Natural Killer–like T-Cell Lymphoma of the Parotid in a Patient Infected With Human Immunodeficiency Virus

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A 42-year-old man with acquired immunodeficiency syndrome developed a mass of the right parotid gland and multiple hepatic masses. Hematoxylin-eosin–stained sections of the parotid lesion showed a diffuse infiltrate of large mononuclear cells with vesicular nuclei and prominent nucleoli, consistent with a non-Hodgkin lymphoma. Immunohistologic stains demonstrated expression of the T-cell markers CD3 and UCHL-1, as well as latent membrane protein 1 and T-cell intracellular antigen 1. Flow cytometry showed surface expression of CD2, CD3, CD7 (dim), CD8, and CD56. CD5 was not expressed. Molecular evaluation by polymerase chain reaction demonstrated monoclonal rearrangement of the T-cell receptor γ gene. Epstein-Barr virus early RNA and human immunodeficiency virus RNA were demonstrated by in situ hybridization. To our knowledge, this is the first reported case of T-cell lymphoma of the parotid in a patient infected with human immunodeficiency virus. After 2 separate chemotherapy regimens, the patient achieved clinical remission for 1½ years; he then developed progressive pulmonary lesions and died.

(REPORT OF A CASE)

In 1985, a 29-year-old white man was diagnosed with HIV infection acquired through homosexual contact. He was treated with a variety of antiviral therapies until March 1998, when his CD4 count was 0 and his viral load was greater than 130,000 viral RNA copies/mL. In July 1998, he was diagnosed with a squamous cell carcinoma of the anal canal and treated with radiotherapy. In August 1998, he underwent surgical resection of a left parotid mass, which revealed an NK-like T-cell lymphoma.

On physical examination, the left parotid gland was extremely tender and demonstrated residual induration associated with the surgical scar. There was no lymphadenopathy or organomegaly. The remainder of the results from the physical examination were unremarkable except for mild perianal erythema from his previous radiotherapy. Lymphoma staging studies were negative except for computed tomographic scan of the abdomen, which revealed multiple small, low-density lesions in the liver, consistent with involvement by lymphoma. The patient was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy starting in August 1998. The residual mass and pain in the parotid promptly resolved, and after 4 cycles of therapy, the liver lesions were no longer visible on computed tomographic scan. Surveillance scanning 3 months after the completion of chemotherapy demonstrated reappearance of the hepatic lesions. Salvage chemotherapy with high-dose cyclophosphamide and etoposide was begun in April 1999, but was discontinued after 1 cycle because the patient experienced an acute myocardial infarction and declined further chemotherapy. Computed tomographic scan of the abdomen in May 2000 showed no radiologic evidence of lymphoma. In October 2000, the patient developed increasing shortness of breath. Computed tomographic scan of the thorax demonstrated multiple bilateral pulmonary nodules. Prior to planned pathologic confirmation of suspected recurrent lymphoma, the patient suddenly died. No autopsy was obtained.

Figure 1. Parotid mass is composed of cells with large vesicular nuclei and prominent nucleoli (hematoxylin-eosin, original magnification ×1000).

Figure 2. Immunoperoxidase staining of parotid mass shows positivity for CD3 (A), UCHL-1 (B), and TIA-1 (C) (all original magnifications ×1000).

Figure 3. Parotid mass exhibits positivity (darkest nuclei) for Epstein-Barr virus early RNA by in situ hybridization (original magnification ×1000).
MATERIALS AND METHODS

Resected tissue was fixed in 10% buffered formalin, embedded in paraffin, and processed for routine histologic examination as well as immunohistochemical and molecular evaluation. Immunohistochemical stains were performed on the Ventana 320 automated stainer (Ventana Medical Systems Inc, Tucson, Ariz), with antibodies and dilutions as follows: CD3 polyclonal and CD20 monoclonal antibodies (1:150 and 1:100, respectively; Dako Corporation, Carpinteria, Calif); UCHL-1 monoclonal antibody (1:130; Zymed Laboratories, South San Francisco, Calif); T-cell intracellular antigen 1 (TIA-1) monoclonal antibody (1:150; Coulter Corporation, Miami, Fla); latent membrane protein 1 (LMP-1) monoclonal antibody (1:100; Dako). In situ hybridization was used to detect EBV early RNA (EBER) and HIV RNA. Epstein-Barr virus early RNA was detected using the BIO-HRP REMBRANDT kit from Kreatech Diagnostics, Amsterdam, The Netherlands. Human immunodeficiency virus RNA was detected using a branched DNA amplification technique as described by Collins et al., except detection was automated on the Ventana Gen II (Ventana Medical Systems). Oligonucleotide probes were from Chiron Diagnostics, Emeryville, Calif. Flow cytometric analysis on single-cell suspensions of fresh tissue was performed at Cytometry Associates (now Exoterix Oncology, Brentwood, Tenn), using a panel of antibodies routinely employed at that facility for the characterization of lymphoid neoplasms. Molecular analysis was performed after DNA was extracted from formalin-fixed, paraffin-embedded tissue. Approximately 1 µg of crude DNA was used per polymerase chain reaction (PCR). T-cell receptor γ gene rearrangement analysis was performed by PCR in a multiplex reaction according to the method of Theodorou et al., except that no GC clamps were added to the primers during their synthesis, and PCR products were electrophoresed on a 2.75% MetaPhor agarose gel (FMC, Rockland, Me), using a 20-bp reference ladder for fine resolution of product size.

