Lymphomatoid granulomatosis

A report of 4 cases

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Summary

Only 1 case of lymphomatoid granulomatosis has previously been reported from South Africa. Experience with 4 such adult patients (2 blacks and 2 whites) is described. These patients were followed up for 15 - 48 months and none developed evidence of a lymphoma during this period. Fever, weight loss, cough and breathlessness were prominent symptoms in all patients. One patient, a black woman, with a diffuse interstitial pattern of lung involvement, had digital clubbing — a rare accompaniment that resolved after therapy. Dilated congestive cardiomyopathy was found in association with pulmonary nodules in a black male patient. All 4 patients were treated with cytotoxic regimens. The 2 patients treated with oral cyclophosphamide and prednisolone responded favourably. The possible explanation for paucity of reports of lymphomatoid granulomatosis from South Africa could be under-reporting, underdiagnosis or a true geographic/ethnic variation in the incidence of this condition.

S Afr Med J 1991; **79:** 274-278.

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Accepted 22 May 1990.

Lymphomatoid granulomatosis is a lymphoreticular proliferative disorder that derives its name from the histological characteristics of an inflammatory granulomatous process in association with features of a lymphoproliferative disease.[1] Although progression to lymphoma was reported to develop in approximately 12% of patients,[2] it is now felt that lymphomatoid granulomatosis is one of a variety of polymorphous T-cell lymphomas *ab initio*.[3] Lymphomatoid granulomatosis was first described in Africa in a white patient by Croft *et al.*[4] in 1980. To the best of our knowledge no further cases have been reported from Africa. We describe a further 4 cases — 2 black and 2 white patients.

Case reports

Case 1

A 59-year-old white man was referred for evaluation of an opacity in the right upper lobe of the lung (Fig. 1). There was a productive cough and weight loss of 1 month's duration. The patient had had a gastrectomy for a peptic ulcer 4 years previously. He was a smoker. On examination there was no clubbing, lymphadenopathy or skin lesions. Sputum examination was negative for malignant cells and acid-fast bacilli. The patient was treated with antibiotics with no improvement. Bronchoscopy was unhelpful and right upper lobectomy was performed. A mass measuring approximately 15 × 6 cm was palpated within the excised lobe. The regional lymph nodes were biopsied. Microscopic examination showed features of lymphomatoid granulomatosis; the lymph nodes were free of disease. The patient was referred to the Oncology Unit where

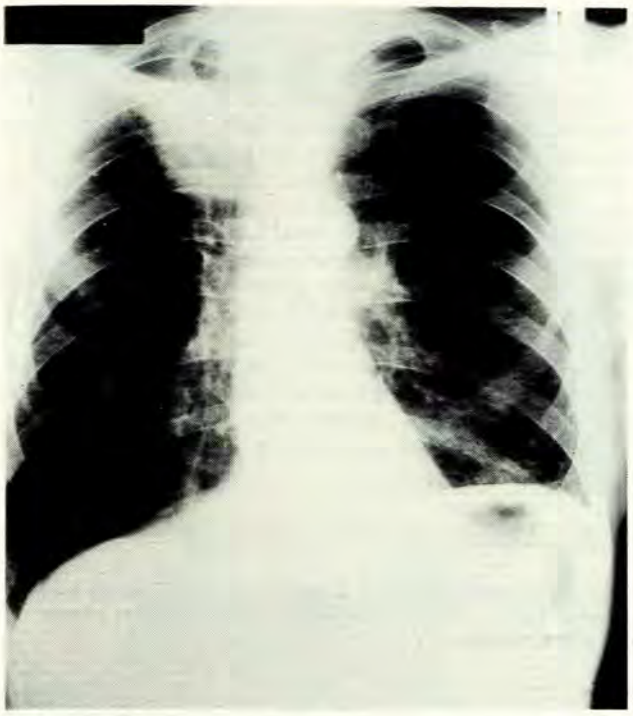

Fig. 1. Case 1 — chest radiograph showing consolidation in the right upper lobe.

it was elected to treat him with the MACOP + B regimen (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisolone and bleomycin) as for lymphoma.[5] He completed 10 courses of this regimen. The patient had two episodes of upper-segment deep-vein thrombosis of his lower limbs and pulmonary embolism. The patient remains free of disease 35 months after initial presentation.

