Reactive Epstein-Barr Virus–Related Polyclonal Lymphoproliferative Disorder in a Patient with AIDS

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Reactivation of Epstein-Barr virus infection and polyclonal expansion of lymphocytes is well-documented in solid organ and hematopoietic stem cell transplant recipients and is considered a potential precursor to lymphoma. We report an analogous case of posttransplantation polyclonal lymphoproliferative disorder in a patient with human immunodeficiency virus infection who was successfully treated with antiretroviral therapy.

Epstein-Barr virus (EBV) has been considered to be a cause of primary CNS monoclonal non-Hodgkin lymphoma, Hodgkin lymphoma, and a subset of cases of systemic non-Hodgkin lymphoma in HIV-infected individuals because of the presence of EBV DNA viral gene expression in these tumors [1]. The presence of a reactive EBV-driven polyclonal lymphocyte expansion is seen in patients who have undergone solid organ or hematopoietic stem cell transplantation, but it is not well-documented in HIV-infected patients. To our knowledge, we present the first reported case of a PTLD-like syndrome in a patient with long-standing AIDS who had not undergone transplantation.

Case report. A 50-year-old man with a long-standing history of HIV infection and AIDS presented with lymphadenopathy and night sweats. His past medical history was significant for chronic obstructive pulmonary disease, narcotic dependence, and homelessness. Examination revealed fever (temperature, 38.3°C) and peripheral muscle wasting. Chest auscultation revealed scattered rales. Diffuse lymphadenopathy of the cervical, axillary, and inguinal areas was noted. His CD4 cell count was 45 cells/μL, up from a nadir of 7 cells/μL. Over the previous 5 years, his CD4 cell count climbed to 121 cells/μL. Over the next few months, his CD4 cell count climbed to 121 cells/μL, and his serum HIV RNA levels decreased to an undetectable value for the first time in 4 years. His serum EBV DNA level became undetectable 2 months after he started antiretroviral therapy, and his symptoms resolved. An additional chest CT was obtained 8 months after his initial scans and showed significant shrinkage of the lymphadenopathy.

Discussion. Pathologic examination showed preservation of the normal architecture, with expansion of the interfollicular region with a mixture of small lymphocytes, plasma cells, and immunoblasts. Several residual germinal centers were present. No granulomas were seen, and the results of acid fast stains were negative. Flow cytometry revealed a polyclonal population of CD19+κ and CD19+λ B cells with normal antigen expression. The CD4+ T cell count was decreased, but those cells present did not exhibit abnormal T cell antigen loss. Immunoperoxidase studies showed polyclonal plasma cells, no evidence of abnormal B cell or T cell immunohistoarchitecture, and no detectable presence of human herpesvirus–8. However, in situ hybridization on paraffin-embedded sections with an oligonucleotide probe specific for EBV-encoded RNA yielded positive results in many small and large cells. The findings of cytogenetic studies, including karyotyping and fluorescent in situ hybridization for the C-myc gene, were normal. No evi-
Figure 1. High-power micrograph with hematoxylin and eosin stain of the excisional axillary lymph node biopsy specimen showing a mixed infiltrate composed of small lymphocytes, plasma cells, and immunoblasts.

dence of a monoclonal lymphoma was noted. Together with the morphology data, these results support the diagnosis of an EBV-associated reactive lymphoid proliferation similar to benign PTLD.

Review of the literature using the Medline database yielded no reports of EBV-related lymphoproliferations analogous to PTLD in HIV-infected patients. Other polyclonal, polymorphic, and B cell lymphoproliferative disorders have been reported in children with HIV infection [2–4]. One report described a 14-year-old boy with congenital HIV infection, lymphadenopathy, and interstitial pulmonary infiltrates. Open-lung biopsy revealed polymorphous lymphoid cells, consistent with polyclonality. The morphology was similar to PTLD in its cellular atypia and prominent mitotic activity, although the results of serologic tests were positive for IgM, consistent with primary EBV infection [2].

Another report described 4 children with AIDS and abnormal lymphoproliferative growth [3]. One patient had lymphoid interstitial pneumonitis, and 3 of the patients were described as having lymph nodes that contained effaced architecture due to a polyclonal, polymorphous lymphoid cell infiltration. The absence of atypia and necrosis suggested a nonmalignant process. EBV was strongly suspected to be the etiologic agent, because a previous report described the presence of EBV DNA in the lung of a pediatric patient with lymphoid interstitial pneumonitis and AIDS. Other cases of lymphoid interstitial pneumonitis in pediatric patients with AIDS have been associated with Salmonella sepsis [4].

