CD4-Positive T-Cell Primary Central Nervous System Lymphoma in an HIV Positive Patient

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ABSTRACT

Objectives: *Primary central nervous system lymphomas (PCNSLs) in patients with human immunodeficiency virus (HIV) are predominantly B-cell lymphomas associated with Epstein-Barr virus (EBV) and rarely CD8-positive T-cell PCNSLs.*

Methods: *Patient history, laboratory results, cerebrospinal fluid (CSF), imaging, and brain biopsy specimens were reviewed and tested for T-cell receptor clonality.*

Results*: A 64-year-old HIV-positive woman sought treatment for lethargy and left-sided weakness. Brain imaging showed regional increased T2 signal with restricted diffusion in cerebral hemispheres. CSF flow cytometry revealed CD4-positive T lymphocytes with loss of CD3, CD5, and CD7. EBV-positive T-cell lymphoma was immunohistochemically confirmed on brain biopsy specimens. Molecular analysis detected clonal T-cell receptor gene rearrangement. The patient received intrathecal methotrexate and whole-brain radiation. She did not respond to treatment and was eventually placed in hospice care.*

Conclusions: *To our knowledge, this is the first report of CD4-positive T-cell PCNSL in an HIV-positive patient and will help to raise clinical awareness of this previously unknown entity.*

Primary central nervous system lymphoma (PCNSL) is defined as extranodal malignant lymphoma rising in the brain, spinal cord, meninges, or eye in the absence of lymphoma outside the nervous system at the time of diagnosis. PCNSL is a common non-Hodgkin lymphoma (NHL) in patients with human immunodeficiency virus type 1 (HIV-1). In patients with AIDS, PCNSL has an incidence of 1,000 times greater than that seen in the general population.[1,2] However, after the introduction of highly active antiretroviral therapy (HAART), the frequency of PCNSL has declined.[3] PCNSLs are predominantly of B-cell origin and are consistently associated with Epstein-Barr virus (EBV) infection.[1,3] To our knowledge, only eight cases of T-cell PCNSL have been reported in the English literature to date. None of these cases were CD4 positive.[4-10] Here, we present the first case of EBV-positive, CD4-positive T-cell PCNSL in a patient with AIDS.

Case Report

A 64-year-old woman with a medical history of HIV-1 infection for 9 years sought treatment at the hospital for chief complaints of gradually progressive lethargy, fever of unknown origin, left-sided weakness, and respiratory distress. The patient was receiving HAART and had a CD4 count of 134 cells/mL and an HIV-1 viral load of less than 40 copies/mL of blood on admission. The initial blood workup was not significant except for mild macrocytic anemia. Blood culture was drawn and empiric antibiotic treatment was initiated. Brain magnetic resonance imaging (MRI) showed scattered regions of increased T2 signal intensity with associated restricted diffusion primarily involving the cerebral white matter and

