Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab

R. Almodóvar, M. Izquierdo*, P. Zarco, F. Javier Quirós, R. Mazzucchelli, B. Steen*

*Rheumatology and *Pneumology Units, Alcorcón Hospital Foundation, Madrid. Spain.*

Raquel Almodóvar MD, Mercedes Izquierdo MD, Pedro Zarco MD, Francisco Javier Quirós MD, Ramón Mazzucchelli MD, Bárbara Steen MD.

Please address correspondence and reprint requests to: Dr. R. Almodóvar, Unidad de Reumatología, Fundación Hospital Alcorcón, Avenida de Budapest s/n. 28922, Madrid, Spain.
E-mail: ralmodovar@fhalcorcon.es

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ABSTRACT

We present a case of a 34 year-old male diagnosed with ankylosing spondylitis. After two years of treatment with infliximab, the patient developed a clinical picture compatible with stage II thoracic sarcoidosis. These findings resulted in the interruption of infliximab therapy. The patient was not administered new treatment since respiratory function testing did not confirm harmful repercussions. After a follow-up of 1 year, the patient is asymptomatic and radiologic tests show complete resolution of pulmonary infiltrates and mediastinal and bilateral hilar lymphadenopathy.

Introduction

Sarcoidosis is a multisystemic disease which is manifested by the formation of non-caseating granulomas. Pulmonary sarcoidosis is one of the most frequent causes of interstitial pulmonary disease. It always requires diagnosis of exclusion consisting in: *a)* compatible clinical-radiological manifestations; *b)* presence of sarcoid-related granulomas in histological samples, and *c)* the exclusion of other causes that may indicate a similar clinical/histological picture, especially granulomatous diseases (1). Although the etiology of the disease is not known, it is thought that certain cytokines such as tumoral necrosis factor (TNF) alpha play an important role in the development of the disease (2, 3). Several cases of sarcoidosis refractory to conventional treatment have been described, with improvement with infliximab treatment (4-9). This case is instructive due to the development of thoracic sarcoidosis in a patient with ankylosing spondylitis (AS) positive HLA B27 treated with infliximab.

Case report

A 34 year-old male, ex-smoker for two years of 10 packets of cigarettes/year, who underwent L5-S1 discectomy in 1992 and varicose vein surgery in the lower extremities in 2000. The patient was diagnosed in 1994 with AS by modified new York criteria, without extra-articular involvement. Physical examination revealed arthritis of knees. The spinal mobility measures were: Schober test: 1.5 cm; occiput to wall distance: 5.2 cm; chest expansion: 3.2 cm and cervical rotation: 45º. The sacroiliac joints showed bilateral radiological sacroiliitis grade III-IV. The patient was initially treated with non-steroid antiinflammatory drugs (NSAIDs) and maintained a stable clinical picture.

In May, 2001 the patient presented inflammatory flare-ups with acute axial pain and stiffness accompanied with increase of acute phase reactants and did not respond to full doses of NSAIDs. Anti-TNF alpha therapy with infliximab was initiated at doses of 5 mg/kg weight every 6 weeks. Mantoux testing and chest x-ray results performed before treatment were normal. The patient showed clinical improvement at 6 weeks with reduction of axial symptomatology and normalization of acute phase reactant levels. In February 2002, the patient presented a clinical picture of middle-lobe pneumonia not bacteriologically characterized, which receded after antibiotic treatment; the patient continued anti-TNF alpha therapy as usual once the infection disappeared.

In September 2003, the patient was admitted in our hospital with a week-long clinical picture of progressive dyspnea on moderate exertion and dorsal pain with pleural characteristics, without other accompanying symptomatology. The last dose of infliximab had been administered on August 19, 2003. Physical exploration revealed dry rales in both bases of the lungs, without alterations at other levels.

Laboratory hemogram, biochemical, proteinogram, rheumatoide factor, antinuclear antibody and systematic urine

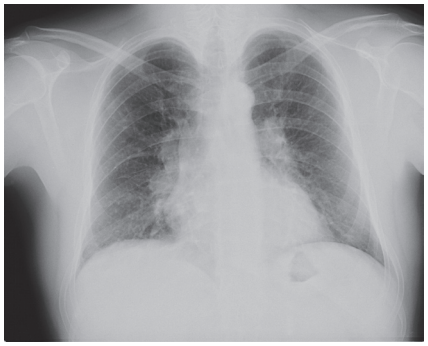

Fig. 1. Chest x-ray: prominent pulmonary hilar vessels, especially right vessel.

