

Plasmablastic Lymphoma of the Maxillary Sinus in an HIV-Positive Patient

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Received: 14 October 2016; Accepted: 13 December 2016; Published: 12 January 2017

Abstract

Plasmablastic lymphoma (PBL) is a rare type of B-cell lymphoma. This tumour shows a strong predilection for the oral cavity and almost always occurs in an HIV seropositive individual. The aetiology and pathogenesis of the disease is unknown, but it is considered to be due to viral infection with concurrent immunosuppression. PBL has an extremely aggressive clinical course linked with a poor prognosis and survival rate. Treatment regimes include radiation and/or chemotherapy. In this case report, we describe a 35-year old male with a two-month history of a swelling in the left maxilla.

We outline the clinical, histological and immunohistochemical characteristics, and describe how a final diagnosis of PBL was determined. Further research regarding the pathogenesis and optimum treatment regimes are necessary to improve an understanding of this entity.

Abbreviations: DLBCL: Diffuse Large B-cell Lymphoma; EBER: EBV-encoded RNA; EBV: Epstein-Barr Virus; HAART: Highly Active Antiretroviral Therapy; IPI: International Prognostic Index; MUM1: Multiple Myeloma Oncogene-1; NHL: Non-Hodgkin's Lymphoma; PBL: Plasmablastic Lymphoma

Introduction

Plasmablastic lymphoma (PBL) is a rare form of non-Hodgkin lymphoma (NHL) that can occur in the oral cavity of immunodeficient patients, most particularly those with HIV infection [1]. PBL was initially thought to be a variant of diffuse large B-cell lymphoma (DLBCL); however the World Health Organisation (WHO) classified it some years ago as a separate entity. PBL accounts for a mere 2.6% of all NHLs and has a strong predilection for the oral cavity [2]. Despite its common appearance in the oral cavity, this malignancy can also be seen in other extra-nodal sites [2]. Distinction of PBL from other NHLs may be difficult based solely on clinical and microscopic features. The expression of specific immunohistochemical markers is essential for a definitive diagnosis [1].

The immune suppression, along with the invasive nature of this tumour, often leads to a very poor prognosis, despite aggressive treatment regimes including radiation and/or chemotherapy [1].

Case Report

A 35-year old male patient presented with a 2-month history of a painful mass in the left maxilla. His medical history revealed that he is HIV seropositive and had refused ARV treatment for the past two years. Blood tests revealed a CD4 count of 301 and a viral load of

73,579 copies/ml. Extra-orally, the patient presented with a swelling of the maxilla extending from the left alar of the nose, to the most lateral point of the zygomatic arch (Figure 1). Intra-orally the mass was fungating and exophytic and involved the entire left side of the hard palate and the buccal vestibule with associated teeth (Figure 2). There was an absence of bleeding or any other visible exudate. Clinically a differential diagnosis of antral carcinoma, lymphoma or a malignant odontogenic tumour was considered. Radiographic examination revealed an ill-defined destructive radiolucent lesion present in the left side of the maxilla. An incisional biopsy of the mass took a specimen measuring 1×1×0.5 cm, and this was submitted for histological evaluation.

Diagnosis

A microscopic examination of sample mass was performed and revealed the presence of a diffuse infiltrate of pleomorphic tumour cells with plasmacytoid features (i.e., abundant basophilic cytoplasm, eccentric large round nucleus, and a prominent central nucleolus). The background infiltrate contained occasional tingible-body macrophages and abnormal mitoses (Figure 3). A differential diagnosis based on the histological features would include plasma cell myeloma and post germinal centre diffuse large B-cell lymphoma (DLBCL).

Additionally, immunohistochemical stains were performed (Figure 4, 5 and 6) and the results are presented in Table 1. From the histological data and immunohistochemical profile a final diagnosis of plasmablastic lymphoma was made.

After the patient was informed of the diagnosis he consented to begin anti-retroviral treatment, but declined a referral for possible chemotherapy. The aggressive tumour resulted in the death of the patient two months later.



Figure 1: Extra-orally the swelling extended from the left alar of the nose to the most lateral point of the zygoma.



Figure 2: Intra-orally the mass had perforated through the hard palate and occupied the entire left side of the palate and buccal vestibule. The mass appeared to be fungating and exophytic.