Case 2

A 39-year-old black woman was referred with a history of a productive cough, progressively worsening dyspnoea, weight loss and swelling of the lower limbs of 4 months' duration. She was class III disabled (New York Heart Association (NYHA)). A skin rash had appeared on her lower limbs 2 months previously. Sputum culture revealed *Klebsiella* sp. and she was treated with chloramphenicol at the referring hospital. Her only other therapy was furosemide for presumed cardiac failure but a detailed cardiac examination, including echocardiography subsequently failed to confirm this. On examination, the patient was in mild respiratory distress with a respiratory rate of 36/min and central cyanosis. Clubbing of the fingers was present. There was an indurated swelling with subcutaneous nodules and overlying macular erythema on the anterior aspect of both shins. Mid-to-late inspiratory crackles were present in both mid and lower zones of the chest.

The chest radiograph taken on admission to hospital showed a reticulonodular infiltrate in both mid and lower zones. The cardiac silhouette was normal. The Mantoux test was 8 mm reactive. Pulmonary function tests showed a severe restrictive ventilatory defect with impaired single breath-diffusing capacity for carbon monoxide. Tests for antinuclear antibody and rheumatoid factor were negative. Biochemical investigations for sarcoidosis, including calcium, phosphate and serum angiotensin-converting enzyme, were negative. The haemoglobin value was 11,8 g/dl and the white cell count $7{,}7 \times 10^9$/l with 38% neutrophils, 48% lymphocytes and 4% eosinophils, and the erythrocyte sedimentation rate was 91 mm/1st h (Westergren).

A transbronchial lung biopsy was unhelpful and an open lung biopsy was performed. Histological examination of the specimen showed features of lymphomatoid granulomatosis. The patient was started on cyclophosphamide 2 mg/kg/d and prednisolone 1 mg/kg on alternate days according to the protocol of Fauci *et al.*[6] There was a dramatic clinical improvement, which was mirrored by the lung function test. The patient returned to work after 6 weeks. Two episodes of haemorrhagic cystitis not responsive to further increases in fluid intake occurred 7 months later and necessitated withdrawal of cyclophosphamide. Features of haemorrhagic cystitis and schistosomiasis were found on histological examination of the bladder-wall specimen obtained at cystoscopy. The patient remains well 19 months after her initial presentation. She has been on prednisolone alone for the last 12 months.

Case 3

A 70-year-old black man was admitted to hospital with a 1-year history of left pleuritic pain, non-productive cough, anorexia and weight loss. Five years previously he had developed dyspnoea, which was attributed to congestive cardiomyopathy and managed with diuretics. His dyspnoea initially improved but recurred to the extent that he was class IV disabled (NYHA) on presentation. He had a 20 pack year history of smoking.

On examination, the patient was apyrexial, emaciated, had generalised hyperpigmentation and peripheral oedema. No clubbing, lymphadenopathy or cutaneous lesions were noted. He was in cardiac failure, with atrial fibrillation and mitral tricuspid regurgitation. There were signs of consolidation of the left lung.

Chest radiography during this admission showed total opacification of the left hemithorax with ipsilateral mediastinal displacement (Fig. 2, left). Radiography 39 months previously had shown 2 nodules, which had increased in size and number 25 months later (Fig. 2, right).

The patient was unable to perform pulmonary function tests. An echocardiogram demonstrated impaired left ventricular function. He was treated with diuretics, digoxin and captopril with good effect.

Tru-cut biopsy of the lung (left lower lobe) was performed and histological examination showed the characteristic features of lymphomatoid granulomatosis.

Chlorambucil at a dose of 0,1 mg/kg/d was begun. Prednisolone and cyclophosphamide were not used because he was in severe cardiac failure. Two months later his disability improved to class III. However, left ventricular contractility remained static on repeat echocardiography and chest radiography showed no change. Bone marrow depression necessitated cessation of chemotherapy and radiotherapy was initiated. The patient could not complete the course owing to his poor clinical condition. He has survived 48 months since the radiographic changes were first noted.

