Spontaneous Regression of Refractory Diffuse Large B-Cell Lymphoma with Improvement in Immune Status with ART in a Patient with HIV: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient:	Male, 55
Final Diagnosis:	Diffuse large B-cell lymphoma • HIV
Symptoms:	Fatigue • weight loss
Medication:	—
Clinical Procedure:	Renal biopsy
Specialty:	Oncology

Objective:	Unusual or unexpected effect of treatment
Background:	Diffuse large B-cell lymphoma accounts for the large majority of AIDS-related non-Hodgkin lymphoma. Traditionally, this lymphoma has been treated with CHOP-like regimens with the recent addition of rituximab. We report a unique case where an HIV-infected patient with diffuse large B-cell lymphoma had complete regression of the lymphoma with continued antiretroviral therapy (ART) after chemotherapy was stopped.
Case Report:	A 55-year-old man who presented with fatigue and weight loss had initial CT findings of bilateral renal masses during his workup. Biopsy revealed diffuse large B-cell lymphoma and subsequently he was also diagnosed with HIV. He completed 6 cycles of CHOP-like (4 cycles of EPOCH-R and 2 cycles of R-CHOP) first-line therapy with significant dose delays and dose reductions due to severe adverse effects. Chemotherapy was stopped due to physical deconditioning and intolerable adverse effects. He had a FDG-PET/CT showing progression of his disease 8 weeks after completing chemotherapy. He was maintained only on ART after finishing 6 cycles of chemotherapy. With this therapy alone and with improvement in his immune status, his lymphoma regressed completely.
Conclusions:	There are very few reported cases in which lymphoma has regressed with treatment of HIV alone, as is regression of diffuse large B-cell lymphoma. This case emphasizes that ART can lead to immune reconstitution of HIV-infected patients and can establish the anti-tumor effect, causing regression of the lymphoma.

MeSH Keywords:	Art Therapy • HIV • Lymphoma, Large B-Cell, Diffuse • Neoplasm Regression, Spontaneous
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Background

Malignancies are a common cause of morbidity and mortality in patients with HIV. More than 40% of HIV-infected individuals are diagnosed with malignancies. [1]. Malignancies are reported to cause 28% of the deaths in this group [2,3]. Non-Hodgkin lymphomas account for 10% of all malignancies in the HIV population and about 70–90% of such patients have diffuse large B-cell lymphoma [1,3,4]. In the early days of the HIV epidemic, very few people were cured of HIV lymphomas. Due to compromised immune status in HIV patients, chemotherapy was not well tolerated in the past. Since the introduction of ART in the 1990s, patient tolerance to chemotherapy regimens has improved and is now comparable to the general population. ART decreases the adverse effects of HIV on the bone marrow and hematopoiesis and, hence, improves the ability of bone marrow to tolerate adequate and effective chemotherapy [5,6]. Currently, ART is considered to be an essential component of the regimen used to treat HIV

lymphomas and has improved overall survival [6]. In a retrospective study by Vaccher et al., patients with HIV lymphomas who received CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and ART combination therapy were compared to CHOP or (CHOP-like regimens) alone. The analysis showed significantly improved survival rates in the combination therapy group [7]. ART leads to immune reconstitution in HIV-infected patients and can reinforce oncolytic ability of the immune system. We report the case of an HIV-positive patient with spontaneous regression of his diffuse large B-cell lymphoma following immune reconstitution with ART after chemotherapy was stopped.