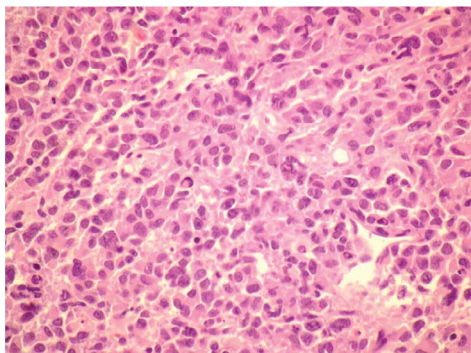


Figure 3: The haematoxylin and eosin stained slide shows a diffuse infiltrate of pleomorphic tumour cells with occasional tingable macrophages, prominent mitoses and cellular debris (Magnification × 40).

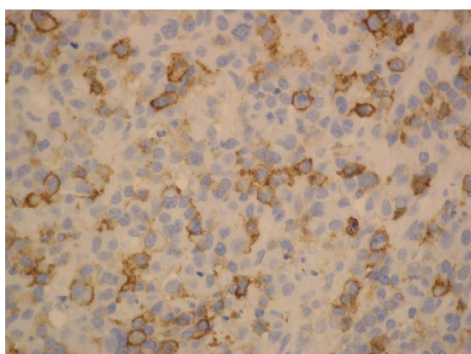


Figure 4: The plasmablastic lymphoma cells show cytoplasmic positivity for CD138 (Magnification × 40).

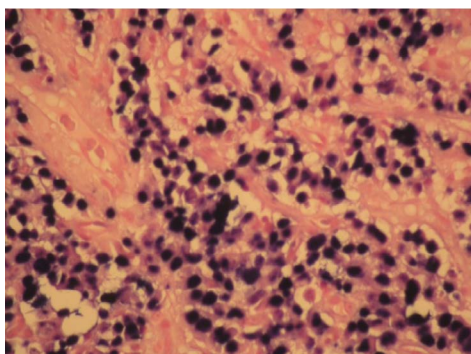


Figure 5: The EBER stains positive for the presence of the Epstein-Barr virus, commonly seen with plasmablastic lymphoma (Magnification × 40).

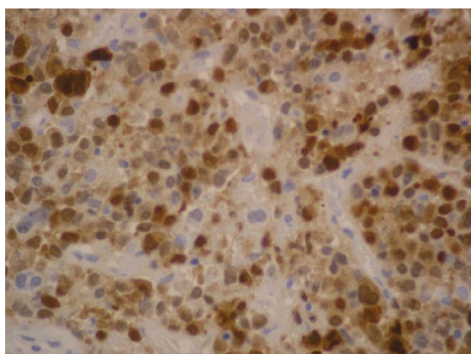


Figure 6: MUM-1 stain displays a nuclear positivity as seen with plasmablastic lymphoma (Magnification × 40).

Table 1: Immunohistochemical Results.

Immunohistochemical Indicator	Presence
CD3	Cytoplasmic positivity
CD20	Negative
CD30	Positive
CD45/LCA	Negative
CD138	Positive
EBER	Positive
MUM1	Positive
PAX5	Negative
HHV8	Negative

Note: The positivity shown by this tumour for CD30 is unusual for a PBL.

Discussion

Plasmablastic lymphoma (PBL) is a rare type of B-cell lymphoma, which was first described in 1997 [1,2]. Initially, PBL was thought to be a variant of diffuse large B-cell lymphoma (DLBCL), a common non-Hodgkin’s lymphoma (NHL) [3-6]. More recently it has been recognized by the World Health Organisation (WHO) as a separate entity [3-7]. DLBCL is the most common type of NHL, affecting 30% of Western populations, while PBL accounts for a mere 2.6% [5,6]. The tumour has a strong predilection for the oral cavity and frequently appears in HIV seropositive patients [2-6]. The reason for the oral tropism of PBL has yet to be explained, but extra-oral sites have recently been implicated as primary locations with concurrent development intra orally [1]. This rare neoplasm has also been described in other sites such as lymph nodes, subcutaneous soft tissue, liver, bones and anorectum [8]. The case in the present study had an epicentre in the antrum with subsequent secondary oral invasion through the palate.

