

Early involvement of the bronchi in patients with malignant lymphoma

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Summary Fibreoptic bronchoscopy in previously untreated patients with malignant lymphoma provided diagnostic information in 8 of 25 cases with radiological evidence of intrathoracic involvement. There was a marked difference in the pattern of endobronchial involvement between Hodgkin's Disease (HD) and Non Hodgkin's Lymphoma (NHL) which specifically infiltrated the bronchus-associated lymphoid tissue.

Bronchoalveolar lavage was abnormal in only one patient with Hodgkin's Disease in whom the presence of many Sternberg-Reed cells suggested occult dissemination of otherwise localised disease.

Pulmonary involvement in patients with malignant lymphoma increases in frequency from 5-10% at initial presentation to ~50% of those dying with the disease (Kaplan, 1980; Peckham, 1973; Rosenberg *et al.*, 1961; Sugarbaker & Craven, 1940). There is good radiological and postmortem evidence that this occurs both by direct invasion from adjacent lymph nodes and by lymphatic or haematogenous dissemination from distant sites (Filly *et al.*, 1976; Robbins, 1953; Stolberg *et al.*, 1964; Vieta & Craven, 1941). However, histological evidence of early intrathoracic spread has been inadequate compared with that available for the involvement of the intrabdominal organs (Kaplan, 1980; Peckham, 1973; Rosenberg *et al.*, 1961; Sugarbaker & Craven, 1940; Filly *et al.*, 1976; Robbins, 1953; Stolberg *et al.*, 1954; Vieta & Craven, 1941; Goffinet *et al.*, 1977).

Fibre optic bronchoscopy with endobronchial and transbronchial biopsies, and limited bronchoalveolar lavage has provided diagnostic information in a variety of other pulmonary disorders (Gribetz *et al.*, 1980; Reynolds & Newball, 1974; Haslam *et al.*, 1980). Therefore, we employed these techniques in a series of newly diagnosed patients with radiological evidence of intrathoracic lymphoma to assess the evidence for further dissemination of the disease and the manner in which it had arisen.

Patients and methods

Patients

Twenty five patients with newly diagnosed

lymphoma and a radiological evidence of intrathoracic involvement were bronchoscoped at the Imperial Cancer Research Fund Department of Medical Oncology, St Bartholomew's Hospital over an 18-month period. (Table I). All gave their

Table I Patient characteristics

		Bronchoscoped	Not bronchoscoped
Total	HD	12	13
	NHL	13	8
Stage	HD II	5	8
	III	3	3
	IV	4	2
	NHL II	2	0
	III	1	0
	IV	10	8
Radiological Abnormalities	HD mediastinum	11	12
	hilum	6	10
	parenchyma	4	2
	NHL mediastinum	10	6
	hilum	6	10
	parenchyma	7	2

consent to an elective fibreoptic bronchoscopy. During the same period an additional 21 patients suspected of having intrathoracic lymphoma were seen but not bronchoscoped because of refusal of consent (1 patient), superior venacaval obstruction (5 patients), and the necessity for more urgent treatment (15 patients). Four controls for the bronchoalveolar lavage were drawn from patients who had normal lungs at diagnostic bronchoscopy for unexplained chest X-ray abnormalities.

Histological diagnosis of lymphoma on lymph node biopsy was confirmed in all cases by Dr A.G.

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Stansfeld and clinical or pathological staging completed as previously described. (Lister *et al.*, 1978; Sutcliffe *et al.*, 1978).

Radiology

Routine postero-anterior chest X-ray with penetrated and lateral views and a computerised tomographic scan of the chest were performed in all patients.

Bronchoscopy

Premedication with papaveretum and scopolamine was followed by topical anaesthesia with 4% lignocaine. The bronchial tree was fully inspected to a subsegmental level with an Olympus BF1-TR fiberoptic bronchoscope. In all patients with directly visible abnormalities specimens for cytological examination were then collected by brush and fine catheter aspiration and plated on glass slides for air dried and formalin fixed preparations. Endobronchial and transbronchial biopsies were collected from those areas which were abnormal on direct inspection or by radiological examination.

Bronchoalveolar lavage

Bronchoalveolar lavage was performed in 10 patients and 4 controls (Table III). The lavage procedure employed 300 ml of sterile saline (buffered to pH 7) introduced in 60 ml aliquots and aspirated into iced siliconised bottles containing 20 ml RPMI 1640 and 1000 units of heparin. The cells obtained by bronchoalveolar lavage were assessed morphologically and by surface markers as previously described. (Habeshaw & Young, 1978; Dorreen *et al.*, 1982).

Results

Radiology

Radiological abnormalities in the chest were equally distributed between those with HD and NHL with the mediastinum being the most common site of involvement (Table I).

Fibre optic bronchoscopy

Fibre optic bronchoscopy was accomplished without complication in all 25 patients. Eight patients (32%) had lymphoma visible in the major airways although the pattern varied markedly with the histological type. (Table II).

