Plasmablastic lymphoma in immunocompetent and in immunocompromised patients: Experience at a regional cancer centre in India

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Abstract

Introduction: Plasmablastic lymphoma (PBL) is a rare lymphoma associated with immunosuppression. It is strongly associated with immunosuppression (human immunodeficiency virus [HIV]) and often occurs within the oral cavity. PBL is also seen in patients receiving immunosuppressive therapy; however, despite its predisposition for the immunocompromised patients, PBL has been diagnosed in immunocompetent patients. **Aim:** This study aims to prognostic factors and outcome of PBL in immunocompromised and in immunocompetent patients. **Materials and Methods:** We conducted a retrospective study at our institute from the year 2008 to 2015. **Results:** A total of 13 patients (8 males and 5 females) with PBL were identified. Eight patients (61.5%) had extraoral PBL (median age 30.2 years) and 5 patients (38.5%) had oral PBL (median age 44 years). Most common extraoral site was gastrointestinal tract. Eight (61.5%) out of 13 patients were HIV positive. More than 50% of patients had Ann Arbor Stage III or IV. All the cases were CD20 negative and CD138 positive. Seven out of 13 patients had Ki-67 more than 80%. Nine patients received cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Three patients were on best supportive care due to poor performance status (PS). One patient received intensive chemotherapy with CODOX-M/IVAC. The median overall survival was 9 months in HIV-positive patients and 6 months in HIV-negative patients. The prognosis was worse in patients with Ki-67 of >80%. **Statistical Analysis:** Survival curves were generated using the Kaplan–Meier method and analyzed using log-rank test and Fisher's *t*-test. **Conclusion:** The present study confirms that PBL in both HIV-positive and in HIV-negative patients has an overall unfavorable outcome. The most important prognostic factors are stage, ki-67, and the Eastern Cooperative Oncology Group PS of the patient at the time of presentation.

Key words: Immunocompetent, immunocompromised, ki67, plasmablastic lymphoma

Introduction

Plasmablastic lymphoma (PBL) is a rare lymphoma associated with immunosuppression. It is strongly associated with human immunodeficiency virus (HIV) infection and often occurs within the oral cavity. PBL is also seen in elderly patients with age-associated immunosuppression and other patients receiving immunosuppressive therapy; however, despite its predisposition for the immunocompromised patients, PBL has been diagnosed in immunocompetent patients.[1]

Since the initial reports of PBL, it has been described in several other sites, including the gastrointestinal tract (GIT), omentum, lung, nasal and paranasal regions, testes, bones, soft tissue, lymph nodes, bone marrow, skin, and CNS.[2]

Materials and Methods

A retrospective observational study was conducted at a regional cancer center in India from January 2008 to December 2015. A total of 560 cases of non-Hodgkin's lymphoma (NHL) were identified, out of which 13 cases (0.023%) were PBL. The patients' medical details were reviewed for information regarding age, gender, presenting complaints, and sites involved by PBL, HIV status, Ann Arbor stage, international prognostic index score, treatment given, response to treatment, complications during treatment, and treatment outcome.

Diagnosis of PBL was established by histopathologic examination and immunohistochemistry (IHC) studies. Complete workup of patients included hemogram, lactate dehydrogenase, complete metabolic profile, bone marrow biopsy, cerebrospinal fluid examination, and computed tomography (CT) scan of neck, chest, abdomen, and pelvis. The Eastern Cooperative Oncology Group (ECOG) scale was used to determine performance status (PS). 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 toxic treatment effects.

Results

We had eight patients diagnosed with extraoral PBL. There were three female and five male (median age 30.2 years; range 10–48 years). Our first patient was a 45-year-old female who had presented with abdominal pain, and after evaluation (CT abdomen and colonoscopy), was found to have a large polypoidal mass in the ascending colon. Histopathological examination (HPE) and IHC studies of the biopsy specimen confirmed the diagnosis of PBL. After complete workup, she was staged I_{EA} according to the Ann Arbor staging system. She received two cycles of rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy after which due to progressive disease she died within 6 months. The second case of extraoral PBL presented a diagnostic dilemma as her clinical, radiological, and laboratory parameters (CA125) strongly favored the diagnosis of ovarian carcinoma, and because fine needle aspiration cytology is contraindicated in ovarian cancer, she underwent cytoreductive surgery for suspected ovarian cancer, and the HPE and IHC studies of excised specimen revealed it to be a case of PBL. She had rapid progression with ascites, pleural effusion, and died before starting chemotherapy. The third case was a boy

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14 years of age who presented with the complaint of the abdomen pain. His CT abdomen revealed a mass lesion at the ileocecal junction, biopsy, and IHC of which was suggestive of PBL. His stage was IIIEB and was given four cycles of CHOP. He responded well to treatment and was in complete response (CR) post four cycles of CHOP; but then, he lost to follow-up for 3 months. He came back with recurrent disease, this time with lung involvement and expired due to respiratory failure. All these patients were HIV negative.

