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Primary lymphoproliferative conditions of lung

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Gibbs, A. R., and Seal, R. M. E. (1978). *Thorax*, **33**, 140–152. **Primary lymphoproliferative conditions of lung.** The clinical, laboratory, and pathological features of six primary lymphoproliferative conditions of the lung are described. These comprise two patients with malignant lymphomas, one with pseudolymphoma, one with lymphoid interstitial pneumonia (LIP), one with lymphomatoid granulomatosis, and one with plasma cell granuloma. We recommend that the term 'premalignant lymphoma' be used for pseudolymphoma since the condition, although tending to remain localised, has a malignant potential.

A combination of dyspnoea, cough, and pyrexia were the presenting features in our cases of premalignant and malignant lymphoma although they may often be discovered accidentally by chest radiography. The patient with LIP presented with the usual symptoms of dyspnoea and cough. The initial manifestations of the patient with lymphomatoid granulomatosis were skin rash and peripheral neuropathy nine months before the pulmonary symptoms, a not unusual occurrence. Plasma cell granuloma is often asymptomatic but our patient presented with cough, chest pain, and haemoptysis.

Premalignant lymphoma tends to pursue a benign course although exceptionally it may become disseminated. Malignant lymphoma may remain localised for many years but a significant proportion metastasise. Lymphomatoid granulomatosis and LIP have a varied course but both may terminate in malignant lymphoma. Plasma cell granuloma is always benign. The interrelationships of these conditions and their differential diagnosis are discussed.

There is a spectrum of ill-understood and rare primary lymphoreticular proliferative conditions of the lung, ranging from obviously benign disease on the one hand to malignant lymphoma on the other. The group comprises plasma cell granuloma, pseudolymphoma, malignant lymphoma, and two recently recognised conditions, viz, lymphoid interstitial pneumonia (Carrington and Liebow, 1966) and lymphomatoid granulomatosis (Liebow *et al.*, 1972). Classification of each entity is difficult, and because of their rarity and short period of observation their precise natural histories have not been evaluated.

We describe six cases within this group (two non-Hodgkin's lymphomas, one pseudolymphoma, one lymphoid interstitial pneumonia, one lymphomatoid granulomatosis, one plasma cell granuloma) and discuss their clinicopathological features and interrelationships. Case 5 was reported in more detail in a previous publication (Gibbs, 1977).

Methods

The cases have been drawn from three Cardiff hospitals. Diagnosis was based on thoracotomy findings with excision or biopsy in five and closed (drill) lung biopsy in one. Thirty-eight cases of lymphoma, which presented initially with pulmonary manifestations, were found in the files but only the six cases described complied with the diagnostic criteria for primary pulmonary lymphoproliferative conditions, that is, involving lung and regional nodes with no evidence of dissemination after three months. No cases of primary Hodgkin's disease of the lung within Saltztein's (1963) definition were encountered. Appropriate histological blocks were taken from the material after inflation

of the lungs or, in the case of biopsies, straightforward fixation with 4% formaldehyde in saline. The following stains in addition to haematoxylin and eosin were used in some cases: aldehyde fuchsin, Verhoeff Van Gieson, orcein and reticulin stain (Gordon and Sweet).

Case reports

CASE 1

This patient, a cleaner, had had numerous admissions since 1953 for episodes of pneumonia, seronegative arthritis, and cardiac ischaemia. Systemic lupus erythematosus was diagnosed in 1954 and confirmed by serological investigations. Since then she had received intermittent courses of cortisone or prednisone for further episodes of joint pains and one episode of bruising associated with thrombocytopenia. In 1971 she was noted to have hypertension (230/110 mmHg) and was treated with bethanidine; a renal biopsy at this time showed the changes of benign arteriolar nephrosclerosis but there was no evidence of glomerulonephritis.

In September 1973, when 57 years old, she was admitted complaining of chest discomfort and dyspnoea. A mass was noted radiographically in the mid zone of the left lung; tomograms showed it to have an irregular outline and to be umbilicated and situated in the lingula (Fig. 1). Review of a chest radiograph taken two years previously indicated a similar but smaller mass in the same position. At thoracotomy in November 1973 a firm, round, grey lesion, 3 cm diameter, was found in the lingula. It was removed as a wedge resection of lingula with what was thought

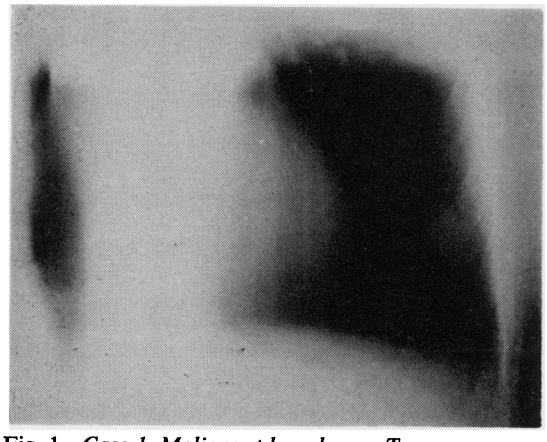

Fig. 1 *Case 1. Malignant lymphoma. Tomogram showing mass in lingula.*

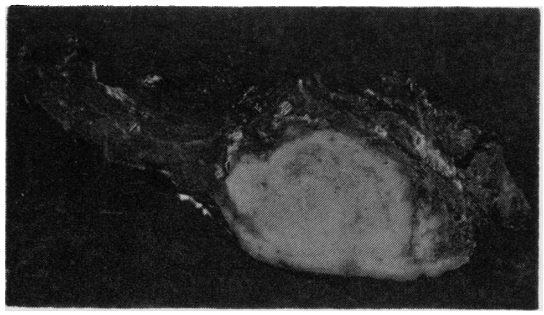

Fig. 2 *Case 1. Malignant lymphoma. Gross appearance of wedge resection of lingula.*

to be adequate clearance (Fig. 2). No lymph nodes were identified.

She is alive with no recurrence or metastasis three-and-a-half years later. She is still receiving a maintenance dose of prednisone (5 mg twice daily) and clonidine for hypertension (bethanidine was stopped and changed to clonidine in November 1972).

Pathology

The surgical specimen consisted of a wedge of lung tissue, 4×3×2 cm, containing a fairly well circumscribed, firm, grey-white, fleshy tumour, 2×2×1½ cm (Fig. 2).

Microscopically the tumour showed a nodular pattern and was made up of a fairly uniform collection of large, poorly differentiated lymphocytes with an occasional reticulum cell (Fig. 3). No germinal centres were identified but invasion of some small arteries and veins was noted. At the edges of the tumour the lymphocytes extended in the lung tissue to surround bronchioles. Normal lung was identified away from the tumour.

Comment

This tumour was interpreted as a poorly differentiated non-Hodgkin's lymphocytic lymphoma.

