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Successful treatment of resistant scleroderma-associated interstitial lung disease with rituximab

SIR, We report the case of a 57-year-old patient who presented with an 18-month history of scleroderma. This had been diagnosed previously in another institution where she was treated with i.v. infusion therapy of methylprednisolone at 10 mg/kg and cyclophosphamide 15 mg/kg. She failed to respond to the initial six courses of therapy, and had a further five infusions. Unrelated to her medical condition, she moved to our region where she presented to the respiratory service in February 2004 with worsening dyspnoea. She reported hand pain, stiffness and swelling and restriction of shoulder movements, with worsening Raynaud’s phenomenon, and was also referred to rheumatology.

When she attended the rheumatology clinic in August 2004, she was wheelchair bound due to dyspnoea and had an intermittent cough, but not productive of sputum. There was no chest pain or haemoptysis. The patient was in respiratory distress and had difficulty talking, with a resting respiratory rate of 40/min and oxygen saturation of 92% on room air. She was not centrally cyanosed and had bibasal coarse crackles, but her jugular venous pulse was not elevated, heart sounds were normal, no murmurs were detectable and she had no dependent oedema. She had puffy scleroderma of the hands with marked synovitis and bilateral shoulder capsulitis. There was extensive telangiectasia on her hands and face, and facial skin tightening with beaking of the nose. She also had symptoms of heartburn and was taking omeprazole 20 mg daily.

The chest X-ray demonstrated signs of pulmonary fibrosis at both bases. Her blood count was normal, ESR and CRP were 30 mm/h and 28 mg/l (normal <10 mg/l), respectively; rheumatoid factor was negative but ANA was strongly positive at a titre of 1:2560 with a homogeneous pattern; extractable nuclear antigens including Scl-70 were negative. High-resolution CT (HRCT) performed before the successful rheumatology review showed basal honeycombing and a ground glass appearance compatible with scleroderma-related interstitial lung disease (ILD). Her pulmonary function test showed a forced vital capacity (FVC) of 1.841 (100% predicted), forced expiratory volume in 1 s (FEV1) to FVC ratio was 88.01, and the diffusing capacity of the lung for carbon monoxide (DLCO) was 1.1 mmol/min/kPa (62.7% predicted).

In September 2004, she was treated with rituximab 1000 mg 2 weeks apart with 100 mg of methylprednisolone premedication prior to the infusions. She improved within 3 weeks and managed to walk up to 500 m. Her FVC improved to 2.01 (109.5%). Her arthropathy resolved completely. She started prednisolone 5 mg daily and cyclosporin 50 mg twice daily. In late 2005, her arthropathy resolved completely. She started prednisolone 5 mg daily and cyclosporin 50 mg twice daily. In late 2005, there was deterioration in her symptoms, and in February 2006 a repeat HRCT showed ground glass changes compatible with mid-zone pneumonitis (Fig. 1A). Her FVC had reduced to 1.691 (93.5% predicted) and her DLCO was 0.622 mmol/min/kPa (34.3% predicted). She was developing cor pulmonale; an echocardiogram performed confirmed an enlarged right ventricle with impaired function with right ventricular systolic pressure of 132 mmHg and raised pulmonary artery pressures. In view of the success of the original infusion she was retreated with the same rituximab regimen. Following therapy she resumed her walking distance of 500 m. Her FVC improved to 2.021 (113% predicted) and 0.844 mmol/min/kPa (48% predicted), respectively, and the repeat HRCT (Fig. 1B) showed an improved air bronchograms evident on HRCT in the upper and mid-zones were less conspicuous following therapy.

Peripheral blood cytometric evaluation using a sensitive assay after the second treatment was determined. Following therapy the B-cells were 0.0001 x 10⁹/l (normal levels 0.06–0.66 x 10⁹/l) and pre-plasma cells 0.0002 x 10⁹/l. The good clinical response noted by the patient and the repeat HRCT in mid-zones demonstrated a reduction of the ground glass appearance and resolution of the air bronchograms in midzones (arrows). At this stage, the lung bases demonstrated irreversible fibrotic changes with honeycombing.

The monoclonal antibody rituximab is directed against the CD20 antigen that is expressed on B lymphocytes. Rituximab has been used to treat non-Hodgkin’s lymphoma where it has good
efficacy and an excellent safety record. Edwards et al. [1, 2] demonstrated good efficacy of B-lymphocyte depletion therapy in RA. Rituximab has also shown great promise in other autoimmune diseases including lupus, myositis and ANCA-associated vasculitis, in addition to showing promise for the haematological associated autoimmune diseases including idiopathic thrombocytopenic purpura and others [3–5].

