An estimated 30 - 40% of HIV-infected patients are likely to develop cancer during the progression of their disease. The occurrence of malignancy among these patients represents a difficult challenge in their care. Kaposi's sarcoma (KS) – currently the most common tumour observed with an estimated incidence of 15 - 20% – represents the first manifestation of AIDS in 30 - 40% of patients. Any organ may be involved, but the gastrointestinal tract and lung remain the most frequently involved locations. The case described here presented a clinical and ethical dilemma where visceral KS, pregnancy and medical complications required multi-disciplinary management.


CASE REPORT
Managing AIDS-related Kaposi’s sarcoma and pregnancy

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An estimated 30 - 40% of HIV-infected patients are likely to develop cancer during the progression of their disease. The occurrence of malignancy among these patients represents a difficult challenge in their care. Kaposi’s sarcoma (KS) – currently the most common tumour observed with an estimated incidence of 15 - 20% – represents the first manifestation of AIDS in 30 - 40% of patients. Any organ may be involved, but the gastrointestinal tract and lung remain the most frequently involved locations. The case described here presented a clinical and ethical dilemma where visceral KS, pregnancy and medical complications required multi-disciplinary management.


A 24-year-old woman was referred to the Division of Oncology at a large academic hospital. She had presented recently at a local hospital with a history of progressive shortness of breath, and had received treatment for atypical, multilobular pneumonia. She was diagnosed with HIV in 2009 when she presented with severe mucocutaneous Kaposi’s sarcoma (KS) as her AIDS-defining disease. She was pregnant at the time of her initial diagnosis, and received 4 cycles of bleomycin/vincristine chemotherapy after delivering a healthy term infant. This was followed by an additional 14 cycles of chemotherapy, which was discontinued when her KS lesions demonstrated a good clinical response.

She returned 6 months later with KS progression and was re-challenged with the ABV regime (doxorubicin, bleomycin and vincristine) for 6 cycles. She reached the tolerance dose of bleomycin, and chemotherapy was discontinued. A large lesion behind her left earlobe was treated with a short course of palliative external beam radiotherapy (EBRT).

In February 2012, KS progression was visible, this time involving the genital area, mouth and lymph nodes. Again, she was challenged with combination chemotherapy containing doxorubicin and vincristine for 4 cycles, with no clinical benefit, and palliative EBRT was offered to problematic lesions of the vulva and left foot.

In June 2012 she was admitted to the high-care unit with a 2-month history of progressive, grade IV dyspnoea, intermittent cough, and bleeding from a palatal KS lesion in her mouth. She was 27 weeks pregnant and had been treated at a local hospital for pneumonia and started on anti-tuberculosis (TB) treatment 2 weeks earlier.

On inspection, the patient was acutely ill with signs of a hyper-dynamic circulation and peripheral oedema. Physical examination revealed bilateral coarse crepitations, wheezes and the use of accessory respiratory muscles. A large, bleeding, nodular KS lesion was observed, involving most of the hard palate and oropharynx. Abnormal laboratory studies revealed reduced haemoglobin (7.8 g/dl), raised C-reactive protein (75.0 mg/l), low albumin (26 g/l), raised fibrinogen (4.4 g/l), raised D-dimer (1.34 mg/l) and raised lactate dehydrogenase (368 U/l) levels and a low CD4 count (137 cells/µl). A standard blood culture was negative. A routine chest X-ray (CXR) revealed bilateral opacities infiltrating predominantly the perihilar peribronchovascular interstitium (these may often be mistaken for opportunistic infections).

Fig. 1. Chest X-ray showing bilateral KS opacities infiltrating predominantly the perihilar peribronchovascular interstitium (these may often be mistaken for opportunistic infections).

According to the AIDS Clinical Trials Group (ACTG) staging system, the patient was classified as a poor-risk stage IV (T1I1S1)
HIV/AIDS patient with a problem list of: (i) HIV-infected since 2009, receiving antiretroviral therapy (ART); (ii) CD4 count of 137 cells/µl; (iii) 2 weeks of anti-TB treatment; (iv) KS since 2009 (for which she received multiple cycles of chemotherapy and palliative EBRT); (v) current presentation of bilateral, multi-lobular infiltrates on a CXR with a high index of suspicion of lung KS involvement; (vi) early signs of early diffuse intravascular coagulation (DIC); and (vii) pregnancy (28 weeks).

Management
A multi-disciplinary team (MDT), comprising a high-care medical team, oncologist, obstetrician and the HIV/infectious diseases personnel, was required for optimal management.

