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Case Report

Adult Squamous Cell Carcinoma of The Scrotum in HIV Positive Patients in Nigeria

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ABSTRACT

Squamous cell carcinoma of the scrotum (SCCS) is rare, particularly in West Africa. It usually affects males older than 60 years. Although it was the first cancer to be linked to environmental factors, the mechanism of action of these risk factors is still not completely understood. We report on 4 men who presented with SCCS at our centre during a 20-month period. Three patients were relatively younger (mean age 43 years) and tested positive for human immunodeficiency virus (HIV) infection. They had no history of exposure to any known risk factor for SCCS. Thus, it seems that SCCS may occur in younger men who have HIV infection.

Key Words: Squamous cell carcinoma, scrotum, HIV

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INTRODUCTION

Malignant tumors of the scrotum are rare. Squamous cell carcinoma is the commonest malignant disorder of the scrotum. It was the first cancer to be directly linked to a specific occupation[1].

Squamous cell carcinoma of the scrotum (SCCS) is exceptionally rare in blacks. After the first report by Pott, less than 10 cases have been reported in black Americans[2]. Predisposing factors include exposure to chimney soot, industrial dyes (textile workers), poor hygiene, psoralens and ultraviolet radiation[3]. The human papilloma virus (HPV) has also been suggested to be an etiological factor. Buschke-Löwenstein tumor, a precancerous condition of the scrotum, has been associated with HPV subtypes 6 and 11.

To our knowledge the occurrence of SCCS in patients infected with the human immunodeficiency virus (HIV) has not been reported previously. Although a report from Lagos University Teaching Hospital anecdotally described a case of fungating SCCS in an HIV-infected Nigerian, proposing the possible association, in our center SCCS is extremely rare, with an average of one case every 5 years[4-5]. However, in the 2-year period (2006–2007) we encountered four cases in Nigerian men, who are described here.

PATIENTS AND METHODS

Patient 1:

A 39 year old clerk presented with a 9 month history of chronic ulcer involving the left hemiscrotum. There was associated weight loss and painful inguinal swelling. He had no history of exposure to any of the known etiological factors for SCCS. The patient claimed to be happily married, but had a history of multiple sexual partners. Examination revealed a fungating mass of about 5 x 9 x 3 cm involving the left

hemiscrotum. The inguinal lymph nodes were enlarged and fixed. Histopathological examination of a biopsy taken from the scrotal ulcer revealed moderately differentiated non-keratinizing SCC. Chest X-ray was normal. The patient could not afford CT scan for further staging. Serological testing for HIV-1 infection using the Western blot technique was positive.

He was referred to the HIV clinic where further investigations for acquired immunodeficiency syndrome (AIDS) were carried out. CD4+ T–lymphocyte count was 238/µl. Viral load was 822,993 (5.92 log 10) RNA copies per milliliter (RNA cpm) of plasma. Haemoglobin was 10.8 gm/dl and the blood glucose was normal.

Triple antiretroviral therapy (ART) with stavudine, lamivudine and nevirapine was started. The treatment led to an increased CD4+ count of 302/µl and reduced viral load with a 2-log reduction to 3,723 RNA cpm after 4 week.. However, there was no significant improvement in the patient's general condition. Moreover, he developed transfusion dependant anaemia.

The scrotal tumor was examined again after about 2 months and was found to be inoperable due to extensive local invasion of the left testis, pubic bone, perineum and inguinal region. The patient received palliative radiotherapy but his condition gradually deteriorated and he died five months after presentation.

Patient 2:

A 47-year old senior military officer presented with a one year history of a chronic, gradually enlarging ulcer involving the left hemiscrotum. Over the preceding few months there had been multiple episodes of bleeding from the ulcer. There was no history of exposure to any of the recognized etiological factors for SCCS. The patient denied a history of weight loss, diarrhea or any of the known symptoms of AIDS. He was married, but had a history of multiple sexual partners.

Examination revealed an ulcer measuring about 7 x 10 cm with fungating edges involving the left hemiscrotum and extending to the root of the penis and inguinal region. The left inguinal lymph nodes were enlarged.

