ORBITAL PLASMABLASTIC LYMPHOMA : A CLINICO-PATHOLOGICAL CORRELATION OF A RARE DISEASE AND REVIEW OF LITERATURE

First Author: Kaustubh Mulay, MD

Second Author: Mohammad Javed Ali MD, FRCS.

Third Author: Vijay Anand Reddy, MD

Fourth Author: Santosh G Honavar MD, FACS.

Affiliations: Ocular Pathology Service (Dr Mulay) , Oncology Service (Drs Ali, Reddy and Honavar), L.V.Prasad Eye Institute, Road No 2, Banjara Hills, Hyderabad – 500034.

Corresponding Author : Santosh G Honavar MD, FACS.

honavar@lvpei.org

ETHICS STATEMENT: This study has been reviewed by the ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from the parents.

FINANCIAL DISCLOSURE: None

CONFLICT OF INTEREST: None

INTRODUCTION

Ocular adnexal lymphomas are relatively rare accounting for 0.1% of all lymphomas [1]. The current WHO classification recognizes plasmablastic lymphoma (PBL) as a distinct subtype of diffuse large B-cell lymphoma (DLBCL) characterized by presence of neoplastic cells resembling B immunoblasts but having immunophenotypic features of plasma cells [2]. Plasmablastic lymphoma (PBL) was first described to involve the oral cavity of predominantly HIV-positive patients [3]. Recently, several reports and case series have published the occurrence of PBL in other anatomical locations and in HIV-negative patients [4-8]. Ocular involvement by PBL is extremely rare with very few reports in literature [9-13]. Its morphological and immunological resemblance to plasma cell myeloma makes it a diagnostic challenge while its clinical course characterized by death and recurrence makes therapy a challenge for clinicians. We present 3 cases of PBL, each of which had distinct clinic-radiological features and and review the literature on orbital plasmablastic lymphomas.

CASE REPORTS

Case 1

A 45 year old previously healthy woman was referred to the ocular oncology clinic with history of proptosis of the right eye for 6 months and diminished vision in the right eye for 2 months. At presentation, her best corrected visual acuity (BCVA) was limited to finger counting in the right eye. Severe proptosis of right eye was noted with restriction of ocular motility in all directions (Figure 1a). Fundus examination of right eye showed macular folds, hyperemic disc and dilated tortuous vessels suggesting globe indentation and compressive optic neuropathy. A firm, hard, non-tender mass was palpable in the superolateral aspect of the orbit on the right side with erythematous skin. Resistance was observed on retropulsion. Computerized tomography of the

orbit showed a well defined, large soft tissue mass, 4.0x3.0x2.6cm in size, confined to the superolateral aspect of the right orbit with significant bony erosion involving the lateral wall with contiguous extension into the temporal fossa (Figure 1b).

Microscopic examination showed a diffuse tumour compose of discohesive large, round lymphoid cells with moderate amount of amphophilic cytoplasm, eccentric to central nucleus and a prominent nucleolus in many. A significant population of tumour cells had a plasmacytoid appearance both, normal and abnormal mitotic figures were seen. Immunostaining revealed a strong, membranous expression of CD138. K67 labeling index was 98%. No immunoreactivity for CD20 and CD45 was observed. A diagnosis of plasmablastic lymphoma was confirmed. Serum electrophoresis was within normal limits. Chest X-ray was normal. A bone marrow aspiration and trephine biopsy were performed which was normal. Our patient was staged as Ann Arbor 1A. HIV screening test performed was found to be negative. The patient died within a week following diagnosis, even before further treatment could be initiated.

Case 2

A 45-year-old Indian male was referred to our Oncology Clinic with protrusion of the left eye with associated redness, watering and pain. At presentation, his BCVA was 20/25 in the right eye and limited to light perception in the left eye. Conjunctival chemosis was observed with severe proptosis of the left eye (Figure 3a). Fundus examination could not be performed. Computed tomography showed a large hypodense mass in the anterior orbit on the superior and superolateral aspect of the globe. The mass indented the globe and was seen causing bony destruction with intracranial extension involving the frontal sinus and the Ethmoid sinus (Figure 3b). Since the patient gave a history of severe weight loss in the past 3 months, a HIV screening test was performed and was found positive.

Microscopic examination of the incision biopsy showed a diffuse tumour composed of a monotonous population of plasmacytoid cells with eccentric nuclei having a conspicuous to

prominent nucleolus. Mitotic activity was brisk. Immunohistochemically, CD3, CD20 and CD5 were found to be negative. The tumour cells expressed strong membranous immunoreactivity for CD138 and weak reactivity for LCA (CD45). Ki-67 index was close to 100%. No light chain restriction was seen. Morphology and immunostaining patterns were confirmative of a plasmablastic lymphoma.

Bone marrow aspiration done as a part of the staging protocol revealed involvement by plasmablastic lymphoma. Ultrasonography of the abdomen revealed multiple deposits in the liver. Serum LDH was normal. Our patient was thus staged as Ann Arbor IV.

