Pulmonary Kaposi’s Sarcoma - Initial Presentation of HIV Infection

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Abstract
Kaposi’s sarcoma is the most common malignancy associated with human immunodeficiency virus. It commonly affects the skin but can present with visceral involvement, including the lungs. A 23-year-old homosexual male presented with fever, intractable cough and dyspnea. On examination, multiple skin lesions were revealed. Chest computed tomography visualized multiple nodules, bronchoscopy showed endobronchial lesions. Histopathological study of the skin lesions showed Kaposi’s sarcoma and the endobronchial biopsy – a proliferative inflammatory process. Diagnosis of Kaposi’s sarcoma was made based on clinical, laboratory, computed tomography and bronchoscopy data as well as on the regression of pulmonary nodules by the combination antiretroviral therapy. The diagnosis of pulmonary Kaposi’s sarcoma is still a challenge due to concomitant occurrence of opportunistic infections. This case emphasizes the need to strongly consider pulmonary KS as a possible cause for respiratory illness in any HIV-positive patient with cutaneous Kaposi’s sarcoma.

Keywords
acquired immunodeficiency syndrome, bronchoscopy, combination antiretroviral therapy, Kaposi’s sarcoma

INTRODUCTION
Kaposi’s sarcoma (KS) is a vascular neoplasm first described by a Hungarian dermatologist, Moritz Kaposi, in 1872.¹ It was initially considered a rare benign tumor commonly occurring in elderly males of Jewish or Mediterranean descent. Later, in the 1950s, the condition was also found in the local population in various Sub-Saharan Africa regions. Kaposi’s sarcoma was brought to the attention of the medical community at the onset of human immunodeficiency virus (HIV) epidemic. In 1981, a cluster of young men having sex with men (MSM) from New York, Los Angeles, and San Francisco were reported to have been afflicted quite inexplicably with an aggressive, disseminated form of Kaposi’s sarcoma.² This form later became known as the epidemic KS or the acquired immunodeficiency syndrome-related Kaposi’s sarcoma (AIDS-KS) which is the most frequent and severest form of that condition. This was followed one year later by the first ever description of AIDS which got KS listed as an AIDS-defining illness. Only a decade later in 1994, Chang Y and More P isolated the genome of herpes virus in biopat taken from an HIV(+) patient.³ This virus was referred to as KS-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8). It is the most oncogenic of all herpes viruses, a necessary but not the only factor that may cause KS to develop further. AIDS-KS may affect skin and mucous membranes, lymph nodes and some internal organs, most commonly the gastrointestinal tract and the lungs. While skin involvement may seem alarming, the internal organ involvement is life-threatening.⁴ The incidence and prognosis of AIDS-KS have been dramatically influenced after the introduction of combination antiretroviral therapy (cART). Still, aggressive forms of AIDS-KS with visceral involvement and lethal outcome keep occur-
They are associated with the immune reconstitution inflammatory syndrome (IRIS) as a direct complication of cART or may result from the KSHV/HHV8-induced hyperinflammation.\textsuperscript{5,6}

There are only a few\textsuperscript{1} reports of KS in patients with HIV infection in Bulgaria.\textsuperscript{7,8} We report a rare case of AIDS-KS with pulmonary involvement and make a review of the relevant literature sources.

**CASE REPORT**

A 23-year-old male was hospitalized at the Clinic of Pulmonology at St George University Hospital, Plovdiv in June 2016 with a 2-week history of fever, sweats, non-productive cough, intensifying dyspnea, and fatigue. The patient was given cefuroxime for 1 week which failed to produce any effect. During the last year he noticed purple lesions on the limbs and the face that have increased in size over the past few months. He unintentionally lost weight for the last 2 months.

On physical examination, the patient had asthenic habitus, pale skin and mucous membranes, Brown-purple raised, well defined, non-painful plaques up to 2 cm, on upper and lower extremities were established. Purple-coloured plaques were seen on his hard palate. Bilateral cervical and axillary lymphadenopathy were also found. The rest of the physical examination was otherwise unremarkable except for the severely weakened vesicular breathing and scant moist rales on the left.\textsuperscript{2}

Laboratory studies showed mild normocytic anemia, leucopenia and moderately elevated erythrocyte sedimentation rate. The patient’s blood cultures were sterile. The result of the serological test for HIV (ELISA) was reactive. The chest x-ray (CXR) showed rounded opacity with sharp contours and average density on the left measuring 3.3 cm in diameter, mesh-like surrounding parenchymal structures, and hilar and axillary lymphadenomegaly. The impression was of lung malignancy. Computed tomography (CT) of the chest with contrast material found a mass, 61/40 mm in diameter with central necrosis, in the third segment of the left lung and a number of ill-defined nodules bilaterally measuring 11 mm to the right and 8 mm to the left. The mediastinal and axillary lymph nodes were enlarged, most less than 10 mm in diameter; enlarged lymph nodes were also seen in both axillae (Fig. 1). There was a suspicion of left pulmonary cancer with metastases.

