Serosanguineous Pleural Effusions in AIDS-Associated Kaposi's Sarcoma*

Richard F. O'Brien, M.D.; and David L. Cohn, M.D.

We describe the clinical course and pleural fluid findings in patients with AIDS-associated pleural KS and survival analysis of cases from the Colorado registry with and without pleuropulmonary KS. Twenty-one of 105 (20 percent) of AIDS cases with KS had pleuropulmonary involvement with KS and 13 (62 percent) had pleural effusions. All cases were homosexual males with cutaneous lesions of KS that antedated pleural involvement by several months. Clinical presentation and physical examination findings were nonspecific. Chest roentgenograms generally showed nonlocalulated bilateral pleural effusions; concurrent parenchymal infiltrates were present in 90 percent. Pleural fluid analysis showed that most effusions were serosanguineous, mononuclear cell-predominant exudates. Pleural fluid was visibly blood-tinged in nine of ten cases, with median RBC counts of 52,000/µl (range 16,000 to 803,000/µl). Cytologic examination of pleural fluid or needle biopsy of the parietal pleura failed to establish the diagnosis. In two cases the effusions were chyloous. Postmortem examination of the lungs typically showed multiple cherry red to purple lesions on the visceral but not parietal pleural surface. In half the cases, progressive pleural effusions led to significant morbidity or mortality. Systemic chemotherapy for disseminated KS was minimally effective; chest tube thoracostomy with attempted tetracycline sclerosis was unsuccessful in controlling pleural effusions in three cases. Median survival from diagnosis of KS to death was 205 and 338 days, respectively, for patients with and without pleuropulmonary KS (p<0.01). Pleural effusions are common in AIDS-associated pleuropulmonary KS, and finding a serosanguineous exudative effusion in an AIDS patient with cutaneous KS is highly suggestive of the diagnosis of pleural KS.

(Chest 1989; 96:460-66)

KS = Kaposi's sarcoma; HIV = human immunodeficiency virus; CMV = cytomegalovirus

Pulmonary disease in the acquired immunodeficiency syndrome (AIDS) is very common and is caused predominantly by opportunistic infections. However, 10 to 15 percent of pulmonary disease in AIDS is caused by noninfectious diseases, which include lymphocytic interstitial pneumonitis, nonspecific interstitial pneumonitis, non-Hodgkin's lymphoma, and KS. Of these entities, KS is clearly the most common noninfectious cause of lung disease in AIDS. Approximately 25 percent of all AIDS cases develop KS as a primary or secondary manifestation. Although the vast majority of these patients have cutaneous KS, 20 to 25 percent of these patients will also develop thoracic involvement. We and others have observed an increasing number of AIDS patients with clinically significant pleural and pulmonary involvement with KS. Several recent reports have summarized the clinical manifestations of pulmonary KS, with particular attention given to endobronchial and pulmonary parenchymal involvement with KS. In addition, it has become apparent that pleural effusions are a common manifestation of disseminated KS in AIDS. No reports specifically have commented on the clinical course or detailed pleural fluid findings of patients with pleural KS. We now report these findings in ten AIDS patients with pleuropulmonary KS.

METHODS

From March 1982 through June 1987, 405 cases of CDC-defined AIDS were reported in Colorado. Of these, 105 patients (26 percent) had KS as an initial or secondary diagnosis in the course of their AIDS illness. Retrospective analysis of available clinical records or communication with physicians revealed that 21 of these 105 (20 percent) patients developed pulmonary parenchymal or pleural involvement with KS. Eight patients had KS involving the pulmonary parenchyma only and are not included in the following clinical descriptions. Of the remaining 13 patients, ten had both parenchymal and pleural KS, and three had only pleural KS. The diagnosis of pleural and/or pulmonary KS was corroborated or established by autopsy in 11 patients, by fiberoptic bronchoscopy showing typical endobronchial KS in four patients, by open lung biopsy in one patient, and by presumptive diagnosis in five patients. A presump-
The diagnosis of pleuropulmonary KS was based on the following criteria: (1) the AIDS patient had extensive cutaneous KS; (2) pleural effusions were consistent with KS (serosanguineous exudate) and no other cause of effusion could be determined (congestive heart failure, infection, etc). Ten of 13 patients with pleural effusions secondary to KS had pre-mortem pleural fluid analysis and form the basis of this report. All ten patients were HIV-antibody positive, and the diagnosis of pleuropulmonary KS was definitive in seven and presumptive in three (Table 1).

