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Intrathoracic lymphoid hamartoma

E. HIRST AND H. B. L. WILLIAMS[1]

From the Departments of Pathology and Radiology, Sydney Hospital, Sydney, N.S.W.

Encapsulated lesions in the mediastinum are apt, if they contain lymphoid tissue, to be regarded as thymomata. Castleman (1954) first distinguished a multinodular lymphoid mass from a thymoma and pointed out that it more closely resembled a lymph node. He thought the lesion was inflammatory and designated it localized mediastinal lymph node hyperplasia (Castleman, 1955). Since then there has been a difference of opinion as to whether the lesion is inflammatory, neoplastic or hamartomatous. Doubt has been expressed that the lesion is a lymph node.

We have been able to find 37 cases recorded in the English literature up to the present. The purpose of this paper is to record a further case, to present observations on the lesion, and to review the literature pertaining to it.

CASE REPORT

The patient, a girl of 14 years, was referred to Sydney Hospital on 7 August 1959 because of an abnormality detected on a miniature chest radiograph obtained six weeks before admission.

There were no complaints of ill health and no symptoms referable to the respiratory system. There was no family history of pulmonary disease and no known exposure to tuberculosis. The patient lived near an abattoir and occasionally played in its grounds. A chest film taken elsewhere six years previously was apparently normal but was not available for review.

Physical examination showed a thin girl. No abnormal physical signs were elicited and neither the spleen nor any peripheral lymph nodes were palpable. A mild degree of dental caries was present.

Radiological examination (Figs 1 and 2) revealed a rounded shadow the size of a hen's egg in the inner part of the right lung near the root. The mass was clearly separated from the mediastinum, and the vessels, seen through the substance of the mass in both planes, showed no distortion. In the lateral radiograph the mass was in the hilar plane. The diagnosis appeared to rest between a thymoma, a developmental cyst of the non-communicating type, and a hydatid cyst. At fluoroscopy the mass was smoothly marginated, showed no pulsation, and did not vary in size or contour on forcible inspiration-expiration. A solid tumour appeared more probable.

[1] Present address: Prince Henry Hospital, Little Bay, N.S.W.

Special investigations showed a negative Casoni test, both immediate and delayed, and an erythrocyte sedimentation rate of 5 mm./hour Westergren. The Mantoux test was positive. Sputum smears were negative for acid-fast bacilli and culture for *Mycobacterium tuberculosis* was negative. The blood count was normal.

At operation the tumour appeared as a rounded, smooth, solid mass occupying the apex of the fissure between the right lower and middle lobes. It was partly embedded in the fissural surface. No enlarged lymph nodes or other abnormality in the area of the tumour or on palpation of the lung or mediastinum were found.

The right lower lobe artery was adherent along the posterior surface of the tumour, and the cardiac segmental artery was adherent anteriorly. However, no vessel of large size entered the mass. There was moderately dense adherence medially to the adjacent bronchus. Clean, relatively easy dissection and removal of the entire mass was possible.

Frozen-section examination of the specimen showed lymphoid tissue with characteristic thick-walled vessels entering the lymphoid follicles. A diagnosis of 'mediastinal lymph node hyperplasia' was submitted. A portion was saved for culture which was negative on ordinary media.

After a mild post-operative pyrexia, convalescence was rapid and uninterrupted, and the patient was discharged 13 days after thoracotomy. She became pregnant in August 1961, had a normal confinement, and the post-natal period was uneventful. She was free from any symptoms, and physical and radiological examination was normal in June 1962. She has remained well since.

PATHOLOGY The specimen was a smooth, ovoid, flattened nodule, $6 \times 4{\cdot}5 \times 4$ cm., and weighed 29 g. (Figs 3 and 4). Much of its surface was covered by a thin, mobile, fibrous capsule, the remainder by shiny pleura. The cut surface was pale and yellowish-pink, resembling lymphoid tissue. It was uniform except for a small central area of fibrosis. There was no necrosis, cyst formation or calcification.

Microscopical examination showed that it consisted of lymphoid tissue with a follicular pattern and was devoid of lobulation. There were numerous, universally distributed, rather small follicles with or without germ centres (Fig. 5). Closer examination of the follicles showed usually a central core of slightly spindle-shaped reticulum cells devoid of cellular

