Successful treatment of ankylosing spondylitis coexisting with pulmonary sarcoidosis by infliximab

Sirs,

Ankylosing spondylitis (AS) is an inflammatory disease that predominantly affects vertebral and sacroiliac joints and sometimes leads to severe morbidity. On the other hand, sarcoidosis is a systemic disease characterized by noncaseating granulomas in various organs. Among a variety of its clinical manifestations, progressive pulmonary sarcoidosis is one of the life-threatening complications. Although the pathogenesis of these diseases is unknown, involvement of TNF-α has been suggested (1, 2). Here we present a rare case of a patient with a combination of AS and sarcoidosis, who was successfully treated with infliximab, an anti-TNF-α monoclonal antibody.

A 36-year-old man from Bangladesh was referred to our hospital in February 2003 with a 4-year history of low back pain, which was worse in the morning and improved with exercise. On admission, the patient had pain and stiffness in the neck and back, difficult breathing, and blurred vision. Shobers test was 3.7 cm and chest expansion was 1.5 cm. X-ray findings showed squaring of the thoracic vertebrae (Fig. 1A) with sclerosis and narrowing in the sacroiliac joints (Fig. 1B). HLA typing revealed A3, A33, B27, B44, DR2 and DR7. CRP (5.3 mg/dl) and ESR (99 mm/hr) were increased. Tests for autoantibodies, including antinuclear antibodies and rheumatoid factor, were negative. Based on the above findings, the diagnosis of AS was established. Interestingly, chest radiograph and CT revealed bilateral hilar lymphadenopathy (Figs. 2A-B) without lung parenchymal involvement (Fig. 2C). However, bronchoalveolar lavage showed a high number of lymphocytes (total cell number: 2.55×10^7, lymphocytes: 61.9%) with a high CD4/CD8 ratio (4.80). Histopathological examination of a transbronchial lung biopsy showed noncaseating granuloma (Figs. 2D-E). Ocular examination showed anterior uveitis with granuloma, which suggested sarcoidosis rather than AS. Taken together, he was also diagnosed with sarcoidosis.

Treatment with salazosulfapyridine was started in combination with NSAIDs, but no improvement was noted. Methotrexate was administered but discontinued due to severe nausea. Since the stiffness and pain were worsened, together with worsening of pulmonary sarcoidosis (Figs. 3A-B), administration of infliximab (3 mg/kg) was started in April 2007 (at weeks 0, 2, 6, and then 8-week interval). Six months after start treatment, the chest radiograph and CT showed marked improvement of lung parenchymal changes and mediastinal lymphnode swell-

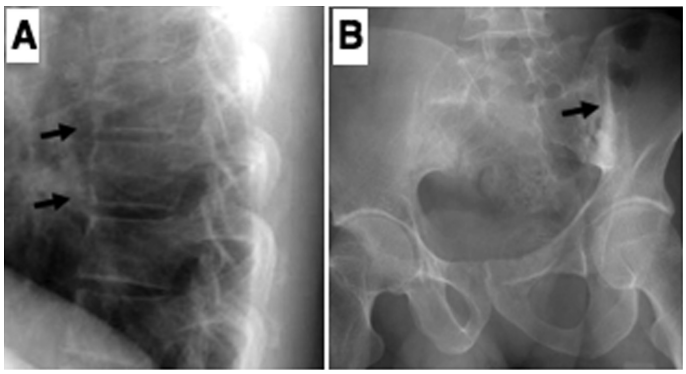

Fig. 1. Findings of x-rays associated with AS.
A: Chest x-ray showed the squaring of vertebrae (arrows).
B: Pelvic x-ray showed sclerosis of the sacroiliac joint (arrow).

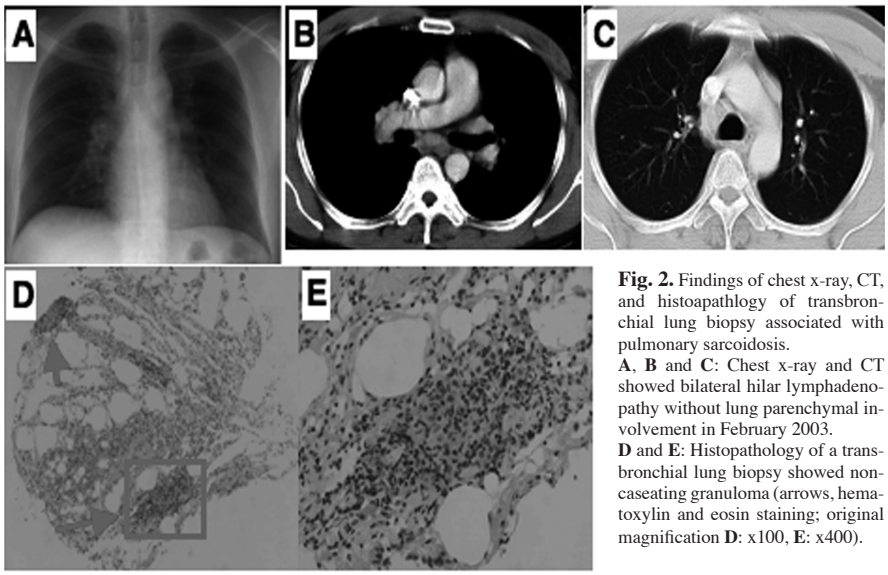

Fig. 2. Findings of chest x-ray, CT, and histoapathlogy of transbronchial lung biopsy associated with pulmonary sarcoidosis.
A, **B** and **C**: Chest x-ray and CT showed bilateral hilar lymphadenopathy without lung parenchymal involvement in February 2003.
D and **E**: Histopathology of a transbronchial lung biopsy showed noncaseating granuloma (arrows, hematoxylin and eosin staining; original magnification **D**: x100, **E**: x400).

