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Spontaneous Regression of an Oral Manifestation of Plasmablastic Lymphoma: Literature Review and Commentary about the Phenomena

Natália Batista Daroit[1], Viviane Palmeira da Silva[1], Bruna Jalfim Maraschin[1], Fernanda Visioli[1], Pedro Bandeira Aleixo[2], Márcia Gaiger de Oliveira[1] and Pantelis Varvaki Rados[1*]

[1]Department of Conservative Dentistry, School of Dentistry, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2492/503, Porto Alegre, RS, 90035-003, Brazil.
[2]Department of Pathology, Universidade Federal de Ciências da Saúde de Porto Alegre, Rua Francisco Ferrer, 400 - Rio Branco, Porto Alegre - RS, 90420-140, Brazil.

Authors' contributions

This work was carried out in collaboration between all authors. Author NBD designed the study, wrote the first draft of the manuscript and collected the patient details. Authors VPS and BJM managed the literature searches and made the photographs. Authors FV and PBA reviewed and corrected the text furthermore collaborated with the image acquisition. Authors MGO and PVR performed the histopathological diagnosis of the case, it followed the help in the writing and discussion of the scientific paper. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Plasmablastic Lymphoma (PBL) is a hematolymphoid malignant disease that has a predilection for the oral cavity and jaw. The aim of this paper is report a total resolution of oral manifestation of PBL without any oncological treatment; this process is extremely rare and we discuss the mechanism which can occur. We present a case of PBL in left maxilla and oral mucosa in a woman HIV-positive patient. After an incisional biopsy an unusual outcome of spontaneous regression of the disease occurred, we reported the diagnostic process, the management and the

**Corresponding author: E-mail: pantelis@ufrgs.br;*
E-mail: nataliadaroit@yahoo.com.br;

follow up of case. We revised the similar cases reported in the literature and we will discuss the hypotheses how the phenomenon can occur. Although the PBLs are aggressive lesions, with questionable prognosis, the spontaneous regression can occur and the patient should be monitored for the risk of metastases and possible recurrence of the disease.

Keywords: Acquired immunodeficiency syndrome; jaw cancer; maxilla; plasmablastic lymphoma; spontaneous neoplasm regression.

ABBREVIATIONS

EBV : Epstein Barr Virus
HAART : Highly Active Antiretroviral Therapy
HHV8 : Human Herpes Virus 8
HIV : Human Immunodeficiency Virus
PBL : Plasmablastic Lymphoma
PET : Positron Emission Tomography
SR : Spontaneous Regression

1. INTRODUCTION

Some neoplasias are classified as Acquired Immunodeficiency Syndrome related cancers, especially Kaposi's sarcoma, high-grade B-cell non-Hodgkin's lymphoma and invasive cervical cancer [1]. Plasmablastic Lymphoma (PBL) is an aggressive form of diffuse large B-cell lymphoma, composed of large cells with morphology of immunoblasts and a plasma cell. History of immunodeficiency especially caused by HIV infection is common in patients with PBL. [2]. Some cases of this disease occurs at extranodal sites, especially in the oral cavity [3].

Even though prognosis is poor, a complete remission of disease without treatment can occur. This finding was reported initially in HIV+ patients that start the use of highly active antiretroviral therapy (HAART) [4,5,6] or yet which interrupted this therapy [7]. This phenomena has been seen in PBL in HIV+ patients with undetectable viral range and with immune system stable after the performance of an incisional biopsy [8,9]. Besides have been reports of spontaneous regression (SR) an HIV negative patient in absence of anti-neoplastic treatment [10,11]. The literature review reported eight cases of PBL SR without anti-neoplastic treatment (Table 1), we herein describe more one case of intraoral PBL that spontaneously regressed in the absence of any anti-neoplastic treatment.

2. PRESENTATION OF CASE

A 66-years-old woman was referred to our Oral Pathology Department showing a nodular lesion involving the maxillary region associated with painful symptoms with a history of approximately 30 days. The patient's medical history revealed HIV infection, hypertension and hypoparathyroidism, treated with HAART - abacavir/ lamivudine/ efavirenz, hydrochlorothiazide, amlodipine, enalapril, levothyroxine, calcium carbonate. Serological investigation presented undetectable viral load for HIV, 6 months ago, CD4 T-lymphocytes=480 cel/μL (29-5827 cel/μL) and CD8 T-lymphocytes=2950 cel/μL (22-4076 cel/μL). Additional clinical or laboratory analyses were unremarkable. The present study was conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki.

