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Prevalence of Undiagnosed HIV Infection in Patients With Ocular Surface Squamous Neoplasia in a Tertiary Center in Karnataka, South India

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Purpose: To evaluate the prevalence of undiagnosed and asymptomatic human immunodeficiency virus (HIV) infection in patients with ocular surface squamous neoplasia (OSSN) in a referral hospital in Karnataka, South India.

Methods: A consecutive series of patients presenting with OSSN were evaluated in an academic center during January 2009 to June 2010. A detailed history was obtained and physical examination in 25 consecutive patients with OSSN was performed. Twenty-three patients (88%) agreed to undergo serological HIV testing. Of these, 2 were excluded from the current study because they had xeroderma pigmentosa, a known predisposing factor for OSSN.

Results: Of the 21 patients, 6 (29%) patients were HIV positive. None of the patients had previous HIV testing. The median age of presentation among HIV-positive patients was 36 years, whereas it was 54 years among HIV-negative patients. The mean CD4 count in HIV-positive patients was 133 cells per mm^3, and all patients were started on antiretroviral treatment.

Conclusions: The conjunctival tumor may be the primary and the only apparent manifestation of HIV in patients presenting with OSSN, and the ophthalmologist needs to be aware of this association.

Key Words: OSSN, HIV, conjunctival tumor

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Asia, home to 60% of the world's population, is second only to sub-Saharan Africa in terms of the number of people living with human immunodeficiency virus (HIV). India accounts for roughly half of Asia's HIV prevalence. Provisional estimates showed that there would be 2.27 million people living with HIV/AIDS in India by the end of 2008, with an estimated adult HIV prevalence of 0.29%.[1] Karnataka has a HIV prevalence of 0.69% and is 1 of the 5 states identified with high prevalence all over India.[2]

In developed countries, the increased cancer risk among immunosuppressed individuals with HIV/AIDS is well described with a relative risk of 100 for Kaposi sarcoma and non-Hodgkin lymphoma. In India, non-Hodgkin lymphoma dominates the profile of recognized cancers, whereas Kaposi sarcoma is rare. There is limited evidence about ocular surface squamous neoplasia (OSSN) in these individuals.[3]

There are numerous reports suggesting a strong association of OSSN with HIV infection in sub-Saharan Africa.[4–12] OSSN includes a spectrum of diseases that range in severity from mild dysplasia to carcinoma in situ and, ultimately, to invasive carcinoma. In European countries, OSSN usually occurs in patients older than 60 years,[13] progresses slowly, and mostly has a favorable prognosis. Traditionally, risk factors for this disease have included ultraviolet (UV) light exposure, petroleum products, heavy smoking, and more recently human papilloma virus (HPV) infection.[14] In sub-Saharan Africa, in contrast, the majority of patients with OSSN seem to be younger (20–50 years), the disease seems to be more aggressive, and HIV has been identified as a major risk factor with a relative risk of 10.[5] However, it has not been well established whether OSSN is seen as a primary, early, or late sign of HIV/AIDS. There are no reports from India showing the association of OSSN in persons with HIV/AIDS.

We investigated patients presenting with OSSN referred to a tertiary center in South India to determine the percentage of patients in whom the conjunctival tumor is the primary manifestation of HIV, and whether it may serve as one of the clinical markers for HIV infection.

METHODS

Patients

From January 2009 to June 2010, 25 patients were referred to our center with a clinical suspicion of OSSN. A detailed medical history was obtained, and all patients underwent physical and ocular examination. Patients underwent slit-lamp examination, dry eye evaluation, best-

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corrected visual acuity, and a detailed fundus examination. All patients were offered HIV testing. After obtaining informed consent, Combaids (radioimmunodot assay for HIV1/2: sensitivity, 100%; specificity, 98.6%) was used to test for HIV infection. Confirmation of the test result was performed by Tri-dot (rapid test for HIV 1 subtype C; sensitivity, 99.48%; specificity, 99.7%) and Tri-line tests (rapid immunochromatographic assay HIV 1/2: sensitivity, 99.9%; specificity, 99.6%) as enzyme-linked immunosorbent assay (ELISA) and Western blot techniques were not available in our laboratory. The size of the tumors was classified as group 1, measuring less than 8 mm or involving less than 3 clock hours and group 2, measuring greater than 8 mm or more than 3 clock hours. All our patients were treated with excisional biopsy conforming to standard excision techniques and cryotherapy with or without adjunctive mitomycin C (0.04% 4 times a day, one to two 1-week cycle.)

Histopathology

Biopsies were fixed in formalin and processed to paraffin embedding, and the sections were stained with hematoxylin, eosin, and periodic acid-Schiff stain. Lesions were categorized as conjunctival intraepithelial neoplasia or invasive squamous cell carcinoma (SCC).

