Thorax 1985;**40**:571–575

Diagnosis of pulmonary complications of the acquired immune deficiency syndrome

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ABSTRACT Forty eight patients with the acquired immunedeficiency syndrome (AIDS) presented to the Mount Sinai Hospital in New York with persistent cough and dyspnoea or an abnormal chest radiograph, or both. Thirty two (67%) were found to have *Pneumocystis carinii* pneumonia, either alone or in combination with another pathogen. Of these patients, eight (25%) had a normal chest radiograph. Abnormalities in the single breath carbon monoxide diffusing capacity and alveolar-arterial oxygen gradient ((A-a) DO_2) suggested infection with *Pneumocystis carinii*. Fibreoptic bronchoscopy with transbronchial biopsy was 100% sensitive in the diagnosis of pneumocytis pneumonia. Fibreoptic bronchoscopy should be undertaken in patients suspected of having a pulmonary complication of AIDS, even if the chest radiograph is normal.

The acquired immune deficiency syndrome (AIDS) is characterised by an unusually aggressive form of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, or other life threatening opportunistic infection in patients who are under the age of 60 and who have no previous history of either illness or treatment causing immunosuppression.[1–7] In addition, cases of lymphocytic interstitial pneumonia[8] and malignant lymphoma[9–11] have been reported in patients with AIDS. The great majority of over 3000 patients with AIDS reported to the Centers for Disease Control in the United States are male homosexuals, but the disorder has also been encountered in intravenous drug abusers,[4 12–14] Haitian immigrants,[15 16] and patients with haemophilia A.[17–20]

Mortality among patients with AIDS is high, most patients succumbing to opportunistic pulmonary infections.[4 21 22] In addition to pneumocystis pneumonia, patients with AIDS have developed pulmonary infections caused by *Mycobacterium avium intracellulare, Mycobacterium tuberculosis, Cryptococcus neoformans, Candida albicans*, cytomegalovirus, and herpes simplex virus.[13 21] Patients are frequently diagnosed as having AIDS because they are found to have pneumocystis pneumonia or infection with another opportunistic pulmonary pathogen. Possibly early detection and treatment of these infections could improve survival. There is still, however, no general agreement on the best diagnostic approach to these patients. In this paper we present the results of diagnostic studies in patients with suspected pulmonary complications of AIDS, and emphasise the value of fibreoptic bronchoscopy in establishing the diagnosis.

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Accepted 21 May 1985

Methods

From December 1981 to December 1983, 64 patients who were at high risk of developing AIDS came to our attention because of persistent cough, dyspnoea, or an abnormal chest radiograph. On the basis of the criteria proposed by the United States Centers for Disease Control,[21] 45 of these patients were shown to have AIDS because of the finding of Kaposi's sarcoma or opportunistic infection. Three additional patients at risk of AIDS were found to have a lymphoproliferative disorder, and are included in this study. The remaining 16 patients proved to have other pulmonary infections not consistent with the diagnosis of AIDS.

Arterial blood gas determinations, spirometric tests, and the single breath test of carbon monoxide diffusing capacity were performed whenever possible. All patients underwent fibreoptic bronchoscopy under local anaesthesia. Brush biopsy specimens were sent for cytological study, Gram staining, and in seven cases Giemsa staining. Transbronchial

forceps biopsy specimens were obtained in all but one patient; touch prints were made of biopsy material for Giemsa staining. Lung tissue was evaluated by haematoxylin and eosin, methenamine silver, and Ziehl-Neelsen staining.

A diagnosis of pneumocystis pneumonia was made if the organisms were identified in brush biopsy specimens, touch imprints made from tissue specimens or glass slides, or lung tissue. Methenamine silver stain was used to identify cyst forms, and Giemsa staining identified trophozoites. Cytomegalovirus infection was diagnosed by the characteristic histological findings in biopsy specimens. Other infections were diagnosed by the use of culture techniques.

