Altered Clinical Course of Malignant Melanoma in HIV-Positive Patients

Lori K. E. Rodrigues, MD; Barbara J. Klencke, MD; Kirsten Vin-Christian, MD; Timothy G. Berger, MD; Richard I. Crawford, MD; James R. Miller III, PhD; Carlos M. M. Ferreira, MD; Mehdi Nosrati, BS; Mohammed Kashani-Sabet, MD

Objective: To determine whether the natural history of melanoma is different in patients who test positive for human immunodeficiency virus (HIV) compared with matched control subjects.

Design: Retrospective cohort analysis.

Setting: Ambulatory care at 2 university-affiliated medical centers.

Patients: Each HIV-positive melanoma patient (n=17) was randomly matched with 2 HIV-negative patients (HIV status unknown, but without risk factors for HIV) based on the melanoma subtype, tumor thickness, Clark level, tumor location, and sex and age of the patient.

Main Outcome Measures: Disease-free survival and overall survival of HIV-positive and HIV-negative melanoma patients were compared using a matched-pairs analysis. CD4 cell counts were recorded at the time of melanoma diagnosis and disease recurrence.

Results: Melanoma patients who were HIV positive had a significantly shorter disease-free survival (P=.03) and overall survival (P=.045) compared with HIV-negative melanoma patients by matched-pairs analysis. There was an inverse relationship between CD4 cell counts and time to first melanoma recurrence.

Conclusions: The natural history of malignant melanoma in HIV-positive patients is more aggressive compared with matched HIV-negative melanoma patients. Altered immune response and comorbid disease may play a role in the poor clinical outcome of HIV-positive patients. These findings have important implications in the management of melanoma in the setting of HIV disease.

Arch Dermatol. 2002;138:765-770

The immune suppression associated with human immunodeficiency virus (HIV) infection may affect the incidence or clinical behavior of a malignant tumor. Patients with acquired immunodeficiency syndrome (AIDS) have been shown to be at greatly increased risk for some cancers, such as Kaposi sarcoma, primary central nervous system lymphoma, non-Hodgkin lymphoma, and cervical cancer.1,2 Cutaneous nonmelanoma neoplasms, such as basal cell carcinoma and squamous cell carcinoma, have also been noted frequently in those with HIV infection.3-6 One study7 suggested that these skin tumors have a more aggressive behavior. The relative risk of a few types of malignancies, such as human papilloma virus–related cancers (eg, anal, penile, and vulvar), Hodgkin disease, and lung cancer, is slightly elevated, although these are not yet designated as AIDS-defining cancers.7

Reports of concurrent melanoma and HIV lead some to speculate that there may be an increased risk of melanoma.8 A few case reports suggest a poor clinical outcome of melanoma in the setting of HIV disease.8-10 whereas others make no comment about outcome.11 Further studies are needed to confirm these results because existing epidemiologic data address the issue of incidence rather than the natural history of the disease.

In this retrospective study, we review the clinical course of 17 HIV-positive patients with melanoma. The presentation and clinical behavior of melanoma in HIV-positive patients are compared with sex- and age-matched HIV-negative patients (HIV status unknown, but without risk factors for HIV disease). We report a reduced disease-free and overall survival in HIV-positive melanoma patients compared with matched controls.

RESULTS

All 17 HIV-positive melanoma patients were men between ages 31 and 75 years, with a mean age of 42 years (Table 1 and Table 2). Subtypes of melanoma in-
PATIENTS AND METHODS

Twenty-six HIV-positive patients with melanoma were initially seen at the University of California, San Francisco, and St Paul’s Hospital, Vancouver, British Columbia. Seventeen HIV-positive patients were ultimately evaluated in our study. The remainder of the patients were excluded for the following reasons: 5 because we were unable to locate the melanoma pathology reports (the patients’ medical records were kept by physicians who have since changed practices or retired); 1 did not have an invasive melanoma; 2 presented with metastatic disease from an unknown primary melanoma; and in 1 case there was a discrepancy between the dates of diagnosis and death. Approval was obtained from the Committee on Human Research at the University of California, San Francisco, to conduct the study. Formal application was not required by the Ethics Review Committee at St Paul’s Hospital for a retrospective review of medical records. Information about a patient’s history of HIV and melanoma was obtained by chart review. Information regarding the melanoma included pathology reports, risk factors, and treatment. Information regarding the HIV history included dates of first diagnosis, CD4 cell counts, medications, and the presence of opportunistic infections.