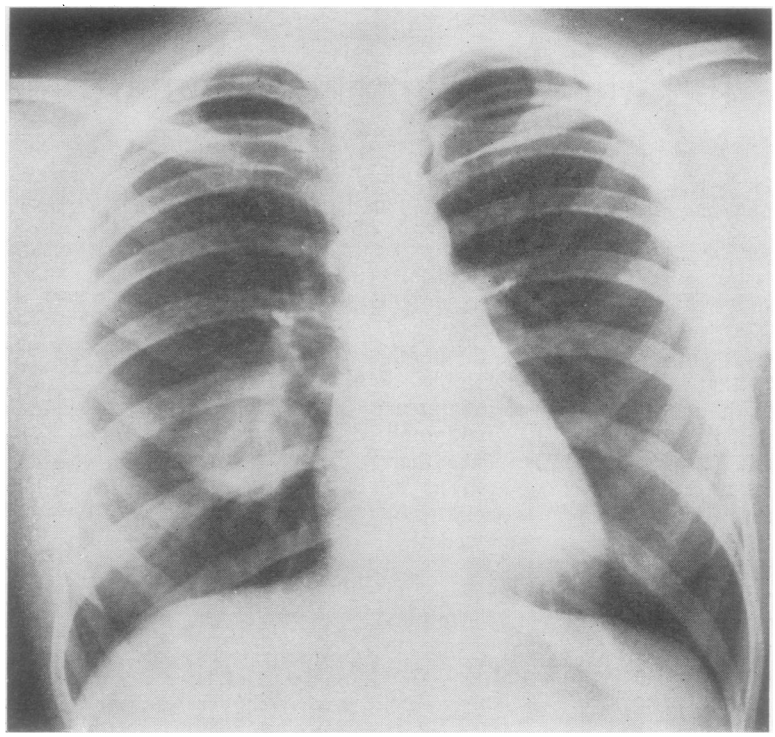

FIG. 1. *Postero-anterior radiograph.*

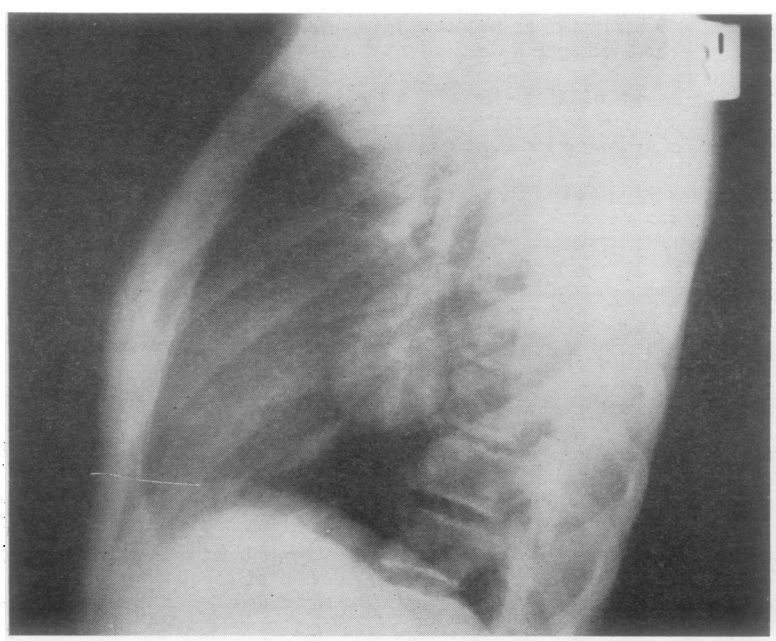

FIG. 2. *Lateral radiograph.*

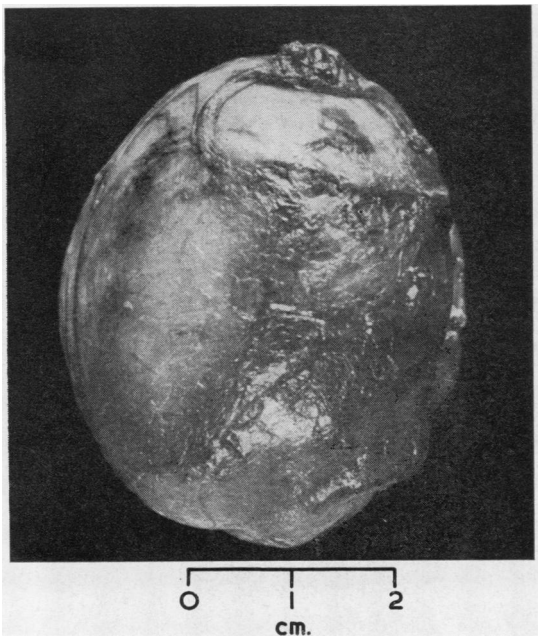

FIG. 3

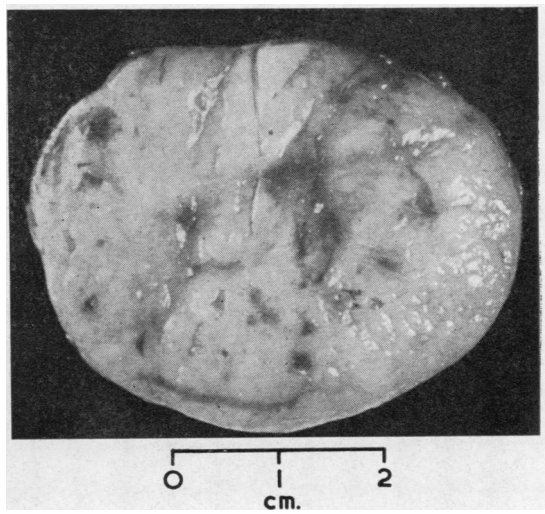