He was commenced on HAART and CHOP regimen. The patient refused chemotherapy and died in 6 months following presentation.

Case 3

A 48–year-old Indian male presented with complains of pain, redness and watering in left eye for past 3 days. At presentation, his BCVA was limited to finger counting and light perception in the affected eye. Clinical examination revealed proptosis with edema, tenderness and edema of the left upper and lower lids with complete mechanical ptosis with restricted motility of the globe in all gazes (Figure 4a). Conjunctival chemosis was observed and rest of the anterior segment details could not be assessed. Severe peri-orbital, non-pitting edema with severe tenderness and bluish discoloration of the overlying skin accompanied by skin blistering was seen (Figure 4a). Upper lip edema with blisters were also noted (Figure 4b). A computerized tomography performed at this moment showed a diffuse mass occupying the entire superior orbit with extension into temporal fossa and orbital apex with globe compression and stretching of the optic nerve (Figure 4c and 4d). An incision biopsy was performed.

Microscopic examination showed a diffuse tumour composed of large plasmablastic cells with eosinophilic to amphophilic cytoplasm and an eccentric vesicular nucleus having prominent nucleoli. Mitotic activity was brisk. Few apoptotic bodies and an occasional binucleate cell were

also seen. Immunohistochemistry reveal a negative staining for CD45 and CD20. Strong membranous positivity for CD138 was observed. Ki67 index was 97-98%. This confirmed the diagnosis of a plasmablastic lymphoma. HIV screening test was performed and found to be positive. Bone marrow aspiration did not reveal involvement by plasmablastic lymphoma. HAART therapy was commenced. Following two cycles of chemotherapy that included Adriamycin, vincristine and cyclophosphamide, the patient is alive at 3 months post-diagnosis with improvement.

DISCUSSION

PBL is a rare subtype of DLBCL accounting for 0.1% of all lymphomas [1]. Ocular involvement by PBL is even rarer. Of all lymphomas diagnosed in our Institute, PBL accounted 0.62 %. A large study showed PBL having a mean age of 39 years at presentation in HIV-positive patients and 54 years in HIV-negative patients [16]. In patients with ocular involvement, including those in this case series, mean age at presentation in HIV-positive patients was 44.8 years. PBL presents more commonly in men than in women [18]. Of all PBL published in literature and having an orbital involvement, 71.4% were males. In our series 66.6% were males. PBL very rarely occurs in children [19-21]. Table 1 summarizes the clinical, radiological and histopathological features of ocular plasmablastic lymphomas reported in the literature.

PBL accounts for 2.6% of all AIDS-related lymphomas [15]. In a literature review of 228 cases of PBL 69% was HIV-positive while 39% were HIV-negative [14]. 6 of 7 (85.7%) PBL affected patients with orbital presentation described in literature were HIV-positive. In the present study 2 of 3 patients (66.6%) were HIV-positive. The association with other immunosuppressive states is conflicting. Some studies have reported some form of immunosuppression in HIV-negative patients with PBL [17] while others found no such immunosuppression [21]. The HIV-negative patient reported by us had no other form of immunosuppression. Despite the growing literature

on PBL, its pathogenesis is still not clear. A large number of molecular and immunohistochemical studies have tried to put light but no definitive pathogenesis mechanisms have been established. PBL is characterized by immunoblastic morphology and plasma cell phenotype. In other words, plasmablasts are lymphoid cells that morphologically resemble B-cell immunoblasts but have acquired a plasma cell immunophenotype. Thus PBL probably develops from post-germinal center, terminally differentiated, active B-cells in transition from immunoblast to plasma cell [18]. Recent studies have shown MYC gene rearrangements in PBL [19-22]. MYC gene rearrangements have not yet been studied on PBL involving the orbit. Most PBL are positive for Epstein-Barr virus (EBV) thus confirming its role in the pathogenesis of PBL. The role of HHV-8 in pathogenesis of PBL remains controversial. Some studies have detected HHV-8 RNA in PBL [23,24] while others have found negative results [25-27]. Some studies have documented simultaneous occurrence of Kaposi sarcoma, Castleman disease and PBL thus suggesting further associations with PBL [28]. None of the PBL involving the orbit has shown a positive association with HHV-8 till date.

Majority of patients having PBL present with diminution of vision and/or proptosis of the effected eye. Conjunctival chemosis [9,10], lid swelling [9], ptosis [10], loss of sensation along the trigeminal nerve [12] are other findings described on clinical examination. Vision is either reduced or lost in the effected eye. Globe motility of mild to severe degree is a consistent finding on examination. The three patients in the present study showed all the clinical findings mentioned above in various combination. Computed tomography reveals a soft tissue mass usually associated with bony destruction. Involvement of paranasal sinuses [9,12,13], intracranial tissues [11,12] nasopharynx [13] and eyelids [10] in contiguity may be seen. Involvement of ethmoid sinus, lid and temporal fossa was seen in the present series. At presentation, involvement of liver, bone marrow or lymph nodes is not uncommon given the highly aggressive nature of PBL [10,13]. Two patients in the present study had an Ann Arbor – stage 1 disease while one patient showed involvement of bone marrow and liver at

presentation. Orbital inflammation was the most common differential diagnosis made clinically at presentation. This reflects the challenge pose to the diagnosing physician.

