Published in final edited form as:

Hum Pathol. 2011 July ; 42(7): 1042–1046. doi:10.1016/j.humpath.2010.10.014.

Adult T-cell leukemia/lymphoma with EBV-positive Hodgkin-like cells

Girish Venkataraman, MD^{1,#}, Jonathan Berkowitz, MD PhD^{2,#}, John C. Morris, MD², John E. Janik, MD², Mark A. Raffeld, MD¹, and Stefania Pittaluga, MD PhD¹

¹ Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD.

² Metabolism Branch, Center for Cancer Research, National Cancer Institute

SUMMARY

Hodgkin-like cells (HLC) have been described in a variety of non-Hodgkin lymphomas (NHL) including chronic lymphocytic leukemia (CLL) and peripheral T-cell lymphoma (PTCL). There have been rare reports in the Japanese population of human T-cell lymphotropic virus-1 (HTLV-1)-associated adult T-cell leukemia/lymphoma (ATLL) harboring HLC; however, no similar cases have been described in western patients. We report a 53-year-old African-American man that presented with progressive weakness and lethargy, and was found to have generalized lymphadenopathy and hypercalcemia. A lymph node biopsy showed involvement by ATLL with scattered Epstein-Barr virus (EBV)-positive cells, some of which resembled Hodgkin cells that had a B-cell phenotype, consistent with an Epstein-Barr virus-lymphoproliferative disorder (LPD). The patient had stage 4 disease with bone marrow involvement. In light of the associated B-cell lymphoproliferative process, the patient was treated with six cycles of intensive chemotherapy that targeted both the ATLL and the EBV-LPD that resulted in a complete response. An awareness of the association of EBV-LPD with Hodgkin-like cells in the context of ATLL is necessary to avoid potential misdiagnosis and to aid in therapeutic decisions.

Keywords

Adult T-cell leukemia/lymphoma; Epstein-Barr virus; flow cytometry; Hodgkin-like; human T-cell lymphotropic virus-1; immunohistochemistry

1. Introduction

Patients with human T-cell lymphotropic virus type-1 (HTLV-1)-associated adult T-cell leukemia/lymphoma demonstrate impairment of the immune system that is manifested as an increased frequency of unusual or opportunistic infections [1]. One study reported a more than 25-fold greater incidence of opportunistic infections in patients with ATLL compared to patients diagnosed with other types of non-Hodgkin lymphoma [1,2]

© 2010 Elsevier Inc. All rights reserved.

Correspondence and reprint requests: Girish Venkataraman, M.D. National Cancer Institute 10, Center Drive Building 10, Room 2N/113 Bethesda, MD 20892 venkataramang@mail.nih.gov.

[#]Both authors contributed equally.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The paradigm for the evolution of Epstein-Barr virus-related lymphoproliferative disease (EBV-LPD) in the setting of immunosuppression is the induction of abnormal B-cell proliferation by EBV. In the transplant setting, EBV is believed to be a causal factor in a subset of cases. Recently, four cases of EBV-LPD were reported in 29 patients with various malignant T-cell lymphoproliferative disorders that were treated in a clinical trial with the anti-CD2 monoclonal antibody, sipilizumab [3]. Despite the associated immunosuppression, outside of patients undergoing allogeneic hematopoietic stem cell transplantation, EBV-LPD has only rarely been reported in patients with ATLL [3-5]. The few reported cases have occurred in Japanese patients with ATLL and were associated with scattered HLC in tumor biopsies. This rare subtype has been incorporated into the new WHO classification of hematopoietic tumors [6]. Herein, we report a western patient with HTLV-1-associated ATLL that was also concurrently diagnosed with an EBV-LPD with Hodgkin-like cells.

2. Case Report

A 53-year-old African-American man presented with 4 weeks of progressive weakness and lethargy to the point where he had difficulty standing. He also complained of intermittent night sweats and a 23 kg weight loss over the previous six months. On physical examination, he was found to have subcentimeter adenopathy in the cervical and inguinal regions. Laboratory examination demonstrated normal blood counts, but his serum calcium was evaluated at 13.8 mg/dL (reference range, 8.5-11.0 mg/dL). Computerized tomography demonstrated enlarged lymph nodes in the mediastinum, supraclavicular fossae, celiac axis, porta hepatis, mesentery and retroperitoneum. Serology for HTLV-1 was positive. A cervical lymph node biopsy was consistent with ATLL. He was referred to the National Cancer Institute (NCI) for evaluation. Staging examination revealed normal blood counts, with involvement of the bone marrow by ATLL. EBV viral titers were measured at 150,000 genome equivalents per one million peripheral blood mononuclear cells by quantitative polymerase chain reaction (PCR).

