HIV-associated malignancies

HIV-associated malignancies have become increasingly important with the spread of HIV infection.

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The biggest challenge facing the majority of clinicians in South Africa today is the explosive HIV epidemic. Just over 5 million South Africans were HIV positive in 2004, which constitutes 11% of the population.[1] Among antenatal attendees the figure was a shocking 29.5%.[2] During that same year 44% of all deaths in the country were attributable to AIDS, and in the 15 - 49-year age group the figure was 70%.[1] The French 'Mortalité 2000' study looked at causes of death among HIV-infected patients on antiretrovirals in 2000 and found 28% to be due to malignancy. AIDS-defining malignancies accounted for 55% of this total, with a median age of 43 years at death.[3]

Sitas *et al.*[4] performed an epidemiological study in Johannesburg in 2000 where they saw an increased risk for the development of Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and vulva and cervix carcinoma among HIV-infected patients. However, they found the relative risks of developing these malignancies to be considerably lower than in the West.[4] At Groote Schuur Hospital we have experienced a yearly increase in the number of AIDS-related lymphomas since we started testing in 2003. In 2006 more than 30% of all new lymphomas seen at our clinic were HIV positive. KS has become the commonest malignancy among men in Uganda and Zimbabwe and the second commonest after cervix cancer among women in Uganda.[5,6] Unfortunately the lack of a cancer registry in South Africa means that we have no idea of the impact of HIV-associated malignancies on our health system.

The World Health Organization clinical staging system denotes KS, aggressive B-cell NHL, primary central nervous system lymphoma and invasive cervical cancer as indicative of stage 4 HIV.[7] Non-AIDS-defining malignancies include Hodgkin's lymphoma, invasive anal carcinoma, squamous carcinoma of the conjunctiva, skin cancers, myeloma, leukaemia and lung cancer.[8,9] These have an increased incidence in HIV-infected individuals but are not necessarily related to the level of immunosuppression.

Immunosuppressed individuals are at an increased risk of developing malignancies compared with the general population. In the HAART era HIV has become a chronic illness due to a reduction in opportunistic infections resulting in longer survival of these patients. A dramatic decrease in the incidence of KS and to a lesser extent of AIDS-related NHL has been seen. However, an increased incidence of non-AIDS-defining malignancies has been noted.[9,10]

AIDS-defining malignancies

Kaposi's sarcoma (Figs 1 - 4)

This is the most common malignancy in HIV-infected patients, occurring 1 000 - 77 000 times more commonly than in the general population. In Europe and North America it is 5 - 10 times more common in homosexual men than in other HIV-infected groups.[8] In Africa it has reached epidemic proportions in men and women alike.[5,6] The rates have declined by 30 - 50% in Europe and the USA since the introduction of HAART.[8] Median survival was 12 - 18 months

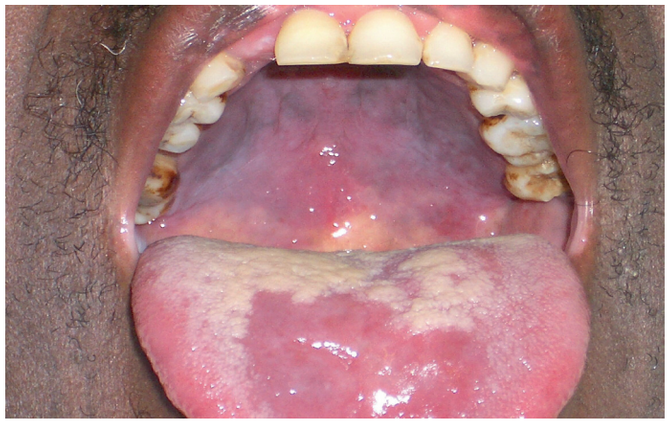

Fig. 1. Oral Kaposi's sarcoma.

