Pulmonary Kaposi’s sarcoma: Diagnostic features and natural history in patients with acquired immunodeficiency syndrome

WILLIS TSAI MD FRCPC, CHARLES K CHAN MD FRCPC FCCP FACCP, FRANCES SHEPHERD MD FRCPC, CAROL SAWKA MD FRCPC
Departments of Medicine, the Wellesley Hospital, the Toronto Hospital, the Toronto-Sunnybrook Regional Cancer Centre; and the University of Toronto, Toronto, Ontario


OBJECTIVE: This retrospective descriptive study was undertaken to highlight the diagnostic features and natural history of pulmonary Kaposi’s sarcoma (KS).

METHODS: Thirty-three patients with symptomatic pulmonary KS were assembled from a cohort of 239 patients with KS. Pulmonary KS was diagnosed by visualization of endobronchial lesions at bronchoscopy or based on clinical-radiological correlation and exclusion of opportunistic infections.

RESULTS: The median time from initial presentation with KS to the development of pulmonary involvement was nine months. Dyspnea (79%) and dry cough (79%) were the most common presenting symptoms. Oral palatal involvement was present in 58% of patients with pulmonary KS. Pulmonary nodules (58%) were the most common radiological finding, but an interstitial pattern was noted in 42% of patients. Pleural effusion was present in 39%. Radiological patterns were not static, as 50% of patients with an initial interstitial pattern progressed to develop poorly formed nodules in the peripheral lung fields. Endobronchial lesions were noted on bronchoscopy in 23 patients. A presumptive diagnosis of pulmonary KS was made in 10 patients, with autopsy confirmation in four. Chemotherapy completely resolved symptoms in nine of 25 treated (36%) patients, and a further nine (36%) experienced a significant reduction in symptoms. Radiological improvement was noted in two of the clinical responders. Median survival from the time of diagnosis of pulmonary KS was only eight months, and symptoms relapsed within six weeks of achieving the best clinical response with chemotherapy.

CONCLUSIONS: Pulmonary KS presents a difficult diagnostic challenge due to a nonspecific constellation of symptoms and radiological findings. Bronchoscopy is diagnostic when endobronchial lesions are visualized but, more important, it can exclude opportunistic infections. In some patients, even with a negative bronchoscopy, the diagnosis may still be established using clinical-radiographic correlation, particularly if there is radiological evolution to a nodular pattern over time. Multidrug chemotherapeutic regimens appear to have some symptomatic benefit, but radiological improvement is extremely limited. Progression of disease occurs in virtually all patients, and the median survival is only eight months from the point of recognition of pulmonary KS. (Pour le résumé, voir page 182)

Key Words: Bronchoscopy, Chemotherapy, Radiographic features

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Correspondence and reprints: Dr Carol Sawka, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, North York, Ontario M4N 3M5. Telephone 416-480-5847, fax 416-480-6002, e-mail carol_sawka@actrf.on.ca

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Kaposi’s sarcoma (KS) is the most common tumour in patients with the acquired immunodeficiency syndrome (AIDS). It has been estimated to occur in 10% to 20% of all cases with AIDS (1). Curiously, there is a marked predilection for homosexual men. Overall, 95% of all AIDS-related KS cases are in homosexual or bisexual men. Furthermore, 15% to 40% of all homosexual men with AIDS will develop KS, as opposed to 4% of intravenous drug abusers (2).

Although the skin is the most frequent site of involvement, visceral spread is common. Pulmonary involvement has been found clinically in 21% to 40% of patients with cutaneous KS (3). In autopsy studies, this number increases to 45% of patients (4). Pulmonary KS is virtually always accompanied by skin involvement, but isolated cases of primary pulmonary KS have been described (5).

Despite the high frequency of pulmonary KS, relatively few studies have provided an overview of the natural history of disease from the time of diagnosis to death. This can be partially attributed to the fact that the disease is difficult to diagnose and treat; thus, KS has not received the same attention as other pulmonary complications of AIDS. Although in the past decade, the proportion of KS cases in AIDS patients has declined, there has been an overall absolute increase in KS-related mortality (6,7). As overall survival in patients with AIDS has improved, KS is becoming an increasingly important factor in limiting further improvements in life expectancy.

The purpose of this retrospective cohort study was to review systematically a relatively large contemporary series of patients with pulmonary KS, and to characterize clinical and radiological aspects of the disease. It is beyond the scope of this descriptive study to assess the effectiveness of chemotherapeutic regimens for KS. Data on treatments used in this study are provided primarily to outline the clinical course.