Each HIV-positive melanoma patient was matched with 2 HIV-negative patients (HIV status unknown, but without risk factors for HIV disease) based on the melanoma subtype, tumor thickness, Clark level, sex and age of the patient, and, when possible, anatomic location of the primary tumor. Controls were randomly selected from the University of California, San Francisco, Melanoma Center data set on the basis of the tumor and patient characteristics mentioned. This data set included patients with a primary melanoma and with 2 years of follow-up or who had documented first relapse. Disease-free survival and overall survival for HIV-positive and HIV-negative melanoma patients were recorded and, when available, the cause of death was noted.

The Wilcoxon matched-pairs, signed rank test and the binomial sign test were used to determine the statistical significance of the overall survival and time to first recurrence between the HIV-positive and HIV-negative patients. Kaplan-Meier analysis was used to assess disease-free and overall survival for the cohort of HIV-positive and HIV-negative patients. The relationship between CD4 cell counts (at initial diagnosis of melanoma) and tumor thickness was examined using regression analysis. The relationship between CD4 cell counts and disease-free survival was also examined. The HIV-positive patients were split into 2 groups: those with low (below the median) and those with high (above the median) CD4 cell counts. Separate Kaplan-Meier curves were produced for low and high CD4 cell counts, with respect to disease-free survival, and the significance of the difference between these 2 curves was tested by the generalized Wilcoxon test and the log-rank test.

Table 1. Summary of the Melanoma Characteristics, Dates of Disease Diagnoses, CD4 Cell Counts, Number of Antiretroviral Medications, and Status for Each HIV-Positive Study Patient

<table>
<thead>
<tr>
<th>No.</th>
<th>Year of Melanoma Diagnosis</th>
<th>Tumor Thickness, mm</th>
<th>Clark Level</th>
<th>Location</th>
<th>Subtype</th>
<th>Year of HIV Diagnosis</th>
<th>HIV Therapy, No. of Medications</th>
<th>CD4 Cell Count at Diagnosis, /µL</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1991</td>
<td>0.4</td>
<td>II</td>
<td>Head and neck</td>
<td>SSM</td>
<td>1991</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Dead from metastatic melanoma</td>
</tr>
<tr>
<td>2</td>
<td>1984</td>
<td>1.5</td>
<td>IV</td>
<td>Trunk</td>
<td>SSM</td>
<td>1984</td>
<td>0</td>
<td>Unknown</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>1999</td>
<td>2.3</td>
<td>IV</td>
<td>Extremity</td>
<td>NM</td>
<td>1985</td>
<td>3</td>
<td>360</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>1990</td>
<td>8.0</td>
<td>IV</td>
<td>Trunk</td>
<td>NM</td>
<td>1990</td>
<td>0</td>
<td>235</td>
<td>Dead from unknown causes</td>
</tr>
<tr>
<td>5</td>
<td>1992</td>
<td>0.5</td>
<td>III</td>
<td>Trunk</td>
<td>NS</td>
<td>1989</td>
<td>0</td>
<td>752</td>
<td>Dead from metastatic melanoma</td>
</tr>
<tr>
<td>6</td>
<td>1991</td>
<td>1.0</td>
<td>NS</td>
<td>Head and neck</td>
<td>NOC</td>
<td>1985</td>
<td>4</td>
<td>554</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>1987</td>
<td>1.3</td>
<td>IV</td>
<td>Trunk</td>
<td>NM</td>
<td>1987</td>
<td>0</td>
<td>119</td>
<td>Dead from metastatic melanoma and AIDS</td>
</tr>
<tr>
<td>8</td>
<td>1997</td>
<td>2.8</td>
<td>IV</td>
<td>Extremity</td>
<td>NM</td>
<td>1997</td>
<td>4</td>
<td>274</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>1992</td>
<td>1.7</td>
<td>IV</td>
<td>Trunk</td>
<td>NM</td>
<td>1989</td>
<td>1</td>
<td>384</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>1998</td>
<td>0.5</td>
<td>III</td>
<td>Trunk</td>
<td>SSM</td>
<td>1997</td>
<td>3</td>
<td>489</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>1986</td>
<td>0.5</td>
<td>III</td>
<td>Trunk</td>
<td>SSM</td>
<td>1985</td>
<td>1</td>
<td>Dead from AIDS</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1996</td>
<td>2.0</td>
<td>IV</td>
<td>Trunk</td>
<td>DPM</td>
<td>1985</td>
<td>3</td>
<td>384</td>
<td>Alive</td>
</tr>
<tr>
<td>13</td>
<td>1997</td>
<td>1.9</td>
<td>IV</td>
<td>Trunk</td>
<td>SSM</td>
<td>1993</td>
<td>3</td>
<td>130</td>
<td>Alive</td>
</tr>
<tr>
<td>14</td>
<td>1997</td>
<td>1.5</td>
<td>IV</td>
<td>Trunk</td>
<td>LMM</td>
<td>1997</td>
<td>3</td>
<td>570</td>
<td>Alive</td>
</tr>
<tr>
<td>15</td>
<td>1994</td>
<td>3.6</td>
<td>IV</td>
<td>Trunk</td>
<td>DPM</td>
<td>1988</td>
<td>0</td>
<td>960</td>
<td>Dead from metastatic melanoma</td>
</tr>
<tr>
<td>16</td>
<td>1996</td>
<td>2.3</td>
<td>III</td>
<td>Trunk</td>
<td>SSM</td>
<td>1991</td>
<td>3</td>
<td>460</td>
<td>Alive</td>
</tr>
<tr>
<td>17</td>
<td>1983</td>
<td>0.9</td>
<td>III</td>
<td>Head and neck</td>
<td>SSM</td>
<td>1983</td>
<td>0</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus; SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; NS, not stated; NOC, not otherwise classified; DPM, desmoplastic melanoma, and AIDS, acquired immunodeficiency syndrome.

