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The diagnostic role of fiberoptic bronchoscopy in immunocompromised patients with pulmonary diseases

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ABSTRACT : Fifty-six bronchoscopies were carried out for the diagnosis of pulmonary diseases in 50 immunocompromised patients with various underlying diseases. In 30 of these patients, bronchoscopy provided useful findings. The diagnostic sensitivities (positive/procedures) for transbronchial lung biopsy bronchoalveolar lavage, aspiration of intra-bronchial sputum and brushing were 55.1%, 29.4%, 8.3% and 0%, respectively. Overall diagnostic sensitivity was higher for non-infectious diseases than for infectious ones. Also, there was a tendency for the diagnostic sensitivity to be higher in cases whose pulmonary infiltrates were extensive. In two samples of lavage fluid positive for the isolation of cytomegalovirus, the virus was not significant etiologically. Complications from bronchoscopy occurred in nine patients, but were not serious. However, no prolonged patient survival was noted with the use of diagnostic bronchoscopy. We consider that bronchoscopy is a safe method for the diagnosis of pulmonary diseases in immunocompromised patients, but that further studies are required in order to confirm the clinical significance of this procedure.

INTRODUCTION

Fiberoptic bronchoscopy has been increasingly utilized for the diagnosis of various pulmonary diseases, and has made diagnosis reliable and accurate. In the late 1970s, bronchoalveolar lavage using bronchoscopy was introduced, allowing the analysis of lung cells, and bronchoscopic laser therapy was also developed. Thus, bronchoscopy has brought about remarkable progress in the diagnosis and treatment of pulmonary diseases. The number of diseases for which bronchoscopy is indicated has also increased. Many investigators have reported the usefulness of bronchoscopy in the diagnosis of pulmonary complications in immunocompromised patients such as those with malignant disease, organ transplant recipients[1−7] or those with acquired immunodeficiency syndrome (AIDS).[8−12]

We have diagnosed pulmonary complications

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using bronchoscopy in 50 immunocompromised patients with various underlying diseases, and have studied the clinical significance of diagnostic bronchoscopy. Our findings are reported in the present paper.

MATERIALS

During the period from March 1977 to June 1986, 50 immunocompromised patients underwent bronchoscopy at the Second Department of Internal Medicine, Nagasaki University Hospital for the diagnosis of pulmonary diseases. They comprised 31 men and 19 women ranging in age from 19 to 78 years, with a mean age of 52 years.

Among the underlying diseases in these 50 patients, hematologic malignancy was the most common condition, and about half of such patients had malignant lymphoma. Seven patients had been treated with steroids; these included four patients with nephrotic syndrome, one with sarcoidosis, one with aplastic anemia and one with autoimmune hemolytic anemia. Three patients had solid malignant tumors; one case each of lung cancer, bladder cancer and breast cancer. The two other patients were a renal transplant recipient and one with myelodysplasia (Table 1).

Table 1. Underlying Diseases of 50 Immunocompromised Patients

Underlying disease	No. of patients (%)
Hematologic malignancy	38 (76)
non-Hodgkin's lymphoma	19
Hodgkin's disease	3
Leukemia	15
Multiple myeloma	1
Disease treated with steroids	7 (14)
Solid malignant tumor	3 (6)
Renal transplant	1 (2)
Myelodysplasia	1 (2)
Total	50 (100)

The radiographic patterns of pulmonary infiltrates are shown in Table 2. In 38 patients, arterial blood gases without supplemental oxygen were determined before bronchoscopy. The relationship between the radiographic patterns and arterial oxygen tension (PaO_2) is shown in Table 2.

Table 2. Radiographic patterns of Pulmonary Infiltrates and Arterial Oxygen Tension (PaO_2)

Pattern	No. (%)	Hypoxemic*	Non-hypoxemic*
Bilateral diffuse	22 (44)	13	6
Unilateral localized	16 (32)	2	8
Bilateral localized	12 (24)	3	6
Total	50 (100)	18[†]	20[†]

*Hypoxemic: $PaO_2 < 60$ torr, Non-hypoxemic: $PaO_2 > 60$ torr

[†]In 38 patients, PaO_2 before bronchoscopy was measured without supplemental oxygen.