All patients underwent at least one diagnostic thoracocentesis, and the initial pleural fluid was analyzed for: RBC count, WBC count and differential, cytologic study, protein, LDH, glucose, pH, and cultures for aerobic, anaerobic, and mycobacterial organisms. In some patients fluid was also analyzed for amylase, cholesterol, and triglyceride levels.

Survival analysis of the 21 patients with pulmonary or pleural KS and 84 patients without pulmonary involvement was performed using the product-limit method and compared number of days from diagnosis of KS to death. At the time of analysis 88 patients had died, and 17 were “censored” at the date when last evaluated by a physician.

**RESULTS**

**Demographics**

All ten patients were homosexual or bisexual males; one homosexual patient additionally had a history of IV drug abuse (Table 1). The average age of the patients at the time of AIDS diagnosis was 33 ± 3 years (± SEM). All patients had a history of cutaneous KS that antedated the diagnosis of pleuropulmonary KS an average of 6 ± 4 months (± SD; range 0 to 12 months). The KS skin lesions appeared to be emerging at an accelerated pace in 50 percent of patients when pleural KS became apparent. Five of ten patients had a prior history of opportunistic pulmonary infections: four with *Pneumocystis carinii* pneumonia and one with CMV pneumonitis.

**Clinical Features**

A clear picture of the clinical presentation of pleural KS alone was difficult to ascertain because most patients had concurrent pulmonary parenchymal KS or past opportunistic pulmonary infection. Pleural effusion was rarely the only clinical manifestation of pleuropulmonary KS, in that nine of ten patients had parenchymal KS, evident by chest X-ray film examination, simultaneous with pleural disease. Most patients with pleuropulmonary KS presented clinically with progressive shortness of breath, nonproductive cough, and fever. Only two patients had pleuritic chest pain, and one patient had hemoptysis secondary to

---

**Table 1 — Demographic and Clinical Data in Patients with AIDS-Associated Pleural Kaposi's Sarcoma**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, Yr</th>
<th>Method of Dx of PPKS</th>
<th>Initial KS Dx to PPKS, mo</th>
<th>Other Diagnoses</th>
<th>KS Treatment</th>
<th>PPKS to Death, mo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>Autopsy</td>
<td>3</td>
<td>PCP, CMV</td>
<td>Methotrexate, Vincristine, Thoracocenteses, Sclerosis†, Radiation</td>
<td>2</td>
<td>Chylous effusion; sclerosis unsuccessful and complicated by pleuropulmonary fistula</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Autopsy</td>
<td>6</td>
<td>None</td>
<td>VB, VP-16, Thoracocenteses, Sclerosis</td>
<td>7</td>
<td>Sclerosis partially successful; empyema secondary to multiple thoracocenteses</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>Autopsy</td>
<td>0</td>
<td>PCP</td>
<td>None</td>
<td>1</td>
<td>Extensive pulmonary and lymph node involvement by KS with limited skin KS; no PCP at autopsy</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>Presumptive</td>
<td>9</td>
<td>None</td>
<td>VB, VP-16, Thoracocenteses, Bilateral chest tubes, sclerosis</td>
<td>3</td>
<td>Chylous effusion; sclerosis unsuccessful</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Autopsy</td>
<td>2</td>
<td>None</td>
<td>ABV</td>
<td>0.5</td>
<td>Diffuse alveolar damage (bleomycin toxicity)</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>Autopsy</td>
<td>4</td>
<td>None</td>
<td>None</td>
<td>1</td>
<td>Severe fibroncular pleuritis at autopsy</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Autopsy</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>0.5</td>
<td>Presented with gingival KS</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>Presumptive</td>
<td>12</td>
<td>MAI, cryptococcal meningitis</td>
<td>Bleo, VB</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>Bronchoscopy</td>
<td>12</td>
<td>PCP</td>
<td>ABV</td>
<td>13</td>
<td>Stabilized by chemotherapy</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>Presumptive</td>
<td>6</td>
<td>PCP</td>
<td>VB, Bleo, VP-16, Thoracocenteses</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Abbreviations: PPKS = pleuropulmonary Kaposi's sarcoma; VB = vinblastine; ABV = adriamycin, bleomycin, vinblastine; Bleo = bleomycin; PCP = *Pneumocystis carinii* pneumonia; MAI = *Mycobacterium avium intracellulare*.
†Sclerosis = tube thoracostomy with intrapleural installation of tetracycline (20 mg/kg).
endobronchial KS. Physical examination results showed typical, and generally extensive, KS skin lesions in all patients (except patient 3); oropharyngeal KS lesions were extensive in four of ten cases. Chest physical examination was remarkable only for signs of pleural effusion; pleural rubs were not heard.