included superficial spreading (8), nodular (4), desmoplastic (2), and lentigo maligna (1). Two melanomas were not otherwise classified. Melanoma tumor thickness ranged from 0.4 to 8.0 mm, with a mean tumor thickness of 1.92 mm. One patient had histologic evidence of ulceration; 4 patients did not have ulceration. Twelve melanoma biopsy specimens were not evaluated for the presence or absence of ulceration.
Three patients had a melanoma located on the head and neck region, 12 on the trunk, and 2 on the extremities. The CD4 cell count at the time of melanoma diagnosis was available for 12 patients; the values were between 119/µL and 960/µL, with a mean of 436/µL.

Fifteen of the 17 HIV-positive patients had a wide excision of their melanoma. One patient was lost to follow-up after the initial biopsy. Documentation of a re-excision was not found in his medical record. Another patient had widespread metastatic disease at melanoma diagnosis and a wide excision was not performed.

The nodal status of the HIV-positive patients was largely determined by clinical examination, because the sentinel lymph node biopsy procedure has only recently entered widespread use. One patient presented with palpable axillary lymphadenopathy confirmed as melanoma. Three patients had histologically negative lymph nodes determined by sentinel lymph node biopsy. The remaining HIV-positive patients had no evidence of lymphadenopathy by clinical examination. None of the HIV-positive patients underwent elective lymph node dissection.

Baseline staging studies including a chest x-ray examination and blood work (complete blood cell count with differential, liver function tests, and lactate dehydrogenase measurements were performed in all but 2 HIV-positive patients). Elevated liver function test results were noted in 3 patients. One patient with a lactate dehydrogenase level almost twice the upper limit of normal had liver metastasis on computed tomographic scanning. Another patient had an elevated lactate dehydrogenase level and concurrent hepatitis C infection.

Follow-up examinations were recommended at a minimum of every 6 months, with surveillance chest x-ray examinations and laboratory studies (complete blood cell count and liver function tests) performed when indicated. One HIV-positive melanoma patient with elevated liver function test results at baseline was followed up and is alive without evidence of recurrent disease. Three patients did not follow through with their physician visits and were lost to follow-up.

Eleven HIV-positive melanoma patients had comorbid illnesses, such as *Pneumocystis carinii* pneumonia, hepatitis B or C, *Mycobacterium avium* complex, herpes simplex infection, central nervous system toxoplasmosis, or cryptococcus and cytomegalovirus infection by the time of their death. There were no reported cases of Kaposi sarcoma.

Ten of the 17 HIV-positive patients were undergoing antiretroviral therapy at the time of melanoma diagnosis (Table 1). Two patients were receiving a single antiretroviral agent, and the remaining 8 patients were undergoing highly active antiretroviral therapy (HAART). The 2 patients who received single-drug treatment for HIV disease are dead; 1 patient died of AIDS and the other of metastatic melanoma and AIDS. The HIV-positive patients who were treated with HAART are alive and currently without evidence of recurrent melanoma. Two patients who received HAART had recurrent disease that was surgically resected and treated with adjuvant therapy. One patient received interleukin 2 and postoperative radiation; the second patient was treated with interferon alfa, which he was unable to tolerate. Seven HIV-positive patients were not treated for HIV disease. Three patients died of metastatic melanoma and 1 died of metastatic melanoma and AIDS. Three patients were lost to follow-up. However, it is likely that 1 of these patients died of metastatic melanoma because he had axillary, mediastinal, and liver masses detected by computed tomographic scanning.

