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CASE REPORT

Invasive conjunctival squamous cell carcinoma as a primary manifestation of AIDS: a case report

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Worldwide, the Acquired Immune Deficiency Syndrome (AIDS) pandemic has affected nearly 40 million people and in 2004 alone more than 3 million died from the disease.[1] Sub-Saharan Africa has the highest incidence of HIV/AIDS in the world and South Africa specifically has the worst and fastest growing HIV/AIDS infection rate.[2] By the end of 2003, 4.7 million South Africans were living with HIV infection and by 2004 AIDS was the leading cause of death in this country.[3] Half of all affected adults become infected before 25 years of age and more than 20% of adults living with HIV/AIDS are between 15 and 49 years of age.[4]

Ophthalmic manifestations are common in HIV and occur in approximately 75% of all HIV patients during the course of their disease.[5] A comparison of ophthalmic manifestations between developed and developing countries show that while HIV microvasculopathy, cytomegalovirus (CMV) retinitis and Kaposi's sarcoma are common in the former group, Herpes Zoster Ophthalmicus (HZO), HIV microvasculopathy, and conjunctival neoplasia are the commonest manifestations in the latter group.[6,7] CMV retinitis appears to be uncommon in Africa, not because of a lower incidence, but due to the shorter survival times of patients in these regions once they develop the condition, that is AIDS (the mean survival time of AIDS patients in Africa who are not on any antiretroviral treatment is 22 days after the diagnosis of CMV retinitis).[8] Orbital manifestations of HIV infection are not seen very often and secondary squamous cell carcinoma of the orbit arising from conjunctival primary is uncommon in Western countries.[9] This paper reports conjunctival squamous cell carcinoma (CSCC) with orbital invasion as the presenting feature of underlying HIV infection.

In November 2004, a 48-year-old male was referred by a local optometrist for "chronic conjunctivitis" to the ophthalmology department of a local Gauteng hospital. At referral he complained of gradual visual deterioration in the right eye over the preceding four months and associated moderate pain, discomfort and epiphora. Systemic symptoms included weight loss, night sweats and general fatigue and lethargy over the last month. Previous ocular, medical and family history was unremarkable. He denied taking any medication or having any allergies to the same. Blood pressure was measured 110/80 mmHg in the right arm while seated and the patient was orientated to person, place and time. He was currently unemployed and previously worked as an office clerk.

On examination the patient was a mentally alert middle-aged male, unstressed, with best-corrected visual acuities of hand movements (right) and 6/6 (left). There was no improvement in acuity with pinhole testing in the right eye. Inspection of adnexae showed right- sided fullness over the orbital rim, boggy upper and lower eyelid oedema, normal skin colour, 3 mm of ptosis and no proptosis. Palpation of the orbital rim and soft orbital tissue revealed

