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CASE REPORT

Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept

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Summary Rheumatoid arthritis (RA)-associated constrictive bronchiolitis is a severe condition with no established efficient treatment. A 55-year-old woman with seropositive RA developed rapidly progressive constrictive bronchiolitis confirmed by lung biopsy. Her clinical condition worsened despite steroids and azathioprine. Treatment with etanercept—a tumor necrosis factor (TNF)-α inhibitor—combined with methotrexate, resulted in a marked improvement of both her clinical condition and pulmonary function tests. Treatment with TNF-α inhibitors and methotrexate may be proposed in RA-associated constrictive bronchiolitis, a severe condition hitherto not amenable to improvement.

Introduction

Constrictive bronchiolitis with airflow obstruction is a rare but severe manifestation of rheumatoid arthritis (RA).[1,2] Treatment with steroids and/or immunosuppressive drugs usually does not prevent evolution toward chronic respiratory failure.

Tumor necrosis factor (TNF)-α inhibition using a chimeric monoclonal anti-TNF-α antibody (infliximab) or a soluble TNF-α receptor (etanercept) has become a major treatment in patients with refractory or steroid-dependent RA.[3] Here we report improvement of refractory RA-associated bronchiolitis in a patient treated with etanercept and methotrexate.

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Case report

A non-smoker woman born in 1947 developed seropositive RA in 1985. She was treated with low-dose prednisone until 1990, when oral methotrexate (10 mg/week) was initiated, with efficient control on clinical symptoms. She never received penicillamine nor tiopronine. In May 2002, basilar inspiratory crackles were found at pulmonary auscultation. There was no dyspnea and pulmonary function tests were normal: forced expiratory volume in 1 s (FEV_1): 2.78 L (105% of predicted); forced vital capacity (FVC): 3.01 L (98% of predicted) (Fig. 1). Methotrexate was stopped with the hypothesis of emerging drug-induced pneumonitis, which was ruled out by high-resolution computed tomography (HRCT) of the chest (which only showed mild branching linear opacities). Bronchoalveolar lavage showed no bacteria. Prednisone 5 mg/d was resumed.

Progressive dyspnea on exertion was noted in September 2002, without exacerbation of the rheumatologic symptoms. PaO_2 at rest was 8.1 kPa. The chest radiograph was normal. HRCT of the chest showed branched opacities (Fig. 2) and mild peripheral cylindric bronchiectases but no mosaic pattern of lung attenuation. Lung function was markedly impaired: in October, FEV_1 was 1.25 L (48% of predicted); FVC 2.49 L (79% of predicted); FEV_1/FVC 50%; residual volume (RV) 2.46 L (130% of predicted), and RV/total lung capacity (TLC) ratio 50%. Videothoracoscopic lung biopsy demonstrated diffuse inflammation of the bronchioles, with a pattern including chronic bronchiolar fibrosis narrowing the bronchiolar lumen and/or bronchiolar destruction, cellular inflammatory bronchiolitis with peribronchiolar inflammation and fibrosis (Fig. 3). A diagnosis of acute and chronic RA-associated constrictive bronchiolitis was made. Prednisone was increased at 1 mg/kg/d and azathioprine 100 mg/d was started in November 2002.

The respiratory condition of the patient continued to deteriorate with worsening dyspnea (NYHA class III). In May 2003, FEV_1 was 0.88 L (34% of predicted), FVC 1.86 L (60%), and RV/TLC ratio 54%. PaO_2 at rest was 7.52 kPa and long-term oxygen therapy was started (18 h/d). Azathioprine was

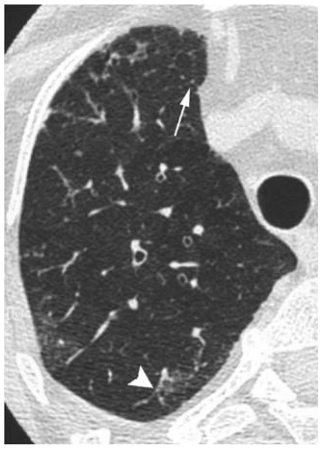

Figure 2 HRCT of the chest (left upper lobe) showing centrilobular nodules (arrow), bronchiectases, and branching linear opacities (arrowhead).

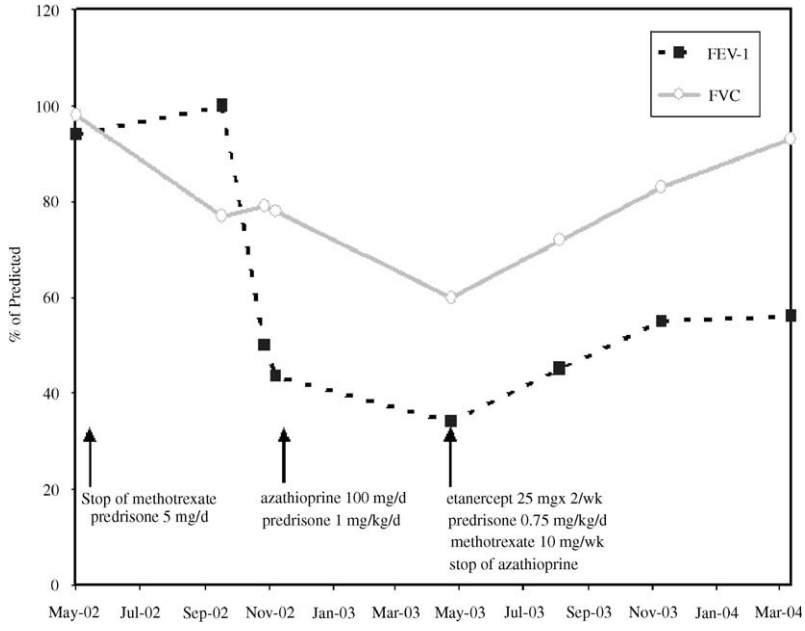

Figure 1 Evolution of post-bronchodilatator FEV_1 and FVC under treatment by etanercept.

