Kaposi’s Sarcoma in Human T-Cell Leukemia Virus Type I-Associated Adult T-Cell Leukemia

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Kaposi’s sarcoma (KS) developed in a patient with human T-cell leukemia virus type I (HTLV-I)-associated adult T-cell leukemia who was treated with a short-term course of monoclonal antibody immunotherapy. The presentation was transient and temporally related to the underlying clinical course. The association of KS in an HTLV-I-infected, but not human immunodeficiency virus (HIV)-infected, individual should alert investigators to the occurrence of KS in retroviral-associated diseases other than acquired immunodeficiency disease syndrome. Recognition of the similarities and differences between HTLV-I and HIV infections may provide insights concerning the angioiopathogenesis of KS.

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KAPOSI’S SARCOMA (KS) is encountered in diverse clinical settings that share frequent associations with neoplasia or immune dysfunction.1-5 KS is a frequent sequela in the acquired immunodeficiency syndrome (AIDS), in which immune status is severely subverted and in which other malignancies frequently arise.1-5 Human T-cell leukemia virus type I (HTLV-I), the first pathogenic human retrovirus discovered,6 is functionally analogous to the human immunodeficiency virus (HIV), the etiologic agent in AIDS.6 HTLV-I infection is associated with an aggressive T-cell malignancy, adult T-cell leukemia (ATL),7 which is frequently accompanied by opportunistic infection,8,9 in which altered cellular and humoral immune responses have been reported in vitro and in vivo.10-12 Despite these similarities, KS develops frequently among the male homosexual AIDS population,13 yet has not been reported among HIV-negative, HTLV-I-associated ATL patients.

We describe the development of KS in a patient with HTLV-I-associated ATL who was treated with a short-term course of monoclonal antibody (MoAb) immunotherapy. Eruptions of disseminated dermal lesions flourished soon after induction of a partial remission of the leukemia. The prominent KS nodules became attenuated at the time of relapse, and during the terminal malignant phase of ATL, the KS lesions were inconspicuous. Although multiple clinical derangements are associated with ATL, KS is not a previously recognized complication of this retroviral-induced hematologic malignancy. The observation of HTLV-I-associated KS in ATL extends the constellation of pathophysiologic states related to this retroviral infection.

CASE REPORT

A 40-year-old black Haitian male living in the United States developed chronic gastroenteritis and weight loss. ATL was diagnosed on the basis of a circulating lymphocytosis of 26,220/μL of abnormal mature lymphocytes (Fig 1); a predominant CD2+, CD3+, CD4+, CD8− T-cell phenotype with 72% monoclonal cells positive for interleukin-2 receptor alpha chain expression (IL-2Ra) (CD25+); elevated soluble IL-2Ra serum level of 40,000 U/mL (normal up to 542 U/mL); and the presence of T-cell clonal expansion on the basis of beta chain gene rearrangement by Southern hybridization (Fig 1). Infection with HTLV-I was affirmed by the presence of circulating antibodies specific for HTLV-I antigens by an enzyme-linked immunosorbent assay (ELISA) and by demonstration of HTLV-I proviral DNA clonally integrated in host genome on Southern hybridization (Fig 1).

The patient was seronegative for antibodies to HIV by ELISA on three separate occasions. Further exclusion of a concurrent HIV infection was aggressively pursued. Genomic DNA isolated from the patient’s peripheral mononuclear cells was subjected to specific gene sequence amplification by the polymerase chain reaction.20 By this technique, genotyping for pol and gag regions of the HIV provirus was negative and effectively ruled out HIV infection (Fig 1). However, the patient was positive for cytomegalovirus infection (high serum antibody titers and virus isolated from urine) and acute hepatitis B viral infection (serum hepatitis B surface antigen positive). In addition, Isospora belli oocysts were recovered from stool, reflecting an ongoing opportunistic gastroenteritis.

The patient was anergic on skin testing against Tetanus and Diphtheria toxoids and Streptococcus group C, tuberculin, Candida, Trichophyton, and Proteus antigens. Thirty-four percent of the peripheral blood lymphocyte population were CD4− and 4% were CD8−. Serum and cerebrospinal fluid protein electrophoresis, immunoglobulin levels, and complement (CH50) were normal.

Immunotherapy consisted of 11 courses over a 7-week period of intravenously administered anti-Tac, an MoAb directed against the 55-Kd peptide alpha chain of the IL-2R.22 A partial remission ensued and the total white blood cell count decreased from 26,200 to 3,000 to 4,000/μL with a parallel decline from over 70% to 1% to 2% circulating abnormal lymphocytes. The number of Tac-positive cells declined from 23,000 to 340/μL (normal up to 500/μL), and the serum level of soluble IL-2Ra decreased from 35,000 to 2,000 U/mL. One month after immunotherapy, delayed-type hypersensitivity developed to six recall skin test antigens to which the patient was previously anergic. I belli gastroenteritis responded well to oral sulfamethoxazole/trimethoprim.10

At a 4-month follow-up the patient appeared in general good health, but was concerned about the interim development of multiple hyperpigmented, firm, nonblanching papules distributed over the chest and extremities. The borders were distinct and some of the lesions had a linear configuration ranging up to 15 mm in the long axis. The lesions were nonpruritic, painless, and did not involve the mucous membranes (Fig 2). Biopsies of right medial thigh and left deltoid lesions showed findings diagnostic of KS (Fig 3).

