Noteworthy Features of HIV-associated T-cell Non-Hodgkin lymphoma

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The incidence of NK/T-cell lymphomas is increased in patients infected with HIV. Their pathogenesis is undefined, but appears to be related to immunosuppression and concomitant oncoviral (EBV, HTLV-I, HTLV-II, HHV8) coinfection. Experience related to the manifestation and management of these aggressive NK/T-cell malignancies in afflicted HIV-positive individuals is limited. We present three varying cases of HIV-associated T-cell lymphoma. The heterogeneity of their clinicopathological features and outcome are discussed in light of the emerging literature on this HIV-related subject.

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**INTRODUCTION**

Lymphoma is a frequent complication of HIV infection. Typically, AIDS-defining lymphomas are aggressive B-cell non-Hodgkin lymphomas (NHL). Lymphomagenesis in the setting of HIV infection is believed to be secondary to oncoviral participation in concert with immunological derangements [1]. Although HIV-associated T-cell NHL was recognized relatively early in the AIDS epidemic [2-4], there are far fewer published reports of these neoplasms compared to B-cell NHL in the HIV infected population. In fact, the occurrence of HIV-associated T-cell lymphoma was previously believed to be exceptional [5]. Many cases of T-cell NHL were included with B-cell tumors in larger series of AIDS-related lymphoma. Since then, the number of published cases of AIDS-related T-cell NHL reports has increased considerably, as has our experience with diagnosing and managing these diverse lymphomas.

There is a growing body of literature that correlates HIV infection with T-cell abnormalities [6, 7], some of which are believed to predispose HIV infected patients to developing NK/T-cell lymphomas. For example, some authors believe that the preponderance of CD8+ lymphocytes seen with chronic HIV infection may facilitate their neoplastic transformation [8]. In addition, there is strong epidemiological data linking HIV infection with an increased risk of developing T-cell lymphoma, of different subtypes [9]. In general, a 15-fold increased risk of T-cell NHL has been estimated in HIV positive persons. T-cell lymphomas can be divided into three major categories: precursor T-cell neoplasms (e.g. precursor T-lymphoblastic lymphoma/leukemia); mature (peripheral) T-cell neoplasms (e.g. adult T-cell lymphoma/leukemia, nodal anaplastic large cell lymphoma, mycosis fungoides/Sézary syndrome, primary cutaneous anaplastic lymphoma, and peripheral T-cell lymphoma unspecified); and T-cell proliferations of uncertain malignant potential (e.g. blastic NK cell lymphoma). However, not all of these T-cell entities have yet been fully characterized in HIV infected patients.

In this paper, we present three different cases of T-cell lymphoma that occurred in HIV-positive individuals. Their varying clinicopathological findings and outcome are discussed in light of the emerging literature on this HIV-related subject.

**CASE REPORTS**

**Case 1**

A 35-year-old male with a history of intravenous drug use, AIDS, prior *Pneumocystis jirovecii* and *Mycobacterium avium* (MAI) infection, presented with a mass on his upper lip almost 4 years after his initial diagnosis of HIV infection. He was on lamivudine, stavudine and nelfinavir. His CD4+ cell count was 10 cells/mm$^3$ and HIV viral load 470,401 copies/mL. Initially, he reported the formation of a large blister on his lip that developed over a 2 week period into an inflamed, painful mass severely limiting his oral intake. Viral cultures submitted from the blister fluid were negative. An open excisional biopsy under general anesthesia was performed for diagnostic and palliative purposes. Microscopically, the subcutaneous tissue showed a diffuse infiltrate of malignant lymphocytes with irregular and convoluted nuclei (Figure 1). A diagnosis of T-cell CD30+ primary cutaneous anaplastic large cell lymphoma (ALCL) was made. Cytotoxic therapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was started and highly active antiretroviral therapy (HAART) was continued as outlined above, along with azithromycin, itraconazole, ethambutol and trimethoprim/sulfamethoxazole for infection prophylaxis. The patient received only one cycle of combined chemotherapy. His course was complicated with multiple admissions for febrile neutropenia and refractory diarrhea, and shortly thereafter developed a new lymphoma lesion in the right groin. He died shortly after this progression.

