Plasmablastic lymphoma: Does prognosis differ with HIV status and site of disease?

**Abstract**

**Background:** Apart from its common occurrence in the oral cavity in HIV-positive patients, plasmablastic lymphoma (PBL) has also been described at extraoral sites and among immunocompetent individuals. There is sparse data quoting prognostication of PBL depending on the site of occurrence and HIV status of patients. **Aims:** The present study was carried out at a tertiary oncology center to address the issue whether PBLs occurring at oral and extraoral sites differ prognostically and whether HIV status of patient has any impact on prognosis. **Materials and Methods:** This was a retrospective observational study conducted at our center on consecutive patients diagnosed with PBL, from January 2008 to December 2012. **Results:** We had four patients with oral PBL; three male and one female. Sites of involvement were oral tongue and buccal mucosa. Two patients died within 6 months of diagnosis due to disease progression while on treatment. One patient was lost to follow-up after achieving complete remission (CR) after chemotherapy. Only one patient completed the prescribed schedule of chemotherapy and radiotherapy and is in CR with 33 months follow-up. There were four extraoral PBL patients; three female and one male. Extraoral sites were ileocaecal region, ovary, clavicle and rectum. Three patients died within 6 months due to progressive disease during treatment. Only one patient has completed chemotherapy and is in CR with 18 months follow-up. Among all these eight oral and extraoral PBL patients, four were HIV positive. Two of them are in CR after treatment (18 months and 33 months follow-up). One patient died during treatment and one patient was lost to follow-up after being in CR. Unfortunately, none of the other four HIV-negative patients could survive for more than 6 months after diagnosis. **Conclusion:** Both oral and extraoral PBLs have aggressive clinical course and an overall unfavorable outcome. Prognosis of HIV-associated PBL seems to be better with addition of highly active antiretroviral therapy to chemotherapy. Further large sample studies are needed to confirm these results.

**Key words:** Extraoral, HIV, non-Hodgkin’s lymphomas, plasmablastic

**INTRODUCTION**

Plasmablastic lymphoma (PBL) is classified as a distinct entity by the World Health Organization and typically occurs in the oral cavity in the clinical setting of HIV infection, accounting for 2.6% of non-Hodgkin’s lymphomas (NHL) in this population.\[1\]

In the original report, 15 of 16 patients were infected with HIV, and all the patients had involvement of the oral cavity.\[1\] More recently, however, several cases of PBL involving the extraoral sites have been reported in immunocompetent individuals.\[2-3\] Clinically, PBLs are rapidly progressive tumors associated with poor response to therapy and an average survival time of 14 months.\[4\]

To address whether PBLs occurring in oral and extraoral locations differ prognostically, we analyzed eight cases diagnosed as PBL and treated at our institute. Herein, we present the clinical features and outcome analysis among oral and extraoral PBL.

**MATERIALS AND METHODS**

This was a retrospective observational study carried out at a tertiary cancer care in South India. With the concurrence of the institutional ethics and review board (IERB), we included consecutive patients diagnosed with PBL from January 2008 to December 2012. Patients’ medical records were...
reviewed for information regarding age and gender, presenting features and sites involved by PBL, HIV status, Ann Arbor stage, International Prognostic Index (IPI) score, treatment instituted, response to therapy, complications during treatment and treatment outcome. Diagnosis of PBL was established by histopathologic examination and immunohistchemistry studies. Complete work up of patients included hemogram; lactate dehydrogenase; complete metabolic profile; bone marrow biopsy and cerebrospinal fluid examination, computed tomography (CT) scan of neck, chest, abdomen and pelvis. Stage was assigned according to the Ann Arbor staging system. The IPI score was assigned whenever possible if all five components constituting the score could be identified in the medical records. The Eastern Oncology Cooperative Group scale was used to determine performance status. Response to treatment was determined as complete if there was elimination of all evidence of lymphoma after therapy. Progression of disease was defined as a growth of more than 25% in size or development of new sites of disease. Overall survival (OS) was defined as the time from disease diagnosis to death due to any cause. Progression-free survival was defined as the time from the date of diagnosis to the date of documented disease progression or death of disease or due to treatment toxic effects.

RESULTS

We had four patients diagnosed with extraoral PBL. There were three females and one male (median age 31.8 years; range 10–45 years). Our first patient was a 45-year-old female who had presented with abdominal pain, and after evaluation (CT abdomen and pelvis, stage was assigned according to the Ann Arbor staging system. The IPI score was assigned whenever possible if all five components constituting the score could be identified in the medical records. The Eastern Oncology Cooperative Group scale was used to determine performance status. Response to treatment was determined as complete if there was elimination of all evidence of lymphoma after therapy. Progression of disease was defined as a growth of more than 25% in size or development of new sites of disease. Overall survival (OS) was defined as the time from disease diagnosis to death due to any cause. Progression-free survival was defined as the time from the date of diagnosis to the date of documented disease progression or death of disease or due to treatment toxic effects.