Abdominal and pelvic CT scan and chest X-ray were normal, but the Hb (done after an episode of major hemorrhage) was 8 gm/dl. Screening for HIV-I was positive and was confirmed by the Western blot method. Histopathology of biopsies from the ulcer edge revealed a well differentiated SCC.

The patient underwent left hemiscrotectomy and left inguinal lymph node dissection within 10 days of presentation. Postoperative recovery was uneventful. Histopathological examination of the lymph nodes was negative for malignant cells. The patient was referred to a hematologist and started ART 2 weeks after surgery. Pre-therapy CD+4 count was 148 cells/µl and viral load was 43,270 cpm. Twenty-eight months postoperatively, the patient was compliant with ART. Currently, he has clinically improved without evidence of tumor recurrence.

Patient 3:

A 55 year old civil servant presented with an 18 month history of right inguinoscrotal swelling. It had started as a pimple on the upper part of the right scrotum, which had ulcerated and continued to increase in size. The lesion bled intermittently. There was associated right pedal edema, weight loss and severe low back pain. The patient had worked as a driver with the Ministry of Transport for about 25 years, where he had occasional physical contact with different petroleum products, especially petrol, engine oil and exhaust soot.

The patient looked ill. Scrotal examination revealed a huge fungating inguinoscrotal mass about 20 x 20 cm, fixed to the underlying structures and perineum, with gross edema of the right lower limb and bilateral matted inguinal lymph nodes. Biopsy of the mass confirmed a diagnosis of a well differentiated

SCC. Serological tests for HIV-I and II were negative.

The tumor was inoperable and the patient was referred for radiotherapy and chemotherapy. However, his condition deteriorated and he eventually died nearly 3 months after presentation.

Patient 4:

A 43year old school teacher and part-time clergyman presented with a nine month history of a right hemiscrotal ulcer that was gradually increasing in size. There were no systemic symptoms. The patient denied a history of multiple sexual partners.

Local examination revealed an 8 x 6 cm ulcer of the right hemiscrotum with everted edges. The right inguinal lymph nodes were palpably enlarged. Biopsy from the ulcer confirmed a well differentiated SCC. Serological testing was positive for HIV-1. Abdominal and pelvic ultrasonography were negative for metastases. The patient was scheduled for surgical excision and referred to the HIV clinic and was then lost for follow up before surgical intervention.

DISCUSSION

SCCS is extremely rare in Nigeria. In an earlier series reported from our center, only 4 cases were seen in 20 years (1979 to 1998). Thus, the incidence was about 1/300,000 new male hospital attendances. All the patients had long-term exposure to known etiological factors for SCCS. None of the patients was younger than 50 years; their mean age was 55.8 years (range 52.2 – 59 years). Two of the patients were tested for HIV and were negative, whereas 2 were not tested. Two patients had surgical excision while 2 were unfit for surgery and were referred to radio- and chemotherapy. All 4 patients died within 2 years.

The present series of 4 patients were seen within only 2 years. The incidence is about 1/55,000 new male hospital attendances at the center. Three of the 4 patients were HIV-positive and they were younger (mean age 43 years). They had no known predisposing factors for SCCS. Two of the lesions were on the left and one on the right. Two were ulcerative and one was fungating. The 4th patient (HIV negative) was 55 years old and had a known predisposing factor. The tumor was fungating and was on the right side.

Although the number of cases is very small, it should be noted that the HIV prevalence in our environment is about 4.4% (previously 5.8%)[6]. Therefore, the finding that 3 of 4 of the patients were HIV-positive indicates that HIV infection may contribute to the occurrence of SCCS in younger patients.

Malignancies associated with HIV infection include SCC at different sites, malignant melanoma, lymphoma and Kaposi sarcoma[7]. To our knowledge the association of HIV/AIDS with SCCS has not been previously reported. This is surprising, because 65-91% of AIDS patients present with visible cutaneous or mucosal lesions, while almost 50% develop cancer[8-11].

