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BRIEF REPORT

Immune Control Despite Protracted Lymphopenia After Chemoradiation in an Elite Controller

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Elite controllers are human immunodeficiency virus-1–positive individuals capable of sustaining undetectable viral loads without treatment. We present the case of an elite controller diagnosed with extensive stage small cell lung cancer who maintained a viral load of <20 copies/mL despite the development of severe treatment-related lymphopenia.

Keywords. elite suppressor; elite controller; treatment-related lymphopenia; chemotherapy; radiation therapy; Human Immunodeficiency Virus; small cell lung cancer

A subset of persons infected with human immunodeficiency virus (HIV)-1 can durably maintain undetectable viral loads (VLs) and normal CD4 counts without receiving highly active antiretroviral therapy (HAART). These individuals, termed elite controllers (ECs), make up less than 1% of the HIV-infected population [1]. The mechanism underlying this phenotype is yet to be fully elucidated due, in part, to the heterogeneity among ECs [1].

Chemotherapy has had variable effects on patients who control HIV-1 without therapy [2–4], with loss of control of viral replication occurring in a long-term nonprogressor treated with chemotherapy [2] and in an EC who received chemotherapy and a stem cell transplant [3]. There are no case reports of ECs who have received radiation or chemoradiation. Therefore, the effect of this treatment on EC status is unknown.

Even in the absence of HIV infection, approximately half of patients develop a protracted treatment-related lymphopenia (TRL) after chemoradiation [5–7] putting them at risk for shorter survival due to progression, not opportunistic infection. In this report, we document the effect of chemoradiation on an EC.

CASE PRESENTATION

A 58-year-old man with a prior history of intravenous drug use, cleared hepatitis C virus infection, and heavy smoking presented with subacute right-sided chest pain. He reported a diagnosis of HIV 17 years before presentation, but he had never received treatment. Laboratory evaluation revealed white blood cells 6.25 k/mm^3 and lymphocytes 37.3%. Human immunodeficiency virus antibody was positive by enzyme-linked immunosorbent assay and Western Blot (all bands positive); CD4$^+$ count was 801 cells/mm^3 (41%) and his VL was <20 copies/mL by the TaqMan COBAS assay. Human leukocyte antigen (HLA) typing revealed the following alleles: HLA-A*1/31, HLA-B*08/57, and HLA-C*7.

Positron emission tomography scan showed 2 foci of activity in the right lung parenchyma and focal activity in the left mediastinal and supraclavicular (SC) lymph nodes. Biopsy of a 4R lymph node and the left SC node revealed a neuroendocrine carcinoma positive for thyroid transcription factor 1 and synaptophysin and negative for p40 and chromogranin. The Ki-67 was >90%. The 4L lymph node was benign. There was no intracranial metastatic disease on magnetic resonance imaging. Radiation therapy with cisplatin (60 mg/m^2) and etoposide (120 mg/m^2) was administered. The thoracic radiation dose was 64 Gy in 32 fractions. Prophylactic cranial irradiation was applied after the completion of systemic therapy (25 Gy in 10 fractions).

The patient's CD4$^+$ count decreased to a nadir of 130 cells/mm^3 (52%) during chemoradiation, but he maintained undetectable VLs for more than 2 months (Figure 1). Due to the initial drop, a 3-month course of HAART with raltegravir, abacavir, and lamivudine was empirically initiated during chemoradiation in spite of the fact that the patient never lost control of viral replication. Highly active antiretroviral therapy was discontinued at the end of chemoradiation in accordance with the patient's wishes, but he maintained VLs of <20 copies/mL over an 18-month period despite the fact that there was no significant rebound in his CD4 or CD8$^+$ T-cell counts. However, due to recent recurrent episodes of community-acquired pneumonia, the patient was eventually given Triumeq. His most recent CD4$^+$ T-cell count was 446 cells/mm^3 (60%) and his most recent imaging, obtained 2 years after treatment, demonstrated no recurrent malignancy.

DISCUSSION

This case suggests that an HIV-1-infected patient with an EC phenotype can maintain viral controller status despite a