There were two patients with HIV-associated extraoral PBL in the present study. The first case was a 10-year-old girl who had clavicular swelling with an expansile lytic lesion at the medial end of the clavicle on X-ray chest and increased uptake in the right clavicle on bone scan. Her work up for multiple myeloma was negative. She underwent open biopsy of clavicular lesion under general anesthesia and was diagnosed to have PBL. During work up, she was detected to be HIV +ve and her CD4 count was 53/mm³. She received CHOP 4 cycles along with ART. She is on regular follow-up, in CR, and disease free for the last 18 months. The other patient was already receiving antiretroviral drugs for the previous 2 years before being diagnosed with PBL (CD4 count 371/mm³; primary site-rectum). He received only supportive care in view of poor performance status and died within 3 months. [Table 1 shows patient details of extra-oral PBL].

There were four patients initially evaluated at the Oral Oncology Department for gradually increasing ulcerative mass in the oral cavity. All were females with an age range of 10 to 45 years. A clinical examination, computed tomography (CT) scan of neck, chest, abdomen and pelvis, metabolic profile; bone marrow biopsy and cerebrospinal fluid examination, and immunohistchemistry studies were done for complete work up. The International Prognostic Index (IPI) score was assigned whenever possible if all five components constituting the score could be identified in the medical records. The Eastern Oncology Cooperative Group scale was used to determine performance status. Response to treatment was determined as complete if there was elimination of all evidence of lymphoma after therapy. Progression of disease was defined as a growth of more than 25% in size or development of new sites of disease. Overall survival (OS) was defined as the time from disease diagnosis to death due to any cause. Progression-free survival was defined as the time from the date of diagnosis to the date of documented disease progression or death of disease or due to treatment toxic effects.

Table 1: Patient details-extraoral plasmablastic lymphoma

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Clinical presentation, primary site and HIV status</th>
<th>IHC</th>
<th>Stage and chemotherapy given</th>
<th>Treatment response and current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>45/F</td>
<td>Abdominal pain; Primary site-ascending colon; HIV-negative</td>
<td>LCA +ve CD138 +ve</td>
<td>IEA; Received 2 cycles R-CHOP</td>
<td>PD after 2 cycles; died within 6 months</td>
</tr>
<tr>
<td>35/F</td>
<td>Abdominal pain; CT abdomen-left solid pelvic mass? Ovarian; CA-125-278 U/mL; Underwent cytoreductive surgery for suspected ovarian cancer; HIV negative</td>
<td>LCA +ve; CD138+CK -ve; CD20 -ve CD30 -ve; HMB -ve CG and SP -ve</td>
<td>IEA; was planned for chemotherapy</td>
<td>Had rapid progression with ascites, pleural effusion and died before starting chemotherapy</td>
</tr>
<tr>
<td>10/F</td>
<td>Clavicular swelling; Primary site-clavicle; Newly diagnosed HIV+ve; CD4-53/mm³</td>
<td>CD 138+; LCA+CD20 -ve; CD30 -ve CD79a -ve; Pax 5 -ve ALK -ve; EMA -ve Desmin -ve; MPO -ve</td>
<td>IIIE A; CHOP 4 cycles ART</td>
<td>On regular follow-up, in CR, DFS 18 months</td>
</tr>
<tr>
<td>39/M</td>
<td>Bleeding per rectum; Primary site-rectum</td>
<td>CD138+ CK-; CD 20- CD 30 -;HMB - Suggestive of PBL-clavicle</td>
<td>IV</td>
<td>Supportive care in view of poor performance status. Died within 3 months</td>
</tr>
</tbody>
</table>