FIG. 4

FIG. 3. *External surface of the lesion.*

FIG. 4. *Cut surface showing homogeneous pale tissue resembling lymphoid tissue.*

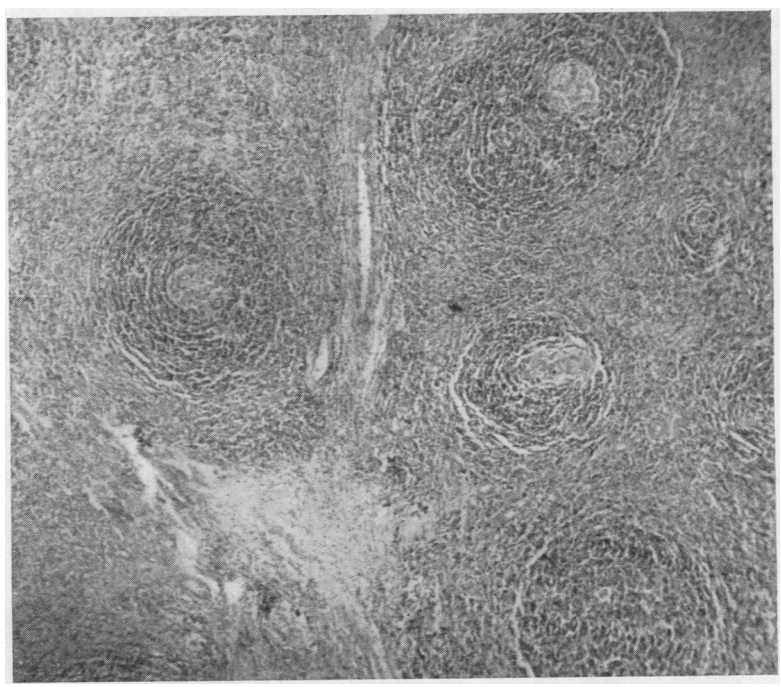

FIG. 5. *Characteristic numerous small follicles. H. and E.,* ×54.