METHODS

Patient population: Thirty-three patients with pulmonary KS were identified from a cohort of 293 patients, who were referred to the Toronto-Sunnybrook Regional Cancer Centre or The Toronto Hospital for assessment and management of KS. These two institutions serve as the principal tertiary care centres for KS in Toronto. They draw from a broad referral base including primary care physicians and other tertiary care centres for patients infected with human immunodeficiency virus (HIV).

Eligible patients in this retrospective review included any individual with pulmonary KS diagnosed between January 1989 and December 1992. The retrospectively assembled study group was followed over time until the study cut-off date of December 1992.

Diagnosis of pulmonary KS: Investigations for pulmonary KS were instituted if the subjects developed inexplicable radiological infiltrates and respiratory symptoms. A few patients were referred with a diagnosis of pulmonary KS already, based on prior investigations of respiratory symptoms instituted by the referring physicians.

Patients were identified as having pulmonary KS primarily by visualization of lesions in the tracheobronchial tree via bronchoscopy. Some were diagnosed based on clinical-radiographic correlation, which was confirmed at autopsy, whenever possible. Twenty-three patients (70%) were diagnosed by positive bronchoscopy. A presumptive diagnosis...
TABLE 1
Patient characteristics at diagnosis of pulmonary Kaposi’s sarcoma (n=33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tr>
<td>Age (years)</td>
<td>median 34</td>
</tr>
<tr>
<td></td>
<td>range 28-55</td>
</tr>
<tr>
<td>CD4 lymphocyte count (cells/mm³)</td>
<td>median 70</td>
</tr>
<tr>
<td></td>
<td>range 3-300</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>median 114</td>
</tr>
<tr>
<td>Prior opportunistic infections</td>
<td>10</td>
</tr>
<tr>
<td>Prior Pneumocystis carinii pneumonia</td>
<td>7</td>
</tr>
<tr>
<td>Oropalatal Kaposi’s sarcoma</td>
<td>10</td>
</tr>
<tr>
<td>Visceral Kaposi’s sarcoma</td>
<td>6</td>
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RESULTS

Demographics: Patients with pulmonary KS formed 11% (33 of 293) of all individuals with KS assessed at the two centres. Table 1 summarizes the patients’ baseline characteristics at the time of diagnosis of pulmonary KS. All patients were male with homosexual contact identified as the risk factor for AIDS. All were between 28 and 55 years of age (median 34). All but one were Caucasian.

Clinical presentation: The median time between initial presentation of KS and the diagnosis of pulmonary involvement was nine months (mean 11, range zero to 38). Respiratory symptoms at the time of the diagnosis of pulmonary KS are summarized in Table 2. All patients were symptomatic at the time of diagnosis because symptoms were the principal indication for investigation. In decreasing order of frequency, these were dyspnea (79%), dry cough (79%), chest pain (12%) blood-tinged sputum (9%) and frank hemoptysis (6%). Fever was noted in four patients.
All patients had skin involvement with KS. Oral mucosa or palatal involvement was noted in 58%. The gastrointestinal tract was found to be involved in 22%.

**Radiographic features**: A summary of the CXR findings at the time of diagnosis of pulmonary KS is presented in Table 3. Pulmonary nodules were the most common radiological findings, present in 58% of patients (Figure 1). Pleural effusion was present in 39%. Interstitial lung disease was observed in 42% of patients (Figure 2). A predominant perihilar pattern was seen in 36% of this group. Interestingly, an increased incidence of interstitial/perihilar disease was observed in the subgroup with positive bronchoscopy (55%). Conversely, the nodular pattern was more common in the group with negative bronchoscopy.

Radiological findings were not static. Of the 14 patients who initially presented with an interstitial or perihilar infiltrate, seven went on to develop superimposed pulmonary nodules.

**Follow-up**: Three patients were lost to follow-up, and were not included in either survival statistics or analysis of response to treatment.

**Overall survival**: Median survival from AIDS-defining illness to death was 23 months (range three to 35). Median time from development of the initial KS lesion to death was 19 months (range three to 35). Median time from diagnosis of pulmonary KS to death was eight months (range one to 20).

**Response to therapy**: Most of the patients were treated with multidrug doxorubicin-containing regimens: DBV (15 patients) and DB (two patients). The remainder were treated as follows: BV (three patients), IFN (two patients), etoposide (two patients), vinblastine (one patient) or no treatment (five patients).

Nine of the 25 treated patients had a complete resolution of symptoms. All patients, including three patients subsequently placed on maintenance therapy, relapsed within six weeks of discontinuing original therapy. Of the remaining group, nine patients experienced a significant reduction in symptoms. Seven patients failed to improve, or else deteriorated further.

