Original Research Paper Oncology

Site as a Prognostic Factor in Plasmablastic Lymphoma: Experience at a Regional Cancer Centre

RUDRESHA AH	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
KC LAKSHMAIAH	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
LINU JACOB ABRAHAM	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
GOVIND BABU K	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
LOKNATHA D	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
SURESH BABU MC	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
RAJEEV LK	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
LOKESH KN	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029
*** ANKIT AGARWAL**	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029 * Corresponding Author
ASHOK S KOMARANCHATH	Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M.H. Marigowda Road, Bangalore, Karnataka – 560029

ABSTRACT

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. However, despite its predisposition for the immunocompromised patients, PBL has been diagnosed in immunocompetent patients. Due to its rarity, trials have not been conclusive about the site being a prognostic factor in PBL.

AIM: To study the site as a prognostic factor in PBL

MATERIAL AND METHODS: We carried out a retrospective study at our institute from the year 2008 to 2015 to identify PBL patients. After detailed clinical history, physical examination, histopathological examination and immunohistochemistry all the patients diagnosed with PBL were included in the study. All the patients were staged according to Cotswald modification of Ann Arbor staging system. Survival curves were generated using the Kaplan Meir method and analysed using the log rank test and Fisher's t-test.

RESULTS: 13 patients (8 males, 5 females) with PBL (plasmablastic lymphoma) were identified. 8 patients(61.5%) had extraoral PBL (median age 30.2years) and 5 patients(38.5%) had oral PBL (median age 44years). Most common extraoral site was GIT. 8 (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 thirteen patients had Ki67 more than 80%. Nine patients received CHOP chemotherapy. Three patients were on best supportive care due to poor PS. One patient received intensive chemotherapy with CODOX-M/IVAC. In our study the median OS was 9.5 months in oral PBL patients and 6 months in extraoral PBL patients (p=0.3). The prognosis was worst in patients with Ki-67 of >80%.

CONCLUSIONS: Our observations confirm that both oral and extraoral variants of PBL are characterized by an overall unfavorable outcome. The important prognostic factors are stage, ki67 and the ECOG PS at the time of presentation. Large randomized trials are needed to further assess the prognosis and the prognostic factors in extraoral and oral PBL.

KEYWORDS | plasmablastic lymphoma, immunocompetent, immunocompromised, ki-67.

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, omentum, lung, nasal and paranasal regions, testes, bones, soft tissue, lymph nodes, bone marrow, skin, and CNS. PBL has also been documented to arise from long-standing sacrococcygeal cysts in HIV-positive persons[2].

Although the clinical and pathologic features of this lymphoma are well characterized, its molecular pathogenesis remains poorly understood, partly owing to its rarity.

The diagnosis of PBL remains a diagnostic challenge given its rarity, peculiar morphology, and an immunohistochemical profile similar to PCM. Additionally, there is a wide differential diagnosis within the subgroup of DLBCL and PCM with plasmablastic morphology that is still a common problem because of the lack of a distinctive phenotype. Distinction between extramedullary plasmablastic neoplasms remains critical for patient management, and correlation with clinical findings is essential.

MATERIAL AND METHODS:

This was a retrospective observational study carried out at a tertiary cancer care in South India. We included patients diagnosed with PBL from January 2008 to December 2015. 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 (IPI) score, treatment given, response to treatment, 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(LDH); complete metabolic profile; bone marrow biopsy and cerebrospinal fluid examination, computed tomography (CT) scan of neck, chest, abdomen and pelvis. The Eastern Oncology Cooperative Group (ECOG) 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. Progressionfree 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 eight patients diagnosed with extraoral PBL (table 1). There were three females and five males (median age 30.2 years; range 10-48 years). Our first patient was a 45yearold 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. HPE and IHC studies of the biopsy specimen confirmed the diagnosis of PBL. After complete work up, she was staged IEA according to the Ann Arbor staging system. She received two cycles of RCHOP chemotherapy after which, unfortunately, she had progressive disease and 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 FNAC 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 14yrs of age who presented with complain of abdomen pain. His CT abdomen revealed a mss lesion at the ileocaecal junction, the biopsy and IHC of which was suggestive of PBL. His stage was IIIEB and was given 4 cycles of CHOP. He responded well to treatment and was in CR post 4 cycles of CHOP but then he lost to followup 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 HIVassociated extraoral PBL in the present study. The first case was a 10yearold girl who had clavicular swelling with an expansile lytic lesion at the medial end of the clavicle on Xray 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 followup, in CR, and disease free for the last 18 months. Second 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. The other threepatients had left tibia, ascending colon and stomach as the primary site of the disease. Patient with tibial involvement was stage IIAE and was started on CHOP regimen. However he expired after 2 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.

