Plasmablastoid Lymphoma in Patients with Human Immunodeficiency Virus: A Diagnosis Challenge

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Abstract

In this era of Highly Active Antiretroviral Therapy (HAART), we see that incidence of neoplastic diseases among patients affected by Human Immunodeficiency Virus (HIV) is increasing. Plasmablastic lymphoma (PBL) is an example of neoplastic condition specific to HIV patients. It is a subtype of diffuse large B-cell lymphoma (DLBCL) recently described in the 2008 WHO classification of lymphoproliferative disorder. PBL is characterized by its aggressive nature and plasmacytic differentiation and usually occurs in the oral cavity or jaw of HIV-infected individuals. However, several cases of PBL involving extraoral sites have been reported in immunocompetent individuals. This entity is a diagnostic challenge and need integration of clinical, pathological, genetic and microbiologic features. Several types of lymphoma present with plasmablastoid differentiation and may give rise to some difficulties for a differential diagnosis. We give some anatomicopathological, molecular and genetic details for each subtype and we will illustrate the difficulty for the diagnosis with two cases. The first case is a patient with plasmablastic lymphoma that present with unusual negative immunoreactivity for CD 138 (10% of PBL cases). The second case has clinical, epidemiological and pathological characteristic of plasmablastic lymphoma but HHV8 positivity is a criteria for considering extra-cavity PEL as the most relevant diagnosis.

Introduction

Plasmablastic lymphoma (PBL) is a relatively new clinical entity described as a distinct subtype of diffuse large B-cell lymphoma (DLBCL), characterized by its aggressive nature and plasmacytic differentiation [1]. There are more and more publications around this topic in the recent years showing the growing awareness and interest of the medical community. Indeed, Castillo described more than 300 articles that were published between 1997 and 2009, and around 300 articles have been published since 2010 (<5 years) [2]. It usually occurs in the oral cavity or jaw of human immunodeficiency virus (HIV) infected individuals [3]. More recently, however, several cases of PBL involving extraoral sites have been reported in immunocompetent individuals [4-7]. PBL is a diagnostic challenge given its morphology and its immunohistochemical profile. Furthermore, PBL is a therapeutic challenge with a high rate of relapse and death with no established standard of care.

The purpose of this article is to relate unusual findings in two cases of plasmablastoid lymphoma in HIV positive individuals making difficult the diagnosis and to compare to the current literature.

Case Reports

The first case is a 41 year old female patient, presenting with a right cervical mass progressing since 10 days accompanied by cough and fever. No history of weight loss or sweating. In her remarkable previous history, we find HIV diagnosed in her native country, Ukraine, in 2006, initially on HAART, but unfortunately stopped on May 2014 due to financial problem. In November 2014, HAART was reintroduced: raltegravir and emtricitabine combined with tenofovir switched to cobicistat, elvitegravir, emtricitabine and tenofovirin order to avoid any drug interaction. At that time, a CD4 cell count of 215/µl (range 410-1590/µl) and a viral load of 173 copies/ml were measured.

Ultrasound showed multiple necrotic adenopathy in the right cervical area. Computed CT of the head and neck confirmed the presence of this multiple and necrotic adenopathy in the right cervical area. A computed tomography of the thorax didn't show evidence of tuberculosis. PET/CT showed hypermetabolic adenopathy in the latero-cervical, subternal and mediastinal areas. A surgical biopsy is performed and immunohistochemistry analyses revealed that the cells were immunoreactive for IRF4/MUM1, CD19, CD45, BCL2 but negative for PAX5, ALK, CD138, CD20, CD3, CD5, CD10, BCL6. Positive expression of c-Myc on fluorescence in situ hybridization (FISH). Detection of Epstein-Barr virus (EBV)–encoded small RNA (EBER) by flow cytometric in situ hybridization assay was positive. HHV-8 antigen was not detected. Immunoreactivity for cytokeratins and EMA were tested: anti CK AE1-AE3, EMA, CAM5.2, CK5.6, CK7 and were all negative. Ki 67 reached 85% immunohistochemical staining. Despite absence of CD138, the most probable diagnose remains plasmablastic lymphoma. Bone marrow biopsy didn't show neoplastic cells. In the laboratory studies, beta2microglobulinemia was elevated (3150 [range<2100µg/l]) without hyper gammaglobulinemia.

She began a chemotherapy with DA-EPOCH on March 2015. After 6 courses, she developed a complete metabolic response. On October 2015, we found recurrence of the disease, despite chemotherapy with DHAP, the patient died from a septic shock after 10 months survival time.