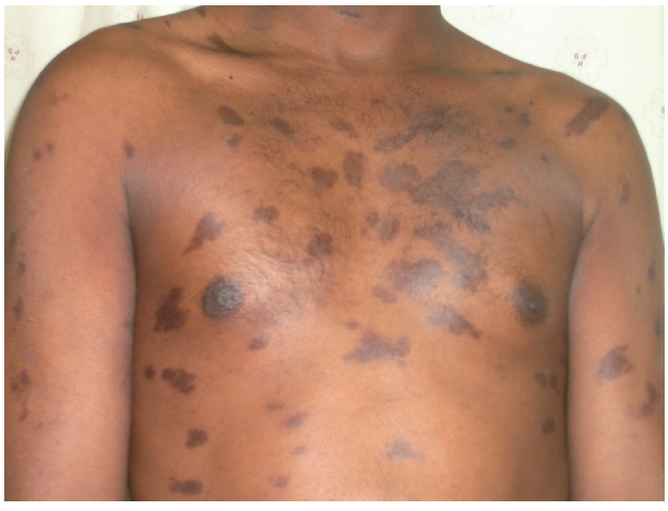

Fig. 2. Cutaneous Kaposi's sarcoma.

Sitas *et al.* performed an epidemiological study in Johannesburg in 2000 where they saw an increased risk for the development of Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and vulva and cervix carcinoma among HIV-infected patients.

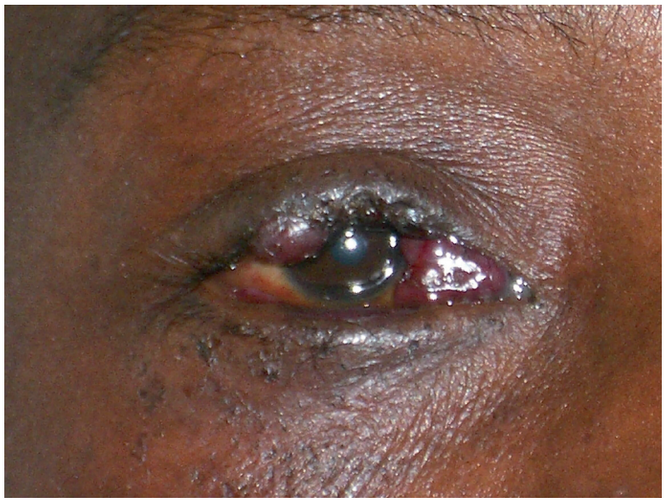

Fig. 3. Kaposi's sarcoma of the eye.

pre-HAART, although deaths were mainly attributable to opportunistic infections. With HAART a 3-year overall survival of 80% has been seen in one series.[10]

Prior to the advent of HIV, KS was an unusual indolent vascular tumour occurring in elderly men of Jewish or Mediterranean ancestry (classic KS). Endemic KS occurs in children in Africa and is most likely due to vertical transmission of the causative organism. Immunosuppressant-related KS is seen in organ transplant patients. HIV-associated KS is aptly termed epidemic KS. The histology of KS is characterised by spindle-shaped cells, neoangiogenesis and an inflammatory infiltrate. KS-associated herpesvirus, also known as human herpesvirus-8 (HHV8), has been found in more than 90% of KS biopsy specimens and is now known to be the main aetiological factor in patients with or without HIV.[5,8]

The clinical spectrum ranges from minimal to extensive disease. It generally involves the skin, most commonly the lower extremities, face and genitalia. Cutaneous KS is usually a purple-red multifocal rash, which in the early stage is papular (patch stage). More advanced disease can be plaque-like (plaque stage), which may develop into ulcerated tumours (nodular stage). It can be associated with significant lymphoedema, particularly in the lower extremities, where the lesions may be confluent and fungating. Extracutaneous KS can involve most organs including the gastrointestinal tract, lungs, lymph nodes, heart, liver, pancreas and testes. In a third of patients lesions involving the mucosa of the oral cavity are seen.[8] During the pre-HAART era AIDS-related KS was staged according to the AIDS Clinical Trials Group (ACTG) classification into good or poor risk according to tumour burden and immune function as measured by CD4 count and the presence of systemic illness. This has been re-evaluated by the ACTG with the advent of HAART and only tumour stage and systemic illness were found to be prognostic. CD4 count is no longer a prognostic factor.[10]

