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Title:**Castleman Disease and Lymphocytic Interstitial Pneumonia: A complex diagnostic and management challenge****Rheumatology Key Message:**

Combined proteasome inhibitor and anti-CD20 therapy effective in treatment-resistant multicentric Castleman Disease

Article:

SIR,

Castleman disease (CD) is a rare lymphoproliferative disorder which in its multicentric form results in systemic inflammatory symptoms, lymphadenopathy, and multi-organ involvement. Interleukin-6 (IL-6) is implicated in CD pathogenesis, inducing B-cell proliferation, hypergammaglobulinemia, and acute phase responses¹. Mediastinal lymphadenopathy is common but other pulmonary manifestations are infrequent^{2,3}. Multiple treatments have been reported¹; unsurprisingly an evolving role of biological therapies is emerging.

We present the clinical course of a 33-year old female of Chinese descent with systemic upset and cystic lung disease due to lymphoid interstitial pneumonia (LIP), subsequently diagnosed as manifestations of idiopathic HIV-negative HHV-8-negative multicentric plasma cell type Castleman disease. We describe her clinical course as influenced by advent of a variety of immunomodulatory therapies.

In 2009 our patient presented with malaise, weight-loss, cough and breathlessness, with normocytic anaemia, hypergammaglobulinaemia (diffuse increase, no paraproteinaemia), hypoalbuminaemia, elevated CRP at 81mg/L (normal range <10mg/L) and ESR 129mm/hr (normal range: 1-12mm/hr). Thoracic CT (Fig 1A) demonstrated multiple thin-walled cysts and mediastinal lymphadenopathy. Tuberculosis was excluded. Lung biopsy confirmed LIP with interstitial infiltration by plasma cells and lymphocytes. Autoimmune disease and immunodeficiency are associated with LIP⁴, but our patient was HIV negative, hepatitis B and C negative, functional/diagnostic antibodies were within reference range. Typically, LIP responds to high-dose corticosteroids, but 1.5mg/kg prednisolone (75mg daily) resulted in only transient, limited symptom improvement. Cough and systemic upset recurred on dose-reduction, with ESR persistently >100mm/hr.

Given lack of treatment response alternative diagnoses were explored. Hypergammaglobulinaemia was notably persisting and rising (IgG being 60g/L (normal range: 6-16g/L) in 2010 rising to 68.2g/L by March 2011, with additional IgA and M rises). Bone marrow aspirate demonstrated excess plasma cells (up to 50% of the cellularity; Fig. 1B), but no clonal lymphocyte population or lymphoma evident. Whole body CT demonstrated persistent thoracic lymphadenopathy and worsening lung involvement but no solid organ

abnormality or non-thoracic adenopathy. Repeat autoantibody and infection screen was negative. Literature review highlighted an association of CD with LIP in patients of Asian ancestry, a feature not readily evident in the Western literature⁴. Lymph node biopsy via mediastinoscopy demonstrated substantial plasmacytic infiltrate (Fig. 1C) consistent with the plasma cell variant of CD. Both HIV and HHV-8 infection are associated with CD, but serum and lymph node tissue demonstrated no HHV-8 infection. Serum free IL-6 levels were not elevated.

Her condition deteriorated with requirement for home oxygen, ongoing weight-loss and IgG rising to 72.9g/L. With IL-6 implicated in CD pathogenesis, the anti-human IL-6 receptor monoclonal antibody Tocilizumab (350mg intravenous monthly infusion) was commenced. Mixed treatment response was seen with only transient symptomatic improvement, mixed immunoglobulin response with partial improvement in IgG, only transient fall in IgA and no improvement in IgM levels (Fig. 1D), no effect on ESR (Fig. 1E) and limited CRP reduction (Fig. 1F). Dosage was increased to twice monthly infusions with no additional benefit. Respiratory disease continued to worsen.

Given lack of elevation in free IL-6 and response to IL-6 blockade in our patient we elected to focus on the hyperglobulinaemia, and accordingly used the proteasome inhibitor Bortezomib (6 cycles of two-weekly subcutaneous injections with dexamethasone; commenced April 2014) to directly target plasma cell immunoglobulin synthesis. Initial improvements were evident with reduction in all immunoglobulins, normalization of CRP and fall in ESR (Fig. 1D-F), improved respiratory function and nutritional status with normalization of weight and albumin. Inflammatory indices began to rise during the treatment course and disease activity recurred shortly after Bortezomib cessation.

B cell targeting was re-attempted via anti-human CD20 monoclonal antibody Rituximab (two 1000mg intravenous infusions; June 2015), in combination with further Bortezomib (6 cycles with dexamethasone). Combination therapy resulted in sustained symptomatic improvement, lung disease stabilization, and marked improvement in all inflammatory indices (Fig. 1D-F). However recent rising inflammatory indices off therapy suggest further courses will be required.

Aside from the complex diagnostic challenge presented by this case and the importance of considering clinical disease in the setting of ethnicity, her management highlights evolving therapies against Castleman disease mediated immune dysregulation. Despite a small prospective study reporting sustained efficacy (median treatment duration of 65-weeks) of tocilizumab in multicentric HIV-negative CD⁵, we achieved only transient response – perhaps commensurate with the low circulating IL-6 levels. Neutralizing antibodies to tocilizumab have been implicated in lack of efficacy, although typically infrequently occur with this agent.

Reports of Bortezomib inducing sustained remission in CD exist⁶. Small prospective studies in HIV-positive CD demonstrate Rituximab maintains sustained response either alone or following chemotherapy⁷. We are unaware of

any previous reports of Bortezomib with Rituximab in HIV-negative CD, a therapeutic combination that we have found to result in effective sustained amelioration of resistant systemic CD manifestations.

Although we have focused on therapeutic targeting of B cell dysregulation and hyperglobulinaemia, we are open to consideration of alternative immune pathways⁸ with comprehensive studies potentially elucidating a complex immunopathogenesis in our patient.

Figure Legend:

Fig. 1 – Radiological, pathological and immunological manifestations in a case of multicentric Castleman Disease

(A) High-resolution CT scan demonstrating multiple thin-walled cysts. (B) Bone marrow trephine stained for CD138. (C) Mediastinal lymph node biopsy stained with hematoxylin and eosin staining. (D) Serum immunoglobulin levels during the course of treatment. IgG normal range: 6-16g/L. IgM normal range: 0.4 – 2.4g/L. IgA normal range: 0.8 – 4.0 g/L. (E) Erythrocyte sedimentation rate (ESR) during course of treatment. Normal range: 1-12mm/hr. (F) C-reactive protein (CRP) during course of treatment. Normal range <10mg/L. (D-F) Boxes relate to treatment periods with Tocilizumab, Bortezomib and Rituximab (with corresponding key shown to right of figure).

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