Intrathoracic Manifestations of Malignant Lymphomatous Disease*.

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Involvement of intrathoracic structures by malignant lymphomatous disease has long been recognized and variations in distribution of lesions described.1,2,3 Despite this background the possibility of malignant lymphoma is often overlooked in the differential diagnosis of pulmonary and mediastinal disease. In an effort to further delineate the clinical pattern of this condition we have reviewed the problem directing particular attention to pulmonary symptoms and signs and to chest films.

**Material**

One hundred cases with the diagnosis of malignant lymphoma confirmed by biopsy or autopsy during the period 1950 through 1958 were selected at random from the files of the North Carolina Baptist Hospital. Autopsy material was available in 16 instances. Five diagnostic categories, modified from Custer's classification,4 were considered to comprise the malignant lymphoma group: Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, giant follicular lymphoma and chronic lymphocytic leukemia. Further subdivision within these groups has not been helpful clinically and has afforded no better understanding of the process. Of the patients studied 35 had Hodgkin's disease, 20 had lymphosarcoma, 26 had chronic lymphocytic leukemia, 12 had reticulum-cell sarcoma and seven giant follicular lymphoma. Of these patients 40 have died and 29 have been lost to follow-up. The average duration of follow-up for the entire series was 22 months. Sex distribution is given in Table 1. Of the entire series, 55 were men, 45 women.

**Symptoms and Signs**

Pulmonary symptoms (Table 2) were infrequent despite a high incidence of intrathoracic involvement as indicated by chest films. Non-productive cough and dyspnea were the most common symptoms but were rarely troublesome in the absence of infection or pleural effusion. Other symptoms encountered were chest pain, usually a non-specific aching, choking, and hoarseness. Pierce et al5 have also noted the infrequency of symptoms referable to intrathoracic lesions despite radiologic evidence of extensive disease.

In the absence of pleural effusion, objective evidence of intrathoracic disease on physical examination was unusual. Two patients who had lymphocytic leukemia with widespread pulmonary dissemination had clubbing of the fingers and toes; one of them was also cyanotic as was another with lymphosarcoma. Distention of the jugular and sublingual

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veins, prominent thoracic venous collateral pattern and edema of the upper extremities suggested superior vena cava obstruction in one with Hodgkin's disease and in another with reticulum-cell sarcoma.

**Radiographic Findings**

Fifty patients had radiographic findings suggestive of malignant lymphoma on the initial chest film and four others subsequently presented x-ray film evidence of pulmonary disease. The site and nature of the lesions are shown in Table 3. Hilary adenopathy was the most common finding in this series being present in 34 of 54 patients with positive films and was more frequently bilateral than unilateral. Twenty-two of them showed enlargement of the paratracheal nodes as well. Parenchymal lesions were present in 23 and were of four types: solitary nodules in two, scattered nodular densities in seven, pneumatic infiltrative lesions in 10 and diffuse lymphatic dissemination in four. Kerley's lines, indicative of interstitial edema or infiltration, were observed twice while cavitation was seen in one patient. Eighteen gave evidence of pleural involvement with effusion present at sometime in all of them. Six presented radiographic findings suggestive of phrenic nerve paralysis, three of the right and three of the left.

In this series, 71 per cent of patients with Hodgkin's disease had chest lesions in contrast to an incidence of 30 per cent in the study of Kirklar and Hefke. In contrast, Vieta and Craver found 74 per cent of their patients with Hodgkin's disease to have x-ray film changes indicative of the process. Parenchymal lesions were present in 23 per cent of our patients with malignant lymphoma whereas Robbins found an incidence of only 7 per cent in a series of 715 cases. Comparison of such series is of questionable value because of differences in pathological classification, methods of treatment and follow-up data.
TABLE 1—DISEASE CATEGORIES RELATED TO SEX AND TO THE PRESENCE OR ABSENCE OF ROENTGENOGRAPHIC EVIDENCE OF LYMPHOMA

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Films +</th>
<th>Films 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>15</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Leukemia</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Retic. Cell</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Giant Foll.</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>100</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

Accessory Clinical Findings

Other clinical findings are presented in Table 4. The most frequent physical finding noted was peripheral lymphadenopathy which was present in 73 patients, 39 with positive and 34 negative chest films. Splenomegaly was present in 47 patients, fever in 45, hepatomegaly in 30, anemia in 29, and eosinophilia in 16, 14 with and two without pulmonary manifestations. Anemia was not found in any patient with lymphosarcoma. Abnormal serum proteins (decreased albumin, elevated globulin or both) were found in 24 of 45 while sedimentation rate was elevated in 44 of 60 patients. Intermediate PPD skin test was positive in seven and negative in two individuals. Two with lymphocytic leukemia presented with exfoliative dermatitis.