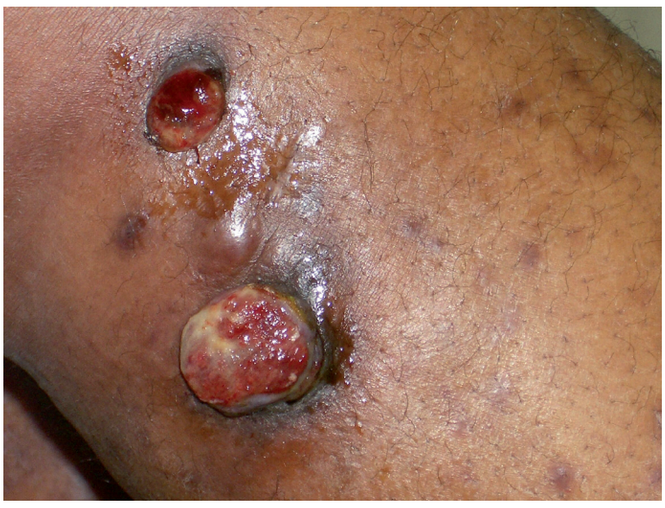

Fig. 4. Ulcerated Kaposi's sarcoma lesions.

Initial management, and often the only treatment required for KS, is HAART. Further treatment is given for symptomatic, systemic or cosmetically unacceptable disease. For localised disease therapeutic options include cryotherapy, intralesional chemotherapy, topical retinoids or, most commonly, radiotherapy. We use a single fraction of 8Gy which can be repeated if necessary. There is a complete remission rate of 50 - 80%, depending on the tumour bulk.[8] Systemic KS is treated with chemotherapy. First-line therapy is liposomal doxorubicin and paclitaxel is second line.[8,10] These are not available in the state sector in South Africa. We use a combination of low-dose adriamycin, bleomycin and vincristine. Response rates are 30 - 50%; however, patients frequently improve symptomatically.

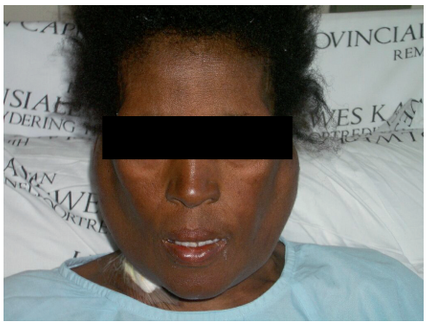

Fig. 5. Non-Hodgkin's lymphoma.

Non-Hodgkin's lymphoma (Fig. 5)

NHL occurs 60 - 200 times more frequently in the HIV-infected population than in the general population.[10,11] Since the introduction of HAART the incidence of AIDS-related lymphomas (ARLs), particularly primary CNS lymphoma, has decreased significantly in Europe and the USA. However, it has increased as an AIDS-defining illness due to a decrease in opportunistic infections and KS.[5,8] Risk factors for the development of NHL include low CD4 count (except Burkitt's where the CD4 count is usually > 200), high viral load, increased age and male gender. ARLs usually present at a more advanced stage with patients having a large tumour burden. It is more frequently associated with B-symptoms and extranodal disease, particularly bone marrow, GIT, liver and leptomeningeal involvement, as well as involvement of unusual sites like the skin or lung. Lymphadenopathy is seen in about one-third of patients.[8,11]

The WHO has subdivided AIDS-related lymphomas (ARLs) into 3 groups:

- Lymphomas also occurring in immuno-competent patients like Burkitt's and diffuse large B-cell (DLBC) lymphomas (90% of ARLs).
- Those occurring more specifically in HIV-infected individuals like primary effusion and plasmablastic lymphoma.

- Those also occurring in other immunodeficiency states such as post-transplant lymphoproliferative disorder.[11]

DLBC lymphoma is the commonest histology, seen in two-thirds of ARLs. Burkitt's comprises 25%, with plasmablastic and primary effusion lymphomas (PEL) occurring less frequently. Epstein Barr virus (EBV) occurs in 80% of DLBC, 30 - 50% of Burkitt's and 100% of primary CNS lymphoma.[11] PEL is associated with both EBV and human herpesvirus 8 (HHV8). It is characterised by malignant effusions without nodal disease and has a very poor prognosis with a median survival of 3 - 6 months despite HAART.[12] Plasmablastic lymphoma is an aggressive lymphoma typically seen in the oral cavity of HIV-infected individuals, but can be found at any site. Median survival was 5.5 months pre-HAART but this appears to have improved with HAART.[12] HHV8 is thought to be the causative factor in the pathogenesis of multicentric Castleman's disease, a lymphoproliferative disorder that behaves very aggressively in HIV-infected individuals.[12]

