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# An Actor with Fatal Violaceous Plaques

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**Abstract : We report a case of homosexual Thai AIDS patient who presented with mucocutaneous Kaposi's sarcoma (KS) and developed pulmonary involvement which rapidly progressed to a fatal outcome. Although AIDS-KS has been reported as the most common cancer occurring in HIV-infected patients, it has rarely been reported in Thai patients. The characteristic mucocutaneous lesions, histopathological and bronchoscopic findings are demonstrated. The clinical differentiation and management are discussed.**

***Key words*** : AIDS-KS, Kaposi's sarcoma, Pulmonary KS

**เรื่องย่อ : ผื่นสีม่วงที่อันตรายถึงชีวิต**

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รายงานผู้ป่วยชายรักร่วมเพศหนึ่งรายที่มาพบแพทย์ด้วยโรคเอดส์และ Kaposi's sarcoma (KS) บริเวณผิวหนังและเยื่อบุในช่องปาก ซึ่งลุกลามไปยังระบบทางเดินหายใจจนกระทั่งเป็นสาเหตุการตาย การวินิจฉัยโรคอาศัยลักษณะทางคลินิก ผลการตรวจทางพยาธิวิทยา และ bronchoscopic findings ซึ่งมีลักษณะจำเพาะที่นำเสนอในรายงานผู้ป่วยรายนี้ รวมทั้งการวินิจฉัยแยกโรคและแนวทางการดูแลรักษาที่เหมาะสม

## INTRODUCTION

Kaposi's sarcoma (KS) is a low-grade multicentric cutaneous and extracutaneous malignant vascular tumor which was first described by Moricz Kaposi in 1872. There are 4 distinct clinico-epidemiological subsets classified as classic KS, African-endemic KS, iatrogenic immunosuppressive drug-associated KS and AIDS-associated or epidemic KS.[1] The first, classic KS, is a disease of elderly men of Mediterranean and Jewish descent

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that tends to involve the lower extremities and usually follows an indolent course even when extracutaneous sites are involved. The second, African-endemic KS, is more systemic in nature and affects only Africans particularly from the Sub-Saharan region who have no evidence of an underlying immunodeficiency.[1] It may present as either an indolent or aggressive form. The third, iatrogenic immunosuppressive drug-associated KS, has been reported to develop in 0.5% of organ transplant recipients at an average of 16.5 months after transplantation. This runs a fairly benign course and may resolve entirely when the immunosuppressive drug is stopped or the dose is reduced.[2,3] The fourth, epidemic or AIDS-associated KS (AIDS-KS) is a disease that occurs almost exclusively in homo- or bi-sexual men, and to a lesser extent in women who have a bisexual male partner and, in less than 1% in men with hemophilia.[4] AIDS-KS has been reported as the most common neoplasm occurring in HIV-infected patients and may be a primary and fatal AIDS-defining illness. Here, we report a case of epidemic or AIDS-associated KS and review the literature.

