

Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A

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Abstract

Lymphoid interstitial pneumonitis (LIP) is a rare clinicopathological entity that may be associated with common variable immune deficiency (CVID) and may lead to respiratory failure and death. Some patients may respond to prolonged corticosteroid treatment. We hypothesised that, in view of the predominant T cell nature of LIP, cyclosporin A would be a more appropriate choice of immunosuppressive agent and report the first case of its successful use in a woman with LIP associated with CVID.

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Lymphoid interstitial pneumonitis (LIP) is a rare clinicopathological entity that is characterised by a diffuse or multifocal reactive lymphoid infiltrate involving the alveolar interstitium.¹⁻⁴ Most cases show a preponderance of lymphocytes.¹⁻⁵ The condition has been associated with a number of diverse systemic illnesses such as AIDS, Epstein-Barr virus infection, autoimmune disorders, and various immunodeficiency states including common variable immune deficiency (CVID), also known as primary antibody deficiency.¹⁻³

The association of LIP with CVID was first reported by Liebow and Carrington in 1973⁶ and up to 10% of patients with LIP may have hypogammaglobulinaemia.^{1,3} The clinical course of non-AIDS LIP is variable but death may occur due to progressive pulmonary fibrosis though some patients may respond to corticosteroid therapy taken for prolonged periods.²⁻⁵ There are only occasional reports of treatment with alternative immunosuppressants.^{2,7} We hypothesised that, in view of the predominant T cell nature of LIP, cyclosporin A would be a more appropriate choice of immunosuppressive agent and report the first case of its successful use in a patient with LIP associated with CVID.

Case report

In October 1995 a 34 year old woman with known CVID diagnosed in 1989 was admitted to our unit complaining of dyspnoea and fatigue for two months. She had been treated with intravenous immunoglobulin replacement therapy since 1989 at a dose of 0.3 g/kg/month in divided doses. She had previously been

diagnosed as having bronchiectasis which was treated with long term antibiotics, and autoimmune haemolytic anaemia which was treated with corticosteroids and splenectomy. As a result of steroid treatment she had developed severe osteoporosis with multiple previous pathological bone fractures.

On admission she complained of fever, sweats, and progressive dyspnoea with nocturnal cough increasing over the preceding two weeks. She had been given several courses of oral antibiotics and inhaled budesonide with no improvement. She had never smoked. On examination she was afebrile with bilateral crackles on auscultation and a splenectomy scar.

Initial investigations showed leucocytosis at $12.9 \times 10^9/l$ (neutrophils $6.5 \times 10^9/l$, total lymphocytes $4.2 \times 10^9/l$, T cells $2.5 \times 10^9/l$, CD4 lymphocytes $1.82 \times 10^9/l$, CD8 lymphocytes $0.68 \times 10^9/l$) and C reactive protein concentrations of 36 mg/l. Chest radiography and high resolution computed tomography (HRCT) showed patchy ground glass opacification, peribronchovascular nodules, discrete nodules, and areas of bronchiectasis. Antinuclear antibodies, *Aspergillus* precipitins, and blood cultures were negative. Her immunoglobulin profile at admission after recent infusion of immunoglobulin (normal ranges) was IgG 14 (6-13) g/l, IgA <0.1 (0.8-3.9) g/l, IgM 1.6 (0.4-2.5) g/l, and IgE 4 (<120) kU/l. Pulmonary function showed a restrictive pattern (forced expiratory volume in one second (FEV₁) 1.72 l (58% predicted), forced vital capacity (FVC) 1.90 l (56% predicted) with reduced gas transfer coefficient (Kco) 62% predicted).

Immediate management included broad spectrum antibiotics but, after no improvement and continued fever, bronchoscopic lavage was performed; this did not identify any bacteria, mycobacteria, virus or fungi on culture. Polymerase chain reaction (PCR) for DNA to Epstein-Barr virus, cytomegalovirus, and *Mycoplasma pneumoniae* was negative. Ten days after admission the patient underwent an open lung biopsy (lingula) for diagnosis.