Intravenous antibiotic therapy (clarithromycin), concurrent ART (tenofovir, efavirenz and lamivudine) and anti-TB (rifabutin) supportive treatment were continued, with the addition of trimetroprim-sulfamethoxazole as *Pneumocystis jiroveci* prophylaxis, as the patient’s current CD4 count was <200 cells/µl. Continuous positive airway pressure (CPAP) was required as she became entirely dependent on the support system to maintain breathing. Sub-cutaneous heparin was administered during her hospital stay.

On day two post admission, she reported no fetal activity and an obstetric consult confirmed an intra-uterine death. She went into spontaneous labour and delivered a premature, stillborn microcephalic fetus (weighing 1.380 g).

Her bleeding KS mouth lesion was controlled with adrenaline gauze. Due to her poor performance status, low CD4 count, resistant KS, extent of KS disease and poor prognosis, no active chemotherapy management was offered. She died 3 hours post delivery due to extensive KS and respiratory failure.

Discussion
In sub-Saharan Africa, where many patients access ART with advanced HIV disease, AIDS-related KS presents with a high tumour burden and rapid disease progression, resulting in a life expectancy of <6 months.[11] KS involving the lung presents as shortness of breath, fever, cough, chest pain and haemoptysis, or as an incidental finding on a CXR.[12]

A prognostic index can guide therapeutic options for AIDS-related KS, including: immune status (CD4 count); patient age; AIDS-defining disease on presentation; and the presence of co-morbid conditions. Patients with a favourable prognostic index can be treated initially with ART alone. Systemic chemotherapy is warranted in advanced, systemic or rapid, progressive KS disease. Several chemotherapeutic agents – e.g. bleomycin, vincristine, vinblastine, and an anthracycline (doxorubicin) – have activity in the treatment of KS, but in the developed world, liposomal doxorubicin and a taxane group constitute the backbone of current systemic chemotherapy against KS.[13,14] In all cases, an objective response of 70 - 80% can be obtained with various combinations of chemotherapy. Partial responses and clinical benefit are frequently observed, but relapses often occur when treatment is stopped.[15,16]

Our patient initially received a combination of bleomycin and vincristine, and was re-challenged with the ABV combination when her KS progressed. Unfortunately, treatment with systemic chemotherapy comes at a cost: both bleomycin and doxorubicin have a maximum tolerable dose before long-term complications become evident. In addition, bleomycin may induce alveolitis and pulmonary fibrosis, and there is evidence of accelerated pulmonary dysfunction in lung KS patients who received bleomycin.[17] Doxorubicin is associated with irreversible cardiac damage (congestive heart failure and cardiomyopathy) when the maximum dose of ≥450 mg/m² is exceeded.

The patient described here had reached the maximum tolerable dose of both bleomycin and doxorubicin. She developed progressive KS during the last 4 cycles of doxorubicin-based therapy; therefore, it may be postulated that her KS became resistant to anthracycline chemotherapy. As both liposomal doxorubicin and the taxane drugs are not available in the public healthcare sector, second-line chemotherapy could not be offered.

The incidence of pregnancy-associated malignancy ranges from 0.02 - 0.10%; the most common malignancies diagnosed during pregnancy are gynaecological, haematological and skin cancers (malignant melanoma). Malignancies in pregnancy present the MDT with an ethical conflict between the optimum management of the cancer and preservation of the pregnancy.[17] For most of these cancers, chemotherapy is necessary to achieve a cure or efficient palliation of cancer-related symptoms. The consequence of chemotherapy and/or EBRT during the first trimester is high (congenital malformation or spontaneous abortion), and termination of pregnancy v. delayed treatment should be discussed with the patient. Chemotherapy treatment during the second and third trimesters follows the standard chemotherapy guidelines, but delivery should be timed during a non-neutropaenic period and care should be taken to time the last cycle of treatment at 32 weeks of gestation. However, patients remain at high risk and this warrants careful monitoring.[18,19]

The patient described in this case presented with a 28-week pregnancy, but had received chemotherapy and EBRT during the first trimester when she was unaware of her pregnant status. This resulted in an intra-uterine death and early clinical DIC that concluded in a spontaneous delivery, probably due to maternal hypoxia and the abnormal fetus (microcephaly). Few studies are available concerning in utero chemotherapy-exposed neonates. In one study, the mean gestational age at delivery was 35.8 weeks, the mean birth weight was 2.647 g, and 4% of infants were born with a congenital abnormality.[19,20]

Conclusion
This case highlights the clinical complications and ethical dilemma associated with advanced KS in pregnancy. The MDT plays an important role in securing optimal care for patients with advanced HIV disease, malignancy and associated pregnancy.

Conflict of interest.
None.

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