Since we originally used rituximab, further evidence for a role for B cells in the pathogenesis of autoimmune pneumonitis has emerged [6]. Given the recent evidence challenging the efficacy of cyclophosphamide and high-dose steroid in scleroderma-related ILD the rationale for formally testing other therapies including B-lymphocyte depletion is considerable [7].

There is very limited data on the role of rituximab for ILD. Adams et al. [8] have reported a stabilization of DLCO with cyclophosphamide and rituximab in a group of six patients with juvenile onset systemic sclerosis [8]. Other options including stem cell transplantation have been tried but would not have been suitable in our case [9]. Thus far, the evidence for anti-tumour necrosis factor blockers including infliximab for ILD is conflicting.

Our patient had clinical scleroderma with a serological profile that was certainly compatible with autoimmune disease, where it has been predicted that drugs in the rituximab class may be efficacious [10]. She had a degree of irreversible pulmonary fibrosis at initial therapy, which may have lessened the benefit of rituximab therapy; so early use may be more beneficial. Since our patient was in extremis at the first clinical presentation, HRCT was not obtained immediately before the initial rituximab therapy. It is possible that rituximab is removing antibodies that are directly pathogenic so could be fundamentally treating a root cause of the clinical manifestations. Formal clinical trials are warranted.

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**Association of Kikuchi–Fujimoto’s disease with SLE**

Sir, Kikuchi–Fujimoto’s disease (KFD) is a rare benign form of necrotizing histiocytic lymphadenitis, typically affecting young women of Asian background. Clinical features include lymphadenopathy, predominantly involving cervical lymph nodes, fever, malaise, anorexia, myalgias and arthralgias [1]. Diagnosis is dependent upon presence of appropriate immunohistology of the lymph node, which typically shows abundant CD68+ plasmacytoid monocytes in the node paracortex, eosinophilic fibrinoid material and apoptotic debris [2]. KFD has been reported in association with a number of autoimmune and infectious diseases [3, 4], including infrequent co-existence with SLE [5]. Differentiation between KFD and SLE is imperative because of significant differences in treatment and prognosis. We report the cases of four patients initially presenting with a diagnosis of KFD who subsequently developed SLE.

A 22-yr-old Asian woman was diagnosed with KFD after she presented with fever, malaise and enlarged non-tender cervical lymphadenopathy that on cytopathological analysis demonstrated features characteristic of Kikuchi’s lymphadenitis. Sequential samples for ANA (Hep1000) and anti-double stranded deoxyribonucleic acid antibodies (anti-dsDNA) (Ctithidia assay) were negative. Treatment with a reducing dose of corticosteroids controlled her constitutional symptoms. Three months later she developed a malar rash, cutaneous vasculitic lesions, strongly positive ANA:1:1280 and antibodies to Sm and Ro antigens, followed by features consistent with lupus cerebritis. Complete recovery was achieved with pulsed i.v. methylprednisolone and cyclophosphamide. She remains in disease remission.

A 39-yr-old Asian woman presented with an acute febrile illness associated with bilateral cervical lymphadenopathy, marked acute-phase responses and negative infectious and immunological serology. Lymph node histological analysis was compatible with a diagnosis of Kikuchi’s lymphadenitis and features of SLE lymphadenitis were absent. Fourteen months later, she developed wide-spread arthralgia, fatigue and subacute cutaneous lupus erythematosus, ANA (1:640) (Hep1000) and antibodies to dsDNA (Ctithidia assay), Sm, Ro and cardiolipin. Repeated samples demonstrated hypocomplementaemia (C3 0.49 g/l, C4 <0.05 g/l) and lymphopenia (0.7 x 10³ cells/l). She was commenced on immunosuppression and low-dose aspirin. She remains in clinical remission.

A 31-yr-old Asian woman presented with a 3-week history of fever associated with bilateral cervical and axillary lymphadenopathy and elevated inflammatory markers. KFD was diagnosed on the basis of negative infectious and autoimmune serology and characteristically lymph node biopsy, without features of lupus lymphadenitis. Six months later, she developed a small joint inflammatory polyarthritis, malar rash, mouth ulcers and an immunological profile consistent with SLE [ANA positive 1:1280]

**Rheumatology key message**

- Rituximab could be therapeutic in scleroderma ILD; studies are warranted to confirm this.