The patient was consulted by a haematologist, dermatologist and infectious diseases specialist, who suspected HIV infection. He was put on medications (cefepime 2×1.0, levofloxacin 0.5, trimethoprim / sulfamethoxasole 2×0.960, fluconazole 0.1), and later discharged in improved condition.

He was admitted to the Clinic of Infectious Diseases at the same hospital for further evaluation where bronchoalveolar lavage (BAL) was performed during bronchoscopy. Tumor infiltration was found at the beginning of B3 sub-segmental bronchus where it was narrowed; similar whitish infiltrations, less pronounced, were seen at the orifice of the upper-right bronchus. The impression was of endobronchial proliferation

![Figure 1. Chest CT scan of the patient. Interstitial thickening and bilateral nodules, hilar and mediastinal lymph nodes.](image-url)
process at left apex and possible metastases to the right. The biopsy revealed chronic inflammation and absence of cancer cells. The BAL was negative for bacterial flora and M. tuberculosis; no Pn. jirovecii and fungal studies were performed. The patient refused re-bronchoscopy.

Histopathological examination of skin punch biopsy revealed epidermis with hyperkeratosis and acanthosis, proliferation of dermal vascular spaces, irregular and split-like lined by endothelial cells. The vessel lamina varied in caliber. Eosinophilic spindle cells and mild chronic inflammatory infiltrates were seen around vascular spaces. Pronounced erythrocyte extravasation and hemosiderin deposition were found. Immunohistochemical staining established CD34-positive spindle cells (Fig. 2). The repeat HIV serological test (ELISA) was again reactive; the result was confirmed by immunoblotting assay at the National Centre of Infectious and Parasitic Diseases in Sofia. The ELISA assay for T. gondii was negative. Specific studies - CD4 count was 12 cells/μL, HIV RNA - 197 282 copies/mL. Treatment was started with antiretroviral medications (dolutegravir, abacavir, and lamivudine) at a fixed dose.

The patient was referred to the oncology panel committee at the district Skin Cancer Dispensary, which determined the stage to be T9N9M9, and recommended local radiotherapy, which was administered to the patient's two necrotic gluteal lesions.

The control CT of the chest at 3 months showed reduction of the number and size of the lung nodules, and persistent mediastinal and axillary lymph nodes. The CT at 9 months revealed only single nodules, of even smaller size, persistent axillary lymph nodes, and absence of lymph nodes in the mediastinum.

The follow-up for the HIV specific studies showed the treatment to be efficacious 2 months later: CD4 count increased (237 cells/μL) and the viral load decreased (HIV RNA 105 copies/mL). Over the following 6 months, the CD4 count gradually decreased to 182 cells/μL, most likely as a result of radiotherapy. Ten months later, the CD4 count increased to 247 cells/μL, and in January 2019 it reached 566 cells/μL. Viral load was undetectable.

DISCUSSION

Kaposi’s sarcoma is an angioproliferative tumor involving blood and lymphatic vessels that etiologically is associated with KSHV/HHV8. There are four clinical variants of Kaposi’s sarcoma each with distinctive clinical and epidemiological characteristics: the classic Kaposi’s sarcoma (as described by Moritz Kaposi), the endemic (or African), the iatrogenic (immunosuppressant therapy related), and the epidemic (or AIDS related) KS. The latter two are associated with immunosuppression. The common features for all four forms are that they are histologically indistinguishable and all have a prior KSHV/HHV8 infection of the host. The major differences are in the extent of anatomic involvement.

Figure 2. Skin biopsy of the patient, haematoxylin and eosin staining, ×100.
of skin and internal organs, the evolution and prognosis of the disease. °

In Western Europe and North America, AIDS-KS is most common in homosexual and bisexual men infected with KSHV/HHV8. The introduction of cART has dramatically reduced the incidence and severity of AIDS-KS.

