Plasmablastic Lymphoma of the Breast in an Immunocompetent Patient: Long-lasting Complete Response Induced by Chemotherapy and Autologous Stem Cell Transplantation

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Abstract. Background: Plasmablastic lymphoma (PBL) is a rare entity which is often causally related to infection by the Human Immunodeficiency Virus (HIV). Despite its predilection for oral cavity involvement, multiple cases of extra-oral involvement have been reported in the literature, more often among immunocompetent individuals. Case report: Herein we present the first case of primary PBL of the breast in an otherwise immunocompetent 36-year-old woman who was successfully treated with consolidation megatherapy and autologous stem cell transplantation. Conclusion: PBL carries a particularly poor prognosis and more intensive treatment is usually warranted. However, no treatment guidelines exist and treatment choices are made based on case reports and small retrospective case series.

First described in 1997 as an oral cavity lesion in Human Immunodeficiency Virus (HIV)-positive patients (1), plasmablastic lymphoma (PBL) is a rare entity with an aggressive clinical course and poor prognosis. Since the original report, the clinicopathological features of PBL have been expanded and the disease has been incorporated in the latest 2008 World Health Organization (WHO) classification of lymphomas (2), but it still remains a diagnostic and therapeutic challenge.

The majority of published cases underscore the connection between this entity and immunodeficiency. Two thirds of the patients are HIV-positive and many of the remaining ones have some other form of immunosuppression. Also, the literature supports the predilection for oral cavity involvement among HIV-positive patients and the frequent extra-oral involvement among HIV-negative patients, in sites such as the lungs, colon, liver, stomach, psoas muscles and humerus (3-8). Herein we present the first case of primary breast plasmablastic lymphoma in an immunocompetent patient that was successfully treated with high dose chemotherapy and stem cell rescue. We, thus, propose this approach as an upfront treatment for carefully selected patients, considering the overall poor prognosis of PBL with conventional chemotherapy.

Case Report

A 36-year-old woman with a medical history of breast fibroadenomas presented with a 5 month history of worsening left thoracic and abdominal pain. She reported no associated symptoms or exacerbating factors. On examination, her abdomen was soft without tenderness. Palpation of the breasts revealed multiple lumps and the rest of the physical examination was unremarkable. Her family history was notable for breast cancer on her maternal grandmother and her mother but no test for the presence of BRAC1/2 mutations had been performed. She did not smoke, drink alcohol or use illicit drugs and she did not take any medication. A chest radiograph revealed the presence of a left hemithorax extrapulmonary but intrathoracic mass, most probably in the pleural space, approximately 4 cm in diameter. Computed tomography (CT) scans with the administration of intravenous contrast material of the chest, abdomen and cervix revealed the aforementioned mass (3.8×1.8 cm), a lymph node block at the posterior mediastinum, multiple unilateral breast masses (Figure 1) with associated axillary lymphadenopathy and multiple enlarged intra-abdominal lymph nodes; transvaginal ultrasound revealed...
a right ovarian hyperechoic mass (3.6×3 cm). Other laboratory tests were only notable for the presence of an IgGκ paraprotein by serum immunofixation, while the patient was tested negative for HIV infection. Tissue samples from the breasts and the intra-abdominal lymph nodes were obtained; the histologic examination revealed a neoplastic diffuse infiltrate composed predominately of plasmablasts and to a much lesser extent plasma cells. The immunohistochemical analysis showed that the tumor cells were CD138-, CD79α-, epithelial membrane antigen (EMA)-, multiple myeloma oncogene 1 (MUM1)- and Clg(κ)-positive, faintly positive for CD45(LCA) and CD20, CD3 and CD45(RO)-negative. In addition, in situ hybridization for small RNA EBV transcripts (EBER) was negative and the proliferation rate, identified with the marker ki67, was approximately 80%. The above morphological and immunohistochemical findings were more compatible with PBL, according to the WHO 2008 classification of tumors of hematopoietic and lymphoid tissues. Bone marrow biopsy was negative for marrow infiltration.

The patient was treated with combination chemotherapy consisting of cyclophosphamide 750 mg/m² (day 1), adriamycin 50 mg/m² (day 1), oncovin 1.4 mg/m² (day 1) and prednisone 40 mg/m² (days 1-5) every 21 days (CHOP-21). She completed 8 cycles uneventfully and a complete radiological and clinical remission was achieved. A Positron Emission Tomography (FDG-PET) scan could not demonstrate any metabolic activity. However, IgGκ paraproteinemia persisted, which was thought to represent minimal residual disease (MRD). Three additional cycles of oncovin, cyclophosphamide and prednisone (COP) were administered but resolution of the paraproteinemia was not achieved. Considering the aggressive nature of the disease and the risk of relapse after first line treatment, a decision was made.