The second case is a 61-year old, homosexual, male patient, who had a known history of HIV since 1996, on HAART, admitted with history of sub and retro-mandibular adenopathy slowly gradually progressing for the last 3 months. An antibiotherapy during one month was provided without improvement. There is no history of fever, neither
weight loss. In his previous medical history, he is also known with hypercholesterolemia treated by simvastatin and with oesophagitis treated by omeprazole. On physical examination, we found a 3 centimeter diameter mass in the right submandibular area and several infracavitary lymph nodes bilaterally. Ultrasound showed in the right cervical area several pathologic adenopathy with irregular and heterogeneous contum as well an irregular parotid mass measuring 2.6 x 1.7 x 2.1 cm but non infiltrative. Computed tomography of the head and neck showed this same mass with a kystic and a solid part confirmed by MRI.

PET/CT showed the hypermetabolic parotidian mass and multiple sus and sub-diaphragmatic adenopathy. The fine needle aspiration of bone marrow was free of disease. Laboratory studies showed normal chemistry, normal serum lactate dehydrogenase, beta 2 microglobulin of 275/µl (range 410-1590/µl) and an undetectable viral load. Laboratory studies showed normal bone marrow was free of disease. A parotidectomy was thus performed.

Chemotherapy with da-EPOCH was begun. After two courses, there was a complete metabolic remission based on PET CT. The patient complete his 6th course maintaining his complete remission and achieved now 17 months of free survival time.

Discussion

Plasmablastic lymphoma (PBL) is an aggressive lymphoma, considered as a subtype of diffuse large B-cell non-Hodgkin’s lymphoma variant. PBL is characterized by weak/absent expression of conventional B-cell markers and by strong expression of plasma cell markers. It has been described as a new disease entity in the WHO classification of lymphoproliferative disorders in 2008 [8], thought to account for approximately 2.6% of all AIDS-related lymphomas (ARLs) [9]. The majority of patients affected are men, particularly the HIV-positive cases. One study found a mean age at presentation of 39 years in HIV-positive patients and 58 years in HIV-negative patients [9]. Delecluse et al. reported 16 cases in the oral cavity oh HIV patients in 1997 [3], originally this first cases have been considered as variant of diffuse large B-cell lymphoma (DLBCL) [3]. PBL is strongly associated with HIV infection, but occurs also in other immunosuppressive situations such as from solid organ and bone marrow transplantation, lymphoproliferative or autoimmune disorders [10,11]. The occurrence of PBL in extra-oral sites have been described [9]. A characteristic feature of PBL is its rapidly progressive clinical course. HIV-positive patients treated with highly active antiretroviral therapy (HAART) and appropriate chemotherapy has a better overall survival than HIV-negative patients [4,10,11]. HIV-associated PBL remains poor prognosis pathology and the impact of more intensive chemotherapeutic regimens in the ART era is not evident [7]. One study found a median overall survival in HIV-positive patients of 10 months [11].

Pathologic features

Morphology is characterized by monomorphic proliferation of round- to oval-shaped cells with plasmablasticoid features (i.e., abundant and basophilic cytoplasm, eccentric nuclei, and a prominent central nucleolus). A plasmablastic morphology, however, may be seen in other lymphoproliferative disorders.

Kane and colleagues proposed simple morphological and immunohistochemical criteria for the diagnosis of PBL of the oral cavity, which includes CD20 negativity and positivity for CD138, PAX5. In situ hybridization showed extensive positivity for Epstein-Barr virus-encoded small RNA (EBER) and c-Myc translocation was present on fluorescence in situ hybridization (FISH). Serologies for hepatitis A, B, and C were negative and polymerase chain reaction for HHV8 in blood was positive.

Fine needle aspiration of the mass was performed and microscopic examination revealed isolated cell without differentiation, prominent nucleolus and high nuclear-cytoplasmic ratio confirming the suspicion of a neoplastic disease. A parotidectomy was thus performed.

Anatomopathologic analysis of the biopsy showed a lymph node with sinus infiltrated by voluminous cell, with abundant basophilic cytoplasm and prominent eccentric nuclei. The cells have a plasmablastoid aspect. Immunohistochemical staining revealed that the malignant cells were immunoreactive for the plasmacytic marker CD38, CD 138 but negative for conventional B cell marker CD20, PAX5. In situ hybridization showed extensive positivity for Epstein-Barr virus-encoded small RNA (EBER) and c-Myc translocation was confirmed on FISH. Immunoreactivity for cytokeratin’s and EMA were negative excluding poorly differentiated carcinoma. Finally, we found that the lymphoma cells were positive for HHV8 latency-associated nuclear antigen 1 (LANA-1).

The clinical presentation, the morphological and immunohistochemistry features were consistent with PBL or extracavitary PEL. The staging was IIIA according to Ann Harbor and 1/3 adjusted IPI.

