Spectrum of Kaposi’s Sarcoma in the Epidemic of AIDS^1

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Abstract

Kaposi's sarcoma (KS) is seen with increased frequency in the course of the epidemic of acquired immune deficiency syndrome. In this population, KS manifests in an aggressive and more disseminated fashion as compared to the classical type. As the epidemic of acquired immune deficiency syndrome continues to spread and more cases of KS are evaluated, a distinct diversity in the clinical presentation and in the course of the disease as well as in variation in the prognosis and response to therapy is being observed. A preliminary description of the spectrum of KS in the epidemic of acquired immune deficiency syndrome is presented here.

Introduction

KS^2 is an interesting model of a possibly virus-associated human tumor (1). It has a special geographical and ethnic distribution. Elderly men from Eastern European countries, children and young adults from certain parts of Africa, and renal transplant recipients have been among those at high risk for developing KS (2). Recently an increasing number of KS cases has been reported in patients with AIDS (3). The high incidence of KS among AIDS victims is such that the presence of this tumor in risk populations is now considered proof of the diagnosis of AIDS.

Considerable variation in clinical presentation, course of the disease, prognosis, and response to therapy have been reported among the classical type of Kaposi’s sarcoma (4). In the epidemic form, seen in patients with AIDS (KS-AIDS), KS is reported to be disseminated and aggressive, even capable of causing death by invading vital organs such as the lung (5). However, the emerging data in a large series of KS-AIDS cases indicate that the manifestations of KS may vary considerably among AIDS victims, suggesting a spectrum of disease presentation. The data presented here summarize our observations of this tumor in a group of patients with AIDS.

Methods

Patient Population. Patients with Kaposi’s sarcoma referred to the dermatology service of Memorial Sloan-Kettering Cancer Center were selected for this study. The diagnosis of KS was confirmed by clinical and histopathological features. Designated criteria by the Center for Disease Control’s “AIDS-Case-Definition” were used to separate KS-AIDS cases from those with classical KS. The majority of KS-AIDS cases were homosexual men. However, 2 cases of i.v. drug abusers, 1 heterosexual case from Columbia, South America, and 1 other case of KS who has denied history of homosexual activity were among the patients evaluated. On their initial admission and prior to initiation of any therapy, each patient was evaluated for the extent of KS tumor, immunological profile, presence of opportunistic infections, and HTLV-III serology.

Extent of Disease

Four major sites were evaluated for the presence of KS tumors. Biopsies of skin, mucous membrane lesions, and enlarged lymph nodes were used for histopathological confirmation of KS. Gastroscopy and colonoscopy were used for documentation of KS in the gastrointestinal tract. Suspected mucosal lesions in the gastrointestinal tract were biopsied for histological confirmation of the diagnosis of KS. Bronchoscopy was used to demonstrate the presence of KS in the respiratory tract. The latter procedure was not routinely performed on all cases and was only used on those cases with respiratory complaints who were suspected to have opportunistic infections of the lung.

Opportunistic Infections

The presence of opportunistic infections was documented by the clinical criteria and by confirmatory laboratory tests, such as bronchial washing for Pneumocystis carinii and atypical mycobacteria and blood and bone marrow cultures for atypical mycobacterial infections.

Immunological Profile

Complete blood counts were performed measuring the numbers of WBC and the numbers and percentages of lymphocytes in each patient. Mononuclear cells were separated on a Ficoll-Hypaque gradient. T-lymphocyte membrane phenotypes were determined on a fluorescent-activated cell sorter (Becton-Dickinson FACScan IV) (6, 7). Monospecific antibodies to helper/inducer (LEU 3a+ or OKT^+^) and to suppressor/cytotoxic (LEU 2a+ or OKT^−^) T-lymphocytes were used to determine the numbers and ratio of these T-cell subsets. In vitro lymphocyte blast transformation in response to stimulation with phytohemagglutinin was determined using previously reported methods (8, 9).