Chest Roentgenogram Patterns

Chest roentgenograms showed interstitial or interstitial-alveolar parenchymal infiltrates in nine patients. This was associated with small unilateral or bilateral pleural effusions in four patients or moderate to large bilateral effusions in five patients. One patient had large bilateral effusions without demonstrable pulmonary parenchymal infiltrates. The pleural fluid did not appear to be loculated, since effusions were free-flowing on lateral decubitus films. Modest hilar or mediastinal adenopathy was present in three patients.

Pleural Fluid Analysis

The initial analysis of pleural fluid obtained by routine thoracocentesis in AIDS patients with pleural KS is shown in Table 2. The typical effusion was a serosanguineous, mononuclear cell-predominant exudate. Pleural fluid was visibly bloody or blood-tined in nine patients and had median RBC counts of 52,000/μl (range 16,000 to 803,000/μl). The WBC counts were generally low, with median counts of 1,400/μl (range 200 to 4,600/μl); counts were moderately elevated (1,000 to 5,000/μl) in five cases and minimally elevated (<1,000/μl) in the other five cases. Differential WBC counts showed a mononuclear cell-predominant pattern (>50 percent lymphocytes, monocytes, and/or macrophages) in all cases. Cytologic examination of pleural fluids was negative in nine cases. Occasional "bizarre" or "reactive" cells were described in two cytology reports, but frankly malignant cells were not seen. Analysis of pleural fluid protein and LDH levels showed that all fluids were classified as "exudates" according to the criteria of Light et al. Glucose and pH values were normal in nine patients. The one exception (patient 6) had extensive pleural KS involvement at autopsy, with low values of pleural glucose and pH (63 mg/dl and 7.02, respectively). In four patients pleural amylase levels were normal. In two patients (1 and 4) pleural fluid analysis was consistent with a chylous effusion in that the fluid was turbid in appearance, cholesterol values were normal and triglyceride levels elevated (334 and 231 mg/dl, respectively). Cultures for aerobic, anaerobic, and mycobacterial cultures were negative in all ten cases. Fungal cultures were negative in six fluid samples submitted.

Diagnosis of Pleural Kaposi Sarcoma

Transthoracic closed needle biopsy of the parietal pleura demonstrated only "reactive" or "normal" pleura in three cases. Thoracoscopy was not performed in any patient. Seven patients underwent autopsy, which confirmed the diagnosis of pleural KS. Postmortem examination of the thoracic cavity typically showed bilateral serosanguineous pleural effusions and multiple small (≤2 cm diameter) cherry red or purple KS lesions that studded the visceral surface of the lungs (Fig 1). Lesions were found on the parietal pleura in only one patient. Significant mediastinal lymph node involvement with KS was seen in three of seven autopsy cases.

Microscopic lung sections showed typical KS lesions in the lung parenchyma along peribronchial, lymphatic, and perivascular areas. The visceral pleural surface was infiltrated with typical KS lesions that extended into subpleural lymphatics. Parenchymal and visceral pleural lesions were often adjacent to one another. In addition, prominent areas of fibrous pleuritis were seen in areas of KS pleural involvement in three cases.

Clinical Course, Therapeutic Attempts, and Survival

The natural history of KS pleural effusions was
characterized by rapid clinical deterioration to death within weeks to months in most cases. Recurrent, progressive, and massive pleural effusions dominated the final days of several patients and contributed significantly to death in five patients. Some patients had their terminal care in a hospice setting, and the contribution of pleural effusions to their ultimate demise could not be ascertained. Therapeutic maneuvers attempted to control disseminated as well as local pleural complications of KS (Table 1). Six patients received various chemotherapy regimens that achieved a partial remission of cutaneous KS and stabilization of pleural effusions in three patients but were ineffective in the other three. Specific measures for local control of pleural disease was attempted with whole lung irradiation in one patient (unsuccessful) and tube thoracostomy with tetracycline sclerosis in three patients (unsuccessful). We resorted to repetitive therapeutic thoracocenteses or chest tube drainage for symptomatic relief of dyspnea in six patients.

Pleurapulmonary KS in AIDS had an extremely poor prognosis. The average interval from the diagnosis of pleural KS to death was 4 ± 3 months (range 0.5 to 13 months). Survival analysis comparing AIDS-associated KS with and without pleuropulmonary involvement is shown in Figure 2. The median survival from diagnosis of KS to death was 205 days (mean 249 days) for patients with pleuropulmonary KS and 338 days (mean 382 days) for those without pleuropulmonary KS (p < 0.01).