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Still, B-cell lymphomas with plasmablastic features may share overlapping in morphologic and immunophenotypic features and need other analyses to their recognition as distinct entities.

Epstein-Barr virus (EBV) infection has been detected in 74% of published PBL cases [7].

EBV can be detected by EBER in situ hybridization, Epstein–Barr virus latent membrane protein 1 (LMP1) is not expressed. In contrast to AIDS-related immunoblastic lymphomas that usually express LMP-1 [13].

The role of Human Herpes Virus 8 (HHV8) in the pathogenesis of PBL is uncertain [7] and PBL is not included in KSHV/HHV8-associated lymphomas defined by WHO. In a large cohort study, around 30% of HIV positive homosexual men were seropositive for HHV8 [14] but several studies have found that PBLs of the oral cavity type do not contain KSHV [15].

The histopathologic aspect of PBL has a diffuse pattern with a high mitotic index [4,5].

MYC translocation has been identified as a prevalent secondary event in plasma cell neoplasms. Up to 10% of DLBCL cases [16,17] have this translocation. Valera and colleagues reported in PBL c-MYC rearrangement in 50% of the cases reviewed and noted a strong association between EBV positivity patients and c-MYC rearrangements [18].
Differential diagnoses

Burkitt and Burkitt-like/atypical Burkitt lymphomas comprise up to 35-50% HIV-associated non-Hodgkin lymphomas [19,20] and thus the highest proportion of this neoplasm. The diagnosis of Burkitt or Burkitt-like lymphoma requires criteria's: a medium-sized CD10-positive B-cell population, a high proliferative rate and demonstration of a translocation involving the MYC gene [19]. A morphological variation that appear unique to AIDS is in some cases, Burkitt lymphomas presents with plasmacytoid differentiation but still the morphology is different and CD20 is negative. EBV-encoded RNA (EBER) can be detected by in situ hybridization in tumour cells in about 30% of Burkitt lymphomas, 50-70% of Burkitt lymphomas with plasmacytoid differentiation, and 30-50% of Burkitt-like lymphomas [21]. But the viral oncongenes LMP-1 and EBNA-2 are not expressed in Burkitt EBER-positive in contrast to EBER-positive immunoblastic DLBCL and PEL [21]. In our two cases, the fact Ki67 is not reaching 100% and CD10 negativity are arguments against Burkitt.

Anaplastic or plasmablastic plasma cell myeloma is characterized by large-sized neoplastic plasma cells containing large hyperchromatic nuclei centrally-located, a high nuclear/cytoplasmic ratio with an increased number of mitoses. Unlike plasma cytomas and myeloma, most PBLs are EBV associated such thus in situ hybridization for Epstein-Barr encoded RNA (EBER) helps to distinguish between these two plasma cell neoplasms [4,22]. Chang et al. reported that EBER +plasmablastic myelomas and plasmacytomias, although rare, existed in immunocompetent patients [23]. By contrast, both patients were immunocompromised and there was no involvement of the bone marrow, neither hypergammaglobulinemia or lytic bone lesions. Furthermore, c-Myc rearrangement is not seen in plasmablastic plasma cell myeloma.

Immunoblastic cell type diffuse large B-cell lymphoma appears in the context of severe immunosuppression, with different clinical patterns. EBV positivity occurs in 80 to 90% of cases, with frequent expression of LMP-1 and EBNA-2, show a non-germinal centre B-cell/activated B-cell phenotype (lack of expression CD138) [21]. It also exist a plasmacytoid variant that can be confusing with PBL. But the B-cell related antigens such as CD20, CD79a are expressed. In the differentiation path from B cell to plasma cell there is a less characterized transient phase represented by the plasmablast. CD79a and bc6 have an extended expression in the post GC/plasmablastic phase of B-cell differentiation make them sometimes not good markers for discrimination between late-stage B cells from plasmablast. PAX 5 and CD 10 have been identified in a recent study [24] as potential good markers and have been integrated in a scoring system to better discriminate between DLBCL that presents with a plasmablastic differentiation and PBL (CD20-, MUM1+). This represent helping tools in the differential diagnosis. Based on this, both cases cannot be confused with immunoblastic cell type diffuse large B-cell lymphoma.

Diffuse large B-cell lymphoma in elderly is considered a provisional entity in the 2008 WHO classification. This is a clonal B cell lymphoproliferative disorder seen in patients>50 years old without known immunodeficiency or prior lymphoma [25].

Plasmablastic lymphoma arising in HHV8+ multicentric Castelman disease. The cells express Ig M lambda and HHV8 and arise in Castelman disease.

