Lung involvement in Hodgkin's disease

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Macdonald, J. B. (1977). *Thorax*, 32, 664-667. **Lung involvement in Hodgkin's disease.** Lung involvement occurred in 43% of 284 patients with Hodgkin's disease in Nottingham during 1960-75. It was commoner than pleural, hilar or mediastinal node involvement, although over three-quarters of patients with any other thoracic manifestation subsequently developed pulmonary involvement. The patients with pulmonary involvement contained significantly fewer with the histological feature of lymphocyte predominance. The commonest radiographic type, peribronchial infiltration, tended to occur early in the course of the disease while less common types, homogeneous or pneumonic infiltrates and nodules, occurred later. Modern chemotherapy was very effective in the treatment of pulmonary Hodgkin's disease. Since two-thirds of the patients who developed lung involvement already had stage IIIB or IV disease, the early use of chemotherapy should reduce the incidence of this common complication.

Lung involvement is common in Hodgkin's disease, occurring in 15-40% of patients (Ellman and Bowdler, 1960). Its radiology has been described in detail by Sheinmel *et al.* (1950) and Wolpaw *et al.* (1944) and its pathology by Stolberg *et al.* (1964). However, these reports and others, such as that of Peckham (1972), have been descriptive rather than analytical. In this paper all the patients attending a large regional centre over a 16-year period were studied and 122 cases of pulmonary involvement were analysed.

Patients and methods

The case notes of all patients with Hodgkin's disease in the Nottingham area from 1960 to 1975 inclusive were assessed. Only patients with unequivocal histological proof of the disease were included, and the standard classification by Lukes *et al.* (1966) was used. All the chest radiographs taken during or after 1969 were reviewed by the author. The criteria for accepting lung involvement in Hodgkin's disease were: (1) presence of a lesion proven by necropsy, lung biopsy or bronchial biopsy to be Hodgkin's disease involving the lung (92 patients); (2) presence of a non-transient radiographic lung lesion responsive only to Hodgkin's disease chemotherapy or to radiotherapy in a patient with Hodgkin's disease (21 patients); or (3) radiographic appearances typical of pulmonary involvement in a patient with

Hodgkin's disease (9 patients). Radiographic and postmortem evidence of hilar or mediastinal node involvement and of other intrathoracic complications was noted. Pulmonary involvement was subdivided radiographically in a simplified version of the classification of Sheinmel *et al.* (1950).

Results

Table 1 shows the type of intrathoracic involvement found. More than half the 284 patients developed intrathoracic involvement at some stage in the disease, and these types of involvement were often associated. In 91 of the 122 cases of lung involvement hilar or mediastinal nodes were also involved. No case of purely pulmonary Hodgkin's disease was found.

PULMONARY INVOLVEMENT

Of the 122 patients with lung involvement, 26 had

Table 1 *Type of intrathoracic involvement in 284 patients*

Involvement	No. of patients
Lung	122 (43%)
Hilar nodes	97 (34%)
Mediastinum	66 (23%)
Pleura	32 (11%)
No intrathoracic involvement	137 (48%)
Total No. of patients	284 (100%)

two types and two patients three types of radiographic appearance. The classification of pulmonary changes is shown in Table 2. All types of change occurred slightly more frequently in the right lung than in the left, especially 'pneumonic' infiltration (15R, 4L) and direct invasion (17R, 7L). About one-third of changes noted were bilateral, although nodules were bilateral in seven out of 12 cases.

Table 3 shows the histological classification in the 276 patients in whom this was known. Three of the eight patients without histological classification had lung involvement. The group with pulmonary involvement contained significantly fewer with lymphocyte predominance ($P < 0.01$). There was no significant correlation between histology and radiographic type of lung involvement. Lung involvement was proven in 92 cases (75%)—by necropsy in 83 patients, by bronchial biopsy in eight patients, and by lung biopsy in one patient. Dyspnoea was the only significant symptom, being reported by 26 patients.

Radiotherapy was given to the involved lung in 13 patients but produced a partial response in only two. However, 29 of the 71 patients given chemotherapy showed complete resolution of the radiographic lesions, with partial response in 34 patients and no response in eight patients. Thus chemotherapy was markedly superior to radiotherapy.

