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Usefulness of transbronchial biopsy in immunosuppressed patients with pulmonary infiltrates

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ABSTRACT In a retrospective study of thirty-one immunosuppressed patients with new pulmonary infiltrates transbronchial biopsy provided a specific diagnosis in 11 of the 31 (36%) patients. In a further five patients, whose biopsy showed non-specific interstitial pneumonitis, a specific diagnosis was established by other means. Overall a specific diagnosis was obtained in 52% of patients. Twelve patients were left with a diagnosis of non-specific interstitial pneumonitis. In three out of 31 (10%) patients insufficient tissue was obtained. The seven patients who had metastatic carcinoma of the lung did poorly. The nine with other specific diagnoses did better in that five of them were alive after more than 11 months of follow-up. Patients with non-specific pneumonitis did well; eight out of 12 (67%) were alive after an average follow-up of 13·4 months. In 27 of the 31 (87%) patients the procedure was felt to have influenced therapeutic decisions. This was true whether the biopsy yielded a specific or a non-specific diagnosis. In our series making a specific diagnosis did not improve the patients' survival. Those with non-specific pneumonitis who were treated empirically did well, as did patients with specific diagnoses other than metastatic carcinoma of the lung.

Transbronchial biopsy has generally been accepted as a useful technique in establishing a diagnosis in pulmonary infiltrates occurring in immunosuppressed patients.[1–4] Diagnostic possibilities include infection (where unusual and opportunistic organisms must be considered), drug or radiation toxicity, and parenchymal lesions caused by the underlying disease. Non-invasive assessment of these patients is not usually diagnostic.[5 6]

High yields of specific diagnoses achieved by transbronchial biopsy reported by some authors are somewhat misleading owing to the inclusion of non-specific interstitial pneumonitis or fibrosis.[1] Only a few studies have examined the outcome in patients in whom a diagnosis of non-specific interstitial pneumonitis has been made.[1 7 8] Are we missing treatable illness in these patients? Should these patients have open lung biopsy?

In our retrospective study we examined the sensitivity of the transbronchial biopsy in establishing a specific diagnosis in 31 immunocompromised patients with new pulmonary infiltrates. The usefulness of the transbronchial biopsy in clinical decision making was examined. We also recorded the outcome in cases where a specific diagnosis was established, as well as those where we reached no specific diagnosis.

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Methods

A retrospective study of 33 consecutive bronchoscopies, with transbronchial biopsy and bronchial washings and brushings, was carried out at the Wellesley Hospital in 31 immunosuppressed patients from January 1979 to December 1980. All procedures were performed by two of the authors (RH and MH). A third observer (SP), who was not concerned with the procedures or the care of the patients, analysed the patients' records. All the patients (14 male and 17 female) were from the Wellesley Hospital or Princess Margaret Hospital, their ages ranging from 19 to 71 years (average 47·7). All patients had new pulmonary infiltrates, 28

Table 1 *Clinical characteristics of the 31 patients having transbronchial biopsy*

Primary diagnosis	*No of patients*	
Lymphoma	9	(1 also had a carcinoma)
Leukaemia	9	(3 had bone marrow transplants, 2 others also had a carcinoma)
Preleukaemia	1	
Carcinoma	6	(5 breast, 1 ovarian)
Collagen disease	6	(1 also had a carcinoma)
	31	

Immunosuppression	*No of patients*
Chemotherapy	7
Steroid treatment	8
Chemotherapy and steroid treatment	13
Other*	3
	31

*Rheumatoid arthritis with gold injections and chloroquine, leukaemia and diabetes mellitus without recent chemotherapy, and untreated leukaemia—one case each.

of them diffuse, on chest radiography (table 1). Twenty-eight of the 31 patients had been on steroids, immunosuppressive agents, or both, before the development of pulmonary infiltrates. Most had symptoms—cough or shortness of breath. Ages ranged from 19 to 71 years (average 47·7); 14 were male and 17 female.

As part of their investigation patients had complete blood counts, including platelets, routine chemistry, and prothrombin (PT) and partial thromboplastin times (PTT). Some patients had serological assays for *Mycoplasma pneumonia, Legionella pneumophila,* and various viral agents. Examination of sputum (where available) by microscopy and culture was performed for bacteria, mycobacteria, and fungi. Other appropriate cultures were obtained. Most febrile patients were being treated empirically with broad-spectrum antibiotics before bronchoscopy. Arterial blood gases were measured in most cases.

Bronchoscopies were done with local anaesthesia in all but two of the patients. Supplemental oxygen and electrocardiographic monitoring were provided for all patients and ear oximetry was used when necessary. All transbronchial biopsies were done in the supine position under fluoroscopic control. When prothrombin or partial thromboplastin times were raised or platelet counts were less than 50×10^9/l they were corrected before transbronchial biopsy with plasma, fresh frozen plasma, or platelet transfusion. Chest radiographs were done before and after the procedure. An Olympus FB 1T bronchoscope was used, with an oral soft latex wire spiral endotracheal tube (Rusch) positioned bronchoscopically.[9] One to 10 biopsy samples were taken, with an average of 4·2 per procedure. Biopsy material was placed in formalin and stained for mycobacteria, fungi, and *Pneumocystis carinii* as well as with routine histological stains. Bronchial washings, for which sterile Ringer's lactate was used, were cultured and examined microscopically for bacteria, mycobacteria, and fungi. Microbiology brush tips (Medi-Tech Inc, Watertown, Massachusetts) were sent for culture in dry sterile jars. In nine of the 31 patients additional biopsy material was sent in viral transport medium for electron microscopy and viral cell cultures. Two of our patients underwent two bronchoscopies with transbronchial biopsies—one because there was no yield on the first attempt and the second because of recurrent infiltrates.