Case 4

A 26-year-old white man presented with a 2-month history of fever, vomiting, pleuritic pain and a cough with occasional haemoptysis while on holiday in Britain. He had lost 16 kg in weight over the 3½ weeks preceding hospitalisation. He was taking no drugs and had never smoked. He was fully investigated at the Royal Free Hospital in London and referred to Durban for follow-up and therapy.

The patient was pyrexial (38°C) on presentation. Chest examination revealed bronchial breathing at the left apex. The

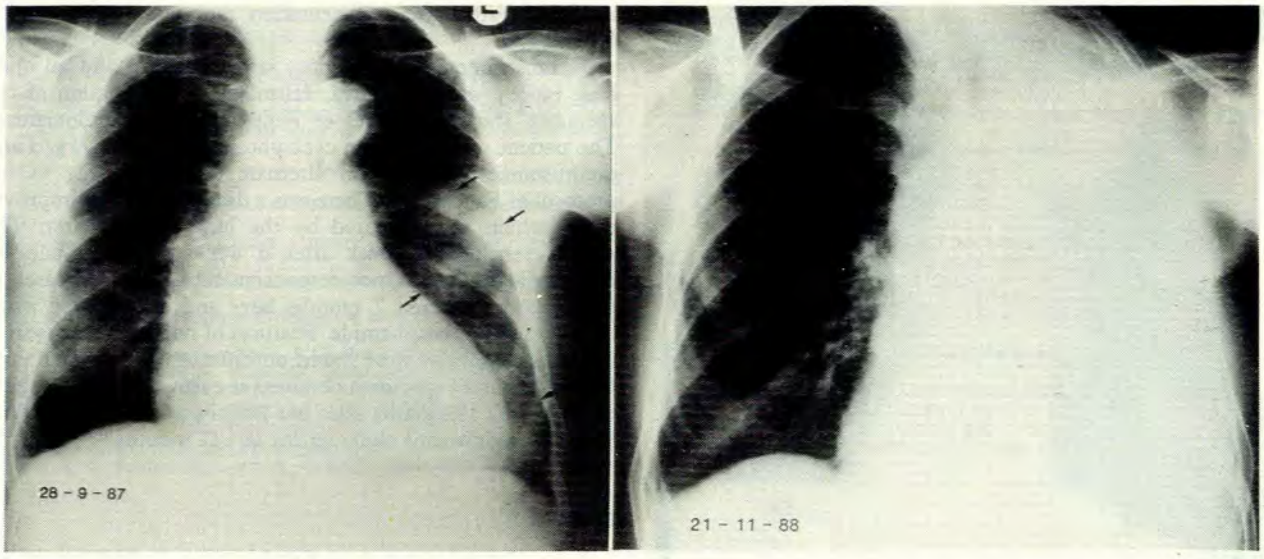

Fig. 2. Case 3 — left: chest radiograph showing cardiomegaly and the nodules (arrowed) in both lung fields, which had increased in size and number from the chest radiograph 25 months earlier. Right: radiograph 14 months later shows progression to complete opacification of the hemithorax with collapse of the left lung.

liver was palpable 2 cm below the right costal margin and the spleen was tipped. The rest of the physical examination showed nothing abnormal.

Chest radiography showed multiple opacities of varying sizes in both lung fields, some of which appeared to be cavitating (Fig. 3).

The haemoglobin value was 11,2 g/dl; leucocyte count 4,5 $\times$ 10^9/l, with 68% neutrophils, 22% lymphocytes, 7% monocytes, 2% eosinophils, 1% basophils, and the platelet count was 202 $\times$ 10^9/l and erythrocyte sedimentation rate 66 mm/1st h (Westergren). Rheumatoid factor and antinuclear antibody tests were negative and sputum examination was unhelpful.

