Impact of highly active antiretroviral therapy in the development and remission of oral plasmablastic lymphoma

Vivian Petersen Wagner¹, Lisley Ortiz¹, Helena Pereira Rodrigues da Silva¹, Luise Meurer², João Julio da Cunha Filho¹, Marco Antonio Trevizani Martins⁴, Manoela Domingues Martins¹⁴

ABSTRACT

Plasmablastic lymphoma (PBL) represents a rare type of non-Hodgkin lymphoma associated with human immunodeficiency virus (HIV) infection. The impact of highly active antiretroviral therapy (HAART) in this tumor is poorly known due to its small incidence. This study reports a case of a 33-year-old HIV-positive woman who was referred to the Stomatology Department complaining about a painful gingival growth and cervical nodule both with 20 days of evolution. The lesions appeared 7 months after the patient stopped HAART. The final diagnosis was PBL. After resuming HAART for 45 days, the gingival lesion presented complete remission. The patient continued with HAART alongside chemotherapy. At 24 months follow-up, the patient was stable. The dental surgeon plays an essential role in orientation and retention in care of HIV patients once the adherence of HAART seems to play an important role in PBL development and response to treatment.

Key words: Acquired immunodeficiency syndrome, B-cell lymphoma, highly active antiretroviral therapy, human immunodeficiency virus infections

According to the Joint United Nations Programme (UNAIDS), there are approximately 34.2 million people infected with human immunodeficiency virus (HIV) worldwide.¹ The reduced immunity among individuals with acquired immune deficiency syndrome (AIDS) increases the chance of developing diseases that originate from opportunistic pathogens. Therefore, infectious diseases, such as candidiasis, necrotizing ulcerative gingivitis, and herpes simplex, are among most prevalent AIDS-associated oral lesions.² Others include neoplastic diseases as AIDS-related lymphomas and Kaposi’s sarcoma. The increment of highly active antiretroviral therapy (HAART) led to a significant decrease of AIDS-related morbidity and mortality.

AIDS-related lymphomas also presented a decline in incidence in the HAART-era coupled with a rise in overall survival when chemotherapy is associated with HAART.³ Despite this considerable decrease in incidence, these lesions are still an important source of morbidity and mortality among HIV patients. AIDS-related lymphomas are predominantly aggressive high-grade B-cell lymphomas, such as Burkitt’s lymphoma, diffuse large B-cell lymphoma, primary effusion lymphoma, and plasmablastic lymphoma (PBL).³ PBL was first described by Delecluse et al. as an aggressive variant of diffuse large B-cell lymphoma in HIV patients, presenting a high tropism for the oral cavity.⁴ This rare lesion accounts for 2.6% of all AIDS-related lymphomas and even in the HAART-era is still associated with poor prognosis, presenting a median survival time of around 5 months.⁴ The aim of the present study is to report a case of PBL diagnosed in an HIV patient who interrupted HAART regimen with 24 months of follow-up. Moreover,

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a discussion of the impact of HAART in AIDS-related lymphomas, particularly in PBL, and the role of the dental surgeon in these cases are offered.

CASE REPORT

A 33-year-old woman was referred to our Stomatology Department complaining about a painful gingival growth with 20 days of evolution. She was diagnosed with HIV-infection 12 years before and had been under HAART regimen (TDF + 3CT + ATZ/r) since then. The patient stopped HAART 7 months earlier due to gastrointestinal adverse effects.

Extraoral examination revealed unilateral lymphadenopathy, with a single right submandibular lymph node palpable, firm, measuring 2 cm × 2 cm, and presenting diffuse pain in the cervical posterior region [Figure 1a]. Intraoral examination revealed an exophytic painful nodule in the gingiva extending from the vestibular region of teeth 45 and 46 to the lingual region [Figure 1b]. The teeth involved presented severe mobility. The patient referred noticing the gingival nodule and the cervical mass at the same time, around 20 days earlier. The periapical radiography revealed a destructive radiolucency with ill-defined borders leading to the erosion of the alveolar bone [Figure 2]. Based on clinical and radiographic aspects, the differential diagnosis included AIDS-related lymphomas, sarcomas, and oral squamous cell carcinoma with regional metastasis. An incisional biopsy of the gingival nodule was performed and the specimen was submitted to histopathological examination. The patient was advised to seek an infectologist to resume HAART.

Histopathological examination revealed a dense neoplastic plasma cell proliferation [Figure 3a]. Immunohistochemical analysis of neoplastic cells disclosed positivity to MUM-1 [Figure 3b] and CD138 [Figure 3c]. The cells showed negativity to leukocyte common antigen, CD3, CD4, CD5, CD7, CD10, CD20, CD79a, Bcl2, Bcl6, and cyclin-D1. Proliferation rate, assessed by Ki67/MIB-1 staining, was 80% [Figure 3d]. The findings were consistent with a PBL and the patient was referred to the Oncology Service for treatment.