Case Report

A 55-year-old man presented to his primary care physician with fatigue and 60-pound unintentional weight loss over a period of 5 months. Initial workup was significant for normocytic
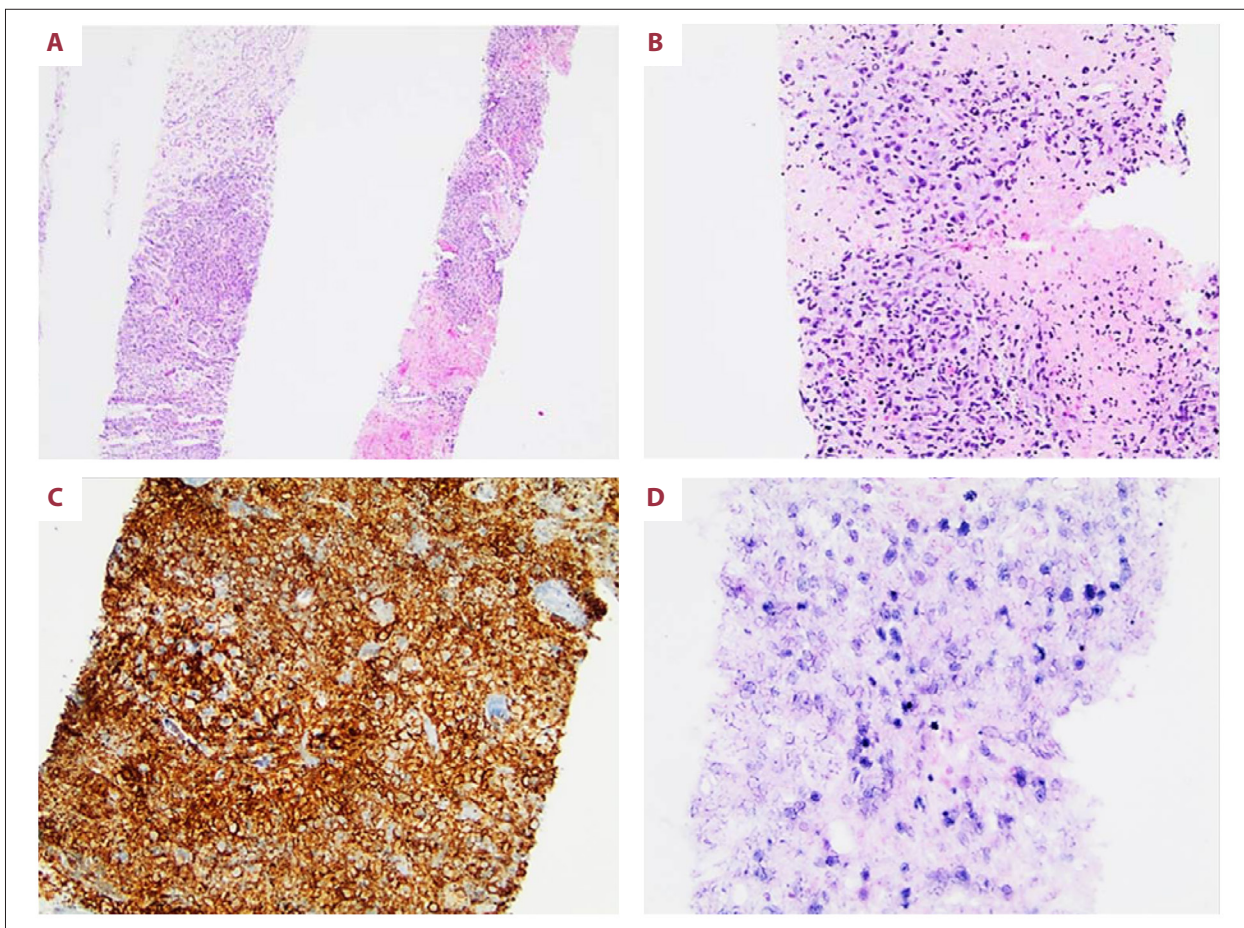