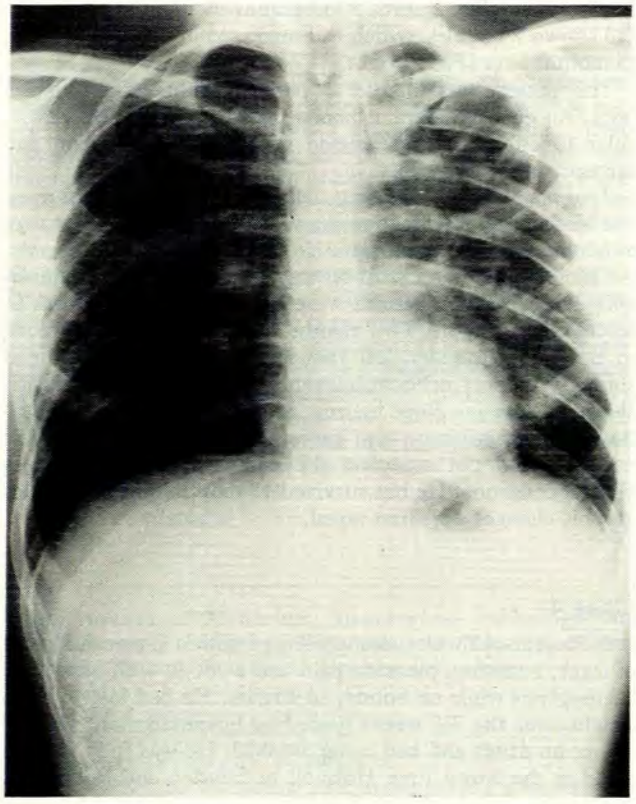

Fig. 3. Case 4 — chest radiograph showing a cavity and multiple nodules in the left lung. A large retrocardiac mass is also present.

Abdominal ultrasonography showed no evidence of intra-abdominal masses. Computed tomography (CT) of the abdomen revealed several small lesions in the liver, most of which were less than 2 cm in diameter. Liver function tests showed nothing abnormal. Low attenuation and solid lesions were also present in both kidneys, but no enlarged abdominal nodes were noted.

In view of the history of hoarseness, the nasopharynx was examined by indirect laryngoscopy. There was a small well-defined lesion on the medial surface of the right vocal cord, which was regarded as benign and therefore not biopsied. Percutaneous lung biopsy showed no evidence of malignant disease or infection. Subsequent bronchoscopy revealed that the apical segment of the right upper lobe was narrowed by necrotic material, but there was no other abnormality of the bronchial tree. Histological examination was unhelpful. A biopsy of the left kidney under ultrasonographic control produced necrotic tissue.

A diagnostic laparoscopy and subsequent laparotomy were performed and multiple biopsies were taken from a large left perirenal mass. Histological examination revealed that the tissue was perirenal fat showing features of lymphomatoid granulomatosis.

The patient was started on therapy with cyclophospamide 2 mg/kg/d orally and prednisolone 1 mg/kg on alternate days according to the protocol of Fauci *et al.*[6] The temperature settled and he has regained weight. Serial chest radiography showed almost complete clearing of the parenchymal lung lesions with a residual thin-walled cavity in the left upper zone. The patient remains well 15 months after initial presentation.

Pathology

Lung tissue was submitted for histological examination in 3 cases. The consolidated lobectomy specimen (case 1), a wedge of lung tissue from an open lung biopsy (case 2) and three cores of a Tru-cut lung biopsy (case 3) were available for histopathological examination. In case 4 the histopathological report was obtained from the Royal Free Hospital, London.

Tissue was fixed in 10% formaldehyde and routine paraffin sections prepared and stained with haematoxylin and eosin, elastic-van Gieson and Masson's trichrome stains.

Light microscopy in all 3 cases showed similar features — vessels invaded by an angiocentric lymphoplasmacytic infiltrate (Fig. 4). Small lymphocytes admixed with polytypic mature and immature plasma cells, histiocytes and occasional atypical large lymphoid cells were seen extending through the vascular wall into the subintimal layer. None of the tissue showed evidence of vascular occlusion or tissue necrosis. The predominant cells, small lymphocytes, showed mild cytological atypia in all 3 cases. In cases 1 and 3 the cellular infiltrate extended from the bronchovascular units into surrounding interstitial parenchyma, while in case 2 the intervening parenchyma was within normal limits. The plasma cell population proved to be polytypic in all cases, with demonstrable staining reactions using both χ- and λ-light-chain antisera (peroxidase-anti-peroxidase; Dakopatts).