## CASE REPORT

A 37-year-old Thai man presented with progressive dyspnea for over a period of 3 months. He was a homosexual man who had been diagnosed as having asymptomatic HIV infection for 14 years. He got no treatment at that time. A couple of years ago he had oral candidosis and *Pneumocystis carinii* pneumonia (PCP). Since then he had continued to take trimethoprim-sulfamethoxazole for secondary prophylaxis of PCP. At the beginning of the previous year he had completed a course of treatment for pulmonary tuberculosis with sputum positive for AFB. About 6 months prior to this admission he had developed several asymptomatic violaceous cutaneous plaques on his trunk and forearms without clinical evidence of visceral organ involvement. Limited KS was diagnosed based on skin biopsy and cryotherapy was given resulting in local complete resolution of the treated area, but new lesions appeared and progressed in other areas without any intercurrent illness. He had developed progressive dyspnea over the past 3 months which led to this hospitalization. Physical examination revealed several violaceous plaques on the face, extremities and oral mucosa with hoarseness and a puffy face (Figure 1). Histopathologic study revealed diffuse dermal infiltration with incomplete slit-like channels lined by plumped endothelial cells (Figure 2A, 2B). He had mild respiratory distress, was tachypneic with inspiratory and expiratory rhonchi. Chest radiography (CXR) showed bilateral hilar nodes enlargement with diffuse patchy nodular infiltrations (Figure 3). The differential diagnosis of his current pulmonary problems included pulmonary KS, lymphoma or a pulmonary infection such as recurrent pulmonary tuberculosis or fungal infection but PCP was less likely to be the cause since medical prophylaxis had been continued and bilateral hilar adenopathy is infrequently seen in PCP. The diagnosis of pulmonary KS in our patient was confirmed by fiberoptic bronchoscopic visualization of characteristic endobronchial lesions. His $CD_4$ count was 109 cells/mm$^3$ (normal range 470-1,404), $CD_8$ count was 746 cells/mm$^3$ (normal range 360-1250), $CD_4$ / $CD_8$ ratio was 0.15 (normal range 0.65-2.49) about 2 months prior to this admission.

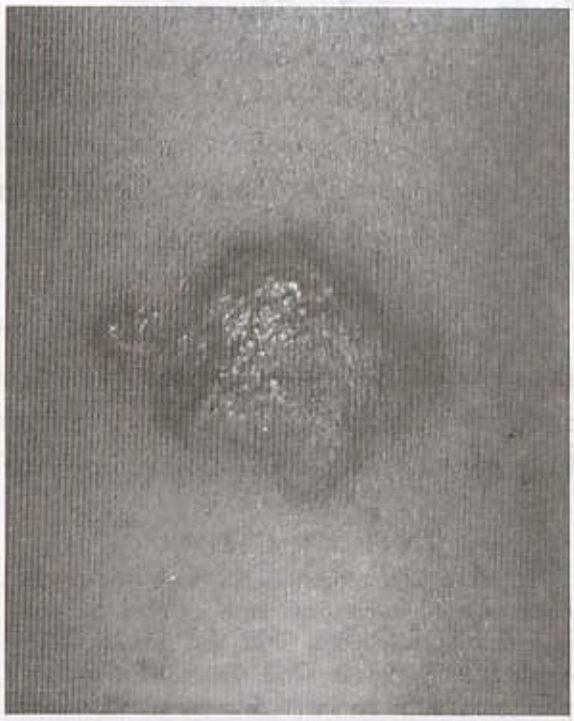

*Figure 1.* A well-defined violaceous plaque at right forearm.

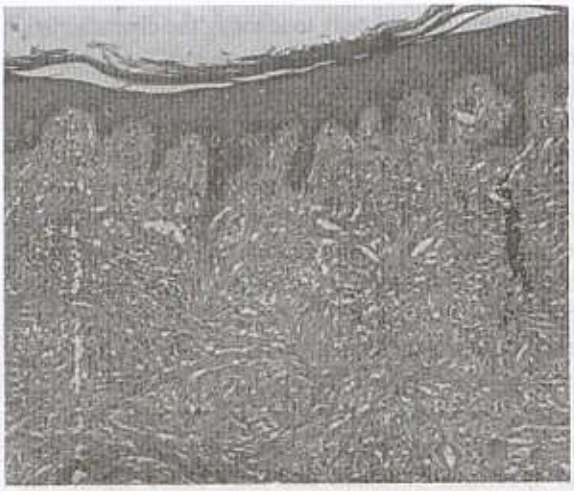

*Figure 2A.* Histopathological findings of skin biopsy from a violaceous plaque at right forearm. (Hematoxylin-Eosin staining, x10)

