Thorax 1992;47:730–733

Pulmonary Kaposi's sarcoma in Africa

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Abstract

Background **A study was carried out to identify the main clinical radiological and bronchoscopic features of HIV related Kaposi's sarcoma of the lung in African patients.**

Methods **Forty seven HIV positive patients with epidemic Kaposi's sarcoma who had clinical or radiological respiratory changes were investigated by simple lung function tests and fibreoptic bronchoscopy.**

Results **The most common respiratory symptoms in the 47 patients were persistent cough in 42, haemoptysis in 23, and breathlessness in 38. A restrictive spirometric pattern was most common. The mean (SD) forced expiratory volume in one second (FEV_1) was 1·88 (0·62) l with a forced vital capacity (FVC) of 2·66 (0·87) l and a FEV_1/FVC % of 73·2 (7·5). On the chest radiograph 26 patients had diffuse reticulonodular shadows, 11 focal nodular shadows, seven a pleural effusion, and one a substantial increase in vascular markings; in two the radiograph was normal. At bronchoscopy characteristic discrete lesions were easily visible in 37 patients and were often bright red. Multiple nodules were seen in 11, flat or early plaque lesions in 12 (14 had both), proximal flat lesions and diffuse infiltration in three, diffuse infiltration alone in four, and masses in two; one had normal appearances at bronchoscopy. One patient had *Pneumocystis carinii* and two had a single bacterial pathogen cultured from the bronchoalveolar lavage fluid. Only two of 29 bronchoscopic biopsies showed classical histological Kaposi's sarcoma. After cytotoxic treatment 20 patients have died, with an overall median survival of 70 days.**

Conclusion **In this African population symptomatic pulmonary Kaposi's sarcoma was common, with lesions seen in all but one patient at bronchoscopy. Coexistent infection was uncommon. Prognosis was poor despite treatment.**

(*Thorax* 1992;47:730–733)

HIV related Kaposi's sarcoma is usually a multicentric tumour and pulmonary lesions are common.[1] Bronchopulmonary Kaposi's sarcoma may not be diagnosed during life,[2] and may present with a clinical and radiological picture resembling opportunist infection.[3 4] In developing countries, where pulmonary Kaposi's sarcoma is easily mistaken for tuberculosis, an accurate diagnosis is important for giving appropriate treatment. Lung lesions may be difficult to confirm both technically and histologically,[5 6] but the bronchoscopic appearance of endobronchial Kaposi's sarcoma is considered characteristic enough to make a presumptive diagnosis.[7] The clinical picture is therefore attributed to Kaposi's sarcoma once opportunist infection has been excluded.[1] As there are few data on pulmonary Kaposi's sarcoma in the developing world we have undertaken a clinical, radiological, and bronchoscopic study of African patients with pulmonary Kaposi's sarcoma and describe the clinical features, the amount of coexisting opportunist infection, and survival after treatment.

Patients and methods

All HIV positive patients in Zimbabwe with epidemic type Kaposi's sarcoma, proved by skin or lymph node biopsy, are referred to our Kaposi's sarcoma clinic for assessment for treatment. From all the patients referred during six months those with clinical or radiological pulmonary abnormalities were recruited into this study. Investigations included a detailed history, clinical examination, chest radiography, simple lung function tests (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF)), blood gas analyses, fibreoptic bronchoscopy, bronchoalveolar lavage, and bronchial or transbronchial biopsy. Patients were tested for HIV antibody with two ELISA tests (an initial antibody screen for HIV-1 and HIV-2 followed by a confirmatory HIV-1 test). Patients were excluded from the study if they refused bronchoscopy, and excluded from lavage and biopsy if they had a disorder of coagulation (platelet count below 60×10^9/l or a prothrombin ratio above 1·5) or a resting arterial oxygen tension (Pao_2) below 8·5 kPa. After bronchoscopy patients were treated with vincristine 1·4 mg/m^2, bleomycin 7·5 mg/m^2 (to a maximum of 200 mg/m^2), and actinomycin D 2·1 mg/m^2, being randomly allocated to treatment with either a single pulse monthly or a five day pulse monthly.