There were five patients with HIV – associated extraoral PBL in our 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 workup for multiple myeloma was negative. She underwent open biopsy of clavicular lesion under general anesthesia and was diagnosed to have PBL. During workup, she was detected to be HIV positive and her CD4 count was 53/mm^3. She received four cycles of CHOP along with ART. She is on regular follow up, in CR and disease free for the last 18 months. The second patient was already receiving antiretroviral drugs for the previous 2 years before being diagnosed with PBL (CD4 count 371/mm^3; primary site-rectum). He received only supportive care in view of poor PS and died within 3 months. The other three patients had left tibia, ascending colon, and stomach as the primary site of the disease. The patient with involvement of tibia was stage IIAE and was started on CHOP regimen. However, he expired after two cycles of chemotherapy due to sepsis. The patient with ascending colon disease had ECOG PS 3, stage IVAE and was planned for best supportive care only with steroids. He expired within 3 months of diagnosis. The patient with stomach involvement was a girl who received CHOP chemotherapy and now is in CR on follow-up regularly.

There were five patients initially evaluated at the Oral Oncology Department for gradually increasing ulcerative mass in the oral cavity and later referred to the Medical Oncology Department as the biopsy specimen confirmed PBL. Three patients were male, and two were female (median age 44.6 years; range 26–58 years). The primary site of involvement was oral tongue in two patients and buccal mucosa in the other three patients. Three of these five 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/mm^3) while the other two patients were diagnosed to be seropositive at the time of lymphoma workup (CD4–264/mm^3 and 272/mm^3). 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 two of the five patients of oral PBL in our study completed the prescribed chemotherapy and radiotherapy schedule. One is alive and disease free with a follow-up of 33 months. The other patient lost to follow-up after 10 months of treatment completion. The details of all the patients are in Tables 1 and 2.

Discussion

PBL is a distinctive B-cell neoplasm showing diffuse proliferation of the large neoplastic cells, which resemble

Table 1: Immunocompetent patients with plasmablastic lymphoma

Case	Age/sex	HIV status	Site	Ki-67 (%)	Ann Arbor stage	Treatment	Outcome
1	26/male	Nonreactive	Gingivobuccal sulcus	80	IEA	CODOX-M/IVAC	Expired during treatment
2	58/male	Nonreactive	Tongue	82	IEA	CT + RT	Dies due to disease progression
3	45/female	Nonreactive	Ascending colon	85	IEA	Progression after two cycles of R-CHOP	Died within 6 months of diagnosis
4	35/female	Nonreactive	Ovary	84	IEA	Expired before starting CT	
5	14/male	Nonreactive	Ileocecal junction	88	IIIEB	CHOP×4 cycles	Recurrence in 5 months

HIV=Human immunodeficiency virus, CT=Chemotherapy, RT=Radiotherapy, CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone

Table 2: Human immunodeficiency virus-positive patients with plasmablastic lymphoma

Case	Age/sex	HIV status	Site	Ki-67 (%)	Ann Arbor stage	Treatment	Outcome
1	10/female	Reactive	Clavicle	72	IIIEA	CHOP×4 cycles	DFS 18 months
2	39/male	Reactive	Rectum	80	IV	Best supportive care	Died in 3 months
3	38/male	Reactive	Left tibia	86	IIEA	2×CHOP	Died during treatment
4	48/male	Reactive	Ascending colon	78	IV	Best supportive care	Died in 2 months
5	12/male	Reactive	Stomach	70	IIIEA	CHOP×4 cycles	DFS 10 months
6	35/female	Reactive	Alveolus	68	IEA	CR after 6×CHOP	Lost to follow-up
7	55/male	Reactive	Tongue	50		CT + RT	CR DFS of 33 months
8	49/female	Reactive	Gingivobuccal sulcus	70		4×CHOP	Died in 9 months of diagnosis