METHODS

All patients were given atropine sulfate, pentazocine, and 4% lidocaine topical anesthesia before the bronchoscopy. The bronchoscope (Olympus BF-B2, 4B2, 1TR, 2TR) was passed transorally into the trachea. Bronchoscopy was done under fluoroscopy in principle and hypoxemic patients underwent bronchoscopy with supplemental oxygen. Transbronchial lung biopsy (TBLB), aspiration of intra-bronchial sputum using a polyethylene tube (Asp), bronchoalveolar lavage (BAL) or brushing was selected. For BAL, the bronchoscope was wedged into an involved subsegment, and 60 to 100 ml of normal saline was instilled in 30- to 50-ml aliquots, each aliquot then being aspirated manually. Chest radiographs were taken routinely on the day after BAL and changes in infiltrates were examined. In some patients, arterial blood gases were determined just before and after bronchoscopy.

Hematoxylin and eosin, silver methenamine and Ziehl-Neelsen staining were carried out on the transbronchial biopsy specimens. The aspirated sputum, lavage fluids and brushings were sent for bacterial, fungal and mycobacterial staining and culture. The lavage fluids were pooled and centrifuged for five minutes at 1,500 rpm. The sediment was smeared and stained with Papanicolaou, silver methenamine and

toluidine blue O stains. Isolation of cytomegalovirus (CMV) from five samples of lavage fluid was done.

A final diagnosis of pulmonary disease was made on the basis of bronchoscopic and autopsy findings and the clinical course including the response to specific treatment. Finally, a specific pulmonary disease was identified in 44 of the 50 patients, and was not identified in six patients. The specific diseases in these 44 patients were classified into infectious diseases (in 26), non-infectious diseases (in 15) and mixed-type diseases (in 3).

RESULTS

Fifty-six bronchoscopies were done in 50 patients (Table 3).

Table 3. Bronchoscopic Procedures Performed in 50 Patients

Procedure	No. of procedures
TBLB alone	22
TBLB+Asp	15
TBLB+BAL	6
TBLB+BAL+Asp	6
BAL alone	4
BAL+Asp	1
Asp alone	1
Asp+Brush	1
Total	56

TBLB = transbronchial lung biopsy; BAL = bronchoalveolar lavage; Asp = aspiration of intra-bronchial sputum; Brush = brushing.

TBLB, BAL, Asp and brushing were performed alone or in combination. TBLB was performed in 45 patients, Asp in 24, BAL in 17 and brushing in one. A specific pulmonary disease was unequivocally diagnosed in 20 patients (40%) by bronchoscopy alone, and was suspected in 10 patients (20%) on the basis of bronchoscopic and clinical findings. In these 10 patients, a specific form of treatment after bronchoscopy was effective, and the usefulness of bronchoscopy for the diagnosis of pulmonary diseases was demonstrated. As a whole, bronchoscopy was useful in 30 patients (60%) (Table 4). In two samples of lavage fluid positive for isolation of CMV, the isolated virus was not significant etiologically. Therefore, CMV was not included among the cases with positive bronchoscopic findings. Histopathological findings in five cases of pneumonia showed infiltration of inflammatory cells and intra-alveolar organization. These five pulmonary infiltrates were localized and disappeared without any treatment or antibiotics. All positive findings, except for three cases of Pneumocystis carinii pneumonia diagnosed by BAL alone, were obtained by TBLB alone or by TBLB combined with other procedures.

Table 4. Diagnostic Findings on Bronchoscopy

Etiologic Diagnosis	No. of patients (%)
Definitive	20 (40)
Pneumocystis carinii	6*
Tuberculosis	3
Cryptococcus	3
Aspergillus	1
(Cytomegalovirus infection	2)
Lymphoma	3
Leukemia	2
Metastatic calcification	1
Pumonary ossification	1
Not definitive, clinically useful	10 (20)
Pneumonia	5
Drug-induced pneumonitis	3
Hypersensitivity pneumonitis	1
Lymphoma	1
Total	30/50(60)

* In one of these, cytomegalovirus inclusion bodies were seen in the lavage fluids. Cytomegalovirus was isolated by bronchoalveolar lavage, but was not significant etiologically. These patients were excluded.
All pulmonary infiltrates were localized, and disappeared without any treatment or antibiotics.

