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HIV-Related Refractory Hodgkin Lymphoma: A Case Report of Complete Response to Nivolumab

Elaine Chang[a,b], **Gustavo Rivero**[a,c], **Niraj R. Patel**[d,e], **Elizabeth Y. Chiao**[b,f], **Syeling Lai**[g,h], **Kelash Bajaj**[a], **John E. Mbue**[i], and **Sarvari V. Yellapragada**[a,c]

[a]Department of Medicine, Section of Hematology & Oncology, Baylor College of Medicine, One Baylor Plaza Mailstop BCM 620, Houston, TX 77030, USA

[b]Center for Innovations in Quality, Effectiveness, and Safety, Michael E. DeBakey VA Medical Center, (USPS mailing address) Houston VA Medical Center (152), 2002 Holcombe Blvd, Houston, TX 77030, USA

[c]Department of Medicine, Section of Hematology & Oncology, Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA

[d]Department of Radiology, Division of Nuclear Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[e]Department of Radiology, Division of Nuclear Medicine, Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA

[f]Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[g]Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[h]Department of Pathology, Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA

[i]Department of Pharmacy, Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA

Introduction

We present a case of a patient with well-controlled human immunodeficiency virus (HIV) infection and refractory classical Hodgkin lymphoma (HL) treated with nivolumab as fifth-line treatment, who achieved complete response (CR) by positron emission tomography–computed tomography (PET/CT). To our knowledge, this is the second case report of a

Corresponding author: Elaine Chang, elainec@bcm.edu.

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patient exhibiting nivolumab's response, and first reported CR in the setting of HIV-associated HL (HIV-HL).

Case history

A 40-year-old veteran was diagnosed with HIV in 2009. His CD4 count was 290 cells/mm^3. After initiation of antiretroviral therapy with efavirenz/emtricitabine/tenofovir disoproxil (Atripla®), he maintained good disease control for the next 6 years, with consistently undetectable viral loads and no serious infections. When he initially noticed a right axillary mass in the summer of 2015, he delayed seeking medical attention. On presentation in the fall of 2015, he had lost 15 pounds over 10 weeks and his CD4 count had dropped from 593 to 353 cells/mm^3.

His HIV physician ordered a computed tomography (CT) scan of the neck and chest which revealed bilateral axillary (up to 3.9 cm), retropectoral, and infraclavicular lymphadenopathy. An excisional biopsy of the left axillary node showed Hodgkin's lymphoma, nodular sclerosis type, Epstein Barr virus (EBV)-LMP1 and Epstein-Barr encoding region in-situ hybridization (EBER-ISH) positive (Figure 1). EBV viral load was not evaluated at this time. His bone marrow biopsy was negative for lymphoma. Scans of the abdomen and pelvis showed no lymphadenopathy below the diaphragm. Erythrocyte sedimentation rate was more than 100 mm/hr.

Thus, he was diagnosed with stage IIB classical Hodgkin lymphoma. His baseline echocardiogram was concerning for a left ventricular (LV) ejection fraction of 45%, which was confirmed on Multigated Acquisition (MUGA) scan. To avoid anthracycline-induced worsening LV function, he was treated with 6 cycles of cyclophosphamide, vincristine, prednisone, and procarbazine (COPP). The post-treatment F-18 fluorodeoxyglucose (FDG) PET/CT scan demonstrated active lymphomatous disease throughout the right cervical, axillary, and subpectoral regions (Figure 2A). Biopsy of the right axillary lymph node confirmed refractory Hodgkin lymphoma.

His primary refractory disease progressed through three more regimens: (1) brentuximab vedotin (hereafter called simply "brentuximab"), (2) brentuximab in combination with gemcitabine, and (3) ifosfamide/carboplatin/etoposide (ICE). The patient was then offered nivolumab. After 8 cycles (3 mg/kg every 2 weeks), the post-treatment PET/CT demonstrated resolution of previous abnormal uptake and nodal size consistent with complete response by International Working Group criteria[1] (Figure 2B). He currently has no lymphoma-related symptoms, and has received a total of 17 cycles by the time of this report. His CD4 count, 391 cells/mm^3 at the start of therapy and now 426 cells/mm^3, has remained stable throughout this time; the viral load has remained undetectable. The antiretroviral regimen was changed from Atripla® to an integrase inhibitor-based regimen, tenofovir alafenamide/emtricitabine/dolutegravir, for noncancer- or chemotherapy-related reasons. However, he developed insulin-dependent diabetes mellitus with the presence of glutamic acid decarboxylase (GAD65) antibodies. He has declined evaluation for autologous stem cell transplant.

