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# Oral plasmablastic lymphoma: A clinicopathological study of 113 cases

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## Abstract

**Background:** Plasmablastic lymphoma (PBL) is an aggressive neoplasm that commonly develops in HIV-positive patients, usually affecting the oral cavity. EBV is present in the majority of cases, therefore, playing an important role in the pathogenesis of this neoplasm.

**Methods:** PBL diagnosed from 2000 to 2020 were retrieved from the archives of the Department of Oral Pathology and Oral Biology at the University of Pretoria, South Africa. The patients' clinical information including gender, age, tumour location and HIV status was obtained from the original histopathology request forms. A morphological description was assessed using H&E-stained slides, with diagnoses confirmed by immunohistochemistry, and EBV detection performed via in situ hybridisation.

**Results:** During the 20 years period investigated, 113 PBL were found. Males outnumbered females (M:F ratio of 3:1), with a median age of 41 years (range 8–62). The gingiva (50 cases or 44.2%) and the palate (23 cases or 20.4%) were the most affected sites. All cases with available information were HIV positive. The tumours were composed of a diffuse proliferation of immunoblasts or plasmablasts in all cases. A starry-sky pattern, tissue necrosis, cellular pleomorphism and mitotic figures were common microscopic findings. IHC for CD3 and CD20 were negative in all cases, while positivity for CD38, CD138 and MUM1 was observed in 70.2%, 79.2% and 98.9%, respectively. EBV was present in 100% of the cases.

**Conclusion:** PBL is a frequent diagnosis in South Africa, due to the country's HIV burden, where it usually affects the oral cavity and is always associated with EBV infection.

KEYWORDS
EBV, HIV, lymphoma, oral cavity, plasmablastic lymphoma

## 1 | INTRODUCTION

Plasmablastic lymphoma (PBL) is defined as an aggressive lymphoid neoplasm comprising of a diffuse proliferation of immunoblasts and plasmablasts that are typically negative or only focally positive for the mature B-cell markers CD20/PAX5. The neoplastic cells may contain variable proportions of plasmacytic differentiation, demonstrating positivity for plasma cell markers such as CD38, CD138, VS38c and MUM1.[1] PBL was first described in 1997 and has since been strongly associated with HIV-positive patients, particularly in

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cases involving the oral cavity.[2] Subsequent studies demonstrated that PBL may develop in immunocompetent individuals, with other extraoral sites also affected.[3]

The pathogenesis of PBL remains poorly understood, but the presence of the Epstein-Barr virus (EBV) in the majority of cases is believed to play an important role in the development of the neoplasm.[4] Moreover, Hassan et al. (2007)[5] demonstrated that the recurrent translocation t(8;14) involving *C-MYC* and *IGH* genes is present in PBL, which was latter demonstrated to be found in approximately 50% of the cases, being considered an important molecular event in the pathogenesis of this malignancy.[6]

South Africa has the highest burden of HIV/AIDS in the world and, for this reason, the incidence of HIV-related lymphomas, including PBL, is high.[7] This article aims to describe a large series of PBLs from a single South African diagnostic centre, with an additional review of the available literature regarding the clinicopathological and molecular data of this aggressive neoplasm. This study forms part of a special issue published by the Journal of Oral Pathology and Medicine covering the most important aspects of haematolymphoid lesions and neoplasms affecting the oral cavity and neighbouring structures.

## 2 | MATERIAL AND METHODS

This study was conducted following approval by the University of Pretoria, Faculty of Health Sciences Research Ethics Committee (Reference no.: 161/2020). All procedures followed the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

All cases diagnosed as PBL affecting the oral cavity from January 2000 to March 2020 were retrospectively retrieved from the pathology archives of the Department of Oral Pathology and Oral Biology, University of Pretoria (South Africa). Using H&E-stained sections, immunohistochemical reactions and in situ hybridisation for detection of EBV, PBLs were diagnosed by at least one oral and maxillofacial pathologist following the World Health Organization (WHO) guidelines for classification of Haematolymphoid neoplasms.[8] Relevant clinical information of each case was obtained from the histopathology request form, including details on gender, age, tumour location and HIV status.

