Thorax, 1977, **32**, 71–79

Lymphomatoid granulomatosis—a condition with affinities to Wegener's granulomatosis and lymphoma

A. R. GIBBS

From the Department of Pathology, University Hospital of Wales

Gibbs, A. R. (1977). *Thorax*, **32**, 71–79. **Lymphomatoid granulomatosis—a condition with affinities to Wegener's granulomatosis and lymphoma.** A case of lymphomatoid granulomatosis of the lung is described in which the presenting features were a skin eruption and peripheral neuropathy. The onset of the pulmonary symptoms of breathlessness and productive cough was delayed nine months but, when apparent, the extent of the radiological changes contrasted with the mildness of the symptoms and the triviality of the physical signs. Biopsy of the affected lung revealed a mixed lymphocytic, plasma cell, and histiocytic infiltrate following a perivascular distribution. This combination of clinical and pathological findings is in every detail that of lymphomatoid granulomatosis as recently identified by Liebow *et al.* (1972).

Additional, previously undescribed, and unexplained findings in this case were persistent hypercalciuria and the presence in three axillary lymph nodes of subcapsular groups of cells resembling those of a benign naevus. This is the first case described in the British literature, and it is important that more cases be reported in order that the prevalence, prognosis, and aetiology of the condition should be further established.

The combination of pulmonary symptoms and signs, far less prominent than the lung radiological change together with skin rash, peripheral neuropathy, and lymphadenopathy would bring to mind a wide differential diagnosis including sarcoidosis, Wegener's granulomatosis, lymphoma, occult carcinoma, collagen disease, and histiocytosis X. To this list should now be added lymphomatoid granulomatosis identified by Liebow *et al.* (1972) and Liebow (1973) while investigating the spectrum of pulmonary disease lying between classical Wegener's granulomatosis and lymphoma. They coined the term 'lymphomatoid granulomatosis' for a condition which clinically and radiologically resembles Wegener's granulomatosis but has histological affinities with lymphoma; frank lymphoma became evident terminally in a number of their cases. In lymphomatoid granulomatosis an infiltrate involves mainly the lungs and follows a predominantly perivascular distribution. It may be associated with vasculitis or vasculonecrosis involving arteries and veins and, where the infiltrate abuts on small bronchi and bronchioles, it results in the histological features of a bronchiolitis obliterans. The infiltrate consists of lymphocytes, plasma cells, histiocytic cells, and atypical cells resembling but not identical with the reticulum cell element seen in Hodgkin's disease. An interesting feature of the condition is the frequent occurrence of cutaneous lesions, nervous system involvement, and renal lesions (which, although showing combinations of cellular infiltration, necrosis, and vascular changes, do not include glomerulonephritis as seen in classical Wegener's granulomatosis).

Lymphomatoid granulomatosis has not been reported previously in the British literature and it would seem important for it to feature as part of the complete differential diagnosis in a number of circumstances.

Case report

A 32-year-old white man, a traffic engineer, first presented in April 1974 with a rapid onset of a skin rash which consisted of red, swollen, papular

lesions on the face, forearms, and legs. There was no associated pain or pruritus. A course of topical prednisone and oral antihistamines was given but without any effect.

Three months later the patient was admitted to hospital for investigation and treatment since the rash had persisted, and he also complained of weight loss, numbness of the left heel, and a tightness over the lower legs. Positive findings on examination were: an erythematous, indurated, polycyclic skin eruption which was most marked over the face and upper limbs; an enlarged, nontender, firm, and mobile lymph node in the left axilla; and loss of sensation to light touch over the lateral aspect of the left calf. Over the next few weeks his muscle weakness became more severe, particularly affecting the hands and toes. Lymphadenopathy of the right axilla was also noted.

Investigations at this time showed: Hb 13·1 g/dl, WBC 10×10^9/l, normal differential, ESR 4 mm/hr, normal bone marrow, bilirubin 10 mmol/l (0·6 mg/mmol), SGOT 12 IU/l, SHBD 185 IU/l, alkaline phosphatase 27 IU/l, total protein 63 g/l, albumin 39 g/l, normal electrophoresis, immunoglobulins: IgG 9·6 g/l, IgA 4·2 g/l, IgM 1·20 g/l, fasting blood sugar 4 mmol/l (72 mg/100 ml), CPK 10 IU/l. Negative or normal findings included: rheumatoid factor, antinuclear factor, smooth muscle antibodies, antimitochondrial antibodies, LE cells, WR and Kahn, fasting lipids, serum amylase, thyroid function tests, viral agglutinins, Mantoux test, Kveim test, and urinary aminoacids. A chest radiograph was normal apart from obliteration of the left costophrenic angle. Radiographs of the hands, intravenous pyelogram, barium meal, and barium enema showed no abnormality.