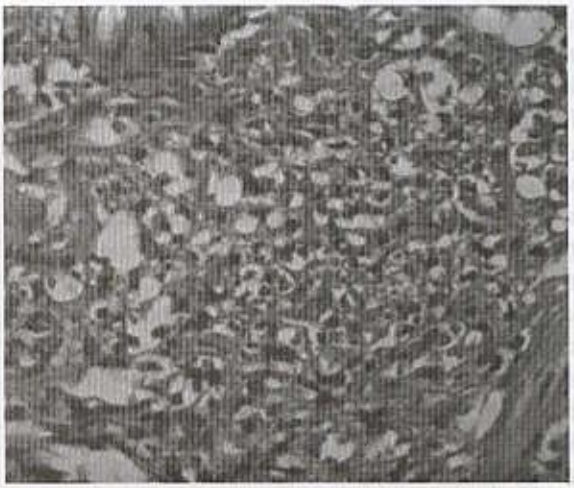

*Figure 2B.* Histopathologic study revealed diffuse dermal infiltration with incomplete slit-like channels lined by plumped endothelial cells. (Hematoxylin-Eosin staining, x40)

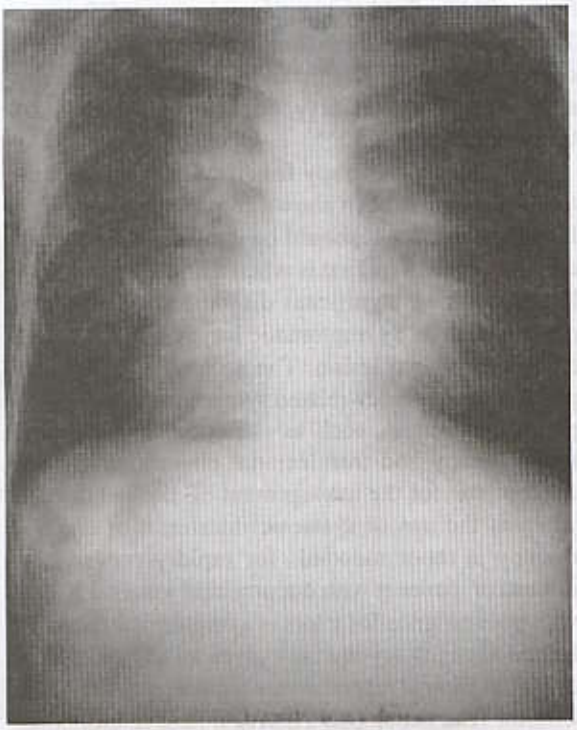

*Figure 3.* Chest radiography showed bilateral hilar nodes enlargement with diffuse patchy nodular infiltration.

## DISCUSSION

AIDS-KS may develop at any point in the course of HIV infection even in the presence of a normal $CD_4$ cell count[1], but 75% of patients in one study had a $CD_4$ count of less than 200 cells/$mm^3$ at the time of diagnosis of KS. The clinical course varies among individual, it may remain quite indolent with only skin and lymph node involvement or rapidly progress to fulminant visceral disease. Patients with AIDS-KS commonly present with characteristic nonpruritic painless mucocutaneous lesions that rarely locally invasive.[1] Confluent lesions may give rise to surrounding lymphedema particularly on the face and extremities. In addition to the mucocutaneous lesions, systemic involvement may be encountered, most commonly in lymph nodes (50-80%), gastrointestinal tract (50-70%), and lungs (20-50%); however, all organ systems including the cardiovascular and nervous systems may be affected.[1]

The histogenesis of KS cells has been the subject of considerable controversy. Current ideas suggest that KS cells are most likely derived from lymphatics and/or follow a lymphatic differentiation. Furthermore, the pathogenesis of KS has not been established and questions still exist as to whether KS

is a reversible proliferative disorder or a true malignancy.[5,6] There are epidemiologic and immunologic data suggesting that it may be caused by an infectious agent other than HIV.[1,7] Beral and colleagues concluded that AIDS-KS was caused by a sexually transmitted organism that is co-transmitted with HIV.[1,4,7] Recent studies have clearly shown that human herpesvirus 8 (HHV 8), designated KS-associated herpesvirus (KSHV) might have an active etiologic role in KS.[5-7] Flamand has shown that KS cell lines do not harbor herpesvirus-like DNA sequences while B cells, CD14 and CD34 cells do, implying that if KS originates from infection with HHV-8, the virus is not necessary for maintenance of the neoplastic state.[8]