Briefly, immunohistochemical reactions were performed on 3µm sections from formalin-fixed paraffin-embedded (FFPE) tissue blocks that were dewaxed and hydrated with distilled water. Antigen retrieval was performed on all sections in a Pascal Pressure Chamber (Dako Cytomation Inc.) in a high TRIS/EDTA pH buffer. Sections were treated with hydrogen peroxide to reduce endogenous peroxidase activity, rinsed and then incubated with the following antibodies: CD3 (Novocastra RTU clone PS1) (Leica Biosystems Newcastle Ltd), CD20 (Dako RTU clone L26) (Dako Cytomation Inc), CD38 (Novocastra 1:100 clone SPC32), CD138 (Dako 1:100 Clone MI15), MUM1 (Dako RTU clone Mum1p) and Ki-67 (Dako RTU clone MIB1) for 120 minutes at room temperature. After rinsing in phosphate saline buffer, detection was performed using the Novocastra Novolink Polymer Kit. Sections were counterstained with haematoxylin and mounted with DPX permanent mountant. Appropriate positive controls were used for each marker, whereas the omission of a primary antibody was used as a negative control for the reactions. Red-brown granular staining either on the cell membrane (CD3, CD20, CD38 and CD138) or nucleus (MUM1 and Ki-67) was considered as positive, which was recorded based on the percentage of positive staining cells as follows: focal (5%–20%), moderate (20%–70%) or diffuse (>70% of cells).

EBV detection was performed in all cases investigated via in situ hybridisation (ISH). Briefly, ISH was performed on 3 µm FFPE tissue sections using the Ventana Benchmark GX (Ventana Medical Systems Inc.) system. EBV mRNA target was retrieved with Ventana Protease 3 enzyme and Ventana CC2 low pH solutions. Hybridisation with Ventana Epstein-Barr Virus Early RNA fluorescein labelled probe (Ventana Medical Systems Inc), followed by detection with the Ventana ISH/iVIEW Blue kit. The sections were then counterstained with Ventana Red Counterstain II, rinsed, dehydrated in acetone, cleared in Xylene and mounted with DPX permanent mountant. Results were recorded as either positive or negative.

## 3 | RESULTS

During the 20 years period investigated, 113 cases diagnosed as plasmablastic lymphoma affecting the oral cavity, with or without extension to neighbouring structures, were identified. Forty-five cases were previously reported by Boy et al (2010). These cases were included in the current series to better demonstrate the clinicopathological features of this neoplasm. Eighty-five cases affected males, whereas 28 cases affected females, leading to a M:F ratio of 3:1. Data regarding patients' age was available for 111 cases, and ranged from 8 to 62 years, with a median age of 41 years. The gingiva was the most commonly affected site (50 cases or 44.2%). The upper gingiva was affected in 22 cases, the lower gingiva in 20 cases and in 8 cases the exact gingival region was not specified. The palate was affected in 23 cases (20.4%), followed by the buccal mucosa (18 cases or 15.9%), retromolar region (1 case or 0.9%) and upper lip (1 case or 0.9%). There were 20 cases (17.7%) affecting the oral cavity with no further details regarding extension to neighbouring structures such as the maxillary sinus, orbit and parotid gland (Figure 1). The HIV status of the affected patients was available for 91 cases, with all cases being seropositive for the disease. In 21 patients, this information was not available.

Microscopically, neoplastic cells were diffusely distributed in the connective tissue of the oral mucosa, commonly infiltrating normal neighbouring structures including minor salivary glands, muscle fibres, nerves and adipocytes. At low magnification, the oral mucosa was frequently ulcerated, with the underlying neoplastic infiltrate showing a so-called starry-sky appearance due to numerous tingible body macrophages. Large areas of tumour necrosis were also a common finding. All cases contained large neoplastic cells with abundant cytoplasm and centrally or more frequently eccentrically located


**FIGURE 1** Clinical manifestations of PBL. (A) A female patient presenting with a large swelling involving the right submandibular region. (B) A male patient exhibiting an aggressive tumour affecting the maxillary gingiva with overlying areas of ulceration and necrosis

nuclei containing a single amphophilic nucleolus, reminiscent of either immunoblasts or plasmablasts. However, smaller cells with eccentric nuclei exhibiting multiple nucleoli at the periphery and a large cytoplasm with a lighter perinuclear hof region were also identified in many cases. These neoplastic cells represented the so-called plasmacytic differentiation of PBL, although some of these cells may also represent a reactive non-neoplastic component. Cellular pleomorphism with bizarre morphology and atypical mitotic figures were common findings (Figure 2).

Immunohistochemically, 100% of the cases were negative for the mature B-cell marker CD20 and the T-cell marker CD3, although a variable amount of positive reactive cells was observed in all cases. All cases were positive for at least one plasma cell marker. Staining for CD38 was available for 94 cases, being negative in 28 cases, focally positive in 18 cases, moderately positive in 6 cases and diffusely positive in 42 cases. The CD138 marker was available for 106 cases with 21 negative, 21 focally positive, 4 moderately positive and 60 diffusely positive. MUM1 protein was available for 87 cases, with only one negative case and 86 diffusely positive cases. EBV via in situ hybridisation was positive in all 113 cases evaluated (Figure 2).