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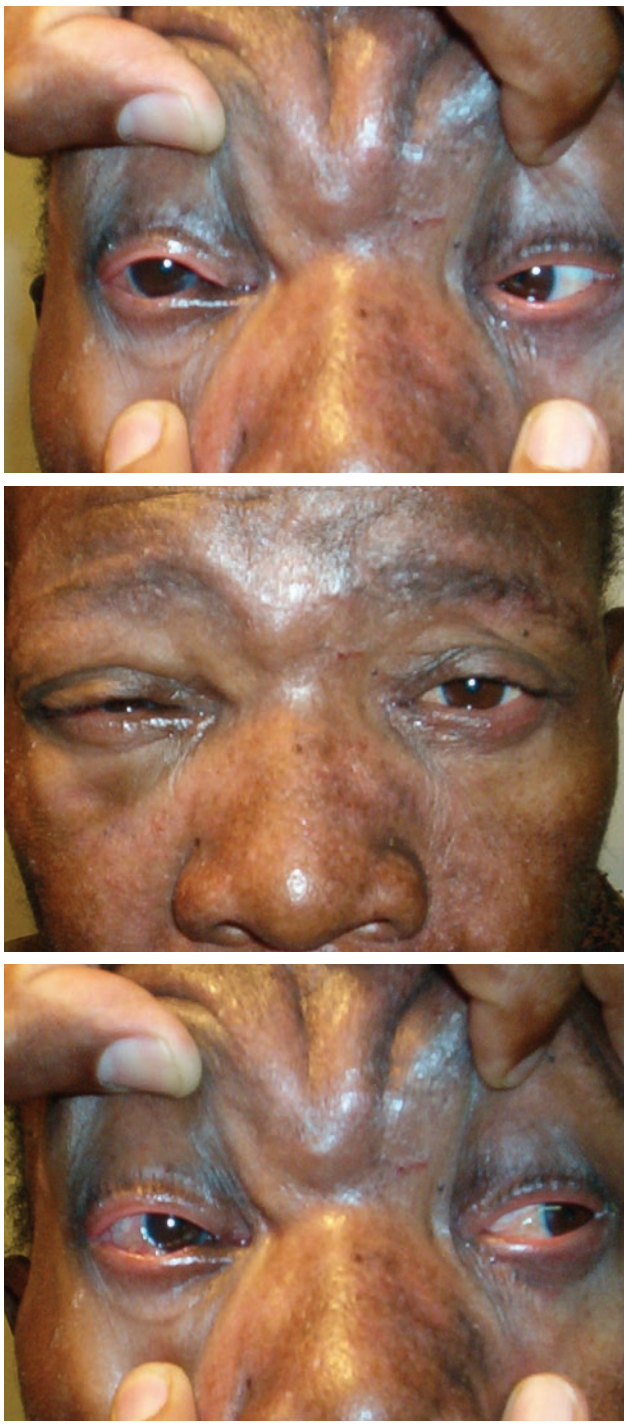


Figure 1. Patient in primary gaze position (middle picture), looking to right and to left

no obvious masses. There was no resistance to retropulsion. On primary gaze the right eye was adducted and there was moderate restriction in elevation and marked restriction in abduction and depression (Figure 1). Confrontation visual fields demonstrated total field loss in the right eye with an apparently normal field in the left.

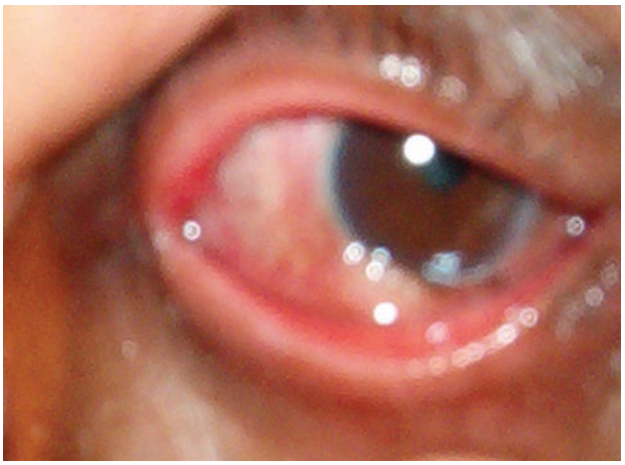
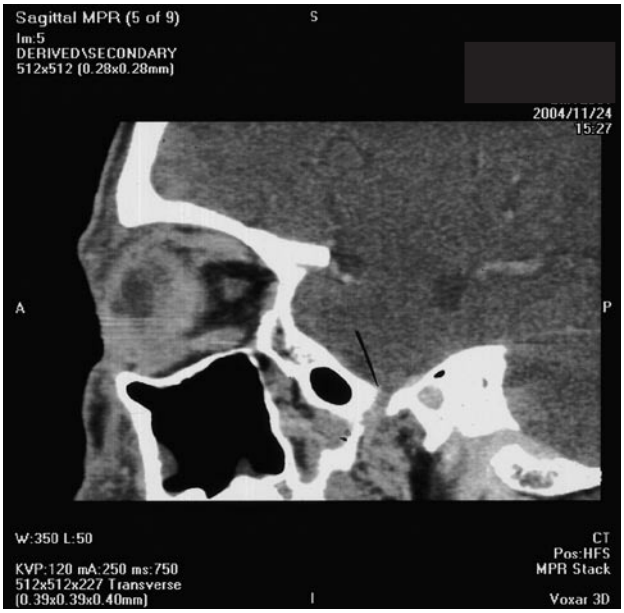