CASE 2

An 18-year-old nurse presented in 1954 with cough and purulent sputum. Physical examination revealed pyrexia and crackles over the right mid zone. Radiologically there was collapse and consolidation of the right middle lobe. These signs were unchanged six months later in spite of antibiotic therapy. Bronchoscopy was normal in March 1955. In May 1955 right upper and middle lobectomy was performed. No gross enlargement of mediastinal lymph nodes was found and the one lymph node obtained showed only reactive

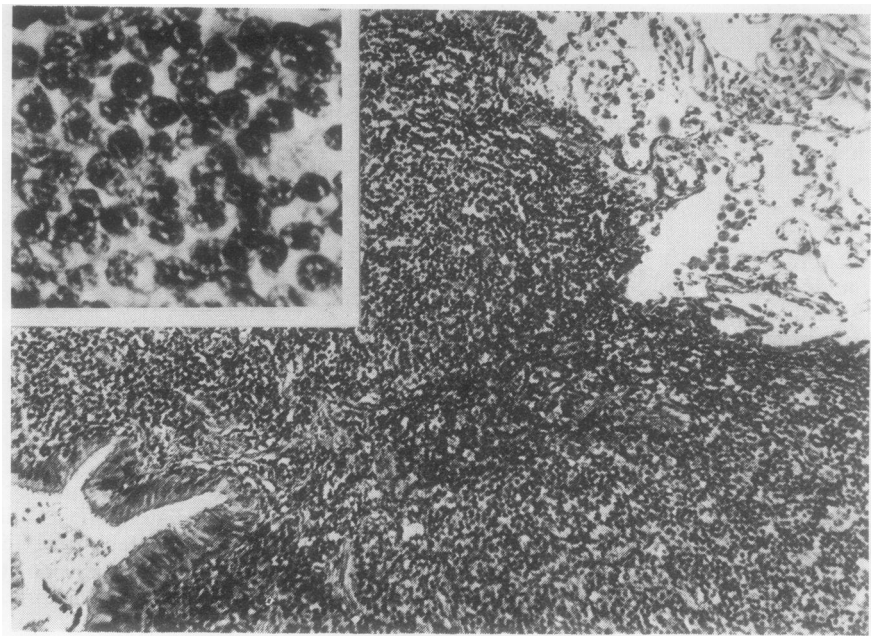

Fig. 3 *Case 1. Malignant lymphoma. This shows a general view of the tumour. Haematoxylin and eosin ×110. Inset shows the tumour to be composed mainly of immature lymphocytes. H and E ×780.*

changes. Since the pathologist reported Hodgkin's disease the patient received radiotherapy.

She is alive and well with no recurrence 22 years later.

Pathology

The specimen was from a right upper and middle lobectomy with the right middle lobe partially collapsed and consolidated. On cut section the middle lobe was completely occupied by a well-demarcated, fairly circumscribed, lobulated, grey, firm tumour which was also occupying part of the anterior segment of the upper lobe (Fig. 4).

Microscopically the tumour showed nodularity and some intervening fibrous tissue. It was composed of large lymphocytes, prominent plasmacytoid cells, and occasional plasma cells and eosinophils (Fig. 5). Some large multinucleate cells were present but these had only a superficial resemblance to Reed Sternberg cells. Some of the bronchiolar epithelium was invaded by tumour. The surrounding lung showed obstructive pneumonitis.

Comment

This is now interpreted as a poorly differentiated non-Hodgkin's lymphoma with plasmacytoid features.

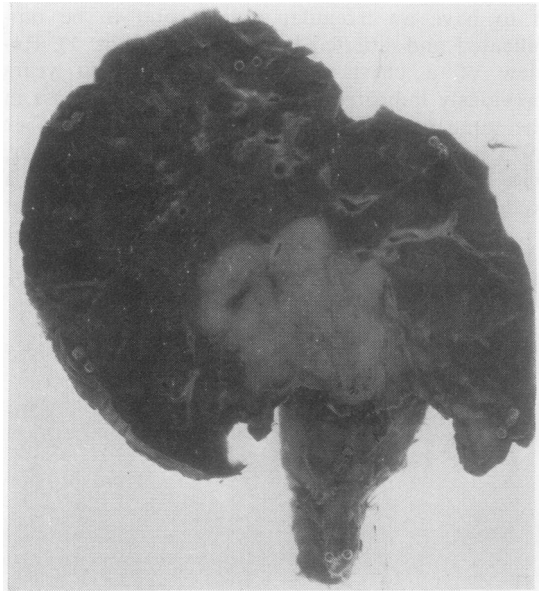

Fig. 4 *Case 2. Malignant lymphoma. Tumour involving anterior segment of right upper lobe.*

CASE 3

A 49-year-old male van-driver developed a febrile illness in June 1975. Chest radiography at this

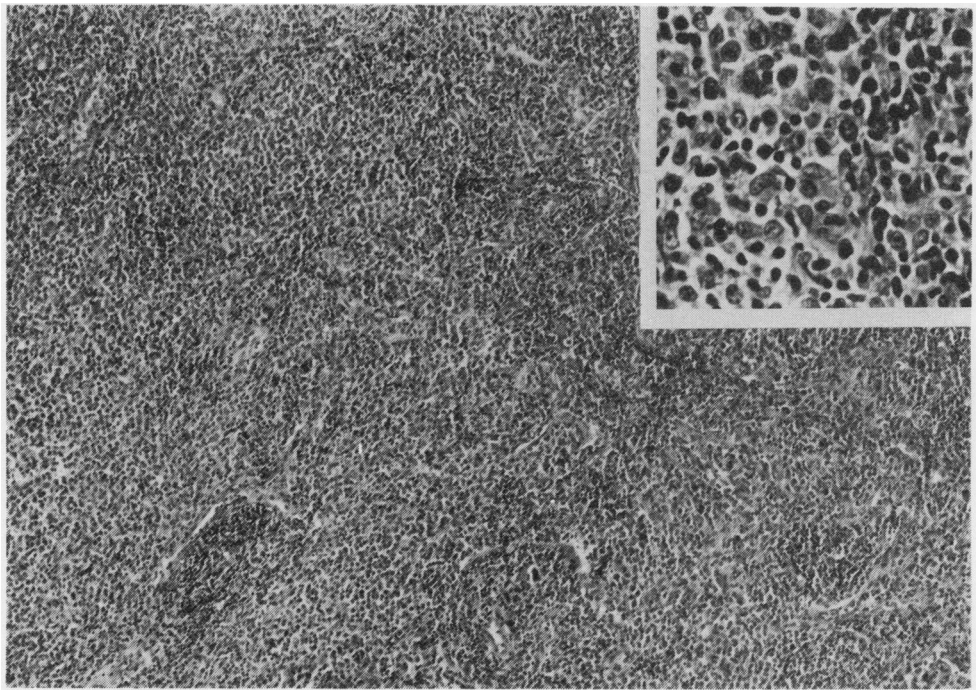

Fig. 5 *Case 2. Malignant lymphoma. H and E ×110. Inset shows pleomorphic nature of the infiltrate. H and E ×350.*

time demonstrated a lesion in the left lower lobe. Since several courses of antibiotics failed to alleviate his symptoms a further film was taken two months later and the appearances were unchanged.