## 4 | DISCUSSION

Plasmablastic lymphoma is a high grade, aggressive malignant neoplasm that was first described by Delecluse et al. in 1997.[2] Since then, the neoplasm has been shown to have a strong predilection for the oral cavity. Several case series are currently available in literature describing the clinical and microscopic features of this important entity, with the main examples summarised in (Table 1). To date, the current series is the largest single centre study specifically describing PBLs affecting the oral cavity. Alli et al. (2017)[7] recently reported 132 cases in their sample; however, the author's main objective was to describe the distribution of all AIDS-related lymphomas of the head and neck region. Therefore, this series did not provide a detailed individual description of their oral PBL cases. In the current series, we demonstrate the strong association of PBL with both EBV- and HIV infection, reinforcing this important biological relationship.[4]

PBL accounts for approximately 2.6%–3% of all lymphomas diagnosed in HIV-positive patients, being considered an AIDS-defining disease. Some of the largest published series on PBL, including the publication by Boy et al in 2010[9] describing 45 cases, were carried out in South Africa.[7,10,11] This can be explained by the high burden of HIV in this country, with over 5 million infected individuals.

PBL is strongly associated with HIV infection, usually developing in patients with CD4+ T-cell counts lower than 200 cell/ml$^3$ and variable viral loads. However, this neoplasm has also been diagnosed in other groups of immunosuppressed patients. This includes post-transplant patients, those affected by chronic immune diseases, and in elderly individuals in which ageing immune senescence may explain the tumour onset.[12] More recently, PBL associated with local chronic inflammatory processes have also been described.[13] Nevertheless, this lymphoma may also be diagnosed in immunocompetent patients as demonstrated in Table 1.

The importance of HIV status for the clinical behaviour of plasmablastic lymphoma remains debatable. Some studies have demonstrated that seropositive patients to carry higher survival rates,[13] whereas the majority failed to obtain any significant association with patient prognosis.[3] Other authors postulate a better prognosis among HIV-positive individuals as these patients are generally younger and therefore respond better to antiretroviral therapy (ART) and chemotherapeutic regimens.[3,13] Several studies have also demonstrated a strong association between EBV-positive PBLs and HIV-positive patients.[3,4] The prognostic importance of EBV is also unclear, with contradictory results currently reported. However, the aetiologic role played by this virus is already accepted, being found in the majority of the cases, and all cases in the current sample. Most EBV-positive cases are classified as latency type I infection, although Morscio et al. (2014)[12] demonstrated the expression of LMP-1 protein, therefore classifying a subset of cases as latency type II, and in rare instances as latency type III. Although a small proportion of cases can be EBV negative, EBV infection is considered a useful diagnostic auxiliary for excluding other histologic mimickers, including plasma cell myeloma and ALK + large B-cell lymphomas. These neoplasms often demonstrate plasmacytic/plasmablastic differentiation, but generally lack EBV infection (rare cases of myeloma might be positive). Interestingly,

**TABLE 1** Clinicopathological features of plasmablastic lymphoma described in the main cases series published in the literature