Figure 2. Subconjunctival mass right inferior fornix extending to limbus

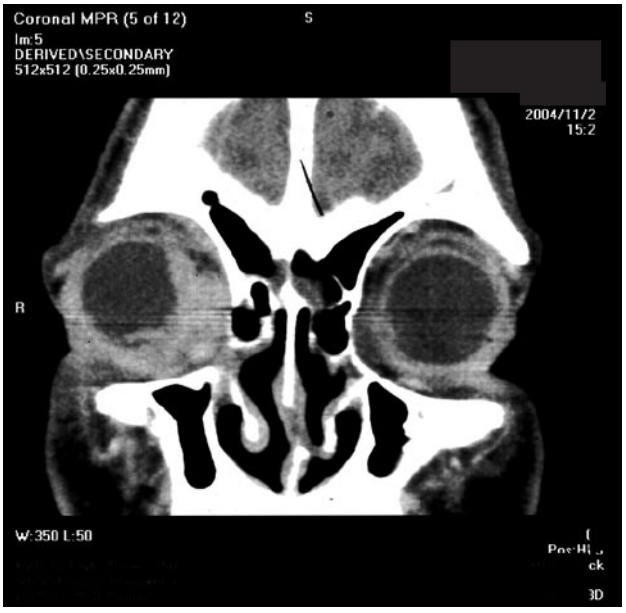
Anterior segment evaluation of the right eye by slit lamp examination revealed bulbar conjunctival and scleral blood vessels that were dilated and tortuous and difficult to adequately visualize, especially nasally. In the lower conjunctival fornix there was a yellowish-white gelatinous mass (5 mm X 5 mm) that extended onto the bulbar conjunctiva up to the lower limbus temporally and nasally (Figure 2). The lower fornix was tender, congested and hyperemic. The medial canthal angle in the right eye was narrow with extended apposition between upper and lower lids. Both corneas were clear with intact sensitivity, irises were brown OU, anterior chamber appeared clear without cells or flare and anterior chamber angle estimates were Grade 4 by Van Herick.

Pupils were regular, round and reactive to light, with no afferent pupillary defect for either eye. Applanation tonometry at 12pm was 16 mmHg (right) and 12 mmHg (left). A dilated fundus examination (by slit lamp with 78D lens and by binocular indirect ophthalmoscopy) revealed a few peripheral cortical opacities of the lens in the right eye, with clear central media of the lenses in both eyes. Fundus assessment revealed well-perfused optic nerve heads with cup to disc ratios of 0.5H/0.5V in the right eye and 0.4H/0.4V in the left. The peripheral nasal fundus of the right eye showed several choroidal folds and no abnormalities were noted in the macular areas of both fundi.

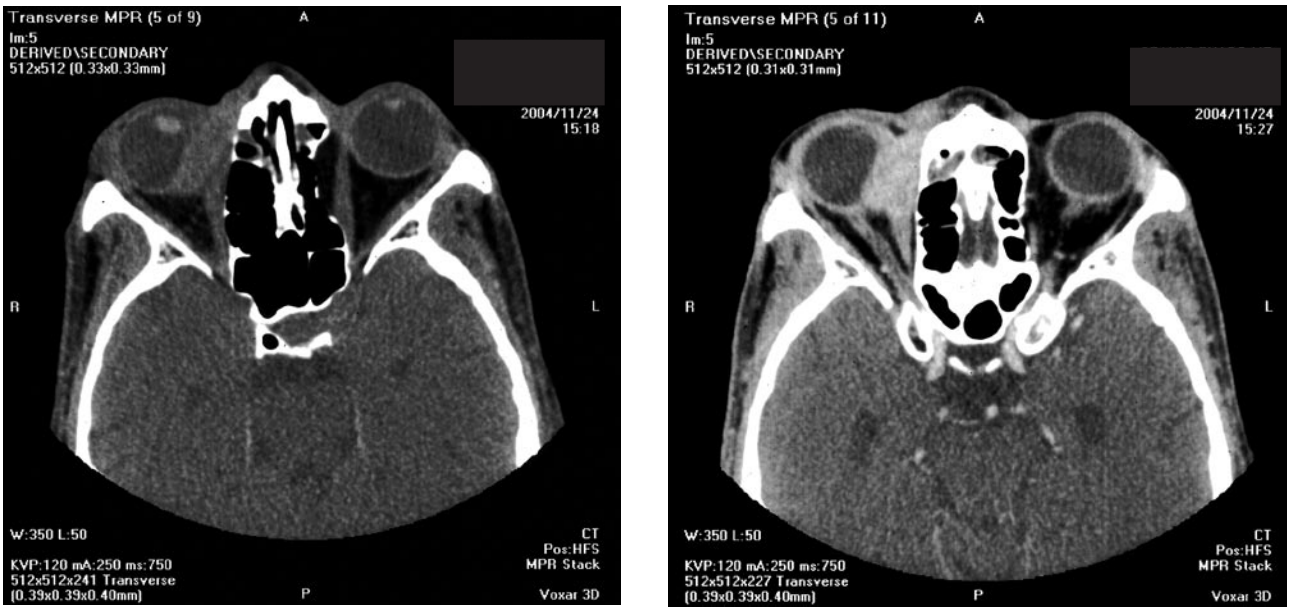
The remaining results of physical examination showed evidence of marked weight loss, "blue-