A positive finding was persistent hypercalciuria on numerous occasions (values ranging from 9·6–11·7 mmol/24 h (384–468 mg/24 h); this was present before the start of steroid therapy. Urinary phosphate excretion and serum calcium, phosphate, and alkaline phosphatase were always normal, however.

Nerve conduction studies supported the diagnosis of a peripheral neuropathy.

His condition remained reasonably static during this admission but, in view of the fact that a question of malignancy had been raised by the findings on the axillary lymph node biopsy, it was decided to perform an exploratory laparotomy. This showed no abnormality apart from some enlarged, mobile mesenteric lymph nodes. These and the liver were biopsied.

Oral prednisone (80 mg daily) was started in the hope that the progression of the neuropathy might be halted. Meanwhile the skin rash had begun to improve and continued to do so during this period of steroid therapy. It never completely cleared, however, and the peripheral neuropathy and hypercalciuria persisted.

In October 1974, the patient was discharged but continued to take oral prednisone. His condition showed little change over the next three months but in January 1975 he developed 'flu-like' illness with complaints of nausea, productive cough with yellowish sputum, and breathlessness on walking. On examination he was febrile (37·8°C), he had a tachycardia (110 beats/min), there were crepitations and bronchial breathing at both lung bases, and there was cervical lymphadenopathy. His neurological state and skin rash remained unchanged. Investigations showed that he still had hypercalciuria. This time his chest radiograph (Fig. 1) showed extensive nodular and confluent areas throughout both lower lobes, lingula, and right middle lobes. The changes were present to a lesser extent in the mid-zone.

The patient was started on antibiotics but, as little improvement occurred over several weeks, bronchoscopy, which was normal, and an open lung biopsy were performed. The latter showed the picture of lymphomatoid granulomatosis and the patient was given oral cyclophosphamide (100 mg daily) in addition to the prednisone. At about the same time his chest condition began to improve although there was no concomitant improvement in the state of his peripheral neuropathy and skin rash. A chest radiograph taken a few days after the beginning of the cyclophosphamide treatment showed considerable clearing of the lung fields but with some discrete rounded shadows still present. A further chest radiograph taken a month later (Fig. 2) showed further clearing but with some fibrotic markings present in the left lower zone.

Since then (12 months) the chest radiological appearances and the patient's skin rash, peripheral neuropathy, and hypercalciuria have remained static. His drug therapy now consists only of prednisone (7 mg on alternate days).

Throughout his illness bacteriology of sputum, pleural fluid, nose, urine, and blood showed no significant abnormality.

PATHOLOGY

Skin Three separate skin biopsies, the first (Fig. 3) taken four months after the onset of the skin rash and the others taken over a further two

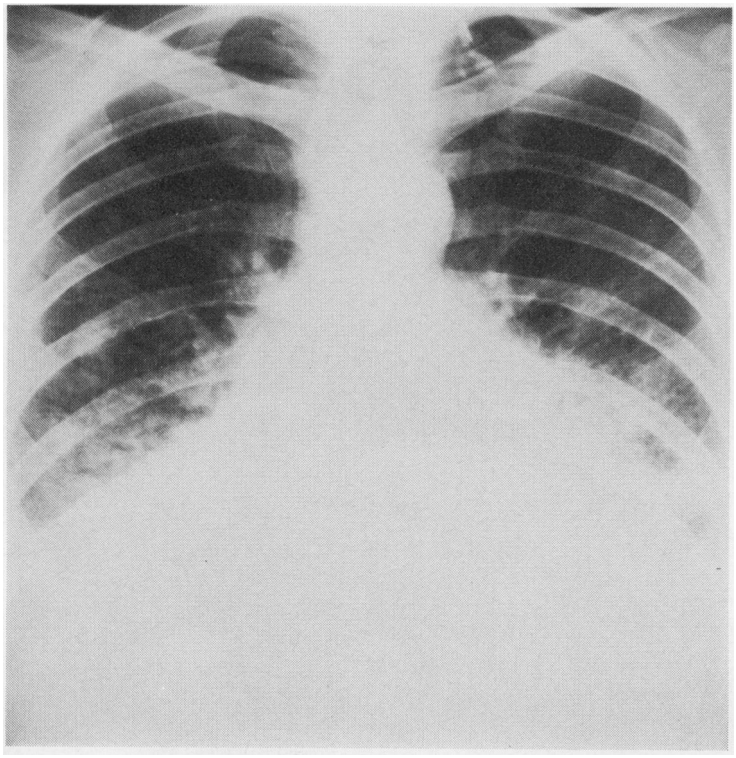

Fig. 1 *Postero-anterior radiograph showing diffuse and nodular bilateral infiltrates in the mid and lower zones.*