| Authors/year | Country | Cases | Sex (M/F) | Age[a] (range) | Site oral (yes/no) | Stage (I+II/ III+IV) | HIV (pos./ neg.) | CD4 count (median) | *MYC* transloc. (yes/no) | EBV (pos./ neg.) | Complete remission | Outcome (Alive/ Dead) | OS time | PFS | Overall survival |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Witte et al., 2020[16] | Germany | 76 | 59/17 | 63 (26–91) | – | 21/55 | 30/46 | – | 35/28 | 42/34 | 18 out of 72 | – | – | – | – |
| Li et al., 2020[26] | China | 8 | 7/1 | 53 (27–69) | 2/6 | 4/4 | 0/8 | – | – | 1/7 | 5 out of 7 | 5/2 | – | – | – |
| Meer et al., 2020[11] | South Africa | 45 | 27/18 | 37.2 (9–59) | 0/45 | – | 29/0 | (11–410) | 10/11 | 37/3 | – | – | – | – | – |
| Miao et al., 2019[21] | China | 13 | 10/3 | 50 (22–66) | 3/10 | 6/3 | 1/12 | – | 3/10 | 8/5 | – | 8/5 | 11.3 | – | 31% at 2yrs |
| Arora et al., 2019[25] | USA | 29 | 21/8 | 50 (25–75) | 9/20 | 9/20 | 26/3 | 87 (9–681) | 12/4 | 27/2 | 12 out of 24 | 11/17 | 15.9 | – | – |
| Zuze et al., 2018[27] | Malawi | 12 | 7/5 | 46 (26–71) | – | 9/3 | 6/6 | 147 (9–460) | – | 5/2 | 5 out of 12 | 5/7 | – | – | 56% at 1yr |
| Rudresha et al., 2017[28 c] | India | 13 | 8/5 | 30.2 (10–48) | 5/8 | 5/6 | 8/5 | 264 (53–371) | – | – | 3 out of 8 | 4/6 | 9 and 6 | – | – |
| Alli et al., 2017[7] | South Africa | 159 | 104/55 | 39.1 (11–84) | 132/27 | – | 89/1 | – | – | 19/24 | – | – | – | – | – |
| Han et al., 2017[29] | China | 6 | 3/3 | 56.8 (43–76) | 0/6 | 2/4 | 0/6 | – | – | 0/5 | – | 6/0 | 10 | – | – |
| Wang et al., 2017[30] | China | 6 | 6/0 | 43.8 (30–74) | 3/0 | 5/1 | 6/0 | 41 (1–381) | 3/3 | 4/2 | 1 out of 3 | 3/1 | – | – | – |
| Montes-Moreno et al., 2017[1] | Spain | 36 | 26/10 | 58 (29–92) | – | 5/15 | 11/25 | – | 12/14 | 21/15 | – | – | – | – | – |
| Pinnix et al., 2016[24] | USA | 10 | 9/1 | 50.5 (28–74) | 1/9 | 10/0 | 2/8 | – | 1/1 | 7/3 | 9 out of 10 | 9/1 | – | 90% at 2 yrs | 100% at 2 yrs |
| Tchernonog et al., 2016[13] | France/ Belgium | 135 | 108/27 | 58 (16–88) | 25/106 | 72/62 | 56/79 | 0.23 (0.13–1.1)[b] | – | 63/39 | – | – | 32.0 | – | – |
| Koizumi et al., 2016[18] | Japan | 24 | 24/0 | 44 (24–59) | 9/15 | 8/16 | 24/0 | 67.5 (1–520) | 5/3 | 20/2 | 10 out of 23 | 10/14 | 15 | – | – |
| Laurent et al., 2016[31] | France | 82 | 62/20 | 62 (22–88) | 26/56 | 22/22 | 28/41 | – | 10/26 | 39/38 | 22 out of 41 | 23/24 | – | 40.8% at 2 yrs | – |
| Noy et al., 2015[32] | USA | 12 | – | 44 (18–60) | 0/12 | 6/6 | 12/0 | 136 (2–514) | – | 8/0 | 7 out of 12 | 12/0 | – | – | 66.7% at 1yr |
| Elyamany et al., 2015[33] | Saudi Arabia | 8 | 6/2 | 51.5 (20–59) | 2/6 | 1/7 | 2/6 | – | 1/7 | 0/6 | 0 out of 6 | 0/8 | 5.5 | – | – |
| Loghavi et al., 2015[3] | USA | 61 | 49/12 | 49 (21–83) | 21/40 | 19/24 | 20/30 | – | 10/5 | 40/17 | 19 out of 39 | 18/43 | 7 | – | – |
| Chapman et al., 2015[14 d] | USA | 15 | 9/6 | 40 (4–60) | 5/10 | 3/12 | 9/6 | 102 (23–458) | 2/2 | 9/6 | – | – | – | – | – |
| Cattaneo et al., 2015[34] | Europe | 24 | 18/6 | 43 (16–63) | – | – | 7/1 | – | – | – | 12 out of 24 | 15/9 | – | 30% at 2 yrs | 53% at 2 yrs |
| Schommers et al., 2015[35] | Germany | 34 | 33/1 | 47 (26–74) | – | – | 34/0 | 0.15 (0–1.1)[j] | – | – | – | 18/15 | – | – | 43% at 2 yrs |
| Morscio et al., 2014[12] | Belgium | 25 | 23/2 | 57.6 (6–79) | 4/21 | – | 2/23 | – | – | 16/9 | – | 11/13 | – | – | – |
| Vaubell et al., 2014[10] | South Africa | 11 | 9/2 | 11.5 (5–18) | 1/11 | 1/5 | 11/0 | 262 (9–800) | 2/1 | 10/1 | 4 out of 9 | 2/5 | 12 | – | – |

(Continues)

