## Case Reports

# Lymphomatoid granulomatosis with long survival

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## ABSTRACT

We present a case of lymphomatoid granulomatosis presenting in a 35-year-old Saudi lady with long survival. She responded to treatment with intermittent cyclophosphamide infusion in addition to corticosteroids. This is the first case of lymphomatoid granulomatosis to be reported in the Arab world. The prolonged survival and response to intermittent cyclophosphamide infusion is discussed.

**Keywords:** Lymphomatoid granulomatosis.

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Lymphomatoid granulomatosis (LYG) is a rare lymphoproliferative and granulomatous disease, which usually affect the lungs, skin, central nervous system (CNS) and kidneys.[1] Histologically, it is characterized by polymorphic infiltration of lymphoid and plasmacytoid cells with granulomatous inflammation in an angiocentric and angio destructive pattern.[1-3] Survival to more than 5 years has been unusual. We report a case of lymphomatoid granulomatosis with prolonged survival, which responded to therapy with intermittent doses of cyclophosphamide and prednisolone.

**Case Report.** A 35-year-old Saudi lady was admitted in May 1995 with a 2-year history of progressive shortness of breath and dry cough. She also had brownish skin lesions on the left forearm and cheek for 10 years, treated with topical corticosteroid by a dermatologist. She had no chest pain, fever or weight loss. The rest of the medical and occupational history was unremarkable. Her examination revealed brownish papulo-macules on the left forearm and left cheek, crepitations and bronchial breathing in the left lower lung. Her white blood cell count (WBC) was 11 x $10^9$/L (Normal range: 4-11 x $10^9$/L, Hemoglobin 121 g/L (Normal range: 120 -160 g/L), Platelets 323 x $10^9$/L (Normal range 140-450 x $10^9$/L), and erythrocyte sedimentation rate (ESR) of 42 mm/hr (range 5-15 mm/hr), renal and liver function tests were normal. Anti-nuclear antibodies (ANA), rheumatoid factors (RF), and anti-neutrophil cytoplasmic antibodies were negative. The patient was confirmed as having depressed cell-mediated immunity as indicated by negative skin reactions to multiple antigens. Sputum cultures, including tuberculosis, were negative. Chest x-ray showed bilateral patchy alveolar infiltrates involving right middle and lower zones and the left lower zone (Figure 1). This was confirmed by computed tomography (CT) of the chest, which also revealed no lymphadenopathy (Figure 2). Bronchoalveolar lavage and brushing did not reveal any microorganisms including tuberculosis. Left forearm lesional skin biopsy yielded non-specific histology. Transbronchial biopsy yielded non-specific results. She then underwent open lung biopsy of the lesions in the base of the left lung and the lingula. The histology of

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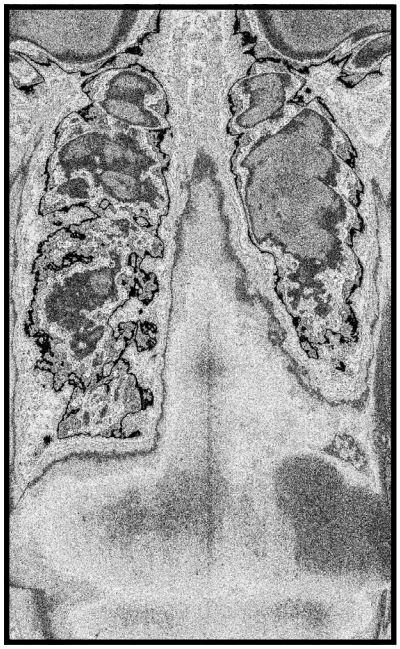

**Figure 1 -** Plane x-ray of the chest showing bilateral patchy alveolar infiltrates of the right, middle and lower zone and left lower zone.

which showed focal interstitial fibrosis with infiltration by round cell infiltrates, mainly lymphocytes with formations of lymphoid follicles with germinal centers. The blood vessels also showed focal dense infiltration of their walls by cellular infiltrate comprising lymphocytes and atypical large lymphoid cells with convoluted vesicular nuclei. Peribronchial inflammation was also noted. Some blood vessels showed severe narrowing or obliteration of the lumen by fibrosis or by some atypical lymphoid infiltrate. These changes were diagnostic for LYG. In addition, other lymphoproliferative diseases including lymphoma were excluded both by the histological picture and by immunohistochemical staining.