Bronchoscopy and bronchography were performed but these were normal and tomography was unhelpful. Left lower lobectomy was performed in October 1975 and this showed the presence of four pseudolymphomas (Fig. 6). The patient is alive with no recurrence 18 months later.

Pathology

Macroscopic examination of the left lower lobectomy specimen showed apparently normal lung apart from four well-demarcated, grey foci of consolidation. These were situated one in the apical segment (1×1=1 cm), one in the subapical segment (3×1=1 cm), and two areas each less than 1 cm diameter in the basal segments (Fig. 6). The bronchi and hilar nodes appeared normal.

Microscopy showed that all four grey areas of consolidation were similar and there were dense collections of mature lymphocytes with some plasma cells, reticulum cells, and Russell bodies (Figs 7 and 8). They showed numerous germinal centres. At the periphery of the lesions the in-

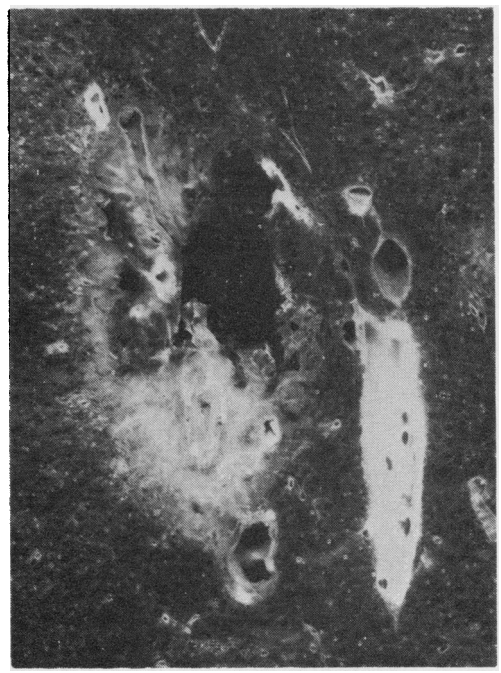

Fig. 6 *Case 3. Premalignant lymphoma. One of the tumours.*

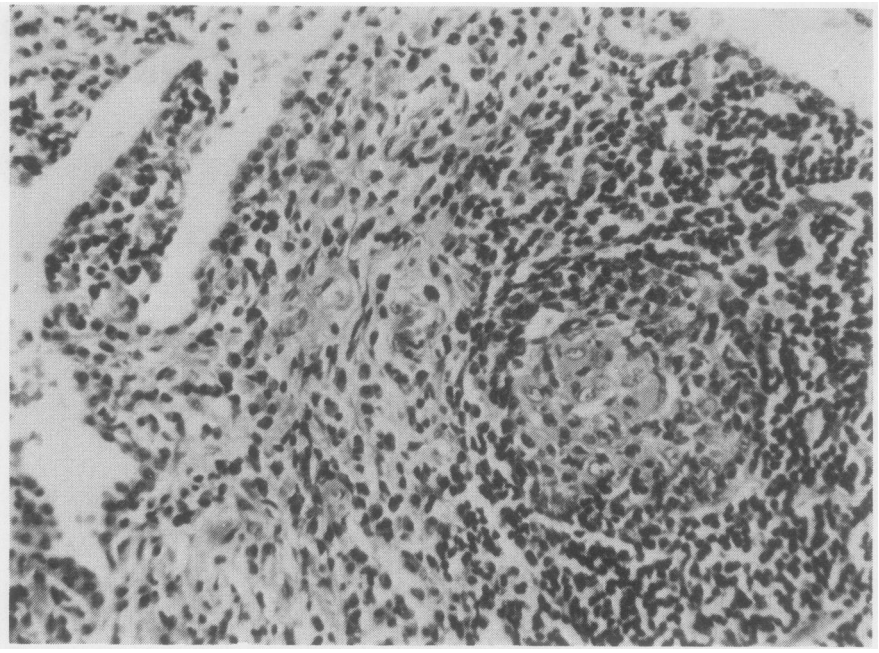

Fig. 7 *Case 3. Premalignant lymphoma. One of the tumours showing a germinal centre. H and E ×155.*

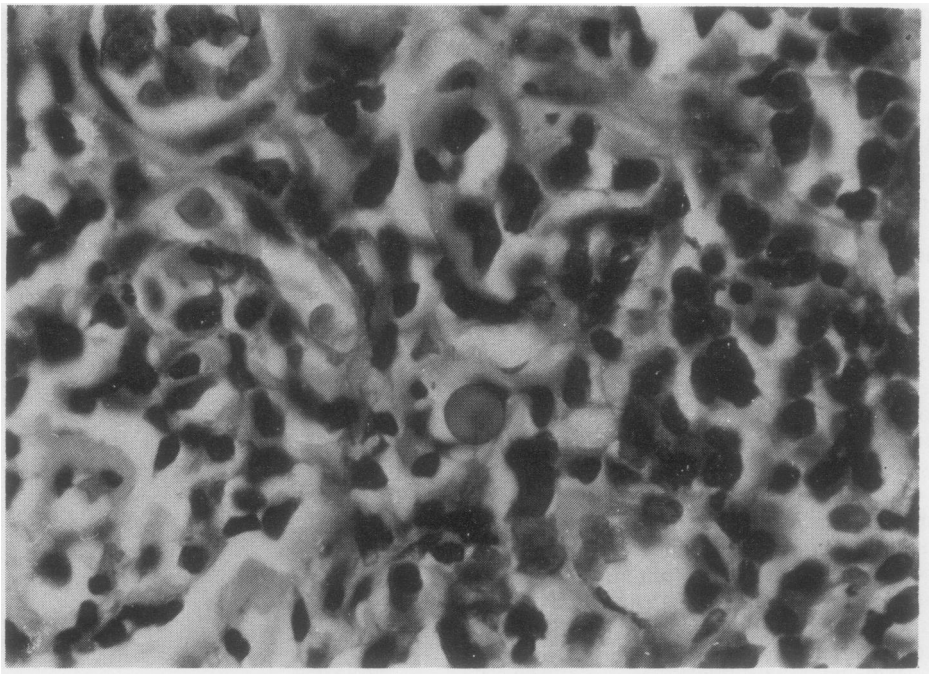

Fig. 8 *Case 3. Premalignant lymphoma. This shows an area where plasma cells are prominent; a Russell body is present near the centre. H and E ×990.*

filtrate was interstitial and surrounded bronchioles and small vessels. It appeared to invade the bronchiolar walls but never breached the bronchiolar epithelium.