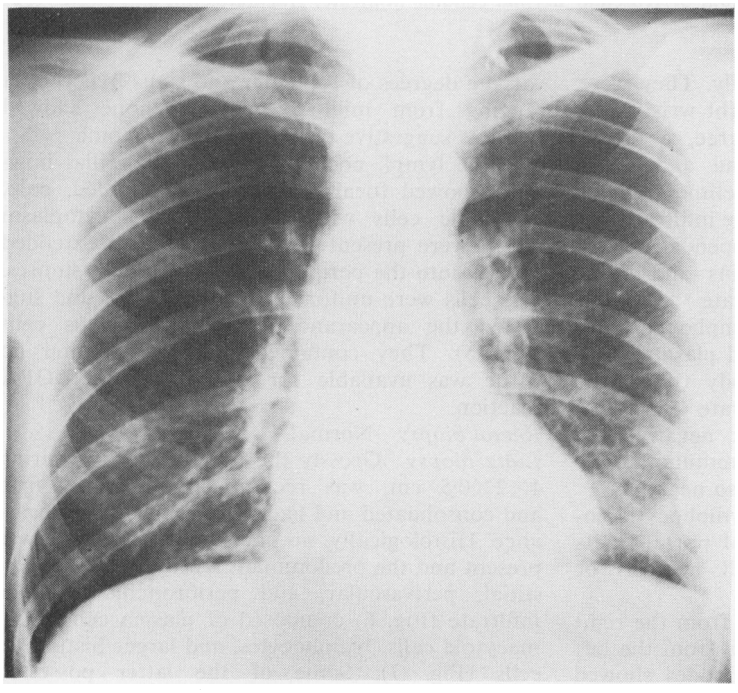

Fig. 2 *Postero-anterior radiograph two months later after administration of prednisone and cyclophosphamide.*

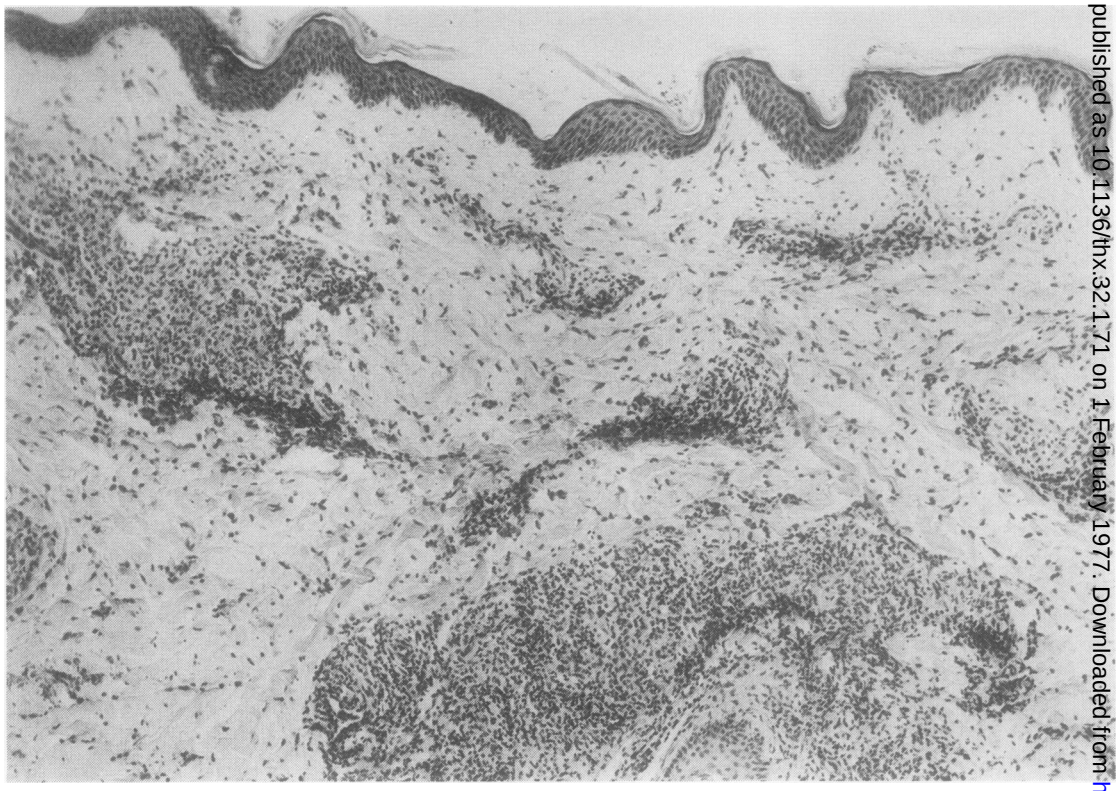

Fig. 3 *Skin showing the periadnexal and perivascular dermal cellular infiltrate. Haematoxylin and eosin* ×32

months, were examined histologically. They were taken from the left forearm and right wrist.