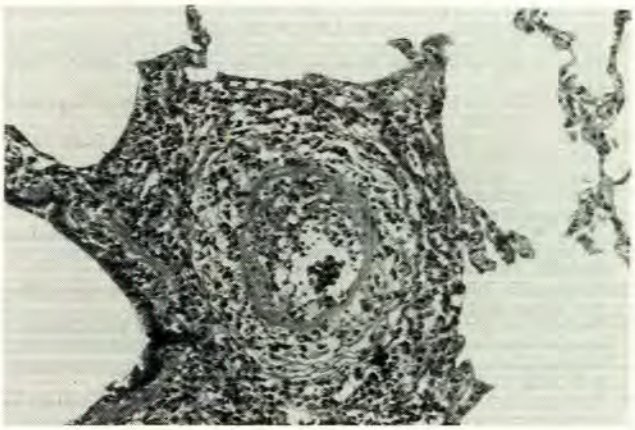

Fig. 4. Case 2 — lymphomatoid granulomatosis of the lung: an angiocentric and angiodestructive lymphoid infiltrate involving a small pulmonary artery.

Discussion

Lymphomatoid granulomatosis is a predominantly pulmonary angiitis with frequent extrapulmonary manifestations. The skin, central nervous system and kidney are commonly involved. Lymph node, spleen and bone marrow involvement are less common.[7] Upper respiratory tract involvement is notably rare.[8,9] More recently,[10,11] lymphomatoid granulomatosis has been grouped under the entity of 'angiocentric immunoproliferative lesions' (AILs). Jaffe[10] believes that AILs are probably neoplastic *ab initio*, with grade I lesions being characterised by a predominance of small lymphoid cells with little or no cytological atypia. Progression from grade I to II and III is characterised by increasing cytological atypia. A recent editorial[3] in *The Lancet* stated that, based on immunological phenotyping and gene re-arrangement studies, most cases of lymphomatoid granulomatosis are, in fact, malignant lymphomas. Angiocentric immunoproliferative lesions are thought to represent a variant of T-cell lymphoma. Wegener's granulomatosis, which is essentially a granulomatous vasculitis, is distinguished from lymphomatoid granulomatosis because of its unique appearance on histological examination and because it does not develop into a lymphoma.[12]

The patients reported here presented with pulmonary symptoms, viz. cough, shortness of breath and chest pain. Cough occurred in 56 - 80%, dyspnoea in 11 - 35% and chest pain in 13 - 15% of patients in three large series of patients with lymphomatoid granulomatosis.[1,2,13] Weight loss, which was also a feature in our patients, occurred in 35 - 58% of patients in these series.

Skin involvement, the commonest extrapulmonary manifestation of lymphomatoid granulomatosis has been reported in 40 - 45% of cases.[2,14] Patient 2 had erythematous macular lesions, with subcutaneous nodules resembling erythema nodosum. The skin lesions in this condition are variable and take the form of subcutaneous nodules, dermal nodules, maculopapular eruptions, macular erythema and ulcers. These may be generalised or localised to the face, trunk, legs or arms and may precede, occur with or follow pulmonary involvement. Recurrences are well documented. The diagnosis of lymphomatoid granulomatosis may be based on the skin biopsy specimen if the characteristic pathological changes of the condition can be demonstrated.[15] The healing of the skin lesions mirrored the resolution of the pulmonary symptoms in our patient.