deep gray structures. There was no significant mass effect or vasogenic edema associated with these lesions. The postcontrast images showed none to modest enhancement associated with some of these lesions **Image 1**. The largest region was in the left posterior temporal lobe, which was subsequently biopsied. All cultures and serology tests failed to detect any infectious etiology except polymerase chain reaction on cerebrospinal fluid (CSF), which detected the presence of EBV. Moreover, the CSF cytology showed a cellular sample with a monotonous population of atypical lymphocytes **Image 2**. The lymphocytes were medium in size with slightly irregular nuclei and variable amounts of cytoplasm. CSF flow cytometry identified a population of atypical T lymphocytes (58% of total cells) that expressed CD2 and CD4 (98% of T cells) with loss of expression of CD3, CD5, and CD7 **Image 3**. The atypical cells were negative for CD8, B-cell markers, CD34, terminal deoxynucleotidyl transferase, and myeloid/monocytic markers. Cytoplasmic CD3 was detectable in 80% of the atypical lymphocytes. Stereotactic brain biopsy was performed. Histologic examination showed a moderate lymphohistiocytic infiltrate in the leptomeninges and a mild although widely distributed lymphohistiocytic infiltrate in fragments of brain parenchyma **Image 4A**. Immunohistochemical stains revealed atypical T cells that were CD2 positive, CD4 positive, and CD8 negative **Image 4B** and **Image 4C**. CD20 was essentially negative. Epstein-Barr encoding region in situ hybridization for EBV-encoded RNA was positive in many small cells and had a similar distribution as the CD2-positive T cells **Image 4D**. Latent membrane protein 1 (LMP-1) immunohistochemical stain showed rare positive cells. Molecular analysis using primers specific for the T-cell receptor γ locus showed clonal T-cell receptor gene rearrangement. The patient did not show any evidence of T-cell lymphoma outside of the central nervous system. A diagnosis of EBV-positive, CD4-positive T-cell PCNSL was made. The patient received intrathecal methotrexate followed by a course of whole-brain radiation. However, following a single fraction of radiation (2 Gy), the patient became vitally unstable and hypotensive, requiring admission to the intensive care unit. The patient was unable to complete her treatment plan. After consulting with her primary team and family, the patient was placed in hospice care and died in less than a month.

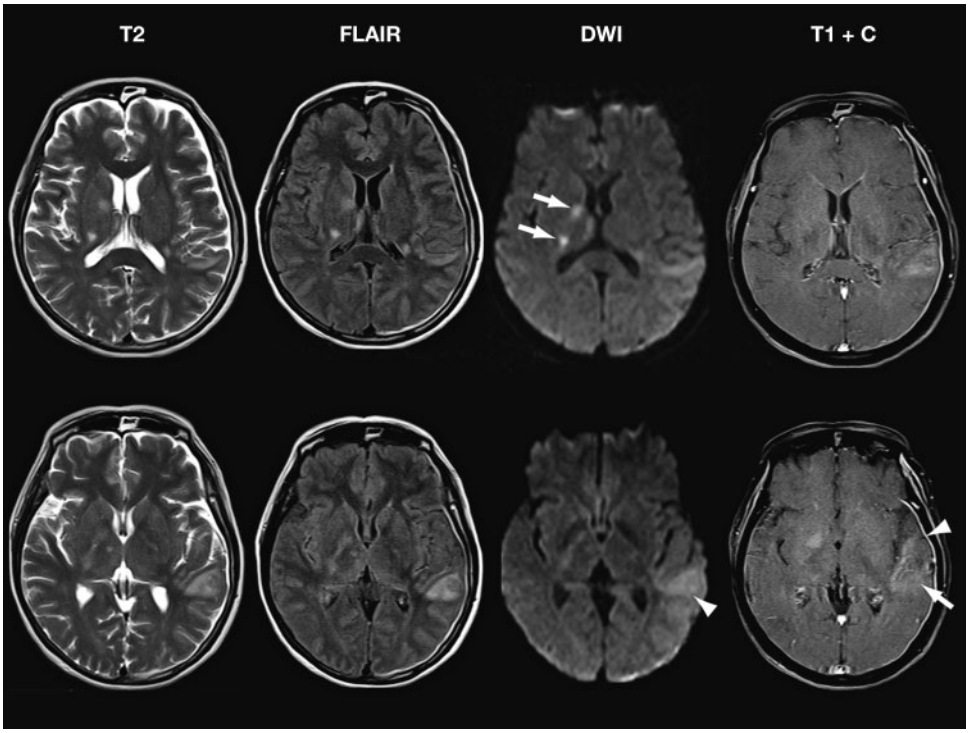

Image 1 Axial T2-weighted (T2), fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and T1 postcontrast images. Note the restricted diffusion in the right periventricular region and basal ganglia (arrows on DWI) and in the left temporal lobe white matter (arrowhead on DWI). There is corresponding hyperintense signal on T2 and FLAIR images to these regions. On postcontrast, most of these lesions show no enhancement or only subtle enhancement (arrow on T1+C), an atypical feature for central nervous system (CNS) lymphoma. Also note dural thickening and enhancement (arrowhead on T1+C) along the left cerebral hemisphere, a feature described in CNS lymphoma.