Measures designed to avoid spread of infection were based on avoiding contact with saliva, respiratory tract secretions, and blood.[23] Disposable mouthpieces were used for pulmonary function tests, and the equipment was thoroughly cleaned after each use. Persons performing fibreoptic bronchoscopy wore gowns, gloves, masks, and protective eyeware, and the bronchoscope was carefully cleaned and gas sterilised after each procedure. Specimens of tissue, blood, and secretions were transported in clearly labelled sealed plastic bags.

Results

Of the 48 patients in this study, 34 men were homosexual or bisexual, seven men and three women were intravenous drug abusers, two men were both homosexual and users of intravenous drugs, one man had haemophilia A, and one man had no apparent risk factors. The mean age at the time of presentation was 35 years, with a range of 24 to 49 years.

CHEST RADIOGRAPHY

In 24 of the 32 patients found to have pneumocystis pneumonia, the chest radiograph showed bilateral diffuse interstitial infiltrations, usually of the reticulonodular pattern. Importantly, eight of the 32 with pneumocystis pneumonia had normal chest radiographs as reported by the hospital radiologists and after subsequent review. Fibreoptic bronchoscopy was performed in these eight patients because of complaints of dyspnoea and cough and the finding of a decreased TLCO or increased (A-a)DO_2, or both, despite the negative chest radiograph.

PULMONARY FUNCTION TESTS

Pulmonary function tests were performed in eight cases before fibreoptic bronchoscopy. None of these patients had a history of lung disease before developing AIDS. The total lung capacity was reduced in one (<80% predicted). Five had a decreased forced expiratory volume in one second (<80% predicted) and decreased forced vital capacity. TLCO was reduced (<60% predicted) in all seven patients tested.

ARTERIAL BLOOD GAS TENSIONS

Twenty seven patients had arterial blood gas determinations before fibreoptic bronchoscopy. In 21 (78%), the partial pressure of oxygen (Pao_2) was less than 80 mm Hg (10.7 kPa). In 26 of the 27 (96%) the (A-a) DO_2 was greater than 20 mm Hg (2.7 kPa).

FIBREOPTIC BRONCHOSCOPY

All 48 patients underwent fibreoptic bronchoscopy during the initial evaluation of suspected opportunistic infection complicating AIDS. The results of bronchoscopy are presented in table 1. The most common pathogen was *Pneumocystis carinii*, which was found either alone or in combination with another pathogen in 32 cases (67%),

The techniques used in establishing the diagnosis of pneumocystis pneumonia in patients with AIDS are set out in table 2. Histological examination of biopsy specimens using silver methenamine stain was the most sensitive indicator of pneumocystis pneumonia in our series, being positive in all 32 patients in whom biopsy was performed. Giemsa stained biopsy touch prints were positive in 28/30 cases (93%). When Giemsa stained preparations of bronchial brushings and washings were studied, they were found to be positive in five of seven cases (71%) each. In several cases empirical treatment with trimethoprim and sulfamethoxazole had been started up to three days before the bronchoscopy was performed without apparent reduction in diagnostic yield.

Cytomegalovirus was recognised by the presence of characteristic intranuclear and intracytoplasmic inclusions in biopsy specimens. This infection was found in three patients (6%), one of whom also had pneumocystis pneumonia.

Cultures of bronchial washings disclosed nontuberculous mycobacteria in two patients (4%). *Staphylococcus aureus* was isolated in bronchial washings in three patients (6%) and *Haemophilus influenzae* and *Histoplasma capsulatum* each occurred in one patient (2%).

One patient with widespread cutaneous Kaposi's sarcoma and bilateral pleural effusions had a nondiagnostic pleural biopsy, but fibreoptic bronchoscopy and colonoscopy both showed intraluminal lesions typical of Kaposi's sarcoma.