Bronchoalveolar lavage fluid was centrifuged at 3000 rev/min for 15 minutes and the deposit stained for bacteria, mycobacteria, fungi, and *Pneumocystis carinii* by standard staining techniques with Gram, Giemsa, Ziehl-Nielson, Kenyoun, Parker blue-black ink in potassium

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Accepted 13 March 1992

Table 1 Clinical, radiological, and bronchoscopic features in 47 African patients with pulmonary Kaposi's sarcoma (number of patients except where otherwise specified)

Clinical		*Radiological*		*Bronchoscopic*	
Age (y): mean (range)	33 (23–51)	Diffuse shadows	25	Multiple nodules	11
		Plus BHL	1		
Sex: M/F	41/6	Focal shadows	10	Multiple plaques	12
		Plus BHL	1		
Cough	42				
Mean (SD) duration (days)	67 (48)	Pleural effusions	7	Multiple nodules and plaques	14
Haemoptysis	23	Increased vascularity	1	Multiple plaques and diffuse infiltration	3
Chest pain	16	Normal	2		
Shortness of breath					
At rest	13			Diffuse infiltration alone	4
Mean (SD) duration (days)	46 (35)			Mass	2
During exercise	25				
Mean (SD) duration (days)	60 (47)			Normal	1
Crackles					
Widespread	27			> 15 lesions visible	35
Localised	6				
Sarcoma					
Widespread					
Cutaneous > 15 lesions	31				
Palatal	36				

BHL—bilateral hilar lymphadenopathy.

hydroxide, periodic acid-Schiff, India ink, toluidine blue-O, and silver-methenamine stains. Lavage fluid specimens were cultured for bacteria, mycobacteria, and fungi but no viral studies were done.

Biopsy specimens were fixed in 10% formal saline and paraffin wax sections were made and stained with haematoxylin and eosin, Gomori's silver and Ziehl-Nielson stains, and periodic acid-Schiff with and without prior diastase digestion.

As patients in Africa may present a long time after the onset of symptoms survival by treatment modality was examined with two starting points—(1) from the time of onset of first symptoms and (2) from the time of bronchoscopic diagnosis.

The Kaplan-Meier method was used to calculate survival and the curves were compared by means of the log rank test.

Results

All patients had AIDS as defined by the Centers for Disease Control.[8] Of 101 patients referred to the clinic, 47 fulfilled the criteria for inclusion in the study and all were recruited. Forty one were men (age range (mean) 23–51 (33) years) and six were women (23–47 (33) years). Unprotected heterosexual intercourse was the only risk factor for HIV infection and none was having antiviral treatment before or during the study. One patient had had pneumonia two years previously and another had been treated eight years previously for sputum positive tuberculosis. Twenty of the men were smokers. The clinical, radiological, and bronchoscopic findings at presentation are summarised in table 1.

Eighteen patients, all sputum smear negative, had been started on antituberculous chemotherapy before pulmonary Kaposi's sarcoma was diagnosed. Treatment was subsequently stopped as none had improved clinically or radiologically after at least two months' treatment. No one had developed pulmonary or extrapulmonary tuberculosis during recruitment or by follow up.

LUNG FUNCTION

Blood gas analysis during the breathing of air showed a mean (SD) arterial oxygen tension (Pa_{O_2}) of 61 (16) mm Hg, a Pa_{CO_2} of 4·0 (0·53) kPa and an alveolar-arterial gradient of 4·0 (1·5) kPa. A restrictive spirometric pattern was seen in most patients. The mean FEV_1 was 1·88 (0·62) l, with an FVC of 2·66 (0·87) l (63% predicted), and FEV_1/FVC was 73 (7·5%). An obstructive pattern was seen in four patients (two smokers), of whom three had widespread endobronchial lesions and one a tracheal mass.

CHEST RADIOGRAPHS

On the chest radiograph 26 patients had diffuse reticulonodular or nodular shadowing. In six the diffuse shadowing was around the hilar regions, four bilaterally and two on the left side only. Eleven patients had focal nodular shadows, mainly in the mid and lower zones. Seven patients had pleural effusions, all blood stained. Two patients had a normal chest radiograph and one had large pulmonary arteries only.