The diagnostic sensitivities for TBLB, BAL and Asp were 55.1%, 29.4% and 8.3%, respectively. All five positive samples of lavage fluid contained Pneumocystis carinii,[1] and cytomegalovirus inclusion bodies were seen simultaneously in one of them. Two positive Asp samples contained tubercule bacilli and Staphylococcus aureus. The diagnostic sensitivities of bronchoscopy for infectious and non-infectious disease were 18/26 (69.2%) and 12/15 (80%), indicating a slightly higher rate for non-infectious disease. The diagnostic sensitivity for

radiographic patterns was 68.2% for bilateral diffuse infiltrates, which was the highest, 66.7 % for bilateral local infiltrates and 43.8% for unilateral local infiltrates (Table 5). Thus, there was a tendency for the diagnostic sensitivity of bronchoscopy to be higher when the pulmonary infiltrate was more extensive.

Table 5. Diagnostic Sensitivity of Bronchoscopy

	Sensitivity (%)
Procedure*	
Transbronchial biopsy	27/49 (55.1)
Bronchoalveolar lavage	5/17 (29.4)
Aspiration of sputum	2/24 (8.3)
Brush	0/ 1 (0)
Disease Category	
Infectious disease	18/26 (69.2)
Non-infectious disease	12/15 (80.0)
Radiographic Pattern	
Bilateral diffuse	15/22 (68.2)
Unilateral localized	7/16 (43.8)
Bilateral localized	8/12 (66.7)

* Sensitivity = positive/procedures (%)
Sensitivity = positive/patients (%)
Two patients, in which cytomegalovirus was isolated in the lavage fluids, were excluded.

The effect of diagnostic bronchoscopy on patient survival was examined retrospectively. However, no prolonged survival was noted with this technique (Table 6).

Table 6. Effect of Bronchoscopy on Patient Survival

Prognosis	Results of Bronchoscopy	
	Diagnostic	Non-diagnostic
Survived	15 (50)	10 (50)
Died	15 (50)	10 (50)
Total	30 (100%)	20 (100%)

Complications from bronchoscopy occurred in nine patients (18%) ; three with pneumothorax and six showing a transient increase in temperature. None of the cases of pneumothorax required tube drainage. The cases of fever occurred in five BAL patients and in one who underwent a combined procedure of TBLB and Asp. The infiltrates showed no worsening on radiographs taken on the day after bronchoscopy. Moreover, no other serious complications occurred.

DISCUSSION

Pulmonary complications occur frequently in the immunocompromised host, and the mortality is high when the infiltrates are extensive.[13] Therefore, it is necessary to find and treat such cases as early as possible. In parallel with changes in underlying diseases, various pulmonary complications are encountered, and discrimination among them is often difficult.[2)8)13)14)] Fiberoptic bronchoscopy has been utilized frequently for the diagnosis of such pulmonary complications, and many investigators have reported its usefulness.[1-12)15)16)] Furthermore, the value of bronchoscopy in patients with AIDS has been confirmed.[8-10)] For the diagnosis of pulmonary complications in immunocompromised patients, bronchoscopy is becoming the procedure of first choice among invasive techniques such as percutaneous needle biopsy and open-lung biopsy.[2-5)10)]

The criteria of indication for bronchoscopy in immunocompromised patients depend on the clinical situation, the underlying disease and the bronchoscopic procedure selected. At the outset, the following three points should be taken into consideration : whether the underlying disease is expected to be subsequently controlled by a certain type of treatment, whether deterioration of the general condition is primarily due to pulmonary complications, and whether pulmonary infiltrate will interfere with any subsequent treatment of the underlying disease. Therefore, bronchoscopy is not indicated at the end-stage of solid malignant tumor. Second, the criteria should fulfill the general standards for which bronchoscopy is indicated.[17)] Most of the present patients had received chemotherapy and some of them had accompanying hypoxemia. Therefore, hypoxemia and hemorrhagic diathesis are important factors to consider among the criteria. Although there is no standard for the level of PaO_2 adequate for bronchoscopy, many investigators have recommended a PaO_2 higher than 50 to 75 torr regardless of whether supplemental oxygen is given.[2)4)18)] After the procedure of combined TBLB and BAL for 12 non-immunocompromised patients in our study, the