Similar small interstitial collections of cells were noted away from the main tumours with normal tissue intervening.

The 10 regional lymph nodes examined showed reactive changes only.

Comment

The differential diagnosis lay between multiple pseudolymphomas and lymphoid interstitial pneumonia. We felt that the separation of the individual lymphoid collections by normal tissue favoured the diagnosis of pseudolymphoma.

CASE 4

A 66-year-old retired crane driver had made an uneventful recovery from a haemorrhoidectomy in April 1971, but investigations revealed an IgM paraprotein in the serum and an ESR of 70 mm/h. A search for a primary tumour was begun because of the known association of paraproteinaemia and malignancy. Clinical examination three months later revealed a vague mass in the right side of the abdomen, and a barium enema showed a filling defect in the caecum. At laparotomy in July 1971 a large tumour was identified at the junction of the caecum and ascending colon. Right hemicolectomy and end-to-end anastomosis was performed.

Pathological examination of the hemicolectomy specimen showed two tumours—a carcinoma and a malignant lymphoma. Fluorescent microscopy of the tumour was negative for IgG, IgA, IgM, and beta-I complement, suggesting that the paraprotein was not secreted by either of the two tumours.

He appeared well after the operation, apart from some morning cough and intermittent production of white sputum. The IgM paraproteinaemia persisted. He showed no signs of a hyperviscosity syndrome.

Chest radiography in December 1973 showed thickening of the right horizontal fissure and filling of the right costophrenic angle. This progressed and by January 1975 there was consolidation of the anterior segment of the right upper lobe, the whole of the middle lobe, and the posterior basal segment of the right lower lobe, with septal lines at both bases (Fig. 9). Physical examination revealed bronchial breathing and crackles over the corresponding areas of the chest.

Needle drill lung biopsy was undertaken in February 1975. Lung function tests at this time

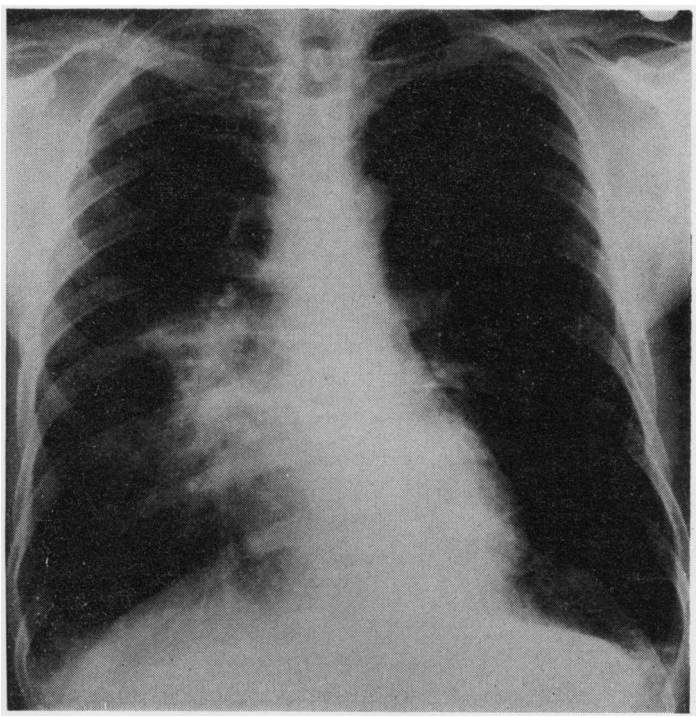

Fig. 9 *Case 4. Lymphoid interstitial pneumonia. Posterior–anterior radiograph showing infiltrate in right lung.*

showed a mild restrictive defect (FEV_1=1·85, FVC=2·85, transfer factor=23). He was treated with chlorambucil. Chest radiography six months later showed considerable clearing. He is alive (two years after lung biopsy) but still has slight cough and sputum. The blood count appeared normal but his paraproteinaemia persists (84 g/l). Investigations for extrinsic allergic alveolitis, Coombs' test, differential agglutinating test for rheumatoid arthritis, and antinuclear factor have been persistently negative. He is on a maintenance dose of chlorambucil (2 mg daily).

Pathology

The specimen was from a right hemicolectomy—2·5 cm length of ileum and appendix attached to a 16 cm length of caecum and colon. The wall of the caecum was diffusely thickened by grey-white, firm tissue over a length of 6 cm. In the proximal end of the caecum there was an ulcerated area, 2·5 cm diameter, with rolled edges. The mesenteric lymph nodes appeared to be enlarged.

Microscopically the ulcerated area was due to a moderately differentiated adenocarcinoma invading the full thickness of the bowel wall.

The thickened area of caecum showed a malignant lymphoma mainly involving the submucosa but which involved the full thickness of the bowel wall in some areas. It had a nodular pattern and consisted mainly of large immature lymphocytes with some plasmacytoid cells and an occasional plasma cell. No evidence of germinal centre formation was seen.

The regional lymph nodes showed mainly reactive hyperplasia but one showed an area suspicious but not diagnostic of malignant lymphoma.

Lung biopsy

Five small cylinders of grey tissue together measured 1 cm.

Microscopically there was a cellular infiltrate involving and expanding the interstitium which in areas formed large round collections (Fig. 10). The infiltrate was composed mainly of mature lymphocytes with a conspicuous admixture of plasma cells and an occasional histiocyte. No true germinal centres were identified but the large round collections of cells had centres composed of epithelioid-like cells. No Langhans' or foreign body giant cells, caseation, mitoses, or vascular invasion were identified.

Comment

We considered that the maturity of the cellular infiltrate and the distribution of the pulmonary lesion favoured a diagnosis of lymphoid interstitial pneumonia rather than pseudolymphoma or secondary malignant lymphoma.