3A. Sagital view of right orbit shows dense mass located inferior to globe



3B. Coronal view shows large scleral enhancing mass in right medial orbit with extension into medial rectus muscle



3C. Pre (left) and post contrast (right) axial views showing right medial scleral enhancing mass with extension into globe and medial rectus muscle

Figure 3. Computed tomography scans of eyeball and orbits

black fingernails", pallor of the mucous membranes, mild hypertrichosis but no oral candidiasis. Head and neck examination showed no cervical or regional lymphadenopathy but there was shotty axillary and inguinal lymphadenopathy and questionable hepatomegaly. There was no evidence of pulmonary infection from sputum samples and chest radiographs appeared normal.

At this stage the differential diagnosis included right anterior scleritis, a medial rectus tumour, orbital lymphoma, orbital pseudotumour, conjunctival lymphoma and squamous conjunctival carcinoma. Results of haemotological investigations showed a leucopenia, (leukocyte count of 3.91 x 109 /l, reference range 4-10), anemia (haemoglobin value of 9.8 g/dl (14.3-18/3), an elevated erythrocyte sedimentation rate of 40 mm in 1 hour (0-10), normal platelet count and

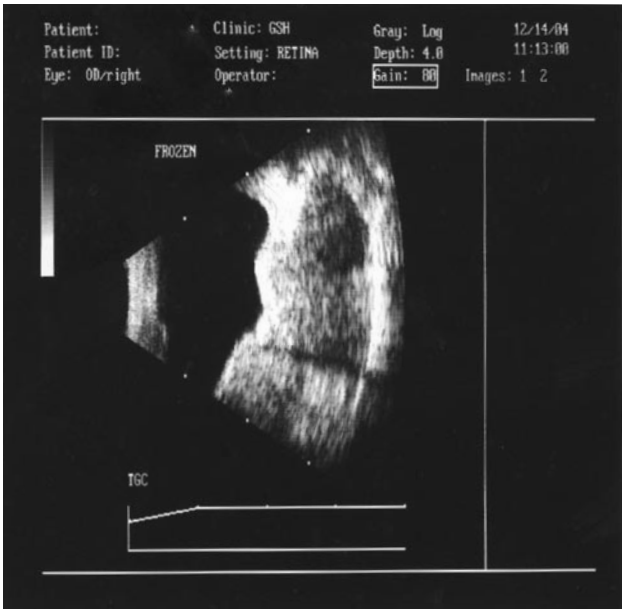


Figure 4. B-Scan showing mass in nasal orbit

morphology. Serum ACE levels were normal and autoantibody screen and syphilis serology were negative. Thyroid function tests were within normal limits. In view of the history and clinical findings of the physical examination, the patient was counseled and consented to HIV testing. HIV serology, that is, HIV antibodies (ELISA), and HIV confirmatory test were positive. The lymphocyte subset showed a T helper cell count (CD4) of 19 cells x 106/l (normal 700-1100 x 106).