Figure 1. (**A, B**) Kidney biopsies showing renal parenchyma distorted by infiltrates of large cell lymphoma and extensive areas of necrosis. (**A** H&E: 20× total magnification; **B** H&E: 100× total magnification). (**C**) Lymphoma cells are diffusely and strongly positive for CD20 (CD20: 100x total magnification). (**D**) EBER (Epstein Barr virus encoded RNA) *in situ* hybridization study shows scattered positivity in the lymphoma cells (EBER ISH: 100× total magnification).
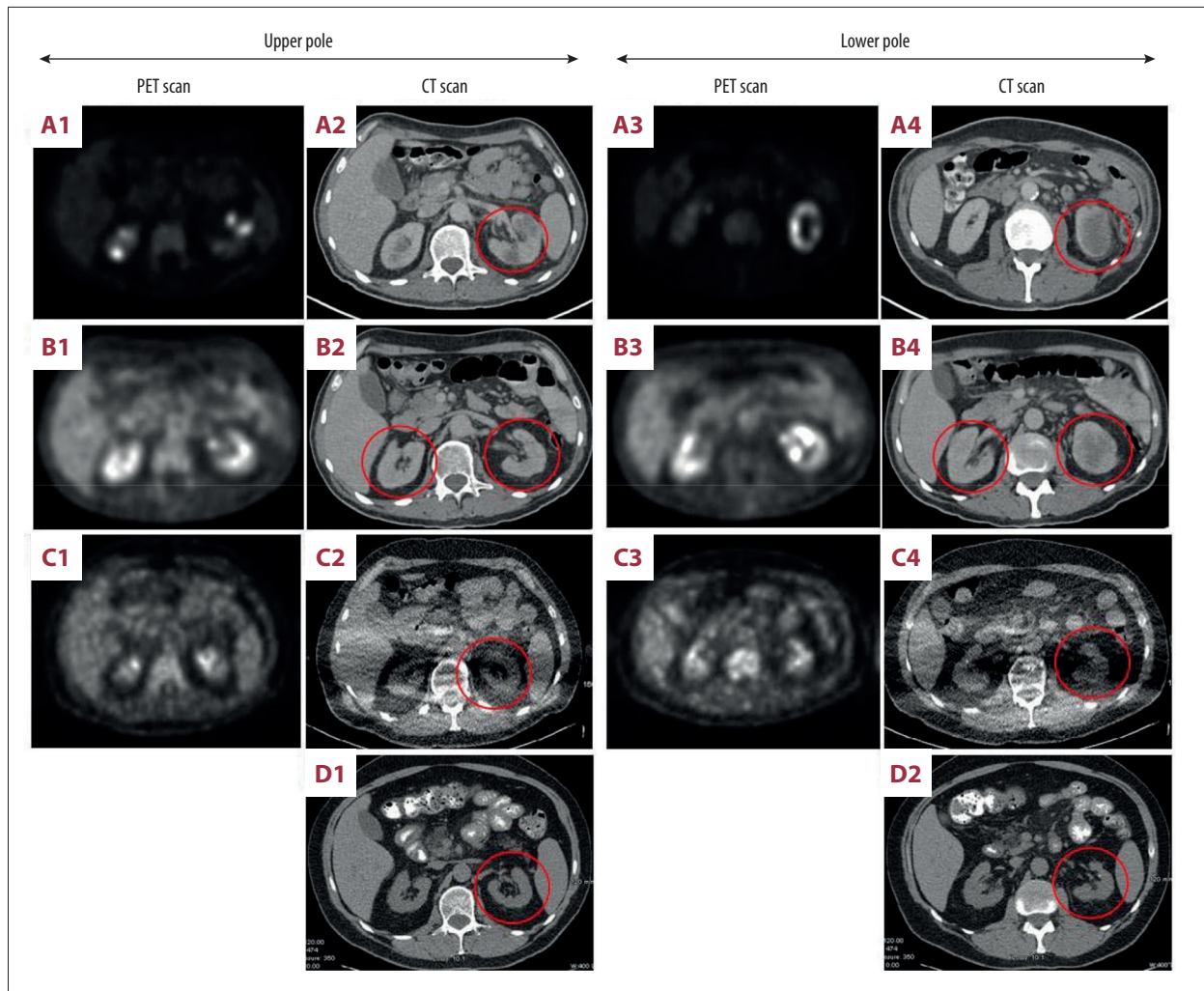
Figure 2. FDG-PET scan with accompanying CT scan of abdomen showing upper and lower poles of Kidneys. **A1–A4** are scans before treatment showing hypermetabolic lesions in both kidneys with visible masses marked with red circles; **B1–B4** are scans after chemotherapy showing worsening hypermetabolism and new masses; **C1–C4** are FDG-PET scans ten months after completion of chemo on ART alone showing complete resolution of hypermetabolism; **D1–D2** are CT scans at seventeen months of completion of chemotherapy showing regression of masses.

anemia, with hemoglobin of 9.5 g/dL. CT abdomen showed multiple abnormal-appearing mass lesions in both kidneys. CT chest and bone scan showed no evidence of metastatic disease. A biopsy of the renal lesions showed EBV-positive diffuse large B-cell lymphoma (Figure 1). The EBV positivity triggered additional testing to assess his immune status. HIV testing was subsequently performed and he was found to be HIV positive. A staging bone marrow biopsy was negative for bone marrow involvement. A staging Fluorine-18 Fluorodeoxyglucose positron emission tomography (FDG-PET)/Computed tomography (CT) showed hypermetabolic lesions in bilateral kidneys with masses (Figure 2A1–A4).