HTLV-Serology

Serum were collected under sterile conditions and were stored at −70°C until they were assayed under code by the ELISA and/or by the Western blot technique. Isolation and characterization of HTLV-III (10, 11) and the detailed procedures for performing ELISA and the Western blot technique (13–15) have been previously reported.

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^2 The abbreviations used are: KS, Kaposi’s sarcoma; AIDS, acquired immune deficiency syndrome; ELISA, enzyme-linked immunosorbent assay; HTLV, human T-lymphotropic virus; OI, opportunistic infections; PHA, phytohemagglutinin.
Results

A total of 214 cases of KS-AIDS was seen in the period of March 1981 through November 1984. The median age of these patients at the time of initial evaluation was 38 yr. Eighty-nine of these cases (41%) have expired, and 125 (59%) were still alive. Twenty-six of the total of 214 were seen only in consultation, and 5 were lost to follow-up.

Of the 183 evaluated cases, only 6 patients demonstrated stable condition and minimal KS tumor. These cases did not show any evidence of AIDS-related complexes prior to their diagnosis of KS. They were not treated, and during the course of follow-up, they have shown no or minimal progression of their KS tumor. These individuals have not developed opportunistic infections and generally demonstrated normal values for their immune parameters. A small number of patients with KS-AIDS presented initially with minimal KS tumor and were generally in good health with normal immune parameters. However, these individuals in a short period of follow-up (usually less than 6 mo) manifested progression of their disease and abnormal immune parameters.

The majority of KS-AIDS cases presented with rapidly progressive and disseminated KS tumor and with abnormal immunological profiles. Most, if not all, of the patients have had some of the symptoms and signs of AIDS-related complexes. Most KS-AIDS patients developed multiple OI, usually with a fatal outcome. The development of KS was also observed as a late manifestation in some AIDS patients presenting with OI (OI-AIDS). KS lesions were observed during the terminal stage of illness of OI-AIDS patients often after the development of several different OI.

The extent of tumor evaluation demonstrated KS tumors to be present on the skin in 70%, in the lymph node in 47%, in the upper gastrointestinal tract in 37%, and in the lower gastrointestinal tract in 33% of cases.

Of the 183 evaluable cases, 74% were alive 12 mo and 50% were alive 24 mo following the time of diagnosis of KS.

In a series of 87 patients who were evaluated for the number of WBC and number and percentage of lymphocytes, it was noted that 55 patients had normal and 32 patients had abnormal WBC. Among those with normal WBC, 71% survived for 12 mo or more, as compared to 61% of those with abnormal WBC. Of the evaluated 87 patients, 77 had normal numbers of lymphocytes, and 10 had abnormal numbers of lymphocytes. The median survival for those with normal lymphocyte counts was 22.2 mo, as compared to 6.2 mo for those with abnormal lymphocytes (P < 0.001). In addition, these data demonstrated that 74% of those with normal lymphocyte counts survived 12 mo, as compared to 13% of those with low lymphocyte count. A progressive decrease in the number of WBC and number of lymphocytes was noted as a general trend in KS-AIDS patients.

A total of 114 patients was evaluated for their T-helper/T-suppressor ratio. There were 15 cases who had a normal ratio of 1.7 or more and 11 cases with ratio of 1.0 to 1.7. Twelve of the 15 cases (80%) with normal ratio were alive 24 mo following their diagnosis of KS-AIDS, whereas only 5 of the 11 (45%) cases with a ratio of 1.0 to 1.7 were still alive 18 mo following the diagnosis of KS-AIDS. Similar observations were made in regards to the blastogenic responses to PHA. KS-AIDS patients with normal PHA responsiveness had a much longer survival period, as compared to those with abnormal PHA responsiveness.

A total of 143 sera was tested for HTLV-III antibodies using the ELISA assay. Thirty-six sera (25%) were negative, while 107 (75%) were positive. Five of the 107 were strongly positive, showing 2 to 3+ positive reactions. These 5 cases appear to have a better prognosis and have not developed OI.

