Alterations in Head and Neck Cancer Occurring in HIV-infected Patients

Results of a Pilot, Longitudinal, Prospective Study

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To assess the impact of human immunodeficiency virus (HIV) infection on the presentation and course of head and neck squamous cell carcinoma (HNSCC), we performed a pilot, prospective, longitudinal study of all patients with HNSCC presenting to our institutions over a 6-month period ($n = 10$). A 60% incidence of HIV infection was seen in this study population, with SCC presenting as the initial manifestation of HIV infection in 2 of the 6 patients. In addition, HIV-infected patients were significantly younger than non-infected patients at ($p = 0.01$). None of the HIV-infected patients had acquired immunodeficiency syndrome (AIDS) at the time of presentation, but 5 of 6 patients had an abnormal CD4 count, compared to none of the non-infected patients ($p = 0.05$). The absolute CD4 count in HIV-infected patients decreased to less than 100×10^9/L in the majority of these patients within 3 months of presentation with HNSCC ($p = 0.05$). Treatment-associated complications were common in HIV-infected patients, occurring in 4 of the 6 cases in contrast to none of the patients without HIV infection ($p = 0.046$). Outcome was significantly poorer for HIV-Infected patients, with 5 patients succumbing to their disease within one year, in contrast to none of the non-infected patients ($p = 0.046$). These data, combined with our previous work, justify further investigation of the relationship between HNSCC and HIV infection and the possibility of its inclusion as an AIDS-defining process.

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The AIDS epidemic continues to exert a significant influence on current medical and social doctrines. The magnitude of its effect can be appreciated by HIV-associated changes in social behaviours, medical treatment, and medical resource allocation. As this epidemic evolves, new processes are being included in the list of AIDS-defining by virtue of alterations in course and implications for prognosis (1). The majority of these processes are opportunistic to the immune dysfunction characteristic of human immunodeficiency virus (HIV) infection. Although infectious processes predominate, neoplastic diseases are beginning to emerge in this population. A recent retrospective study suggested that head and neck squamous cell cancer (HNSCC) may be one such process.

SCC has traditionally been the most common head and neck malignancy. However, at our institution, in face of HIV infection, SCC is the third most common head and neck cancer, after Kaposi's sarcoma and non-Hodgkin's lymphoma, (2, 3). Our experience suggests that these tumors have a unique course in the HIV-infected population (4). Head and neck SCC occurs in a younger population and may be associated with a poorer overall survival. This study was performed as a pilot study to identify the incidence of head and neck SCC in HIV infection in our patient population, and to relate to the level of immunosuppression at which it occurs.

MATERIAL AND METHODS

This study was of prospective, longitudinal design, including all patients with SCC of the head and neck presenting to the King's County Hospital Center and the Veterans' Administration Medical Center-Brooklyn during the period February 1995 to May 1995. All patients were questioned about risk factors for HIV infection and SCC development and underwent a complete head and neck examination. Tumor staging was based on the TNM classification system and HIV-infection staging was based on the Center for Disease Control staging system for HIV

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infection. The tumor stage was confirmed in every case by intraoperative direct visualization, and corroborated by pathology reports. All patients underwent a metastatic work-up (liver function tests, alkaline phosphatase, and chest radiography), CT examination of the neck, and endoscopy with biopsy, prior to receiving any definitive therapy.

After appropriate counseling and obtaining informed consent, CD4/CD8 levels and HIV status were determined in all cases. Patients were treated according to currently accepted guidelines for the location and stage of the tumor. The CD4 count was repeated in all HIV-infected patients within 3 months of treatment completion. The occurrence of any treatment-associated complications and their outcome was recorded. All patients were followed for a minimum of 12 months to assess tumor recurrence and survival.

Statistical significance was defined as a two-tailed p-value less than or equal to 0.05. Fisher's exact test was performed suing StatXact software for exact non-parametric inference (5). All other statistical calculations were performed using the Epistat statistical software package (6).

RESULTS

Eleven patients presented with SCC of the UADT. One patient refused any work-up and treatment and was excluded from the study. All study patients were males with a median age of 55 years (range 36–77). All patients had a history of tobacco (> 10 packs/year) and/or alcohol use (> 2 drinks per day). Risk factors for HIV infection were present in 6 cases (intravenous drug use (5 cases); multiple sexual partners (3 cases)). At presentation, the presence of HIV infection was documented in 4 cases, none of whom met the criteria for AIDS. HIV testing was performed in the remaining 6 patients, with positive results recorded in 2 of these cases, both of whom reported risk factors for HIV infection. The overall incidence of HIV infection was 60% in the study population.

At the time of presentation with SCC of the UADT, all patients with HIV infection were at an early stage in the course of infection (see Table 1). The majority of these patients had CDC stage A1 disease (83%), while one patient had stage A3 disease (17%). The CD4 count at presentation was normal ($> 500 \times 10^9$/L) in all HIV-negative patients, but was below normal range in 5 of 6 patients with HIV infection (Fisher's exact test; $p = 0.05$). In addition, the CD4 level decreased to less than 100 ($\times 10^9$/L) in all HIV-positive patients within three months of presentation with SCC of the UADT (Mann-Whitney U-test; $p = 0.05$).