Initial radiographs of the skull, orbits and sinuses were unremarkable. A computed tomographic scan of the brain, orbits, sinuses, eyeballs and adnexae (pre and post contrast) revealed a right medial scleral enhancing mass with extension into globe and medial rectus muscle (Figure 3). No gas collections were seen within the mass. The other extraocular muscles and optic nerve were not involved. The gaze of the eye was directed medially and there was no associated proptosis. The brain showed generalised involutional changes causing prominence of ventricles, cisterns and sulci. There was no evidence of any focal lesions, raised intracranial pressure, midline shift, bleeding or abnormal calcification. At this stage, a strong suspicion of orbital lymphoma or aggressive conjunctival squamous cell carcinoma was considered and B-scan ultrasonography was done to rule out any intraocular extension. The B-scan showed an extensive mass located in the right nasal orbit with no intraocular extension (Figure 4).

An excisional biopsy of the subconjunctival mass was performed for histological analysis. Macroscopically the mass measured 5 X 2 X 2 mm and was processed in its entirety. Microscopic section showed full thickness severe dysplasia, cytologically atypical poorly differentiated tumour cells with squamous cell carcinoma. A total exenteration of the right orbit was performed after appropriate counseling. The patient was referred to physicians for assessment and initiation of antiretroviral treatment.

Discussion

Squamous cell carcinoma of the conjunctiva is a malignant epithelial neoplasm characterized by basement membrane invasion to involve subepithelial tissue or distant metastasis.[10] Pathophysiologically it arises from limbal stem cells and presents as a mass in the interpalpebral fissure at the nasal or temporal limbus. Lesions that involve the basal one third of the conjunctiva are classified as mild, those involving the inner two-thirds are classified as moderate, and lesions that are full thickness are termed severe dysplasia.[11] Classically, CSCC has been described as a slow-growing, well-differentiated tumour of low-grade malignancy with little potential for local invasion and metastasis.[9, 12]

Aetiology

The precise aetiology of CSCC is unknown, however, it is believed that the abnormal maturation of conjunctival epithelium results from a combination of factors such as ultraviolet light exposure, human papilloma virus infection and infection with the human immunodeficiency virus.[11, 13, 14] The pathogenesis of CSCC in AIDS patients is not clear and two different hypotheses currently exist. Firstly it is suggested that immunosuppression results in reduced effectiveness of the immune surveillance system to suppress tumour growth. Secondly, immunosuppression by HIV may enable coinfection with the human

papilloma virus, which is a known causative agent for CSCC.[15] The association of HIV with other conjunctival malignancies, such as non-Hodgkin's lymphoma and Kaposi's sarcoma has been well documented.[13 - 16]

Epidemiology

Data regarding the incidence and prevalence of CSCC or ocular surface squamous neoplasia vary dramatically with regard to geographical area, race, age, and association with HIV/AIDS, especially between developed and developing countries. The trend in developed countries is that CSCC is a rare finding with a reported incidence of 0.13 to 1.9 per 100 000 people.The lesion occurs in sun damaged ocular surfaces, with a reported male preponderance of 56% to 97% and typically affects the elderly (mean age at time of presentation has been reported to be 56 years).[14] In these countries, the lesions are usually not aggressive, carry a reasonably good prognosis since most are detected early and surgically excised before metastasis occurs.[16 - 20] In the United States, it has a reported incidence of 0.13 per 100 000 persons per year with a five fold higher rate among elderly (older than 60 years) white males.[21] In a ten year incidence study in Australia, the incidence rate was estimated at 1.9/100 000 population. No significant increase in the number of cases per year was observed over the ten-year period.[22] However, the rate was much lower than for squamous cell carcinoma of the skin (600/100 000). Although incidence and prevalence data from developing countries are scarce, studies from these areas show a different epidemiological picture for CSCC. In developing countries a definite association has been documented between HIV and CSCC.[23, 24] Studies from Africa show that over the last ten years there has been an alarming increase in the number of conjunctival lesions diagnosed as CSCC. A recent study in Uganda demonstrated a 10 fold increased risk of conjunctival carcinoma in HIV infected individuals.[25] Prior to the AIDS epidemic, studies within the same country reported an average incidence of 0.13/100 000.[26] Recently, a hospital based Zimbabwean study reported a CSCC rate of 2/100 patients examined.[27] In Malawi, one study showed a 10-fold increase in the number of conjunctival tumours removed there between 1989 and 2002. The number of exenterations for CSCC has also increased significantly over the same time period.[23] Furthermore, it has been noted that the general impression of these lesions in HIV infected individuals is that they occur in young persons and behave in an unusually aggressive manner with frequent metastasis into eyeball, eyelids and orbit.[25, 27 - 30]