The interval between diagnosis of Hodgkin's disease and the first evidence of pulmonary involvement ranged up to 11 years, with a mean of

17.6 months. In 44 of the 122 patients (36%) pulmonary involvement was present at diagnosis. Peribronchial involvement occurred earlier than other types (mean 12.5 months) while homogeneous infiltrates occurred later (mean 29 months). Homogeneous infiltration always developed after diagnosis, and nodulation was present at diagnosis in only two of 12 cases.

Survival rates after the development of pulmonary involvement were calculated by the method of Bradford Hill (1971). Table 4 shows that survival rates were better for patients with late involvement and markedly better for patients receiving chemotherapy. Survival was particularly poor in patients with 'pneumonic' infiltration.

In order to assess at what stage of Hodgkin's disease the lung involvement occurred the clinical stage of the disease immediately before the development of lung involvement was noted, using the standard staging criteria of Rosenberg *et al.* (1971). The results shown in Table 5 demonstrate that lung involvement provided the first evidence of extralymphatic spread in 90 (74%) of the 122 patients.

Table 4 Survival rates after the development of lung involvement

	Onset		Chemotherapy	
	Present at diagnosis	Developed later	Given	Not Given
At 2 years	23%	39%	60%	20%
At 5 years	13%	17%	31%	5%

Table 2 Type of radiographic change seen in pulmonary involvement

	No. of cases
Direct invasion from hilar or mediastinal nodes	36 (30%)
Peribronchial or endobronchial infiltrates	74 (61%)
Substantial homogeneous infiltrates	6 (5%)
Patchy 'pneumonic' infiltrates	24 (20%)
Nodules	12 (10%)
Total No. of patients	122 (100%)

Table 3 Histological classification of patients with and without pulmonary involvement (276 patients)

	Pulmonary involvement		Significance
	With	Without	
Lymphocyte predominant	8 (7%)	29 (19%)	$P < 0.01$
Nodular sclerosis	32 (26%)	49 (32%)	NS
Mixed cellularity	49 (40%)	45 (29%)	$0.05 < P < 0.1$
Lymphocyte depleted	33 (27%)	31 (20%)	NS
Total	122 (100%)	154 (100%)	

Table 5 Clinical stage of disease immediately before lung involvement (122 patients)

	Stage			
	I	II	III	IV
A	0	20	18	3
B	0	7	45	29
Total	0	27	63	32

HILAR NODE INVOLVEMENT

Of the 284 patients with Hodgkin's disease, 97 (34%) had enlarged hilar nodes at some stage. Node enlargement was bilateral in 69 of the 97 patients. Seventy-six of these patients also developed lung involvement. No specific histological type was significantly associated with hilar node enlargement. Radiotherapy or chemotherapy was given to 96 patients: in 17 patients the node enlargement disappeared completely, in 52 patients

the nodes became smaller and in 27 patients no response was seen. Comparison of responses to radiotherapy and chemotherapy showed no significant difference.

MEDIASTINAL NODE INVOLVEMENT

Enlargement of mediastinal lymph nodes (excluding superior and inferior tracheobronchial nodes) was seen in 66 of the 284 patients (23%). Paratracheal nodes were involved in 34 cases, anterior mediastinal nodes in 20 cases, and posterior mediastinal nodes in two cases. Involvement of both paratracheal and anterior mediastinal nodes occurred in only four cases, and the node group was not recorded in 14 cases.

Mediastinal node enlargement was strongly associated with both hilar node enlargement (47 of 66 cases) and pulmonary involvement (47 of 66 cases). Mediastinal nodes showed similar response rates to radiotherapy and chemotherapy, and again no histological type predominated.

OTHER INTRATHORACIC INVOLVEMENT

Of the 284 patients, 32 (11%) developed pleural effusions which persisted or disappeared only on specific treatment. Twenty-three of these patients also had pulmonary involvement. The effusion was unilateral in all but three of the patients. Pleural plaques were seen in 24 patients—20 of these had pulmonary involvement. Rib erosions were seen in nine patients, leading to pathological fracture in two patients. Sternal erosions developed in two patients and two patients had pericardial effusions.