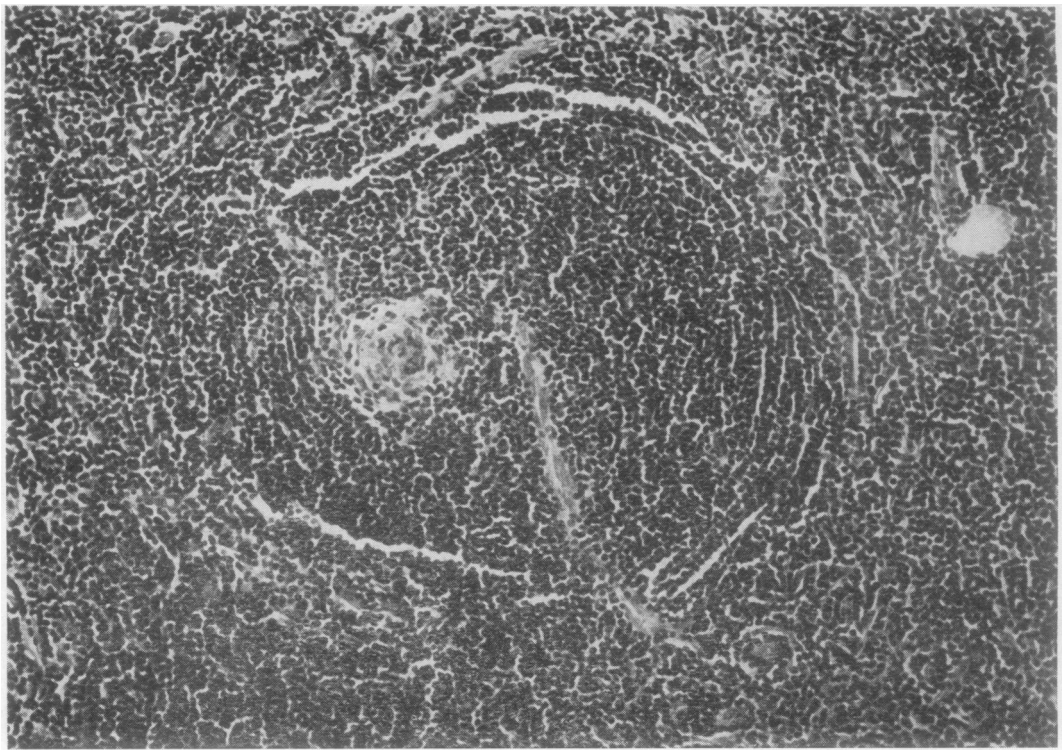

FIG. 6. *Vessel entering follicle radially. H. and E.,* ×213.

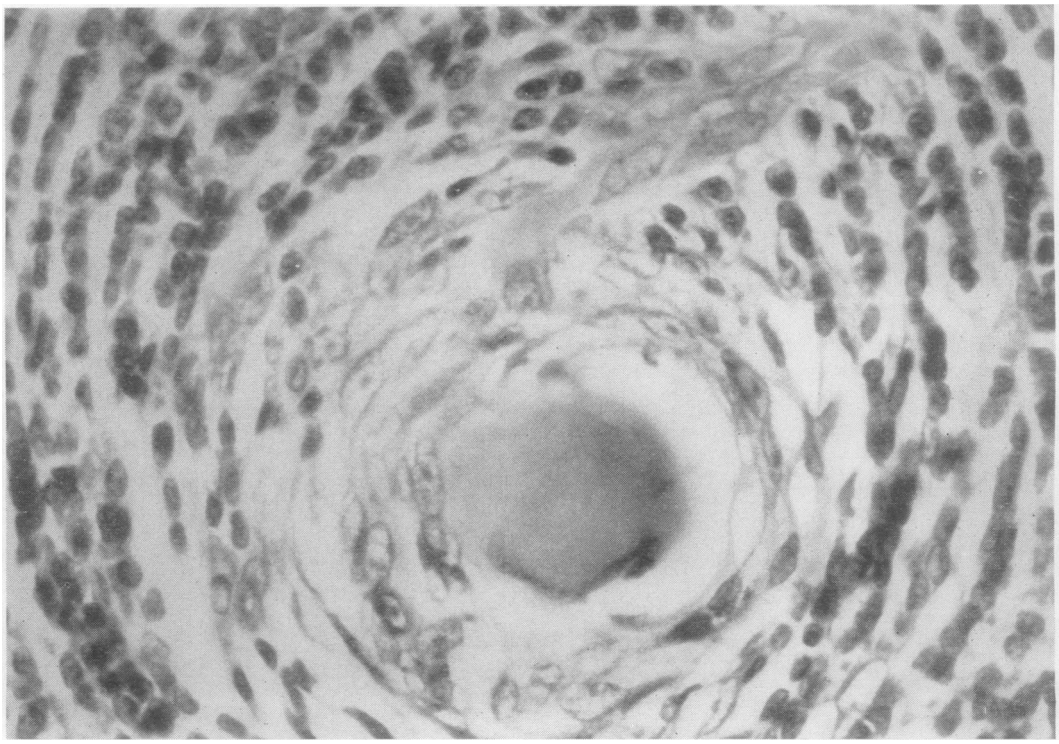

FIG. 7. *Centre of follicle with hyaline structure resembling Hassall's corpuscle, concentrically arranged lymphocytes, and vessel entering radially. H. and E.,* ×811.