decline in PaO_2 ranged from 0.8 to 33.0 torr (average 19.6 torr). Thus, such a decline in PaO_2 after bronchoscopy should be taken into consideration. A platelet count greater than 50,000 to 70,000/mm^3 is desirable for TBLB.[2)4)] In two patients with a platelet count lower than 20,000/mm^3, we were able to perform TBLB with safety after platelet transfusion. BAL is applicable to patients on mechanical ventilation and those with hemorrhagic diathesis.[4)10)11)18)] Taking the above-mentioned points into account together with the choice of bronchoscopic procedure, the indication for bronchoscopy should be examined carefully in each patient.

The timing of bronchoscopy is important for the early diagnosis and treatment of pulmonary complications. When a difinitive diagnosis has not been made through non-invasive examinations, it is necessary to rely upon empirical treatment. If pulmonary complications are not improved by empirical treatment, then the point at which bronchoscopy should be performed becomes a critical consideration. It is difficult to arrive at a clear conclusion at present because of the variety of pulmonary complications. One investigator has proposed that invasive examinations should be done one to three days after the start of empirical treatment.[8)] Because it is frequently difficult to predict pulmonary complications from chest radiographs, efforts should be made to find them at an early stage using gallium-67 scintigraphy and periodic measurements of PaO_2.[1)9)10)19)] When PaO_2 is significantly reduced or when diffuse accumulation of gallium is observed in the lung, bronchoscopy should be positively undertaken because of its high diagnostic sensitivity for diffuse pulmonary lesions.

Various bronchoscopic procedures such as TBLB, BAL, brushing, Asp and bronchial washing can be selected. The choice of appropriate procedure depends on the clinical situation, suspected diagnosis and the diagnostic sensitivity of the selected procedure. As shown in the present study, TBLB usually has the highest diagnostic sensitivity among the various procedures, and combination of TBLB with other procedures raises the sensitivity still.[3)4)10)11)16)] In the present study, TBLB had a sensitivity of 55.1%, being especially high for non-infectious pulmonary disease. BAL has a high diagnostic sensitivity for Pneumocystis carinii pneumonia, mycobacterial disease, cytomegalovirus infection, legionnaire's disease and fungal pneumonia, and is also useful for pulmonary hemorrhage, pulmonary infiltration of hematologic malignancy and drug-induced pulmonary disease.[1)4)9)10)12)16−18)] Therefore, we think that BAL should be employed as actively as TBLB.

For the early diagnosis of pulmonary complication, specimens should be treated by rapid and sensitive methods. In our two positive fluid samples for isolation of CMV, three to four weeks was required for the diagnosis. Recently, a rapid laboratory method for the detection of CMV using a sensitive and specific monoclonal antibody against CMV was developed. Using this method, the clinical significance of the detection of CMV in pulmonary complications in immunocompromised patients has been investigated.[7)20)] The further development of new and rapid methods for diagnosing various pulmonary diseases is thus desirable.

Complications from bronchoscopy occurred in 9/50 (18%) patients, but did not become serious. No serious complications have been reported in previous studies.[2)4)5)10)11)] Reported complications have included pneumothorax, hemorrhage, transient increase in temperature, worsening of pulmonary infiltrate and hypoxemia.[1)4)10−12)] We think that bronchoscopy is a safe diagnostic method for use in immunocompromised patients, if such patients are carefully selected.

Some investigators have doubted the usefulness of bronchoscopy, since diagnostic bronchoscopy does not necessarily prolong patient survival.[2)5)15)21)] In the present study, no prolonged survival was noted following diagnostic bronchoscopy, reflecting the fact that 80% of the diagnosed patients had hematologic malignancy, and that this ratio was greater than 70% for non-diagnosed patients.

In order to evaluate the significance of bronchoscopy in immunocompromised patients, it is necessary not only to equalize the background factors of the patients but also to take the following points into serious consideration:

indication, timing of bronchoscopy, choice of bronchoscopic procedure, treatment of specimens, complications, and effect on patient survival. After these problems have been solved, the usefulness of this technique can be confirmed.

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