Discussion

Before the advent of chemotherapy pulmonary involvement was regarded as a late complication of Hodgkin's disease, giving a poor prognosis (Levinson *et al.*, 1957). The survival rates without chemotherapy in the present study confirm this finding. However, lung involvement responds well to chemotherapy, with a massive rise in two- and five-year survival rates. A considerable proportion of the patients in this study had received chemotherapy before the modern chemotherapy regimens were standardised. Thus current survival figures are likely to be even better than those presented. Of patients given modern chemotherapy, those with lung involvement appear to fare as well as those without. However, small numbers prevent detailed analysis of this point.

The present study shows that lung involvement is a common feature in Hodgkin's disease—perhaps commoner than is often realised. It occurred

more frequently than hilar node involvement, and over three-quarters of patients with hilar node enlargement also developed lung involvement. In one-third of all patients studied, lung involvement provided the first evidence of stage IV disease. Thus the role of the routine chest radiograph in monitoring the progress of Hodgkin's disease is well founded. Most previous studies have noted a strong association between hilar and lung disease but that lung involvement without mediastinal disease does occur occasionally (Sheinmel *et al.*, 1950; Ellman and Bowdler, 1960; Kern *et al.*, 1961). However, a recent study by Whitcomb *et al.* (1972) noted hilar lymphadenopathy in all 29 patients with lung involvement and felt that, without hilar nodes, lung involvement is distinctly unlikely. In the present series 31 patients had lung manifestations without hilar or mediastinal node enlargement, and 23 of these cases were supported by postmortem findings. Thus hilar node enlargement is by no means a prerequisite for lung involvement. This can be important practically, in the differential diagnosis of a lung lesion in a patient with Hodgkin's disease. Some authors such as Verse (1931) and Kern *et al.* (1961) have noted cases of Hodgkin's disease confined solely to the lungs, but none was found in this study and this presentation is likely to be very rare.

While the radiological appearances of pulmonary Hodgkin's disease are well described, the frequency of occurrence of the various radiological types is less well documented. The present results fit in well with the theory of Wolpaw *et al.* (1944) that the distribution of involvement is primarily governed by the location of the lymphoid tissue within the lung. The major site of organised lymphoid tissue is at points of bifurcation of bronchi and pulmonary vessels (Stolberg *et al.*, 1964; Murray, 1976), and infiltration occurs along peribronchial and perivascular lymphatics. In the present study this is indeed much the most common type of involvement seen radiographically. Direct spread along peribronchial lymphatics from hilar nodes is another variant whose predicted frequency seems to be confirmed in practice. Small clusters of lymphocytes are also distributed throughout the lung in connective tissue. The less common radiological appearances—nodules, 'pneumonic' or homogenous infiltrates—may arise either in these aggregates or in more peripheral peribronchial or perivascular nodes. With a relative abundance of local lymphoid tissue one might expect peribronchial involvement to occur earlier in the disease than other types, and the present findings confirm this. Conversely, more peripheral involvement such as 'pneumonic' and homogene-

ous infiltrates tend to occur relatively late. In this series 36% of patients had lung involvement at presentation. This figure is considerably higher than the 4.4% found by Peckham (1972) and nil noted by Fisher *et al.* (1962). These series are from highly specialised units serving areas within a large city. The present study is of a whole region and may give a more representative cross-section.

The type of histology in patients with lung involvement is somewhat controversial. Most studies were reported before the Lukes classification (Lukes *et al.*, 1966) was adopted. The present study shows that patients with lung involvement are less likely to have lymphocyte predominance than those without pulmonary involvement. However, Whitcomb *et al.* (1972) showed 26 of 29 patients with lung involvement to have the nodular sclerosing type. This study in a military hospital included only young adult patients with a mean age of 25 years, compared to the present study of a whole regional population with a mean age of 43 years. My finding that a substantially higher proportion of patients under the age of 40 years with lung involvement had the nodular sclerosing type may well explain this discrepancy.

At the onset of pulmonary involvement over two-thirds of patients already had stage IIIB or stage IV disease. In two-thirds of these patients the diagnosis had been made at least two months before pulmonary involvement occurred. Thus nowadays almost half the patients would have started chemotherapy before their lung involvement had a chance to occur. Since chemotherapy treats this complication effectively, the incidence of lung involvement is likely to fall with modern chemotherapy regimens.

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