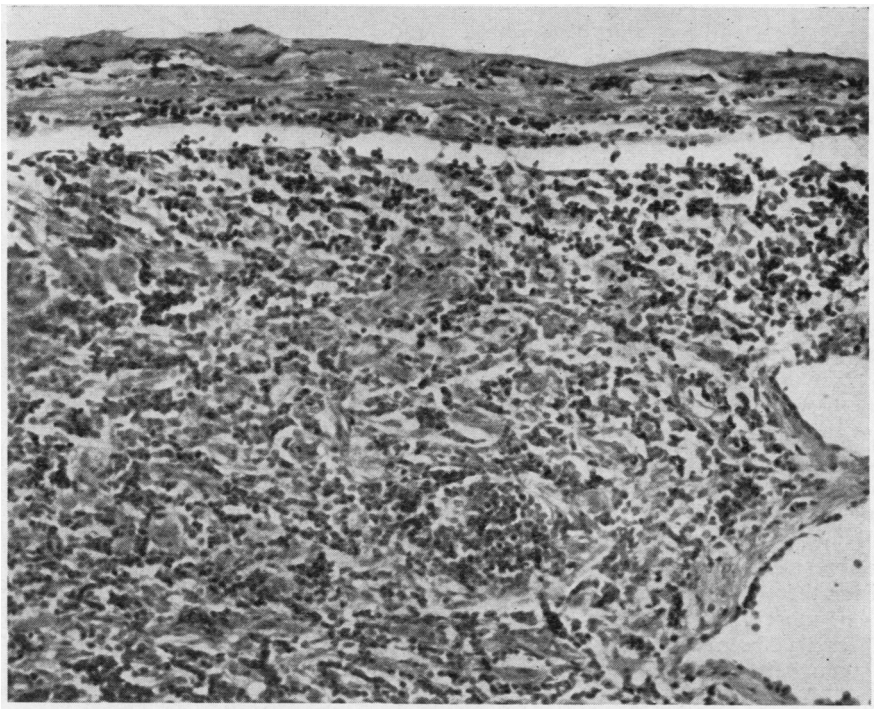

FIG. 8. *Rudimentary peripheral space. H. and E.*, ×213.

debris. Many of the follicles contained a varying degree of hyaline fibrosis, and in blocks from the centre of the specimen many of the follicles were entirely replaced by concentric rings of hyaline fibrosis. A notable feature was the presence of vessels which entered the follicles radially (Figs 6 and 7). These vessels had practically no lumen and were lined by prominent endothelial cells. The walls of these vessels showed patchy hyalinization, more marked in the centre of the follicle or at one side. Often in the centre of the follicle there was a hyalinized structure superficially resembling a Hassall's corpuscle (Fig. 7). Whether they contained a germinal centre or not, the follicles were often composed of rings of lymphocytes concentrically arranged (Fig. 7).

The tissue between the follicles was composed of lymphocytes with scattered, larger, pale, clear (reticulum) cells and was traversed by numerous compressed capillaries without lumina and with prominent endothelial cells. There were no mitoses or abnormal cells of the Sternberg-Reed type.

Examination of many blocks showed only a few areas with rudimentary peripheral spaces (Fig. 8) which could not be identified as lymph sinuses. These spaces contained only a few lymphocytes. No medullary lymph sinuses were found. There was no carbon pigment and no giant cells.

Reticulin stains showed that the interfollicular tissue was traversed by a network of reticulin fibres which tended to outline the numerous vessels, and this was even more marked along the vessels entering the follicles. Sections stained for metalophil cells (Marshall, 1956) showed almost complete absence of these cells both in the follicular and in the intervening tissue. Neither syncytial nor solitary metalophil cells were found.

The microscopical appearances were not those of any of the known forms of inflammation, including toxoplasmosis (Palmer, 1962). Nor was the pattern similar to that of any of the malignant lymphomas including follicular lymphoma. In view of the fact that there was a mild grade of lymphocytic infiltration of the 'capsule' and an increased number of follicles without phagocytosis, it is notable that there was no other similarity to follicular lymphoma.

REVIEW OF THE LITERATURE

Of the 38 cases the sex incidence has been almost equal. The youngest patient was 14 years and the eldest 58 years. There is a striking preponderance in the sesquidecade 15 to 30 years (24 cases). In addition some cases occurring in patients over 30 years were known to have been present before that age. Thus in more than 70% of the patients the lesion was first noted before the age of 30 years.

The presentation was usually as an abnormal finding on routine chest radiographs (24 cases). In six the complaint was chronic cough, in three

'colds', in two fatigue (in one this disappeared after operation), and in three patients an aching or discomfort in the retrosternal area. Facial oedema was reported in one patient. Back pain was reported once (Inada, Kawai, Katsumura, and Nakano, 1959), but this patient showed many unusual features and will be referred to later. One patient (Harrison and Bernatz, 1963) had repeated haemoptyses and nodular pulmonary fibrosis of unstated cause. In one case the lesion presented as a supraclavicular mass (Iverson, 1956).

In 19 instances the lesion had been observed before operation for periods of from three months to 16 years, 12 of these for periods of three years or longer. In three of these cases it was thought to have increased in size, but in at least one instance it was considered to have remained stationary over a period of five and a half years (Harrison and Bernatz, 1963). In many instances information is not given regarding the size of the mass during observation.

After excision there has been a follow-up period of two years or more in 16 cases, the longest for 12 years. There has been no evidence of recurrence, even though in two cases (Chipman and Dolan, 1961 ; Harrison and Bernatz, 1963) it was considered to have been incompletely removed.