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Fig 1. Diagnosis of HTLV-I–associated ATL. (A) Peripheral blood smear from the patient demonstrates ATL lymphocytes with characteristic multibilobated nuclei, dense chromatin, and inconspicuous nucleoli (Wright stain; original magnification ×450). (B) Southern blot hybridization of patient’s mononuclear cell genomic DNA probed with a 9-kilobase (kb) SacI-SacI HTLV-I proviral insert (lanes 1 and 2), and with a 770-base pair (bp) sequence to the human T-cell receptor β chain constant region (lane 3) after endonuclease digestion with EcoRI (lanes 1 and 3) or PstI (lane 2). Clonal integration of HTLV-I proviral genome is indicated by the greater than 9-kb EcoRI band and the composite PstI cellular-proviral bands of 3.5 and 10-kb generated in lanes 1 and 2, respectively. T-cell clonal expansion is shown by the unique 8-kb TcRβ chain band generated in addition to the 4- and 11-kb germline bands (lane 3). (C) Spot blot hybridization of patient’s mononuclear cell genomic DNA that has been amplified by polymerase chain reaction (PCR) for regions within the HIV gag and pol domains and then hybridized with internal HIV gag and pol radiolabeled probes. Positive HIV-infected control generates strong signals to both regions amplified. Patient’s PCR amplified material was negative, excluding a coinfection with HIV.

At 1 year from the time of treatment no additional KS lesions developed, and the previous lesions were visibly less prominent, having become lighter and macular in nature. At this time the ATL, previously in partial remission, became more active. Repeat skin biopsies showed an atypical dermal lymphoid infiltrate morphologically and phenotypically consistent with ATL (Tac-positive). The dermis also demonstrated a spindle cell proliferation with extravasated red blood cells consistent with KS. The patient reverted to his prior state of anergy to the six recall antigens previously examined. Despite additional treatment with anti-Tac MoAb, scrotal and left lower extremity swelling developed secondary to femoral vein compression caused by inguinal adenopathy. Lymph node biopsy showed diffuse replacement by a malignant lymphoid infiltrate consistent with ATL. At 16 months from his initial presentation the KS lesions were markedly attenuated, reflecting progressive resolution of the KS. Chest and abdominal computerized tomography showed massive lymph node tumor burden, and despite aggressive chemotherapy the patient died after a rapidly deteriorating clinical course.

**DISCUSSION**

KS, either presaging other manifestation of AIDS or presenting as a sequela of AIDS, is a frequent consequence of infection with the human retrovirus HTLV-I has been previously reported. Here we report a case of KS in an HTLV-I–infected individual with ATL. Negative serologies for antibodies to HIV and the inability to amplify HIV gag and pol gene sequences by PCR excluded a concurrent infection with HIV.

The clinical and histologic features of KS observed in this case are characteristic of the patch or plaque stage of early KS often observed in association with AIDS and other immunodeficiency states. so-called epidemic or acquired KS. The endemic form of KS reported in equatorial and southern Africa is similar, presenting with extensive cutaneous disease and a predilection for lymph nodes. In contrast, classical KS in patients of European descent commonly presents with nodular disease involving primarily the lower extremities. Thus, the presentation of KS in the HTLV-I–infected ATL individual in the present report is more reminiscent of AIDS-related KS.

While the natural history of KS in individuals with AIDS is variable, the development of KS in our HTLV-I–infected ATL patient was biphasic. The florid presentation and subsequent attenuation of lesions corresponded with a partially induced remission and subsequent relapse, respectively, of the leukemic state. Most ATL patients, as with AIDS
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Fig 2. Clinical presentation of KS. Hyperpigmented papules developed at multiple sites. Discrete lesions are displayed over the medial aspect of the right lower leg (A and B) and over the left superior deltoid region (C and D). Lesions at a distance (A and C) and close-up (B and D) are presented for perspective.

patients, are anergic when skin-tested with standard recall antigens. In this regard the in vivo cellular immunity of our patient was distinctive. Our ATL patient was anergic during an active phase of his leukemia before anti-Tac therapy and before the appearance of KS lesions. He subsequently developed delayed-type hypersensitivity responses during the presentation of KS and while in an anti-Tac induced state of partial leukemic remission, but became anergic once again during the terminal malignant course. Coincidentally, with the recurrence of the ATL the KS greatly resolved and many of the lesions were subsequently infiltrated with leukemic cells. This variable presentation of KS in relation to the clinical course of ATL is suggestive of a secondarily induced, multicentric proliferative response of endothelial and spindle cell elements.