Three categories of plasmablastic lymphoma have been described in literature [13,29,30]. Plasmablastic lymphoma of oral mucosa-type has a monomorphic population of plasmablasts with minimal or no plasmacytic differentiation. They are found largely in the oral mucosa but may also occur in other nodal or extranodal sites. Plasmablastic lymphoma with plasmacytic differentiation is composed predominantly of plasmablasts but exhibits a greater differentiation to mature plasma cells. These cells are round to oval with abundant eosinophilic to amphophilic cytoplasm, eccentric nucleus and a prominent nucleolus. Sometimes, a perinuclear Hof may be seen [18]. The third type is plasmablastic lymphoma associated with Castleman disease and is typically nodal or splenic in its location [31,32]. Syndecan-1 (CD138), CD38, VS38c and multiple myeloma oncogene [MUM1] are consistently expressed by PBL. Staining for CD45 and other B-cell markers CD20 or CD79a varies from absent to weak immunoreactivity. Reports on CD10, CD56 and Bcl-6 are conflicting [5,10,12,25]. Ki-67 is usually around the 100% mark, thus explaining the highly aggressive nature of PBL. Positive regulatory domain 1 (PRDM1/BL IMP1) protein and activated transcription factor x-box binding protein in 1(XBP 1) are proteins recently described to identify PBL reliably [33] as they are involved in terminal B-cell differentiation. Plasma cells myeloma (PCM), Burkitt lymphoma, DLBCL, ALK-positive large cell lymphoma with plasmacytoid features and primary effusion lymphoma (PEL) are other lymphoproliferative lesions that may exhibit a plasmablastic morphology. Detection of paraproteinemia in blood and/or excess light chains (Bence-Jones proteins) in urine, lytic bone lesions, and hypercalcemia or anemia favors the diagnosis of plasma cell myeloma over PBL. Negative or weak staining for PAX5 and CD20 coupled with positive staining for PAX5 and CD20 coupled with positive staining for PRDM1/BLIMP1 and XBP-1 help differentiate PBL from DLBCL as such a staining pattern is seen in <5% of DLBCL [34]. Strong expression of CD20 and CD79a help to differentiate Burkitt lymphoma from PBL. ALK expression and/or ALK-rearrangement

confirm an ALK-positive large cell lymphoma with plasmacytoid features while HHV-8 immunoreactivity helps to differentiate PEL. EBV- encoded RNA (EBER) ISH has been positive in majority of PBL involving the orbit, although it can be negative in a minor population of HIV-positive and a large proportion of HIV-negative patients with PBL [14]. We suggest a strong CD138, VS38c immunoreactivity coupled with a negative/weak CD20, CD79a reactivity and detection of EBER to be confirmative of PBL.

PBL is a fatal disease with a rapid clinical course characterized by relapse or early death despite treatment. Of all cases of PBL with orbital presentation described in literature, only two survived beyond a period a period 10 months past-diagnosis. No long term follow-up is available. Two patients in the present study died within 6 months post-diagnosis while 1 is on remission at 3 months post – diagnosis.

No validated guidelines are available for treating PBL. Most clinicians end up treating PBL like other lymphomas. CHOP and CHOP–like regimens have been tried with varying intensities. However intensifying the CHOP regimen has not be shown to improve overall survival [20]. Rituximab added to the CHOP regimen (R-CHOP) does not have a role in the treatment of PBL given the CD20-negative nature of these tumours although it could be added in those with a weak CD20 expression. Chemotherapy has been shown to induce overall response rate of 77%. HIV-positive patients who discontinue or do not initiate highly active retroviral therapy (HAART) show a higher rate of relapse [20]. A combination of HAART and chemotherapy increases the response rate [35,36]. EPOCH, CODOX-M/IVAC, DHAP, PmitCEBO and BEAM have been tried in PBL with little or no success [9,20]. Autologous stem cell transplantation has been experimented in PBL but the follow-up data is not long enough to conclude its effectiveness [37]. Responses to bortezomib have been encouraging but the data available is limited [38]. Overall, the treatment of PBL is quite puzzling. It thus poses a therapeutic challenge to clinicians. The recent advancement has been the identification of loss of p16 and MDR-1 in PBL (39).