Chemotherapy was initiated with dose adjusted EPOCH-R (Etoposide, Prednisone, Vincristine, Cyclophosphamide,

Doxorubicin, Rituximab) along with ART (Darunavir, Ritonavir and Truvada). Bactrim and Azithromycin were administered for antimicrobial prophylaxis. He responded well to ART with improvement in CD4 counts as depicted in Figure 3.

The patient had severe pancytopenia, fatigue and neuropathy with each cycle of dose adjusted EPOCH-R. After four cycles of EPOCH-R, his regimen was switched to R-CHOP. He received two cycles of R-CHOP to complete a total of six cycles of chemotherapy. FDG-PET/CT scan done 8 weeks after completion of this treatment showed progression of his lymphoma with appearance of new lesions on the kidneys (Figure 2B1–B4).

Further chemotherapy was held for several months due to cytopenias and severe physical deconditioning. He was also
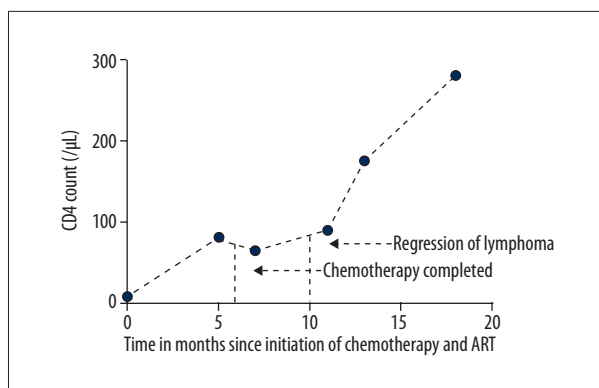
Figure 3. CD4 count with disease progression and ART.

felt to be a poor candidate for an autologous stem cell transplant given his poor functional status. He continued to receive ART and was followed with periodic CT and FDG-PET scans. His FDG/PET scan done at 10 months after he stopped chemotherapy showed complete resolution of his lymphoma (Figure 2C1–C4).

Discussion

HIV is associated with various human malignancies. In particular, non-Hodgkin lymphoma (NHL) is primarily encountered in patients with more advanced HIV infection [8,9], and a CD4 count that is usually below 100 cells/μL [10–12]. A history of a low CD4 count nadir may also be a significant risk factor for the development of NHL [13]. Retrospective and prospective studies have demonstrated an association between a lower most recent CD4 count and a higher risk of systemic NHL in patients who had or had not received prior antiretroviral therapy (ART) [14–16].

The pathogenesis of NHL in the setting of HIV infection is thought primarily due to immune deregulation leading to loss of control of viruses, such as Epstein-Barr virus (EBV). There is significant B-cell proliferation induced by infection with EBV in the setting of chronic immunosuppression and decreased T cell immune surveillance. To some degree, there is also progressive impairment of dendritic cell function and the resulting functional disorganization of lymph nodes that occurs with HIV infection [17,18]. This progression likely results from the increased production of cytokines (e.g., interleukin-6 and interleukin-10) from the damaged dendritic cells that are known to drive lymphoid cells [17,19]. Another factor that plays a role in the genesis, progression, and spread of AIDS-related lymphomas is the enhanced adhesion of neoplastic lymphocytes to HIV infected endothelial cells. When neoplastic cells are brought in close proximity to growth factors produced by the endothelial cells, it results in accelerated extravasation of the malignant cells into the tissues [20,21]

In diffuse large B-cell lymphoma (DLBCL) tumors, the majority demonstrates increased expression of the B-cell lymphoma 6 (BCL-6) gene. The increase in expression is the result either of mutations (often near the gene transcription initiation site) or of translocations that place the gene under the control of a new promoter [22]. Overexpression of BCL-6 in B-cell lymphoma cell lines leads to downregulation of BCL-6 target genes, including the p53 tumor suppressor gene. This may be a way in which BCL-6 protects cells from undergoing apoptosis in response to DNA damage. Other mechanisms important in the pathogenesis of a minority of DLBCL include aberrant somatic hypermutation, BCL-2 activation, and c-myc overexpression.