The patient consulted the infectologist and resumed HAART after the first visit at the Stomatology Department. At the first appointment in the Oncology Service, the patient was under HAART for about 45 days and presented complete remission of the gingival lesion [Figure 4]. Submandibular and submental palpable lymph nodes were detected. At this time, CD4 counting, CD4/CD8 ratio, and viral load were 314 cells/µL, 0.45, and 28.26 log 4.45, respectively. The patient referred losing 15 kg during the past 3 months, correspondent to 14.58% of her body mass. The patient was diagnosed with Stage IB and started treatment with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone associated with methotrexate, arabinoside-C, and dexamethasone for central nervous system chemoprophylaxis. At 24 months follow-up, the patient was stable and submandibular and submental palpable lymph nodes were not perceived; furthermore, new lesions were not clinically identified.

DISCUSSION

HIV infection when untreated is inevitably fatal, with a median survival time from seroconversion of 8–10 years. Nevertheless, since the mid-1990s, the introduction of HAART led to a dramatic reduction in mortality in HIV patients. For this reason, HIV has now come to be considered more as a chronic disease instead of a fatal disease. In Brazil, the first middle-income country to provide free and universal access to HAART in 1996, the mortality rates declined 66.4% in HAART-era compared to non-HAART-era. However, this improvement cannot be achieved without long-term optimal adherence and retention in care, which are the greatest challenges in the management of HIV/AIDS.

HAART adherence failure is directly associated with low survival rates in HIV patients. In the present case, the patient decided to stop HAART regimen approximately 1 year after having her second child due to severe gastrointestinal effects.
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It is important to notice that the patient underwent HAART regimen for 11 years before this decision. A retrospective clinical cohort demonstrated that postpartum period is associated with an increased risk of nonadherence to HAART, probably due to lifestyle changes or postpartum depression. As a result of the central role that adherence plays in the effectiveness of HAART, it is extremely important to clarify to HIV patients about the potential consequences of nonadherence. The dentist, as a health-care provider, must be aware of this aspect. Dental practitioners usually have more knowledge about routes of HIV transmission than HIV pathogenesis, complications, and advances in treatment. It is known that long-term interventions based on repetition and reinforcement are required to produce long-lasting adherence. Therefore, HIV patients should benefit from all opportunities with dental practitioners for reinforcement of the gravity of HAART nonadherence.

Non-Hodgkin lymphoma risk is still greatly elevated in HIV-positive individuals compared to the general population; nevertheless, AIDS-related lymphomas experienced a noticeable decline in incidence in the HAART-era, demonstrating the effectiveness of recovering immune function on the pathogenesis of these lesions. PBL represent only 2.6% of AIDS-related lymphomas. It presents a marked male predilection (5.7:1) and in the majority of cases presents with intraoral involvement at the time of initial diagnosis. PBL is strongly associated with HIV-infection and among those cases, around 74% with EBV infection present.

Previous reports in literature demonstrated that HAART interruption was associated with PBL development and recurrence. Herein, the patient noticed that the lesion appeared about 7 months after stopping HAART treatment. These findings suggest that the reduction in immune response experienced by patients during HAART interruption might be determinant for the development of malignant tumors, such as PBL. In the present case, the patient presented complete remission of the gingival lesion only with HAART resumption. Nevertheless, the nodal lesion was still present after 45 days on HAART regimen. Corti et al. reported a case of a PBL patient that responded to HAART alone and remained in remission after 10 months without requiring chemotherapy. Similar events were reported by others, which demonstrated that even after established malignant disease, recovery of immune function may be decisive on partial, as describe herein, or total remission of HIV-associated PBL.

The median survival time for PBL is around 4 months after diagnosis. At first description of PBL, Delecluse et al. found that all PBL patients were deceased at 12 months follow-up. Cohort studies fail to demonstrate an improvement on PBL prognosis in HAART-era, while the overall survival of other types of AIDS-related lymphomas increased more than two-fold in HAART-era. PBL is an extremely rare tumor, leading to small samples as consequence. Guan et al., in a meta-analysis comprehending 10 randomized clinical trials, were able to demonstrate that prognosis and survival of PBL patients receiving HAART in addition to chemotherapy and/or radiotherapy were improved compared to patients receiving chemotherapy and/or radiotherapy alone. In the present study, the patient was stable with 24 months of follow-up. This finding translates what was reported herein by other authors who also found that HIV-positive PBL patients treated with chemotherapy associated with HAART present longer survival rates. The reason for this may rely on the fact that antiretroviral therapy can restore immune surveillance allowing a more efficient anticancer effect of chemotherapy.
Reduction in immune response seems to play a role in PBL pathogenesis. Moreover, immune reconstitution secondary to HAART was associated with partial remission and appears to be related with improvement of overall survival. These findings reveal the major importance of HAART adherence regarding the development and treatment of PBL. The presence of oral diseases can be a signal of decline in immune system function. The role of dental surgeon, however, goes beyond the diagnosis and is also associated with orientation and retention in care of HIV patients, thus improving both quality of life and survival for these patients.

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Conflicts of interest
There are no conflicts of interest.

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