HIV-infected patients (median 45.5 years) were significantly younger than non-infected patients (median- 66.5 years; Mann-Whitney U-test; $p = 0.01$). SCC lesions usually involved the oral cavity (3 cases), oropharynx (3 cases), larynx (3 cases), and the hypopharynx (1 case). Most HIV-infected patients had TNM stage IV disease (83%) at presentation, while one patient was in stage II cancer (17%). Two non-HIV-infected patients each were in TNM stage III (50%) and stage IV (50%) at presentation. Owing to the small number of patients in this study, no inferences on tumor location or stage in HIV-infected and non-infected patients could be made.

Surgical treatment was used with curative intent in all patients. In addition, 9 of 10 patients received postopera-

Table 1

Characteristics of study population

Patient No.	Age	Sex	HIV risk factors	Alcohol/ tobacco use	Anatomic location	TNM Stage	HIV status	CDC stage	CD4 count -preop. ($\times 10^9$/L)	CD4 count @ 3 mo ($\times 10^9$/L)	Complications	Status @ 1 year
1	54	M	(+)	(+)	Oral cavity	II	(+)	B3	178	98	Thrush	NED
2	36	M	(+)	(+)	Oral cavity	IV	(+)	A1	330	87	(−)	NED
3	77	M	(−)	(+)	Oral cavity	IV	(−)	–	539	–	(−)	NED
4	48	M	(+)	(+)	Oropharynx	III	(+)	A1	378	89	Mucositis	DOD
6	37	M	(+)	(+)	Oropharynx	IV	(+)*	A1	471	58	(−)	DOD
7	56	M	(−)	(+)	Oropharynx	IV	(−)	–	896	–	(−)	NED
5	43	M	(+)	(+)	Larynx	IV	(+)*	A1	273	81	Infection; ORN	DOD
8	63	M	(−)	(+)	Larynx	III	(−)	_	1169	–	(−)	NED
9	70	M	(−)	(+)	Larynx	IV	(−)	–	1051	–	(−)	NED
10	53	M	(+)	(+)	Hypopharynx	IV	(+)	A1	520	80	Infection	DOD

* HIV infection initially detected at presentation

Abbreviations: CDC = Center for Disease Control stage of human immunodeficiency virus infection; ORN = osteoradionecrosis; NED = no evidence of disease; DOD = Dead of disease.

tive radiation therapy. The neck nodal status was over-estimated clinically in 2 of 6 HIV-infected patients. In contrast, week nodal status under-staged in 2 of 4 non-infected patients. Treatment-associated complications were seen in 4 of 6 of HIV-infected patients but in none of the non-infected patients (Fisher's exact test; $p = 0.046$). Two HIV-infected patients developed wound infection, which was resolved with local care and antibiotics. One patient developed a mucositis during radiation therapy that was resolved with improvement of oral hygiene. Oral thrush developed during the postoperative course of one patient, which was resolved with oral nystatin treatment. One of the patients with HIV infection developed osteoradionecrosis of the mandible, requiring surgical debridement and flap reconstruction. Four of 6 HIV-infected patients succumbed to cancer within 12 months of presentation, in contrast to none of the non-infected patients (Fisher's exact patients (Fisher's exact test; $p = 0.046$).

DISCUSSION

The most common neoplastic neoplastic processes in HIV-infected patients, Kaposi's sarcoma and non-Hodgkin's lymphoma, were identified early in the course of the epidemic (2, 3, 7). More recently, cancer of the cervix has been added as an AIDS-defining process, (8, 9). A casual relationship between the development of cervix cancer and human papilloma virus (HPV) infection has already been established. However, the carcinogenic potential of HPV appears to be accelerated in patients with HIV infection, as the majority of patients with HIV, with cervical cancer present at a younger than expected age (7, 8).

Our preliminary study shows trends in SCC of the UADT that resemble those seen in HIV-associated carcinoma of the cervix. First, all of our patients were exposed to oncogenic factors predisposing to the development of SCC (alcohol and/or tobacco). Second, the cancer develops earlier, with all patients under the age of 55 presenting with SCC having concomitant HIV infection ($p = 0.005$). In addition, our previous retrospective study showed that 21% of the patients under 45 years of age with SCC were HIV infected, similar to the 19% incidence of HIV infection in patients with cervical cancer who are under 50 years of age (4). Although SCC development may seem to be accelerated, the anatomic location of the disease process has not changed compared to non-infected patients (4).