cavity and later referred to the Medical Oncology Department as the biopsy specimen confirmed PBL. Three patients were male and one was female (median age 43.5 years; range 26-58 years). The primary site of involvement was oral tongue in two patients and buccal mucosa in the other two patients. Two of these four oral PBL cases were HIV positive. One of the patients was a previously diagnosed case of HIV infection taking ART for 15 months before lymphoma diagnosis (CD4 - 249/mm³) while the other patient was diagnosed to be seropositive at the time of lymphoma work up (CD4 - 264/mm³). After a multidisciplinary team discussion, all these patients were planned for chemotherapy followed by radiotherapy. Intensive high-dose chemotherapy in the form of CODOX-M/IVAC protocol (Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide and Cytarabine) was instituted to a 26-year-old male with PBL of the right gingivobuccal sulcus; however, he did not tolerate the chemotherapy and later on received palliative radiotherapy. The remaining of our oral PBL patients received CHOP chemotherapy. Two patients died during treatment and one patient was lost to follow-up after being in CR after six cycles of chemotherapy and did not come for radiotherapy. Only one of the four patients of oral PBL in our study completed the prescribed chemotherapy and radiotherapy schedule and is alive and disease free with a follow-up of 33 months. [Table 2 shows the patient details of oral PBL].

DISCUSSION

PBL is a distinctive B-cell neoplasm that shows diffuse proliferation of the large neoplastic cells, most of which resemble B-immunoblasts and have immunophenotype of plasma cells. PBL was originally described as a rare variant of diffuse large B-cell lymphoma (DLBCL) involving the oral cavity and occurring in the clinical setting of HIV and latent Epstein–Barr virus (EBV) infection. PBL has been described, less commonly, in extraoral locations and immunocompetent settings.

The pathogenesis of PBL is poorly understood and is likely dependent on a variety of molecular events and pathways. Based on immunohistochemical, molecular and genetic studies, PBL is thought to derive from the post-germinal center, terminally differentiated, activated B cells, probably in transition from immunoblast to plasma cell. By definition, these cells have undergone class switching and somatic hypermutation; however, there are chromosomal aberrations in these processes likely associated with the development of malignancy. A recent study has shown recurring rearrangements involving MYC, a well-known oncogene, and the immunoglobulin gene. PBL has a strong association with EBV infection. In HIV-associated PBL, 74% of the cases show presence of EBV within the tumor cells. EBV infection is demonstrated based on the expression of EBV-encoded RNA (EBER). The association between PBL and HHV8 at this time is unclear. Few studies have demonstrated expression of HHV8-associated proteins in PBL; however, other studies do not support such an association. PBLs usually have a characteristic immunophenotype; they are negative for the typical B-cell antigens, e.g. CD20, and positive for the plasma cell markers such as MUM1, EMA, CD38 and CD138. PBLs characteristically display a high rate of mitotic activity by the Ki-67 proliferation index.

More recently, several cases of extraoral PBL have been reported. Extraoral PBL has been described in both HIV-positive and -negative patients. In HIV-positive cases, the most commonly affected extraoral sites are the gastrointestinal tract, lymph nodes and skin. [Table 2 shows the patient details of oral PBL].

Table 2: Patient details-oral plasmablastic lymphoma

<table>
<thead>
<tr>
<th>Age/ gender</th>
<th>Clinical presentation, primary site and HIV status</th>
<th>HPE</th>
<th>Stage and CT given</th>
<th>Treatment response and current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/M</td>
<td>Oral cavity mass; Primary site- gingivobuccal sulcus; HIV –ve</td>
<td>LCA+CD138 + CK – CD 20 – CD 30 – HMB – Suggestive of PBL</td>
<td>IEA; CODOX-M/IVAC; local RT in view of poor chemotherapy tolerance</td>
<td>Died during treatment</td>
</tr>
<tr>
<td>58/M</td>
<td>Ulceroproliferative tongue growth; Primary site-tongue; HIV –ve</td>
<td>LCA+CD138+CK–CD20–CD30–HMB–Suggestive of PBL</td>
<td>IEA; CHOP 3 cycles</td>
<td>Died due to disease progression</td>
</tr>
<tr>
<td>35/F</td>
<td>Oral cavity mass; Primary site- alveolus; HIV +ve CD4-249</td>
<td>LCA+CD138+CK–CD20–CD30–</td>
<td>IEA; CHOP 6 cycles; ART</td>
<td>CR after chemotherapy; lost to follow-up after that</td>
</tr>
<tr>
<td>55/M</td>
<td>Ulceroproliferative growth; Primary site-oral Tongue; HIV +ve CD4: 264, HIV RNA: &gt;90,000 copies</td>
<td>LCA+, CD138+CD20-, CD3-, CD7-</td>
<td>IEA; CHOP 6 cycles followed by RT- 6 Mv photon beam 50 Gy/25; ART</td>
<td>CR after CT+RT On follow-up; DF for 33 months</td>
</tr>
</tbody>
</table>

A similar pattern is seen in patients with HIV-negative PBL, with the gastrointestinal tract being the most commonly involved extraoral site.[14] Other less common extraoral sites reported include the central nervous system,[15,16] paranasal sinus,[17] mediastinum,[18] lungs[19] and testes.[20] Our study results are consistent with the previously published literature with two of our extraoral PBL patients being HIV-negative and two being HIV-positive. In the present study also, the most common site of extraoral PBL was the gastrointestinal tract (colon and rectum in one patient each). Other extraoral PBL locations encountered were the ovary and clavicle.