The contribution of monoclonal immunotherapy to the development of KS is uncertain, although it is unlikely that the KS arose secondary to a state of induced immunosuppression. Indeed, cellular immunity, reflected by delayed-type hypersensitivity skin testing, normalized after treatment with anti-Tac, and subsequent treatment with anti-Tac at a time when KS lesions were resolving was not followed by an exacerbation of KS. In contradistinction to the receptor blocking effects of anti-Tac, the simultaneous administration of IL-2 and β-interferon has been associated with exacerbation of epidemic KS. Finally, in 60 patients treated with anti-Tac MoAb to date (T.A. Waldmann, unpublished observations, February 1990), there has been no other occurrence of KS. Thus, we do not feel that the development of KS is secondary to direct effects of anti-Tac immunotherapy.

It has been postulated that the aberrant viral transactivation of host genes may lead to specific pathophysiologic states associated with retroviral infection. In this regard, KS-like lesions develop in mice transgenic for the HIV LTR-tat construct, growth of AIDS-KS-derived cells are supported by factors released from HTLV and HIV-infected T-cell lines, and cultured AIDS-KS cells produce autocrine and paracrine growth factors with angiogenic activity. Alternatively, the elaboration of potent KS-associated growth factors may result from activation of an as yet uncharacterized KS oncogene. Finally, it is possible that the mesenchymal cell elements were directly stimulated by factors released from the killing of leukemic cells after therapy, although we have no evidence for this particular process. Collectively, these findings suggest that retroviral-associated KS is not a malignancy of clonal origin, but rather a secondary hyperproliferation of vascular and lymphatic elements in response to cellular-derived paracrine or autocrine growth factors.
Fig 3. Skin lesion from right thigh involved by KS. (A) Sections of skin biopsies at the time of partial ATL remission show a spindle cell proliferation involving superficial and deep dermis surrounding skin appendages (H & E; original magnification ×13.5). Extravasated red blood cells are prominent. Occasional cells are noted to contain periodic acid-Schiff (PAS)-positive globular inclusions, and in some areas the spindle cells appear to enclose fully formed vascular elements. The spindle cells have elongated nuclei with finely distributed chromatin; cytologic atypia was not present. These findings are diagnostic of KS. (B) Dermis is infiltrated by irregular meshwork of spindle cells interspersed with numerous extravasated red blood cells and contained a scant lymphocytic infiltrate without cytologic atypia (H & E; magnification ×132). Immunohistochemical stains performed on frozen sections using the ABC immunoperoxidase technique disclosed a predominant T-cell population expressing CD3+, CD5+, and CD2+ (not shown here). Approximately 85% of the cells also expressed CD7+. There was an admixture of CD4+ and CD8− cells (ratio approximately 3:1). The cutaneous lymphoid infiltrate was not positive with anti-Tac, but occasional positive cells were seen with 7G7/B6, an MoAb that also detects the IL-2Ra. Sections stained only with goat anti-mouse immunoglobulin were negative, failing to show residually bound anti-Tac that had been administered therapeutically. The lymph node biopsy obtained 16 months after presentation showed diffuse replacement by malignant lymphoma composed of pleomorphic lymphoid cells consistent with ATL12,13 (not shown here). Immunohistochemical analysis on frozen sections of the lymph node demonstrated T-cell markers characteristic of ATL: CD3+, CD2+, CD5−, CD7+. The cells were weakly and focally positive for CD4 but totally negative for CD8. The cells were strongly positive with both anti-Tac and 7G7/B6. No staining was observed for B-cell-associated antigens CD20, CD19, and CD22, and surface immunoglobulin heavy and light chains.
The inverse relationship between ATL and KS disease activity in the present case, although not defined, may provide a clue to the pathogenic mechanism underlying HTLV-I infection. During active ATL, suppression of certain T-cell functions parallels the absence of expression among clonal circulating ATL cells of the messenger RNA for the transactivating element, whereas the pX transcriptional element is expressed in the polyclonal cells of non-ATL individuals infected with HTLV-I. Thus, development of KS during ATL remission may reflect up-regulation of the retroviral transactivator element and consequent Tax-induced cytokine expression. Remission of KS at the time of ATL recurrence may reflect eclipse of Tax expression with consequent down-regulation of T-cell-derived products that may act as paracrine factors stimulating Kaposi cell proliferation.

Recent advances have suggested that AIDS-related KS represents a secondary proliferative response of spindle cell elements to paracrine growth factors. This process may not be unique to retroviral infection with HIV. The documentation of HTLV-I-associated ATL-related KS may suggest that a similar mechanism of retroviral induction of cellular growth factors by HTLV-I is possible.

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