Radiologically, this lesion occurs in about equal incidence on each side and in two distinct forms. The less common (nine cases, including the present case) consists of a mass, usually the size of a small hen's egg, arising at the level of the hilar vessels but separated from the mediastinum by a band of lung up to 1 cm. thick. This intrapulmonary form is notable for its fairly constant relation to the lung fissures, on the right side especially to the horizontal fissure. All these cases showed a mass which was approximately circular in outline, sharply marginated, and of homogeneous density. In this form neither calcification nor pulsation has been described. So consistent is the appearance and situation of this tumour in the published radiographs that the possibility of lymphoid hamartoma should be considered, especially in the age group 15 to 40 years.

The second and more common form of presentation (29 cases) is less distinctive. It consists of a solitary or (rarely) slightly lobulated mass within the mediastinum with no predilection for any mediastinal compartment. Nor does the lesion occur more commonly at any particular depth of the thorax. Thus it has been found in intimate relation to the trachea, the azygos vein, both sides of the aortic arch, the heart, and major bronchi. In some cases (Lattes and Pachter, 1962 ; Katz and Dziadiw, 1960) the lesion was so posterior as to cause pressure erosion of the dorsal vertebrae and adjacent ribs. Features that may be of help in suggesting the diagnosis include the distinct margination, the broad base of attachment to one pleural surface or another (as may be seen at tomography (Jamplis, North, and Johnson, 1961)), and the general homogeneity of the mass.

At fluoroscopy transmitted pulsation has been noted on two occasions. On the one occasion when the Valsalva manœuvre was carried out, the findings were misleading in that reduction in size appeared to favour a cyst, but the lesion was solid. There has been no movement on swallowing in the few cases where this sign has been sought.

Special methods of investigation have included tomography (Bloch and Peck, 1962), angiography, and studies of the barium-filled oesophagus. Two cases have shown calcification (Inada and Hamazaki, 1958 ; Inada *et al.*, 1959), which took the form of amorphous calcified nodules within the substance of the lesion. Angiography has disclosed no abnormality in the pulmonary circulation (Castleman, 1954 ; Jamplis *et al.*, 1961). Barium swallow (Cohen, 1957 ; Harrison and Bernatz, 1963) demonstrated slight oesophageal displacement in two cases where the mass was in close relation to this structure. Tracheal displacement has been recorded on two occasions (Cohen, 1957 ; Inada *et al.*, 1959), indentation once (Chipman and Dolan, 1961), and compression of the right main bronchus once (Harrison and Bernatz, 1963). It will be seen that no special method of investigation is very helpful in the group where the mass is mediastinal, and this is well illustrated by the wide variety of diagnoses proposed, *viz.*, bronchogenic cyst, mediastinal teratoma or dermoid, hydatid cyst, tuberculoma or abscess, thymoma, carcinoma, malignant lymphoma, mesothelioma, bronchial adenoma, retrosternal thyroid, neurogenic tumour, intrathoracic meningocele, lipoma, and pulmonary 'hamartoma'.

A diagnostic pneumothorax seems on theoretical grounds to offer the greatest chance of a precise diagnosis, as it should be possible by this procedure to define the broad base of attachment with greater certainty. On the other hand, the absence of lymph sinuses suggests that lymphangiography would have only negative value.

Laboratory examination has not been helpful. In five instances the tuberculin test has been negative. In our own case it was positive, and in that reported by Inada and Hamazaki (1958) there was tuberculin conversion.

A mild anaemia has been reported in two patients. In both of these the erythrocyte sedimentation rate was raised (53 mm. and 120 mm./hr.) and both of these patients had symptoms. In the remainder of the patients the blood count and the sedimentation rate where recorded have been normal.

Except in the unusual cases quoted by Inada *et al.* (1959) and Harrison and Bernatz (1963) bronchoscopy has been negative. In the former case there was a marked stenosis of the left main bronchus and in the latter compression of the right main bronchus.

In some of the reported cases it is difficult to be certain of the exact situation of the lesion at operation. They have been divided into mediastinal and peribronchial types (Harrison and Bernatz, 1963). Most have been situated near the root of the lung. In the intrapulmonary form the lesion lies near the fissures, beneath the visceral pleura, adjacent and often adherent to the bronchus, and rarely covered by adherent lung. The more medial lesions are usually partly in the superior mediastinum near the trachea and pulmonary artery. However, some have been situated entirely in the anterior mediastinum where they may be adherent to the sternum. More posteriorly, they have been reported near the posterior chest wall (Lattes and Pachter, 1962) and adherent to the ribs and surrounding the sympathetic chain (Katz and Dziadiw, 1960; Chipman and Dolan, 1961). Due to the close relation and adherence to the hilar structures, removal of the mass has entailed a lobectomy in three cases (Castleman, Iverson, and Menendez, 1956; Abell, 1957; Inada and Hamazaki, 1958) and a pneumonectomy in one (Castleman *et al.*, 1956). In two of the patients excision was considered to have been incomplete (Chipman and Dolan, 1961; Harrison and Bernatz, 1963). In the unusual case of Inada *et al.* (1959) the superior vena cava was torn at operation. However, in the remaining instances there has been no difficulty in removing the lesion intact.

