Plasmablastic Lymphoma in a Previously Undiagnosed AIDS Patient: A Case Report

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Abstract Background Plasmablastic lymphoma (PBL) is an unusual non-Hodgkin lymphoma (NHL) most commonly found in the head and neck region. The majority of cases are seen in adult HIV-positive patients, although PBL has been reported in HIV-negative patients. The diagnosis of PBL serves as an AIDS-defining illness. Methods We report a case of PBL localized to the oral cavity in a previously undiagnosed AIDS patient. The lesion manifested as solitary, ulcerated, and markedly tender. PBL was confirmed by immunohistochemical profile and subsequent tests confirmed AIDS diagnosis. The patient was prescribed highly active antiretroviral therapy (HAART) and concomitant local low dose radiation therapy prior to initiation of chemotherapy. Results Complete local clinical response was observed after 4 weeks of treatment with HAART and radiation therapy. The response sustained in this patient in the subsequent 11 months following diagnosis. Conclusions The diagnosis of PBL has a unique immunophenotypic profile and should raise suspicion for AIDS in these patients. HAART added to treatment has shown improved survival.

Keywords Plasmablastic lymphoma · Non-Hodgkin lymphoma · Radiotherapy · HIV · AIDS · HAART

Introduction

The epidemiology and prognosis of AIDS has changed tremendously since the first description of disease in 1980 [1]. The introduction of effective therapy and prophylaxis for opportunistic infections has significantly reduced mortality [2, 3]. Highly active antiretroviral therapy (HAART), introduced in 1996, has not only reduced the complications associated with AIDS, but also significantly improved survival [4–6]. However, secondary malignancies continue to be a major cause of AIDS-related morbidity and mortality [5].

Recent reports have shown a significant decrease in the incidence of non-Hodgkin lymphoma (NHL) in AIDS patients on HAART [7, 8], but the incidence still remains much higher than that of the general population [3, 9, 10]. The prevalence of AIDS-related malignancies is expected to increase as AIDS patients continue to live longer [4, 5, 8]. Therefore, PBL is expected to be seen more frequently among the spectrum of AIDS-defining illness [11].

PBL was first described by Delecluse et al. in 1997 as an oral cavity large B-cell lymphoma with unique immunohistochemistry occurring in HIV patients; 15 of 16 were HIV-positive in the series [1, 12]. Addition of HAART therapy to the treatment regimens which include chemotherapy and/or radiation therapy depends on the extent of disease.
PBL characteristically presents as a tender, ulcerated lesion in the oral cavity that may precede the diagnosis of AIDS [13]. The natural history of PBL without adequate treatment is progression from local to systemic disease and subsequent death. More recent observations regarding the role of co-infection of HIV and Epstein-Barr virus (EBV) in NHL oncogenesis confirm that lymphoid cells that actively replicate in response to viral antigens remain at a higher risk for NHL, unless their immune function can be restored. Since HAART therapy does not restore the immune system to normalcy [2, 4], the risk of secondary NHL is not completely eliminated. However, improved immune status will also result in improved remission and survival rates for NHL [5, 8, 14, 15]. The response to HAART therapy is measured by CD4 count and viral load. Positive prognostic indicators include an elevated CD4 count, low viral load and localized versus systemic disease at initial presentation [1, 8].

Case Report

A 38-year-old female presented to the oral surgery clinic with history of a painful mouth ulcer of 4 months duration. After initial treatment with antibiotics for a suspected dental abscess yielded no clinical improvement, the patient was referred to our head and neck cancer clinic for further evaluation. A complete history and physical examination was performed.

She reported local throbbing pain and associated odynophagia secondary to the lesion but denied dysphagia, hoarseness, dyspnea, fever, night sweats, or weight loss. Her past medical history included asthma but no other major medical problems. An extensive social history included an 11-pack year history of smoking, daily alcohol use, and crack-cocaine use for several years. Upon examination of the oral cavity a 4 × 1.5 cm firm, solitary, tender non-ulcerated lesion (Fig. 1a) was appreciated. Extension was noted from the mid-line mucosal surface of the upper lip across the superior alveolar ridge onto the anterior maxilla. A biopsy of the lesion was performed.

Laboratory investigation showed a WBC count of 3,500/m³ with normal differential, hemoglobin 10.3 g/dl, MCV 74.8 fL, platelets 189,000/mm³, total serum protein 9.3 g/dl, albumin 3.4 g/dl, and calcium 8.9 mmol/l. Quantitative IgA, IgG, and IgM were in the normal range. No monoclonal protein was seen on serum or urine protein electrophoresis. Bone marrow biopsy was normocellular with no evidence of lymphoma. A total body skeletal survey was normal. Contrasted computed tomography (CT) scans of the head, neck, chest, abdomen, pelvis, and extremities were performed. The head CT showed localized osteolytic infiltration by the lesion, with erosion of the maxillary alveolar ridge (Fig. 1b). The remaining images showed no evidence of extended disease.

Histopathologic evaluation of the biopsy specimen revealed many plasmacytoid tumor cells with eccentrically placed nuclei, amphophilic cytoplasm and some cells showing cytoplasmic hoff (pale area representing golgi apparatus.) One or more nucleoli could be seen, either placed centrally or along the nuclear membrane. In many areas of the tumor, the sprinkling of tingible-body macrophages produced a starry-sky appearance (Fig. 2). Mitosis and apoptosis were brisk.