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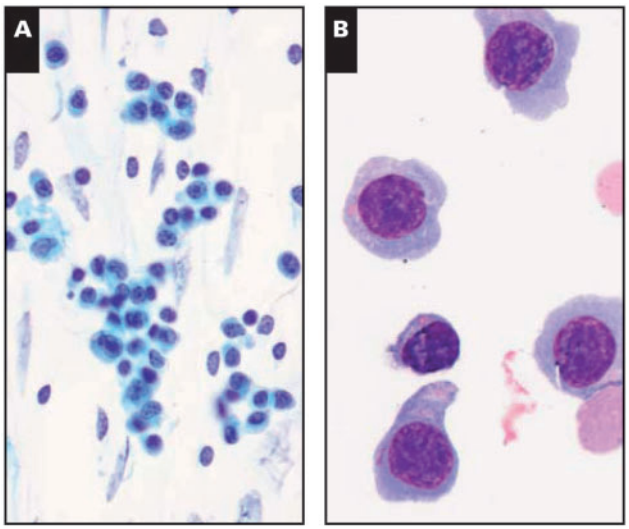

Image 2 **A**, Cerebrospinal fluid (CSF) cytology showing atypical small- to medium-sized lymphocytes with irregular nuclei and variable amounts of cytoplasm (Papanicolaou stain, ×400). **B**, CSF cytospin reveals morphologically similar cells (Diff Quik, ×1,000).

Discussion

Lymphoma is one of the most common HIV-related malignancies and can be divided into NHL, which is an AIDS-defining malignancy, and Hodgkin lymphoma (HL), which is a non–AIDS-defining malignancy. The most common NHLs in this patient group are Burkitt lymphoma and diffuse large B-cell lymphoma, followed by primary effusion lymphoma, plasmablastic lymphoma, marginal zone lymphoma of mucosa-associated lymphoid tissue, and peripheral T-cell lymphoma.[11] After introduction of HAART and improvement in immune function in patients with AIDS, the incidence of AIDS-defining malignancies has significantly decreased. However, NHL is still one of the main causes of death among patients with AIDS.[12,13]

A number of studies have shown that there has been a steady increase in the incidence of non–AIDS-defining malignancies such as HL, suggesting that HAART provides insufficient protection against HL in patients with HIV.[14-16] Interestingly, HLs in these patients are almost always EBV related.[17] Most HIV-associated lymphomas are of B-cell origin (95%). Very few CD8-positive T-cell lymphomas are reported in HIV-positive patients. The most common T-cell lymphomas are peripheral T-cell lymphoma and anaplastic large cell lymphoma–ALK negative, both of which have a very poor prognosis.[18] It is extremely rare to have CD4-positive T-cell lymphoma in patients with HIV, since HIV infection results in depletion of CD4-positive T cells.

Only one case has been reported in the literature of CD4-positive T-cell lymphoma in a patient with HIV.[19] The patient