Figure 1. Mammogram at initial diagnosis, showing multiple breast masses. Mediolateral oblique images right (A) and left (B). Craniocaudal images right (C) and left (D).
to proceed to high-dose chemotherapy with autologous stem cell rescue in order to eradicate the MRD. The conditioning regimen consisted of melphalan 180 mg/m² and etoposide 1,700 mg/m². The autologous stem cell transplantation was complicated by a single episode of febrile neutropenia but was otherwise uneventful and repeat immunofixation was negative for the presence of paraprotein, 10 months after the initial diagnosis. Today, 8 years after the transplantation, the patient is alive and well, in complete remission by clinical, imaging and immunofixation criteria.

Discussion

The rarity of PBL implies that any conclusions regarding its biological and clinical features are derived from case reports and small case series. As stated above, PBL is closely-related to immunodeficiency. In the largest literature review of 228 cases, 69% were HIV-positive (9). Of the HIV-negative patients, approximately one third have some other form of immunosuppression, for example during the post-transplantation period (10). Our patient did not have any apparent cause of immunodeficiency.

The pathological hallmark of PBL is the diffuse proliferation of large neoplastic cells most of which resemble B-immunoblasts, but in which all tumor cells have the immunophenotype of plasma cells and express plasmacytic markers such as CD138, CD38, Vs38c and MUM1, but not mature B-cell markers such as CD20 and PAX5. However, no marker is specific enough to lead to the diagnosis of PBL on itself (2). Two recurrent features are immunoglobulin gene rearrangements and MYC oncogene rearrangements (11). The postulated cell of origin of the plasmablastic...
lymphoma is the plasmablast \textit{i.e.} a blastic proliferating B-cell that has switched its phenotype to the plasma cell gene expression program (2). Also, Epstein Barr Virus infection (EBV) is frequently documented and EBV-DNA levels have been successfully used to monitor treatment response in a patient with PBL (12). The relationship between PBL and human herpesvirus 8 is less well-established. No morphological and genomic differences have been described between the HIV-positive and HIV-negative PBL patients. The differential diagnosis of the plasmablastic lymphoma includes other B-cell lymphomas with plasmablastic features, such as the anaplastic lymphoma kinase–positive large B-cell lymphoma, large B-cell lymphoma arising in human herpesvirus 8–associated multicentric Castleman disease, the primary effusion lymphoma and immunodeficiency-associated lymphoproliferative disorders (11).

In a recent case report and literature review of HIV-negative PBL patients, no previous cases of primary breast disease were identified and to our knowledge this is the first case reported (13). The presentation of a young female patient with a positive family history for breast cancer with multiple palpable breast lumps and axillary lymphadenopathy was highly suspicious for breast cancer. As shown in this case, definitive pathological diagnosis is the cornerstone of proper management and should precede any therapeutic approach. Since PBL is usually disseminated at the time of diagnosis, it is not known whether the primary site affects disease outcomes.

Another unique feature of our case is the treatment approach. Our patient achieved a complete response by imaging criteria, but had residual paraproteinemia which was thought to be due to MRD. This fact led to our decision to administer high-dose chemotherapy with stem cell rescue as consolidation treatment before disease relapse and this is the second published case with this treatment approach (14). Since there are no established therapeutic guidelines, the management of PBL patients relies on the physician’s preference. Treatment options are summarized in a recent review of the literature (15). CHOP-like regimens result in decent response rates, but are usually short-lived. More intensive regimens such as Hyper-CVAD (the combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine) have been shown to induce higher response rates and may lead to long-term disease-free survival (15). The use of autologous or allogeneic transplantation has not been adequately assessed and the increased toxicity must be weighed against the potential benefits in selected patients. In the few published reports, autologous stem cell rescue has been used mainly as salvage treatment, but there is one case report where it was used as consolidation therapy after complete remission, as was the case with our patient (14). In HIV-positive patients the use of Highly Active Anti-retroviral Therapy (HAART) is recommended as it improves outcomes. Other treatment approaches include the use of the proteasome inhibitor bortezomib with mixed results and the use of the anti-CD20 monoclonal antibody rituximab if the malignant cells express this marker.

In conclusion, we herein present the first case of an immunocompetent patient with plasmablastic lymphoma of the breast which was successfully treated with autologous stem cell transplantation as consolidation after attaining a complete remission with chemotherapy. With this case report we contribute to a growing body of literature regarding this rare entity and we propose a more aggressive therapeutic approach in selected patients.

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References


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