Pulmonary infiltrates - diagnostic problems in lymphoma

J.H. Campbell,¹ V. Raina,² S.W. Banham,¹ D. Cunningham² and M. Soukop²

Department of ¹Respiratory Medicine and ²Oncology, Glasgow Royal Infirmary, Glasgow G31 2ES, UK.

Summary: The use of invasive investigations in immunocompromised patients with pulmonary infiltrates is controversial. We report a series of 22 pulmonary lesions occurring in 19 patients with underlying Hodgkin's (7) and non-Hodgkin's (12) lymphoma in whom invasive investigations were performed. The principle techniques used were fiberoptic bronchoscopy, bronchoalveolar lavage and transbronchial lung biopsy. A specific diagnosis was made on 12 occasions (55%). Involvement of the lung with lymphoma (6) and cytotoxic drug induced pneumonitis (4) were the commonest diagnoses, infection being found on only one occasion. In 15 of these 22 procedures (68%) the information obtained made a positive contribution to patient management.

Introduction

Pulmonary lesions developing in patients with Hodgkin's and non-Hodgkin's lymphoma pose considerable diagnostic and management problems.¹ Involvement of the lung with the lymphomatous process occurs in 5–20% of patients at diagnosis and eventually in 20–60%.^{2–6} In addition, both the underlying condition with its associated altered immune status and the effects of complex aggressive treatment policies may result in a wide range of pulmonary complications including infection, drug-induced pneumonitis and pulmonary haemorrhage.^{1,7–10} The clinical presentation and chest X-ray appearances are often poor pointers to the underlying pathology.^{1,7,11}

This paper reviews our experience of Hodgkin's and non-Hodgkin's lymphoma patients with an unexplained pulmonary lesion requiring specialist respiratory investigation. We have attempted to examine diagnostic yield and the effect on management pertaining to these investigations.

Methods

Between August 1984 and January 1988, 137 new patients with Hodgkin's and non-Hodgkin's lymphoma attended a lymphoma clinic. Of these, 19 patients (12 male, mean age 50 years, range 22–79) initially or subsequently presented with pulmonary infiltrates which required specialized respiratory investigation. Three patients had two separate periods of investigation; on each occasion the chest X-ray was distinctly different and the admissions were more than

2 months apart. These episodes have been considered separately, making a total of 22 episodes investigated. On 10 occasions, the patient had previously been treated with broad spectrum antibiotics but the infiltrates were unresponsive. At the time of referral, 8 patients were receiving combination cytotoxic chemotherapy and 9 patients had completed antitumour therapy (4 chemotherapy alone, 1 radiotherapy alone, 4 combination chemotherapy and radiotherapy). The radiation field had included the lung in 4 patients. Five patients were as yet untreated. Clinical details are summarized in Table I.

Investigations included bacterial culture of blood and sputum, and viral, mycoplasma and legionella serology testing. In each episode, fiberoptic bronchoscopy and bronchial wash were performed. The bronchial wash was performed with sterile saline (20–60 ml), instilled into a segmental bronchus. Samples were cultured for bacteria, mycobacteria and fungi, and examined cytologically. Transbronchial lung biopsy (TBLB) was performed on 21 occasions

Table I Clinical presentation of pulmonary infiltrates (22 episodes) in 19 patients with lymphoma

	n %
Cough	7 (27)
Breathlessness	8 (36)
Fever	9 (41)
Malaise	3 (14)
Haemoptysis	2 (9)
Arterial $PO_2 < 8$ kPa (60 mm Hg)	6 (27)
White cell count under $1.0 \times 10^9/l$	2 (9)
Broad spectrum antibiotics	10 (45)
(High dose co-trimoxazole)	3 (14)

Correspondence: J.H. Campbell, M.R.C.P.(UK).
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and one episode was investigated with a percutaneous fine needle aspirate.

Results

Of the 22 episodes investigated, a specific diagnosis was made in 12 (55%). These are summarized in Table II. Transbronchial lung biopsy was the principle technique by which a specific diagnosis was made (9 of 21 episodes, 43%). In the remaining cases this technique gave non-specific changes or normal lung and in one case inadequate tissue.

Lymphoma was the most common single diagnosis (6 patients). In two of these the bronchoscopic technique was the means of establishing the initial diagnosis of a lymphoma. In the remaining 4 patients, the pulmonary infiltrate represented recurrent or progressive disease. In this group analysis of broncho-alveolar lavage fluid did not detect any abnormal lymphocytes - although immunological marker studies were not performed.

On 4 occasions, patients receiving combination chemotherapy for intermediate or high-grade non-Hodgkin's lymphoma (International Working Formulation) were found to have cytotoxic drug-induced pneumonitis. None of these patients had previously received radiotherapy. The chemotherapeutic regimes had included bleomycin and this was thought to be the most likely causative agent. Three patients were seriously ill; 2 of these responded well to high-dose steroids with rapid and major clearing of the infiltrates as assessed clinically and radiologically. The third patient, who had not received steroids, died from cytotoxic drug-induced pneumonitis.