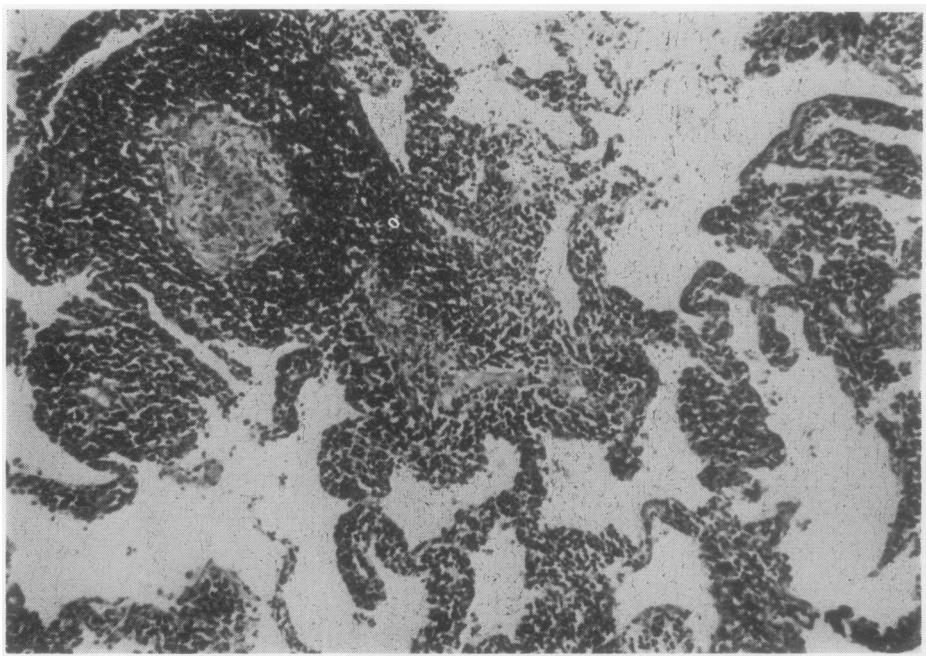

Fig. 10 *Case 4. Lymphoid interstitial pneumonia. Interstitial lymphoid infiltrate with centres of focal collections formed by epithelioid-like cells. H and E ×60.*

CASE 5

A 32-year-old male traffic engineer first presented in April 1974 with a rash followed three months later by peripheral neuropathy. At this time axillary lymphadenopathy was noted. Oral prednisone therapy was begun and the skin condition improved but the degree of peripheral neuropathy remained the same.

In January 1975 he developed a 'flu-like' illness —crackles and bronchial breathing were noted at both lung bases. There was now also cervical lymphadenopathy. Chest radiography showed nodular and confluent consolidated areas throughout both lower lobes, the lingula, and the right middle lobe. Little improvement occurred with antibiotics, so bronchoscopy was performed a few weeks later (this was normal) followed by open lung biopsy. The latter showed the features of lymphomatoid granulomatosis. Oral cyclophosphamide was started in addition to prednisone. After this there was considerable improvement in the chest radiological appearances and a chest radiograph taken one month later showed further clearing but with some residual fibrotic markings in the left lower zone. Since then the patient's condition has remained static, his only drug therapy now being oral prednisone (7 mg every other day).

Pathology

The lung biopsy specimen measured 4×2×0·5 cm and was rectangular, firm, consolidated, and greyish-yellow in colour.

Histologically there was no unaffected lung tissue present and there was a marked interstitial, perivascular, and peribronchial cellular infiltrate composed of plasma cells, plasmacytoid cells, lymphocytes, and large histiocytic cells. Some of the latter resembled the atypical reticulum cells of Hodgkin's disease (Fig. 11). Many of the small muscular arteries and veins showed involvement of their media and adventitia by this infiltrate and some showed intimal fibrosis. There was also some necrosis of vessels. Areas of fibrosis were developing in association with the cellular infiltrate.

Secondary effects such as bronchiolitis obliterans and endogenous lipid pneumonia were present.

Comment

The histological picture was that of lymphomatoid granulomatosis. It is not uncommon for skin and nervous system involvement to precede the pulmonary manifestations.

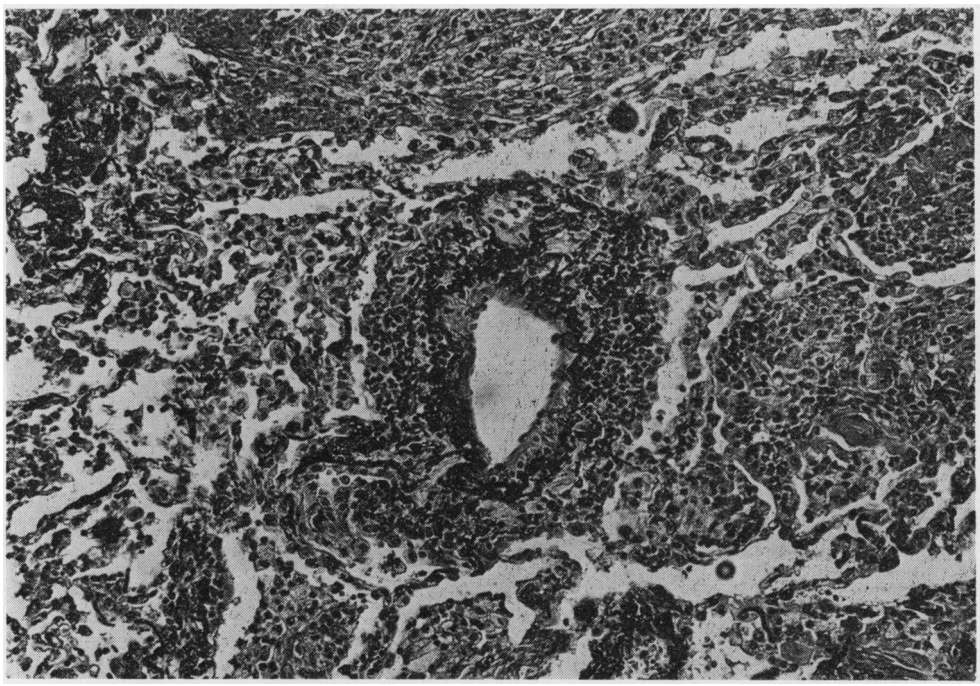

Fig. 11 *Case 5. Lymphomatoid granulomatosis. This shows the interstitial and perivascular lymphoid infiltrate. Orcein ×115.*

CASE 6

A 66-year-old man, who had spent a few years as a stone mason, was admitted in December 1972 complaining of cough with right-sided chest pain for three months. He had also coughed up a small amount of bloodstained sputum.

Examination revealed a dull percussion note and bronchial breathing on the right side posteriorly. Radiological examination confirmed consolidation of much of the right lower and middle lobes with patchy involvement of the anterior segment of the right upper lobe (Fig. 12). Bronchial biopsy revealed an area of squamous metaplasia but bronchography was normal. Right pneumonectomy was performed on 20 December 1972.

Pathological examination showed a plasma cell granuloma involving the right lung and silicotic changes in the hilar nodes. He made an uneventful postoperative recovery but while on holiday in Canada, three months later, he developed a pneumonic illness and died. An account of the necropsy was obtained and no plasma cell lesion was found in the left lung; the cause of death was extensive pulmonary tuberculosis. Histopathology of the lung was examined by one of us, confirming extensive, poorly encapsulated, caseous tuberculosis in which many acid-fast bacilli were identified.

Pathology

The specimen was from a right pneumonectomy showing firm, grey consolidated areas involving most of the middle lobe, part of the anterior segment, and a 3×4 cm ill-defined zone in a basal segment. The hilar nodes were slightly enlarged, hard, and grey. There were no parenchymal silicotic nodules and no lesions within bronchi (Fig. 13).

Microscopically the consolidated areas were composed of numerous plasma cells with lymphocytes, large mononuclear cells, fibroblasts, and eosinophils set in a fibrous stroma (Fig. 14). Areas of hyalinisation were present. The hilar nodes were suggestive of silica exposure.