The diagnosis of PBL is often indicative of an initial manifestation of the acquired immunodeficiency syndrome (AIDS) [5,6]. HIV/AIDS patients are said to have a 60 times greater chance of developing a lymphoma of any sort [6]. The immune suppression, along with the invasive nature of this tumour, often leads to very poor prognosis despite intensive treatment [3-6,9].

The aetiology of the malignancy is unknown but it is considered to be due to oncogenic viral infection or immunosuppression [10]. Some authors have reported a strong association in the majority of cases with the Epstein-Barr virus (EBV), along with the HIV [9,11,12]. PBL commonly affects adults in the 3rd and 4th decades of life and displays a slight male predominance [2,3]. Most patients present in the advanced stages of the malignancy, often with an International Prognostic Index (IPI) score of intermediate or high-risk [7,13]. The tumour progresses rapidly and has an aggressive clinical course [5,6]. PBL are classified into intra- and extra-oral subtypes depending on the site of origin. Lymphomas are generally submucosal and may be without ulceration, unless perforation occurs [10]. When originating from soft tissue in the oral cavity, the mass is soft to touch with possible overlying ulceration, but can be characterised by an absence of other symptoms [10]. Intra-osseous lesions within the oral cavity, although unusual, present with tooth mobility, alveolar bone loss, pain, swelling and paraesthesia of the lip due to nerve involvement [10]. From these clinical features a differential diagnosis can be made, while further tests are necessary for a definitive diagnosis.

The term ‘plasmablastic’ refers to the morphology of cells within a heterogenous group of lymphomas having different clinical and biologic features [6]. The complex histological and immunophenotypical patterns of these lymphomas make diagnosis challenging [6]. Microscopic examination shows a diffuse lymphoid proliferation composed of large cells [3,12,13]. These large neoplastic cells have either a single prominent centrally located nucleolus, termed immunoblasts, or with

Table 2: Differential Diagnosis of Plasmablastic Lymphomas*.

	Plasmablastic lymphoma	Diffuse Large B-cell lymphoma	Burkitt's lymphoma
Size of tumour cell	Large	Large	Intermediate
Plasmablastic differentiation	+	- to -/+	-
CD20	- to -/+	+	+
CD45 (LCA)	- to -/+	+	+
VS38c	+	- to -/+	-
MUM1	+	+	-
EBER	+	+	+
BCL-6	- to -/+	+50%	+100%

Abbreviations used: +: expression of the antigen in majority of cells; -: absence of antigen expression; - to -/+: weak antigen expression.

*Adapted from the publication by Delecluse, et al. [4].

several peripherally located nucleoli, termed centroblasts [3,4,6]. Interspersed are the presence of necrosis, mitotic figures and numerous apoptotic bodies with abundant macrophages which can result in a 'starry sky' appearance [3-5,12].

From an immunophenotypical perspective, approximately 50-85% of PBL are positive for CD79a, with weak/negative expression of CD45, CD20 and PAX5 [3,4,6,9,11]. These tumours also characteristically show a strong positive expression of VS38c, multiple myeloma oncogene-1 (MUM1) and CD138 [3,4,6,11,12]. Several tumour entities share similar immunophenotypical profiles and should be taken into account in the differential diagnosis of PBL (Table 2). Careful clinico-pathological correlation is required. PBL shows a weak or partial expression of BCL-6 compared with a DLBCL and Burkitt's lymphoma which both frequently show a positive expression for this marker [4,1]. CD56 may also be useful but not definitive in separating PBL from multiple myeloma as it is preferentially expressed in the former [4,11]. Most AIDS-related PBL cases have immunophenotype and tumour expression profiles similar to those of plasmablastic plasma cell myeloma [11]. Also PBL, in common with myeloma, may show immunoglobulin light chain restriction [11]. Differentiation should therefore be made between PBL and plasmablastic plasma cell myeloma. PBL shows a strongly positive expression for EBV-encoded RNA (EBER) compared with only 6.7% in plasmablastic plasma cell myeloma cases [4,11,12].

Due to the rarity of PBL and a lack of clinical trials, there is as yet no standard treatment approach for the condition [5]. Treatment options depend on the staging and generally include radiotherapy or chemotherapy or a combination of these treatments [3,13]. Presently, the most common treatment regimes consist primarily of combination chemotherapy, immune modulating therapy, with the occasional use of radiotherapy for larger tumours [9,10]. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) are currently the most widely used chemotherapy regimes [6,9]. Prognosis can be improved by the addition of highly active antiretroviral therapy (HAART) in combination with chemotherapy if the patient is HIV seropositive [5,10]. Patients already on HAART should avoid Zidovudine as it can accentuate the myelosuppression of the cytotoxic drugs [6].