Using the Western blot technique, 82 sera were tested; only 7 sera were found to be negative by both ELISA and Western blot assays. Those KS-AIDS patients whose sera were negative in both ELISA and Western blot assays also appear to be doing well with or without treatment. These cases have mostly been shown to have stable disease, without signs of rapid progression.

The distributions of various HTLV-III antigens (Table 1) were also determined in a series of 82 patients. As shown in Table 1, antibody to Mr 41,000 protein seems to be most frequently (97%) found in these patients whereas antibodies to viral antigen Mr 18,000 protein seems to be least frequent (59%).

Comments

It is generally believed that AIDS, as defined by the Center for Disease Control, is a progressive disease with a fatal outcome. While the majority of the KS-AIDS cases seen by our group have demonstrated an aggressive course, there are those cases who appear to have slow and indolent disease and others who have minimal but stable tumors. Thus, KS in the epidemic of AIDS manifests a wide spectrum of disease presentation. This is very much similar to the spectrum of KS seen in Africa, where the tumor is aggressive and fatal in children, but manifests a wide range of presentation in adults (4).

One may speculate that those AIDS cases who have a milder form of KS and do not go on to develop OI have developed specific means to combat their HTLV-III infection and to control their KS tumor. In addition, such cases may indirectly suggest the possible existence of immunity to HTLV-III infection. Certain host factors, such as the presence of neutralizing antibodies or absence of certain predisposing factors, may play a role in the disease pathogenesis in these cases. In fact, those cases who have a higher titer of anti-HTLV-III antibodies in the ELISA assay appear to have a better prognosis. On the other hand, virally related factors, such as route of infection or presence of less virulent form of HTLV-III, may be responsible.

As previously reported, there may be as high as a 25% false-negative rate with the ELISA assay. On the other hand, the
Western blot assay seems to be more sensitive and specific. The 7 cases of KS that have been negative in both ELISA and Western assay may represent classical KS. However, it is possible that these cases have failed to develop antibodies to HTLV-III. Isolation of HTLV-III from the peripheral blood or bone marrow in these cases will allow distinction between KS-AIDS and classical KS and may shed light on the immunopathogenesis of the HTLV-III infection.

HTLV-III serology performed on KS-AIDS demonstrates a sequential development of antibodies against different viral antigens. Correlation of the clinical data and the result of HTLV-III serology seems to suggest that patients with higher titer antibodies to M, 24,000 protein may have a better prognosis. In addition, decreasing HTLV-III antibody titers are seen with progression of the disease.

It is noteworthy to mention here that, since KS-AIDS cases have been seen in individuals over age 60, it is not possible to use an arbitrary age limit to separate classical KS from KS-AIDS. The use of HTLV-III serology and viral isolation appears to be a more reliable means for this purpose.

Demonstration of a normal T-helper/T-suppressor ratio and normal levels of lymphocyte blastogenic responses to PHA in a few cases of KS-AIDS indicates that these immune abnormalities are not prerequisite for the development of KS.

The data presented here suggest that the absolute number of lymphocytes, the T-helper/T-suppressor ratio, and the lymphocyte blastogenic capacity all have prognostic value in cases of KS-AIDS. While the immune deficiency in these cases seems to be progressive, the presence of normal or near-normal values for the above parameters indicates a less severe immunopathology caused by the HTLV-III infection.

Studies of the extent of the disease in this group of patients suggest that the disease prognosis is not dependent on the tumor burden or on the number of sites involved. The initial site of development of KS tumor does not appear to affect the prognosis. Involvement of vital organs, such as the lung, seems to suggest a worse prognosis.

In conclusion, the diversity of the clinical features, the immunological profile, and the virologic data suggest that KS-AIDS manifests a wide spectrum of disease presentation.

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