Very little data exists on the epidemiology of CSCC in South Africa. Although no incidence or prevalence data is available, a recent hospital based study in Kwa-Zulu Natal demonstrated similar findings to other African countries, that is, CSCC occurs commonly in HIV positive patients, in a predominantly younger age group and in a more aggressive manner.[31] There is strong evidence to suggest that both the spectrum of ocular complications of HIV/AIDS as well as their prevalence differ substantially between developing and industrialized countries.[8, 32] These variations are most likely as a result of differences in socioeconomic conditions, availability of basic health care, access to antiretroviral treatment and differences in endemnicity of other opportunistic disease present before the HIV epidemic.[32, 33] They may also signify a need for greater emphasis on patient education and counseling in developing countries on common ocular manifestations of HIV/AIDS and the consequences of neglecting such lesions.

Clinical presentation and differential diagnosis

Most patients with CSCC complain of a growth on the eye that is progressively increasing in size. Symptoms may vary from a mild foreign body sensation, to a red painful eye.[27] However, presenting symptoms will correlate with the extent of ocular or orbital penetration. If intra ocular extension occurs, patients can complain of reduced vision. If orbital involvement occurs, as is the case reported here, diplopia can be a presenting complaint because of extraocular muscle involvement. Most CSCC lesions present as slightly elevated lesions situated at the limbus with well-defined or ill-

defined borders.[13, 15] They commonly straddle the nasal limbus between the palpebral fissure, but can occur temporally. They may, however, be restricted solely to the conjunctiva or less frequently the cornea.[10, 11] The lesion is usually more than 2 mm in vertical height and may contain areas of necrosis.[15] At the base of the lesion there are commonly feeder blood vessels, and, depending on the vascularity of the tumour, the lesion may appear pearly gray to reddish gray. Macroscopically the lesion is described as being one of three types: leukoplakic, gelatinous, or papilliform, of which the gelatinous is the most common.[11, 14] In this patient, the lesion was a gray yellow gelatinous mass located in the inferior limbus extending to the fornix with orbital extension (as demonstrated by CT scans and ultrasound B scan).The extension into the orbit could in part be attributed to the aggressive nature of CSCC described in HIV/AIDS patients or simply represent a case of longstanding neglect with delay in seeking appropriate care.

The differential diagnosis of CSCC includes unilateral chronic conjunctivitis, pterygium, pinguecula, atypical conjunctival papilloma, nevus, pyogenic granuloma, dermoid, pannus, vitamin A deficiency, benign intraepithelial dyskeratosis, keratocanthoma, malignant melanoma (especially in patients with racial melanosis), conjunctival Kaposi's sarcoma and conjunctival lymphoma.[10, 11, 13 - 15]

The morbidity from CSCC relates to the ocular side effects of the disease and its treatment, as well as regional orbital sequelae, periorbital spread, periorbital sinus involvement, and intracranial involvement. If treatment is delayed, the tumour can metastasize or invade the brain by direct extension.[9, 11, 29]

The management of CSCC includes local resection with topical chemotherapy, cryotherapy or irradiation.[34] Enucleation is indicated in cases of intraocular invasion and for advanced cases with orbital involvement, exenteration is the procedure of choice.[13, 17 - 19]

Conclusion

The severe effect of the HIV epidemic in sub-Saharan Africa has been demonstrated not only by the rising number of HIV patients, but also by a dramatic increase in the incidence of both CSCC and other AIDS related malignancies.[23, 29] Optometrists are commonly the first health professionals to be approached by patients for common eye conditions such as pterygia, pinguecula and other causes of red eye. It is important for optometrists to recognise the different ocular manifestations of HIV/AIDS and appreciate that patients in this country may not typically present with features commonly found in more industrialized nations. Finally, a high index of suspicion is required for atypical presentations of commonly encountered conjunctival lesions, since early recognition could identify underlying immunosuppression and with early referral, reduce associated morbidity and mortality.

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