Patients suffering from PBL have a poor prognosis due to the aggressive disseminating behaviour of the tumour and the disappointing response to treatment [5,11]. Whilst initial response to therapy is encouraging, a high relapse rate is seen with short survival thereafter [3,11]. A considerable problem is the late patient presentation in ARV-

naïve patients. The mean survival rate of HIV-negative patients with PBL is approximately 12 months and less in HIV-positive individuals with severe immunosuppression [5,6,14].

Conclusion

PBL may arise in the oral cavity and surrounding structures and often occurs in an HIV seropositive patient. Due to its low incidence and a corresponding lack of clinical studies, no standard treatment approach exists. Patients with PBL have poor prognosis and a short survival rate. Further studies should be designed to explain pathogenetic mechanisms involved in this malignant neoplasm and to help improve the treatment modalities. Early recognition, aggressive chemotherapy and better management of HIV can increase survival rate [4].

Consent

Written informed consent was obtained from the patient for publication of this report and the accompanying images.

References

1. Tsachouridou O, Christoforidou A, Metallidis S, Papaioannou M, Kollaras P, Kolokotronis A, et al. Plasmablastic lymphoma of the oral cavity, a B cell-derived lymphoma associated with HIV infection: a case series. *Eur Arch Otorhinolaryngol*. 2012; 269:1713-1719.
2. Hewson I. Oral plasmablastic lymphoma: a case report. *Australian Dental Journal*. 2011; 56:328-330.
3. Duarte ECB, da Silveira-Júnior JB, Gomez RS, Paes RAP, de Lacerda JCT, Mesquita RA. Plasmablastic lymphoma of oral mucosa type: A case report. *Oral Oncology EXTRA*. 2005; 41:121-124.
4. Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, et al. Plasmablastic lymphomas of the Oral cavity: A new entity associated with the human immunodeficiency virus infection. *The American Society of Hematology*. 1997; 89:1413-1420.
5. Hansra D, Montague N, Stefanovic A, Akunyili I, Harzand A, Natkunam Y, et al. Oral and extraoral plasmablastic lymphoma. *American Journal of Clinical Pathology* 2010; 134: 710-9.
6. Horváth E, Krenács L, Bagdi E, Pávai Z, Macarie I, Nagy EE, et al. Plasmablastic lymphoma associated with human immunodeficiency virus. *Romanian Journal of Morphology and Embryology*. 2008; 49:309-314.
7. Miranda R, Khoury J, Medeiros L. *Atlas of Lymph Node Pathology*. New York: Springer; 2013:265.
8. Minué G, Campitelli A, Narbaitz M, Gilardi L, Corti M. An aggressive plasmablastic lymphoma of the oral cavity as primary manifestation of acquired immunodeficiency syndrome: Case report and literature review. *Int Arch Otorhinolaryngol*. 2015; 19:354-358.
9. Saraceni C, Agostino N, Cornfield DB, Gupta R. Plasmablastic lymphoma of the maxillary sinus in an HIV-negative patient: A case report and literature review. *SpringerPlus*. 2013; 2:142.
10. Cawson R, Odell E. *Cawson's Essentials of Oral Pathology and Oral Medicine*. Edinburgh: Churchill Livingstone; 2008:340.
11. Adwani DG, Arora RS, Bhattacharya A, Bhagat B. Non-Hodgkin's lymphoma of the maxillary sinus: An unusual presentation. *Annals of Maxillofacial Surgery*. 2013; 3:95-97.
12. Vatca M, Robbins K, Grier DD, Cappellari JO, Naik S. Plasmablastic lymphoma presenting as proptosis and impending visual loss. *Community Oncology*. 2013; 10:27-32.
13. Gorczyca W. *Atlas of Differential Diagnosis in Neoplastic Hematopathology*, 3rd Edition. Taylor and Francis Group. 2014:383-384.
14. Bibas M. Current knowledge on HIV-associated plasmablastic lymphoma. *Mediterranean Journal of Hematology and Infectious Diseases*. 2014; doi:10.4084/mjhidd.2014.064.