


Granulomatous lymphocytic interstitial lung disease: limiting immunosuppressive therapy—a single-centre experience

Thomas J. Beaton¹ , David Gillis¹, Karen Morwood¹ & Michael Bint²

¹Department of Clinical Immunology and Allergy, Sunshine Coast University Hospital, Birtinya, QLD, Australia.

²Department of Respiratory Medicine, Sunshine Coast University Hospital, Birtinya, QLD, Australia.

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Correspondence

Thomas J. Beaton, Department of Clinical Immunology and Allergy, Sunshine Coast University Hospital, 6 Doherty Street, Birtinya, QLD 4575 Australia. E-mail: thomas.beaton2912@gmail.com

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Abstract

Granulomatous lymphocytic interstitial lung disease (GLILD) is characterized by lymphocytic and granulomatous pulmonary infiltration occurring in common variable immunodeficiency (CVID). It is associated with increased mortality compared with CVID patients without GLILD. There are no treatment guidelines due to the low prevalence and the heterogeneity of the condition. A case review of three patients diagnosed with GLILD was performed from a single Australian centre. Patients met the European Society of Immunodeficiency criteria for CVID and a diagnosis of GLILD was confirmed by a multidisciplinary team. Patients were managed with immunoglobulin (Ig) replacement and immunosuppressive agents if required: the decision for immunosuppression was made on the basis of symptoms and declining pulmonary function. All patients clinically improved. One patient had immunosuppressive treatment ceased. GLILD responds to varying immunosuppressive regimes when IgG monotherapy fails. Immunosuppressive therapy can be discontinued following improvement, but patients require close observation. This series helps inform future GLILD treatment guidelines.

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiencies of unknown aetiology characterized by idiopathic hypogammaglobulinaemia and recurrent infections [1]. CVID results in varying amounts of immune dysregulation and non-infectious complications including granulomatous lymphocytic interstitial lung disease (GLILD).

GLILD is an interstitial lung disease associated with lymphocytic infiltrate and/or granulomatous inflammation. It may include pathology consistent with lymphocytic interstitial pneumonitis (LIP), follicular bronchiolitis, lymphoid hyperplasia, and granulomatous lung disease [2]. On lung biopsy, T- and B-cell lymphocytic infiltrate is typical with predominance of CD4-positive cells and a notable absence of FOXP3-positive regulatory T cells [3]. Tertiary lymphoid structures with evidence of

germinal centres have been described [4]. Radiological features are consistent with histopathological findings and they include nodular changes (random or bronchocentric), interlobular septal thickening, and areas of consolidation. Bronchiectasis can be present [5].

GLILD is normally associated with multisystem inflammation and high rates of immune cytopenias, polyarthritis, inflammatory liver disease, lymphadenopathy, and splenomegaly have been observed [6]. Development of GLILD in CVID patients is predicted by the presence of hypersplenism, polyarthritis, and reduced forced vital capacity (FVC) [6].

Non-infectious complications as a result of immune dysregulation are associated with higher mortality compared with patients with infectious complications only [7]. Individuals with GLILD have lower survival (13.7 years) compared with CVID patients with other pulmonary disease or no pulmonary disease (28 years) [2].

No guidelines exist for use and duration of immunosuppressive treatment in GLILD, although various immunosuppressive regimes have been reported with improved outcome. It is accepted that immunosuppression is required in patients with reduced pulmonary function [8]. There are no reports, to our knowledge, of successfully ceasing immunosuppressive therapy in a patient who presented with aggressive GLILD after response to immunosuppressive therapy.

Case Series

Case 1

A 42-year-old female presented in 2011 with inflammatory polyarthritis and progressive thrombocytopenia. There was a history of recurrent sinopulmonary infections. Prednisone therapy of 1 mg/kg was instituted for immune thrombocytopenia purpura (ITP). On weaning corticosteroid therapy, progressive dyspnoea, hypoxia, lymphadenopathy, and splenomegaly developed.