AIDS-related DLBCL displays several genotypic differences compared with DLBCL in the immunocompetent host [23]. First, BCL-2 activation is generally not seen in AIDS-related DLBCL as compared to ones with an immunocompetent host. Second, mutations resulting in deregulation of the BCL-6 proto-oncogene are seen in only 20% of AIDS-related DLBCL [23,24]. Third, c-MYC translocations occur in approximately 20% of AIDS-related DLBCL, which is much more than in an HIV-seronegative population [23].

The pathogenesis of neoplasms in HIV-infected patients is conceptually similar to that observed in solid organ transplant recipients who receive chronic immunosuppressive agents, as well as in patients with profound cell-mediated immune deficiencies. Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and/or plasmacytic proliferations that occur in the setting of solid organ or allogeneic hematopoietic cell transplantation as a result of immunosuppression. The degree of immunosuppression is considered a major determinant in the development of PTLD [25]. In particular, the degree of T-cell immunosuppression appears to be more important than the degree of overall immunosuppression due to the impairment of EBV-specific T-cell-mediated immunity [26]. Management has varied significantly based on the type of lymphoproliferative disease as well as institutional differences. However, immunosuppression reduction is the cornerstone of therapy. The phenomenon of immune reconstitution leading to regression of malignancy is very well documented in this group of patients. A previous case of spontaneous regression of HIV-related NK/T-cell lymphoma in the brain relapsing during intensive chemotherapy but regressing after chemotherapy stopped while on ART alone highlights the important role played by T-cells in tumor regression [30].

After the widespread implementation of ART, the incidence of NHL has decreased [27,28]. This decline in incidence appears to reflect improvements in CD4 counts [29]. The prognosis of HIV-infected patients with DLBCL has also improved significantly during the ART era. Traditionally, DLBCL in the setting of HIV has been treated with CHOP-like regimens with the recent

addition of rituximab. With CHOP-like regimens, disease-free survival rates are 35–45% at 4 years. Dose-adjusted EPOCH is preferred for patients with AIDS-related DLBCL and certain markers of poor prognosis [31]. A multicenter randomized phase II trial from the AIDS Malignancies Consortium (AMC034) explored dose-adjusted EPOCH plus rituximab in 101 patients with AIDS-related B-cell NHL [32]. Tumor histology was DLBCL in 71%, and Burkitt or Burkitt-like lymphoma in 29%. When compared with sequential rituximab, concurrent rituximab resulted in a higher complete response rate (73% *vs.* 55%, respectively) and similar rates of 2-year progression-free (66% and 63%, respectively) and overall survival (70% and 67%, respectively). Another phase II trial of 33 patients with AIDS-related lymphoma treated with short-course EPOCH plus dose-dense rituximab for a minimum of 3 cycles reported 5-year rates of progression-free and overall survival of 84% and 68%, respectively [33]. It is also suggested that for patients with CD4 count over 50/μL with high proliferative index (Ki 67 index >80%) or plasmablastic histology, dose-adjusted R-EPOCH is better.

The treatment of diffuse large B-cell lymphoma (DLBCL) continues to evolve, as researchers seek to improve upon the current standard of care.

Conclusions

We present a unique case of diffuse large B-cell lymphoma in a patient with HIV whose lymphoma continued to progress after 6 cycles of chemotherapy, but spontaneously regressed once his immune system and CD4 count improved with ART alone. There are very few reported cases in which lymphoma has regressed with treatment of HIV alone, as is regression of diffuse large B-cell lymphoma. This case emphasizes that ART can lead to immune reconstitution of HIV-infected patients and can establish oncolytic immune-surveillance, causing regression of the lymphoma. Our report stresses the significance of starting ART in the HIV-infected patient with lymphoma without any delay.

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