To assess the value of the procedure in decision making and the effect on survival the diagnostic results were divided into specific and non-specific categories. Changes of treatment based on the results of the procedure and the patient's state at follow-up were recorded.

Results

The results of 33 bronchoscopies with transbronchial biopsies performed in 31 patients are shown in table 2. A specific diagnosis was established in 11 out of 31 patients (36%) and 12 out of 33 (36%) procedures. Seventeen of 31 (55%) patients had non-specific interstitial inflammation or fibrosis. Of the latter, in five out of 17 (29%) a specific diagnosis was established by an alternative means (table 2). In three of the 31 patients (10%) insufficient tissue (no alveoli) was obtained. Overall, bronchoscopy with transbronchial biopsy, washings, and brushings, as

Table 2 *Results of transbronchial biopsy in the 31 patients*

(1) *Specific diagnosis established by transbronchial biopsy (11 patients)*	
Metastatic carcinoma*	7
Pneumocystis carinii infection	1
Pneumocystis carinii and *Pseudomonas* infection	1
Tuberculosis	1
Drug toxicity (busulfan)	1
(2) *Non-specific diagnosis from transbronchial biopsy (17 patients)*	
(a) Specific diagnosis established by alternative means (one case of each)	5
Respiratory syncytial virus infection (serology)	
Cytomegalovirus infection (serology and open lung biopsy)	
Toxoplasmosis (serology and clinical response)	
Pseudomonas aeruginosa infection (sputum culture)	
Graft-versus-host disease (comparison with open lung biopsy specimens and clinical response)	
(b) No specific diagnosis made	12
(3) *Insufficient tissue* (3 patients)	

*Six out of seven had a known primary tumour.

well as other diagnostic tools, provided a specific diagnosis for 16 patients (52%) and a non-specific diagnosis for 12 (39%).

High-risk factors for biopsy included: hypoxaemia (PaO_2 < 60 kPa) in 15 patients; thrombocytopenia (platelet count < 100 × 10^9/l) in six; abnormal coagulation indices (raised PT, PTT, or both) in five patients; and azotaemia in one patient.

Complications occurring during or immediately after the procedure were: pneumothorax, in each case requiring a chest tube, in five patients (15%); minor bleeding in four (12%); arrhythmia, not requiring treatment, in two (6%); pulmonary oedema in one patient (3%); bronchospasm in one (3%); and cross-contamination of specimens with acid-fast bacilli in one (3%).[10] There were no deaths which were causally related to the procedure.

Of the 11 patients (12 out of 33 procedures) where transbronchial biopsy yielded a specific diagnosis, four had bronchial washings or brushings giving positive results. Although in one patient brushings and washings helped in making a diagnosis of infection with *Pseudomonas aeruginosa* when transbronchial biopsy yielded only *Pneumocystis carinii,* in no case did brushings and washings give positive results when the transbronchial biopsy gave a negative one. Transbronchial biopsy samples were sent for electron microscopy and viral cell cultures in nine of the 31 patients but no positive results were obtained.

An average of 3·8 biopsy samples per procedure were taken in the 11 patients in whom a specific diagnosis was made by transbronchial biopsy, compared with 4·5 per procedure in the 20 patients in whom a non-specific diagnosis was made.

Changes in management resulting from bronchoscopy and transbronchial biopsy are summarised in table 3. In 27 of the 31 patients (87%) the procedure was of some value in decision making. In 20 patients (65%) it led to an alteration in therapeutic approach, including new treatment in four cases. In seven patients (23%) it ruled out infection only, thereby helping to guide the therapeutic approach.

Of the 11 patients in whom a specific diagnosis was made by transbronchial biopsy, nine were dead or in their preterminal illness at follow-up. Eight of these nine died an average of 13·6 weeks after transbronchial biopsy and one was suffering from preterminal illness 10 months later. Of these nine, six had metastatic carcinoma of the lung and one died of *Pseudomonas* pneumonia and progressive respiratory failure. The other two patients (tuberculosis, busulfan lung) died of their leukaemia.

In five patients a specific diagnosis was established by other means (table 2) after non-specific findings at transbronchial biopsy. Four were alive after an average follow-up of 11 months. One died five months later of leukaemia and septicaemia despite initial clinical and radiological improvement.