Comment

The pulmonary lesion was considered to be classical of plasma cell granuloma. No evidence of tuberculosis was identified in this lung either at the initial examination or at re-examination after the postmortem findings of pulmonary tuberculosis.

Discussion

Several reports of so-called primary lymphomas can be found in the literature but, as Saltzstein (1963) and Papaioannou and Watson (1965) point

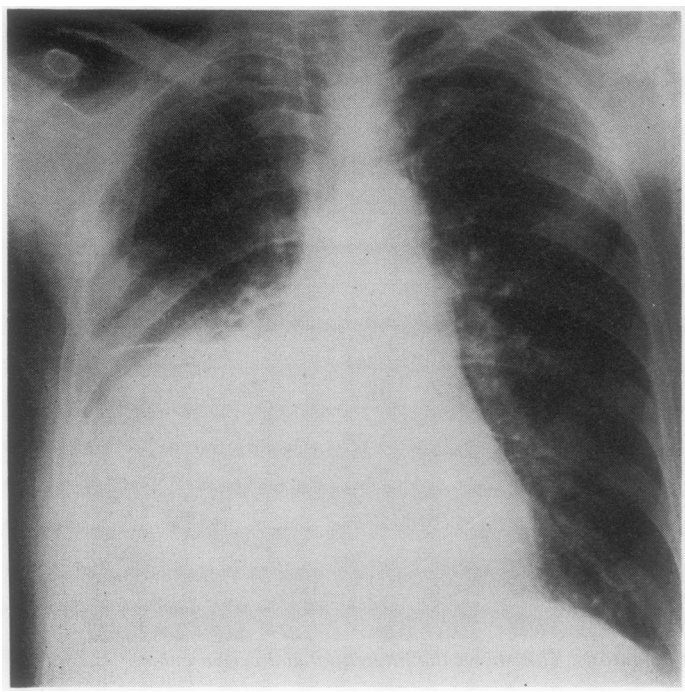

Fig. 12 *Case 6. Plasma cell granuloma. Posterior–anterior radiograph of mass in right lung.*

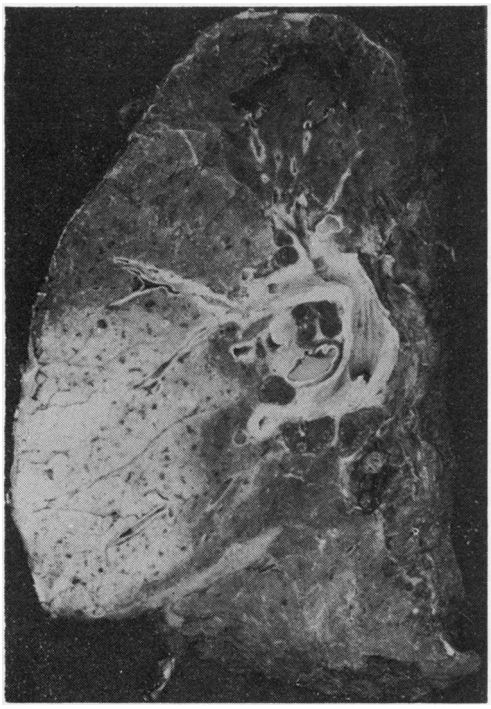

Fig. 13 *Case 6. Plasma cell granuloma. Right pneumonectomy specimen.*

out, many have to be ignored because precise criteria were not used for their diagnosis and they include disseminated malignant lymphomas involving the lung. Saltzstein defines a primary malignant lymphoma or pseudolymphoma of lung as one which originally involves only the lung, or the lung and its regional lymph nodes, and in which there is no evidence of dissemination of the tumour for at least three months after the diagnosis has been established. We have adhered to this definition, and our cases of pseudolymphoma (1) and malignant lymphoma (2) comply with this definition.

It was Saltzstein (1963) who first coined the term 'pseudolymphoma' for a pulmonary tumour which has similarities to malignant lymphoma but which he regarded as a benign inflammatory process with, consequently, a good prognosis. Features which, in his opinion, favoured a diagnosis of pseudolymphoma were: (1) the tumour was composed of a mixed cell infiltrate, mature lymphocytes predominating but with variable proportions of plasma cells; (2) the presence of germinal centres; (3) absence of lymph node involvement. Features favouring malignant lymphoma were: (1) a relatively uniform infiltrate of lymphocytes (especially poorly differentiated lymphocytes); (2) lymph node involvement by tumour; (3) pleural

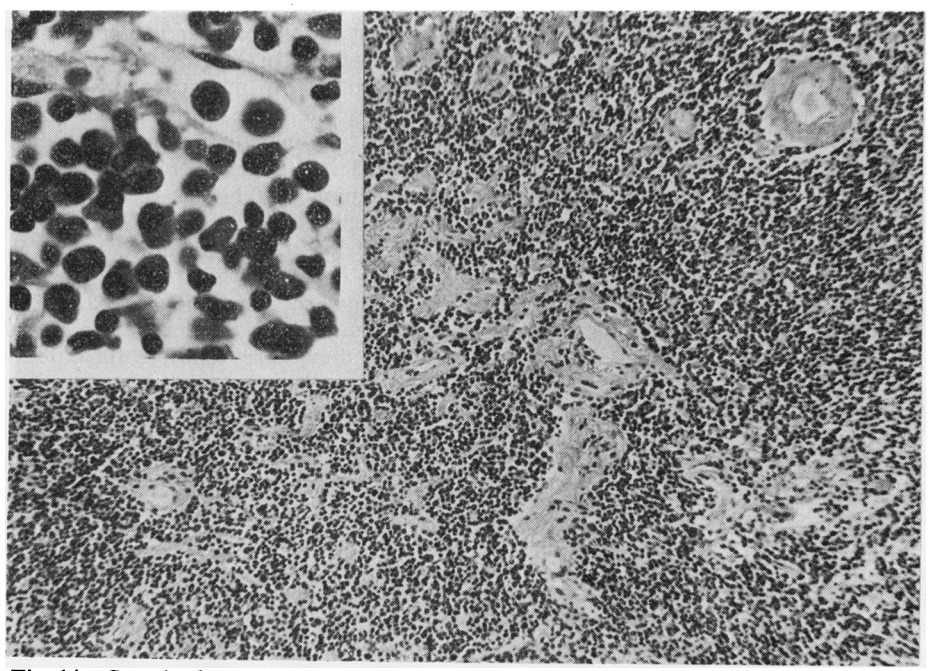

Fig. 14 *Case 6. Plasma cell granuloma. This shows diffuse infiltrate with hyalinised areas. H and E ×120. Inset shows the plasma cell nature of the infiltrate. H and E ×865.*

seeding by the tumour. We think that the term 'pseudolymphoma' should be replaced by the term 'premalignant lymphoma' since occasionally it has been documented as progressing to malignant lymphoma (case 3 of McNamara *et al.*, 1969; one case of Strimlan *et al.*, 1976). Secondly, malignant lymphoma of the lung may remain limited for many years without dissemination (Al-Saleem and Peale, 1969). Our two cases of malignant lymphoma have remained well after resection of the tumours for periods of from 3½ years (case 1) to 22 years (case 2). We would agree with Rubin (1968) and Papaioannou and Watson (1965) that hilar lymph node involvement is more important prognostically than the histology of the lesion.