3. Microscopic Findings and Ancillary studies

Pathological review of his lymph node biopsy showed effaced architecture with two distinct components. The more apparent ATLL component was characterized by sheets of intermediate-sized atypical lymphoid cells expressing CD3, CD4, CD25 and lacking CD7, CD8 and CD30. The other component comprised atypical B cells with marked plasmacytoid differentiation and admixed HLC that had prominent eosinophilic nucleoli, and were positive for CD30, CD15 and PAX-5. *In situ* hybridization for EBV was strongly and diffusely positive in the HLC as well as in many smaller lymphoid cells with spatial distribution corresponding to the B-cell areas (Figure 1), consistent with the presence of an associated EBV-associated lymphoproliferative disorder. The staging marrow biopsy showed obvious involvement of the marrow by large hypercellular foci of atypical lymphoid cells with a CD4⁺/CD25⁺ phenotype, consistent with involvement by ATLL. Peripheral smear examination on a specimen (the earliest available) within the first week of treatment showed rare atypical cells consistent with “flower cells”. Corresponding flow cytometry of this peripheral blood sample confirmed the presence of an abnormal T-cell population with an ATLL phenotype: TCR- $\alpha\beta^{\text{dim}}$, CD2⁺, CD3^{dim}, CD5⁺, CD7[–], CD25^{bright}, CD26[–], CD27⁺, CD52⁺, CD56[–], CD4⁺, and CD8[–] (Figure 2A and 2B). Although the absolute lymphocyte count was 2300/mm³, 37% of the lymphoid cells were malignant T-cell by flow cytometry, consistent with the lymphomatous form of ATLL wherein the peripheral blood does not harbor a significant proportion of the disease burden. TaqMan-PCR identified clonal T-cell receptor gene rearrangement (Figure 2D) and HTLV-1 proviral sequences.

The patient was treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) chemotherapy with rituximab (chimeric anti-CD20) [7]. He received six cycles of treatment resulting in a reduction of both his lymphadenopathy and the circulating EBV load from 150,000 to 88 genome equivalents per one million peripheral blood mononuclear cells.

4. DISCUSSION

The presence of Hodgkin-like cells in ATLL was originally reported in the Japanese population by Ohshima et al [8], and these cells were thought to be part of the ATLL in view of a T-cell phenotype demonstrable in the HLC similar to the surrounding ATLL cells. A subsequent study observed similar cells in 18 patients with incipient ATLL, half of whom went on to develop overt ATLL [4]. The Hodgkin-like cells with a CD30+/CD15+ phenotype were EBV-infected in at least half of the cases and single cell PCR showed oligoclonal/polyclonal IgH rearrangements, while the background small CD4+ T-cells had clonal T-cell receptor gene rearrangements [4]. Furthermore, the same group carried out gene expression analysis examining cases of classical Hodgkin lymphoma (cHL) and ATLL with HLC and identified some ATLL with EBV+ HLC cases clustered with the mixed cellularity subtype of cHL; additionally they observed that increased expression of CCR4 (the ligand for TARC) was common to both cHL and ATLL (also demonstrated previously in ATLL cell lines [9]), their study could not however clarify the biologic role of HTLV-1 infection in the formation of HLC in ATLL [10].

Our case in this study presented as an overt ATLL involving blood, bone marrow, and lymph nodes. The presence of EBV in surrounding smaller cells spatially corresponding to the B-cell areas as part of the EBV-associated lymphoproliferative disorder is notable and most likely stems from the underlying immunodeficiency state precipitated by HTLV-1 infection. However, the role of EBV in supporting the growth of ATLL cells is unclear as yet. CD21 is the EBV-receptor and is reported to be over expressed in CD4+ T cells in ATLL as a result of the stimulatory influence of the HTLV-1 Tax protein; however, evidence of EBV DNA integration could not be demonstrated in these cells, questioning the role of EBV in the ATLL leukemogenesis [11]. In contrast, a recent study purports that coinfection with HTLV-1 and EBV may be associated with a greater likelihood of organ involvement and a more aggressive course through the enhanced expression of adhesion molecules via increased IL-4 signaling [12].

The frequency of co-infection EBV in ATLL has been reported as 17%. [11,12]. Plausibly patients with ATLL may be more susceptible to this infection than patients with other types of lymphoma due to the levels of immunosuppression [1]. While the underlying mechanism of this impaired immunity has not been elucidated, ATLL patients have been shown to have defective cytotoxic T-lymphocytes (CTL). This was suggested in an experiment in which CTL obtained from nine EBV-seropositive ATLL patients were unable to induce regression of foci of EBV-transformed B-cells *in vitro* [13]. However, the same assay using CTL from 10 healthy EBV-seropositive patients resulted in the regression of these foci. In a recent report, four patients that received sipilizumab (anti-CD2) in a clinical trial and developed EBV-LPD demonstrated significantly lower peripheral blood NK cell numbers than those patients that did not. No meaningful differences were noted in the T-cell populations between these two groups although the development of EBV-LPD following sipilizumab was thought to be dependent on the combination of T- and NK-cell depletion [3].