At the beginning of HIV epidemic, AIDS-KS was diagnosed only in patients with low CD4 count and high HIV viral load, but in the cART period, AIDS-KS patients appear to have relatively preserved immune status. 1 Occasional flares can occur as a result of steroid therapy administered for different reasons or as a manifestation of IRIS. 1,12 Therefore it is clear that the challenges AIDS-KS presented at first are still not completely removed by cART.

The clinical picture of AIDS-KS differs significantly from that of the classic form and appears to have more malignant characteristics. It is characterized by multiple skin lesions and, in 14% of all affected patients – by involvement of the internal organs. Lesions appear not as a result of the primary lesion distribution but occur independently of each other in a multi-focal pattern.

Skin involvement usually precedes the visceral involvement, but it is quite possible that internal organs may become involved in isolation. Typical skin lesions are raised reddish-brown non-painful symmetrical papules and plaques. Their size ranges from a few millimetres to a few centimetres in diameter. As seen in this case, they are localized mostly on the lower extremities 5, on the face (tip of the nose), and on the oral mucosa (hard palate). The oral mucosa is often affected in the disseminated and rapidly progressing forms. These skin lesions often ulcerate. Swellings occur frequently, especially on the face and extremities, possibly due to secondary obstruction of the lymph vessels. 13

The gastrointestinal tract and the lungs are the organs that become most often afflicted. Gastrointestinal involvement is usually asymptomatic but is an indicator of a progressing disease. It is detected in 40% of the patients diagnosed with AIDS-KS and in up to 80% of the cases at autopsy, even without skin manifestations. The progressing process usually is manifested by dysphagia, nausea, vomiting, abdominal pain, hematemesis, melena or intestinal obstruction. Gastroscopy or colonoscopy can be crucial for diagnosing of the disease although these techniques are not always capable of detecting sarcoma because of the submucosal location of the tumor. 14

Pulmonary AIDS-KS presents with skin involvement and rarely (15%) become detected as a primary manifestation. 6 The skin and mucosal manifestations are usually asymptomatic, but are easily noticeable and therefore possible to be diagnosed early. The pulmonary lesions are also present but are visualized only when the pulmonary symptoms progress and become evident. On the other hand, due to the prevalence of opportunistic pulmonary infections in HIV (+) patients, pulmonary KS is not quite prominent in the physician’s clinical reasoning. In many cases, it is detected postmortem in HIV (+) persons with skin involvement. The symptoms suggested by the respiratory system are indistinguishable from those that are manifested by other respiratory processes such as cough, shortness of breath, haemoptysis, chest pain, less frequently night sweats, and fever. The process encompasses the tracheobronchial tree, the pulmonary parenchyma, the pleura and/or the intrathoracic lymph nodes. Some researchers believe that the pleural involvement in such cases implies parenchymal localization of the KS. 15 Conventional CXR shows patchy reticular opacities in a peribronchial distribution and ill-defined nodular densities. It is usually followed by CT of the chest to evaluate abnormalities noted on radiography. Characteristically, it visualizes hilar densities extending into the parenchyma along perivascular or peribronchial pathways and a characteristic septal or nodular pattern with concomitant effusions. 16 Similar nodules were visualized in the patient presented. Bronchoscopy is a very sensitive technique for detecting endobronchial KS lesions and obtaining BAL samples for direct microscopy and bacterial culture, M. tuberculosis, fungal studies and cytology exam to exclude the presence of tumors other than KS. The most common endobronchial lesions in HIV (+) patients are the KS lesions – they have a characteristic appearance. The bronchoscopic appearance of KS is quite distinctive; the lesions appear as violaceous slightly raised lesions that easily bleed, and are located along the bronchi, esp. branching point, less often along the trachea (Fig. 3).
They may be isolated or may involve diffusely the tracheobronchial tree. The bronchoscopic image of endobronchial nodules in AIDS-KS, if adequately known, is characteristic enough to make a presumptive diagnosis. A specific histopathological finding may be established by biopsy (see below). Ideal locations for biopsy of KS are at tracheal carina subdividing segmental orifices - the lesions there are seen as barely noticeable erythema plaques. Of note, they may be mistaken for bronchoscope-induced trauma. Endobronchial biopsy has a low diagnostic yield for KS and at the same time poses a risk of hemorrhage (up to 30% of patients). Bronchoscopy of the airways may fail to yield a diagnosis of pulmonary KS for several reasons: technique of the procedure (distal airway are not detectable), KS may not involve the bronchi, the lesions may not extend into the submucosal space to be visible and the interstitial involvement of KS may be microscopic. To avoid the risk of bleeding at the presence of typical clinical and bronchoscopic findings, some researchers prefer not to perform any biopsy. In advanced AIDS-KS, the endobronchial lesions in the parenchyma of some patients may not be visible in bronchoscopy. This would explain the discrepancy in the radiological and bronchoscopy data.

