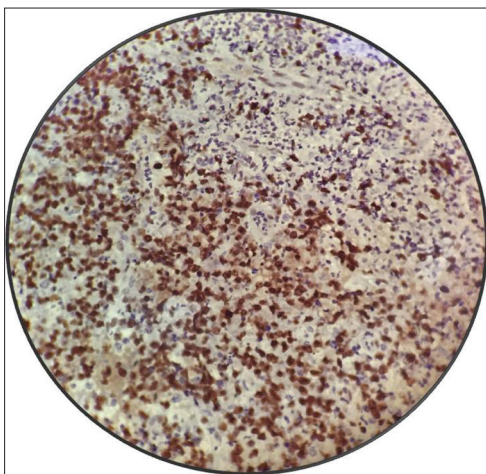


Figure 7: CD138 marker

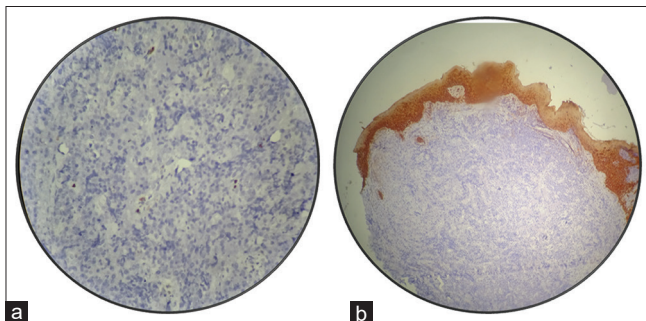


Figure 8: (a) Leukocyte common antigen and (b) cytokeratin negativity

Plasma cells maintain the antibody pool which is secreted when exposed to any antigen. Once the antigen enters the body, other than the macrophages, the biggest cell of the immune system and the B-cell or “the antibody” starts its action to form the antigen-antibody complex. Soluble antibodies circulating throughout the body helps achieve this. Migration of plasma cells does not occur from tissue to tissue, hence are situated in tissues.^[1]

Plasmablasts are precursors of short- and long-lived plasma cells and are known to be a proliferating fraction of antibody-secreting cells found in the bloodstream emigrating to organs.

Plasma cells are differentiating noncycling antibody-secreting. They remain in the organs for life. Plasma cells are distinguished from mature B-cells by different morphological appearances. The nucleus to cytoplasm ratio is high, less rough endoplasmic reticulum and uncondensed nucleus, whereas plasma cells are small, dense with eccentric nucleus with large cytoplasm containing enlarged Golgi bodies and prominent rough endoplasmic reticulum.

The molecular process of maturation and differentiation of plasma cells is essential for development, transition and maturation. The differentiation is carried out by B-lymphocyte-induced maturation protein (BLIMP-1 protein). Cytokine removal pauses the process while its activation further activates the BLIMP-1 protein which helps in the further maturation, thus proving the significance of cytokines. BLIMP-1 suppresses B-cell-specific transcription and is not detected by memory B-cells. It also induces the regulation of mRNA and syndecan-1 protein synthesis (differentiating molecules for plasma cells). Other molecules such as CD44 (adhesion molecule) play an important role by which plasma cells maintain contact with the bone marrow. The process is detected by an increase in the overall size, which can be studied and detected by flow cytometry.

The process then progresses to maturation by the following changes in the phenotypes of bone marrow plasma cells-

1. Gain of syndecan-1
2. Loss of B-cell phenotype
3. Gain of Bcl-2 survival factor
4. Loss of death receptor (CD95)
5. Gain of adhesion molecule (VLA-4 and CXCR4).

The antibody-secreting cells secrete peak levels of antibodies after 3 days, while the bone marrow plasma cells reach the peak after 3 weeks in a linear fashion.^[1]

Finally, the activation and proliferation of B-cells results in the formation of two types of plasma cells-the short-lived ones and the long-lived ones. The short-lived plasma cells form the secondary lymphoid tissues, whereas the long-lived plasma cells form the germinal centers.^[1] The diffuse large B-cell lymphoma (DLBCL) also has a tendency for extranodal presentation. The involved nodes are enlarged, homogeneous and are individualized with little or no necrosis.

It progresses rapidly and has a poor prognosis if left untreated. There have been excellent results obtained with chemotherapy.^[12]

Pathogenesis

Reviewing the pathogenesis, the cell of origin in PBL is a plasmablast which is an activated B-cell that has undergone somatic mutation and class switching recombination. It is actually a B-cell which is in the process of becoming a plasma cell. The main pathogenesis highlights the rearrangements which take place in the *Myc* gene.^[13] The molecular pathogenesis of AIDS-related NHL have their connections with the histogenetic features or the phenotypes which are variable in expression. It depends on the host's immune deficiency by which it selects the type of AIDS lymphoma which will develop. Furthermore, the clinicopathological types originate from different B-cell subtypes which are associated with different pathways of the pathogenesis. The lymphomas can be a primary manifestation because they can develop in the presence of sustained CD4-positive cell counts. The different pathways of pathogenesis link to the various heterogeneity with which the lymphomas present themselves. Two main pathways are responsible for the DLBCL, in which the PBL is subcategorized.^[14]

1. Centroblastic DLBCL is characterized by the mild host immunodeficiency, in which the genetic lesions are characterized by the expression profile of BCL-6 and syndecan-1 (CD138) throughout the physiological maturation process of B-cells. This pathway is exhibited by the B-cells within the germinal centers and is featured by the centroblastic morphology of the cells, which display large noncleaved cell morphology. They can be associated with the EBV virus
2. Immunoblastic DLBCL, originate from the postgerminal center, preterminally differentiated B-cells, which display the BCL-6 and syndecan-1 phenotype. It is characterized by genetic lesions in hosts with marked immunodeficiency. They can be associated with the EBV/HHV8 viruses.^[14]

The first recognized and published case series of PBL in 1997 by Delecluse *et al.*, described the primary lesions which appeared in the oral cavity, without the involvement of the extranodal lymph nodes. The various sites in the oral cavity, which were reported as primary lesions were the gingiva, floor of the mouth, palate and tonsils, with or without infiltration of the surrounding jaw bone.^[7]

As many years have passed since then, the prognosis of the disease is still listed in the poor category. Many articles have reported the overall mean age of survival of HIV-positive patients with PBL in the range of 9 months to 2 years.

HIV-positive patients with PBL are commonly subjected to chimeric antigen receptor T-cell therapy, and spontaneous regression was observed in many cases. As the prognosis is already dismal, no standard therapeutic drugs or dosages have been officially prescribed in the literature. The use of cyclophosphamide, doxorubicin, vincristine and prednisone is still inadequate and requires more vigorous regimens.

Regimens of more intensity include EPOCH (infusional etoposide, vincristine, doxorubicin and methotrexate) have been prescribed.^[15]

More recently, the use of stem cell transplantation is being assessed. The use of antimyeloma drugs or agents has also been prescribed based on the basis of plasmacytic differentiation of PBL-cells, but not many cases have been reported using this therapy.^[16,17] Immunomodulator lenalidomide has been used in cases of relapse of PBL.^[18]

CONCLUSION

Although PBLs are commonly seen in HIV-positive patients, the oral cavity being the primary manifestation should be noted.^[19] Knowledge of its radiographic features before histopathology is mandatory. The ambiguous histopathology which sometimes may give a false appearance of oral squamous cell carcinoma should be ruled out. MIB1, CD3 and CD138 positivity give a definite diagnosis of PBL of the oral cavity associated with the underlying human immune deficiency virus infection.^[20]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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