TABLE 1 (Continued)

| Authors/year | Country | Cases | Sex (M/F) | Age[a] (range) | Site oral (yes/no) | Stage (I+II/ III+IV) | HIV (pos./ neg.) | CD4 count (median) | *MYC* transloc. (yes/no) | EBV (pos./ neg.) | Complete remission | Outcome (Alive/ Dead) | OS time | PFS | Overall survival |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cattaneo et al., 2014[19] | Italy | 17 | 14/3 | 36 (25–54) | 7/10 | 3/14 | 17/0 | 241 (13–727) | 5/3 | 13/0 | 14 out of 15 | 11/6 | – | 53% at 3 yrs | 66.7% at 3 yrs |
| Schommers et al., 2013[23 e] | Germany | 18 | 18/0 | 44 (26–70) | – | 8/10 | 18/0 | 85 (0–1100) | – | 12/2 | 6 out of 18 | 6/12 | 5 | – | – |
| Liu et al., 2012[17] | Japan | 10 | 8/2 | 68 (45–86) | 1/9 | 5/5 | 0/10 | – | 4/4 | 10/0 | 6 out of 9 | 8/2 | 21 | – | – |
| Castillo et al., 2012[15] | International | 50 | 39/11 | 43 (19–66) | 12/38 | 15/33 | 50/0 | 206 (5–683) | 9/12 | 35/2 | 25 out of 38 | 15/33 | 11 | 23% at 5yrs | 24% at 5yrs |
| Boy et al., 2010[9] | South Africa | 45 | 31/12 | 41 (29–58) | 45/0 | – | 33/1 | – | 26/17[f] | 43/2 | – | – | – | – | – |
| Zimmermann et al., 2012[37] | Germany | 8 | 6/2 | 47 (30–67) | 2/6 | 2/6 | 0/8 | 463 (259–730) | 2/4 | 5/3 | 5 out of 8 | 3/5 | – | – | – |
| Hansra et al., 2010[38] | USA | 13 | 8/5 | 40 (4–52) | 6/7 | 1/11 | 7/6 | 181.4 (57–458) | 1/2 | 6/7 | 4 out of 11 | 3/7 | 6 | – | – |
| Valera et al., 2010[6] | International | 42 | 33/8 | 48 (11–86) | 11/31 | – | 27/10 | – | 20/41[g] | 24/17 | – | 6/10 | – | – | – |
| Montes-moreno et al., 2010[39] | Spain | 37 | 23/9 | 48 (31–84) | 8/29 | 10/18 | 20/9 | – | – | 29/6 | 13 out of 26 | 13/16 | 23 | 42% at 2yrs | 42% at 2yrs |
| Kane et al., 2009[40 h] | India | 32 | 22/10 | 36 (5–85) | 25/7 | – | 28/4 | – | – | 4/0 | – | – | – | – | – |
| Gurjal et al., 2008[41] | India | 34 | 24/10 | 39 (12–70) | 25/9 | – | 34/0 | – | – | 5/8 | – | – | – | – | – |
| Dong et al., 2005[42 i] | USA | 13 | 11/2 | 41 (28–44) | 5/8 | 6/5 | 13/0 | – | – | 11/0 | 9 out of 10 | 0/11 | 7 | – | – |
| Colomo et al., 2004[43] | Spain/USA | 39 | 28/11 | 50 (11–86) | 13/26 | 7/12 | 21/18 | – | – | 27/12 | – | 7/12 | – | – | – |
| Teruya-Feldstein et al., 2004[44] | USA | 12 | 12/0 | 39.5 (23–73) | 2/10 | 3/9 | 6/5 | 130 (10–450) | – | 8/3 | – | 7/5 | – | – | – |
| Gaidano et al., 2002[45] | Spain/Italy | 12 | 10/2 | 34.8 (25–68) | 12/0 | 5/5 | 12/0 | – | – | 10/2 | 5 out of 10 | 3/7 | – | – | – |
| Delecluse et al., 1997[2] | Germany | 16 | 15/1 | 41.1 (27–75) | 16/0 | 11/5 | 15/1 | – | – | 9/6 | – | 2/9 | – | – | – |

Abbreviation: OS, Overall survival time.

[a]Mean or median age, (range) in years.

[b]The authors provided the CD4 data using G/L values.

[c]Median survival for HIV+ (9 months) HIV− (6 months) patients.

[d]The authors also used a smaller validation set of PBL comprising 12 cases with a mean age of 42.8 years (30–59), all males, all HIV+ and EBV+, and 4 of them diagnosed in the oral cavity.

[e]It is unclear if the 18 patients described were also included in the series described by Schommers et al. (2015)[35] containing 34 PBL cases.

[f]Data obtained from Boy et al. (2011)[36] that used the same sample to investigate PBL molecular features.

[g]The authors also observed 3 out of 3 cases with *MYC* rearrangement using conventional cytogenetics.

[h]It is not clear if some cases described by Kane et al. (2009)[40] and Gurjal et al. (2008)[41] are present in both series since the authors used cases retrieved from the same database in a similar period.

[i]The authors originally described 14 cases, but one of them stained positively for HHV8. Important to highlight that 6 cases were positive for HHV8 by PCR.

[j]The authors used $10^9$/L as unit.