Examination of pleural fluid in six cases revealed clear yellow fluid in five and colorless in one. Counts were done twice, one showing 2800 white cells and the other 1300 cells/cu. mm. Lymphocytes predominated and no eosinophilia was noted. Cytologic studies of pleural fluid in five instances were not helpful while cultures for acid fast bacilli were negative on two occasions. Chylothorax, a frequently noted complication, was seen once.

FIGURE 2

FIGURE 3

Differential Diagnosis

Intrathoracic lymphoma may mimic many benign or malignant conditions including tuberculosis, carcinoma, sarcoidosis, "collagen" disease, tularemia, infectious mononucleosis, substernal goitre, dermoid cyst, thymoma and other mediastinal tumors so that tissue diagnosis is mandatory. Conditions with intrathoracic manifestations and peripheral eosinophilia which must be differentiated from lymphoma include: Loeffler's syndrome, coccidioidomycosis, parasitic infestations, polyarteritis nodosa and carcinoma.

The following case reports present some of the problems which arise when only intrathoracic manifestations are present.

Case 1. This 38 year-old white married woman was referred with a six-week history of dyspnea and left pleural effusion. Prior to the onset of her illness, she had been in good health. Physical examination revealed an alert woman with obvious respiratory distress and signs of massive left pleural effusion. The blood pressure was 110/80 and the pulse was 120. Liver and spleen could not be palpated and no peripheral node was felt. Laboratory studies revealed hemoglobin of 16.4 gm. per cent, white blood cells 8,000 and normal differential count. An intermediate PPD skin test was recorded as three plus. During thoracentesis, 1800 cc. of straw colored fluid containing 2800 cells/ cu. mm. with 89 per cent lymphocytes and 11 per cent neutrophiles were obtained. Cytological examination of the fluid was not helpful. A right apical infiltrate and massive left pleural effusion were seen on chest film (Fig. 1) and the diagnosis of tuberculosis was strongly considered. She was then transferred to a tuberculosis sanatorium for further study where unusually rapid re-accumulation of pleural fluid led to supraclavicular node biopsy which revealed lymphoblastic lymphosarcoma. She was then returned to this institution where intrapleural and parenteral nitrogen mustard therapy was given without response. Her course was progressively downhill and she expired at home six weeks later.

Comment: This represented a problem in the differential diagnosis of pleural effusion in the presence of a positive intermediate PPD skin test, an apical lesion suggestive of tuberculosis and a normal pleural fluid cytology. The rapid massive re-accumulation of pleural fluid following thoracentesis is more typical of malignancy and this observation led to the correct diagnosis. In retrospect, left scalene fat pad or pleural biopsy might have led to an early diagnosis. The "feel" and thickness of the

FIGURE 4. Case 4: At autopsy this patient was found to have Hodgkin's disease involving the right lower lobe, right hilar nodes and liver and lipoid pneumonia of the right middle and lower lobes.
TABLE 2—RELATION OF SYMPTOMS TO ROENTGENOGRAPHIC EVIDENCE OF DISEASE

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chest Film</th>
<th>Hodgkin’s</th>
<th>Lympho-</th>
<th>Lymphocytic</th>
<th>Retic.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>+</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>+</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>+</td>
<td>4</td>
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<td>1</td>
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<td>Choking</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Hoarseness</td>
<td>+</td>
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<td>0</td>
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<td>1</td>
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<td></td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms</td>
<td>+</td>
<td>12/25</td>
<td>5/10</td>
<td>4/9</td>
<td>4/7</td>
<td>25/54</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1/10</td>
<td>1/10</td>
<td>2/17</td>
<td>0/5</td>
<td>4/46</td>
</tr>
</tbody>
</table>

None of the seven patients with giant follicular lymphomas had pulmonary complaints.

pleura observed on inserting the aspirating needle at times suggests extensive infiltration. When these findings are present, a needle biopsy of the pleura is often helpful.

Case 2. A 49 year-old woman was first admitted because of a 3 cm. “coin lesion” in the left upper lobe which had been noted on a routine chest film (Fig. 2). Physical examination was within normal limits while laboratory data included hemoglobin of 13.2 gms. and white blood cells of 8,000 with a normal differential count. Exploratory thoracotomy was done and the pathologic diagnosis of lymphosarcoma made. She did well following a course of postoperative irradiation but a nine-month follow-up chest film showed recurrence of her disease (Fig. 3). At that time she was asymptomatic. A second course of radiation therapy was given with a good response which has been maintained for 21 months.