CONCLUSION

Orbital involvement by PBL, although rare, is not uncommon with a higher prevalence in HIV-positive individuals. Recent studies on MYC translocation and positive identification of EBER have tried to explain the pathogenesis of PBL and its aggressive nature. Yet, the exact pathogenic mechanisms remain elusive. Morphological and immunohistochemical overlapping with other lymphoproliferative lesions pose a diagnostic challenge to the pathologist. Though the treatment has been revolving around CHOP and CHOP–like regimens, no validated treatment is currently available. Features at presentation simulate an inflammatory process thus making PBL a clinical challenge. Further research is recommended to develop an effective treatment. Lastly, given the aggressive nature of PBL and its propensity to early death despite treatment, early clinical diagnosis might increase the overall survival of such patients.

REFERENCES

1. Norton AJ. Monoclonal antibodies in the diagnosis of lymphoproliferative diseases of the orbit and orbital adnexae. Eye. 2006; 20:1186-88.
2. Swerdlow SH, Campo E, Harris NL et al. Tumour of hematopoietic and lymphoid tissues. In World Health Organization classification of tumors. 2008, Vol 4, IARC Press, Lyon, France
3. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood. 1997; 89:1413–1420.

4. Chabay P, De Matteo E, Lorenzetti M, et al. Vulvar plasmablastic lymphoma in a HIV-positive child: a novel extraoral localization. J Clin Pathol. 2009;62:644-6.
5. Thakral C, Thomas L, Gajra A,. Plasmablastic Lymphoma in an Immunocompetent Patient. J Clin Oncol. 2009;27:78-81.
6. Khurana A, Jalpota Y. Plasmablastic lymphoma in a human immunodeficiency virus negative patient. Ind J Pathol Microbiol. 2010;53:368-9.
7. Brahmania M, Sylwesterowic T and Leitch H. Plasmablastic lymphoma in the ano-rectal junction presenting in an immunocompetent man: a case report. *Journal of Medical Case Reports* 2011;5:168.
8. Kim JE, Kim YA, Kim WY, et al. Human immunodeficiency virus-negative plasmablastic lymphoma in Korea. Leuk Lymphoma. 2009;50:582-7.
9. Morley AM, Verity DH, Meligonis G, et al. Orbital plasmablastic lymphoma--comparison of a newly reported entity with diffuse large B-cell lymphoma of the orbit. Orbit. 2009;28:425-9.
10. Valenzuela AA, Walker NJ, Sullivan TJ. Plasmablastic lymphoma in the orbit: case report. Orbit. 2008;27:227-9.
11. Degnan AJ, Levy LM. Orbital plasmablastic lymphoma with remission following chemotherapy. Radiology Case. 2011;5:1-7.
12. Barkhuysen R, Merkx MA, Weijs WL, et al. Plasmablastic lymphoma mimicking orbital cellulitis. Oral Maxillofac Surg. 2008;12:125-8.
13. Colomo L, Loong F, Rives S, Pittaluga S et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogenous group of disease entities. Am J Surg Pathol. 2004; 28:736-47.
14. Castillo JJ, Winer ES, Stachurski D, Perez K, et al. Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma. Leuk Lymphoma. 51, 2047-53.

15. Carbone A and Gloghini A. Plasmablastic lymphoma: one or more entities? Am J Hematol. 2008;83:763-4.
16. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. Am J Hematol. 2008;83:804-9.
17. Rafaniello Raviele P, Pruneri G, Maiorano E. Plasmablastic lymphoma: a review. Oral Dis. 2009; 15:38-45.
18. Castillo JJ, Reagan JL. Plasmablastic lymphoma: A systematic review. The Scientific World J. 2011;11:887-98.
19. Dawson MA, Schwarer AP, McLean C, et al . Aids-related plasmablastic lymphoma of the oral cavity associated with an IgH/MYC translocation–treatment with autologous stem-cell transplantation in a patient with severe haemophilia-A. Hematologica. 2007;92:11-12.
20. Castillo JJ, Winer ES, Stachurski D, et al. Prognostic Factors in Chemotherapy-Treated Patients with HIV-Associated Plasmablastic Lymphoma. The Oncol. 2010;15: 293-9.
21. McGlaughlin KL, Bajel A, Mow CD. A case of plasmablastic lymphoma harbouring an IgH/MYC translocation in a HIV negative individual. 2010;42:697–9.
22. Bogusz AM, Seegmiller AC, Garcia R, et al. Plasmablastic lymphomas with MYC/IgH rearrangement: report of three cases and review of the literature. Am J Clin Pathol. 2009;132:597-605.
23. Dong HY, Scadden DT, de Leval L, et al. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. *Am J Surg Pathol.* 2005;29:1633-41.
24. Carbone A, Gloghini A, Gaidano G. Is plasmablastic lymphoma of the oral cavity an HHV-8-associated disease? *Am J Surg Pathol*. 2004;28:1538-40.