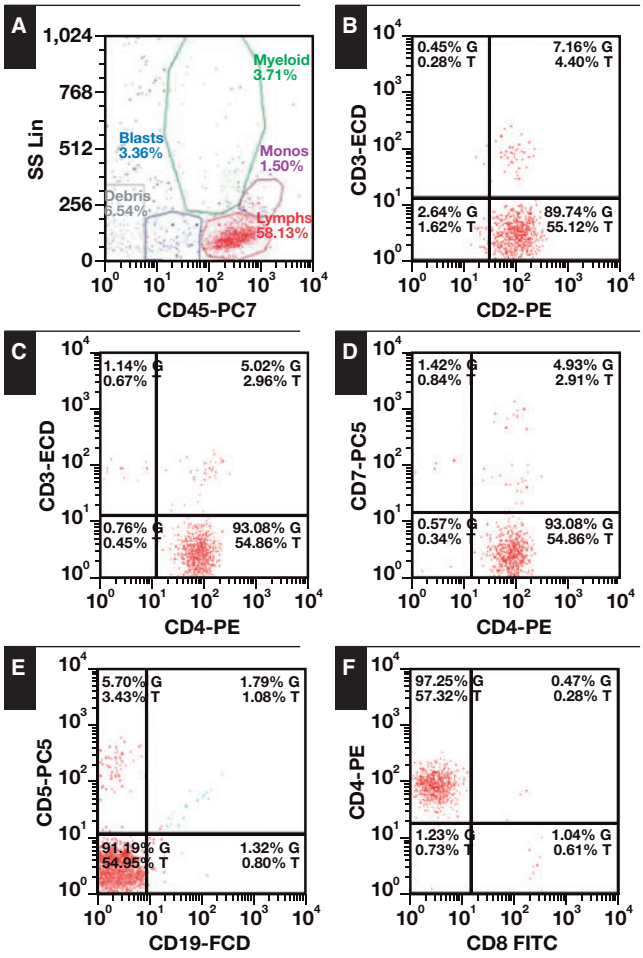

Image 3 Cerebrospinal fluid flow cytometry showing a population of cells with low side scatter and bright CD45 expression, consistent with lymphocytes (58% of total cells) (**A**). Analysis of the lymphocyte gate shows that approximately 90% of lymphocytes are atypical T cells with expression of CD2 (**B**) and CD4 (**C, D**) and loss of expression of CD3 (**B, C**), CD5 (**E**), and CD7 (**D**). The atypical T cells are negative for CD8 (**F**) and CD19 (**E**). G, gate; T, total.

was a 45-year-old man with respiratory symptoms. On examination, he had pleural effusion and generalized lymphadenopathy with a CD4-positive cell count of 45 cells/mL. Microscopic examination of the pleural fluid and hilar lymph node biopsy specimen revealed a high-grade T-cell lymphoma expressing CD45, CD4, and CD5 with loss of CD3. No expression of EBV was identified. The patient died within 7 days after admission.

AIDS-related NHLs can be divided into three main categories according to their site of origin: systemic lymphoma, primary effusion lymphomas, and PCNSL. Systemic lymphomas comprise approximately 80% of cases. They usually present as widely disseminated disease with a high incidence of extranodal involvement.[2] Primary effusion