The episode of viral pneumonitis was diagnosed by a positive fluorescent antibody test for influenza B on material from TBLB, the patient subsequently devel-

oped a pleural effusion, the cytology of which revealed Reed Sternberg cells.

On 10 occasions, no definitive diagnosis was made (45%). In 3 of these episodes, improvement was seen clinically and radiologically following treatment with broad-spectrum antibiotics and these were therefore presumed to have been due to pneumonia. In two instances, with non-specific inflammatory changes on TBLB, radiological resolution occurred without any form of treatment and the patients have remained well 12 months later. One patient with Hodgkin's disease had an initial TBLB showing vasculitis, the significance of this was uncertain. He relapsed with evidence of endobronchial Hodgkin's disease 14 months later.

Three of the patients in whom TBLB and respiratory investigations failed to produce definitive diagnoses died whilst in hospital. One patient who had undergone two TBLB three months apart, the first showing normal lung and the second non-specific fibrosis, was found to have cytotoxic drug-induced pneumonitis at autopsy. Autopsies of the remaining 2 patients revealed bronchopneumonia and residual lymphoma not involving the lung in one patient and a previously undiagnosed lymphoma, including lung involvement, in the other. No major complications occurred during or immediately after the procedures: three patients had minor bleeding, and one a pneumothorax not requiring a chest tube.

Changes in management resulting from these investigations are shown in Table III. In 15 of these 22 procedures (68%), the information obtained made a positive contribution to patient management. On 8 occasions (36%) specific treatment was instituted; in 4 chemotherapy (responsible for drug-induced pneumonitis) was stopped, and on 3 occasions serious infection was ruled out. On only one occasion, investigation failed to detect lymphomatous infiltration of the lung, the diagnosis being made at autopsy.

Table II Specific diagnoses reached in 22 episodes of pulmonary infiltration

	Hodgkin's disease	Non-Hodgkin's lymphoma
Number of episodes	8	14
Diagnosis:		
Hodgkin's: Endobronchial	1	
Parenchymal	2	
Pleural	1	
Lymphoma: parenchymal		2
Viral pneumonitis	1	
Cytotoxic induced pneumonitis		4
Lung cancer		1
Diagnostic yield	62.5%	50%

Discussion

The use of invasive investigations in immunocompromised patients with pulmonary infiltrates remains controversial.^{12,13} Robin *et al.*¹³ make the point that, despite the extensive literature, there is no adequate prospective trial which analyses the benefit of lung biopsy in these patients. If patient survival is used as the outcome measure few, if any, of the published series demonstrate a clear benefit from invasive investigations. However, in our experience pursuit of a histological diagnosis did significantly alter management and outcome largely because of the relatively high incidence of tumour involvement of the underlying lung.

In this study TBLB provided the diagnosis in 9 of

Table III Treatment decision made following bronchoscopy

	No. (%) episodes
New treatment started	8 (36)
Toxic chemotherapy stopped	4 (23)
Serious infection excluded	3 (14)
Recurrent disease excluded	5 (23)
None	1 (5)
Incorrect diagnosis	1 (5)

the 12 episodes where a specific diagnosis was established, and with a yield of 43% the results for this technique are similar to many other reported series,¹⁴⁻¹⁸ although yields in excess of 70% have occasionally been reported.^{19,20} In marked contrast to most other published series, however, was the rarity of infection as a proven aetiology for the pulmonary lesion.^{1,7,14,16,21} Several explanations can be clearly identified. Firstly, few of our patients were severely neutropenic. Secondly, where infection was suspected patients had received broad spectrum antibiotics prior to referral. Thirdly, the higher prevalence of fungal infection in North America could account for the overall higher reporting of infective aetiology in their patient series. In addition to these points, however, it is noticeable that most published series include patients

with a range of malignancies (including acute leukaemia) and are orientated towards the appearance of pulmonary infiltrates in the context of acute life-threatening episodes. Such pooled data whilst valuable in stressing the common aspects of differential diagnosis (particularly infection and treatment related pneumonitis) may mask other more disease-specific complications. Our findings are similar to another British series by Phillips *et al.*²⁰ who performed 56 fiberoptic bronchoscopies on 42 patients with underlying Hodgkin's, non-Hodgkin's lymphoma or leukaemia and diagnosed infection in only 3 cases.

Such considerations have practical significance with regard to the choice of sampling techniques performed in association with flexible bronchoscopy. In recent years broncho-alveolar lavage (BAL) has proved to be an extremely effective method for rapid diagnosis of many pulmonary infections in the immunocompromised host and indeed the major change in our practice during the course of this series has been the adoption of formal BAL rather than a simple bronchial washing in the routine investigation of these patients. Pulmonary lymphoma has now been diagnosed from immunological marker studies of lavage lymphocytes^{22,23} but until such techniques are fully validated transbronchial lung biopsy remains a most important investigation where pulmonary lesions are found in the context of lymphoma and in our experience makes a direct and worthwhile impact on management policy.

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