During the pre-HAART era median survival with ARLs was 5 - 8 months and patients were generally treated with reduced-dose chemotherapy. Currently patients are treated with HAART and standard-dose chemotherapy, which has resulted in response rates approaching those seen in non-HIV-infected individuals.[12] Adverse effects of chemotherapy include neutropenia resulting in opportunistic infections and drug interactions between chemo-agents and antiretrovirals. The anti-CD20 antibody Rituximab has shown promising results after initially being found to result in more deaths due to infections. Stem cell transplant is currently being investigated for relapsed or refractory ARLs.[12]

Primary central nervous system lymphoma (PCNSL) is an extranodal presentation of DLBC lymphoma confined to the craniospinal area. This constitutes 30% of all DLBC lymphoma occurring in this population.[11] It is diagnosed by imaging but can be confused with cerebral toxoplasmosis, therefore a histological diagnosis or demonstration of lymphomatous cells in the CSF is essential.[8,11] EBV DNA is detectable in the CSF of nearly all patients in contrast to non-HIV PCNSL.[12] It is associated with a very low CD4 count (< 50) and carries a very poor prognosis. Management is mainly palliative, consisting of intrathecal chemotherapy and whole-brain radiotherapy. However, with HAART, patients are being successfully treated with high-dose methotrexate as in the non-HIV group.[8]

Invasive cervical cancer

Cervical cancer was relatively rare in the USA until 1990 when Maiman *et al.* reported a series of HIV-infected women with invasive cervical cancer. This disease was resistant to therapy and all the patients died, with a mean survival time of 10 months.[13] This prompted the Centres for Disease Control to call it an AIDS-defining illness. In sub-Saharan Africa there is no proof of increased rates of invasive cervical cancer in the HIV-positive population yet.[6] In KwaZulu-Natal during 2003 Moodley *et al.*[14] found that 21% of patients with invasive cervical cancer were HIV positive in contrast to 38.7% of antenatal attendees. A study conducted in the Western Cape from 1998 to 2001 revealed an increased risk of cervical pre-cancer but not of invasive cervical cancer in HIV-positive patients.[15]

Human papillomavirus is the major aetiological factor. It is more prevalent in the HIV-infected population as the risk factors are similar and HIV-induced immunosupression alters the patients' ability to resist the HPV infection.[10] In the KwaZulu-Natal study HIV-positive patients with invasive cervical cancer were younger by 13 years, and had lower BMIs and haemoglobin levels than the HIV-negative group. 21% of the HIV-positive group had CD4 counts < 200.[14] Management should involve regular screening Pap smears. Patients are treated in the same way as HIV-negative patients. If the CD4 count is < 200 patients should be on HAART. The prognosis appears to be worse than in non-infected women.[10] There is ongoing debate whether cervical cancer is an AIDS-defining malignancy as the incidence is not affected by level of immunity or the introduction of HAART. A vaccine against HPV should decrease the risk of HPV-associated malignancies like cervix and anal carcinoma in HIV-positive individuals.[9]

Non-AIDS-defining malignancies

Hodgkin's lymphoma

This is the most common non-AIDS-defining malignancy, occurring 8 times more commonly in the HIV population. It is associated with EBV in 80 - 100% of patients.[11] The occurrence of disease increases with the degree of immunodeficiency. Patients are more likely to present with B-symptoms, advanced stage and extranodal disease, with bone marrow involvement in more than 50%.[8] Management consists of HAART and chemotherapy. Although the prognosis has improved since the advent of HAART it is still worse than in the general population.[12]

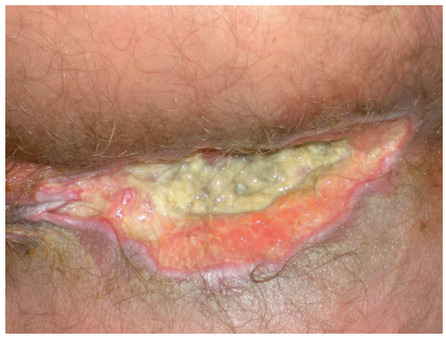

Fig. 6. Anal carcinoma.

Invasive anal carcinoma (Fig. 6)

This is related to HPV infection generally acquired during anal intercourse, although it has been seen in HIV-positive individuals in the absence of receptive anal intercourse. The incidence in HIV-positive homosexual men is twice that in HIV-negative homosexual men. The rates are higher in patients with low CD4 counts.[9] It is managed with chemotherapy and radiotherapy in the same way as the general population. Patients with CD4 counts < 200 experience more treatment-related toxicity and should be on HAART.