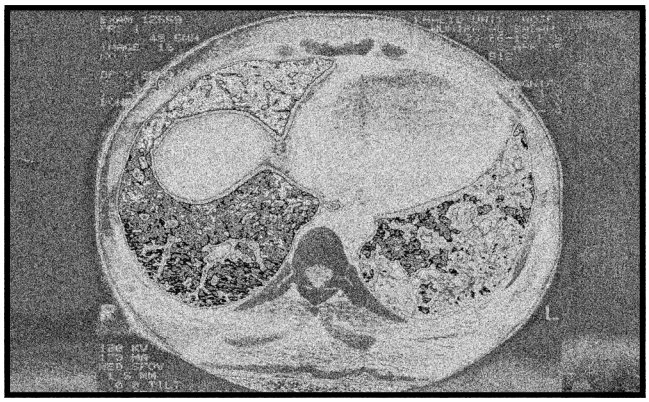

**Figure 2 -** Computerized tomography scan of the chest showing infiltrative lesions in the lungs with no lymphadenopathy.

She was treated with 250 mg intravenous methyl prednisolone daily for 3 days, followed by 70 mg/day oral prednisolone. One dose of cyclophosphamide 1100 mg was administered intravenously over one hour. She was discharged and scheduled for admission for monthly intravenous cyclophosphamide. However, she presented to the emergency room with increasing shortness of breath 10 days following her last discharge from hospital. She was dyspneic at rest, her blood pressure (BP) was 130/80, pulse rate of 85/min and respiratory rate of 22/min. She had decreased air entry and increased resonance on the left side of her chest. An urgent chest x-ray revealed the presence of a large pneumothorax on the left side and mediastinal shift. She was immediately managed by inserting a chest drain, which improved her dyspnea markedly. The chest drain was removed a few days later with no recurrence. During the same admission, she was given the 2nd dose of cyclophosphamide 1000 mg intravenously with adequate hydration. Her investigations revealed normal complete blood count (CBC), ESR dropped to 3 mm, anti-double stranded deoxynucleic acid (anti-DNA) and ANA were negative, the 3rd complement (C3) was 0.99 (Range 0.7 - 1.3 g/L) and the 4th complement (C4) was 0.66 (range 0.2 - 0.5 g/L). Chest x-ray showed improving chest infiltrate and no pneumothorax. She subsequently had scheduled admissions to hospital for a further 13 doses of cyclophosphamide. During this period, she showed improvement clinically and radiologically and was able to function normally.

In total, the patient was given 15 doses of cyclophosphamide over a period of 30 months. For the first 8 doses, the gap was one month apart, and the rest of the doses were given with a gap of 3 months. The prednisolone was tapered gradually and stopped completely over the first year. She showed clinical and laboratory remission (improving hemoglobin and reduced ESR) after the 4th cyclophosphamide dose and remained so during the rest of the follow-up. A repeat CT chest at 24 months from diagnosis revealed anterior and mediastinal masses. These were biopsied using CT-guided fine needle aspirate (FNA). However, the results were non-diagnostic and so the patient underwent mediastinoscopy, and biopsy which proved to be benign reactive changes with no signs of malignancy. Following the completion of the 15th dose of cyclophosphamide, she was judged to be in remission with no signs and symptoms, no new radiological changes and normal biochemical and hematologic parameters. She was off all medication and so was followed in the outpatient clinic every 2

months. She is now ending her 5th year following the diagnosis and 7 years from start of the chest symptoms and has been off all medication for 2.5 years. She was married 6 months ago.

**Discussion.** Our case showed prolonged survival of 5 years from presentation. Her survival extended even longer when considering her chest and skin complaints for years prior to presentation. The median survival in the largest series was only 14 months.[1] Others reported survival up to 54 months.[4] Her response to therapy is also interesting. She was treated with intermittent intravenous low dose cyclophosphamide and prednisolone with excellent results. Therapy of LYG ranged from a short course of corticosteroids following resection of the lesion to intensive chemotherapy.[5,6] Others used cyclosporine after failure of chemotherapy.[7] Fauci et al, in their prospective study, used oral cyclophosphamide and oral prednisolone.[8] In their study, the mean duration of cyclophosphamide treatment in those who attained remission was 37 ± 6 months, while the mean duration of prednisolone treatment in the same group was 26.3 ± 4.1 months. We elected to use intravenous cyclophosphamide intermittently, due to its lower toxicity profile, its good response rate in the treatment of Wegener's granulomatosus and vasculitis, due to the disease in our patient being confined to the lungs and skin and due to the variable natural history of the disease in previously reported cases. The favourable outcome and long survival in our case is most likely due to the limited nature of the disease, being confined to the lung and skin. This is in line with observations seen in Liebow et al's original series and others.[1,2,4,9] Poor prognosis of LYG has been associated with CNS involvement, aged less than 25 years at presentation, hepatomegaly, raised WBC and atypical lymphoreticular cell histologically.[1,2] The WBC in our patient was slightly raised (11,000) but it did not seem to have a major effect prognostically.

In conclusion, we report this case of LYG with prolonged survival and good response to intermittent intravenous cyclophosphamide and prednisolone.

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