Comment: The solitary circumscribed pulmonary nodule presents a recurring problem to the physician. Mitchell and Taylor reported an operative series of such cases in which the incidence of malignancy was 39 per cent and pointed out that exploratory thoracotomy is often necessary to establish the correct diagnosis.

Lymphosarcoma, without parenchymal extension or regional adenopathy, was found at surgery; whether this case represents primary lymphosarcoma of the lung is problematical. Resection was thought to have been adequate but extensive recurrence without symptoms was noted nine months later.

Case 3. A 62 year-old white woman was admitted with a history of non-productive cough and progressive dyspnea for one year. For 25 years, she had used oily nose drops excessively. Exploratory thoracotomy elsewhere six months earlier revealed extensive disease in the right lung. Biopsy was reported as lipoid pneumonia and no resection was carried out. Her symptoms persisted and she was admitted to this institution for further evaluation. Physical examination revealed blood pressure of 130/40, temperature 106°F, and pulse 108. Rhonchi and scattered moist and coarse rales were audible throughout both lung fields while dulness and diminished breath sounds were noted at the right lung base. The remainder of the examination was unremarkable. Laboratory data included hemoglobin of 7.4 gms. and white blood cells of 16,300 with a normal differential. Her chest film is shown in Fig. 4.

She was given penicillin and whole blood preparatory to re-exploration of her chest which she declined. She deteriorated rapidly thereafter and expired within two months. Autopsy revealed lipoid pneumonia of the middle and lower lobes of the right lung and Hodgkin’s disease involving the lower lobe of the right lung, the hilar nodes and the liver.

Comment: The coincidental occurrence of lipoid pneumonia and Hodgkin’s disease was not detected ante-mortem despite exploratory thoracotomy. In this instance, the

TABLE 3—SITES OF INTRATHORACIC INVOLVEMENT IN 54 PATIENTS WITH POSITIVE CHEST FILMS

<table>
<thead>
<tr>
<th>Hodgkin’s (25)</th>
<th>Lymphosarcoma (10)</th>
<th>Leukemia (9)</th>
<th>Retic. Cell (7)</th>
<th>Giant Poll. (3)</th>
<th>Total (54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>7</td>
<td>5</td>
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<td>5</td>
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</tr>
<tr>
<td>Parenchymal</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hilar</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Paratracheal</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
presence of lipoid pneumonia seemed an adequate explanation for her symptoms, although her anemia is difficult to account for on this basis. Unfortunately, a second thoracotomy was declined.

One is tempted to speculate that the use of oily nose drops might have contributed to the development of lymphoma, but there is no clinical or experimental grounds for yielding to such temptation.11 The pulmonary tissue response to lipoid substances is fibrous and granulomatous and fat is diffusely distributed in most instances.11 This patient presented an atypical story of lipoid pneumonia, symptoms rarely being this marked. The distribution of lesions suggests that a tumor might have been primary in the chest and that early resection might have been warranted.

**Autopsy Material**

Thirty-eight patients died during the follow-up period as a result of their disease and two from unrelated conditions, one from carcinoma of the stomach coexistent with Hodgkin's disease of the stomach and the other with myocardial infarction. Autopsy, performed in 16 cases, 13 of whom had positive and three negative chest films, confirmed radiographic impressions in all. Five patients at autopsy, however, were found to have cardiopericardial disease whereas only one was suspected of having these changes during life. No symptom was recorded which suggested such involvement, an experience similar to that of Nabarro10 who reported physical findings, chest film and electrocardiogram of little help in making an ante-mortem diagnosis. He reported 16 of 60 lymphoma patients to have cardiopericardial involvement at autopsy.

**Relation of Intrathoracic Manifestations to the Natural History of the Disease**

Analysis of such a series as this is difficult though these data suggest that x-ray film findings of intrathoracic lesions portend greater dissemination of disease. Anemia, fever, and enlargement of the liver and spleen are more common with intrathoracic lesions but the latter are even more frequent than any single one of these findings. There is general agreement that pulmonary involvement indicates widespread disease but feelings are mixed about the prognostic importance of such findings.2,13,14 Mortality in this series was greater in the group with positive chest films but conclusions cannot be drawn from this because data are insufficient to relate duration of disease to film findings and to the type of disease present.