HIV=Human immunodeficiency virus, CT=Chemotherapy, RT=Radiotherapy, DFS=Disease-free survival, CR=Complete response, CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone

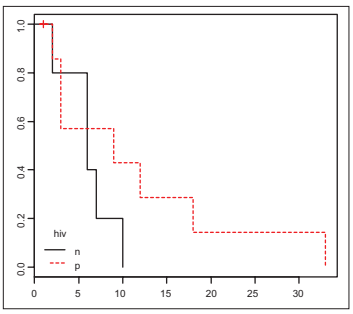

Figure 1: Survival analysis for human immunodeficiency virus positive versus negative

Human immunodeficiency virus	*n*	Observed	Expected	(O-E)^2/E	(O-E)^2/V
Negative	5	5	3.42	0.734	1.34
Positive	8	7	8.58	0.292	1.34

χ^2=1.3 on 1° of freedom, *P*=0.247

B-immunoblasts and have immunophenotype of plasma cells.[3] PBL was originally described as a rare variant of diffuse large B-cell lymphoma involving the oral cavity and occurring in the clinical setting of HIV and latent Epstein–Barr virus infection.[1] PBL has been described, less commonly, in extraoral locations and immunocompetent settings. PBLs usually have a characteristic immunophenotype; they are negative for the typical B-cell antigens, for example, CD20, and positive for the plasma cell markers such as MUM1, EMA, CD38, and CD138.[4] PBLs characteristically display a high rate of mitotic activity by the Ki67 proliferation index. More recently, several cases of extraoral PBL have been reported. Extraoral PBL has been described in both HIV-positive and HIV-negative patients. In HIV-positive cases, the most commonly affected extraoral sites are the GIT, lymph nodes, and skin.[5]

A similar pattern is seen in patients with HIV-negative PBL, with the GIT being the most commonly involved extraoral site. Other less common extraoral sites reported include the central nervous system, paranasal sinus, mediastinum, lungs, and testes. In the present study, out of five HIV-negative patients, three had extraoral primary, and two had oral site as the primary. In the present study also, the most common site of extraoral PBL was the GIT (five out of eight patients had GIT as the primary). Other extraoral PBL locations encountered were the ovary, tibia, and clavicle. In both HIV-positive and HIV-negative patients, 60% of the patients present with an advanced clinical stage (i.e., Ann Arbor Stage 3 or 4). In the present study, we found that most cases presented with advanced Ann Arbor stage. B symptoms have been reported in 33% of HIVpositive and 50% of HIV-negative patients at diagnosis. Interestingly, only one of our patients had B symptoms at presentation. Bone marrow involvement has been reported at 30% in both HIV-positive and HIV-negative patients.[5] In the present study, bone marrow involvement was noted in only one patient with PBL of the rectum who was HIV positive. The median survival of PBL patients without chemotherapy is 3 months.[6]

PBL shows an overall response rate to chemotherapy of 77%, with 46% of patients achieving a CR, and 31% a partial response. Median survival with CHOP and CHOP-like regimens is 14 months. We had given RCHOP to the patient with PBL of ileocecal 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. Three of our extraoral PBL patients could not receive chemotherapy due to rapid disease progression before starting chemotherapy and poor PS and succumbed to their illness within 3 months of diagnosis. We had five patients with PBL of the oral cavity, three being male and two females. After completion of staging workup, all the patients fell into stage IAE (according to the Ann Arbor staging) except one patient who was stage IIIAE. In the oral cavity NHL, Ann Arbor staging does not appear prognostic, and the patients with Stage I disease should be treated the same as those with systemic disease. Chemotherapy, radiotherapy or both are used in the treatment of NHL of the head and neck region.[7] In the present study, the median OS was 9 months in HIV-positive patients and 6 months in HIV-negative patients (P = 0.2). The prognosis was worst in the patients with Ki-67 of >80%. The survival analysis is shown in Figure 1.

Conclusion

The present study shows that PBL has an unfavorable prognosis in both immunocompetent and immunocompromised patients. The most important prognostic factors are stage, ki-67, and the ECOG PS of the patient at the time of presentation. Further prospective, randomized studies are required to delineate proper guidelines for the treatment of this disease.

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Conflicts of interest

There are no conflicts of interest.

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