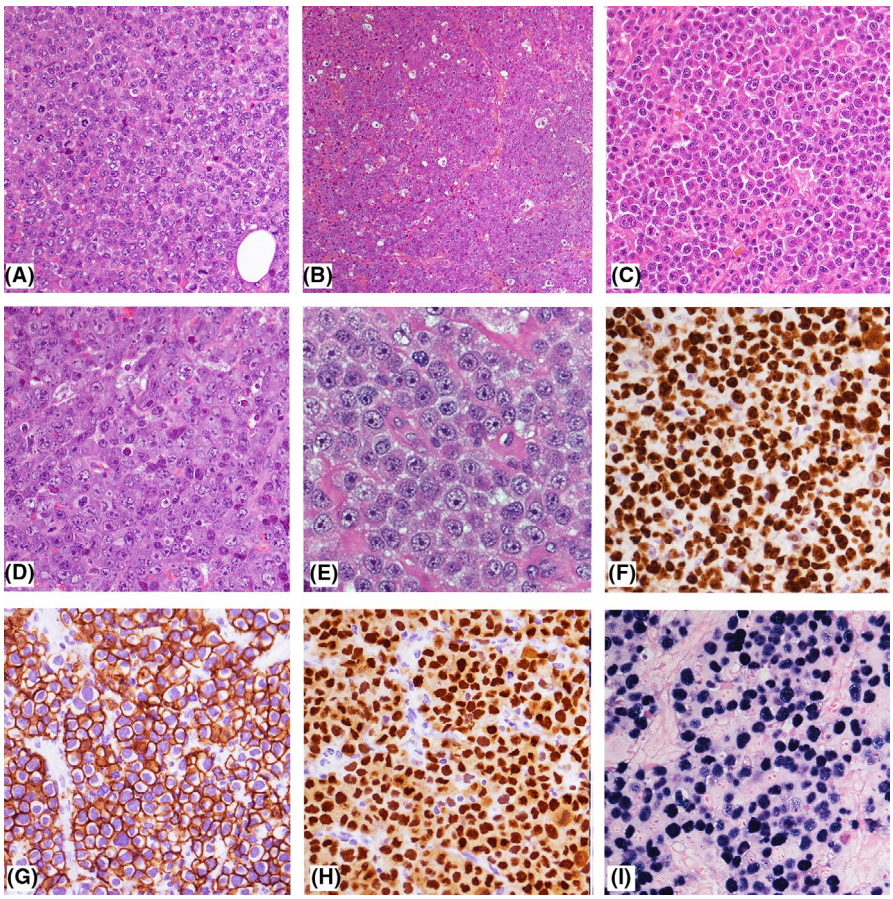


**FIGURE 2** Microscopic, immunohistochemical and in situ hybridisation features of PBL. (A) The neoplasm is characterised by a diffuse proliferation of tumour cells (H&E; 100X). (B) A starry-sky pattern is frequently observed due to the high proliferative potential of the neoplastic cells. Tingible body macrophages phagocytose the apoptotic bodies (H&E; 100X). (C) Plasmacytic differentiation is often observed in PBL and is characterised by smaller tumour cells closely resembling plasma cells (H&E; 100X). (D) Neoplastic plasmablasts are large tumour cells that carry different grades of pleomorphism with prominent nucleoli (H&E; 200X). (E) Immunoblasts may also be present in PBL, characterised by abundant cytoplasm with centrally located nucleoli (H&E; 200X). (F) PBL usually demonstrates a very high proliferative index measured by Ki-67 expression, frequently achieving more than 90% (DAB; 100X). (G) A plasma cell immunophenotype is confirmed by the expression of several markers, such as membranous expression of CD138 protein (DAB; 200X) and (H) nuclear expression of MUM1 protein (DAB; 200X). (I) EBV is usually present in the majority of the cases, but in the current South African sample was present in all cases. Strong nuclear staining of EBER via in situ hybridisation (in situ hybridisation; 100X)

from a molecular biology perspective, neither HIV- nor EBV infection was shown to alter the gene expression profile of PBLs.[14]

Male patients are by far the most affected by this aggressive neoplasm,[12] as also shown in the current sample. This may be related to the higher incidence of HIV-positive patients in this group. It has also been speculated that cancer/antigen-proteins, more commonly expressed in males, possibly play an important role in the pathogenesis of the neoplasm. Although the majority of the patients are adults, with a median age of approximately 45–50 years, there are several cases affecting infants that may or may not be infected by HIV.[10] In the current sample, 3 patients were younger than 15 years of age. The oral cavity is the most frequently affected location, although the cause of this oral tropism remains unknown. However, many other sites may also be affected, especially the gastrointestinal tract, lymph nodes and the skin, while bone marrow involvement is very rare. The relative increase in the number of cases diagnosed extraorally might be a consequence of a higher suspicion among pathologists regarding this entity in other regions. Most cases are found in advanced stages, usually being classified as Ann Arbor III and IV neoplasms, which negatively affects patient prognosis.[12,15,16] In most series, patients usually do not demonstrate B-symptoms,[17-19] but Witte et al. (2020)[16] recently described these systemic manifestations in 45 out of their 76 patients, while Castillo et al (2012)[15] found B-symptoms in 30 out of 42 cases.