| TABLE 4—ACCESSORY CLINICAL FINDINGS RELATED TO INCIDENCE OF INTRATHORACIC LESIONS |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Chest Film | Anemia | <10.5 gms. Fever | Liver | Spleen | ESR >15 | Eosinophilia >5 per cent |
| Hodgkins | + (25) | 12 | 18 | 9 | 13 | 16/20 | 9 |
| | 0 (10) | 3 | 5 | 3 | 3 | 5/6 | 1 |
| Lymphosarcoma | + (14) | 0 | 4 | 3 | 3 | 2/2 | 5 |
| | 0 (10) | 0 | 0 | 1 | 2 | 3/6 | 0 |
| Leukemia | + (9) | 4 | 6 | 5 | 8 | 4/5 | 0 |
| | 0 (17) | 3 | 4 | 3 | 13 | 5/11 | 0 |
| Retic. Cell | + (7) | 1 | 4 | 2 | 3 | 3/3 | 0 |
| | 0 (5) | 3 | 2 | 2 | 1 | 4/4 | 0 |
| Giant Foll. | + (3) | 2 | 1 | 2 | 1 | 0/1 | 0 |
| | 0 (4) | 1 | 1 | 0 | 0 | 2/2 | 1 |
| Total | + (54) | 19 | 33 | 21 | 28 | 25/31 | 14 |
| | 0 (46) | 10 | 12 | 9 | 19 | 19/29 | 2 |
Discussion

Several points deserving emphasis emerge from this study. The history and physical examination are of little help in determining the presence or absence of chest disease in lymphoma although the chest film is frequently helpful, particularly when both hilar and paratracheal nodal enlargement is apparent. That intrathoracic findings were present in 54 per cent of our patients and were more frequent than such well recognized features as hepatosplenomegaly, fever, anemia and eosinophilia enhances the value of the routine chest film in diagnostic study. No clinical syndrome or roentgenographic pattern characteristic of any one of the types of malignant lymphoma were encountered.

SUMMARY

In 100 random, pathologically proved cases of malignant lymphoma, 54 presented evidence of intrathoracic disease. Lack of symptoms or signs referable to these lesions was striking.

Hilar adenopathy was the most frequent radiographic finding noted and when associated with paratracheal nodal enlargement was most suggestive of the final diagnosis. Parenchymal and pleural lesions were non-specific in appearance. Eosinophilia when present usually indicated the presence of intrathoracic disease.

Patients who presented positive roentgenographic signs on initial chest studies tended to have more diffusely disseminated disease and seemed to have a slightly worse prognosis than those who presented with normal chest films.

RESUMEN

En 100 casos tomados al azar de linfoma maligno demostrado anatomicopatológicamente, 54 tenían evidencias de enfermedad intratorácica. Es sorprendente la falta de síntomas o signos atribuibles a esas lesiones.

La adenopatía hilar fue el hallazgo más frecuente y cuando se encontró asociado a crecimiento paratraqueal de ganglios, fue lo mas sugestivo del diagnóstico final. Las lesiones parenquimatosas y pleurales fueron no específicas en apariencia. La eosinofilia cuando se presentó generalmente indicó la presencia de enfermedad intratorácica.

Los enfermos que presentaron signos radiológicos positivos inicialmente tendieron a tener enfermedad mas difundida o diseminada y parecieron tener un pronóstico ligera-mente peor que los que tenían radiografía normal de tórax.

RESUMÉ

Dans 100 cas de lymphome malin, choisis au hasard, et prouvés par l'anatomie pathologique, 54 s'accompagnaient d'une atteinte intrathoracique. L'absence de symptômes ou signes attribuables à ces lésions est frappante.

Une adénopathie hilare est la constatation radiographique la plus fréquente, et lorsqu'elle est associée à une hypertrophie ganglionnaire paratraîchée, elle est plus évocatrice du diagnostic définitif. Les lésions parenchymateuses et pleurales se présen-tèrent sans caractère de spécificité. L'eosinophilie, quand on la trouve de façon con-stante, est en faveur d'une atteinte intrathoracique.

Les malades, chez qui on décèle des signes radiographiques positifs lors des premiers examens thoraciques, ont tendance à être l'objet d'une dissémination et semblent avoir un pronostic légèrement plus mauvais que ceux qui se présentent avec des films thor-aciques normaux.

ZUSAMMENFASSUNG

Von 100 unausgewählten, pathologisch-anatomisch bestätigten, Fällen maligner Lymphome boten 54 Anhaltspunkte für eine intrathorakale Erkrankung. Auffallend war das Fehlen von auf solche Befunde sich beziehenden-subjektiver und objektiver Krankheitszeichen.


Kranke, bei denen gelegentlich der ersten Thoraxuntersuchung bereits röntgenologische Befunde vorlagen, hatten die Tendenz zu mehr diffus ausgebreiteter Erkrankung und zeigten eine etwas schlechtere Prognose zu haben, als diejenigen, die mit einer normalen Thorax-Röntgenaufnahme zur Vorstellung kamen.
REFERENCES

1 Jackson, H., Jr., and Parker, F., Jr.: *Hodgkin's Disease and Allied Disorders*, 1947, Oxford University Press, New York.


