Relapsed Plasmablastic Lymphoma in a HIV negative patient: pushing the envelope

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Abstract

We report a case of Plasmablastic Lymphoma occurring in a 45-year-old HIV-negative woman involving extra nodal sites including ovary, breast and adrenal glands. Prognostic outcomes are generally dismal. On relapse, she received conventional as well as novel therapies and is disease free now, two years post allogenic haploidentical transplantation.

Keywords:
PLASMABLASTIC LYMPHOMA, RELAPSE, NOVEL THERAPIES, DARATUMUMAB, HAPLOIDENTICAL TRANSPLANTATION

Key Clinical Message:
This case emphasises that, with the availability of novel agents (Daratumumab), and repurposed use of bortezomib, even relapsed PBL could be treated successfully and consolidated with an allogeneic haploidentical hematopoietic cell transplantation.

Introduction:
Plasmablastic lymphoma (PBL) is a rare and aggressive CD20-negative B-cell Non-Hodgkin Lymphoma (B-NHL) associated with modest outcomes in HIV positive, and poor outcomes in the HIV Negative. HIV-negative PBL patients are known to present with an advanced clinical stage (less common bone marrow involvement), B symptoms, and have significantly poorer outcomes when compared to HIV- positive patients (1). Multiple studies have shown median survival times of 12–18 months.(1, 2)

Case Presentation:
A 45-year-old Chinese Indian woman presented in Feb 2015 with complaints of ‘persistent’ back pain and a recent history of total hysterectomy for an ovarian mass diagnosed as ovarian plasmacytoid neoplasm. She had no other localizing symptoms, no B symptoms and informed us of a family history of breast cancer (mother). Examination revealed bilateral (B/L) breast lumps (3cms max). CT thorax and abdomen showed additional lesions including few small left axillary lymph nodes, nodular lesions in bilateral adrenal glands (4.2cm max) and altered signals in L1 vertebrae with an associated paravertebral soft tissue mass (5.3cm max) compressing the conus. HIV test (by ELISA) was negative. Biopsy of the breast lumps showed lymphoproliferative neoplasm with plasmacytoid histology [positive for CD138, EBER-ISH, and kappa light chain restriction] s/o Plasmablastic Lymphoma. Bone marrow (BM) aspirate showed 6% plasma cell with no atypical cells. Cytogenetics on Marrow was FISH 17p deleted in 8% plasma cells. Baseline Protein electrophoresis was not done. She received local RT for pain control in the dorso-lumbar region. With a curative intent, she was treated with 6 cycles of dose-adjusted EPOCH (daEPOCH). After 6 cycles of
PBL is a rare type of high-grade B-NHL, frequently involving extra nodal sites (1). Our patient had multiple extra-nodal site sites of involvement at presentation (ovary, breast, adrenal gland, vertebra and para-vertebral soft tissue). An important differential diagnosis for PBL is plasmablastic myeloma. Absence of bone marrow involvement with abnormal plasma cells, or myeloma related end-organ dysfunction makes plasmablastic myeloma an unlikely diagnosis (3). We reviewed literature and found that CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens like Hyper-CVAD-MA (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and high-dose methotrexate and cytarabine), CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine), COMB (cyclophosphamide, oncovin, methyl-CCNU, and bleomycin), and infusional EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) have been used (4). Polychemotherapy achieves more than 50% complete remissions (CRs) in patients with disseminated disease (2). Though the role of infusional EPOCH has not been proven effectively, its use is supported by the impressive results achieved in HIV-associated Non-Hodgkin's Lymphoma. This has become the treatment of choice in many institutions (5). Short series have been reported on the role of AHCT in both HIV and immunocompetent patients. A multi-center Phase II GIGAT group study included 5 patients with PBL, among other lymphoma types, who underwent an AHCT after first CR. Four of them maintained CR after 13–83 months (6). Considering the aggressive course, PBL patients with high-risk features should be considered for consolidation with AHCT in first-line setting (7). Our patient received daEPOCH chemotherapy and was consolidated with AHCT in CR1. She remained in remission for 1 year and 4 months, which is consistent with the median overall survival (OS) reported elsewhere (8). Factors affecting survival in PBL are the following: achieving complete remission (CR), performance status, clinical stage, MYC gene rearrangements, and International Prognostic Index (9). Our patient relapsed in the breast in Jan 2017 and had insignificant response to 3 cycles of salvage chemotherapy (DHAP). She was started on bortezomib and lenalidomide (VR). A literature review by Guerrero-Garcia TA et al, on the use of bortezomib along with chemo regimens in PBL patients observed higher response and survival rates in the frontline setting, and impressive transient responses in relapsed cases (10). Other agents like lenalidomide, brentuximab vedotin, and Interleukin 6 directed agents have been shown to benefit in PBL in a few case reports (11, 12). Few case reports of daratumumab, an antibody directed against CD38, have shown activity in patients with relapsed PBL (13). Daratumumab was added along with VR from cycle 3. After 4 cycles of combination DaraVR...
and Radiation therapy, PET CT was in cMR. There are very few cases of successful AlloHCT in PBL in HIV positive patients (14). She underwent an AlloHCT with haplo-identical sibling brother. She developed limited gut and skin GVHD which responded to steroids. She is alive now 4 years post diagnosis of PBL and more than 2 years post AlloHCT with no evidence of disease, and is off immunosuppression. The emergence of biology driven approaches like novel B-cell targets and immunotherapeutic approaches like cellular immunotherapy (CD30 directed CAR T-cell); anti-PD-1 or anti-PDL-1 monoclonal antibodies; EBV directed antiviral agents (arginine butyrate, ganciclovir), bromodomain extra terminal (BET) inhibitor for MYC gene positive cases; and PI3K/Akt/m-TOR pathway inhibitors hold promise (15). This case exemplifies the fact that when clinical compulsions push treating teams to explore options other than the conventionally tried methods in a hard to treat cancer, outcomes can be rewarding occasionally. This patient received both conventional and novel therapies, and was later consolidated with a haploidentical AlloHCT.

Conclusion:

1. This case emphasizes that with the availability of novel agents (Daratumumab) and use of bortezomib, even refractory PBL could be treated successfully.
2. This case signifies that daEPOCH followed by upfront autologous stem cell transplant in CR1 is a suitable option in primary PBL giving durable remission.
3. To the best of our knowledge this is the first reported case of a relapsed HIV negative PBL treated with AlloHCT who is disease-free for more than 2 years.

References:


Author Contributions: VSR and RN: conceived and lead the idea for the case report; VSR, MK and RN wrote the manuscript, contributed to the design and editing the manuscript. IA and JD contributed pathology and imaging inputs (respectively), pictures and edited the manuscript. VSR, RN, MK, SB, MR, JK, and MC: examined and treated the patient, and edited the manuscript.

Figure Legends:

Figure 1. A) and B): Hematoxylin and Eosin stain shows tumour cells in sheets with rounded nuclei, coarse chromatin, single nucleoli and moderate cytoplasm, low power and high power images respectively. C) CD38 immunohistochemistry (IHC) stain

Figure 2: A to F - Comparative whole-body PET CT images of the patient at various stages of treatment and post allogenic stem cell transplant. In A image the inset view shows bilateral breast tumour indicated by two white arrows and a lytic lesion of the rib indicated by yellow arrow

Conflicts of Interest: None of the authors have any conflicts of interest to report in relation to the case work submitted

Data Sharing: Not applicable