The presumptive diagnosis of pulmonary AIDS-KS is often clinical, based on epidemiological data (e.g., geographic location, MSM), presence of mucocutaneous KS lesions, degree of immunodeficiency, radiographic appearance, appearance of endobronchial lesions, and exclusion of other infections and neoplasms. Although tissue diagnosis is not necessary to confirm pulmonary KS, transbronchial lung biopsy is required in atypical clinical, radiographic and/or bronchoscopic findings. According to Aboulafia there are three traits of pulmonary KS: 1) the development of mucocutaneous lesions nearly always precedes the respiratory involvement; 2) the frequency of pulmonary involvement that can be documented at autopsy (50%) is higher than that detected clinically (33%); 3) approximately two thirds of patients with KS who present with new pulmonary findings have coexisting, usually treatable opportunistic infections.

Histopathologically, KS has three characteristics, both in skin and visceral sites: angiogenesis, inflammation and spindle cell proliferation. Immunohistochemical stain for HHV8 latent nuclear antigen (LNA-1) is considered a “gold standard” in diagnosing KS because of its high specificity and sensitivity. The newly formed vessels are devoid of basal membrane, which predisposes to microhemorrhages and hemosiderin deposits. The skin biopsy findings in the presented patient are consistent with those described above.

The major goals of treatment are reducing the symptoms, number of lesions, alleviation of edema, prevention of disease progression and the psychological stress for the patient. The antiretroviral therapy is indicated for all AIDS-KS patients, both newly detected and those already initiated on cART. For patients with asymptomatic pulmonary KS typically cART is recommended without concomitant chemotherapy. With decreasing HIV plasma viremia and immune reconstitution, many KS lesions stabilize or even resolve completely without any specific treatment. In those with progressive disease (especially IRIS), with clinical manifestations in visceral localization or lymphoedema, cART should be combined with cytotoxic chemotherapy. In the case presented, after cART was initiated, regression of KS pulmonary nodules, fading of skin lesions and decreasing their size have been documented. For systemic use, liposomal doxorubicin, liposomal daunorubicin and doxorubicin paclitaxel are recommended. Prognosis is good even in advanced disease. For 140 KS patients with visceral involvement treated with cART and liposomal anthracycline, the 5-year overall survival was 85%. Local therapy is more cost-effective and is well tolerated by patients. Cryosurgery, intralesional injections of Vinca alkaloids, and radiotherapy are also used. Novel therapeutic approaches include antiviral agents (valganciclovir) and angiogenesis inhibitors (lenalidomide, sirolimus everolimus). These latter drugs are still in the phase of clinical trials.

This case emphasizes the need to strongly consider pulmonary KS as a possible cause for respiratory illness in any HIV-positive patient with cutaneous KS.

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REFERENCES


Лёгочная саркома Капоши с лёгочной локализацией - начальное проявление ВИЧ-инфекции

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Абстракт

Саркома Капоши является наиболее распространённым злокачественным новообразованием, связанным с вирусом иммунодефицита человека. Она часто поражает кожу, но может вызывать и поражение внутренних органов лёгких. У 23-летнего мужчины с гомосексуальной ориентацией наблюдалась лихорадка, постоянный кашель и одышка. Обследование выявило множественные поражения кожи. Компьютерная томография молочной железы показала множественные узлы, а бронхоскопия выявила эндобронхиальные поражения. Гистопатологическое исследование поражений кожи выявило саркому Капоши, а эндобронхиальная биопсия - пролиферативный воспалительный процесс. Диагноз саркомы Капоши был поставлен на основании клинических, лабораторных, компьютерных томографических и бронхоскопических данных, а также регрессии
лёгочных узлов после комбинированной антиретровирусной терапии. Диагноз саркомы Капоши с лёгочной локализацией всё ещё остаётся проблемой из-за сопутствующих оппортунистических инфекций. Этот случай подтверждает необходимость рассматривать СК с лёгочной локализацией в качестве возможной причины респираторных заболеваний у любого ВИЧ-позитивного пациента с саркомой Капоши.

Ключевые слова
сарcoma Капоши, синдром приобретённого иммунодефицита, комбинированная антиретровирусная терапия, бронхоскопия