25. Vega F, Chang CC, Medeiros LJ, et al. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. *Mod Pathol.* 2005;18:806-15.
26. Brown RS, Power DA, Spittle HF, et al. Absence of immunohistochemical evidence for human herpesvirus 8 (HHV8) in oral cavity plasmablastic lymphoma in an HIV-positive man. *Clin Oncol*. 2000;12:194.
27. Carbone A, Gloghini A, Canzonieri V, et al. AIDS-related extranodal non-Hodgkin's lymphomas with plasma cell differentiation. *Blood*. 1997; 90: 1337-1338.
28. Cioc AM, Allen C, Kalmar JR, et al. Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. *Am J Surg Pathol*. 2004;28:41-6.
29. Teruya-Feldstein J. Diffuse large B-cell lymphomas with plasmablastic differentiation. *Curr Oncol Rep*. 2005;7:357-63.
30. Tavora F, Gonzalez-Cuyar LF, Sun CC, et al. Extra-oral plasmablastic lymphoma: report of a case and review of literature. *Hum Pathol*. 2006;37:1233-6.
31. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000; 95:1406-12.
32. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood*. 2002;99:2331-6.
33. Schebesta M, Harvey B, Busslinger M. Trancriptional control of B cell development. Curr Opin Immunol. 2002;14:216-23.
34. Montes – Moreno S, Gonzalez M , Singh A, et al. Aggressive large B-cell lymphoma with plasma cell differentiation: Immunohisto-chemical characterisation of plasmablastic lymphoma and diffuse large B-cell lymphoma with partial plasmablastic phenotype. Hematolegica. 2010;95:1342-9.

35. Teruya-FeldsteinJ, ChiaoE, et al. CD-20 negative large cell lymphoma with plasma blastic features: a clinically heterogenous spectrum in both HIV-positive and HIV negative patients. Oncol. 2004;15:1673-79.
36. Lester R, Li C, Philips P et al. Improved outcome of HIV-associated plasmablastic lymphoma of oral cavity in era of highly active anti- retroviral therapy : a report of two cases. Lark lymphoma. 2004;45:1881-5.
37. Goto H, Hagiwara S, Hirai R, et. al. Case of relapsed Aids – related PBL treatment with autologous stem cell transplantation and HAART. Rare tumours. 2011; 3:11.
38. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood. 2009; 113: 6069-76.
39. Matsuki E, Miyakawa Y, Asakawa S, et al. Identification of loss of p16 expression and up regulation of MDR-1 as genetic events resulting from two novel chromosomal translocations found in plasmablastic lymphoma of the uterus. Clin Cancer Res. 2011; 17: 2101-9.

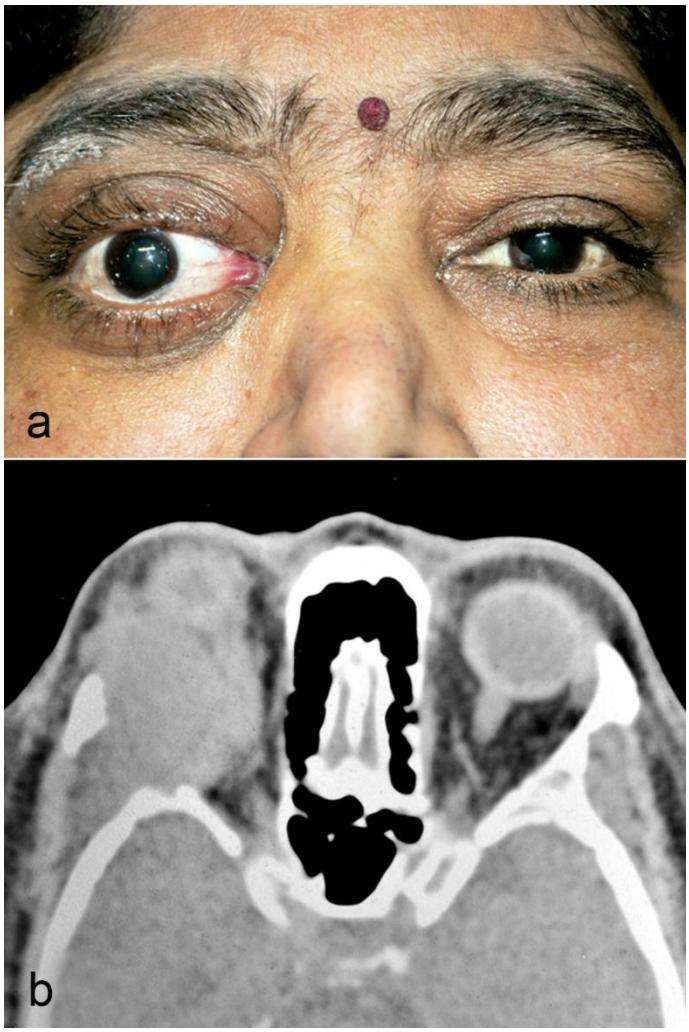

FIGURE 1: External photograph of the patient showing right eye proptosis with periocular swelling and mild conjunctival congestion (Fig 1a). CT Scan axial cut of the same patient showing a large mass occupying the lateral quadrant of the orbit with erosion of the lateral wall and extension into the temporal fossa (Fig 1b).