A lymphoproliferative disorder affecting the pulmonary parenchyma was diagnosed by transbron-

Table 1 *Diagnosis established with fibreoptic bronchoscopy in 48 patients with AIDS*

	No (%)
Pneumocystis pneunomia	30 (63)
Pneumocystis pneumonia with *Haemophilus influenzae*	1 (2)
Pneumocystis pneumonia with cytomegalovirus	1 (2)
Cytomegalovirus	2 (4)
Mycobacterium avium intracellulare	1 (2)
M kansasii	1 (2)
Staphylococcus aureus	3 (6)
Histoplasma capsulatum	1 (2)
Kaposi's sarcoma	1 (2)
Lymphocytic interstitial pneumonitis	1 (2)
Lymphoma	1 (2)
No specific diagnosis	5 (10)
Total	48 (99)

*The total of 99% is due to rounding of individual percentages.

chial biopsy in two patients. One had lymphocytic interstitial pneumonitis and the other immunoblastic lymphoma. Bronchoscopy was not diagnostic in the remaining five patients (10%).

Most patients tolerated bronchoscopy well. Two patients, however, developed pneumothoraces requiring thoracostomy tube drainage after transbronchial biopsy. One of these patients was successfully treated but the other had a persistent bronchopleural fistula until he died of staphylococcal sepsis. One patient with haemophilia A had haemoptysis (50 ml of blood) after a bronchial brush biopsy. Bleeding subsided spontaneously and forceps biopsy was not carried out.

OPEN LUNG BIOPSY

Two patients who had no specific diagnosis after fibreoptic bronchoscopy underwent open lung biopsy. Pulmonary infiltration with Kaposi's sarcoma was diagnosed in one; but in the other patient open lung biopsy did not lead to a diagnosis. A third patient, with lymphocytic interstitial pneumonitis diagnosed by bronchoscopy, also had an open lung biopsy, which confirmed this diagnosis.

NECROPSY

Thirteen patients had complete necropsies; the pulmonary findings are listed in table 3. No case of pneumocystis pneumonia was discovered at the time of necropsy that had not been diagnosed during life. Two cases of cytomegalovirus infection, two cases of Kaposi's sarcoma, and one case of immunoblastic lymphoma affecting the lungs were, however, discovered only at necropsy. One patient with a premortem diagnosis of disseminated infection with acid fast bacilli died before identification of the organism was possible. He was treated with isoniazid and rifampicin. Both *M tuberculosis* and *M avium intracellulare* were cultured from the lungs at the time of postmortem examination.

Table 2 *Yield from fibreoptic bronchoscopy in 32 patients with AIDS and Pneumocystis carinii pneumonia*

Technique	*No of positive/total procedures*	*% positive*
Transbronchial biopsy	32/32	100
Touch preparation	28/30	93
Bronchial brush	5/7	71
Bronchial wash	5/7	71

Table 3 *Results of necropsy in 13 patients with pulmonary complications of AIDS*

Patient No	*Clinical diagnosis*	*Pulmonary necropsy diagnosis*
1, 2, 3, 4	Pneumocystis pneumonia	Pneumocystis pneumonia
5	Resolved pneumocystis pneumonia, central nervous system lymphoma	Cytomegalovirus, central nervous system lymphoma
6	Staphylococcal pneumonia	Staphylococcal pneumonia
7	Resolved pneumocystis pneumonia, bacterial pneumonia	Adult respiratory distress syndrome, disseminated *Aspergillus* and *Candida*
8	Disseminated acid fast bacillary infection	*M tuberculosis* and *avium intracellulare* (postmortem cultures)
9	Staphylococcal pneumonia	Staphylococcal pneumonia, Kaposi's sarcoma
10	*Mycobacterium avium intracellulare*	*M avium intracellulare*, Kaposi's sarcoma
11	Pneumocystis pneumonia	Pneumocystis pneumonia, cytomegalovirus
12	Immunoblastic lymphoma	Immunoblastic lymphoma
13	*M kansasii*, pneumocystis pneumonia	Immunoblastic lymphoma; no evidence of active *M kansasii* or pneumocystis infection

Discussion

By far the most common pulmonary complication of AIDS was pneumocytis pneumonia, occurring alone or in combination with another infection in 32 of the 48 patients (67%) during the initial evaluation.