**Figure 1A.** Subcutaneous primary cutaneous anaplastic large cell lymphoma with associated edema (H&E stain, magnification ×200)
A 35-year-old man with known HIV infection presented with fevers, pancytopenia and splenomegaly. His white blood cell count was 1400 cells/mL and his peripheral blood smear had a leukoerythroblastic picture (i.e. myelocytes, metamyelocytes and nucleated red blood cells were present). In addition, his hemoglobin level was 9.1 mg/dL and platelet count 10,000 cells/mL. A bone marrow biopsy was performed as an initial diagnostic procedure. The marrow cellularity was greater than 90%, and most of the marrow space was replaced by sheets of malignant immunoblasts. No granulomas were present. Lymphoma cells were CD45+, focally CD3+ and CD20 negative. A diagnosis of high-grade T-cell immunoblastic lymphoma was made. Unfortunately, no further history was available. This patient died shortly after his lymphoma diagnosis.

Case 3

A 16-year-old male with HIV infection he acquired during the perinatal period had a history of multiple opportunistic infections including CMV, MAI and pulmonary aspergillosis. He presented with tender unilateral, posterior occipital lymphadenopathy. An excisional biopsy showed partially effaced lymph node architecture due to lymphoma involvement (Figure 2). Immunohistochemical studies confirmed a diagnosis of nodal peripheral T-cell lymphoma (PTCL) that was CD3+, CD43+ and weakly CD45RO+. Staging CT scans found no additional evidence of lymphoma. At that time of his presentation, the patient was on lamivudine, stavudine and nelfinavir, as well as ethambutol and clarithromycin for prophylaxis. Chemotherapy was initiated to treat PTCL using a combination of cyclophosphamide, doxorubicin, etoposide, methotrexate, cytarabine and hydrocortisone with G-CSF support. A complete response was achieved with six cycles of this chemotherapy regimen. As of today, he has no further evidence of lymphoma by CT scan assessment. His last CD4 count was 81 cells/mm³.

Discussion

The three cases presented here illustrate several key features of HIV-associated T-cell lymphoma; viz. T-cell lymphomas usually present with advanced HIV disease and frequent prior opportunistic infections, a broad morphological spectrum with a heterogeneous clinical presentation (extranodal and nodal) is likely to be encountered, and in general such lymphomas are likely to exhibit an aggressive clinical course with a poor prognosis. While case 1 (treated) and case 2 (untreated) died soon after presentation, case 3 was successfully treated with HAART and chemotherapy. In a review of 25 cases collected during 8 years in San Francisco, researchers described two forms of

![Figure 1B](image1.png) Higher power shows a diffuse infiltrate of malignant lymphocytes with irregular and convoluted nuclei (H&E stain, magnification ×600)

![Figure 1C](image2.png) Lymphocytes demonstrate strong CD30 membranous immunoreactivity (CD30 immunohistochemical stain)

![Figure 2](image3.png) An effaced lymph node due to CD3 positive peripheral T-cell lymphoma cells (CD3 immunohistochemical stain)
HIV-associated T-cell lymphoma [10]: (I) Epstein-Barr virus (EBV)-negative epidermotropic T-cell NHL with an indolent course arising in patients with high (600 cells/mm$^3$) CD4 counts and (II) CD30$^+$ large cell lymphomas that harbored EBV, had epidermotropism, and were associated with severe immunosuppression (CD4 count of 50 cells/mm$^3$) and a poor prognosis.

In a recent review of 93 published cases of NK/T-cell lymphoma in HIV-positive individuals, it was shown that afflicted patients were of median age 38 years (range, 1-63 years) at presentation, exhibited a 4:1 male predominance, and had a median CD4 count of 184 cells/mm$^3$ [11]. Up to 54% of these reviewed cases had a prior AIDS-defining illness. In our small series, all individuals were relatively young males with advanced immunosuppression and opportunistic infections. The male predominance, as seen with other lymphomas such as Burkitt lymphoma, is interesting, but may simply reflect a Western HIV-infected population. NK/T-cell neoplasms are uncommon, even in the non-HIV population. They bear significant differences in incidence in different parts of the world. In general, T-cell lymphomas are more common in Asia. Adult T-cell leukemia/lymphoma (ATLL) is more common in regions with a relatively high prevalence of HTLV-1, such as the Caribbean basin and South Japan. However, reports of HIV-associated NK/T-cell neoplasms have been documented worldwide including the USA, Europe, South America, and Asia [11].