**DISCUSSION**

This series describes our experience with AIDS-associated pleuropulmonary KS with emphasis on pleural manifestations. In general, pleural effusions are common (~50 percent incidence), occur concurrently with lung parenchymal KS lesions, are characterized as serosanguineous (blood-tinged) exudates, and are associated with a poor prognosis.

The extensive pleuropulmonary involvement seen in AIDS-associated KS differs from the clinical pattern of classic (non-AIDS) KS. Classic KS is a relatively indolent cutaneous neoplasm involving the lower extremities and has a fair prognosis. Internal organ metastasis is estimated to occur in only 10 to 20 percent of classic KS patients, most commonly to the GI tract and lymph nodes. Pulmonary parenchymal and/or pleural involvement are uncommon but not rare late complications of classic KS. Nonbloody pleural effusions have also been described in two patients with classic KS and extensive intrathoracic lymphadenopathy. Pleural fluid cell counts and chemistry values have not been reported.

In contrast to classic KS, extensive and disseminated internal organ involvement in AIDS-associated KS is the rule. It is therefore not surprising that pleural disease in AIDS-associated KS is quite common. Our data and those of others suggest that approximately 20 percent of AIDS patients with KS develop pleural and/or lung parenchymal KS. Based on this report

**FIGURE 1.** Postmortem examination showing multiple 1-2-cm violaceous lesions on visceral pleural surface of lung.

**FIGURE 2.** Product-limit survival analysis of AIDS-associated Kaposi's sarcoma with and without pleuropulmonary disease, showing survival from time at diagnosis of Kaposi's sarcoma to death. From Colorado AIDS surveillance registry of cases reported from May 1982 to July 15, 1987.
and eight other studies, 56 of 119 (47 percent) cases with pulmonary KS\(^7\)\(^{10.25-26} \) had pleural effusions believed secondary to KS. Consistent with the general epidemiology of KS in AIDS, pleural KS involvement has occurred almost exclusively in homosexual or bisexual men. Kaposis sarcoma has rarely been reported in IV drug users, hemophiliacs, or children with AIDS, comprising less than 5 percent of all reported cases of AIDS-associated KS.\(^{26-31} \) Pleuropulmonary KS tends to be a relatively late manifestation of disseminated KS. It generally occurs several months after the diagnosis of cutaneous KS and is associated with evident lung parenchymal KS. All of our patients and more than 90 percent of previously reported cases of pleuropulmonary KS had evident KS skin lesions. From autopsy studies and isolated case reports\(^{32-33} \) extensive internal organ dissemination (including the lung) with KS may occur rarely in the absence of cutaneous disease.

The chest roentgenogram is helpful in suggesting the diagnosis of pleuropulmonary KS in AIDS. Bilateral mixed interstitial/alveolar infiltrates are the most common radiographic pattern reported, yet this does not distinguish KS from infiltrates caused by \(P\) \textit{carinii} pneumonia,\(^20\) the most common cause of pulmonary disease in AIDS. Two additional radiographic findings, namely, intrathoracic adenopathy and pleural effusions, are highly suggestive of pleuropulmonary KS. One series emphasized intrathoracic adenopathy as a major radiographic finding in as many as two-thirds of pleuropulmonary KS cases\(^6\); we found only 30 percent of our cases had mediastinal and/or hilar adenopathy.

The finding of pleural effusions in AIDS patients is unusual. \(P\) \textit{carinii} pneumonia is the major cause of pulmonary morbidity in AIDS but very rarely causes pleural effusions. Likewise, other opportunistic pulmonary infections with CMV, \textit{Cryptococcus neoformans}, and \textit{Mycobacterium avium intracellulare} are rarely associated with effusions. Possible causes of pleural effusion in AIDS patients include bacterial pneumonia, \(M\) \textit{tuberculosis}, KS, non-Hodgkin’s lymphoma, and congestive heart failure. Furthermore, one can limit the differential diagnosis of pleural effusions in AIDS patients by considering the transmission category of the patient. Since KS and non-Hodgkin’s lymphoma are found predominantly in homosexual men, these would be the most likely causes of effusion in that group. On the other hand, IV drug users rarely develop KS, and the differential diagnosis of pleural effusion would likely be: \(M\) \textit{tuberculosis}, bacterial pneumonia, non-Hodgkin’s lymphoma, and endocarditis-induced heart failure.