DISCUSSION:

PBL is a distinctive Bcell neoplasm that shows diffuse proliferation of the large neoplastic cells, most of which resemble Bimmunoblasts and have immunophenotype of plasma cells.[3] PBL was originally described as a rare variant of diffuse large Bcell lymphoma (DLBCL) involving the oral cavity and occurring in the clinical setting of HIV and latent Epstein–Barr virus (EBV) infection.[1] 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 postgerminal 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 wellknown oncogene, and the immunoglobulin gene.[4] PBL has a strong association with EBV infection.[4] In HIVassociated PBL, 74% of the cases show presence of EBV within the tumor cells.[4] EBV infection is demonstrated based on the expression of EBVencoded RNA (EBER). The association between PBL and HHV8 at this time is unclear. Few studies have demonstrated expression of HHV8associated proteins in PBL.[4] PBLs usually have a characteristic immunophenotype; they are negative for the typical Bcell antigens, e.g. 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 HIVpositive and negative patients. In HIVpositive cases, the most commonly affected extraoral sites are the gastrointestinal tract, lymph nodes and skin.[4]

A similar pattern is seen in patients with HIVnegative PBL, with the gastrointestinal tract being the most commonly involved extraoral site.[4] 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 gastrointestinal tract (five out of eight patients had GIT as the primary). Other extraoral PBL locations encountered were the ovary, tibia and clavicle. In both HIVpositive and 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 HIVnegative patients at diagnosis.[4] Interestingly, only one of our patients had B symptoms at presentation.. Bone marrow involvement has been reported at 30% in both HIVpositive and negative patients.[4] 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.[4]

PBL shows an overall response rate (ORR) to chemotherapy of 77%, with 46% of patients achieving a CR and 31% a partial response (PR). Median survival with Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and CHOPlike regimens is 14 months.[4] Because of the disappointing survival rates, the NCCN guidelines recommend against CHOP in favor of more intensive regimens, such as infusional EPOCH, HyperCVAD or CODOXM/IVAC. We had given RCHOP to the patient with PBL of ileocaecal region who had progressive disease after two cycles and died within 6 months of diagnosis. CHOP was given to a 10yearold girl with PBL of the clavicle who had excellent response and is in CR with regular followup 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 performance status, 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 work up, all the patients fell into stage IEA (according to the Ann Arbor staging) except one patient who was stage IIIEA. 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. 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.[4] 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[14]. Our observations confirm that both oral and extraoral variants of PBL are characterized by an overall unfavorable outcome (figure 1). In our study the median OS was 9.5 months in oral PBL patients and 6 months in extraoral PBL patients (p=0.3). The prognosis was worst in patients with Ki-67 of >80%.

CONCLUSION:

PBL has an unfavorable outcome even with intensive chemoregimens and studies have shown that 5 year survival is only 25% with treatment. The most important prognostic factors are stage, ki67 and the ECOG PS of the patient at the time of presentation. In our study we conclude that PBL has an unfavourable prognosis irrespective of the site of disease. Further Prospective randomized studies are required to delineate proper guidelines for the treatment of PBL.