Intraoral inspection showed an exophytic erythematous nodule with ulcerated areas on the maxillary left ridge, measuring approximately 3x4 cm. On palpation the lesion had a fibrous consistency and the superior left first molar presented increased mobility (Fig. 1A). The panoramic radiograph revealed bone resorption in the left side of maxilla probably due to periodontal disease in the superior left first molar (Fig. 1B). During the clinical evaluation no lymphadenopathy was detected. On the basis of these findings the clinical diagnoses were: malignant neoplasia or deep fungal infection. An incisional biopsy was performed. During the surgical procedure, the tissue was bleeding and friable.

The specimen was submitted to histopathological analysis, which revealed a diffuse proliferation of large, round to oval cells, with typical plasmablastic features (i.e., immunoblastic morphology with abundant basophilic cytoplasm, occasional paranuclear hofs and prominent central nucleolus). Frequent apoptotic bodies and mitotic figures were seen (Fig. 2). Immunohistochemistry identified expression of CD138, CD38 and MUM1 by the neoplastic cells. No staining was seen with CD20, TDT, PAX-5, HHV8 and EMA (Table 2). Proliferative index accessed by Ki-67 reached more than 95% of the tumor cells. With these histopathologic and immunophenotypical findings the diagnosis of a plasmablastic lymphoma was established. The patient was referred to an oncologic center for appropriate treatment.

Table 1. Spontaneous regression of PBL cases without anti-neoplastic therapy

Author year	NASTA 2002	LESTER 2004	GILABERTE 2005	ARMSTRONG 2007	GARCÍA-NOBLEJAS 2013	CORTI 2011	IGAWA 2015	WAGNER 2016	Present case
Gender	Male	Male	Male	Male	Female	Female	Male	Female	Female
Age	44	50	44	35	78	55	80	33	66
Site	Mediastinum	Palate	Arm	Maxilla	Buccal Mucosa	Oral	Maxilla	Mandible	Maxilla
HIV	+	+	+	+	-	+	-	+	+
EBV	-	+	+	+	+	-	+	NI	-
HHV8	+	NI	+	NI	NI	+	NI	NI	-
HAART before PBL	Yes	Yes	Yes	Yes	No	No	No	Yes, but the therapy was interrupted	Yes
Therapy	HAART	HAART	HAART	HAART	Decrease of Methotrexate	HAART	None	HAART	HAART
Recurrence	Yes	Yes	Yes	No	No	No	No	No	No

NI- Not informed

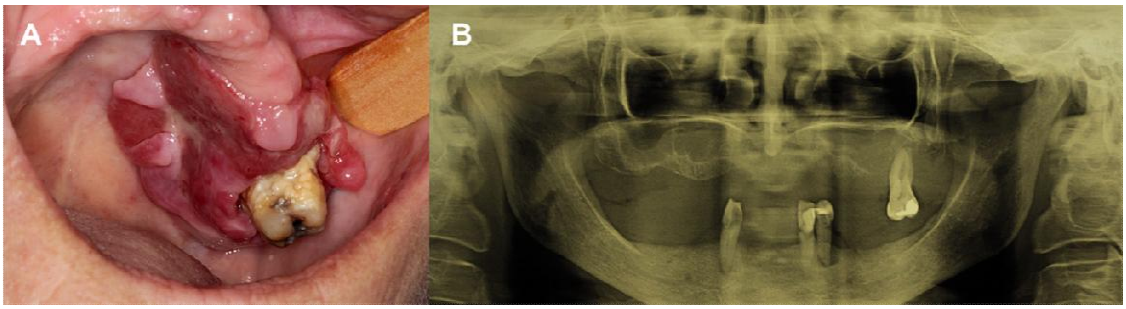

Fig. 1. A) Clinical appearance of the PBL in the first exam – exophytic erythematous proliferation adjacent to superior molar. B) Radiograph exam of the jaws, slight bone resorption associated a tooth