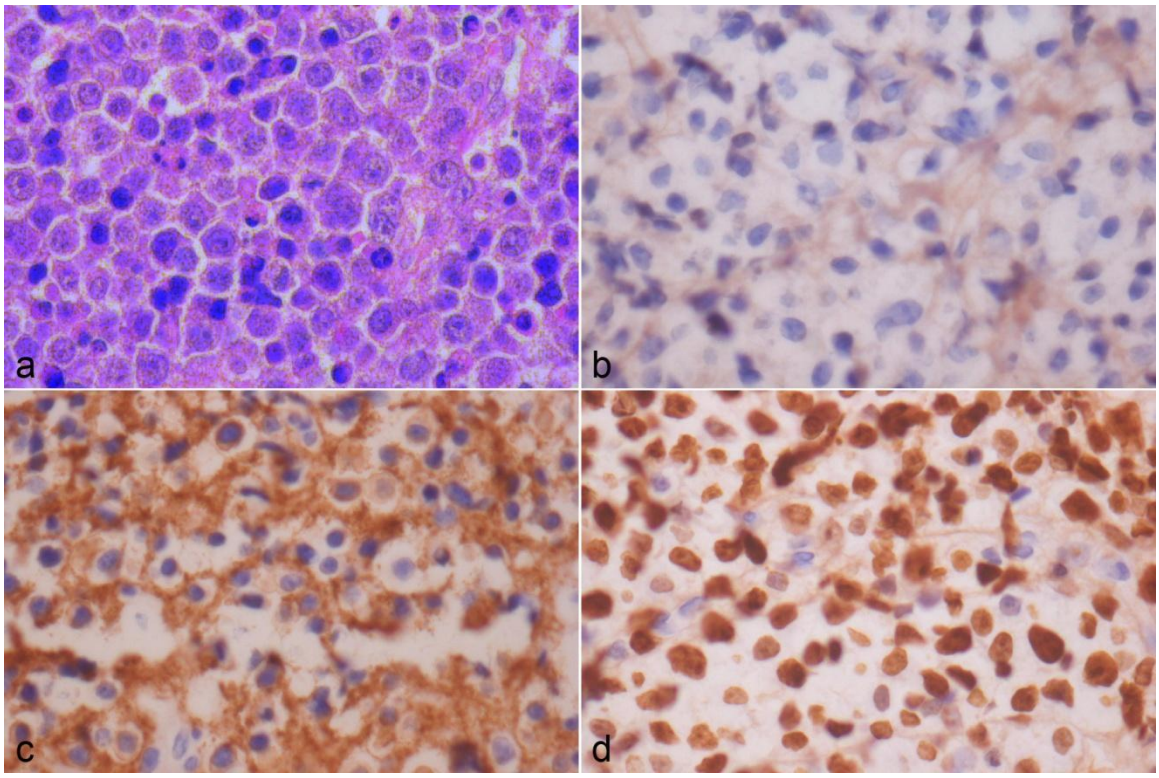

FIGURE 2: Microphotograph showing atypical plasmacytoid tumors cells with abundant amphophilic cytoplasm and a large eccentric vesicular nucleus having a prominent nucleolus (HE x400) (Fig 2a). Immunohistochemical staining shows lack of immunoreactivity for CD20 (x400) (Fig 2b), Strong membranous CD138 immunoreactivity (x400) (Fig 2c). Strong Ki-67 immunoreactivity in almost all tumors cells (x400) (Fig 2d).