All 3 patients with HD showed direct invasion of the trachea or main bronchi by lymphoma from the surrounding node masses. (Figure 2). All 5 patients

Table II Bronchoscopy

Patient	Diagnosis	X ray	Bronchoscopy	Biopsy
F.C.	HD IV _B MC	m,h,p,ple	mass R.middle and lower main bronchi	MC. HD.
M.D.	HD II _A NS	m	masses in mid trachea	NS. HD.
P.S.	HD IV _A MC	m,h,p	mass R. middle and upper main bronchi	not diagnostic
A.C.	NHL IV Ib	m,h	multiple submucosal masses	Ib NHL
M.C.	NHL IV Ib	h,p	multiple submucosal masses	Ib NHL
E.H.	NHL IV Cb	m,h	submucosal masses	Cb NHL
S.S.	NHL IV Ib	m,h,p,ple	submucosal masses	Ib NHL
H.T.	NHL IV Lpc	m	submucosal masses	Lpc NHL

MC=mixed cellularity; NS=nodular sclerosing; Ib=immunoblastic; Cb=centroblastic; Lpc=lymphoplasmacytoid; m=mediastinal nodes; h=hila nodes; p=parenchymal infiltration; ple=pleural effusion.

with NHL had multiple submucosal masses visible at each division of the bronchial tree in the normal sites of bronchus-associated lymphoid tissue. (Figure 1).

Endobronchial biopsies of similar histological appearance to that of the diagnostic lymph node specimens were obtained in 7/8 patients from the sites of visible involvement and in the eighth patient the transbronchial biopsy was positive. In both HD and NHL the mucosal epithelium was intact over the lymphomatous mass in the submucosa. (Figures 1-6). In one patient the appearance of the endobronchial specimens was inconclusive.

The routine cytological specimens were entirely normal in keeping with the intact epithelium.

Bronchoalveolar lavage

Bronchoalveolar lavage produced an average return of 120 ml with 10⁶ to 10⁸ cells. The relative proportions of macrophages and T and B lymphocytes are given in Table III.

In only one patient (MD) with Hodgkin's Disease was there a marked abnormality of the lavage fluid, with decreased macrophages, many Sternberg-Reed (S-R) like cells and a high proportion of T lymphocytes. The binucleate S-R like cells were not E rosette or surface immunoglobulin positive, did not pinocytose neutral red nor have Fcγ or C3d receptors, but were positive for HLA A, B & C and DrW antigens.

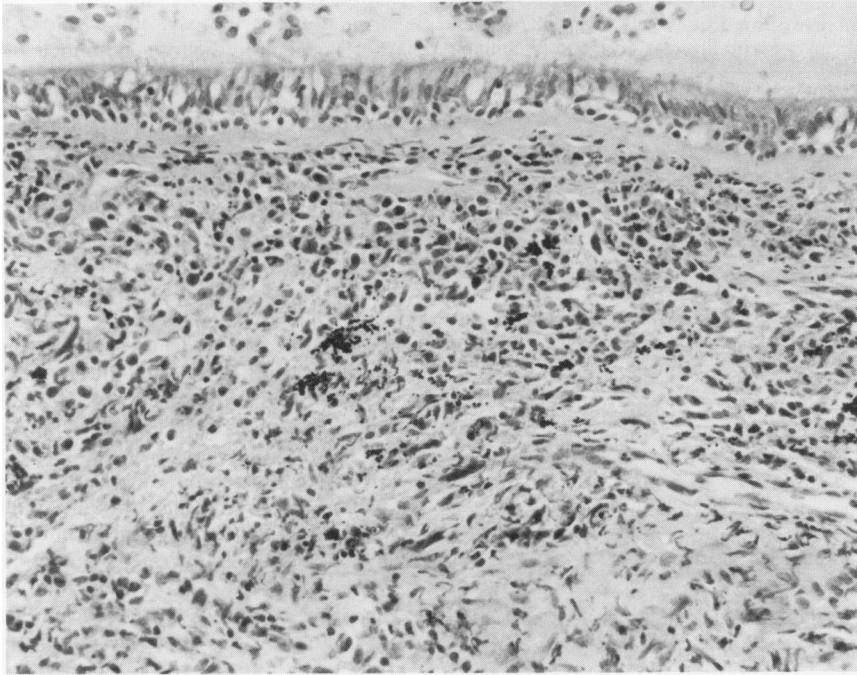


Figure 1 Infiltration of the normal bronchus-associated lymphoid tissue by immunoblastic Non Hodgkin's Lymphoma. H and E $\times 250$.