PBLs typically consist of large neoplastic plasmablasts as demonstrated in the current series. Although plasmablastic differentiation may also be observed in ALK + large B-cell lymphoma, primary effusion lymphoma and anaplastic plasma cell myeloma, these mimickers can usually be excluded based on clinical, immunohistochemical and EBV/HHV-8 statuses.[8] Plasmacytic differentiation is a common finding, which is not restricted to extraoral cases as previously believed. This variability may represent a continuum of morphological differentiation

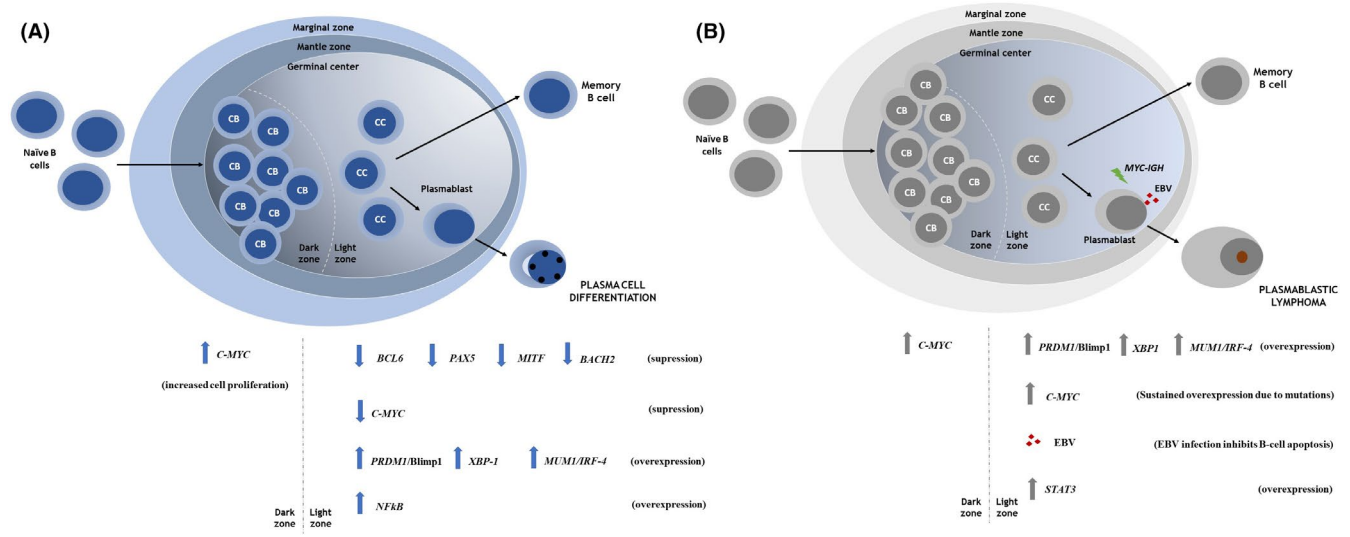


**FIGURE 3** Schematic models summarising the main molecular events for the development of physiological plasma cells and plasmablastic lymphoma. (A) Naïve B cells enter in the germinal centre to undergo somatic hypermutation stimulated by antigen exposure. In the dark zone of the germinal centre, centroblasts (CB) express the c-Myc protein that favours their proliferative potential. After moving towards the light zone of the germinal centre, centrocytes (CC) move towards either memory B cells or terminally differentiated plasma cells. For the development of the latter, B cells in the light zone overcome the regulatory function of *PAX5*, *BCL6*, *MITF* and *BACH2* genes that repress plasma cell differentiation, leading to the overexpression of *PRDM1* (and its protein Blimp1), *XBP1 and MUM1/IRF-4* genes, all them strongly associated with plasmacytic differentiation. Expression of *PRDM1*/Blimp1 suppresses c-Myc protein expression and contributes to the silencing/repression of *PAX5 and BCL6*. A higher expression of *NF-kB* also contributes for plasmacytic differentiation. (B) In the neoplastic scenario, the occurrence of t(8;14)(q24;q32) involving the genes *MYC* and *IGH* together with the presence of EBV infection (both events present in the majority of the PBL cases), contribute to the pathogenesis of the disease. Neoplastic cells carry an immunophenotype consistent with the plasmacytic differentiation with the expression of CD38, CD138, MUM1, EMA and VS38c; however, mutations in both *MYC* and *PRDM1* genes lead to sustained overexpression of c-Myc and Blimp1, respectively. Therefore, the expression of both proteins is believed to be the main molecular events that cause a high proliferative potential and the plasmablastic differentiation observed in PBLs. EBV-infection results in defective B-cell apoptosis. In addition, *STAT3* mutations have recently been reported in PBL, which may possibly contribute with c-Myc overexpression