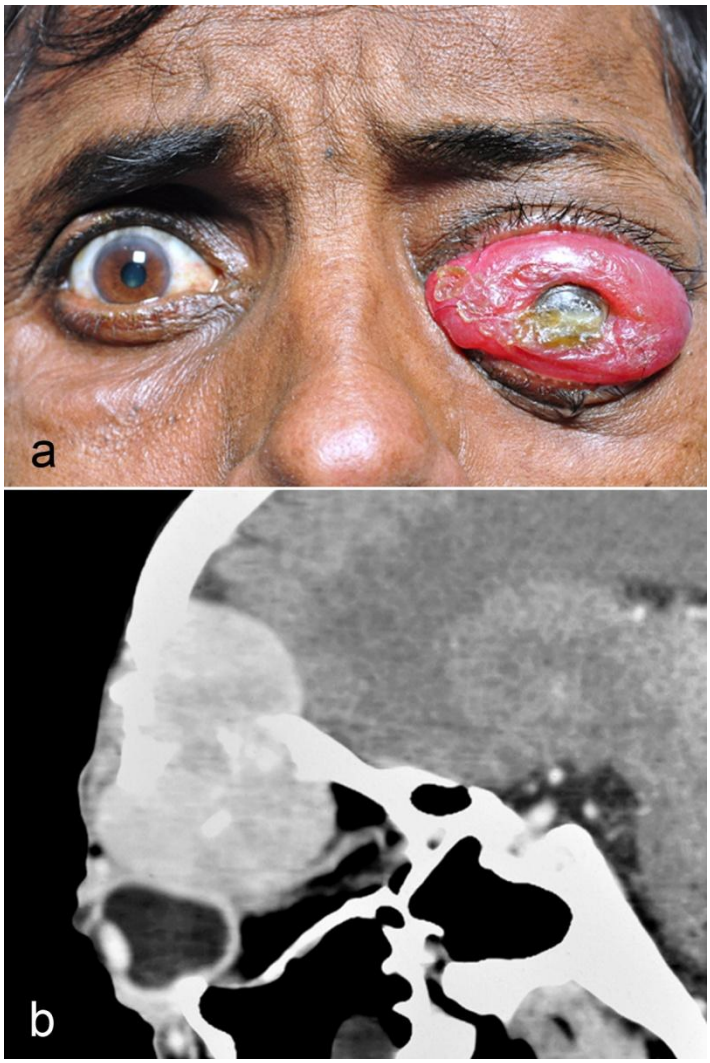

FIGURE 3: External photograph of the patient showing gross proptosis of the left eye with severe conjunctival chemosis (Fig 3a). CT scan with saggital reconstruction showing a large mass lesion in the superior orbit with extension into the frontal sinus and intracranial space (Fig 3b).

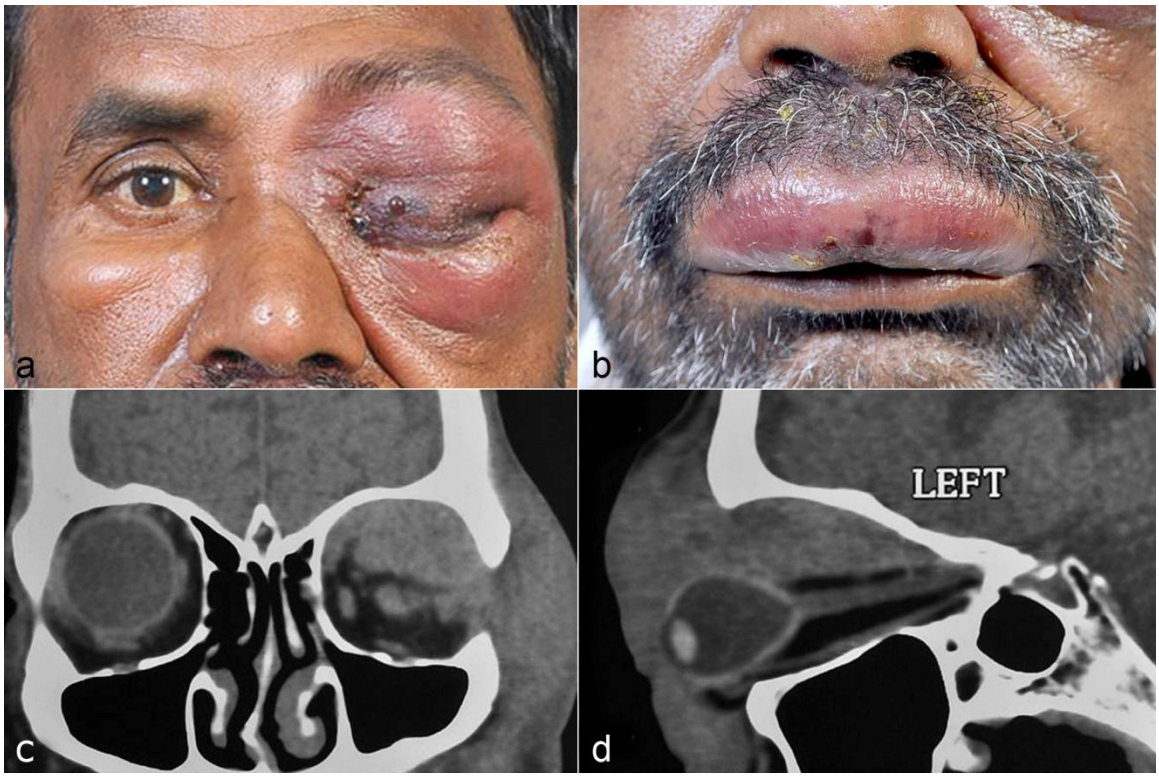

FIGURE 4: External photograph of the patient showing left periocular edema with total ptosis, skin induration and blisters (Fig 4a). External photograph showing upper lip edema with blisters (Fig 4b). CT Scan coronal cut of the same patient shows a diffuse ill-defined mass involving the entire superior orbit with superolateral bony erosion and extension into the temporal fossa (Fig 4c). CT Scan with saggital reconstruction showing diffuse mass involving the entire superior quadrant up to the apex with indentation of the globe and optic nerve stretch (Fig 4d).