Discussion

The pathogenesis of lymphoma in HIV is complex. HIV not only increases the risk of cancer through immunosuppression, but is also a carcinogen in itself.[2] While the distribution of histologic subtypes may have shifted slightly in the last 20 years with the widespread use of ART,[3] the overall incidence of HIV-HL has not significantly decreased, in contrast to dramatic decreases in the rates of Kaposi's sarcoma, primary central nervous system lymphoma, and diffuse large B cell lymphoma, suggesting that ART-mediated immune reconstitution is not adequate to prevent Hodgkin lymphomagenesis in the HIV-infected population.[4] Additionally, the observation that EBV is invariably detectable in HIV-HL regardless of histology,[5-7] and only seen in 20-40% of cHL cases in the HIV-uninfected population, has sparked research interest in the tumor microenvironment of HIV-HL in search of the unique role of EBV in this disease. In the meantime, HIV-HL is treated under the same guidelines as cHL in the general population. Among HIV-HL patients with nodular sclerosis or mixed cellularity histology who receive chemotherapy, survival is comparable to patients without HIV. However, because treatment in HIV-infected patients is more frequently withheld, outcomes for HIV-HL are worse than those seen in HIV-uninfected patients on average.[3]

Immune checkpoint blockade emerged as an important new treatment option for patients with relapsed or refractory HL in 2015, after a pivotal single-arm multicenter trial of nivolumab monotherapy demonstrated an impressive objective response rate of 87%.[8] In 2016, nivolumab was granted FDA approval for relapsed or refractory HL after autologous SCT, followed by publication of a second single-arm, multicenter trial demonstrating an objective response rate of 66%.[9] However, the safety and efficacy of nivolumab in HIV-associated HL (HIV-HL) are still unknown, since the first trial excluded patients with HIV infection and the second trial did not report HIV status.

The scientific rationale for checkpoint therapy in HL is clear, as chromosome 9p24.1/PD-L1/PD-L2 alterations, increasing the abundance of the PD-L1 and PD-L2 ligands, are seen when evaluated by FISH assay in nearly all HL patients. Furthermore, these copy number alterations are a defining feature of the disease. Interestingly, EBV induces PD-L1 expression even in patients with normal 9p24.1 copy numbers in HL.[10] The role of EBV in inducing PD-L1 expression is further demonstrated outside HL. In one study, 100% of EBV-positive immunodeficiency-associated DLBCLs were found to express PD-L1.[11] This is particularly significant given the three-fold stronger association with EBV in HIV-HL compared to cHL in HIV-uninfected patients. Our patient's tumor was strongly positive for EBV by both LMP1 immunohistochemistry (IHC) and EBER ISH suggesting a "primed" state for immune checkpoint response.

Finally, HIV infection itself seems to induce a state of immunosuppression and immune evasion mediated by the PD-1–PD-L1 axis.[12, 13] In patients with chronic HIV infection, longitudinal assessment shows that HIV-specific CD8+ T cells upregulate PD-1 expression over time, resulting in anergy. Furthermore, blockade of the PD-1–PD-L1 pathway *in vitro* results in regain of HIV-specific CD8+ T cell effector function.[14] It is hypothesized that HIV-specific dysfunctional CD8+ T cells gradually accumulate and prevent the renewal of a

more competent, less anergic, HIV-specific CD8+ repertoire.[14] This is consistent with findings that the gradual loss of CD4 cells in HIV infection is due to an immune-based mechanism rather than a direct HIV cytopathic effect.[15] Our patient's CD4 count is stable-to-increasing on anti–PD-1 therapy, supporting our hypothesis that nivolumab may actually improve HIV-related immune dysfunction.

This data suggests that it is possible that EBV and HIV induce PD-L1 expression which leads to escape from immune surveillance, as well as diminished immune surveillance, allowing the two viruses to synchronously contribute to the pathogenesis of HL.[13] Because, the degree of PD-L1 expression did not predict nivolumab response in clinical trials,[8] testing for PD-L1 expression was not requested on our patient's tumor.