A characteristic feature of pleural effusions in AIDS-associated pleural KS is that the fluid is a serosanguineous exudate. The initial thoracocentesis fluid was blood-tinged in nine of ten cases, and RBC counts were elevated in all patients. This observation is in accord with recent series of AIDS-associated pleuropulmonary KS\(^7\)\(^{10.25-26} \) where effusions were described as “bloody,” “serosanguineous,” or “hemorrhagic.” We were unable to find any evidence for other routine causes of hemorrhagic effusions (traumatic thoracocentesis, carcinoma, pulmonary embolism, chest trauma, etc) in these patients. Postmortem examination of patients with KS pleural effusions, however, have shown a significant number of nonbloody effusions.\(^8,28\) We observed nonbloody effusions in two patients but only several weeks after the initial thoracocentesis in association with a preterminal state.

The pathogenesis of bloody exudative effusions in AIDS-associated KS is probably twofold. First, the visceral pleural surface of affected lungs are studded with hemorrhagic KS lesions that can release blood into the pleural space. Secondly, gross and microscopic findings at autopsy suggest that lymphatic obstruction of lung parenchymal tissue and mediastinal lymph nodes occurs. Of note, two patients in our series had chylous pleural effusions, commonly associated with diseases causing lymphatic obstruction. Schulman and Grimes\(^44\) reported one case of AIDS-associated metastatic KS and bilateral chylothorax. Therefore, both visceral pleural lesions and lymphatic obstruction probably account for effusions in these patients.

The WBC counts were modestly elevated (mean 1,400 cells/\(\mu\)l) and were predominantly mononuclear cells. This finding was not particularly helpful since other diagnoses such as tuberculosis pleurisy and lymphoma are possible. The initial diagnostic thoracocentesis fluid in all cases was an “exude” using the strict criteria of Light et al.\(^16\) Absolute protein levels \(\geq 3\) g/dl and LDH levels \(\geq 200\) U/L were found in only eight and five cases, respectively. However, when pleural/serum ratios were calculated, all ten patients had “exudates” (Table 2). Glucose, pH, and amylase values were basically normal. We encountered “transudative” effusions in two patients on subsequent thoracocenteses, usually in association with a preterminal clinical state and severe hypoalbuminemia.

A pathologic diagnosis of pleural KS, like that in lung parenchymal KS, is extremely difficult to make antemortem. Including three cases from this series closed needle pleural biopsy specimens were negative in 14 cases.\(^3,8,10,11,27\) This is undoubtedly due to the patchy nature of KS infiltration and because KS is rarely found in the parietal pleura, the site actually biopsied with the Cope needle. The definitive diagnosis of pleural KS, unfortunately, is made at autopsy in the majority of cases. Thoracotomy with open lung and visceral pleural biopsy offers the only opportunity for an antemortem diagnosis of pleural KS. Pleuroscopy could theoretically establish a definitive diagnosis of pleural KS, since the lesions are uniquely localized.
on the surface of the visceral pleura. Our data indicate that finding a serosanguineous exudative pleural effusion in an AIDS patient with cutaneous KS is highly suggestive of pleural KS.

Once the diagnosis of pleural KS has been established therapeutic options are very limited. Since pleural KS is usually but one of several sites of disseminated KS, systemic chemotherapy has been the mainstay of therapeutic attempts. Modest temporary objective responses have been obtained in at least 50 percent of advanced cases utilizing α-interferon or combination of agents such as Adriamycin, bleomycin, and vincristine. Because the prognosis of pleuropulmonary KS is extremely poor, with survival averaging only three to six months, aggressive chemotherapy should be considered only in patients with a reasonably good functional status.

Specific therapeutic measures for pleural disease include chest tube thoracostomy with tetracycline pleurodesis or whole lung irradiation. In our experience with three patients, attempted sclerosis of the pleural space with tetracycline was unsuccessful. This may be analogous to the poor response seen in lymphomatous pleural effusion, where lymphatic obstruction contributes to the pathogenesis of effusion. Experience with radiation therapy is extremely limited, but two reports have documented improvement of pulmonary infiltrates and pleural effusions following whole lung irradiation. Radiation therapy has a reasonably sound theoretical basis in that both cutaneous and oropharyngeal KS lesions are radiosensitive. In addition, if the lymphatic obstruction analogy to lymphomatous effusions is correct, it is logical to expect some improvement in effusions following irradiation. Further investigation is needed to evaluate the efficacy and toxicity of radiation therapy for pleuropulmonary KS.

ACKNOWLEDGMENTS: We thank Carol A Bujonit for obtaining follow-up information on patients in the study; Arthur M. Davidson, M.D., for statistical analysis; and Vicky Maltezos and Debbie Gomez for typing the manuscript.

REFERENCES


30. Jarlais DC, Marmor M, Thomas P, Chamberland M, Zolla-
36 Nobler MP. Pulmonary irradiation for Kaposi's sarcoma in AIDS. Am J Clin Oncol 1985; 8:441-44.