Each showed, to a varying degree, a mixed cellular infiltrate affecting the mid and lower dermis predominantly but also sometimes extending into the subcutaneous tissue. The infiltrate was situated predominantly around appendages, but in some areas infiltration of veins and small arteries could be seen. The infiltrate consisted mostly of mature and immature lymphocytes and also larger pale histiocytic cells and plasmacytoid cells. A few scattered foreign body type giant cells were also present in the infiltrate (Fig. 4).

Direct immunofluorescence was negative for IgG and complement; indirect immunofluorescence on the patient's blood was also negative.

Liver There was a mild focal lymphocytic infiltration of the parenchyma and of portal tracts but there was no associated cell necrosis or disturbance in the architecture.

Lymph nodes Three lymph nodes from the right axilla, three out of six lymph nodes from the left axilla, and the mesenteric lymph nodes showed varying degrees of follicular and sinus hyperplasia ranging from mild to marked; none showed features suggestive of malignant lymphoma.

Three lymph nodes from the left axilla, however, showed focal collections of rounded, pale, basophilic cells with poorly defined cytoplasm which were present in the capsule and extended slightly into the peripheral and medullary sinuses. The cells were uniform, lacked mitoses, and suggested the appearance of benign naevus cells (Fig. 5). They contained no pigment, and no tissue was available for testing by the DOPA reaction.

Rectal biopsy Normal.

Lung biopsy Grossly the lung tissue, measuring 4×2×0·5 cm, was rectangular in shape, firm and consolidated and had a greyish-yellow appearance. Histologically, no unaffected lung tissue was present and the predominant feature was an interstitial, perivascular, and peribronchial cellular infiltrate (Fig. 6) composed of plasma cells, plasmacytoid cells, lymphocytes, and larger histiocytic cells (Fig. 7). Some of the latter possessed

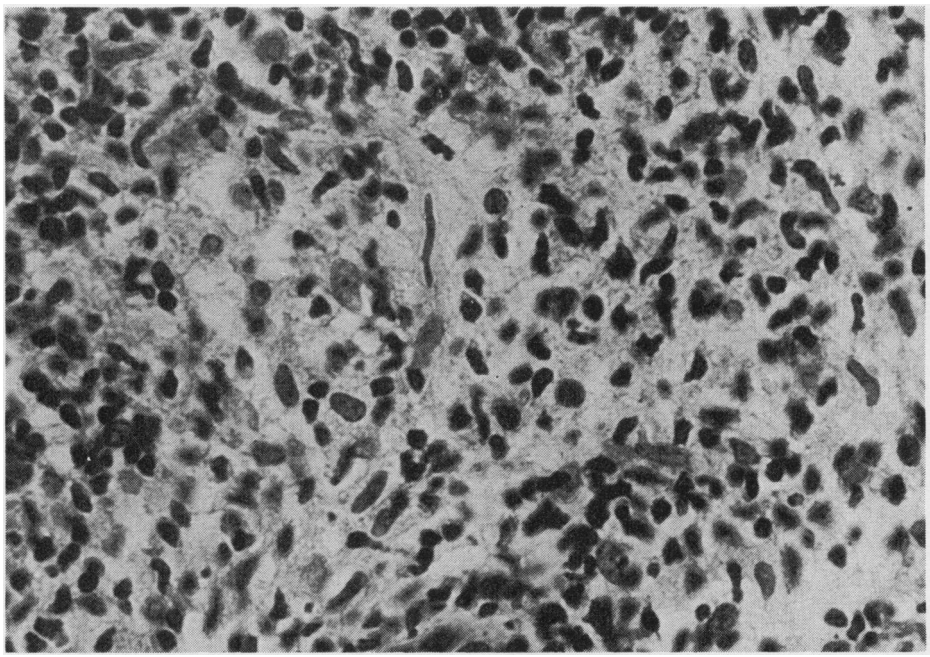

Fig. 4 *Skin showing the predominantly lymphocytic and histiocytic nature of the cellular infiltrate. H and E* ×*365*

acidophilic cytoplasm and contained large, pale, vesicular nuclei with prominent acidophilic nucleoli not unlike the atypical reticulum cells of Hodgkin's disease. There was little mitotic activity and eosinophils were almost completely absent. 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 minimal vasculonecrosis. Fibrosis was developing in association with the infiltrative process.

A secondary obstructive effect upon the airways was apparent (Fig. 8) as bronchiolar obliteration by granulation tissue (bronchiolitis obliterans). As part of the obstruction there was marked alveolar accumulation of lipid-laden macrophages (endogenous lipid pneumonia). Cuboidal metaplasia of the alveolar lining cells occurred.