of tumour cells. However, the true nature of this plasmacytic component may not be easily determined, as many of these cells may represent a reactive component rather than true neoplastic cells.[9]

Although PBL is currently defined as an independent entity derived from the broader category of diffuse large B-cell lymphomas (DLBCLs), it does not express the mature B-cell markers CD20 and PAX5, and shows variable staining for CD79a. Tumour cells usually exhibit positivity for at least one of the plasma cell markers CD38, CD138 and MUM1. However, as demonstrated in the current sample, there is often variability in the expression pattern of these plasmacytic antigens, with some of them being negative in rare cases.[15] This variability is believed to be a consequence of malignant transformation of plasmablasts in different stages of their normal maturation process. Proliferative index measured by Ki-67 is always very high, with most cases exhibiting a proliferation index of greater than 90% in the neoplastic cells. This proliferation index is also a useful diagnostic tool since plasma cell myeloma usually does not present with such a high proliferative potential. This high proliferation index is also indicative of pathogenic events, since PBL is associated with a higher expression of c-Myc and p53 proteins, and a lower expression of p27 and p16 cell cycle regulators,[20] ultimately leading to cellular proliferation.

The molecular basis of PBLs remains poorly understood, but the recurrent t(8;14) translocation involving *C-MYC* and *IGH* genes has been shown to be present in approximately 50% of the cases.[6] Miao et al. (2019)[21] reported that the *C-MYC* translocation was significantly associated with HIV-positive patients; however, such association and the prognostic significance of this chromosomal abnormality remain to be fully validated.[6,15,16,20] A gene expression profile study by Chapman et al. (2015)[14] has shown PBL to be significantly different from DLBCL, further justifying its classification as an independent entity. In contrast, Chang et al. (2009)[22] demonstrated via comparative genomic hybridisation that PBLs were more similar to DLBCLs than plasma cell myelomas. The plasmablastic differentiation of the neoplasm seems to be strongly associated with mutations in *PRDM1* and *XBP1* genes, which are important regulators of terminal B-cell differentiation. Although *PRDM1* is mutated, its protein (Blimp1) is still overexpressed in PBL. This does not result in an impairment of the proliferative potential of c-Myc, which would be expected in normal physiological circumstances. Therefore, it is believed that *PRDM1* and *C-MYC* mutations are significantly associated with plasmablastic differentiation and the high proliferative potential of the neoplasm[1] (Figure 3).

Several prognostic parameters have been suggested for patients affected by PBL. Unfortunately, most systems are based on weak evidence, usually from small retrospective studies, since prospective or clinical trials are difficult to perform given the low incidence of the neoplasm from a populational perspective. Treatment approaches vary with many chemotherapeutic schemes being reported in literature, most frequently CHOP or CHOP-like regimens, but also other more intense schemes like EPOCH. Despite the absence of CD20 expression in tumour cells, some authors have advocated the use of rituximab. ART is also very important for HIV-positive patients, with rare cases showing impressive tumour involution following ART introduction. Adjuvant radiotherapy and bone marrow transplantation have also been described in some studies.[13,23–25]

Although complete remission can be obtained in rare cases, survival rates are generally short, ranging from 6 to 12 months. A large number of the patients included in a previous series died of the neoplasm or from complications of the oncological treatment.[15,23] Therefore, the prognosis is still very poor with the overall survival rate achieving no more than 67% at 3 years, and a progression-free survival of 42% at 2 years follow-up. Pinnix et al. (2016)[24] found higher survival rates, possibly because their sample comprised earlier stage tumours.

In conclusion, PBL is an aggressive malignancy that in a South Africa population is almost exclusively diagnosed in HIV-positive patients and has a strong association with EBV infection. The molecular basis of this neoplasm is still poorly understood, but mutations in *C-MYC* and *PRDM1* have shed light in understanding the pathogenesis of this neoplasm. Future studies are necessary to validate prognostic parameters able to stratify patients according to their risk of death.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, and all authors have read and approved the final draft.

## PEER REVIEW

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Full list of reference used for this article can be found on Table S1.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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