Pulmonary KS has been reported in about 1/3 of patients with mucocutaneous KS[9] but only 15% of patients had pulmonary KS in the absence of mucocutaneous involvement.[10] Median $CD_4$ lymphocyte count was usually in the lower range. In one study of 168 patients with pulmonary KS, the median $CD_4$ count was 19 cells/mm$^3$.[10] Pulmonary KS may involve the parenchyma, tracheobronchial tree, pleural tissue and intrathoracic lymph nodes with various manifestations ranging from cough, shortness of breath, dyspnea on exertion, chest pain, hemoptysis, hoarseness, wheezing, and upper airway obstruction to respiratory failure.[9] CXR usually shows some abnormalities except in cases of isolated endobronchial lesion. The CXR findings vary from bilateral, symmetrical nodular or linear opacities that are predominant in perihilar area along bronchovascular bundles, Kerley's B line (interlobular septal thickening), solitary nodule, hilar and mediastinal node enlargement to pleural effusion.[11] High-resolution computerized tomo-graphy (HRCT) of the chest also gives the same findings but is more sensitive.[9] Nevertheless, no radiographic finding is pathognomonic for pulmonary KS. KS lesions usually show increased uptake on a thallium scan but not on a gallium scan. Both of these scans are seldomly used in clinical practice to diagnose pulmonary KS due to their cost and lack of availability.[12]

A diagnosis of mucocutaneous KS is established by biopsy of a suspicious lesion while bronchoscopy with bronchoalveolar lavage is the most appropriate diagnostic tool to diagnose pulmonary KS, not only to identify the characteristic endobronchial lesion of pulmonaryKS but also to rule out other infections which may co-exist.[13] Endobronchial KS has been reported in about 30% of patients with pulmonary KS. It may produce hemoptysis, focal wheeze or endobronchial obstruction. It is usually diagnosed by endoscopic examination, which shows characteristic violaceous or bright red, flat or slightly raised lesions on the bronchial mucosa especially at the carina subdividing segmental orifices.[14] The finding of a characteristic endobronchial lesion is sufficient for diagnosis. Endobronchial biopsy or transbronchial biopsy usually gives a low yield due to a small size of specimen obtained and may cause significant bleeding complications. Biopsy should be reserved for patients with an atypical presentation such as the patient with an endobronchial lesion but no other organ involvement.[14] Recently, there have been a few studies suggesting the use of a polymerase chain reaction (PCR) assay for HHV8 in bronchoalveolar lavage (BAL) fluid to identify pulmonary KS cases. Tam and colleagues demonstrated that HHV8 detection in BAL fluid provided 100% sensitivity and 98.9% specificity for the diagnosis of tracheobronchial KS.[15]

Specific therapy for AIDS-KS is not curative and has not been shown to prolong survival.[1,6] However, treatment should be carried out in 2 main circumstances. The first is when a limited number of lesions causing significant discomfort or cosmetic distress such as a symptomatic laryngeal lesion, or a disfiguring facial lesion. The second is directed at palliation of disease –related symptoms. Local therapeutic modalities, such as radiation, cryotherapy, laser therapy and intralesional chemotherapy are appropriate for the management of limited disease whereas the use of systemic interferon or chemotherapy is recommended for rapidly progressive disease or patients with documented visceral KS or with poor prognostic factors or symptomatic edema.[16] Liquid nitrogen cryotherapy gives an 85% complete or partial clinical response rate according to the AIDS Clinical Trial Group (ACTG), regardless of individual CD4+ cell counts, and lasts up to 6 months in the majority of patients.[16] The use of systemic single agent chemotherapy should be considered in patients