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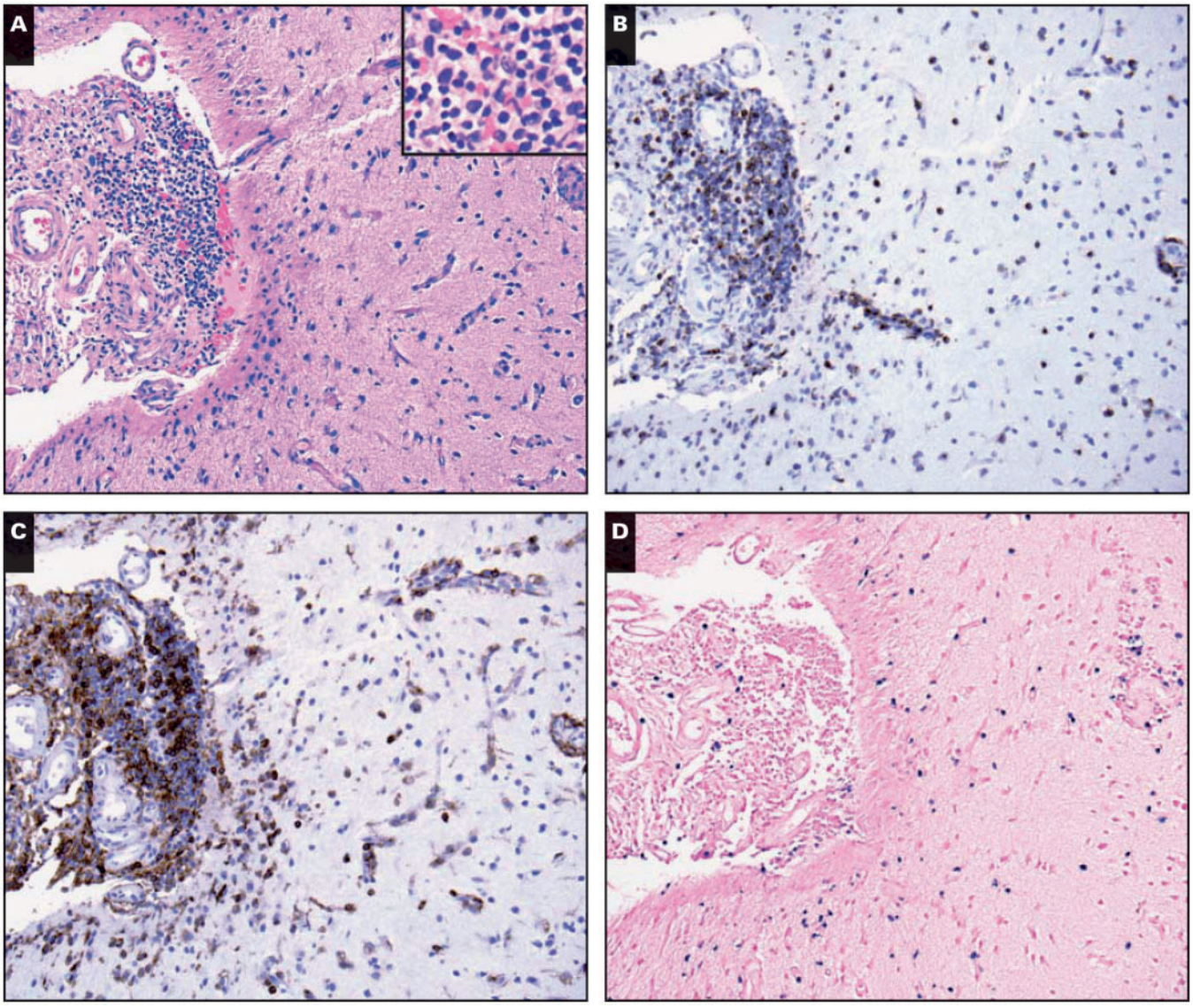

Image 4 **A**, Microscopic examination of the brain biopsy specimen shows perivascular and intraparenchymal lymphohistiocytic infiltration (H&E, ×200). Inset: Lymphocytes are atypical with irregular nuclear contours and larger nuclei in comparison to normal lymphocytes (H&E, ×600). Immunohistochemical staining shows the atypical lymphocytes are positive for (**B**) CD2 (×200) and (**C**) CD4 (×200). **D**, Epstein-Barr encoding region in situ hybridization shows positive lymphocytes in the same distribution as CD2-positive lymphocytes (×200).

lymphoma is a rare subtype of NHL. It is limited to the body cavities and universally associated with Kaposi sarcoma–associated herpesvirus/human herpes virus 8 (HHV-8) infection. Coinfection with EBV is common, especially in patients with HIV. However, rare cases of HHV-8–negative primary lymphomatous effusions have been described in both HIV-positive and HIV-negative patients, known as HHV-8–unrelated primary effusion lymphoma–like lymphoma.[20] PCNSLs comprise approximately 15% to 20% of cases.