Discussion

Of these cases of lymphomatoid granulomatosis so far described (Liebow *et al.*, 1972; Liebow, 1973; Allen, 1974; Kay *et al.*, 1974) most cases presented in early middle age with cough, fever or dyspnoea. In a small proportion of cases, however, the patients presented with a skin rash, lymphadenopathy or nervous system involvement and did not show the pulmonary involvement until later. All showed pulmonary involvement at some time.

Cutaneous involvement occurred in approximately 50%, renal involvement in 45%, central nervous system involvement in 23%, and peripheral neuropathy in 15% of cases. The renal lesions were usually discovered only at necropsy and consisted of wedge-shaped infarcts or rounded tumour-like masses which often bulged the capsular surfaces. The histology of the renal lesions was that of a mixed lymphoreticular infiltrate following for the most part a perivascular distribution in combination with varying degrees of necrosis and vascular occlusion, a similar histological picture to that seen in the lungs. In the other organs involved by the disease process the histological pattern of cellular infiltration, necrosis, and vascular changes was similar.

Although the pathological features of lymphomatoid granulomatosis resemble lymphoma, in so far as the nature of the cellular infiltrate and the nodular gross appearance of the lesions are concerned, the condition shows several differences. It tends to affect the lungs early while the lymph nodes, spleen, and bone marrow are spared and it shows a much higher incidence of central nervous

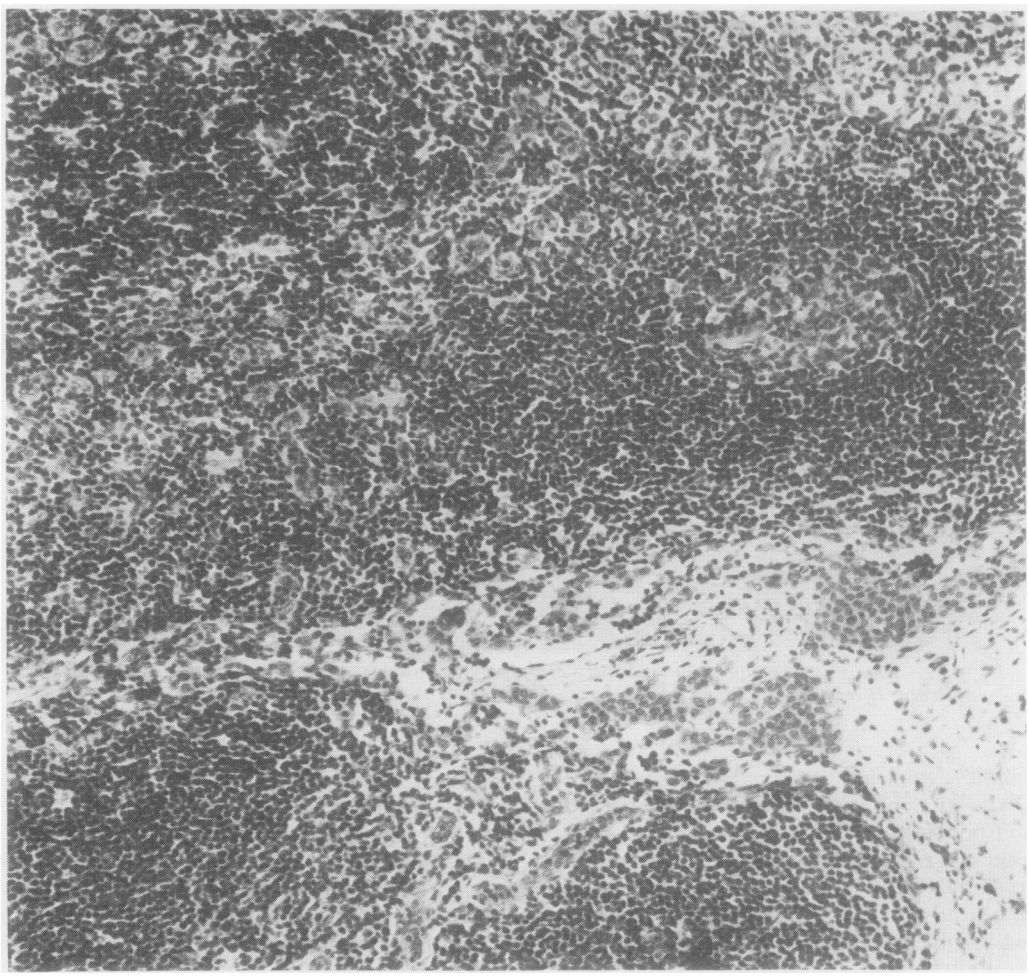

Fig. 5 *Lymph node containing the subcapsular groups of naevus cells. H and E ×143*

system involvement than occurs in lymphoma. The tendency to a perivascular distribution of the cellular infiltrate in lymphomatoid granulomatosis with concomitant vascular occlusion and vasculonecrosis also differs from that seen in lymphoma. In the minority of patients who have exhibited lymphadenopathy in lymphomatoid granulomatosis the lymph nodes have shown atypical hyperplasia, but in five out of the original 40 cases described by Liebow *et al.* (1972) there was progression to an atypical lymphoma which could not be assigned to one of the usual histological classes.