with a large number of lesions. Response rates varying from 40% to 88% for intralesional cytotoxic chemotherapy with etoposide, vinblastine, doxorubicin or interferon-alpha (IFN-α) have been reported.[16] IFN-α is useful in patients with primary mucocutaneous disease or asymptomatic visceral involvement. IFN-α alone or in combination with zidovudine produces a response in approximately 30-70% of patients with AIDS-KS who have good prognostic factors according to the ACTG staging system, especially with a CD4 count of more than 250 cells/mm$^3$.[16] Although systemic combined-chemotherapy provides the best overall response rate for patients with disseminated life-threatening disease, however, many patients are unable to tolerate the toxicity associated with systemic AIDS-KS treatment.[16] Several regimens employing various combinations of doxorubicin, bleomycin, etoposide, and vinca alkaloids give response rates of up to 40-80% depend on the extent of the disease.[1]

The response rates of liposomal daunorubicin trials have been reported ranging from 30% to a peak of 70-90%.[7] Concomitant antiretroviral therapy with chemotherapy significantly lowers the incidence of opportunistic infection. Baseline CD4 cell count is the single most important determinant of response particularly for IFN-α. Our patient developed disseminated mucocutaneous disease with facial lymphedema and symptomatic pulmonary involvement, so systemic chemotherapy and highly active antiretroviral therapy (HAART) was indicated.[7] The subacute onset of progessive dyspnea suggested that infectious diseases should be ruled out.

The prognosis of KS depends on the age of the patient, the underlying AIDS condition, level of CD4 cell count at diagnosis, and the extent and rate of progression of KS.[7] A unique TIS staging system was established by the National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group on the basis of tumor extent(T), immunologic function(I), and presence or absence of systemic symptoms(S)[17]. Lymphadenopathy may be seen very early in the course and has no prognostic significance whereas lung involvement is the most life-threatening condition. According to the ACTG's staging classification for AIDS-KS, our patient had all poor prognostic indicators, which, justified combined systemic chemotherapy which has been reported to induce tumor regression even in patients with poor prognostic indicators.[7] Despite their wide toxicity profile, such combinations are reasonably safe and certainly more effective than vinca alkaloids alone for the palliative management of a patient with advanced KS. Recently, several studies with liposomal encapsulated doxorubicin and daunorubicin, for both AIDS-KS and the classic variants, have shown promising results. Moreover, the introduction of HAART therapy in the management of HIV infection has dramatically decreased the incidence of AIDS-KS which may be attributed to its supportive effect on the immune system which prevents its' occurrence.

In our patient, adjuvant radiation therapy was recommended for symptomatic treatment of localized facial lymphedema. However, the patient died before this was able to be provided. Our patient and his family refused further intervention at the time he progressed to respiratory failure. He died 48 hours after initiation of chemotherapy.

## CONCLUSION

We report a case of AIDS-KS who initially presented with mucocutaneous disease and rapidly developed advanced pulmonary KS that caused death 6 months after disease onset. Early recognition of the mucocutaneous lesion which is the most common clinical presentation of KS and thorough evaluation of staging will provide optimal management for the patient. Although AIDS-KS is incurable, palliative treatment may improve the patient's quality of life.

## COMMENT

This case is an example of HIV infection in a young Thai person. HIV infection is not only a simple infectious disease, but is a disease related to socioeconomic status and human behavior. AIDS-KS is one of the late manifestation of HIV infection in those who have not received HAART therapy in the early period of infection. The treatment modalities available at present can not cure AIDS-KS. A sympathetic explanation of the real situation to the patient and his family could help reduce their distress and anxiety. A good counseling team can help both the patient and his family during this time of distress.

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