RESULTS

The entire group included 25 cases. Four cases were excluded from the study; 2 cases had xeroderma pigmentosa, a known risk factor for OSSN, and the other 2 cases refused HIV testing and further treatment. Of the 21 cases, there were 17 men and 4 women with a mean age of 45 years (range, 23–80 years) at presentation. The mean age in HIV-positive patients was 36 years (range, 31–40 years; median, 36 years, 4 men to 2 women) and in HIV-negative patients it was 52 years (range, 23–80 years; median, 54 years; 13 men to 2 women).

The duration of symptoms before the patients presented to the eye hospital ranged from 3 days to 1 year, with the duration ranging from 1 to 4 months in HIV-positive patients. All cases had involvement of the exposed ocular surface, of which 15 cases involved the ocular surface temporal to the cornea while six cases had involvement of the surface nasal to the cornea. Six cases were included in group 1 based on tumor size and 15 cases in group 2. All the HIV-positive cases were in group 2 representing tumors greater than 8 mm at presentation.

Of the 21 cases who underwent HIV testing, 6 (29%) were positive. Histopathology reports of 20 cases were available (1 case was treated with only mitomycin C as the patient refused any surgery). Nine cases had well differentiated SCC, 5 cases moderately differentiated SCC, 1 case had basi-squamous SCC, and 5 cases had conjunctival intraepithelial neoplasia. All HIV-positive patients had well-differentiated SCC.

None of the patients had undergone previous HIV testing elsewhere before they presented to our eye hospital; thus, the detection of OSSN and the subsequent serology test led to the initial HIV diagnosis. All patients underwent detailed physical examination, and 2 patients were detected to have pulmonary tuberculosis though they denied having any symptoms. CD4 counts were evaluated in all patients, and the mean CD4 count was 133 cells per mm^3 (range, 54–179 cells per mm^3). All patients underwent a detailed ocular examination, and none had any other ocular pathology such as dry eye or any posterior segment changes.

DISCUSSION

The epidemiology of OSSN is changing,[15] with recent reports from Africa suggesting it is an aggressive tumor affecting a younger population. In our study, 29% of patients with OSSN were HIV positive, and OSSN was the only detectable manifestation of an HIV-related condition in these patients. In Africa, the incidence seems to be higher; the study of Spitzer et al[16] reported that 79% of patients with OSSN were HIV positive. In their study, the patients were tested by ELISA and reconfirmed by ELISA (sensitivity, 99.7%; specificity, 98.5%), which might include some false-positive cases.

In this study, the mean age of presentation of OSSN in HIV patients was 36 years, whereas in HIV-negative individuals it affected the older population with a mean age of 54 years, which is comparable with the African studies.[15]

The CD4 counts in all our patients were below 200 cells per mm^3 with a mean of 133 cells per mm^3, which was indicative of AIDS status, and all patients were started on antiretroviral therapy. The median CD4 count of 111 cells per mm^3 in HIV-positive people at diagnosis of conjunctival tumor reported in a study by Wadell et al[17] correlates with our study.

The exact etiologic role of HIV in OSSN still remains unclear. Important cofactors in HIV-associated OSSN may be UV light–induced DNA damage and HPV infection.[5,14] Sunlight-related mutations of p53—a protein that has a crucial role in tumor suppression and cell cycle control—have been identified with high frequency in HIV-positive patients with OSSN.[18] In India, for reasons of occupation, UV exposure may be high and may be a contributory factor in conjunctival tumor. HPV is associated with a variety of anogenital cancers and seems to be an important contributor to cancer risk in India. The prevalence of HPV infection is high in India and may contribute to the development of OSSN.[3] HIV infection itself is a major risk factor leading to a 10 fold increase in conjunctival tumours in Africa.[5,7,19]

Ocular manifestations occur in 50% to 75% of the patients with HIV infection sometime during the course of the disease. The most common ophthalmic manifestations associated with HIV infection in India have been reported to be HIV retinopathy, cytomegalovirus retinitis (20%), and opportunistic infections.[20–24] Sudharshan et al[25] reported 4 cases of OSSN as part of their study of anterior segment manifestations in HIV. However, to the best of our knowledge, no study has reported the prevalence of HIV in OSSN in India.

The management of OSSN involves excisional biopsy with cryotherapy with antimetabolites and interferon-2B used as adjunctives.[15] Antiretroviral treatment alone was shown to cause tumor regression in a case reported by Holkar et al.[26] Most studies reported a low recurrence rate[15] after excision,

and the conjunctival tumors carry a good prognosis when treated early.

A limitation of our study is the small number of patients, and being a referral hospital we may find more aggressive cases being referred to us.

OSSN may not rank very high in the overall clinical presentation in HIV/AIDS, but with the changing epidemic and improved antiretroviral treatment facilities in India we may find a decline in the opportunistic infections and a tendency toward increased cancers. In conclusion, OSSN may be the first apparent manifestation of HIV, and the ophthalmologist needs to be aware of this association because this warrants a work up for immunosuppression in all patients presenting with OSSN, especially individuals younger than 60 years. Early recognition and treatment of immunosuppression may aid in reducing morbidity and mortality in these patients.

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