Lymphomatoid granulomatosis has similarities to Wegener's granulomatosis in the distribution of lesions and the combination of a focal granulomatous disease with destructive vascular change. The age distribution is approximately the same and the radiographic appearances are similar. However, lymphomatoid granulomatosis rarely involves the upper respiratory tract and there is absence of glomerulonephritis. In addition, lymphomatoid granulomatosis shows a much higher frequency of central nervous system and skin involvement than does Wegener's granulomatosis. Histologically, lymphomatoid granulomatosis shows a much more marked lymphoid character to the cellular infiltrate and the cells are more atypical and mitotically active than those usually seen in Wegener's granulomatosis. Also the tuberculoid lesions showing necrosis and giant cell formation, often present in Wegener's granulomatosis

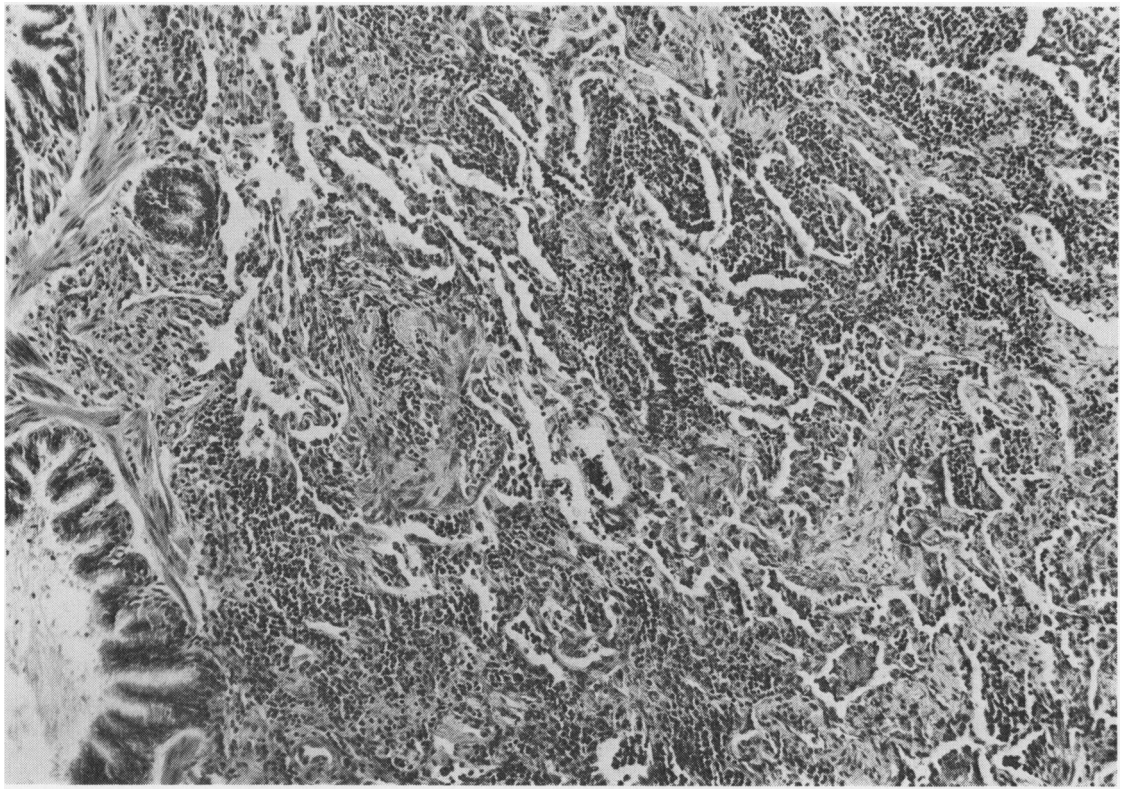

Fig. 6 *Lung showing the interstitial and perivascular cellular infiltrate. H and E* ×*35*

(Wegener, 1936; Wegener, 1939; Godman and Churg, 1954), are rarely seen in lymphomatoid granulomatosis.

The pulmonary radiological picture of lymphomatoid granulomatosis usually shows bilateral, nodular densities predominantly in the mid and lower lung fields. They tend to wax and wane and often became confluent, cavitation occurring in approximately one-third of cases. Enlargement of hilar lymph nodes occurs in very few patients. The radiological changes of lymphomatoid granulomatosis, although overlapping with those of Wegener's granulomatosis, show slight differences, for example, the lesions are more numerous and peripherally situated, less well-defined, and often more confluent in lymphomatoid granulomatosis.