The resected specimen has varied from 3·5 to 16 cm. in maximum extent. They are almost always 'encapsulated', and in three instances a thin fibrous capsule has been described. The external surface is smooth, occasionally lobulated, and the cut surface is homogeneous, usually salmon-pink. Sometimes there are thin fibrous trabeculae coursing through the mass. One instance of doubtful cystic change and three of calcification or ossification (two visible radiologically) have been reported. The microscopical features have been well described by Lattes and Pachter (1962). Briefly, they show lymphoid tissue with a follicular pattern. The follicles are universally distributed and may or may not have germinal centres. There is a distinctive vascular pattern in the follicles and in the interfollicular tissue. Lumenless capillaries enter follicles where their walls often become hyaline. These hyalinized vessels form a structure that resembles a Hassall's corpuscle. Plasma cells and eosinophils may be found. There is no evidence of anaplasia or lymphoma.

Some of the cases were previously diagnosed as thymoma (Thorburn, Stephens, and Grimes, 1952; Forsee, Farinacci, and Black, 1953; Crane and Carrigan, 1953; Inada *et al.*, 1959; Mason, 1959; Smith, 1956).

A review of 50 thymomata by Iverson (1956) and of 138 by Harrison and Bernatz (1963) revealed five and three cases respectively of lymphoid hyperplasia (hamartoma). Castleman *et al.* (1956) have admirably put the case for the rejection of the lesion as a thymoma, namely, the usual position away from the mid-anterior mediastinum, the follicular pattern, the erroneous identification of Hassall's corpuscles, and the occurrence of similar lesions outside the chest. To these may be added the absence of lobulation which is seen in thymomata without myasthenia gravis (Iverson, 1956). On the other hand, the common situation close to the tracheo-bronchial tree and the follicle-laden lymphoid tissue suggested lymph node. Also, Castleman *et al.* (1956) reported a case with satellite masses around the solitary lesion, lending weight to the suggestion that neighbouring lymph nodes were involved.

Plasma cells and eosinophils have been found in some of the lesions, and later cases with rare giant cells (Iverson, 1956) and carbon pigment (Jamplis *et al.*, 1961) were reported. These findings tended to support the suggestion of some form of lymphadenitis.

However, the lymph node hypothesis has been contested. Confirmation of a similar affection in neighbouring lymph nodes is absent. Indeed, in three reported cases where adjacent nodes were taken for biopsy, they showed only mild hyperplasia, lymphadenitis, or were normal, failing to reproduce the histological features of the lesion (Inada and Hazaki, 1958; Zettergren, 1961; Harrison and Bernatz, 1963).

Many reports state that the lesion is a 'lymph node,' but only Mason (1959) and Iverson (1956) have claimed the presence of a sinusoidal architecture. In these cases pictorial evidence is absent,

and in the former case there is some doubt because of the opinion of other pathologists that it is a thymoma. It may be assumed that, as in the present case, a sinusoidal architecture is absent. This has been confirmed by Chipman and Dolan (1961), by Zettergren (1961), and by Harrison and Bernatz (1963). Lattes and Pachter (1962) have put the case for rejection of the lesion as a hyperplastic or inflamed lymph node, adding evidence from reticulin-stained sections and the distinctive histological pattern.

The view that the lesion is a form of benign lymphoma (follicular lympho-reticuloma) has been advanced by Zettergren (1961).

Extrathoracic lesions of apparently similar structure (Cohen, 1957 ; Beskid, 1959 ; Zettergren, 1961 ; Lattes and Pachter, 1962) show a distribution in the sesquidecade 15–30 years of about 70% in 13 cases.

The findings in the present case support the view that the lesion, though lymphoid, is not a lymph node. Lattes and Pachter (1962) have developed the suggestion, first put forward by Abell (1957), that the lesion, being composed of lymphoid tissue of abnormal structure, is a hamartoma. The predominance of the lesion in a young age group, the failure of some of the lesions to enlarge after considerable periods of time, and the absence of recurrence after incomplete excision support this conception.

SUMMARY

A well-defined mass was found in the lung of a young girl on a routine chest radiograph. On pathological examination it was found to consist of lymphoid tissue formerly regarded as mediastinal lymph node hyperplasia and now believed to be intrathoracic lymphoid hamartoma. There was no recurrence four years later. This is the thirty-eighth case of this lesion, which is found to have a marked preponderance in the sesquidecade 15–30 years. In one of its forms it shows a distinctive radiological appearance. It is usually but not always easy to remove. A review of the cases reported indicates that, although composed of the elements of lymphoid tissue, it lacks the structural features of a lymph node and possesses histological characteristics not found in ordinary lymph nodes.