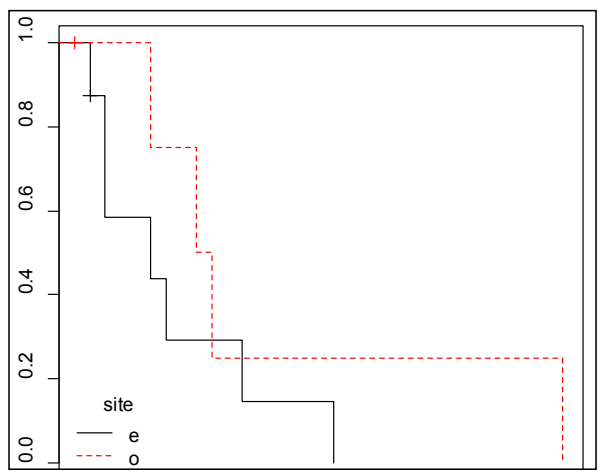

Figure 1 – survival analysis as per site – oral (o) or extraoral (e) N Observed Expected (O-E)^2/E (O-E)^2/V site=e 8 7 5.43 0.452 1.07 site=o 5 4 5.57 0.441 1.07 Chisq= 1.1 on 1 degrees of freedom, p= 0.301

Table 1: EXTRAORAL PLASMABLASTIC LYMPHOMA

case	Age/ sex	HIV status	Site	Ki67	stage	treatment	outcome
1.	45/F	Non reactive	Ascending colon	85%	IEA	Progression after two cycles of R-CHOP	Died within 6 months of diagnosis
2.	35/F	Non reactive	Ovary	84%	IEA	Expired before starting CT	
3.	14/M	Non reactive	Ileocaecal junction	88%	IIIEB	CHOP * 4 cycles	Recurrence in 5 months
4.	10/F	reactive	Clavicle	72%	IIIEA	CHOP*4 cycles	DFS 18mths
5.	39/M	reactive	Rectum	80%	IV	Best supportive care	Died in 3 months
6.	38/M	reactive	Left tibia	86%	IIEA	2* CHOP	Died during treatment
7.	48/M	reactive	Ascending colon	78%	IV	Best supportive care	Died in 2 months
8.	12/M	reactive	Stomach	70%	IIIEA	CHOP*4 cycles	DFS 10 months

Table 2: ORAL PLASMABLASTIC LYMPHOMA

case	Age/sex	HIV status	Site	Ki67	Stage	Treat-ment	out-come
1.	26/M	Non reactive	Gin-givo-buccal sulcus	80%	IEA	CO-DOX-M/ IVAC	Expired during treat-ment
2.	58/M	Non reactive	Tongue	82%	IEA	CT+ RT	Dies due to disease pro-gres-sion
3.	35/F	Reac-tive	Alveo-lus	68%	IEA	CR after 6* CHOP	Lost to F/U
4.	55/M	Reac-tive	Tongue	50%		CT+RT	CR DFS of 33 mths
5.	49/F	Reac-tive	Gin-givo-buccal sulcus	70%		4* CHOP	died with-in 9 months of diagno-sis

REFERENCES:

[1] Cattaneo C, Facchetti F. Oral cavity lymphomas in immunocompetent and human immunodeficiency virus infected patients. Lymphoma 2005;46:77-81.

[2] H. Y. Dong, D. T. Scadden, L. de Leval, Z. Tang, P. G. Isaacson, N. L. Harris ***etal***. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. The American Journal of Surgical Pathology 2005;29:1633-41.

[3] Stein H, Harris N, Campo E, Swerdlow S, Campo E, Harris NL ***etal***. WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC 2008:256-57.

[4] Kilger E, Kieser A, Baumann M, Hammerschmidt W. Epstein–Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J 1998;17(6):1700-09.

[5] Hsi ED, Lorsbach RB, Fend F, Dogan A. Plasmablastic lymphoma and related disorders. Am J Clin Pathol 2011;136(2):183-94.

[6] Vega F, Chang CC, Medeiros LJ. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol 2005; 18(6):806-15.

[7] Blood, 9 April 2015 x Volume 125, Number 15

[8] Castillo J, Pantanowitz L, Dezube BJ. HIVassociated plasmablastic lymphoma: lessons learned from 112 published cases. Am J Hematol 2008;83(10):804-09

[9] F. Vega, C. C. Chang, L. J. Medeiros. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Modern Pathology 2005;18:806-15.

[10] R. Lester, C. H. Li, P.Phillips. Improved outcome of human immunodeficiency virus-associated plasmablastic lymphoma of the oral cavity in the era of highly active antiretroviral therapy: a report of two cases. Leukemia and Lymphoma. 2004;45:1881-85.