According to data collected by the Centers for Disease Control and Prevention, HIV-AIDS is the most common risk factor for the development of PCNSL, which has an incidence that is 1,000 times greater in patients with AIDS than in the general population.[1,2] After the introduction of HAART, the overall incidence of PCNSL has declined.[3,16,21] PCNSL can present in any location in the central nervous system, can be monofocal or multifocal, and can have either homogeneous contrast enhancement or ring enhancement on MRI. The most common location is the cerebral hemispheres, but PCNSLs also frequently occur in the cerebellum, basal ganglia, and brainstem.[2,22] Stereotactic brain biopsy is the modality of choice for diagnosis. On histology, the tumor cells resemble centroblasts and often have a perivascular distribution. Tumor cells may be admixed with small reactive lymphocytes,

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Table 1
Review of T-Cell Primary Central Nervous System Lymphoma in Patients With HIV

Case (Referece No.)	Age, y[a]	Sex	Clinical Presentation	Primary Site	Presenting Lesions	HAART	CD4 Cell Count[b]
1 (9)	30	F	Ataxia	Cerebellum	Single	NA	NA
2 (9)	36	M	Seizure	Cerebrum	Multiple	NA	NA
3 (6)	36	M	Headache, dysarthria, and discoordination	Cerebellum	Single	Yes	<50
4 (7)	38	M	Headache, hearing loss, and amblyopia	Cerebrum	Multiple	NA	28-90
5 (8)	43	M	Fever and seizure	Cerebrum	Single	Yes	NA
6 (4)	43	M	Nausea, headache, and facial twitching	Cerebrum	Multiple	No	78
7 (5)	23	M	Nausea and acute confusion	Cerebrum and cerebellum	Multiple	Yes	NA
Current case	64	F	Lethargy and left-sided weakness	Cerebrum	Multiple	Yes	134

EBV, Epstein-Barr virus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ITC, intrathecal chemotherapy; NA, no data available; WBR, whole-brain radiation.
[a]Age and follow-up since the first diagnosis.
[b]Number of CD4 cells per 1 mL of blood.
[c]HIV viral load based on number of copies per 1 mL of blood.
[d]EBV status based on polymerase chain reaction –>or Epstein-Barr encoding region in situ hybridization –>study.

macrophages, and reactive astrocytes.[23] Based on current data, there are no characteristic radiologic or histologic features to distinguish B-cell PCNSL from T-cell PCNSL. Immunophenotyping or molecular analyses are required. Immunophenotypically, PCNSLs are predominantly of B-cell origin and are almost always associated with EBV expression.[3] CSF EBV DNA load has been shown to have a sensitivity of 100% and a specificity of 66% for the diagnosis of PCNSL in patients with HIV.[24]

To our knowledge, only seven T-cell PCNSL cases have been reported in patients with HIV in the English literature.[4-9] None of these cases were reported as CD4-positive lymphoma, and EBV status was available for only two cases, which were both positive **Table 1**. The treatment strategy is similar to that for immunocompetent patients, which entails high-dose methotrexate or other combined chemotherapy, with or without whole-brain radiotherapy.[25-27] Even with the introduction of HAART, the overall survival of patients with PCNSL remains poor.[28] The mechanism of HIV lymphomagenesis is still unclear, but high levels of HIV-1 plasma-viremia and low CD4 cell counts are both risk factors for the development of NHL.[29] Chronic immune activation and polyclonal B-cell stimulation may cause subsets of B cells to be susceptible to additional events leading to transformation and may be key to B-lymphomagenesis.[3,30]