Radiological response to therapy was less frequent. Only two patients demonstrated a reduction in x-ray lesions. No patients had a complete resolution of radiological findings. On the other hand, all patients showed some reduction in skin manifestations.

**Complications**: Major complications resulted in the delay of therapy, but did not necessitate discontinuation of treatment. Major complications were as follows: febrile neutropenia (two patients), pneumonia (two patients), line sepsis (one patient) and thromboembolism (two patients). However, it should be noted that one of the individuals with thromboembolism had a history of recurrent deep vein thrombosis preceding commencement of chemotherapy.

**Causes of death**: Four patients were still alive at the study cut-off date. Table 4 summarizes the cause of death of the 26 patients who died. The most common cause of death was respiratory failure (58%). Eighty per cent of these patients did not have any evidence of infection. Pulmonary hemorrhage and airway obstruction accounted for one death each. A generalized decline with no clear cause of death was found in 19%. The remaining causes of death are summarized in Table 4.

**Prognostic factors**: Multivariate analysis, using SAS statistical software (SAS, North Carolina), was performed on the baseline characteristics. None of the baseline factors evaluated affects survival in a statistically significant manner; however, caution should be exercised when interpreting these results. The data are not presented, since the patient numbers were too small to derive meaningful conclusions.
DISCUSSION

The incidence of pulmonary involvement in our retrospective cohort of patients with KS was 11%. This figure may be slightly less than those quoted in the literature because, in our series, only symptomatic patients underwent invasive respiratory evaluation. Although up to 45% of patients with KS have lung involvement in autopsy studies, most cohort studies describe a figure of approximately 20% (3,8). The latter figure is more likely to be relevant because autopsy tends to be carried out in patients with more extensive disease, and thus the prevalence based on autopsy is heavily influenced by selection bias.

The most common symptoms on presentation were dyspnea, dry cough, blood-tinged sputum, hemoptysis and chest pain. These respiratory symptoms are nonspecific, but can often serve as an indicator for further investigation.

CXR findings were classically described by Sivit et al (9) as a diffuse pattern of either poorly defined nodules or linear/interstitial markings, which may be predominantly perihilar. The latter can occasionally mimic Pneumocystis carinii pneumonia (PCP), thus creating a diagnostic dilemma, especially when combined with a nonspecific symptom complex as described above. In a review of several studies, the classic nodular pattern only occurs in a minority of patients (28.8%) (10), compared with 58% noted in our study. Pleural effusion has been reported as relatively common, occurring in up to 60% of cases with pulmonary KS (10); however, a large number of subsequent studies report occurrences in approximately one-third of cases (9,11). Hilar adenopathy has quite a variable incidence depending on the study centre, but should be sought. Both features can be useful in differentiating between pulmonary KS and PCP because both pleural effusion and hilar adenopathy are rare in PCP (11).

In our study population, pulmonary nodules were noted more frequently than the interstitial pattern. This may reflect the inclusion in the cohort of patients with cutaneous KS, a nodular pattern on CXR and exclusion of opportunistic infections, regardless of endobronchial lesions at bronchoscopy. In contrast, patients with an undifferentiated interstitial pattern and a negative bronchoscopic assessment were not included. Since endobronchial visualization is only 45% sensitive (13), patients who presented with linear/interstitial disease may have been excluded due to incomplete assessment. To date, endobronchial visualization is still the most sensitive diagnostic method of detecting lung involvement, short of open lung biopsy. Bronchoscopic biopsies have a notoriously poor yield (10% to 20%) (14). The chance of bronchoscopy confirming endobronchial KS is highest in patients with perihilar/interstitial changes. Those with peripheral nodules may not have any obvious endobronchial lesions.

The use of high resolution computed tomography (HRCT) to aid in the diagnosis of pulmonary KS is promising, but the overall sensitivity and specificity is not known. Lung involvement has been classically described as hilar densities of an interstitial or nodular nature extending into adjacent lung parenchyma along bronchovascular bundles (10). Although still investigational and time-consuming, the use of sequential thallium and gallium scanning may be of benefit (15). Pulmonary KS is described to be thallium-positive/gallium-negative, in contrast to infections or lymphoma, which are thallium-negative/gallium-positive and thallium-positive/gallium-positive, respectively.

Interestingly, radiographic findings were not static. Of the 14 patients who presented with an interstitial/perihilar pattern, seven went on to develop pulmonary nodules, one of whom had an initially negative bronchoscopy. Therefore, patients presenting with a nonspecific interstitial pattern, even in the presence of initially negative investigations, may develop a more diagnostic nodular presentation making the diagnosis apparent with observation over time.