Myeloma

The risk of multiple myeloma is 4.5 times higher than in the general population. Patients are generally younger (< 40) and have atypical disease compared with the general population. Optimal management is unknown as this is an extremely aggressive disease with patients dying within weeks to months of diagnosis from the disease itself or treatment-related toxicity.[8]

Lung cancer

A recent epidemiological study demonstrated an increased incidence of lung cancer in this population. The disease is different compared with the general population. The median age at diagnosis is lower and the commonest histology is adenocarcinoma. Incidence is not related to the level of immunosupression and smoking is the main aetiological factor.[16] Diagnosis may be delayed due to the signs and symptoms being similar to opportunistic infections. Patients generally present with advanced disease (55% with metastases at diagnosis). Management includes controlling the HIV infection and using the same

Non-AIDS-defining malignancies include Hodgkin's lymphoma, invasive anal carcinoma, squamous carcinoma of the conjunctiva, skin cancers, myeloma, leukaemia and lung cancer.

therapeutic strategies as for the general population. The prognosis is very poor, with a median survival of 6 months.[16]

Other non-AIDS-defining cancers

Skin cancers like squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) have an increased incidence in the HIV-positive population. BCC is generally multicentric, superficial and occurs on the trunk. SCC usually occurs in the head and neck area and behaves much more aggressively than in the general population. Risk factors, as in HIV-negative individuals, include sun exposure, family history and fair skin with blue eyes. [9]

SCC of the conjunctiva is a unique AIDS-associated neoplasm seen in sub-Saharan Africa.[6] The combination of chronic HIV and hepatitis B virus infection occurs often and results in increased rates of hepatocellular carcinoma.[9] An increased incidence of acute myelogenous leukaemia has been described in association with HIV. Leiomyomas and leiomyosarcomas occur with increased frequency in children with AIDS.[9]

Conclusion

Young patients who have aggressive tumours with unusual features should be tested for HIV. In South Africa ARVs are initiated once the CD4 count is below 200 in the absence of other AIDS-defining illnesses, in other words only once patients have stage 4 HIV. In developed countries ARVs are initiated when the CD4 count drops below 350 and this has been shown to prolong survival. Increased voluntary testing and earlier initiation of ARVs should decrease the incidence of KS and ARLs. Effective screening and early treatment of HPV-associated malignancies as well as use of an HPV vaccine could reduce the rates of invasive cervix and anal carcinomas. Avoiding causative agents like smoking or excessive sun exposure is also important to prevent non-AIDS-defining cancers.[9]

With HAART the oncologist's goal in treating HIV patients has changed from a palliative to a curative intent. In South Africa today we still require an extensive palliative care network for these patients.

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In a nutshell

- The AIDS-defining malignancies are Kaposi's sarcoma, aggressive B-cell lymphoma, primary CNS lymphoma and cervix carcinoma.
- Non-AIDS-defining malignancies like Hodgkin's lymphoma and anal carcinoma occur more frequently in the HIV-positive population but are not necessarily related to the level of immune suppression.
- Kaposi's sarcoma is a vascular tumour caused by human herpesvirus 8 and occurs mainly in the skin and mucous membranes but can involve any organ.
- Management of Kaposi's sarcoma starts with HAART and, if clinically indicated, either local therapy like radiotherapy or systemic chemotherapy.
- AIDS-related lymphomas present at an advanced stage, are usually associated with B-symptoms and extranodal disease, and often involve unusual sites.
- The commonest histologies are diffuse large B-cell and Burkitts's lymphoma. Those seen almost exclusively in HIV are plasmablastic and primary effusion lymphoma.
- Primary CNS lymphoma in HIV is associated with a CD4 count < 50, EBV in the tumour and CSF, and a very poor prognosis.
- Cancer in HIV-infected individuals is usually associated with a viral cause, e.g. HPV in cervix and anal carcinoma and EBV and HHV8 in ARLs.
- Patients with unusual and aggressive cancers should be tested for HIV.
- With HAART the incidence of AIDS-defining malignancies has decreased but non-AIDS-defining malignancies are increasing as HIV has become a chronic disease.