Thirty-four control patients were included in our study, and their clinical and histologic characteristics are summarized in Table 2. All patients were men between ages 28 and 77 years, with a mean age of 47 years. Melanoma subtypes included superficial spreading (19), nodular (9), desmoplastic (4), and lentigo maligna (2). The average tumor thickness was 2.01 mm, with a range of 0.35 to 8.00 mm. Fourteen patients had histologic evidence of ulceration, 19 did not have ulceration, and 1 patient’s ulceration status was unknown. Melanoma was located on the head and neck in 10 patients, on the trunk in 21, and on the extremities in 3. There were fewer HIV-positive patients with head and neck melanomas compared with HIV-negative patients. The discrepancy was due to a lack of HIV-negative patients with desmoplastic and lentigo maligna melanoma located in the same anatomic region as the HIV-positive patients. Therefore, the cases were matched with controls from the database with similar histologic features but located on the head and neck. Given the potentially more aggressive behavior of melanomas located in the head and neck, this selection criterion would worsen the survival results for the controls, thereby masking a survival difference between the 2 groups. All patients had wide excision of their melanomas.

### DISEASE-FREE SURVIVAL

Fourteen HIV-positive patients and 18 matched HIV-negative melanoma patients had a median follow-up of 48 months (range, 3-155 months) and were included in the final analysis. Patients were followed up at least every 6 months or more closely if they presented with a thick melanoma or had evidence of metastatic disease. Radiographic and laboratory studies were performed at least...
annually and more frequently when clinically indicated. Seven (50%) of 14 HIV-positive patients developed metastatic melanoma compared with 12 (67%) of 18 HIV-negative patients when followed up for a median of 48 months. The percentage of HIV-negative patients who had a melanoma relapse is higher than one would expect for this cohort because they were selected from a data set that was skewed toward relapses. The HIV-positive patients had a reduced disease-free survival compared with the HIV-negative patients (Figure 1). This reduction in disease-free survival showed a trend toward statistical significance when the 2 Kaplan-Meier survival plots were compared under the assumption that the 2 samples were drawn independently of one another (P = .06, 1-tailed log-rank test). However, when HIV-positive and HIV-negative patients were matched using the variables described, a Wilcoxon matched-pairs, signed rank test showed the reduction in disease-free survival to be significant (P = .04). The median disease-free survival was 16 months for HIV-positive patients compared with 42 months for HIV-negative patients.

OVERALL SURVIVAL

The overall survival of HIV-positive melanoma patients was significantly reduced when compared with matched HIV-negative melanoma patients (Figure 2; P = .002, 1-tailed log-rank test; P = .045, 1-tailed Wilcoxon matched-pairs, signed rank test). Seven of 14 HIV-positive patients died during follow-up compared with 9 of 18 HIV-negative patients. The median overall survival was approximately 2.8 years for HIV-positive patients vs 6.4 years for HIV-negative patients. The cause of death in the HIV-positive patients was due to metastatic melanoma in 3 (43%) of 7 cases. Only 1 HIV-infected patient died of AIDS-related illness in the absence of metastatic melanoma. Three died of metastatic melanoma and concurrent AIDS.

CD4 CELL COUNTS

There was no association between CD4 cell counts and tumor thickness in HIV-positive melanoma patients at the time of melanoma diagnosis (Figure 3). The association between initial CD4 cell counts and overall survival in HIV-positive melanoma patients was not statistically significant. However, patients with lower CD4 cell counts seemed to have shorter overall survival compared with patients with higher CD4 cell counts.

Seven HIV-positive melanoma patients had CD4 cell counts measured at the time that their melanoma metastasized. Patients with higher CD4 cell counts had a significantly prolonged time to melanoma relapse determined by a regression scale (P = .04).

COMMENT

At least 22 cases of melanoma associated with HIV disease have been reported in the literature. Many of these case reports suggest that the natural history of melanoma in HIV-positive patients is more aggressive and associated with a poorer prognosis compared with HIV-negative patients. Our study supports the suggestions of previous reports by demonstrating a significantly shorter
disease-free survival and overall survival for HIV-positive patients with melanoma.