BRONCHOSCOPY, BRONCHIAL BIOPSY, AND BRONCHOALVEOLAR LAVAGE

Lesions were easily seen at bronchoscopy and tended to be more numerous proximally. Macular lesions and plaques varied from 6 to 15 mm, being well circumscribed and usually bright red. The number of lesions varied from one to many, 35 (75%) patients having more than 15 lesions visible. There was no relation between the extent of tracheobronchial disease

*Table 2 Pathogens identified in bronchoalveolar lavage fluid from 28 patients**

	No†	
MICROSCOPY		
Gram positive cocci	8	
Gram negative rods	5	
Fungal hyphae	1	
Pneumocystis carinii	1	
CULTURE		
Streptococcus α haemolytic	2	(1)
Staphylococcus aureus	3	(1)
Staphylococcus epidermidis	1	
Klebsiella spp	2	
Pseudomonas aeruginosa	1	
Candida albicans	5	(2)
Cladosporium spp	1	(1)

*In addition, one patient had *Histoplasma* sp identified on a transbronchial biopsy specimen.
†Numbers in parentheses indicate pure isolates, the rest being mixed cultures.

and clinical respiratory severity or any significant association between the extent of cutaneous lesions and the extent of tracheobronchial lesions.

Twenty eight patients underwent bronchoalveolar lavage; the fluid was bloodstained in 13. The results of staining and culture are shown in table 2. One patient had *Pneumocystis carinii* and nine had bacteria isolated but these were pure growths in only two cases.

Of the 21 patients who had bronchial biopsy and the eight who had transbronchial biopsy, only two showed the classical histological changes of Kaposi's sarcoma. The remaining mucosal biopsy specimens showed oedema, chronic inflammation, and mononuclear pseudogranulomatous infiltrates with paucicellular alveolar wall thickening or distinct nodularity or both. Eleven biopsy specimens were consistent with and six highly suspicious of Kaposi's sarcoma; six were negative and four were inadequate for interpretation. Typical yeast cells of *Histoplasma* sp was seen in one biopsy specimen. No other infection was identified.

TREATMENT AND SURVIVAL

Nineteen patients had single pulse and 16 five day pulse chemotherapy. Two patients died before treatment was randomised and 10 refused treatment. Median survival from the onset of first symptoms was 95 days in the no treatment group, 154 days in the single pulse group, and 205 days in the five day treatment groups; median survival from bronchoscopy was 60 days, 108 days, and 121 days respectively. The mean time from onset of symptoms to bronchoscopy was 67 days. There was no significant difference in survival between the two regimens used. The overall median survival was 70 days.

Discussion

This study shows that bronchopulmonary lesions are common in patients with HIV related Kaposi's sarcoma in Zimbabwe—they occurred in all patients with clinical or radiological evidence of respiratory disease. The overall frequency of Kaposi's sarcoma of the lung in studies in the developed world has varied from 3·4% to 35%.[1 9] At least 46% of our group had lung lesions, perhaps because patients tend to present late. The proportion may be higher as we do not know how many of the 54 patients with no respiratory symptoms and a normal chest radiograph had pulmonary Kaposi's sarcoma as they did not have bronchoscopy.

A definitive diagnosis of pulmonary Kaposi's sarcoma is rarely made during life but finding the characteristic lesions of endobronchial Kaposi's sarcoma at bronchoscopy is strongly associated with parenchymal Kaposi's sarcoma.[7] The absence of endobronchial disease, as occurred in one of our patients, does not exclude parenchymal lesions.[10] Some series suggest that open lung biopsy should be performed to make a definitive diagnosis,[11 12] but the role of transbronchial biopsy may have been underestimated.[13] These procedures are usually necessary only if endobronchial lesions are absent. The histological appearance of bronchoscopic biopsy specimens is often inconclusive and in our study only two had classical changes of Kaposi's sarcoma. Difficulties in obtaining histological proof are due to the patchy nature of the disease, to the size of the specimens required, and to the granulomatous or chronically inflamed appearance of early lesions.[14 15]

As in other series, chronic cough and breathlessness were the most common presenting symptoms of lung lesions.[3 4 14] These presenting symptoms may be indistinguishable from those of opportunist infections; but the poorly defined chest pain, which occurred in over a third of these patients, is less likely to be related to an opportunist infection. Although no one had massive or fatal haemoptysis,[16 17] haemoptysis was common—perhaps reflecting the severity of the disease, due to late presentation in this rural community.