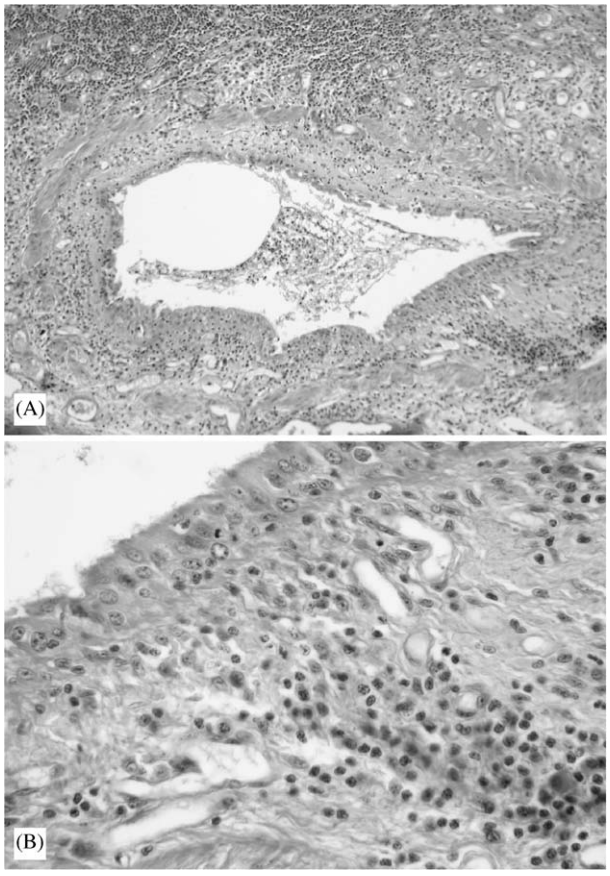

Figure 3 Bronchiolitis: (A) inflammatory cells in the mucosa, submucosa, and bronchiolar wall, with dense peribronchiolar lymphoid infiltrates (HES, $\times 25$); (B) lymphoid cells, capillaries, and fibrosis of the bronchiolar wall at high magnification (HES, $\times 40$).

discontinued, and etanercept treatment (Enbrel, Immunex, Seattle, WA) was instituted (25 mg twice a week subcutaneously) in association with methotrexate 10 mg/week in order to increase the efficacy of etanercept. Prednisone was progressively tapered to 0.75 mg/kg/d. In March 2004, the respiratory clinical condition of the patient had improved markedly: she could cope again with her domestic activities and was able to walk 1 km. Dyspnea was NYHA class II, FEV_1 was 1.43 L (56% of predicted) (Fig. 1), FVC 2.93 L (98%), and RV/TLC ratio 48%. PaO_2 at rest was 9.6 kPa and oxygen therapy could be stopped. The patient had no joint pain. Etanercept treatment was continued with methotrexate 10 mg/week and prednisone 0.5 mg/kg/d. Both drugs were well tolerated by the patient.

Discussion

This is the first report documenting subjective and objective improvement using a TNF-α inhibitor and methotrexate in a patient with biopsy proven RA-associated constrictive bronchiolitis. Our patient presented with typical characteristics of constrictive bronchiolitis including female gender, age (50–60 years), long-standing RA, branched opacities on HRCT of the chest and severe airflow obstruction unresponsive to prednisone and immunosuppressive drugs.

Etanercept is a dimeric fusion protein which specifically binds to TNF-α, blocking its interaction with cell-surface TNF-α receptors, thereby rendering TNF-α biologically inactive. The role of TNF-α in the pathogenesis of bronchiolitis has been assessed in animal models of post-transplant obliterative bronchiolitis with either lung, tracheal, or bronchial allografts.[4–6] In a mouse model of tracheal transplantation, expression of inflammatory cytokines including TNF-α was increased in the transplanted airways during the course of obliterative bronchiolitis. Blockade of TNF-α with TNFR:Fc (equivalent to etanercept) significantly decreased tracheal obliteration and reduced ciliated epithelial injury.[4] In a porcine model of post-transplant obliterative bronchiolitis, TNF-α inhibition with infliximab reduced inflammation, epithelial loss, fibrosis, and obliteration early in the development of obliterative bronchiolitis.[5]

TNF-α inhibitors combined with methotrexate have become a standard treatment of several inflammatory diseases, such as RA[3] or Crohn's disease. TNF-α has also been implicated as a mediator in the pathogenesis of lung fibrosis or sarcoidosis. Case reports suggest the potential efficacy of TNF-α inhibitors in some pulmonary disorders. Positive responses to anti-TNF-α have been observed in Wegener's granulomatosis[7] and sarcoidosis.[8] In addition, infliximab tested in six patients with RA-associated interstitial lung disease induced stabilisation of the pulmonary disease in most cases.[9,10]

In conclusion, we report a beneficial effect of TNF-α blockade in a patient with biopsy proven RA-associated bronchiolitis, a condition hitherto not amenable to improvement.

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