Data for HIV-induced T-cell lymphomagensis are very limited due to the rarity of this entity. A few studies suggest HIV may integrate upstream of the c-fes oncogene, which results in upregulation of Fes and increased clonal proliferation of infected T cells or macrophages.[31,32] This clonal proliferation may subsequently result in cellular transformation of T cells and/or secondary proliferation of surrounding B cells, leading to development of lymphoma.[32] Other studies have shown that HIV-induced gut-associated lymphocyte depletion may lead to intestinal microbial translocation into the bloodstream, leading to increased risk of NHL via chronic immune activation.[33,34] Giaqulli et al[35] showed that HIV-1 P17 protein can activate the PI3K/Akt signaling pathway by maintaining PTEN in an inactivated phosphorylated form, which may lead to increased B-cell proliferation. EBV has been linked to many human neoplasms, including hematopoietic, epithelial, and mesenchymal tumors.[36] Although EBV is mainly B-lymphotropic, it can also infect T cells and epithelial cells.[36,37] The most common EBV-associated T-cell lymphomas are extranodal natural killer (NK)/T-cell lymphoma–nasal type, angioimmunoblastic T-cell lymphoma, and EBV-positive T-cell lymphoproliferative disorders of childhood. EBV has both latent and lytic life cycles, which helps it evade immune clearance and facilitates maintenance of infection for the life of the host. Both latency and lytic replication have pathogenic importance for cell transformation and growth of EBV-associated malignancies.

Most data regarding EBV lymphomagenesis are derived from studying EBV-positive B-cell lymphomas, partly due

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HIV Viral Load[c]	EBV Status[d]	Immunophenotype	Treatment	Follow-up[a]
NA	NA	Positive for pan–T-cell markers (UCHL-1), negative for pan–B-cell markers (CD22)	NA	NA
NA	NA	Positive for pan–T-cell markers (UCHL-1), negative for pan–B-cell markers (CD22)	NA	NA
NA	NA	Positive for CD45 and T-cell markers (UCHL-1), negative for B-cell markers (CD74, CD75, and 4KB5)	WBR	Died after 5 wk
<100	Positive	Positive for CD3, negative for CD20	No lymphoma treatment due to poor general condition	Died after a few months
NA	Positive	Positive for CD2, CD3, CD56, perforin, and CD45; negative for CD4, CD5, CD8, and CD20	No lymphoma treatment due to poor general condition	Died in a few days
>500,000	NA	Positive for CD3 and CD45, negative for CD20	WBR	Stable disease for 31 mo
NA	NA	Positive for CD3 and CD8, negative for CD2, CD4, CD5, and CD20	WBR and ITC	NA
<40	Positive	Positive for CD2 and CD4, negative for CD3, CD5, CD7, and CD20	WBR and ITC	Died after 1 mo

to the difficulty of infecting T cells with EBV in vitro.[38] LMP-1 is the main oncogenic protein of EBV and is essential for tumorigenesis. LMP-1 activates many pathways, which result in the induction of antiapoptotic proteins and cytokines to contribute to growth and differentiation of infected cells.[39] Recent studies showed LMP-1 activates human telomerase reverse transcriptase (hTERT) at transcription level, through nuclear factor κB and MAPK/ERK1/2 pathways.[40] hTERT is the catalytic component of the telomerase complex, which is critically involved in maintaining telomere length and is crucial for the acquisition of unlimited replicative potential and neoplastic transformation.[41] Furthermore, studies have shown that even after HAART and immune reconstitution (normalization of CD4-positive cells), patients with HIV may still lack EBV-specific CD4-positive T-cell function, which may leave these patients prone to EBV infection and development of EBV-associated malignancies such as PCNSL.[42]

On the other hand, other studies have shown that patients receiving HAART who have a virologic response (decline in HIV plasma-viremia) have a decline in EBV plasma-viremia, regardless of immune reconstitution.[43] This may partially explain the lower incidence of NHL in patients with HIV after the introduction of HAART. In general, T-cell lymphomas and particularly T-cell PCNSLs are extremely rare, even in HIV-positive patients. To date, there are no characteristic features to distinguish T-cell PCNSL from B-cell PCNSL based on clinical presentation, imaging findings, or histomorphologic features. Moreover, there are no significant differences in the treatment plan between these two categories. Therefore, more reports of these extremely rare cases of T-cell PCNSL will help raise clinical awareness, improve diagnosis, and ultimately improve the prognosis of patients.

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