In spite of two cases where excision was incomplete, no case of recurrence has been reported.

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REFERENCES

Abell, M. R. (1957). Lymphnodal hamartoma versus thymic choristoma of pulmonary hilum. *Arch. Path.*, **64**, 584.
Beskid, M. (1959). Przypadek Rozrostu Wezla Chlonnego O Utkaniu Grasiczaka. (A case of hyperplasia of the lymph node with the structure of thymoma.) *Pat. pol.*, **10**, 507.
Bloch, C., and Peck, H. M. (1962). Localised benign lymph node hyperplasia. Right hilum. Castleman's disease. *J. Mt Sinai Hosp.*, **29**, 364.
Castleman, B. (1954). Case records of the Massachusetts General Hospital. *New Engl. J. Med.*, **250**, 26.
—— (1955). *Atlas of Tumor Pathology*. Sect. V—Fascicle 19: Tumors of the thymus gland. Armed Forces Institute of Pathology, Washington, D.C.
—— Iverson, L., and Menendez, V. P. (1956). Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer*, **9**, 822.
Chipman, C. D., and Dolan, F. G. (1961). Localized lymph node hyperplasia in the mediastinum. *Canad. med. Ass. J.*, **84**, 900.
Cohen, H. (1957). Tumor-like proliferations of lymphoid tissue. Occurrence in deltoid muscle and mediastinum. *J. Mt Sinai Hosp.*, **24**, 750.
Crane, A. R., and Carrigan, P. T. (1953). Primary subpleural intrapulmonic thymoma. *J, thorac. Surg.*, **25**, 600.
Effler, D. B., and McCormack, L. J. (1956). Thymic neoplasms. *Ibid.*, **31**, 60.
Forsee, J. H., Farinacci, C. J., and Black, H. A. (1953). Ectopia of primary thymic tumors. *Ann. Surg.*, **138**, 922.
Harrison, E. G., and Bernatz, P. E. (1963). Angiofollicular mediastinal lymph-node hyperplasia resembling thymoma. *Arch. Path.*, **75**, 284.
Horie, A. (1962). On the so-called "Lymph node hyperplasia" (Castleman). *Kyushu J. med. Sci.*, **13**, 105.
Inada, K., and Hamazaki, M. (1958). Localized mediastinal lymph-node hyperplasia resembling thymoma. A case report. *Ann. Surg.*, **147**, 409.
—— Kawai, K., Katsumura, T., and Nakano, A. (1959). Giant lymph node hyperplasia of the mediastinum. Case report with a review of the literature. *Amer. Rev. Tuberc.*, **79**, 232.
Iverson, L. (1956). Thymoma. A review and reclassification. *Amer. J. Path.*, **32**, 695.
Jamplis, R. W., North, F. S., and Johnson, W. D. (1961). Benign interlobar hyperplastic lymph node resembling thymoma. *Arch. Surg.*, **83**, 894.
Katz, I., and Dziadiw, R. (1960). Localized mediastinal lymph node hyperplasia. Report of a case with roentgen findings simulating posterior mediastinal neurofibroma. *Amer. J. Roentgenol.*, **84**, 206.
Lattes, R., and Pachter, M. R. (1962). Benign lymphoid masses of probable hamartomatous nature. *Cancer*, **15**, 197.
Marshall, A. H. E. (1956). *An Outline of the Cytology and Pathology of the Reticular Tissue*. 1st ed., pp. 25, 29. Oliver and Boyd, Edinburgh and London.
Mason, C. B. (1959). Giant intrathoracic lymph nodes. *J. thorac. Surg.*, **37**, 251.
Palmer, A. A. (1962). Personal communication.
Smith, P. W. (1956). In discussion of Chesney, J. G., in Effler & McCormack.
Thorburn, J. D., Stephens, H. B., and Grimes, O. F. (1952). Benign thymoma in the hilus of the lung. Case report. *J. thorac. Surg.*, **24**, 540.
Zettergren, L. (1961). Probably neoplastic proliferation of lymphoid tissue (follicular lympho-reticuloma). Reports of four cases with a survey of literature. *Acta path. microbiol. scand.*, **51**, 113.

ADDENDUM

A further case has been published in English (Horie, 1962). In a boy of 15 years a well-defined round density in the right hilar region was found on a routine chest radiograph. After increasing in size for four years it was enucleated without difficulty.