Despite multiple reasons for immune checkpoint implementation in HIV-related lymphomas, no data from clinical trials have yet been published. A phase I clinical trial evaluating the safety of combination checkpoint blockade with nivolumab and ipilimumab in the treatment of solid malignancies added an expansion cohort for HL (NCT02408861). Additionally, a second phase I clinical trial is evaluating the safety of pembrolizumab in patients with HIV infection and recurrent or refractory malignancies, including HL, NHL, and almost any solid cancer (NCT02595866). A literature search yielded only one case report of a patient with HIV infection and HL who was treated with nivolumab.[16] This patient was diagnosed with both cHL and Burkitt lymphoma (both EBV-associated) at 42 years of age, with a baseline CD4 count of 155 cells/mm^3 and bone marrow infiltration by cHL. The Burkitt lymphoma was responsive to first-line therapy, but the cHL continued to be refractory to salvage regimens including brentuximab. In spite of liver failure complicated by encephalopathy, he was treated with nivolumab, and had an excellent partial response (PR). The duration of response apparently was at least 1 year, by the time of the writing of the case report, and he had experienced no immune-related adverse effects.

Conclusion

We present the first reported case of a CR to nivolumab in a patient with HIV-HL. There has been only one previous case report of a patient with HIV infection and HL who achieved PR after salvage treatment with nivolumab. Of note, that patient also experienced a disease response of at least 1 year. Unfortunately, our patient developed autoimmune diabetes mellitus which was possibly related to nivolumab toxicity. Further prospective studies need to address the role of nivolumab for HIV-HL, currently limited post-transplant relapsed refractory settings, given the strong association with EBV and multi-faceted biological and mechanistic justifications. Additionally, the risk of irAEs needs to be further characterized.

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Clinical Practice Points

- We present a case of a veteran with well-controlled human immunodeficiency virus (HIV) infection and primary refractory classical Hodgkin lymphoma (HL) who, after multiple prior lines of therapy, received nivolumab with a complete response. He also developed autoimmune diabetes mellitus after one year of nivolumab.
- HIV-associated HL is currently treated under the same algorithm as HL in the general population, but its unique biology, particularly the near-universal association with Epstein Barr Virus, regardless of histology, suggests that immunotherapy may have an important role in the management of this disease.
- Most clinical trials highlighting checkpoint inhibitors have excluded HIV-infected patients. More prospective data is clearly needed to delineate the risks and benefits of immunotherapy in this population with increased autoimmunity at baseline.

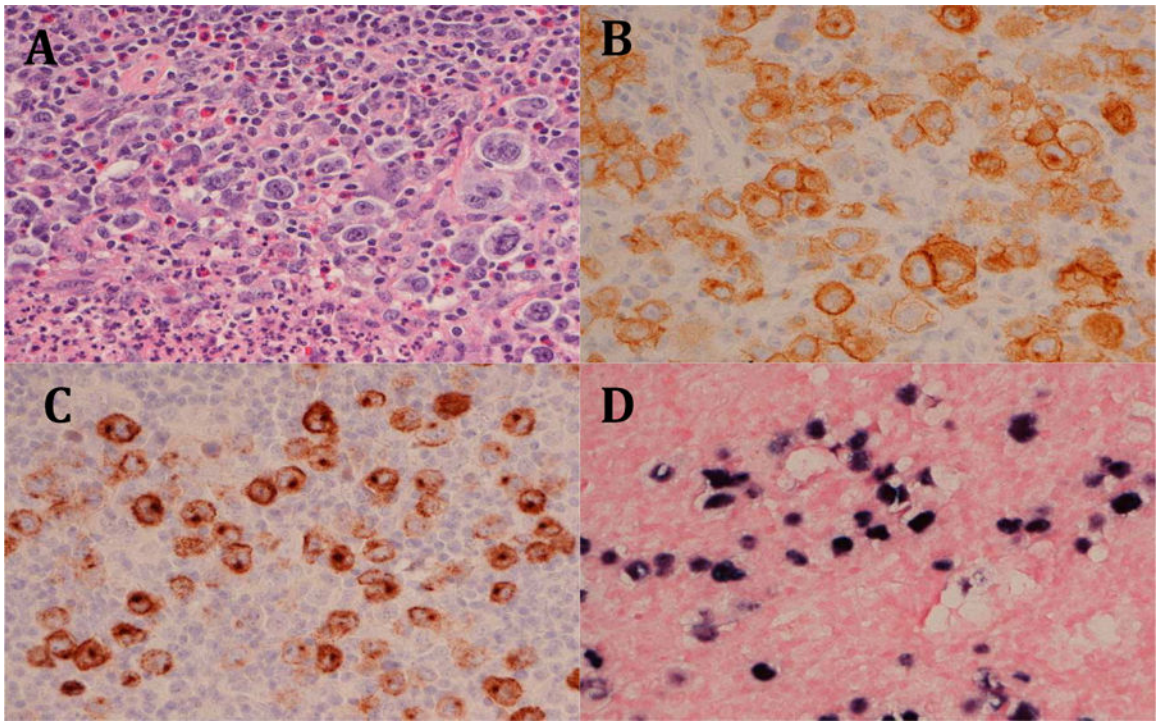

Figure 1. Pathologic Analysis, with H&E (A), CD30 (B), LMP1 (C), and EBER ISH (D)

A. Multiple Reed-Sternberg cells and Hodgkin cells are surrounded by a mixed cellular infiltrate with neutrophils, eosinophils, histiocytes, and lymphocytes (H&E stain, 400×).