Immune dysfunction occurred in 5 of 6 HIV-infected patients (83%) in our study population, the level of which was only mild to moderate at presentation, as reflected by the CD4 counts ($p = 0.05$). In addition, the development of SCC preceded the development of AIDS in all patients and was the initial manifestation of HIV infection in two of these cases (33%). The majority of the HIV-infected patients were classified as Center of Disease Control stage A1 (83%) for HIV infection. However, within 3 months of presentation, a significant drop in CD4 count was seen in all HIV-infected patients, advancing all of them to stage A3 or B3 for HIV infection ($p = 0.05$). The drop in CD4 count probably reflects the stress of undergoing treatment and HIV-associated factors in conjunction with other factors. The deleterious effects of lower CD4 counts on the survival of HIV-infected patients, is well documented, as evidenced by only 2 patients (33%) surviving one year in our study population (10).

SCC of the UADT in HIV-infected individuals may be more aggressive than that in non-infected patients. The majority of patients present with advanced disease. In our overall experience with 30 cases of SCC of UADT in HIV-infected patients, stage III or IV cancer occurred in all but one patient at presentation. In contrast, advanced stage occurred in only 49% of our non-infected population ($n = 515$) (4). Tumor-related survival was 57% at 1 year and 32% at 2 years in HIV-infected patients, compared with 74% and 59% in non-infected patients (4). Since the natural course of HIV infection for patients without AIDS may be well over 10 years, survival is obviously influenced by the development of SCC. Accordingly, the treatment of head and neck SCC must be contemplated in all HIV-infected patients, with some special considerations.

Operative therapy may be associated with a small risk for transmission to healthcare providers. The risk to the average surgeon performing 500 procedures per year, even with an inflated HIV prevalence rate of 30% and transmission rates of 0.3% per injury, is estimated to be 0.001% per year (11). This can be further minimized with the use of appropriate precautions (12). Wound-healing problems are also common in the HIV-infected population, and are worsened by a poor nutritional status (13). Accordingly, nutritional optimization should be considered early in the course of treatment. In addition, alterations in the presentation of infectious complications may be seen, making it especially important meticulously to monitor the wounds in all these patients. Finally, the use of radiation therapy may cause an aggressive mucositis which could delay treatment. This can be minimized with the use of good oral hygiene.

Several aspects of this study deserve comment. It is the only study prospectively to examine patients with SCC of the UADT for the presence of HIV infection. The study identified several differences between SCC of the UADT in HIV-infected and non-infected patients. However, this is a pilot study and is limited by the small sample size. Specifically, the precision and generalizability of this study are limited. The exact magnitude of the observed differences and their implications for the general population with HNSCC need definition.

Nonetheless, based on this data and our overall experience, we recommend routine HIV counseling and testing for all young patients presenting with SCC of the head and

neck in high-risk populations. In regions with lower prevalence of HIV infection, HIV testing should be considered in younger patients having an atypical course or with a history of risk factors predisposing to HIV infection. We feel that our preliminary data support further consideration of SCC of the head and neck in HIV-infected patients as a potential AIDS defining process. Similar to cancer of the cervix, SCC of the head and neck affects a younger than normal population and presents at a more advanced stage. This process develops early in the course of HIV infection, and its treatment prompts a decline in CD4 cells, correctly reflecting the significantly decreased survival. In addition, the optimal treatment in this populations needs to be determined.

REFERENCES

1. Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance and case definition of AIDS among adolescents and adults. MMWR 1992; 41: 1–19.
2. Safai B, Diaz B, Schwartz J. Malignant neoplasms associated with human immunodeficiency virus infection. CA Cancer J Clin 1992; 42: 75–95.
3. Beral V. The epidemiology of cancer in AIDS patients. AIDS 1994; 5 (Suppl): S99–103.
4. Singh B, Balwally AN, Shaha AR, et al. Upper aerodigestive tract squamous cell carcinoma: the HIV connection. Arch Otolaryngol Head Neck Surg 1996; 122: 639–43.
5. Metha C, Patel N. StatXact User Manual Version 2. CYTEL Software Corporation, Cambridge, MA: 1991.
6. Gustafson TL. True Epistat reference manual. 5th ed. Epistat Services, Richardson, TX: 1994.
7. Singh B, Har-El G, Lucente FE. Kaposi's sarcoma of the head and neck in patients with acquired immunodeficiency syndrome. Otolaryngol Head Neck Surg 1994; 111: 618–23.
8. Maiman M, Fruchter RG, Guy L, et al. Human immunodeficiency virus infection and invasive cervical carcinoma. Cancer 1993; 71: 402–6.
9. Maiman M. Cervical neoplasia in women with HIV infection. Oncology 1994; 8: 83–94.
10. Rabeneck L, Wray NP. Predicting the outcomes of human immunodeficiency virus infection. How are we doing? Arch Intern Med 1993; 153: 2749–55.
11. Bartlet JG. HIV infection and surgeons. Curr Prob Surg 1992; 29: 199–280.
12. Wong ES, Stotka JL, Chinchilli VM, et al. Are universal precautions effective in reducing the number of occupational exposures among health care workers? JAMA 1991; 265: 1123–8.
13. Keusch GT, Thea DM. Malnutrition in AIDS. Med Clin North AM 1993; 77: 795–814.