Adults with AIDS and generalized lymphadenopathy frequently have detectable EBV in their nodes, the presence of which can sometimes be predictive of lymphoma development [5, 6]. However, EBV in the lymph nodes of HIV-infected patients without progression to non-Hodgkin lymphoma has been documented [5]. Shibata et al. [5] investigated the lymph nodes of patients with HIV infection. Thirty-seven percent of patients had detectable EBV DNA, compared with none of the HIV-uninfected control subjects. Three EBV-positive patients had malignant lymphoma at the time of biopsy, and another 2 subsequently developed lymphoma a median of 12 months into follow-up. In contrast, none of the EBV-negative patients developed lymphoma [5]. This and other reports in the transplantation literature suggest that a premalignant state can be generated by uncontrolled EBV-infected B cell proliferation. The significance of EBV infection in patients with lymphadenopathy unrelated to lymphoma is unclear. Quantification of EBV DNA levels in similar patients, when compared with levels in those who have lymphomas, has revealed much lower copy numbers [6].

EBV-related lymphoma in patients with HIV infection is thought to be due in part to the loss of EBV-specific immunity [7]. Studies have shown a decrease in EBV-specific cytotoxic T lymphocyte activity in patients with AIDS [8]. A longitudinal
investigation of patients with AIDS and non-Hodgkin lymphoma that used major histocompatibility I tetramers and IFN-γ enzyme-linked immunospot assays showed that HIV-positive individuals have a lower number of functional EBV-specific cytotoxic T lymphocytes, compared with HIV-negative individuals. It also showed that patients with AIDS and non-Hodgkin lymphoma have a loss of EBV-specific cytotoxic T lymphocytes at the functional level, as measured by the enzyme-linked immunospot assay. This loss of EBV-specific cytotoxic T lymphocyte activity was directly related to lower CD4+ T cell counts [9].

The value of measuring EBV DNA loads in the blood is unclear. EBV DNA loads in transplant recipients tend to increase with the occurrence of PTLD [10]. With receipt of antiviruss virus therapy, the DNA levels may decrease but do not always correlate with tumor response to treatment [11]. Some studies performed before the advent and use of effective combination antiretroviral therapy showed that EBV DNA levels in blood samples obtained from patients with HIV infection were higher, compared with those in healthy control subjects [13, 14]. Antiretroviral therapy, HIV suppression, and CD4 cell counts seem to make no difference [1, 15]. Some authors have suggested that EBV DNA plasma loads may be useful as a marker for the diagnosis of EBV-related non-Hodgkin lymphoma [16], but longitudinal studies of EBV DNA load in both PBMCs and serum samples obtained from HIV-infected patients have found no specific correlation with the development of non-Hodgkin lymphoma [17]. The plasma EBV DNA load in our patient seemed to coincide with EBV expansion and was an accurate marker of disease in follow-up.

Transplant recipients have presented with polyclonal EBV-driven lymphocyte proliferation resembling mononucleosis, with numerous interfollicular plasma cells and immunoblasts, although an analogous situation has not been clearly documented in patients with AIDS [18]. This particular patient had pathology and a clinical course consistent with a poorly controlled EBV infection similar to nonmonoclonal PTLD with fewer immunoblasts. With improved adherence to his antiretroviral therapy regimen, his CD4 cell counts increased, and his HIV load decreased. Subsequently, his EBV load also decreased, and the lymphadenopathy began to resolve. In PTLD, first-line therapy is often a reduction in immunosuppression, leading to lymph node shrinkage in >60% of patients [19]. One explanation for this finding would be an increase in EBV-specific immunity. Immune reconstitution to viral antigens with an increase in functional EBV-specific cytotoxic T lymphocytes after initiation of ART has been documented in at least 1 HIV-infected patient [9].

It is unclear why this syndrome has not been reported in patients with AIDS before. In this particular patient, adherence to opportunistic infection prophylaxis and intermittent use of antiretroviral therapy resulted in a prolonged level of immu-
nosuppression over many years, possibly predisposing him to such an unusual manifestation of EBV-related disease. In other cases, however, less florid reactive hyperplasia as a consequence of immunosuppression may be subclinical. It is also conceivable that lymph nodes containing EBV DNA in HIV-infected patients are transient in nature or that they progressed to lymphoma after the follow-up period utilized in previous studies. It is also possible that the presence of a small amount of latent EBV DNA in the lymph nodes of these patients was a bystander to another process. Most cases of EBV reactivation result in only spotty EBV-encoded RNA positivity within germinal centers or rare scattered cells. In the case presented, there was extensive staining of most lymphoid cells in the tissue.

Patients with AIDS who present with lymphadenopathy have a broad differential diagnosis. Polyclonal EBV-driven lymphoproliferative disorders similar to PTLD and the potential development of non-Hodgkin lymphoma need to be considered. It is likely that the EBV-specific immune deficiency that led to this patient’s presentation resulted from an unusually prolonged period of immunosuppression, and similar patients who do not develop immune reconstitution after the initiation of antiretroviral therapy may be equally susceptible. In this scenario, plasma EBV DNA PCR is of possible value for following the patient’s course, and immune reconstitution through the use of antiretroviral therapy and HIV suppression may improve the EBV-related lymphoproliferation. Whether this will lower the risk for subsequent lymphoma is unknown.

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References