Histological examination showed an extensive lymphocytic infiltrate of the lung parenchyma with peribronchial germinal centre formation and epithelialisation of some alveoli (fig 1). Immunohistochemistry showed the lymphocytes to be predominantly T cells with only sparse representation of B cells. Most of the T cells were CD4 positive with only a few CD8

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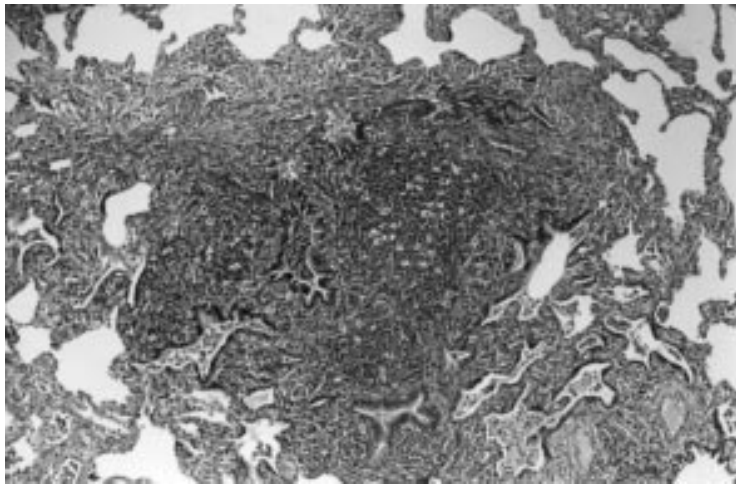


Figure 1 Lymphocytic infiltration of alveolar walls with peribronchiolar lymphoid follicles and germinal centre formation. Epithelialised alveoli are also present. Stain: H & E (\times medium power).

positive cells. There was no evidence of a monoclonal proliferation to suggest transformation to malignant lymphoma.

A diagnosis of LIP was made and she was recommenced on prednisolone 40 mg/day. Over the following three months the patient's symptoms improved and there was resolution of crackles and improved lung function (FEV_1 2.12 l; FVC 2.42 l; Kco 79% predicted) with reduction in the extent of nodularity and ground glass opacification on the HRCT scan, and the dose of corticosteroids was reduced. She continued to receive immunoglobulin replacement (0.7 g/kg/month), though at weekly intervals to maintain a higher trough level.

In January 1996 when prednisolone was down to 10 mg/day she developed identical features as at presentation associated with a fall in FEV_1 (from 2.1 l to 1.9 l) and FVC (from 2.41 to 2.15 l) and the prednisolone was increased back to 30 mg/day with rapid improvement in symptoms and lung function. A further relapse occurred in June when down to 15 mg prednisolone on alternate days, again responding to higher doses. In view of her known osteoporosis it became clear that a steroid-sparing agent would be necessary to reduce further morbidity from corticosteroids. In view of the T cell features of LIP, cyclosporin A was chosen and she commenced treatment at a dose of 150 mg/day in July 1996.

The patient had a good response over the following months and the prednisolone was reduced to 7.5 mg on alternate days. At an early stage cyclosporin levels were higher than planned at 190 ng/ml and the cyclosporin dose was reduced to 75 mg/day. The serum levels began to fall gradually and it was decided to allow the level to fall to undetectable levels without any change in dose and with the patient unaware of the fall. Thus, a blinded "n-of-one" trial to assess the efficacy of cyclosporin was performed.

In May 1997 the patient developed a further identical relapse of symptoms with crackles and falling lung function (FEV_1 1.85 l; FVC 2.18 l; Kco 66% predicted). This was associ-

ated with bilateral new pulmonary nodules and increased ground glass opacification on the HRCT chest scan. She remained on prednisolone in a dose of 7.5 mg on alternate days and the dose of cyclosporin was increased to 125 mg/day with a subsequent improvement in clinical symptoms and lung function (FEV_1 2.32 l; FVC 2.61 l; Kco 93% predicted). There was associated resolution of the chest radiograph and CT scan infiltrates and nodules. Currently the patient is in remission on prednisolone in a dose of 7.5 mg on alternate days with a serum cyclosporin level of 76 ng/ml.