High-resolution computed tomography (HRCT) imaging was typical of GLILD with nodules, organizing pneumonia, and interstitial thickening (Fig. 1A). Pulmonary function tests deteriorated over time with forced expiratory volume in 1 sec (FEV₁) 63% predicted, FVC/FEV₁ ratio 0.75, and diffusion capacity of carbon monoxide (DL_{CO}) 40% predicted at nadir.

CVID was diagnosed due to undetectable immunoglobulin (Ig) G and IgA, and reduced IgM (0.1 g/L). Bone marrow examination was normal. Further immunological testing was not carried out prior to IgG replacement therapy due to profound hypogammaglobulinaemia and infections. Total lymphopaenia of $0.6 \times 10^9/L$ was present with normal CD4:8 ratio.

Bronchoscopy with bronchoalveolar lavage (BAL) identified no evidence of infection or malignant cells. Axillary lymph node biopsy showed lymphoid tissue with mixed B- and T-cell infiltrate and no evidence of monoclonal proliferation. Open lung biopsy had polyclonal lymphoid infiltrate with mixed B and T cells. Patchy organizing pneumonia was present along with non-necrotizing interstitial and airspace granulomas.

IgG levels normalized with replacement therapy resulting in a reduction of infections. Despite this, two years following initial presentation, she developed progressive pulmonary infiltrates, with declining lung function and hypoxic respiratory failure and as a result immunosuppression was instituted with prednisone 1 mg/kg and rituximab 1 g \times 2, two weeks apart. Prednisone was weaned to 5 mg over six months and recurrent 500 mg doses of rituximab were used at six monthly intervals over two years. There was significant clinical improvement with

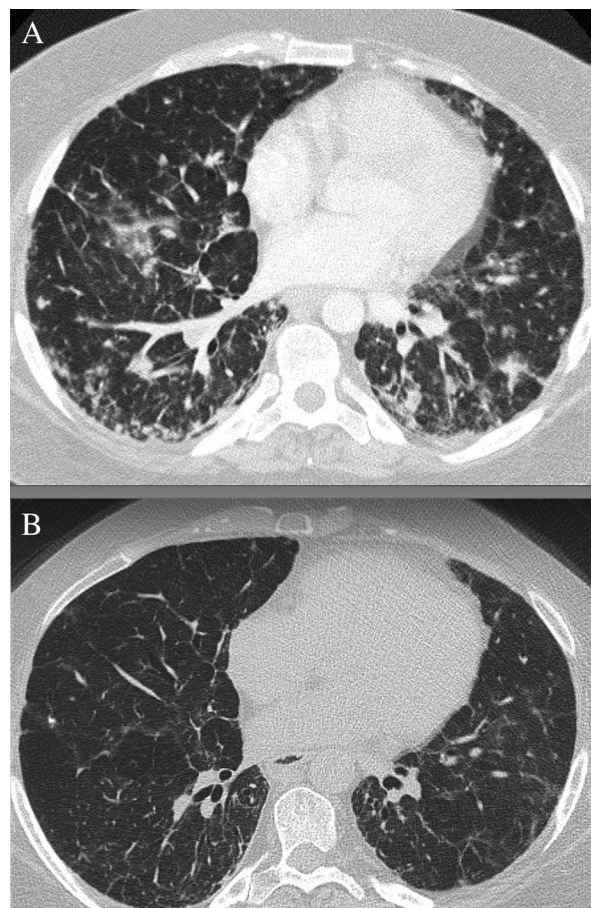


Figure 1. Computed tomography (CT) imaging of case 1 pre- and post-immunosuppression. (A) Pre-immunosuppression with typical features of GLILD including nodular infiltrate, consolidation, and septal thickening. (B) Improved parenchymal changes with ongoing septal thickening 18 months following cessation of immunosuppression.

increased exercise tolerance, resolution of hypoxia, and improvement in lung function, with FEV₁ improving to 90% predicted and DL_{CO} to 50% predicted. HRCT imaging improved dramatically (Fig. 1B). Azathioprine at 2 mg/kg was used as maintenance therapy for 2 years with ongoing disease stability. Due to neutropenia, azathioprine was ceased with no relapse 18 months following cessation of therapy.