The most common clinical findings in HIV-associated NK/T-cell lymphomas include lymphadenopathy, B symptoms, erythrodema and pruritus [11]. Mature NK/T-cell lymphomas infrequently involve lymph nodes, even with recurrences. Frequent spread to other extranodal sites, especially the skin, is commonly seen. Indeed, most (74%) HIV-related T-cell lymphomas are extranodal, with at least 50% involving skin [11]. Apart from T-cell NHL, other causes of erythrodema to consider in patients with HIV infection are drug-related eruptions, infections, and photodermatitis. Additional dermatoses in HIV+ persons characterized by lymphocyte-rich infiltrates include (seborrheic, contact, atopic and interface) dermatitis and psoriatic erythrodema. Many of the clinical manifestations of T-cell NHL can be related to cytokine expression from lymphoma cells. A cytokine profile was not available for review in our cases. Staging in 60 reported HIV-infected patients was found to be stage IV (53%) > I (27%) > III (17%) > II (3%) [11].

While many T-cell subtypes have been recorded in HIV+ patients, their exact frequency is difficult to ascertain as several lymphomas were not classified according to the current WHO classification. Moreover, some atypical cases (so-called pseudo-Sezary or cutaneous T-cell lymphoma stimulant) proved difficult to categorize [12]. Nevertheless, the NK/T-cell lymphoma subtypes presently documented in HIV-infected patients include, from most to least frequently reported [11], PTCL (n = 36), cutaneous T-cell lymphomas (CTCL) including Mycosis fungoides (n = 25), ALCL (n = 13), ATLL (n = 8), NK-cell neoplasms (n = 4), and various others (enteropathy-associated, primary effusion and intravascular lymphoma of T-cell phenotype). A case of HIV-associated T-cell lymphoblastic lymphoma has also been documented [13].

In case 1 the patient was diagnosed with primary cutaneous CD30$^+$ ALCL. In non-HIV individuals, this particular lymphoma usually presents in individuals over 50 years of age, has an indolent course, and in up to 25% of cases may regress spontaneously. Our patient with ALCL was considerably younger (35-years-old), did not tolerate CHOP, and consequently died soon after his lymphoma diagnosis. In another series involving four patients with CD30$^+$ ALCL, investigators similarly reported aggressive disease with patients dying at a median of 3 months [14]. Severe immunosuppression, more than any other factor, seems to result in a similar clinical course in both CD30$^+$ and CD30$^-$ ALCL patients [15]. Case 3 had a nodal PTCL unspecified. Contrary to our case, this wastebasket (unspecified) category presents usually with high stage disease and an overall aggressive course. Case 2, a high grade immunoblastic lymphoma, was not easily classified according to the proposed WHO scheme, most likely due to the limited studied performed at the time of diagnosis.

In contrast to B-cell lymphomas, cytologic grade is not useful in predicting the clinical course of NK/T-cell neoplasms. Moreover, unlike B-cell NHL, there are no convenient immunophenotypic markers to readily demonstrate monoclonyality. The presence of an aberrant immunophenotype is often used to indicate a NK/T-cell malignancy. Most NK/T-cell NHL to date have expressed CD45RO and CD3 antigens, CD4 > CD8, and CD3 in a subset of cases [11]. CD45RO and CD3 are highly sensitive lineage markers for NK/T-cell neoplasms. Clinicians should be aware that in patients with a CD4+ Sezary syndrome, an increased peripheral CD4+ count may cause problems in following HIV-related immunodeficiency [16]. Patients with advanced AIDS and a low CD4+ T-cell count have been shown to present with large reactive skin infiltrates comprised largely of CD8+ T lymphocytes, a process that may mimic CTCL [17]. While CD30 expression is required for the diagnosis of ALCL, it may be found in several extranodal T-cell lymphomas. In cutaneous lymphomas, CD30 expression is prognostically important; since CD30$^+$ cases are generally associated with a favorable prognosis [18].