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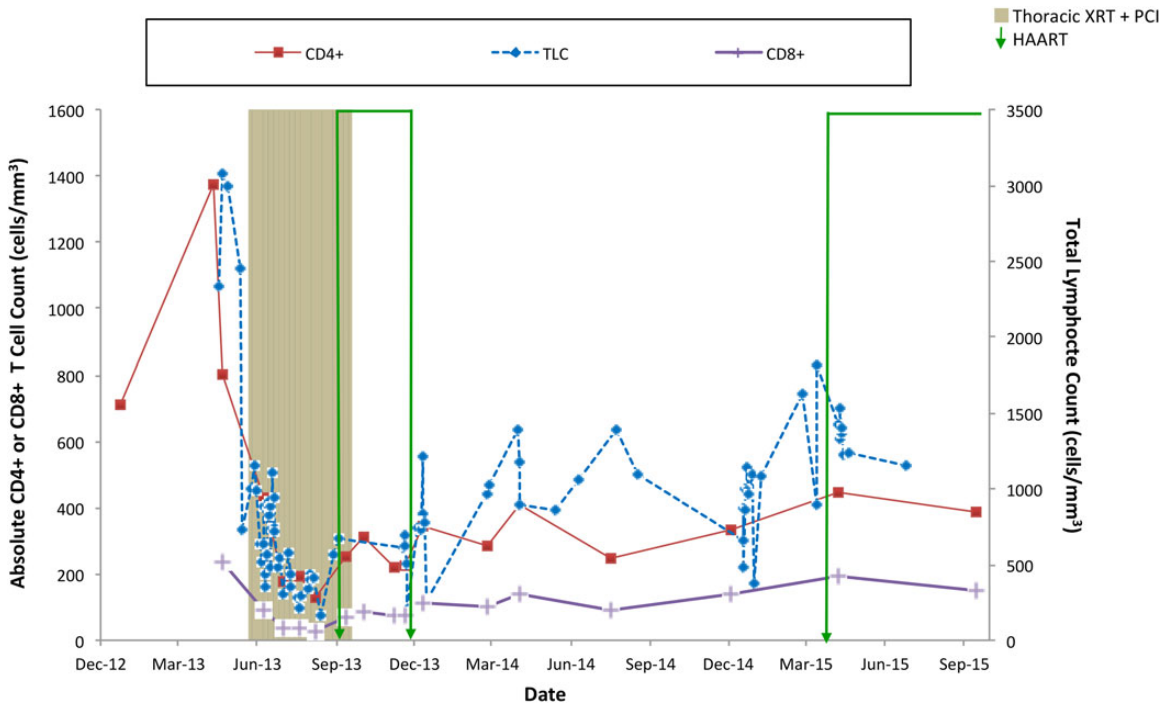

Figure 1. Absolute CD4$^+$ T-cell count (red solid), CD8$^+$ T-cell count (purple solid), and total lymphocyte count (blue dashed) over the course of treatment for small cell lung cancer and follow up to date. Shaded area indicates the duration of thoracic radiation therapy (XRT), and prophylactic cranial irradiation (PCI) therapy and highly active antiretroviral therapy (HAART) duration are denoted by the green arrows.

treatment-induced, long-lasting CD4$^+$ and CD8$^+$ T-cell count reduction. This is interesting because CD8$^+$ T-cell responses are thought to play a major role in the control of HIV replication in ECs who have protective HLA alleles (in this case HLA-B*5703) [8]. It is possible that the remaining peripheral CD8$^+$ T cells were sufficient to control viral replication in this patient. It is unfortunate that we were not able to study the patient's HIV-specific immune response or to determine whether chemoradiation caused any subtle changes in residual viral replication.

It is well recognized that even in the absence of underlying immunodeficiency, chemoradiation results in severe and protracted lymphopenia in 40% of patients [9]. This has been demonstrated across multiple malignancies in which the combination of chemotherapy and radiation is often given, such as gliomas [5], lung cancers [6], and pancreatic cancer [7]. This effect can last for years and is independently associated with decreased survival due to tumor progression rather than infections.

CONCLUSIONS

Our case illustrates that one may retain EC status despite the development of iatrogenic TRL, which affects immunocompetent as well as immunocompromised patients receiving radiation for solid malignancy. However, given reports of transient [3] or permanent [2] loss of control of viral replication in some patients treated with chemotherapy, empiric HAART should probably be considered in these cases.

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References

1. O'Connell KA, Bailey JR, Blankson JN. Elucidating the elite: mechanisms of control in HIV-1 infection. Trends Pharmacol Sci **2009**; 30:631–7.
2. Huang KH, Bonsall D, Katzourakis A, et al. B-cell depletion reveals a role for antibodies in the control of chronic HIV-1 infection. Nat Commun **2010**; 1:102.
3. Smith NM, Mlcochova P, Watters S, et al. Proof-of-principle for immune control of global HIV-1 reactivation in vivo. Clin Infect Dis **2015**; 61:120–8.
4. Gaillard S, Dinoso JB, Marsh JA, et al. Sustained elite suppression of replication competent HIV-1 in a patient treated with rituximab based chemotherapy. J Clin Virol **2011**; 51:195–8.
5. Grossman SA, Ye X, Lesser G, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. Clin Cancer Res **2011**; 17:5473–80.
6. Campian JL, Ye X, Brock M, Grossman SA. Treatment-related lymphopenia in patients with stage III non-small-cell lung cancer. Cancer Invest **2013**; 31:183–8.
7. Wild AT, Ye X, Ellsworth SG, et al. The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. Am J Clin Oncol **2015**; 38:259–65.
8. Migueles SA, Connors M. Success and failure of the cellular immune response against HIV-1. Nat Immunol **2015**; 16:563–70.
9. Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. J Natl Compr Canc Netw **2015**; 13:1225–31.