TABLE 1: Summary of Clinical, Radiological and Histopathologic features of Ocular Plasmablastic lymphomas reported in literature.

Parameter	Morley et al. Case 1	Morley et al. Case 2	Barkhuysen et al.	Valanzuela AA	Degnan AJ	Colomo et al.	Colomo
Age	40	49	50	41	43	37	55
Sex	M	M	F	F	M	M	M
Race	West African	White		Caucasian	Caucasian		
Presentation	Nasal congestion & discharge, tender swelling over right cheek. Vision rapidly deteriorated to blindness in last 3 days.	2 months toothache, intermittent nasal discharge, prominence of left eye, true binocular diplopia on left gaze.	Proptosis, visual loss, ophthalmoplegia.	Upper lid induration. K/c/0 PBL of buccal region.	Proptosis, headache, eye pain. Jaw abscess 3 months ago.		Orbit, eyelid, maxilla
Laterality	Right	Left	Left	Right	Left		
BCVA	Blind		Reduced		-		
Pupils	Poorly reacting mid-dilated		Isocore. Dir pupillary reflex almost absent.		-		
IOP	33 mm Hg				-		
Fundus	Macular folds				-		
Proptosis	8 mm	2mm left	26mm		-		
Conjunctiva	Chemosis	Eyelids swollen	Anesthesia of left maxillary & ophthalmic branches of trigeminal nerve.	Chemosis Complete ptosis	-		
Retropulsion	Resistant				-		
Globe motility	Restriction of right ocular ductions	Restricted in all gazes		Restricted	-		
CT scan	Soft tissue mass in the posterior 1/3 of orbit, extension through superior orbital fissure.	Mass in the maxillary and ethmoidal sinus with bony erosion with orbital mass	Abscess in infratemporal fossa with extn to post cranial fossa, temporal fossa, maxillary sinus & orbit. Destruction of skull base.	Inhomogenous moderately circumscribed mass in the anterior orbit extending from preseptal tissues of upper lid to the lacrimal gland involving the extraconal tissues. Globe displaced	Retro-orbital mass with bony erosion into the sphenoid wing. Mass effect on globe. Mass in left temporal lobe and right fossa of Rosenmuller	Primary maxialry origin	
Hepatomegaly	+	Absent	-	+ Pulm, GIT Liver	-		
Lymphadenopathy	absent	Absent	-	+	Neck, abdomen, pelvis		
HIV status	Positive. CD4>200mm^3 Viral load undetectable	???	Positive	K/c/0 HIV for 10 years	Positive CD34 530/mm^3	Positive	Positive
Histopath	Plasmacytoid cells	Plasmacytoid cells	-	Large malignant lymphoid cells. Immunoblastic	Medium to large sized lymphoid cells	Large lymphoid cells with immunoblastic features	Large lymphoid cells with immunoblastic features
Initial Clin Diag	Cellulitis	Cellulitis	Abscess		-		
CD45		Weak	Poitive	Positive	-	Negative	Negative
CD20	Negative	Negative	Negative	Negative	-	Negative	Negative
CD138	Positive	Positive	Weak	Positive	Positive	+	+
CD79a	Negative	Negative	Weak	Negative	Weak	Negative	Negative
Vs38c	Positive	Positive	-	-	-		
Ki67	Nearly 100%	Nearly 100%	-	100%	-		

Parameter	Morley et al. Case 1	Morley et al. Case 2	Barkhuysen et al.	Valanzuela AA	Degnan AJ	Colomo et al.	Colomo
Other markers		-	Neg CD56, CD30, CD10	Weak CD10, Bcl6. Neg CD3, bcl2, Alk-1, CD30, CD56	CD10 positive		
EBV-LMP1	Negative	-		-	-		Negative
HHV-8	Negative	-		-	-		
EBER	Positive (ISH)	-	Positive ISH	Positive ISH	-	Negative	Positive
Bone marrow	Involved	Negative	Negative	Positive	-		
CSF		Positive	-	-	-		
Stage	4	1	1	4	-		1
Death	3 months	3 months	Alive at 13 months	Second day	Alive at 10 months		7 months
Treatment	CHOP followed by fractionated EBRT	CHOPx10, DHAP, PMitCEBO	HAART. R-CHOP. 18 cyc of IT-Mtx alternated with cytarabine/DAF. RT to skull	Could not be initiated. Was on HAART	EPOCH & Pegfilgrastim		
Course in FU	Lymphadenopathy Pleural effusion	Mesentric & paraaortic node++, nose mass, frontal sinus extension	Skull base reossification and regression of lymphoma.	Bleeding & ulceration from GI lymphoma. Succumbed on table.	Size reduced in 2 mnths, 5 mnths clear. 10 months lesion in retromandibular and cervical nodes and a new lesion in the fossa of Rosenmuller		