The chest radiograph showed bilateral diffuse interstitial densities in most of the patients with pneumocystis pneumonia, although eight patients with proved pneumocystis pneumonia had normal chest radiographs. Most patients were too ill to undergo pulmonary function tests, but when they were performed a diffusing capacity of less than 60% was found, confirming that this is a sensitive indicator of pneumocystis pneumonia. Arterial blood gas determinations were also sensitive indicators of pneumocystis infection.

Several other diagnoses besides pneumocystis pneumonia were established by means of fibreoptic bronchoscopy, including infection with cytomegalovirus, *M avium intracellulare*, *M kansasii*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Histoplasma capsulatum*. Pulmonary Kaposi's sarcoma, immunoblastic lymphoma, and lymphocytic interstitial pneumonitis were also diagnosed by fibreoptic bronchoscopy. But, in contrast to its high sensitivity in diagnosing opportunistic infections in patients with AIDS, fibreoptic bronchoscopy played little part in demonstrating Kaposi's sarcoma in the lungs.

There is no general agreement on the best technique for establishing the diagnosis of diffuse lung disease in immunocompromised patients. While some centres prefer to obtain lung brushings, biopsy specimens, and lavage fluid through the fibreoptic bronchoscope as the first diagnostic procedure,[24] other authorities prefer to proceed directly to open lung biopsy, citing its higher diagnostic yield.[25 26] This uncertainty is reflected in case reports of patients with AIDS with diffuse lung disease, where both fibreoptic bronchoscopy and open lung biopsy have been used in the diagnosis of opportunistic infections.[4 12 27 28] In our series AIDS was either previously diagnosed or suspected in all cases, and they underwent fibreoptic bronchoscopy because of a suspected opportunistic pulmonary infection. A specific diagnosis was established by bronchoscopy in 43 patients (90%).

In this series the sensitivity of transbronchial biopsy in the diagnosis of pneumocystis pneumonia was 100%. This is in general agreement with the findings of Coleman and coworkers,[29] who found transbronchial biopsy to be 79% sensitive in diagnosing pneumocystis pneumonia in patients with AIDS. Giemsa stains of touch preparations were positive for pneumocystis pneumonia in 28/30 cases (93%), and because of the rapidity of the staining procedure they had the advantage of enabling the diagnosis to be made within hours of the bronchoscopy. Giemsa stains of bronchial brushings and washings were positive in 5/7 cases (71%). It is noteworthy that no diagnosis of pneumocystis pneumonia was made from any of three open lung biopsies and 13 necropsies that had not already been established by fibreoptic bronchoscopy.

We conclude that when a patient is suspected of having a pulmonary complication of AIDS an early and determined attempt to reach a diagnosis is in order, even when the chest radiograph is normal. Measurement of diffusing capacity and arterial blood gas tensions provide useful information during the initial evaluation, as both are highly sensitive indicators of the presence of pneumocystis pneumonia. If the result of either of these tests or the chest radiograph is abnormal, the patient should undergo fibreoptic bronchoscopy with transbronchial biopsy, touch preparation of biopsy specimens, and bronchial brushings and washings. In addition to routine histopathological studies, special staining for pneumocystis pneumonia and acid fast bacilli should be performed. Specimens should also be cultured for bacterial pathogens, mycobacteria, and fungi.

Bronchoalveolar lavage has been proposed as a useful technique in the diagnosis of opportunistic infection in patients with AIDS.[30] Although we did not perform this procedure in any of our patients, we agree that this technique is potentially useful, particularly in patients with bleeding disorders or requiring mechanical ventilation, in whom transbronchial biopsy may be contraindicated because of the high risk of uncontrolled bleeding or tension pneumothorax.

Fibreoptic bronchoscopy should be the first invasive procedure in establishing the diagnosis of a pulmonary complication of AIDS. The procedure is safe, well tolerated by the patients, and highly sensitive, particularly in the diagnosis of pneumocystis pneumonia. Open lung biopsy should be reserved for those patients in whom fibreoptic bronchoscopy is non-diagnostic.

This work was supported by the Catherine and Henry Gaisman Foundation. We would like to thank Ms Sarah Lyon for her expert assistance in the preparation of this manuscript.

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