Our study design controlled for differences in clinical and histologic characteristics (by matching variables such as tumor thickness, melanoma subtype, Clark level, and patient age and sex) between HIV-positive and HIV-negative patients to eliminate factors that may influence overall melanoma prognosis. Despite this, the clinical course of melanoma in HIV-positive patients was more rapidly progressive than that of the matched pairs. The aggressive nature of the melanomas may be secondary to factors such as an altered host immune response to tumor due to immunodeficiency and comorbid illnesses. In our study, HIV-positive patients with a more severe immune deficiency (as evidenced by CD4 cell counts) experienced an earlier relapse of their melanoma. Although an inverse relationship between CD4 cell counts at melanoma diagnosis and tumor thickness has been reported,12 this relationship was not observed in our study. In fact, the HIV-positive patients had a relatively high median CD4 cell count at the time of melanoma diagnosis; this might suggest that there is no significant influence of HIV disease on tumor initiation.

The median overall survival for HIV-positive patients in this study was shorter (2.8 years) compared with HIV-negative patients (6.4 years). At least 40% of the HIV-positive patients died of metastatic melanoma and almost 30% died as a result of metastatic melanoma and AIDS, even though 8 patients had concurrent opportunistic infections at the time of death. Most deaths were observed in the HIV-positive patients who were not treated for HIV or received only single-agent antiretroviral therapy. This suggests that immune reconstitution with HAART may improve the prognosis of malignant melanoma in HIV-positive individuals.

Although the exact mechanism of how HIV disease affects melanoma is unknown, several lines of evidence point to the effects of immune modulation on the biology of melanoma. Currently, interferon alfa-2b and interleukin 2 are immunotherapeutic agents approved by the Food and Drug Administration for the treatment of melanoma. Several phase 3 clinical trials evaluating the efficacy of tumor vaccines in the adjuvant therapy of melanoma have been undertaken. In addition, the incidence of melanoma in HIV-infected individuals. A prospective study of 1000 patients with HIV disease noted as much as a 100-fold higher incidence of melanoma compared with the general population.21 Despite this, epidemiologic studies using cancer and AIDS registries or other prospective cohort studies have not demonstrated a significantly increased incidence of melanoma.22-25 Beral et al7 formed an international collaboration of epidemiologists to address the risk of AIDS-defining cancers and non–AIDS-defining cancers in HIV-infected patients. Using primary data, 20 prospective cohort or case-control studies of HIV-infected individuals, representing 90% of the world’s literature on AIDS malignancy, were analyzed to determine the risk of AIDS-defining cancers and 13 other non–AIDS-defining cancers. The meta-analysis showed a relative risk of 0.9 (99% confidence interval, 0.4-1.6) for melanoma in those with AIDS compared with controls.

In conclusion, this study suggests that HIV-positive melanoma patients have a more aggressive clinical course of melanoma, as evidenced by a shorter disease-free and overall survival compared with matched HIV-negative melanoma patients. Our findings may have several implications regarding the management of HIV-positive melanoma patients. These patients may be candidates for sentinel lymph node biopsy at a lower tumor thickness than that used for HIV-negative melanoma patients. These patients should undergo closer surveillance to detect the presence of metastatic disease. Our results suggest that patients undergoing HAART may have an improved clinical outcome. Therefore, initiation of HAART should strongly be considered in HIV-positive patients with malignant melanoma. Finally, the role of adjuvant immunotherapy, such as interferon alfa or interleukin 2, should be explored in this cohort given its potential beneficial effects on melanoma and HIV infection.

Accepted for publication August 7, 2001.

Corresponding author and reprints: Mohammed Kashani-Sabet, MD, University of California, San Francisco, Melanoma Center, UCSF Comprehensive Cancer Center, 1600 Divisadero St, San Francisco, CA 94115 (e-mail: kashanisabet@orca.ucsf.edu).

REFERENCES


CME Announcement

CME Hiatus: July Through December 2002. CME from JAMA/ARCHIVES will be suspended between July and December 2002. Beginning in early 2003, we will offer a new online CME program that will provide many enhancements:

- Article-specific questions
- Hypertext links from questions to the relevant content
- Online CME questionnaire
- Printable CME certificates and ability to access total CME credits

We apologize for the interruption in CME and hope that you will enjoy the improved online features that will be available in early 2003.