The actual pathogenesis of T-cell lymphomas in HIV is incompletely understood [19]. EBV is usually associated with extranodal NK/T-cell lymphomas and NK-cell leukemias. However, EBV has only been detected in around 20% of HIV-associated NK/T-cell cases [11, 20, 21]. Human T-cell leukemia virus (HTLV-1), etiologically linked to ATLL, has rarely been reported with HIV infection [2, 22]. HTLV-II, which is especially prevalent among intravenous drug abusers, has been noted with CTCL in a patient with HIV-1 infection [23]. Unfortunately, the EBV and HTLV status in all three of our cases was unknown. A case of human herpesvirus 8 (HHV8) associated T-cell lymphoma has been reported in a HIV-positive man in a lymph node with concurrent peritoneal effusion [24]. The HIV genome has also been detected in malignant T-cells, leading researchers to believe that HIV infection itself may have a central role in lymphocyte transformation [25, 26].

No standard therapeutic approach has been proposed for the management of HIV-associated NK/T-cell NHL. Therapy in published cases to date constituted both single-modality (46%) and multimodal (17%) treatment [11]. A minority of cases (12%) were also untreated [11]. Treatment of these malignancies is challenging. Based largely upon the collective experience in the treatment of HIV-related B-cell lymphomas, HAART and combination chemotherapy should be offered to patients who present with advanced stage NK/T-cell NHL [27]. The extranodal nature of HIV T-cell lymphomas requires additional creative ways of managing earlier stage disease, such as surgery, phototherapy, radiation therapy, chemotherapy and/or immunotherapy. Local irradiation has been used to successfully manage AIDS-related CTCL [28]. Autologous stem cell transplantation has been shown to be effective and safe in the treatment of HIV B-cell lymphomas [29]; the experi-
ence has not been the same for non-HIV T-cell lymphomas [30, 31]. There are no data supporting the use of autologous stem cell transplantation in HIV T-cell lymphomas. The role of HAART needs to be further explored.

Clinically, NK/T-cell neoplasms are among the most aggressive of all hematopoietic and lymphoid neoplasms. Therefore, it is not surprising that death occurred in up to 55% of reviewed patients, with a median overall survival in 83 patients of 1.1 years from the time of HIV-related NK/T-cell lymphoma diagnosis [11]. Factors that likely contribute to the aggressive clinical behavior of this particular subgroup of malignancies include advanced clinical lymphoma stage at presentation, marked HIV-related immunosuppression, and chemotherapeutic resistance. There is published evidence that the prognosis of HIV-related lymphomas treated with HAART and combination chemotherapy depends more upon tumor-related factors (such as achievement of complete response, International Prognostic Index score and lymphoma histological subtype) than on HIV-related factors [32]. Unfortunately, in patients with T-cell lymphomas, who accounted for a minority (3.8%) of these studied cases, the complete response rate was poorer than B-cell counterparts resulting in a worse prognosis.

In conclusion, a NK/T-cell neoplasm should always be entertained in patients manifesting with an AIDS-defining NHL. Explicit immunohistochemical markers (e.g. CD56 or N-CAM, granzyme B, TIA-1, perforin), molecular studies (e.g. T-cell receptor gene rearrangement) and the demonstration of EBV positivity (e.g. EBER) in malignant cells along with clinical follow up should be employed to help establish the diagnosis. HIV-infected persons diagnosed with a NK/T-cell lymphoma are likely to be young males with AIDS who have a CD4 count under 200 cells/mm³ at presentation [11]. They are also prone to present with extranodal disease, frequently skin involvement, and at an advanced stage. A standard treatment approach is required, as the incidence of these neoplasms appears to be increasing and their prognosis even in the HAART era remains poor.

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