I found in our case, as in the other cases described, that the diagnosis depended on the clinical features taken together with the pulmonary histological changes rather than on the laboratory investigations.

I report this case of lymphomatoid granulomatosis because it illustrates many of the features of a condition which is, as yet, not widely known, viz, the onset of skin and nervous system manifestations, which may precede the onset of pulmonary involvement by a considerable period of time, and the histological features, which although not pathognomonic, when taken together with the clinical features combine to form a distinct clinicopathological entity. Secondly, this case shows features not previously mentioned in association with the condition—unexplained persistent hypercalciuria and the presence in three lymph nodes of subcapsular groups of benign appearing naevus-like cells. The latter feature has been described previously (Stewart and Copeland, 1931; Stewart, 1960; Johnson and Helwig, 1969) and it is interesting that in most of the cases the abnormality occurred in axillary lymph nodes. It was suggested that this could represent a variation of normal anatomy, although this is unlikely, or be the result of aberrant migration of naevus cells from

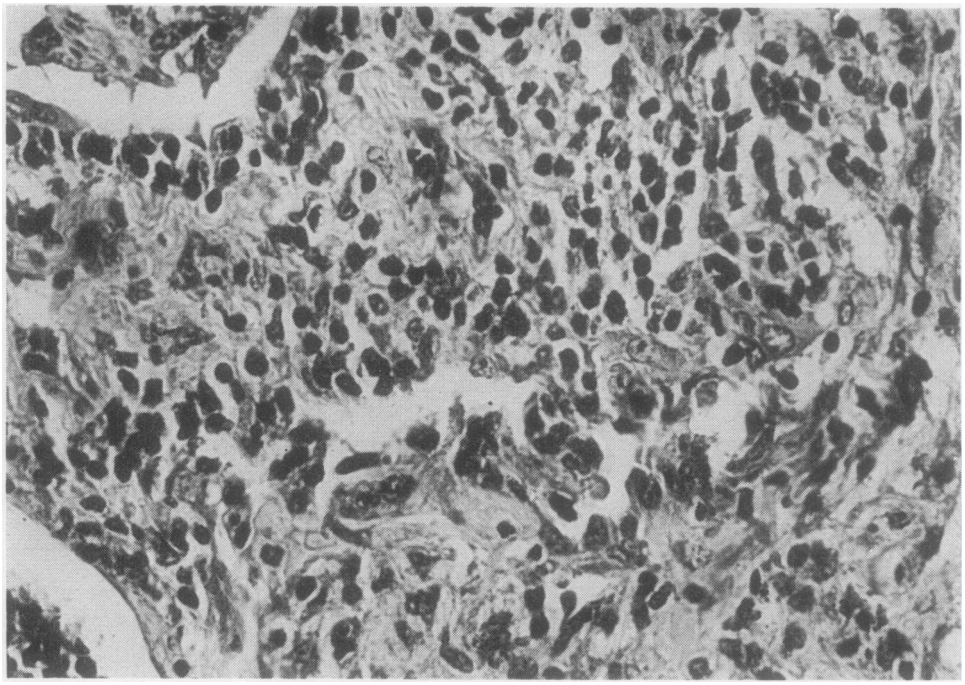

Fig. 7 *The pulmonary infiltrate showing lymphocytes, plasma cells and histiocytic cells, some with pale nuclei and prominent nucleoli. H and E ×370*

the neural crest. A third unlikely possibility is that the cells migrate from a naevus in the skin.

Of the 40 original cases of lymphomatoid granulomatosis described by Liebow *et al.*, 28 had died and pulmonary involvement was the major cause of death in 14, central nervous system involvement accounting for four. In four cases the chest films cleared and there was no further evidence of disease. The longest survivor, who was apparently well, had lived for 17 years after the onset of disease. In eight patients evidence of healing of the lung lesions was found at necropsy but it must be stated that the disease process may still continue in other organs.

The precise role of steroids and immunosuppressives in the treatment of this condition has yet to be established. Certainly in our case the pulmonary manifestations appeared to improve with cyclophosphamide. Also there was initial improvement in the skin condition following prednisone administration but since then it has remained static. The nervous system involvement has shown no change with either steroids or cyclophosphamide. Most of the cases described by Liebow *et al.* received steroids and/or immunosuppressives but the results were variable and, in one case, there was a seven-year remission from the disease without any treatment whatsoever. At present no clinical or histological features have been found to help in assessing prognosis in this condition.

The only large series of cases has been described by Liebow *et al.* (1972) in the USA. This, however, is the first reported case in Britain. This may reflect a genuine difference in frequency of occurrence, or it may be that until now the disease has been overlooked. It is important, therefore, that more people should be aware of the condition and that more cases should be reported. Only from a larger world series of cases can lines of division within the spectrum of diseases described by Liebow and his colleagues, be evaluated.