There is a strong association between HIV positivity and the development of clinical tuberculosis.[18 19] Before bronchoscopy tuberculosis was the presumptive diagnosis in many of our patients because of their prolonged respiratory symptoms and haemoptysis. None, however, had been sputum smear positive or had improved clinically or radiologically with antituberculous treatment, and none was subsequently found to have active tuberculosis. We believe that any HIV positive patient with a clinical diagnosis of sputum negative tuberculosis not responding to treatment should be carefully re-examined for lesions of Kaposi's sarcoma, and if any are found the diagnosis should be reconsidered.

As in other series, there was no relation between the extent of tracheobronchial and cutaneous disease and the severity of respiratory symptoms.[20–23] Palatal lesions were common and they might be a marker for lung lesions.[23]

Chest examination confirmed only the radiological findings of focal or localised disease, and blood gas estimates and lung function tests helped only to define disease severity. Major airway obstruction may occur,[4] and was caused by an intrathoracic mass in one of our patients.

Alveolar, interstitial, mixed alveolar-interstitial, and nodular patterns are the major radiographic features of pulmonary Kaposi's sarcoma, nodules being the most com-

mon.[3 4 9 24 25] Reticulonodular shadows have been shown to have the highest predictive value for intrathoracic Kaposi's sarcoma[21] and were widespread in 26 of our patients. In contrast to other series, our patients with a pleural effusion had no other notable radiological features, though all had visible bronchoscopic lesions. Pleural effusions are thought to be more suggestive of Kaposi's sarcoma than of opportunist pneumonia, but cytological examination of pleural fluid and histological examination of closed pleural biopsy specimens are rarely conclusive.[4 25]

Computed tomography may show perivascular and peribronchial infiltrates but may not add much to the diagnostic strategy in the developed world,[7] though it may help where pneumocystis pneumonia is the major differential diagnosis. It is expensive and rarely available or appropriate in the developing world.

Bronchoalveolar lavage was performed to exclude accompanying opportunist infection, but fluid was not examined for haemosiderin laden macrophages as this test is neither sensitive nor specific.[7] The one patient who had pneumocystis pneumonia, which is uncommon in Africa, had typical perihilar shadowing on the chest radiograph. It was surprising that more coexistent infection was not found as initial reports suggested that Kaposi's sarcoma in the lung is unusual in the absence of opportunist infection.[8] This association, however, has not been supported by later studies,[1 14] any more than by ours; and there is debate about whether cytomegalovirus, which is often found in the lungs of patients with Kaposi's sarcoma, is a pulmonary pathogen.[26]

Survival was worst in the no treatment group, in which patients either were too sick and died before chemotherapy could be started or discharged themselves to rural areas for "traditional" treatment. In Zimbabwe in patients with all stages of HIV related Kaposi's sarcoma the six month survival from date of diagnosis was 35% in the group having the five day pulse treatment and 51% in the group having single pulse treatment,[27] though there was no significant difference in survival between the groups having the two treatments in this series. These data suggest that despite treatment pulmonary Kaposi's sarcoma appears to confer a worse prognosis, perhaps because of the large visceral tumour load.

Pulmonary Kaposi's sarcoma is a major cause of morbidity and mortality and was the direct cause of death in 27% of patients in one study.[4] Half the patients in this series have died from their disease but because of cultural beliefs and legal procedures no necropsy data are available and coexisting pulmonary lesions may have been missed.

The clinical features of pulmonary Kaposi's sarcoma in Africa are similar to, but more advanced than, those seen in the developed world. Patients with cutaneous or lymph node Kaposi's sarcoma who develop unexplained pulmonary or radiographic signs or who have not responded to antimicrobial treatment for pneumonia or tuberculosis should ideally undergo fibreoptic bronchoscopy so that an opportunist infection can be excluded. The endobronchial lesions of Kaposi's sarcoma are characteristic and confirm pulmonary lesions, though histology may be unhelpful. Prognosis is poor despite cytotoxic treatment and cheaper palliative measures are perhaps all that can be offered in many parts of the developing world.

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