In terms of prognosis, patients with Hodgkin-like ATLL were noted to have an improved survival compared to other ATLL variants, including the small cell and pleomorphic variants [14]. Our patient has responded favorably to dose adjusted EPOCH-R, although he

continued to have persistence of HTLV-1 in the peripheral blood by PCR and flow cytometry. In conclusion, pathologists need to be attuned to the presence of HLC in the context of ATLL.

REFERENCES

1. White JD, Zaknoen SL, Kasten-Sportès C, Top LE, Navarro-Roman L, Nelson DL, et al. Infectious complications and immunodeficiency in patients with human T-cell lymphotropic virus I-associated adult T-cell leukemia/lymphoma. *Cancer*. 1995; 75:1598–1607. [PubMed: 8826916]
2. Bishop JF, Schimpff SC, Diggs CH, Wiernik PH. Infections During Intensive Chemotherapy for Non-Hodgkin's Lymphoma. *Annals of Internal Medicine*. 1981; 95:549–555. [PubMed: 7294544]
3. O'Mahony D, Morris JC, Stetler-Stevenson M, Matthews H, Brown MR, Fleisher T, et al. EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, sipilizumab, in patients with T-cell malignancies. *Clin Cancer Res*. 2009; 15:2514–2522. [PubMed: 19293260]
4. Ohshima K, Suzumiya J, Kato A, Tashiro K, Kikuchi M. Clonal HTLV-I-infected CD4+ T-lymphocytes and non-clonal non-HTLV-I- infected giant cells in incipient ATLL with Hodgkin-like histologic features. *Int J Cancer*. 1997; 72:592–598. [PubMed: 9259396]
5. Tanaka Y, Kondo T, Kishimoto W, Kanda J, Tashima M, Mizumoto C, et al. [Epstein-Barr virus-associated B cell lymphoproliferative disorder complicated in adult T-cell leukemia]. *Rinsho Ketsueki*. 2008; 49:263–269. [PubMed: 18516870]
6. Swerdlow, SH.; Campo, E.; Harris, NL. Lyons. IARC press; France: 2008. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues.
7. Wilson WH, Dunleavy K, Pittaluga S, Hegde U, Grant N, Steinberg SM, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008; 26:2717–2724. [PubMed: 18378569]
8. Ohshima K, Kikuchi M, Yoshida T, Masuda Y, Kimura N. Lymph nodes in incipient adult T-cell leukemia-lymphoma with Hodgkin's disease-like histologic features. *Cancer*. 1991; 67:1622–1628. [PubMed: 2001551]
9. Yoshie O, Fujisawa R, Nakayama T, Harasawa H, Tago H, Izawa D, et al. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood*. 2002; 99:1505–1511. [PubMed: 11861261]
10. Ohshima K, Karube K, Hamasaki M, Suefuji H, Tutiya T, Yamaguchi T, et al. Imbalances of chemokines, chemokine receptors and cytokines in Hodgkin lymphoma: classical Hodgkin lymphoma vs. Hodgkin-like ATLL. *Int J Cancer*. 2003; 106:706–712. [PubMed: 12866030]
11. Ohtsubo H, Arima N, Tei C. Epstein-Barr virus involvement in T-cell malignancy: significance in adult T-cell leukemia. *Leuk Lymphoma*. 1999; 33:451–458. [PubMed: 10342573]
12. Ueda S, Maeda Y, Yamaguchi T, Hanamoto H, Hijikata Y, Tanaka M, et al. Influence of Epstein-Barr virus infection in adult T-cell leukemia. *Hematology*. 2008; 13:154–162. [PubMed: 18702873]
13. Katsuki T, Yamaguchi K, Matsuoka Y, Hinuma Y. Impairment of T-cell control of Epstein-Barr virus infected B-cells in patients with adult T-cell leukemia. *AIDS Res*. 1986; 2(Suppl 1):S125–130. [PubMed: 3030343]
14. Ohshima K, Suzumiya J, Sato K, Kanda M, Simazaki T, Kawasaki C, et al. Survival of patients with HTLV-I-associated lymph node lesions. *J Pathol*. 1999; 189:539–545. [PubMed: 10629555]

Figure 1. ATLL with Hodgkin-like cells

A, Effaced nodal architecture with sheets of medium sized atypical cells. **B**, Scattered large atypical lymphoid cells resembling Hodgkin/Reed-Sternberg cells (inset) are noted. **C**, The ATLL component strongly expressed CD4 and CD25 (inset). **D**, HLC express moderate PAX-5, while the small B-cell component is strongly positive. **E**, HLC component additionally expresses CD30. **F**, Numerous EBV-positive cells are identified in the background small lymphocytes and HLC (inset). **G**, Coexpression of EBV in a subset of B-cells (Double stain: CD20-brown-membrane; IHC/EBER-blue-nuclear; ISH).

Figure 2. Peripheral blood flow cytometry and molecular diagnostics
A-B, Distinct CD3^{dim}+CD4⁺ population expressing CD25. **C**, Polyclonal Framework-III-IGH PCR **D**, Strong bi-allelic clonal peaks in the T-cell study.