The tumor cells were negative for CD45, CD20, CD3, and CD30 on immunohistochemical analysis. Diffuse and strong reactivity was seen with VS38c, CD138 (Fig. 3) antibodies, and surface lambda light chains. In-situ hybridization using the EBV-encoded small RNAs (EBER)
1 and 2 probes also showed strong positivity for EBV (Fig. 4).

Based on the information gained from her extensive work-up, a diagnosis of PBL was made. Further testing for HIV was performed (ELISA) and confirmed (Western blot) positive for HIV, at that time CD4 count was 360.

Due to the localized disease and severity of pain, the patient was treated with local radiation therapy (23,400 cGy in 13 fractions) and concomitant HAART was initiated. An evaluation at week 4 after start therapy showed complete local tumor involution (Fig. 5a). Bone resolution was observed on CT scan at 6 months (Fig. 5b).

The patient unfortunately refused the planned chemotherapy, however, she remained disease-free for 11 months, followed by relapse in the gynecologic tract several months after interruption of antiretroviral therapy. She underwent surgical hysterectomy with bilateral

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**Fig. 2** PBL with tumor cells showing blast-like nuclear features, central or peripherally placed nucleoli, abundant amphophilic cytoplasm and admixed tingible body macrophages (H&E ×400)

**Fig. 3** Lymphoma cells strongly and uniformly stained with CD138 (×400)

**Fig. 4** In-situ hybridization for EBV shows strong staining (×400)

**Fig. 5** (a) Four weeks after receiving 23,400 cGy of the gengival-labial lesion. Patient achieved complete resolution of the gengival-labial lesion. (b) Post-treatment contrast CT scan, showing complete resolution of the bone lesion after 6 months of treatment
salpingo-oophorectomy and subsequent chemotherapy. Remission was maintained at her follow-up at 31 months since her initial diagnosis.

Discussion

The World Health Organization (WHO) classifies PBL as a non-Hodgkin B-cell lymphoma, predominantly occurring in HIV-positive patients. Originally PBL was described in the oral cavity region although, many reports of patients without HIV and outside the head and neck area have been recently presented in the literature [10, 13, 16–19].

PBL presents an aggressive behavior mostly in immunosuppressed HIV-positive patients who are co-infected by EBV. Interestingly, once antiretroviral therapy is initiated a more favorable and indolent response is observed.

On light microscopy, PBL reveals soft tissue infiltration by large plasmacytoid lymphoma cells with blast-like features. The tumor cells have eccentric nuclei with prominent nucleoli and give a starry-sky appearance at low power because of the admixture of tingible-body macrophages (Fig. 2), indicative of a high tumor cell turnover rate. PBL cells are not immunoreactive with CD3, CD20, or CD45, may weakly/focally express CD79a, but show stronger expression of plasma cellular immune markers VS38c and CD138. In situ hybridization for EBER (EBV encoded small RNA) is usually positive (Fig. 4) and the tumor cells also strongly express lambda or kappa light chains.

Once PBL is confirmed, work-up tests for HIV should be included due to this strong association [4, 6, 11–13, 20–22]. In case the test results confirmed PBL-AIDS associated, there is evidence that initiating HAART improves prognosis, decreases incidence of systemic complications, and improves survival [4, 14, 19, 20, 23].

Treatment

Not many reports are currently available on optimized treatment regimens for localized PBL in the head and neck area.

Currently there is agreement that HIV-positive patients with PBL must commence HAART [14, 19, 20, 23, 24], since it has shown improvement in survival rates. Chemotherapy is the standard treatment for PBL but controversy still remains regarding when starting chemotherapy regimens, such as CHOP, EPOCH, or other protocols in severely immunocompromised patients undergoing HAART. When these regimens are added, some authors recommend the optimal dose should be adjusted to avoid toxicity [4, 5, 8, 9, 24–28]. Other protocols also require the interruption of HAART during chemotherapy to decrease adverse interactions [9, 15, 26].

Literature regarding inclusion of radiation therapy for the treatment of PBL is sparse. In indolent NHL, treatment with localized radiation therapy showed evidence of efficacy.

In our case we observed the useful role of radiation therapy in this stage I localized but tender lesion in combination with HAART to promote local disease and pain control while in the re-acquisition of immune function period (which normally takes several months) before subsequent chemotherapy. The rational is to avoid poor compliance resulted from drug interaction and toxicity from HAART and chemotherapy.

Conclusion

The diagnosis of PBL presents peculiar morphological and immunohistologic profile and should raise awareness for AIDS-defining illness [12, 13, 22].

PBL is strongly associated to EBV [1, 4, 6, 10, 20, 29, 30] and is not necessarily confined to head and neck area as once believed [1, 10, 16, 30–34].

Chemotherapy is the standard treatment for NHL and should be used in combination with HAART. However, toxicity, drug interactions, and poor compliance with antiretroviral and antineoplastic drugs are still a challenge [27].

Literature regarding inclusion of radiation therapy for the treatment of PBL is sparse. There appears to be a role for radiation therapy in stage I PBL lesions in combination with HAART to promote local disease control during reacquisition of immune function and proceed with subsequent planned chemotherapy. Patients should be kept under close vigilance for detection of systemic manifestations of PBL. The optimal dosage for radiation therapy needs further investigation and should be encouraged through prospective studies.

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