B. Immunohistochemical staining for CD30 highlights Reed-Sternberg cells and Hodgkin cells.

C. Immunohistochemical staining for EBV LMP1 is strongly positive.

D. EBV-infected Reed-Sternberg and Hodgkin cells show strong nuclear EBER expression by in situ hybridization.

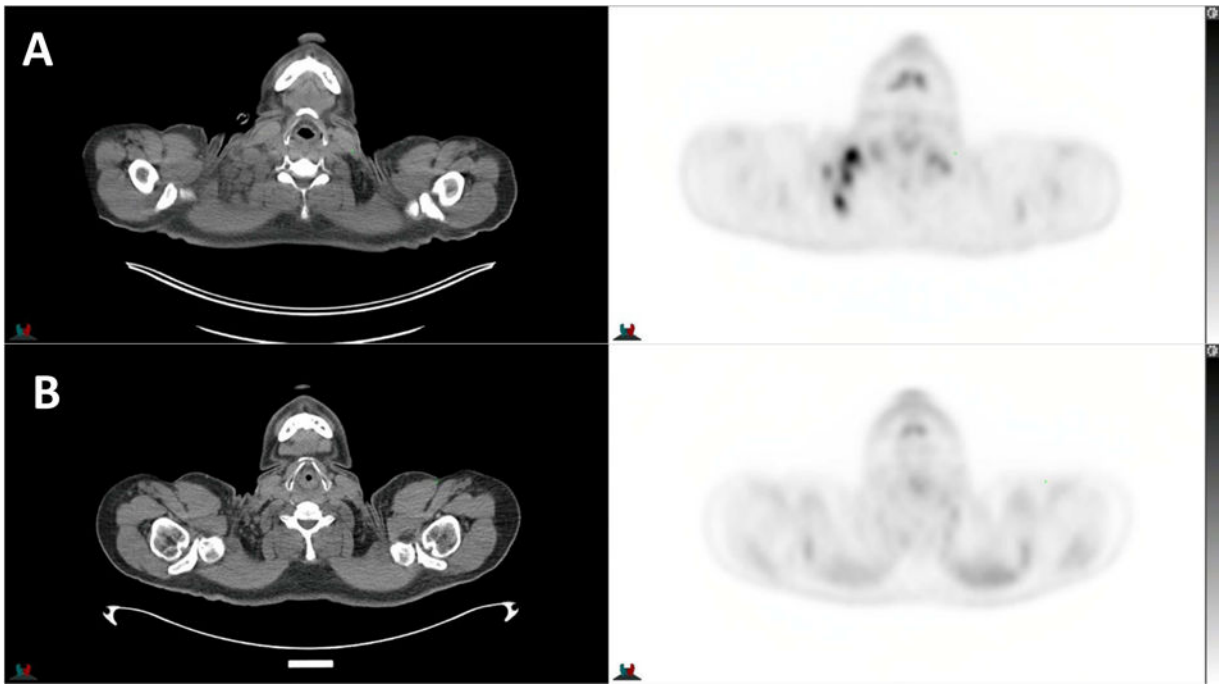

Figure 2. Non-contrast Computed Tomography (CT) and F-18 FDG Positron Emission Tomography (PET) Showing Lymphadenopathy Before Nivolumab (A) and Complete Resolution After Nivolumab (B)

A: The largest lymph node is 1.3 cm in short axis and associated with marked FDG uptake (maximum SUV of 7.7). Additional prominent to mildly enlarged lymph nodes with marked uptake are seen in the right supraclavicular fossa.

B: In a similar plane as (A), after 8 cycles of nivolumab, the 1.3 cm lymph node has decreased in size, measuring 0.6 cm in short axis, and is no longer FDG-avid (maximum SUV of 0.9), consistent with complete response to therapy. Additional sites of previous lymphadenopathy in the right supraclavicular fossa are also decreased in size and no longer avid.