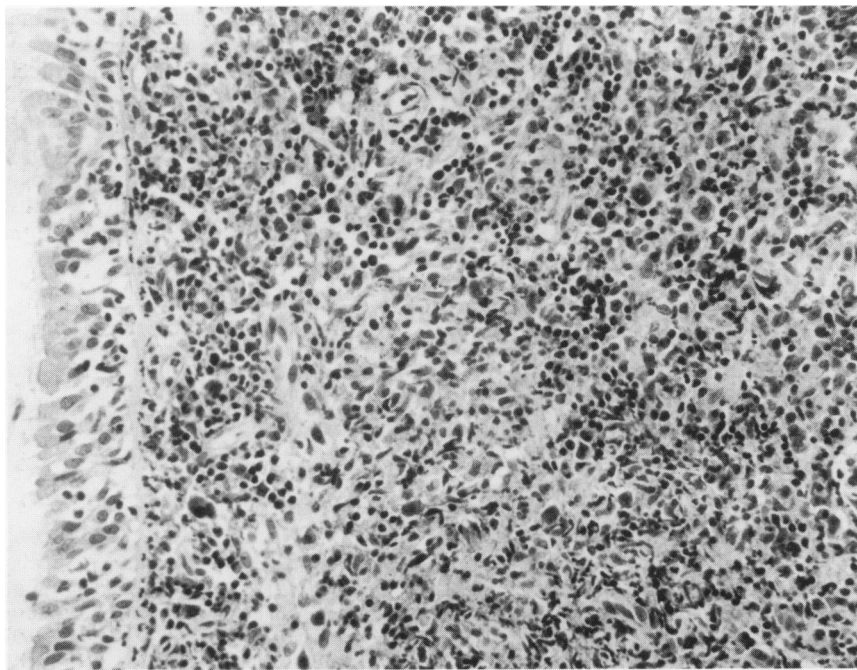


Figure 2 Infiltration of the tracheal wall by Hodgkin's Disease beneath an intact surface epithelium. H and E $\times 165$.

Table III Relative proportions of macrophages and lymphocytes from broncho alveolar lavage in lymphoma

Patient	Diagnosis	Smoking history	No. cells	Percent			
				macro-phages	T cells	B cells	
M.D.	HD II _A NS	NS	10 ⁸	27	53	4	
P.S.	HD IV _A MC	S	10 ⁸	92	6	1	
L.T.	HD IV _B NS	S	10 ⁸	92	2	1	
F.W.	HD II _A NS	NS	10 ⁶	75	20	2	
L.W.	HD II _B NS	NS	10 ⁶	70	21	5	
M.B.	NHL II Ib	S	10 ⁸	80	10	2	
P.C.	NHL IV cc	S	10 ⁸	90	5	1	
E.H.	NHL IV Cb	NS	10 ⁷	70	25	3	
H.S.	NHL IV cc	S	10 ⁸	90	5	1	
S.S.	NHL IV Ib	NS	10 ⁶	65	29	6	
Controls (average of two)			S	10 ⁸	85	10	2
Controls			NS	10 ⁷	65	20	5

For abbreviations see **Table II**.

Discussion

Fibre optic bronchoscopy disclosed a higher incidence (8/25, 32%) of endobronchial disease at presentation in patients with malignant lymphoma than has previously been appreciated (Gribetz *et al.*, 1980; Phillips *et al.*, 1980).

The pattern of lymphomatous involvement varied with the histological type. All 3 patients with HD showed direct extension into the lumen from the surrounding nodal mass, whereas the 5 patients with NHL showed disseminated involvement of the "bronchus-associated lymphoid tissue" (Bienenstock, 1973) at each bronchial orifice. Patients with HD and a positive bronchoscopy, had lymphoma which was confined to the thorax, whilst in NHL all but one patient had widely disseminated disease outside the chest. Although there are reports of the diagnosis of both HD and NHL on sputum cytology (Giangreco *et al.*, 1980; Supron & Kross, 1964) these have all been in patients with advanced disease. By contrast in this group with newly diagnosed lymphoma the appearances at

bronchoscopy, biopsy, and cytology all showed that the surface epithelium remained intact over the lymphomatous deposits.

Bronchoalveolar lavage has been used to investigate the pulmonary lymphoid tissue in both health and in a variety of diseases (Haslam *et al.*, 1980; Hunninghake *et al.*, 1979; Danielle *et al.*, 1977) but not previously in lymphoma. Alveolar macrophages and lymphocytes were present in normal proportions in lymphoma except in one patient with mediastinal nodular sclerosing HD. In this patient the Sternberg-Reed cells may have been shed from the associated infiltrating mass in the tracheal wall; however, the overlying respiratory epithelium was intact. Alternatively, they may have entered the alveoli from the blood stream as do the normal cellular constituents (Hocking & Golde, 1979; van Blusse and van Furth, 1979). This implies dissemination from the thoracic duct lymph which has been observed to contain Sternberg-Reed cells in association with mediastinal disease (Young, 1956; Watne *et al.*, 1960). In this case the peripheral blood was normal, and no other disease was found at staging laparotomy therefore treatment was given by mantle radiotherapy. However, relapse has occurred 16 months later with disseminated extranodal disease requiring chemotherapy.

In conclusion, bronchoscopy in newly diagnosed patients with malignant lymphoma with radiological evidence of ML demonstrated a previously unrecognised incidence of endobronchial disease which had arisen by direct infiltration in those with HD in comparison with lymphatic spread in those with NHL. If confirmed by further investigation these findings may provide an explanation for the worse prognosis of some patients with apparently localised Hodgkin's Disease (Mauch *et al.*, 1978; Lee *et al.*, 1980).

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