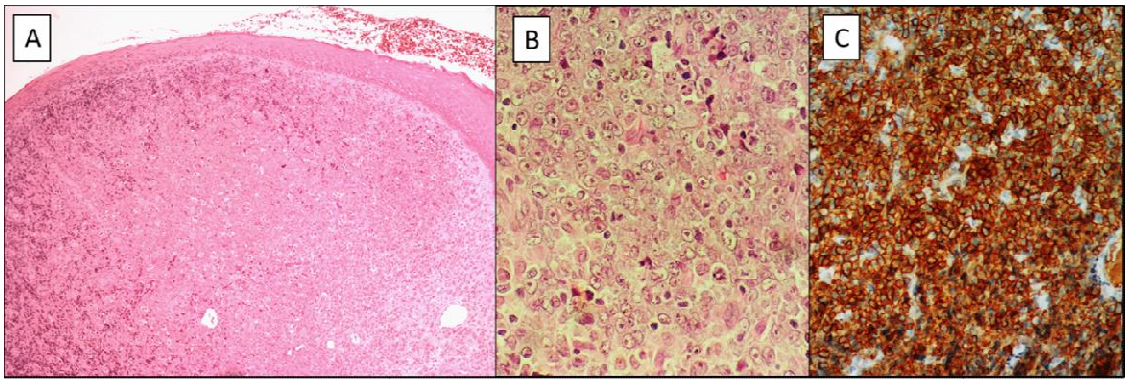

Fig. 2. A) Photomicrography shows the epithelial surface; in the connective tissue underlying was observed an intense hematolymphoid proliferation (H/E, 100x). B) The plasmablastic cells show vesicular nuclei, prominent nucleoli, and amphophilic cytoplasm (H/E, 400x). C) The main immunohistochemistry labeling for the final diagnoses was CD-138 membranous immunostaining (200x)

Table 2. Immunohistochemistry panel of the lesion

Antibody	Result	Localization
CD 138 (MI15)	+	Membran Neoplastic B cells
CD38 (SPC32)	+	Neoplastic B cells
MUM1 (MUM1P)	+	Nucleus Neoplastic B cells
CD79 (HM57)	-	Tumor cell
CD 20 (L26)	-	Tumor cell
PAX-5 (1EW)	-	Tumor cell
CD 3 (2GV6)	-	Tumor cell
CD 2 (11F11)	-	Tumor cell
ALK (ALK1)	-	Tumor cell
HHV8 (13B10)	-	Tumor cell
EMA(E29)	-	Tumor cell
TDT(Polyclonal)	-	Tumor cell
EBV (CSL/CS2/CS3/CS4)	-	Tumor cell
KI 67 (30-9)	>95%	Tumor cell

During the hospital admission, a fine-needle biopsy was performed by a general oncologist and the diagnosis of PBL was confirmed. The patient was then referred to a hematolymphoid oncologist for specific treatment. While waiting for the consultation, the patient informed that she applied olive oil and *Malva sylvestris* tea on the lesion four times/day every day. Surprisingly, at

the moment of specialized oncologist appointment (one month later) the lesion disappeared clinically; in face of this finding, no oncologic therapy was performed at the time, only Positron Emission Tomography (PET) Scan was requested and it did not show any evidence of metastasis.

During follow-up period, the patient underwent upper left first molar extraction with uneventful healing (Fig. 3). Fig. 4 shows the correlation between serological examination, the clinical lesion (appearance and regression) and the HAART therapy of the patient. The patient showed no recurrence of the oral lesion for 12 months. However, in medical follow-up during the PET-Scan, it was diagnosed tumor bone metastasis (bilateral humerus, right frontal region, costal arcs with pathological fracture of femur and radius) and the patient started chemotherapy (three courses of EPOCH chemotherapy).