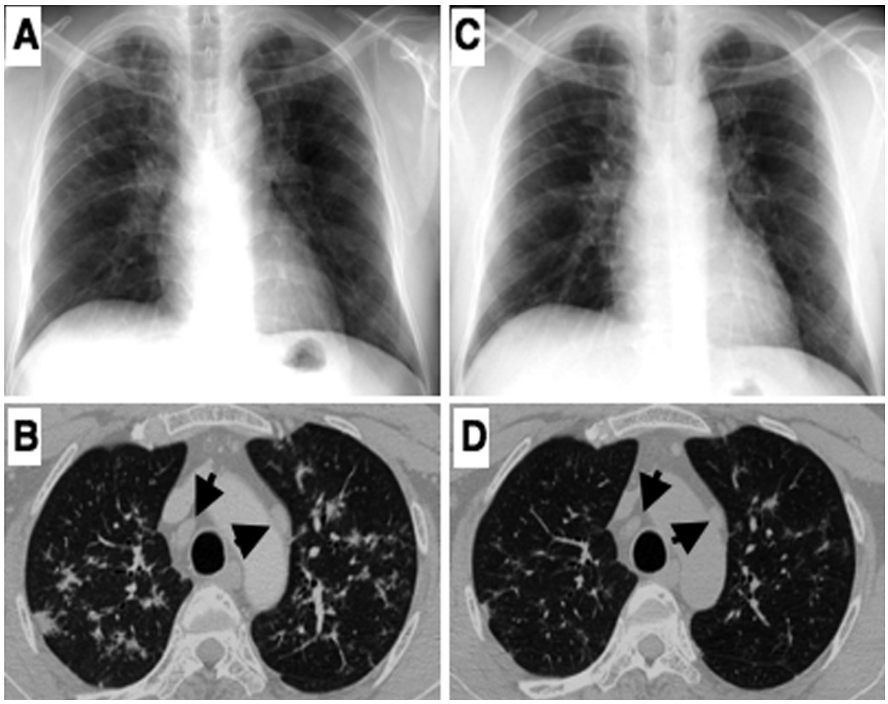

Fig. 3. Effect of infliximab on pulmonary sarcoidosis.
A and **B**; Chest x-ray and CT showed progression of parenchymal infiltration in the bilateral upper fields before infliximab treatment in March 2007. **C** and **D**; Pulmonary involvement and mediastinal lymphnode swelling (arrows) were improved by infliximab therapy in September 2007.

ing (Figs. 3C-D), as were the AS-related symptoms [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): from 6 to 2.75; Bath Ankylosing Spondylitis Functional Index (BASFI): from 2.4 to 0.75] and CRP became negative. No significant adverse effects were observed. Treatment with infliximab has been continued without recurrence of both diseases. The appropriate consent for this report was obtained from the patient.

TNF-α is a pro-inflammatory cytokine that might contribute to the pathogenesis of several autoimmune diseases. A number of large placebo-controlled clinical trials have shown that infliximab is effective and well tolerated in patients with AS (3, 4). Although TNF-α might also play a critical role in sarcoidosis pathogeny, especially for granulomatous process, and TNF-α polymorphisms correlate with the disease phenotype (5), the efficacy of the anti-TNF therapy in sarcoidosis is controversial (6). In a clinical trial for chronic sarcoidosis with pulmonary involvement, treatment with infliximab resulted in only modest improvement of percent of predicted forced vital capacity, but not in any improvement of other parameters (7). Moreover, another anti-TNF therapy, etanercept, failed to demonstrate any clinical benefit of pulmonary sarcoidosis (8). Interestingly, Toussirot *et al*. reviewed eleven cases developed sarcoidosis during anti-TNF therapy, including infliximab, adalimumab and etanercept (9). However, our patient showed exacerbation of clinical manifestations of AS and sarcoidosis simultaneously, although sarcoidosis is known for its fluctuating course and it may relapse and remit spontaneously. Moreover, treatment with infliximab ameliorated the clinical features of both conditions. These findings suggest the two diseases have a common etiological or pathogenic background, and furthermore, infliximab could be a potential therapy for the patients with coexisting AS and sarcoidosis.

Although AS and sarcoidosis share some common clinical manifestations such as sacroiliitis and uveitis, only seventeen cases with coexistence of the two diseases have been reported (10-13). The patients were 41.2±14.3 years old (mean ± SD), and fourteen patients were male. Fifteen out of the 17 patients developed sacroiliitis. However, it was reported that only 6.6% of sarcoidosis patients had sacroiliitis (14). Seven patients were treated with corticosteroids. The present case is the first report that was treated with infliximab. Interestingly, 10 of the patients were reported from France, and 2 Switzerland, 1 Belgium, Italy, Netherlands, Morocco, and Turkey. Analysis of the available information showed only three out of 8 patients were HLA-B27 positive, although it is generally known that about 90% of AS are B27 positive. It was reported that HLA-A1, -B8, and -DR3 were associated with sarcoidosis (15). One patient with coexistence of the diseases was positive for all the HLAs (A1, B8, and DR3) together with B27 out of 4 cases who are available all HLA typing. Genetic and/or regional background may also affect the development of the two diseases. Our patient presented B27, but did not have the sarcoidosis associated HLA-subtypes.

In summary, we present a case of AS and sarcoidosis successfully treated with infliximab. The clinical course suggested the etiological and/or pathogenic association between AS and sarcoidosis, and that infliximab is a promising therapy for such intractable manifestations.

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