Although the mechanism of AIDS associated malignancy is not fully understood, most authors believe that depression of the immune system is the major cause[12]. The destruction of CD4-helper cells, which help in activating natural killer (NK) cells, may be the main factor. NK cells are known for their capability to destroy tumor cells. Impairing function of the NK cells invariably leads to impaired resistance to tumor growth and spread. Brunner et al[3] documented the association of scrotal cancer with HPV type 18. HIV infection may be associated with HPV related anogenital neoplasms. The risk of all HPV-associated cancers and in situ precursor lesions in both men and women is increased with all HIV exposure categories[13].

HPV-associated oncogenesis results from up-regulated expression of viral encoded transforming proteins from HPV16 and 18, particularly E6 and E7[13-14]. E6 appears to bind cellular tumor suppressor protein p53 leading to its rapid degradation, which results in chromosome instability, DNA mutations

and aneuploidy, while E7 phosphorylates the PRB retinoblastoma protein leading to the release of transcription factor E2f that activates mitosis[10]. These events result in up-regulated cell cycle progression, deficient DNA repair and eventually malignant transformation[13-14]. HIV infection may predispose affected patients to rapid development of SCC from the pre- existing lesions[13-14].

Unlike the three HIV-positive patients described here, SCCS is most frequent in the 6th and 7th decades. Most patients have had long-term exposure to risk factors and there is usually a latent period of 10 to 25 years before cancer develops. Apart from their age and lack of exposure to known predisposing factors, the clinical presentation in the three patients described here was consistent with the literature on SCCS. All presented 8-12 months after the onset of symptoms. The tumors started as nodular lesions which later ulcerated.

Only one patient underwent surgical excision. He was treated with hemiscrotectomy, ipsilateral inguinal lymphadenectomy (lymph node negative for malignant cells) and ART and 2 years post-treatment the patient had no evidence of local recurrence. It will be useful to know the actual incidence and characteristics of SCCS in HIV-positive patients and, conversely, the incidence of HIV in SCCS patients. More information may be available in future if physicians managing HIV-positive patients have a high index of suspicion and carefully examine the scrotum of their patients.

In conclusion, SCCS is rare condition that occurs in older males. In association with HIV infection; it seems to be more common in younger men.

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Editorial Comment:

Acquired immunodeficiency disease (AIDS) is known to be associated with a significantly high rate of genitourinary neoplasm, possibly due to the destruction of cellular immunity, oncogenic DNA viruses and production of HIV-1 protein Tat. The authors reported an increased incidence of scrotal squamous cell carcinoma (SCC) in AIDS patients occurring at a younger age, although none of the three patients reported had been exposed to any of the known environmental or occupational risk factors that predispose to scrotal SCC. This clue may indicate changes in the biological behavior of that rare oncological entity in AIDS patients. To elucidate this point, it is necessary to look for coincidental infection with human papilloma virus (HPV) in such patients. The possibility of synergism between HIV and HPV in the oncogenesis of scrotal SCC should also be considered. To establish whether there is synchronization between the two viruses, or one precedes the other inducing acceleration of malignant transformation requires further study.

While appropriate staging of scrotal SCC should be done diligently, the authors examined the patients clinically and performed only US and/or CT, which are not very specific and of limited value. We suggest the assessment of the pelvic lymph node status, as it is essential for proper staging and proper treatment, whereas abdominal and pelvic CT and chest X-ray should be done in every case. Moreover, the testes and spermatic cord should be investigated by MRI for tumor invasion. In addition, dynamic scintigraphy may be useful for studying sentinel lymph nodes using Tc99m and patent blue dye.

Finally, adequate information on this oncological entity may become clearer with further experience and larger numbers of patients.

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Authors' Reply:

We do agree with the points raised in the editorial. The major limitations faced in the management of these patients (who were entirely responsible for the cost of their health care); included poverty and very late presentation, except in patient number 2, the senior military officer. As a result, some investigations had to be excluded. We have no other response.

Dr. Habeeb Tijani