Lymphoid interstitial pneumonia was the name given by Carrington and Liebow (1966) to a rare condition in which there is a diffuse interstitial pulmonary infiltrate composed predominantly of mature lymphocytes but with varying admixtures of plasma, plasmacytoid, and reticulum cells. Germinal centres are conspicuous, and they state that an individual microscopic field is identical with that of pseudolymphoma (Liebow and Carrington, 1973). The condition is usually but not always bilateral and is not infrequently associated with Sjögren's syndrome and/or dysproteinaemia. The condition may progress slowly, and commonly leads to interstitial fibrosis and honeycombing. However, it may uncommonly evolve into a disseminated malignant lymphoma (Halprin *et al.*, 1972).

Lymphomatoid granulomatosis was defined by Liebow *et al.* (1972) as an angiocentric, angiodestructive, lymphoreticular, proliferative lesion which predominantly involves the lungs but frequently affects other organs, such as skin, central nervous system, and kidneys. The infiltrate is composed of lymphocytes, plasma cells, histiocytic cells, and atypical cells resembling the reticulum cell element of Hodgkin's disease. The condition clinically resembles Wegener's granulomatosis in terms of its multisystem involvement, but histologically the cellular infiltrate resembles malignant lymphoma (Liebow *et al.*, 1972; Liebow, 1973; Gibbs, 1977). The clue to the histological diagnosis of lymphomatoid granulomatosis is the pronounced perivascular distribution of the infiltrate with concomitant vascular occlusion and necrosis. Thus elastic stains are very useful. The course of lymphomatoid granulomatosis is variable—most patients die of respiratory insufficiency—but in approximately 10% of cases there is progression to malignant lymphoma (Liebow *et al.*, 1972; Liebow, 1973).

Our case of plasma cell granuloma showed many of the typical features of the condition, viz, numerous plasma cells admixed with lymphocytes, histiocytes, and polymorph neutrophils set in 'hyaline' stroma. The condition appears always to be benign (Bahadori and Liebow, 1973) and has a distinct natural history. Of course it must be distinguished from malignant proliferations of plasma cells (plasmacytoma), pseudolymphoma (premalignant lymphoma) (since the latter may have a prominent plasma cell component), and sclerosing haemangioma.

The association of tuberculosis with the plasma cell granuloma in our patient was probably fortuitous although it is possible that it had some immunological basis. There was certainly a predisposition to tuberculosis because of the history and pathological evidence of silica exposure. No association has been noted before between silica exposure and plasma cell granuloma.

Our cases (see Table) demonstrate several interesting features. Case 1 shows a pulmonary malignant lymphoma developing in a patient with systemic lupus erythematosus (SLE). Several reports have described malignant lymphoma in patients with SLE (Cammarata *et al.*, 1963; Miller, 1967; Smith *et al.*, 1970) but, so far as we are aware, this is the first report of pulmonary malignant lymphoma associated with SLE. Oleinick (1967) found no evidence of increased susceptibility to malignant lymphoma in patients with SLE, but Goldenberg *et al.* (1969) found a suggestive increase of diffuse connective tissue diseases in patients with malignant lymphoma. Case 2 illustrates the long survival that may occur in histologically malignant lymphoma when resected.

Case 3 had four macroscopically recognisable premalignant lymphomas (pseudolymphoma) but microscopically several smaller similar lesions could be identified with normal lung intervening between each. Is this perhaps an intermediate stage between lymphoid interstitial pneumonia and premalignant lymphoma? We considered that because they were multiple focal lesions rather than diffuse lesions it was better to classify them as premalignant lymphomas.

Case 4 illustrates the diagnostic difficulties frequently encountered in these disorders. The clinical history would have suggested that the pulmonary lesion was a metastasis from the large bowel malignant lymphoma. However, the maturity of the pulmonary infiltrate and its diffuse distribution make the diagnosis of lymphoid interstitial pneumonia more tenable. It is interesting that this patient showed an IgM serum paraprotein. There is a well-known association between dysproteinaemia and LIP (Liebow and Carrington,

Table *Clinical summary of cases*

Case	*Sex/Age*	*Presentation*	*Diagnosis*	*Operative procedure*	*Other treatment*	*Course*
1	F 57	Dyspnoea	Malignant non-Hodgkins, poorly differentiated lymphocytic lymphoma	Wedge resection of lingula	Prednisone for SLE and clonidine for hypertension	No recurrence 3½ years
2	F 18	Cough and sputum	Malignant non-Hodgkins, poorly differentiated lymphocytic lymphoma	Right upper and middle lobectomy	Radiotherapy	Alive with no recurrence 22 years
3	M 49	Dyspnoea, pyrexia, malaise, and cough	Pseudolymphomas (premalignant lymphomas)	Left lower lobectomy	Nil	Alive with no recurrence 18 months
4	M 68	Cough and sputum	Lymphoid interstitial pneumonia with previous malignant lymphoma and carcinoma of large intestine	Closed drill biopsy	Chlorambucil	Alive 3½ years. Paraprotein-anaemia persists
5	M 32	Skin rash and peripheral neuropathy preceded pulmonary symptoms of dyspnoea, cough, and pyrexia	Lymphomatoid granulomatosis	Open lung biopsy	Prednisone and cyclophosphamide	Alive 2½ years —condition remains static
6	M 66	Cough, chest pain, and haemoptysis	Plasma cell granuloma	Right pneumonectomy	Nil	Died 3 months later with pulmonary tuberculosis

1973; Montes *et al.*, 1968; Moran and Totten, 1970). Disturbances of immunoglobulins have also been reported, but much less frequently, in pulmonary malignant lymphoma (Hurt and Kennedy, 1974; Jenkins and Salm, 1971) and in pseudolymphoma (Strimlan *et al.*, 1976). Another interesting feature of the case was the coexistence of a large bowel malignant lymphoma and a carcinoma. This has been seen only rarely (Cornes, 1960). In fact, this present case was reported by Bolton *et al.* (1973) before the pulmonary lesions had become apparent.

Diagnosis of these conditions depends mainly on biopsy, since bronchoscopy and bronchography are of little value, but a thorough knowledge of the clinical and laboratory features is essential since there is considerable overlap between these disorders. Recently, Weisbrot (1976) reported a fascinating case of LIP and Sjögren's syndrome which, after a period of 15 years, changed into lymphomatoid granulomatosis. In this case immunoglobulin disturbances were minor, and at necropsy foci of fibrosed LIP were found adjacent to foci of lymphomatoid granulomatosis.