I thank Dr. R. Marks for permission to publish details of the case, Dr. J. G. Leopold for helpful advice, and the staff of the Department of Pathology of the University Hospital of Wales.

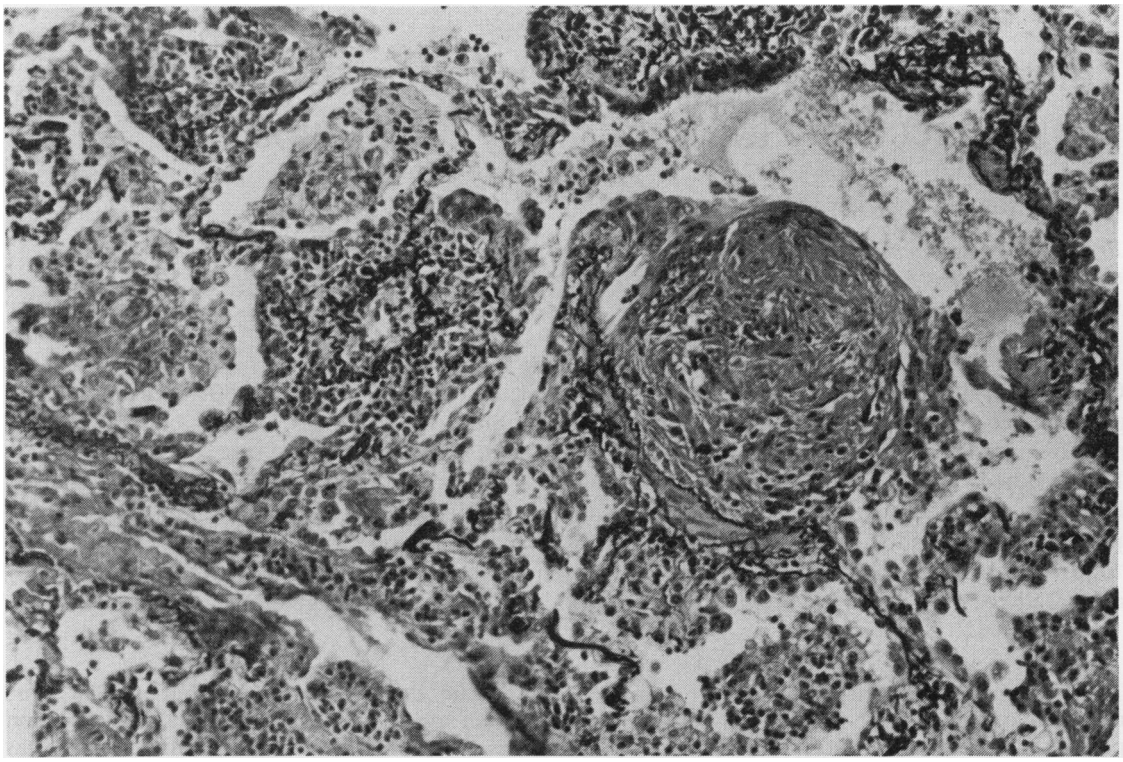

Fig. 8 *Bronchiole showing obliteration by a rounded mass of cellular fibrous tissue; the adjacent vessel (left centre) shows surrounding lymphoid infiltrate. The obstructive pneumonitis can also be seen. Aldehyde-fuchsin* ×215

References

Allen, P. W., ed. (1974). A case of chronic lymphadenopathy and bilateral pulmonary nodules (Conference). *Medical Journal of Australia*, **1**, 231–237.

Godman, G. and Churg, J. ((1954). Wegener's granulomatosis. Pathology and review of the literature. *Archives of Pathology*, **58**, 533–553.

Johnson, W. T. and Helwig, E. B. (1969). Benign nevus cells in the capsule of lymph nodes. *Cancer*, **23**, 747–756.

Kay, S., Fu, Y., Minars, N., and Brady, J. W. (1974). Lymphomatoid granulomatosis of the skin: light microscopic and ultrastructural studies. *Cancer*, **34**, 1675–1682.

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

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

Stewart, F. W. (1960). Early cancer (Tayer lecture, Johns Hopkins University) as quoted by Wood, S., Jr (1961), *Canadian Cancer Conference*, **4**, 172. Academic Press, New York.

Stewart, F. W. and Copeland, M. M. (1931). Neurogenic sarcoma. *American Journal of Cancer*, **15**, 1235–1320.

Wegener, F. (1936). Über generalisierte septische Gefässerkrankungen. *Verhandlungen der Deutschen Gesellschaft für Pathologie*, **29**, 202.

Wegener, F. (1939). Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. *Beitrage zur pathologischen Anatomie und zur allgemeinen Pathologie*, **102**, 36–68.

Requests for reprints to: Dr. A. R. Gibbs., Department of Pathology, University Hospital of Wales, Cardiff.