Case 2

A 27-year-old female presented in 2018 with mild dyspnoea, widespread lymphadenopathy, splenomegaly, and elevation of liver enzymes. There was a history of frequent sinopulmonary infections, recurrent warts, cutaneous fungal infections, and herpes zoster at age 16. There was no family history of immunodeficiency.

HRCT showed bronchocentric pulmonary nodules with surrounding ground-glass opacities (GGO), interstitial thickening, and lymphadenopathy. Pulmonary function demonstrated FEV₁ 78% predicted with a reversible component, FEV₁/FVC ratio 0.7 and DL_{CO} 72% predicted.

CVID was diagnosed with unexplained hypogammaglobulinaemia of IgG (3.2 g/L), IgA (0.6 g/L), and IgM (0.2 g/L), and low isotope-switched memory B cells and high immature B cells.

BAL demonstrated lymphocytosis that comprised 50% total cells, suggesting lymphoproliferative or granulomatous lung disease. There was no monoclonal cells or evidence of infection. Other differentials for BAL lymphocytosis were excluded on clinical grounds with no exposure or drug history that would predispose to pneumonitis and no clinical evidence of connective tissue disease. Endobronchial biopsy of hilar lymph nodes showed polyclonal lymphocytic infiltrate with no granuloma. Liver biopsy demonstrated mild granulomatous hepatitis.

Ig replacement was instituted. There was reduced frequency of infections and pulmonary function normalized: FEV₁ increased to 90% predicted and DL_{CO} to 82% predicted. No immunosuppression was instituted with stable respiratory function over 18 months and improved HRCT changes with Ig replacement therapy alone.

Case 3

A 60-year-old female with a history of ITP and recurrent sinopulmonary infections presented in 2014 with dyspnoea, liver enzyme elevation, and lymphadenopathy. Splenectomy had been undertaken 15 years prior to presentation for ITP and had imaging evidence of splenunculi.

HRCT showed changes consistent with GLILD noting an absence of GGO and presence of mild bronchiectasis (Fig. 2A). BAL had no evidence of infection and transbronchial biopsy showed mixed lymphocytic parenchymal infiltrate. Liver biopsy displayed evidence of nodular regenerative hyperplasia and superimposed lobular and periportal lymphocytic inflammatory change with non-necrotizing granulomas. Pulmonary function was FEV₁ 108% predicted, FEV₁/FVC ratio 0.84, and DL_{CO} 65% predicted. Further investigation revealed unexplained hypogammaglobulinaemia with low IgG (3.4 g/L), IgA (0.9 g/L), and IgM (0.3 g/L) levels, and low isotope-switched memory B cells, confirming CVID.

Ig replacement resulted in reduction in infections. Mycophenolate 500 mg twice daily was commenced, not tolerated at higher doses. Pulmonary function, although within normal limits at baseline, improved to FEV₁ 117% predicted and DL_{CO} to 70% predicted. HRCT changes improved (Fig. 2B) requiring no further treatment.