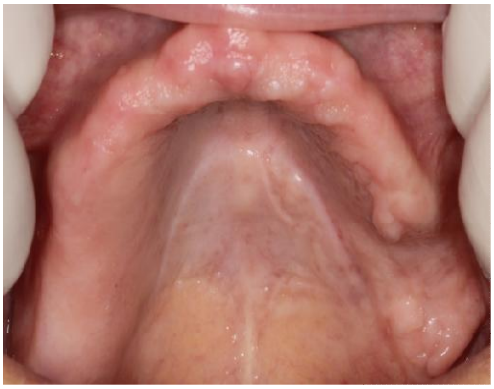

Fig. 3. The clinical follow-up of maxillary region with no signals of recurrence

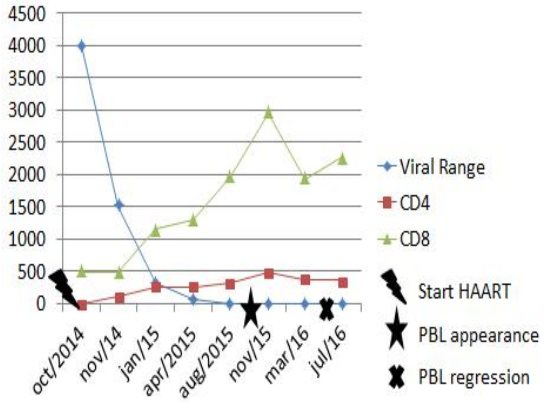

Fig. 4. Serological exams and correlation with clinical oral manifestation of PBL

3. DISCUSSION

Plasmablastic Lymphoma affects, predominantly, males in their fourth decade of life, usually in HIV-positive patients. PBL commonly affects extranodal sites, predominantly the oral cavity, gastrointestinal tract and the skin [3]. Contrasting, in the present case, our patient is a female patient and had a more advanced age than most seropositive patients. The best prognosis is associated with younger patients, early stage of the disease and no lymph node involved [12].

The literature proposes that a SR of tumors can be related to the efficiency of the immune system. This behavior may act by different ways: blocking cell growth or proliferation, inducing apoptosis and activating natural killer cells [13]. One hypothesis to explain SR of lymphomas is that the local trauma caused by the incisional biopsy triggers the local immune system to the healing response, and to resolve the tumor [14]. The radiation hypothesis suggests that doses received by the patient from imaginologic procedures can contribute to SR of PBL [15]. In our case the patient was submitted to a single digital panoramic radiograph with an average dose of 100 mGy. Furthermore, the patient reported the use of phytotherapic ointment: olive oil and Malva sylvestris topically, several times. These substances act as anti-inflammatory agents contributing with the lesion regression [16,17].

PBL resolution without any form of intervention such as surgery, radiotherapy, chemotherapy is rare. In the few cases reported of PBL SR (Table 1) it was not possible to propose a patient profile, even when considering multiple viral infections (EBV, HHV8 and HIV) to try predicting this phenomenon.

HAART can present a dual behavior in seropositive patients regarding the manifestation of PBL. Reported cases describing - patients with high viral load and decompensated immune system with PBL; after HAART, they regularized CD4/CD8 rates and the spontaneous resolution of the neoplasia occurred. A possible explanation is immune function reconstitution and the viral load control [4,5]. On the other hand, the use of HAART might trigger the Immune Reconstitution Inflammatory Syndrome, [18] and this phenomenon results in the uncontrolled production of inflammatory cells leading to development of PBL [5,19]. In the present case,

the clinical lesion appearance and SR occurred after the HAART, when the viral load was undetectable and the patient immune system was already reestablished (Fig. 4).

Differential diagnosis of ulcerated swelling at oropharyngeal mucosa in immunosuppressed patients (post-transplant or HIV positive) may consider lymphoproliferative disorders as EBV-positive mucocutaneous ulcers. Histologically shows lymphocytes, immunoblasts plasma cells, histiocytes and eosinophils with atypical large B-cell blasts, plasmacytoid apoptotic cells, with immunopositivity for CD20+, CD79a+, PAX5+, Oct-2+ and Bob.1+ [20]. Complete remission of this disease when immunosuppressant were reduced or when immune system are recovered are reported in the literature [21]. The reported case is negative for EBV and for CD20 and the patient was immunocompetent since the appearance of the oral lesion, thus we discarded the EBV driven lesion diagnostic.

Metastases can occur after the complete remission of primary tumor; in our case the patient presented metastasis of the oral PBL in bones with femur and radius fracture; other case report related oral metastasis in breast and bone marrow after 2 months [22]; for this reason the PBL patient's follow-up is mandatory. The metastatic appearance may be identified by MMP value study as also by computerized tomography imaging (CTi) and colonoscopy in abdominal cases [23,24], in our case report, the metastasis was diagnosed by PET-scan exam.

4. CONCLUSION

Lymphomas are common in seropositive patients, but SR of these hematopoietic tumors, especially PBL, remains a dilemma. The mechanism involved includes factors that host co-infections and immune system recovery. A bigger number of cases may contribute to clarify possible associations. There are no defined protocols to manage these patients yet, even though there is a consensus which recommends a long term follow-up because of a recurrence risk and possibility of distant metastases.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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