RESULTS

Hematoxylin-eosin-stained sections of the parotid gland demonstrated a dense infiltrate of large, cytologically malignant lymphoid cells with vesicular nuclei and prominent nucleoli (Figure 1). Immunohistochemical stains showed positivity for CD3, UCHL-1, and TIA-1 (Figure 2), as well as for the EBV-associated LMP-1. Both EBER (Figure 3) and HIV in situ hybridization studies demonstrated viral RNA in the cells of interest. Flow cytometric analysis on single-cell suspensions of CD2, CD3, CD7 (dim), CD8, CD56, and HLA-DR, but not CD4, CD5, CD30, or CD16. Molecular analysis showed monoclonal rearrangement of the T-cell receptor γ gene. These results are consistent with an NK-like T-cell lymphoma involving a population of cells infected by both EBV and HIV.

COMMENT

To our knowledge, this case represents the first report of primary T-cell lymphoma of the parotid gland in an HIV-infected patient, and we believe it represents the first reported AIDS-associated T-cell lymphoma displaying the distinct T/NK phenotype. Non-Hodgkin lymphomas occurring in HIV-positive individuals are typically aggressive large B-cell lymphomas or Burkitt/Burkitt-like lymphomas that tend to involve extranodal sites. T-cell lymphomas also occur in HIV-infected patients, but with a much lower frequency than their B-cell counterparts. In a review of 84 AIDS-related lymphomas at San Francisco General Hospital, only 2 cases were found to be definite T-cell lymphomas and 3 were suspicious for a T-cell derivation.

The parotid is an uncommon site of primary non-Hodgkin lymphoma in the general population. In a review of primary parotid lymphomas experienced during a 15-year period at the University of Texas M. D. Anderson Cancer Center, 39 adult cases were identified, representing 1% of all new lymphomas seen and 8.6% of all new parotid tumors.4 According to a recent review of lymphoid proliferations of salivary glands, approximately one third of salivary lymphomas are of the large B-cell type, one third are follicular lymphomas, and one third are low-grade, small cell lymphomas, usually of the mucosa-associated lymphoid tissue type.5 Ioachim et al.6 reported on 6 cases of primary lymphoma of the salivary gland in HIV-infected patients. All 6 lymphomas were high-grade B-cell tumors, including Burkitt, large cell immunoblastic, and “large cell polymorphous” types. Five of the 6 lymphomas showed evidence of EBV infection, with positivity for EBER or for LMP, a protein product of EBV.

In contrast, T-cell lymphomas of salivary glands are distinctly rare. Chan et al.7 performed detailed immunohistochemical and molecular studies on 6 T- and T/NK-cell lymphomas of the salivary gland in Hong Kong and alluded to 6 other cases reported in the medical literature prior to 1997. In that series, 3 cases expressed a T-cell phenotype and were CD56 negative. Two of these 3 cases demonstrated T-cell receptor gene rearrangement by the PCR technique, indicating monoclonality. None of these 3 T-cell lymphomas demonstrated infection by the EBV virus as assessed by EBER. The other 3 cases were CD56 positive and appeared to represent true NK-cell lymphomas (T-cell receptor gene rearrangement negative). These 3 CD56-positive NK-cell lymphomas demonstrated production of EBER transcripts by in situ hybridization. These results are in keeping with previous findings by the same group, which reported EBER expression exclusively in CD56-positive but not T-lineage lymphomas. Our case represents a lymphoproliferative disorder derived from the NK-like T cell, a normally occurring hybrid between NK and T lymphoid cells typically present in low numbers in the blood and bone marrow. The cells in this patient’s malignancy expressed the NK cell markers CD56 and TIA-1, while also demonstrating immunohistochemical and molecular evidence of T-cell origin. The demonstration of EBER transcripts in our case is in keeping with the concept that EBV infects almost exclusively those T/NK-cell nasal and nasal-like lymphomas which exhibit surface CD56 expression.

The exact relationship between EBV infection and the development of non-Hodgkin lymphoma is uncertain. The identification of EBV in up to 80% of B-cell lymphomas in HIV-positive patients and the distinctive patterns of latent viral expression in this setting suggest a possible etiologic role for EBV. Similarly, in T/NK-cell lymphomas of the upper aerodigestive tract, the EBV genome has been identified with such a high frequency that its role in the pathogenesis of these EBV-associated lymphomas is strongly suspected. It has been shown that transfection of cord blood T lymphocytes by EBV DNA can result in immortalization of the lymphocytes.8 The EBV may gain access to T lymphocytes via the C3D receptor (CD21), which is expressed early in the ontogeny of T lymphocytes. In a recent study of lymphomas of the upper respiratory tract, 23 cases expressing T-cell and/or NK-cell antigens were identified.9 Nineteen of the 23 cases expressed EBER transcripts, and all 19 were positive for EBV-encoded LMP-1, an oncogenic protein known for its ability to transform
lymphocytes. Our case was positive for both EBER transcripts and LMP-1.

The role of coinfection by HIV in the transformed cells of this case is unclear. Some authors have reported increased HIV virion expression in cells infected by EBV. The coexpression of these viruses has been theorized to play a possible role in the evolution of HIV infection in AIDS, but an etiologic role in the transformation of lymphoid cells has not been established.

The following scenario seems plausible in this patient: a previous primary infection with EBV occurred, and the virus persisted in the parotid gland. Concurrent HIV infection and resultant immunosuppression permitted the EBV infection to progress. With the development of full-blown AIDS and continued deterioration of immune surveillance, an EBV-positive, CD56-positive T/NK-cell lymphoma of the parotid eventually emerged.

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References