Table 3 *Decisions made as a result of bronchoscopy**

Treatment decisions	*No (%) of patients*
New treatment instituted†	4 (13)
Antibiotic treatment changed (including discontinuation of unnecessary antibiotics)	7 (23)
Initiation of antibiotics prevented (infection only ruled out)	7 (23)
Active treatment discontinued	2 (6)
Chemotherapy or steroid treatment changed (including initiation of new chemotherapy)	7 (23)
None	4 (10)
	31

*Each patient allocated to only one category.
†*Pneumocystis carinii* infection, tuberculosis, pulmonary fibrosis, and graft-versus-host disease.

Of 12 patients with a diagnosis of non-specific pneumonitis on transbronchial biopsy and without a specific diagnosis made by other means, eight were alive at follow-up. These patients had an improved or stable chest radiograph after eight to 18 months (average 12·7 months). Four died an average of 17·3 weeks after transbronchial biopsy.

Discussion

Although open lung biopsy is the most definitive invasive investigation and can be done safely even in critically ill patients,[12,13] transbronchial biopsy is simpler, with less morbidity and expense, and it is generally considered sensitive and specific in excluding treatable disease, despite the limitations of small specimen size.[7] Limitations of the open lung biopsy are the delay often encountered in its organisation, difficulty with surgical access to centrally located infiltrates, and the reluctance of physicians to use it in patients with recurrent lung infiltrates. Open lung biopsy provides a specific diagnosis in 55–65% of patients.[12,14] The yields from transbronchial biopsy are generally slightly below this. In our study 11 out of 31 (36%) patients had a specific diagnosis established by transbronchial biopsy and 16 (52%) had a specific diagnosis established with the help of all diagnostic methods. This is similar to the results of several other recent studies, which have reported yields for specific diagnoses of 48% (bronchial brushings and transbronchial biopsy),[5] 48% (transbronchial biopsy alone),[7] 32% (bronchial washings and transbronchial biopsy),[8] and 42% (transbronchial biopsy).[1] Some studies have produced rates over 70%.[2,3,11]

Some investigators question the sensitivity of

transbronchial biopsy. In one study[8] six out of 15 patients with a non-specific result from bronchial washings and brushings and transbronchial biopsy specimens had a specific diagnosis established by other means. In our study five out of 17 patients with non-specific results from bronchoscopy had a diagnosis established by other means (table 2). In one of these, however, the comparison of transbronchial biopsy material with that obtained from a previous open lung biopsy led to a clinical diagnosis of graft-versus-host disease that was subsequently supported by response to treatment. We found that bronchial washings and brushings did not increase our diagnostic yield significantly. Although some studies have found brushings useful, particularly for fungi and viruses,[3 5 8] most studies do not find bronchial washings very helpful, particularly in the diagnosis of malignancy.[4 5 15–17]

In our series, patients who had a diagnosis of non-specific pneumonitis did well when treated empirically. Eight out of 12 were alive after an average follow-up of over 12 months. An important question arises over those patients in whom a specific diagnosis was made. Did they do better than they would have done if no invasive tests had been performed? Several studies[11 18] have found a high mortality rate in patients with a specific diagnosis. In our series many of the patients who had a specific diagnosis established by transbronchial biopsy had metastatic carcinoma. Although this information strongly influenced subsequent management decisions, these patients fared poorly. Their high mortality rate makes the overall outcome of patients with a specific diagnosis obtained by transbronchial biopsy difficult to interpret. In those nine patients who had a specific diagnosis which was not carcinoma, regardless of how this diagnosis was made, five were alive after an average follow-up of more than 11 months. Moreover, two of the patients in this group of nine died of leukaemia and not of the superimposed lung disease. This suggests a much more favourable prognosis in these patients.

Secondary malignancy was the most common specific diagnosis in our patients, although others have reported a high percentage of opportunistic infection.[2 3 13] In some of these reports there was a high mortality rate in patients with a diagnosis of an infectious, potentially reversible process. Only eight out of 19 (42%) survived in one study despite specific treatment. Some investigators suggest that there has been no decrease in mortality in their patients with the advent of the transbronchial biopsy.[18]

These reports raise the controversial issue of whether invasive investigations of pulmonary infiltrates change the mortality of immunosuppressed patients. The reports do not provide a clear answer to this problem. Some authors feel that lung biopsy improves survival[14 18]; for example, Phillips and coworkers[11] describe a change in treatment due to bronchoscopy in four of 18 survivors. The claims of decreased mortality, however, are generally modest and this is in part due to small numbers and the inevitable lack of control cases.

The small size and heterogeneity of the study population in our series make the effect of a specific diagnosis on mortality difficult to interpret. The nature of the underlying disease had a large influence on the observed mortality. We conclude nevertheless that transbronchial biopsy was useful in the management of our patients, frequently facilitating clinical decision making. The biopsy results often led to modification of treatment or use of specific treatment. Changes included discontinuation of costly or potentially toxic antibiotics, as well as modification or initiation of steroid, antimicrobial, or antineoplastic treatment. The procedure was also useful in determining prognosis (patients with non-specific pneumonitis generally did well). Furthermore, specific biopsy results early in the course of an illness may increase the chance of survival. In our hands there were no deaths from the procedure and the morbidity was less than that of open lung biopsy.

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