Cardiac involvement was noted in 11% (8 out of 72 patients) of Katzenstein *et al.*'s[2] autopsy series. Our patient 3 had dilated congestive cardiomyopathy at the time the chest radiography showed pulmonary nodules (Fig. 2). Because primary congestive cardiomyopathy is the commonest cause of cardiac failure in our environment, we believe the association of cardiomyopathy with lymphomatoid granulomatosis in patient 3 may be incidental. The clinical manifestations of cardiac involvement with lymphomatoid granulomatosis have not been described. The pathology of cardiac involvement has been described by Liebow *et al.*[1] The coronary arteries were involved by a necrotising angiitis and an atypical lymphoreticular infiltrate in 1 of their patients. The myocardium was also infiltrated by lymphocytes and larger atypical reticulo-endothelial derivatives. It is conceivable that if the myocardium is diffusely involved it may manifest as cardiomyopathy. However, a myocardial biopsy would have been necessary to prove this in our patient. The ECG did not reflect any evidence of coronary artery disease.

Clubbing is a rare physical sign in lymphomatoid granulomatosis with only 1 case report of this sign having been published.[16] Patient 2 presented with clubbing, which improved with therapy, a feature documented in the previously reported case.

The wide range of chest radiography findings in our patients reflect the spectrum of lung involvement with lymphomatoid granulomatosis. Each of the patients in our series had a different chest radiographic picture. Patient 1 presented with a unilateral mass lesion in the upper lobe of the lung (Fig. 1). This was noted in 1 out of 24 and 2 out of 16 patients in two published reviews of chest radiography in lymphomatoid granulomatosis.[17,18] Lymphomatoid granulomatosis is included in the differential diagnosis of diffuse interstitial lung disease and was a feature in case 2.[15] The most common chest radiography finding in lymphomatoid granulomatosis is multiple nodules, which may be unilateral or bilateral.[17,18] The radiographs of patient 3 in our series showed multiple unilateral nodules (Fig. 2), which progressed to total opacification of the left lung field over a period of 39 months without therapy (Fig. 2). Patient 4 had multiple nodular opacities, some of which appeared to cavitate — a feature that has been well documented.[17,18]

In case 4 the diagnosis of lymphomatoid granulomatosis was made on histological examination of the biopsy of a perirenal mass, which turned out to be perirenal fat involved with lymphomatoid granulomatosis. Liebow *et al.*[1] reported the involvement of abdominal fascia at necropsy in 1 patient in their original series. Our patient appeared to have, in addition, involvement of the liver as noted on CT and his spleen was clinically enlarged.

The therapy of lymphomatoid granulomatosis remains controversial. This is because the condition is relatively rare and most case series are retrospective studies. Although the

clinical course is variable, with a propensity for evolving into a lymphoma, long-term survival without therapy has been documented.[19] Steroids alone appear inadequate to induce and/or maintain remission. A combination of cyclophosphamide 2 mg/kg/d body weight daily and prednisolone 1 mg/kg on alternate days appeared to be effective in inducing and maintaining complete remission in 7 out of 13 patients in a prospective therapeutic trial.[6] Malignant lymphoma developed in 7 out of the 8 patients who died and within this group only 2 had received therapy over an adequate period of time. The lymphoma that develops is refractory to therapy. Patient 1 in our series is disease-free 35 months after initial presentation. Cyclophosphamide and prednisolone were used with success in patients 2 and 4. However, haemorrhagic cystitis, a known complication of cyclophosphamide therapy[20] necessitated premature withdrawal of this drug in patient 2. Patient 3 survived 48 months without therapy although the disease progressed radiographically.

The prognosis in lymphomatoid granulomatosis is extremely poor with a mortality rate of 65 - 90%.[6] The median survival time in Katzenstein *et al.*'s[2] series was 14 months and 94% of the deaths occurred by 36 months. Early recognition and adequate chemotherapy may alter this poor prognosis.[6]

We have added 4 cases to the only other reported case of lymphomatoid granulomatosis from South Africa. The spectrum of disease demonstrated in our patients is similar to that reported in other series. Clubbing, which appears to be rare, was present in 1 patient. The association of lymphomatoid granulomatosis with cardiomyopathy, which was present in case 3, has not been previously documented. The favourable response to oral cyclophosphamide and prednisolone supports the findings of Fauci *et al.*[6] During the follow-up period of 15 - 48 months, none of the patients in our series developed evidence of a lymphoma.