Surgical excision is agreed to be the best choice for pseudolymphoma and malignant lymphoma (Saltzstein, 1963; Rubin, 1968; Jenkins and Salm, 1971) and plasma cell granuloma (Bahadori and Liebow, 1973). Steroids and immunosuppressants, either alone or in combination, appear to have a role in the treatment of LIP (Liebow and Carrington, 1973) and lymphomatoid granulomatosis (Liebow, 1973; Lee *et al.*, 1976).

At present the aetiology of these lymphoproliferative conditions is unknown but they may represent varied responses to similar stimuli. The natural history of these conditions, apart from plasma cell granuloma, is also poorly understood because of their rarity and relatively short period of observation. However, it is apparent that premalignant lymphoma, LIP, and lymphomatoid granulomatosis have a potential to evolve into malignant lymphomas. More debatable are the relationships between LIP and lymphomatoid granulomatosis and LIP and premalignant lymphoma (Fig. 15). Accurate documentation of more of these cases is essential to define the natural histories of these conditions and to establish their validity as clinicopathological entities.

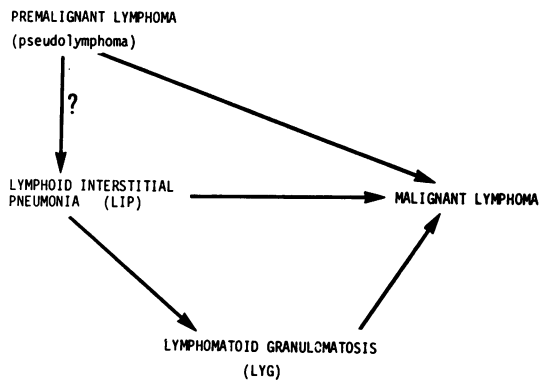

Fig. 15 *Diagram to show interrelationships of primary lymphoproliferative conditions of lung.*

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References

Al-Saleem, T., and Peale, A. R. (1969). Lymphocytic tumors and pseudotumors of the lung. *American Review of Respiratory Diseases*, **99**, 767–772.

Bahadori, M., and Liebow, A. A. (1973). Plasma cell granulomas of the lung. *Cancer*, **31**, 191–208.

Bolton, P. M., Kaufman, B. M., and Fortt, R. W. (1973). Colonic neoplasia and paraproteinemia. *Diseases of Colon and Rectum*, **16**, 59–63.

Cammarata, R. J., Rodnan, G. P., and Jensen, W. N. (1963). Systemic rheumatic disease and malignant lymphoma. *Archives of Internal Medicine*, **111**, 330–337.

Carrington, C. B., and Liebow, A. A. (1966). Lymphocystic interstitial pneumonia (abstract). *American Journal of Pathology*, **48**, 36a.

Cornes, J. S. (1960). Multiple primary cancers: primary malignant lymphomas and carcinomas of the intestinal tract in the same patient. *Journal of Clinical Pathology*, **13**, 483–489.

Gibbs, A. R. (1977). Lymphomatoid granulomatosis—A condition with affinities to Wegener's granulomatosis and lymphoma. *Thorax*, **32**, 71–79.

Goldenberg, G. J., Paraskevas, F., and Israels, L. G. (1969). The association of rheumatoid arthritis with plasma cell and lymphocytic neoplasms. *Arthritis and Rheumatism*, **12**, 569–579.

Halprin, G. M., Ramirez, J. R., and Pratt, P. C. (1972). Lymphoid interstitial pneumonia. *Chest*, **62**, 418–423.

Hurt, R. L., and Kennedy, W. P. U. (1974). Primary lymphosarcoma of the lung. *Thorax*, **29**, 258–261.

Jenkins, B. A. G., and Salm, R. (1971). Primary lymphosarcoma of the lung. *British Journal of Diseases of the Chest*, **65**, 225–237.

Lee, S. C., Roth, L. M., and Brashear, R. E. (1976). Lymphomatoid granulomatosis—A clinicopathological study of four cases. *Cancer*, **38**, 846–853.

Liebow, A. A. (1973). Pulmonary angiitis and granulomatosis. *American Review of Respiratory Diseases*, **108**, 1–18.

Liebow, A. A., and Carrington, C. B. (1973). Diffuse pulmonary lymphoreticular infiltrations associated with dysproteinaemia. *Medical Clinics of North America*, **57**, 809–843.

Liebow, A. A., Carrington, C. B., and Friedman, P. J. (1972). Lymphomatoid granulomatosis. *Human Pathology*, **3**, 457–558.

McNamara, J. J., Kingsley, W. B., Paulson, D. L., Dandade, P. B., Race, G. J., and Urschel, H. C. (1969). Primary lymphosarcoma of the lung. *Annals of Surgery*, **169**, 133–140.

Miller, D. G. (1967). The association of immune disease and malignant lymphoma. *Annals of Internal Medicine*, **66**, 507–521.

Montes, M., Tomasi, T. B. Jr., Noehren, T. H., and Culver, G. J. (1968). Lymphoid interstitial pneumonia with monoclonal gammopathy. *American Review of Respiratory Diseases*, **98**, 277–280.

Moran, T. J., and Totten, R. S. (1970). Lymphoid interstitial pneumonia with dysproteinemia. *American Journal of Clinical Pathology*, **54**, 747–756.

Oleinick, A. (1967). Leukemia or lymphoma occurring subsequent to an autoimmune disease. *Blood*, **29**, 144–153.

Papaioannou, A. N., and Watson, W. L. (1965). Primary lymphoma of the lung: An appraisal of its natural history and a comparison with other localised lymphomas. *Journal of Thoracic and Cardiovascular Surgery*, **49**, 373–387.

Rubin, M. (1968). Primary lymphoma of lung. *Journal of Thoracic and Cardiovascular Surgery*, **56**, 293–303.

Saltzstein, S. L. (1963). Pulmonary malignant lymphomas and pseudolymphomas: Classification, therapy and prognosis. *Cancer*, **16**, 928–955.

Smith, C. K., Cassidy, J. T., and Bole, G. G. (1970). Dysgammaglobulinaemia, systemic lupus erythematosus and lymphoma. *American Journal of Medicine*, **48**, 113–119.

Strimlan, C. V., Rosenow, E. C., Divertie, M. B., and Harrison, E. G. (1976). Pulmonary manifestations of Sjögren's syndrome. *Chest*, **70**, 354–361.

Weisbrot, I. M. (1976). Lymphomatoid granulomatosis of the lung associated with a long history of benign lymphoepithelial lesions of the salivary glands and lymphoid interstitial pneumonitis. *American Journal of Clinical Pathology*, **66**, 792–801.

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