Anaplastic diffuse large B-cell lymphoma show a marked anaplastic cells and again B-cell related antigens such as CD20 and CD79a. In anaplastic T cell lymphoma ALK negative: T-cell markers such as CD2, CD3, CD5, CD7, CD8 and CD30 are expressed. ALK-positive large B-cell lymphoma is a B-cell neoplasm characterized by plasmablastic morphologic features and a unique molecular pathogenesis consisting in the translocation of the ALK gene in 100% of cases. Immunophenotypically, the tumor cells express terminal PC differentiation markers. The association with EBV is unclear.

Primary effusion lymphoma is also quite new lymphoproliferative disorder occurring almost exclusively in HIV-infected patients, associated with human herpesvirus 8 (HHV-8) infection, that is directly involved in the pathogenesis. Most PEL affected patients are coinjected with EBV. It is difficult to confirm sometimes the B-cell lineage because PEL lacks expression of most B-cell associated antigens including CD19, CD20, CD79a and immunoglobulins. On the other hand, immunophenotypically, less specific plasmacytic differentiation marker are frequently expressed, such as CD30, CD45, EMA, CD71, MUM1, and CD138 [19,20,26] even the most common site of involvement are the pleural, pericardial and peritoneal cavities. Making differential diagnosis even more difficult, rare cases of an extracavitary variant of PEL have been observed without lymphomatous effusions [27,28]. In the first case, the differential diagnosis is difficult, specially because HHV8 is positive. Even though, Session 2 of the 2009 Society for Hematopathology-European Association for Haematopathology Workshop [29], consider HHV8 positivity as an exclusion criteria for PBL, several cases of AIDS-related lymphoma including plasmablastic lymphomas if located in the oral cavity have been associated with HHV 8 [30].

In our first case, remain the overlap between a plasmablastic lymphoma and an extracavitary PEL. In both, we find HIV and EBV positivity. Morphologically and immunophenotype we can have the same findings. As discussed below, if we consider HHV8 positivity as a criterion to discriminate between this two entities, extracavitary PEL would be the diagnoses. But considering all this elements: oral location typical of PBL, several cases reported HHV8 association with AIDS-related lymphomas of the oral cavity, translocation of c-Myc, PBL of the oral cavity cannot be excluded. This issue would need further investigations because a grey zone remains.

In the second case, eventhough CD138 is negative, the PBL remains the only possible diagnoses. Burkitt can not be considered because of Ki67 not reaching 100%, morphologic aspect, CD10 and CD20 negativity. Negativity for CD20, PAX5, CD79a is against an immunoblastic DLBCL with plasmacytoid features. ALK is negative. The dissociation between CD20 and CD79a is in favor of a plasmacytic differentiation. In the plasmablastic plasma cell myeloma, we find a medullar invasion and lytic bone lesions that was not present in our patient. She was HIV positive and EBV positive. And finally, c-Myc rearrangement was present. PEL cannot be considered because of HHV 8 negativity. In a recent review, 10% of plasmablastic lymphoma were found negative for CD138 [2].

To make the correct diagnosis, the clinical history (immune deficiency), disease site, tumor cell phenotype, high proliferation index HHV8 status and EBER in situ hybridization have to be integrated.

Treatment and prognosis

The most common chemotherapeutic regimen used is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) but there is no standard regimen due to the aggressive and rapidly
progressive disease. When more intensive regimens have been used such as Hyper CVAD, CODOX-M/IVAC and EPOCH, there was no difference in overall mortality. A bias cannot be excluded considering the use of intensive regimens in more advanced cases. Castillo estimated the ORR at 77% but the OS time remains short at 14 months. Most cases having died due to infectious complications or progression of disease. Early stage of disease and complete response to chemotherapy and use of HAART are good prognostic factors of remission include. The presence of MYC rearrangement is on the other hand a negative prognostic indicator. As PBL express less CD20, there is no rational and no evidence in favour of Rituximab use so it is not considered a therapeutic standard. But it could benefit in a subgroup of HIV-positive individuals with CD20-positivity, CD4 counts>100 CMM, and MYC rearrangements [7]. Treatment of relapsed PBL are still under discussions, rare cases of autologous stem cell after high dose chemotherapy transplantation and bortezomib combined with dose-adjusted EPOCH have shown efficacy [31,32].

Conclusion

PBL is a diagnostic challenge with clinical and histopathological features that could be confusing with other neoplasm described in our article. In order to obtain a right diagnosis, an exhaustive integration of different aspects are needed: clinical, morphological, phenotypical and molecular. Given the poor prognosis of PBL, a correct diagnosis should be performed, especially in the future with the potential development of targeted therapy.

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