A presumptive diagnosis of pulmonary KS was made in 10 patients based on a nodular radiographic appearance, compatible clinical presentation, and exclusion of concomitant infection with bronchoscopy. Despite the lack of endobronchial lesions, of the four presumptively diagnosed patients who underwent autopsy, all were determined to have pathologically confirmed pulmonary KS. Consequently, pulmonary involvement may be frequently missed if the diagnosis is absolutely dependent on finding endobronchial lesions at bronchoscopy.

We were comfortable initiating treatment in compatible symptomatic patients with pulmonary nodules on CXR, even in the absence of endobronchial lesions. The autopsies provide some validation to this approach. However, no data are available with regard to patients with the more nonspecific interstitial pattern. A decision to proceed with open lung biopsy would have to be made on an individual basis. However, HRCT might be of some benefit in these situations.

Once a diagnosis of pulmonary KS is established, no clear treatment guidelines exist. Single drug regimens involving vincristine, vinblastine or doxorubicin showed some degree of palliation, but prognosis was poor (16). Overall survival did not differ greatly from the two to four months of untreated pulmonary KS as described by Meduri et al (4). Multidrug regimens demonstrate increased survival compared with historical controls. Gill et al (17) demonstrated an overall 10-month survival in a cohort of patients who received doxorubicin alone, bleomycin and vincristine, or doxorubicin, bleomycin and vincristine. A response rate of 85% was noted. Single drug therapy, using newer agents such as paclitaxel, show promise in limited case series (18).

<table>
<thead>
<tr>
<th>TABLE 4 Causes of death</th>
<th>n</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Total patients followed</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Generalized decline</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Airways obstruction</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>
In our study, median survival from the diagnosis of pulmonary KS was eight months, which is in keeping with more recent series. Symptom reduction was good, with 31% achieving a complete reduction in symptoms and a further 38% receiving significant reduction in symptoms. However, symptoms recurred in all patients within six weeks of discontinuing therapy. Although all responders noted a decrease in skin lesions, radiological improvement was unimpressive. None of the patients demonstrated complete resolution of x-ray lesions, and only two patients demonstrated any significant improvement.

Of the 26 patients who died by the study cut-off date, the majority died of respiratory failure (58%). One patient died of massive hemoptysis and another of airway obstruction. The remainder were thought to have died from KS contributory conditions.

The median time to death from the time of diagnosis of the initial KS lesion was 19 months, compared with the previously described median survival of 17 months in uncomplicated KS (19). As mentioned earlier, the median time to death from the diagnosis of pulmonary KS was eight months. Despite the previously held belief that a diagnosis of pulmonary KS implies imminent death, patients are living longer than their historical controls. Nevertheless, it is not possible to determine whether this is the direct result of chemotherapy, changes in the pattern of overall care, a change in the nature of the disease or possibly lead time bias from heightened awareness and early diagnosis.

Because of the method of patient accrual, only symptomatic patients were investigated for pulmonary involvement with KS. This would select for a sicker population of patients because asymptomatic, and presumably healthier, patients would not be included. However, our approach may be more reflective of reality. In the current absence of data supporting definite survival benefits, it would be hard to justify treating asymptomatic patients.

Unfortunately, there are no prospective studies that randomize patients to either treatment or nontreatment groups. This is in part due to a lack of sufficient patient numbers, difficulty with early identification, and the short interval between time of presentation with pulmonary KS and death.

CONCLUSIONS

Although pulmonary involvement occurs quite commonly in KS, it is only symptomatically significant in a small minority of patients. Symptoms are typically nonspecific and serve primarily as a cue for further investigations. Short of open lung biopsy, endobronchial visualization via bronchoscopy is still the best diagnostic test, particularly because it has the additional advantage of excluding infective processes. Radiological findings may be equivocal, often mimicking infections such as PCP. Nevertheless, they may develop a distinguishing nodular pattern over time. Due to limitations in the sensitivity of current tests, a diagnosis may depend on clinical suspicion. This is particularly true in patients with cutaneous KS, those in whom infective processes have been excluded, and in those with peripheral nodules on CXR. The latter may only become apparent following a period of observation. HRCT scanning or sequential thallium/gallium scans may also aid in the diagnosis.

This investigation was not designed to determine therapeutic efficacy, and further study is necessary to evaluate the role of chemotherapy in terms of patient selection, clinical response and impact on overall survival. However, multidrug chemotherapeutic regimens appear to be useful in the reduction of symptoms in a subset of patients, despite a lack of radiologic improvement. Unfortunately, treatment is limited by progression of disease, despite a reasonable initial therapeutic response. The median length of survival was only eight months from the time of diagnosis with pulmonary KS.

REFERENCES