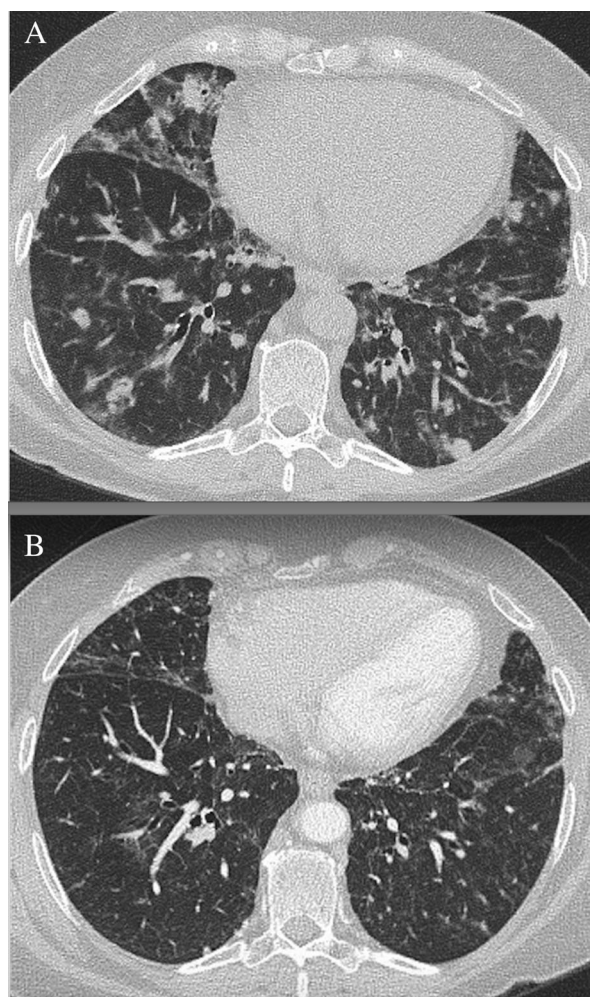


Figure 2. Computed tomography (CT) imaging of case 3 pre- and post-immunosuppression. (A) Pre-immunosuppression including nodular infiltrate, consolidation, and septal thickening. (B) Improved parenchymal changes.

Discussion

This case series informs as to the safety of cessation of treatment for GLILD albeit in small series. Case 1 had immunosuppression discontinued despite severe disease at onset. Case 2 did not require immunosuppression and case 3 clinically improved with Ig replacement and low-dose mycophenolate. The series supports limiting immunosuppression therapy and cessation of therapy in some patients with GLILD with careful monitoring.

GLILD is associated with increased mortality compared to other patients with CVID [2]. Despite increased mortality, the natural history is unclear with GLILD can remain physiologically stable for a prolonged period in some patients and rapidly progressive in others. Our series suggests that a proportion of GLILD patients will not continue to have progressive disease. Baseline pulmonary

function tests, high IgM levels, and thrombocytopenia have been associated with GLILD progression [9].

Given the variation in disease presentation and progression, there is potentially different pathogenic mechanisms in GLILD. An atypical immune response to infection is a possible explanation in some patients. Development of lymphoproliferative disease in CVID has been suggested to be associated with viral infections [10]. Infectious association potentially explains the response to Ig replacement therapy alone in patient 2 in this series and another reported case [11]. It is unclear if increased doses of Ig, above normal replacement targets, would improve response.

It is accepted that immunosuppression is required for GLILD patients with deteriorating pulmonary function [8]. Optimal immunosuppressive treatment is unclear and multiple immunosuppressive regimens have shown efficacy in case reports and series. Prednisone therapy is considered first line [8]. Although often with only partial response [12], improvement of radiological changes and pulmonary function has been reported with a range of other immunosuppressive agents in patients with GLILD who have not responded to Ig and prednisone therapy. The largest reported series targeted T and B lymphocytes with combination therapy of rituximab and azathioprine (or mycophenolate) [13]. Other authors have hypothesized that B cells are required to maintain tertiary lymphoid structures central to inflammation in GLILD and reported success with rituximab monotherapy [14,15].

Other non-infectious complications of CVID commonly associated with GLILD such as granulomatous liver disease, immune cytopenias, and potential for malignant lymphoproliferative disease require consideration when deciding on immunosuppressive therapy.

This report, however, highlights that despite increased mortality associated with GLILD, aggressive immunosuppression is not always required. In the setting of progressive lung disease, immunosuppressive therapy is regularly effective although there are limited data to guide choice of agent. Although this is a small, retrospective case series that is prone to selection bias, our experience suggests it is appropriate to wean and consider cessation of immunosuppressive therapy when disease is stable.

Further research is required into the pathogenesis, natural history, and optimal treatment of GLILD in larger multicentre cohorts. Areas of research should include comparison of immunosuppressive regimens as well as timing and safety of discontinuing immunosuppressive medications.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case series and accompanying images.

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