The possible explanation for the paucity of reports of lymphomatoid granulomatosis from South Africa could be under-reporting or under-diagnosis — the condition being eclipsed by a high background prevalence of tuberculosis in blacks or, less likely, a true geographic/ethnic variation in incidence in this part of the world.

The authors thank the doctors of the Royal Free Hospital in London for referring patient 4, and are grateful to Ms Previna Ramhorry for secretarial assistance.

REFERENCES

1. Liebow AA, Carrington CRB, Friedman PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972; **3:** 457-558.
2. Katzenstein AA, Carrington CB, Liebow AA. Lymphomatoid granulomatosis — a clinicopathologic study of 152 cases. *Cancer* 1979; **43:** 360-373.
3. Editorial. Trends in lymphoma diagnosis. *Lancet* 1989; **1:** 249-250.
4. Croft C, Benatar SR, Uys CJ. Lymphomatoid granulomatosis with fulminant course: a case report. *S Afr Med J* 1980; **58:** 736-738.
5. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large cell lymphoma. *Ann Intern Med* 1985; **102:** 596-602.
6. Fauci AS, Haynes BF, Costa J, Katz P, Wolff SM. Lymphomatoid granulomatosis: prospective clinical and therapeutic experience over 10 years. *N Engl J Med* 1982; **306:** 68-74.
7. Vath RR, Alexander CB, Fulmer JD. The lymphocytic infiltrative lung diseases. *Clin Chest Med* 1982; **3:** 619-634.
8. Gupta S, Gupta OP. Lymphomatoid granulomatosis of the oropharynx. *Ear Nose Throat J* 1980; **59:** 152-154.
9. Gardiner GW. Lymphomatoid granulomatosis of the larynx in a renal transplant recipient. *J Otolaryngol* 1979; **8:** 549-555.
10. Jaffe ES. The lymphoid system. In: Henson DE, Albores-Saavedva J, eds. *The Pathology of Incipient Neoplasia.* Philadelphia: WB Saunders, 1986: 95-97.
11. Jaffe ES. The morphologic spectrum of T-cell lymphoma. *Am J Surg Pathol* 1988; **12:** 158-163.
12. Batsakis JG, Luna MA. Midfacial necrotizing lesions. *Semin Diagn Pathol* 1987; **4:** 90-116.
13. Israel HL, Patchefsky AS, Saldana MJ. Wegener's granulomatosis, lymphomatoid granulomatosis and benign lymphocytic angiitis and granulomatosis of the lung. *Ann Intern Med* 1977; **87:** 691-699.
14. James WD, Odom RB, Katzenstein AA. Cutaneous manifestations of lymphomatoid granulomatosis: report of 44 cases and a review of the literature. *Arch Dermatol* 1981; **117:** 196-202.
15. Krumpe PE, Lum CCQ, Cross CE. Approach to the patient with diffuse lung disease. *Med Clin North Am* 1988; **72:** 1225-1246.
16. Prabhu R, Berger HW, Subietas A, Lee M. Lymphomatoid granulomatosis: report of a patient with severe anemia and clubbing. *Chest* 1980; **6:** 883-885.
17. Hicken P, Dobie JC, Frew E. The radiology of lymphomatoid granulomatosis in the lung. *Clin Radiol* 1979; **30:** 661-664.
18. Wechsler RJ, Sternes RM, Israel NL, Patchefsky AS. Chest radiograph in lymphomatoid granulomatosis: comparison with Wegener's granulomatosis. *AJR* 1984; **142:** 78-83.
19. Firstater E, Yust I, Topilsky M, Tartakowsky B, Segal S, Abramov A. Lymphomatoid granulomatosis with impaired cellular immunity: eight-year survival without treatment. *Chest* 1983; **84:** 777-746.
20. Plot PH, Klippel JH, Decker JL *et al.* Bladder complications in patients receiving cyclophosphamide for systemic lupus erythematosus or rheumatoid arthritis. *Ann Intern Med* 1979; **91:** 221-223.