In both HIV-positive and -negative patients, 60% of the patients present with an advanced clinical stage (i.e. Ann Arbor stage 3 or 4).[21] In the present study, both HIV-negative patients with extraoral PBL had stage IIE disease, one patient with HIV-associated PBL had stage IV disease and the remaining one HIV-associated PBL patient was staged as IIIIE. A. B symptoms have been reported in 33% of HIV-positive and 50% of HIV-negative patients at diagnosis.[22] Interestingly, none of our patients had B symptoms at presentation. PBL has been reported as the initial presentation of HIV infection in approximately 5% of the cases.[23] In the present analysis, of the two HIV-positive patients with extraoral PBL, one patient was already receiving antiretroviral drugs for the previous 2 years before being diagnosed with PBL (CD4 count 371/mm³) while a 10-year-old girl was detected to be HIV-positive during work up at our institute (CD4 53/mm³). Bone marrow involvement has been reported at 30% in both HIV-positive and -negative patients.[22] In the present study, bone marrow involvement was noted in only one patient with PBL of rectum who was HIV positive.

Median survival of PBL patients without chemotherapy is 3 months.[24] PBL shows an overall response rate (ORR) to chemotherapy of 77%, with 46% of patients achieving a CR and 31% a partial response (PR).[25] Median survival with Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and CHOP-like regimens is 14 months.[26] Because of the disappointing survival rates, the NCCN guidelines recommend against CHOP in favor of more intensive regimens, such as infusional EPOCH, HyperCVAD or CODOX-M/IVAC.

We had given R-CHOP to the patient with PBL of ileo-caecal region who had progressive disease after two cycles and died within 6 months of diagnosis. CHOP was given to a 10-year-old girl with PBL of the clavicle who had excellent response and is in CR with regular follow-up for the last 18 months. Two of our extraoral PBL patients could not receive chemotherapy due to rapid disease progression before starting chemotherapy and poor performance status, and succumbed to their illness within 3 months of diagnosis.

We had four patients with PBL of the oral cavity, three being male and one female (median age 43.5 years; range 26-58 years). After completion of staging work up, all the patients fell into stage IEA according to the Ann Arbor staging. In the oral cavity NHL, Ann Arbor staging does not appear prognostic, and patients with stage I disease should be treated the same as those with systemic disease.[27] Chemotherapy, radiotherapy or both are used in the treatment of NHL of the head and neck region. Gustavsson et al suggested that combination therapy is needed for aggressive head and neck NHL.[28] Shah et al. also reported the use of CHOP chemotherapy, followed by radiotherapy 45 Gy/25 fractions in the management of primary extranodal NHL of the oral cavity.[29] After multidisciplinary team discussion, all our patients were planned for chemotherapy followed by radiotherapy. We used the CODOX-M/IVAC protocol (Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide and Cytarabine) in a 26-year-old male with PBL of the right gingivobuccal sulcus; however, he did not tolerate the chemotherapy and later on received palliative radiotherapy. The remaining of our oral PBL patients received CHOP chemotherapy. Two patients died during treatment and one patient was lost to follow-up after being in complete remission after six cycles of chemotherapy and did not come for radiotherapy. Only one of the four patients of oral PBL in our study completed the prescribed chemotherapy and radiotherapy schedule and is alive and disease free with a follow-up of 33 months.

Our observations confirm that both oral and extraoral variants of PBL are characterized by an overall unfavorable outcome. In our series, the death rate in HIV-positive patients was less as compared with HIV-negative patients. Our data are consistent with the observation of prior literature, indicating that the prognosis of HIV-associated PBL can be significantly improved by the addition of highly active antiretroviral therapy to chemotherapy.[30,31] Further studies are needed to examine whether PBL of the oral mucosa and extraoral PBL exhibit distinct responses to therapy and prognoses.

CONCLUSION

Both oral and extraoral PBL are characterized by a generally aggressive clinical course, relative resistance to a variety of chemotherapy regimens and an overall unfavorable outcome. Prognosis of HIV-associated PBL can be significantly improved by the addition of highly active antiretroviral therapy to chemotherapy. Further large sample studies are needed to confirm these results.

REFERENCES


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