Discussion

Lymphoid interstitial pneumonitis (LIP) is by definition a reactive lymphoid infiltrate involving the pulmonary interstitium¹⁻⁴ and is also known as diffuse hyperplasia of the bronchus associated lymphoid tissue (BALT).³ BALT is thought to be an important factor in the immunological response to inhaled antigens landing on the mucosal surfaces and is part of the more widely recognised mucosa associated immune system. The entity of LIP may be seen in association with a variety of conditions such as paediatric AIDS, primary immunodeficiency, Sjögren's syndrome, myasthenia gravis, chronic liver disease, and dysproteinemic states including hyper- and hypogammaglobulinaemia.¹⁻⁴ A small number of cases may in fact be a diffuse interstitial low grade B cell lymphoma with microscopic foci resembling LIP.¹ Up to 80% of patients with LIP will have evidence of dysproteinemia, most frequently hypergammaglobulinaemia due to elevation of IgM and IgG.³ However, hypogammaglobulinaemia occurs in about 10% of adults with this condition, and the association of LIP with CVID has been documented for over 20 years.^{1,3}

Histologically, LIP associated with hypogammaglobulinaemia is characterised by infiltration of the alveolar interstitium by T lymphocytes and also plasma cells, fibroblasts, and scattered macrophages.¹⁻⁴ In non-AIDS patients the lymphoid infiltrate is centred on the airways but invariably infiltrates the interstitium and lymphoid follicles, usually peribronchiolar, are present in many cases.¹ The pattern is similar to that seen in reactive lymph nodes, suggesting that the lung is acting like a giant lymphoid organ. In cases of LIP associated with CVID the cells consist largely of T cells, particularly CD4+ T helper cells.¹ It is important to exclude monoclonality in the cell populations which would favour an alternative diagnosis of lymphoma, also a recognised association with CVID.^{3,5}

CVID is primarily a defect in the function of B lymphocytes, usually characterised by the presence of low or normal numbers of B cells which fail to mature into plasma cells when exposed to antigens or mitogens.⁸ Most patients have normal T lymphocyte CD4:CD8 ratios, although a rare subgroup with CVID have a reduced ratio with a lymphopenia primarily due to CD4+CD45 RA+(unprimed) T cells suggesting persistent activation.⁸

The optimal treatment for LIP is not well established and, due to the small number of cases, there are no controlled trials. However, most patients are treated by prolonged courses of corticosteroids which may control the process or induce remission,²⁻⁵ and a few reports have described the additional use of the immunosuppressive agents methotrexate,² azathioprine,² and chlorambucil⁷ in conjunction with corticosteroids.

The various immunosuppressive agents currently available have a variety of actions. Methotrexate inhibits diverse cell types and functions, especially neutrophils and responses to inflammatory mediators, but may inhibit B lymphocyte differentiation.⁹ Azathioprine reduces the numbers of both T and B lymphocytes,⁹ and the precise action of chlorambucil is poorly understood.⁹ Cyclosporin A has a complex action but the principal immunosuppressive effect is by inhibition of CD4 positive Th2 lymphocyte activation and the related release of IL-4 and IL-5, thus inhibiting clonal expansion of T cells without directly affecting B cells.⁹

In view of the known predominance of T cells in LIP, and the need to minimise generalised immunosuppression in a patient already antibody deficient, we hypothesised that cyclosporin A may be more appropriate than methotrexate or azathioprine whilst still allowing a steroid sparing effect. This was particularly important in our patient who already had significant morbidity from corticosteroid induced osteoporosis. The relapse of LIP when

the cyclosporin levels became undetectable and the subsequent improvement with an increased dosage of cyclosporin A alone seem to confirm the efficacy of this drug in our patient. Furthermore, this therapeutic effect seems to occur at a low serum cyclosporin concentration of <100 ng/ml, and hence at a level where cyclosporin A toxicity can be kept to a minimum.

We conclude that low dose cyclosporin A may be a useful aid in the suppression of LIP, particularly in patients where steroid treatment presents particular problems.

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