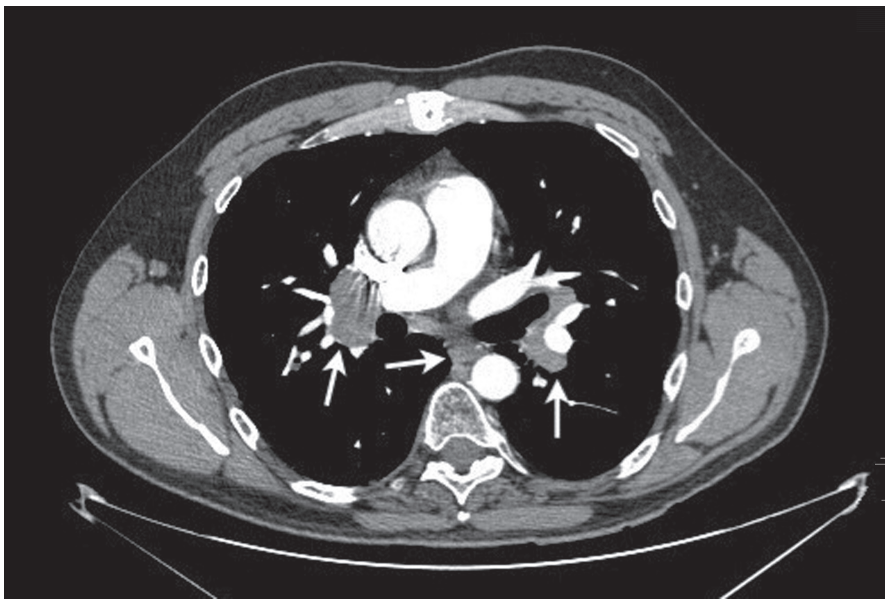

Fig. 2. Helicoidal chest CT: shows hilar and mediastinal adenopathy in aortopulmonary window (arrows).

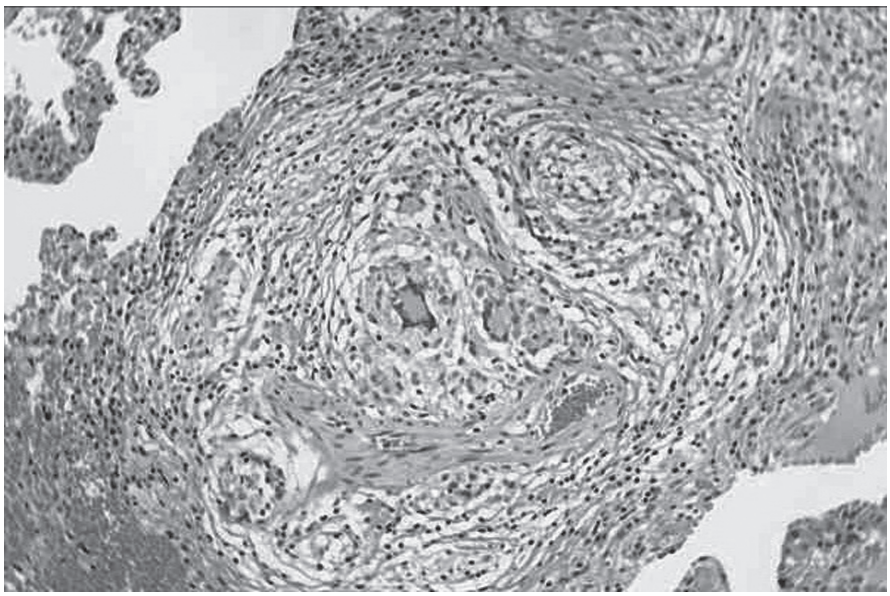

Fig 3. Sarcoid granulomas: Histology from patient showing non-caseating granulomas.

test results were normal. Globular sedimentation rate was 21 (0-20) and C-reactive protein was 23.2 mg/l (0-5). Basal arterial gasometry showed hypoxemia with pO2 of 70 mm/Hg (75-105 mm/Hg).

Electrocardiagram showed sinus bradycardia of 55 beats per minute and incomplete blockage of right branch.

Chest x-ray (Fig. 1) confirmed prominent pulmonary hilar vessels, especially right vessel. The study was completed with helicoidal chest CT (Fig. 2) which revealed hilar and mediastinal adenopathy in aortopulmonary window, and small areas in ground-glass attenuation in superior pulmonary lobes and signs of venous thrombosis in left popliteal vein, without signs of pulmonary thromboembolism. These findings led to determining causes due to infection, tumor and sarcoidosis as possible diagnoses. Borderline high value of angiotensin-converting enzyme 60.9 U/L (8-55) was confirmed. New mantoux testing and Lowenstein culture of sputum were performed with negative results. Tumor markers, antiphopholipid antibodies and anticardiolipin antibodies were normal. Respiratory function test results were also within normal values. Bronchoscopy and bronchoalveolar lavage was performed and samples were sent to the microbiology and pathologic anatomy units. Transbronchial biopsy was not performed due to the friability of the mucosa, and video-assisted thoracoscopy was performed and pulmonary biopsy samples were taken. All the cultures for bacteria, micobacteria and fungi were negative. Histological findings revealed the presence of non-caseating granulomas (Fig. 3), confirming diagnosis of Stage II thoracic sarcoidosis.

Infliximab treatment was terminated. Corticosteroid treatment was not initiated due to the normal results observed in respiratory function. The only treatment administered was dicumarinic anticoagulant during 6 months for profound venous thrombosis of inferior right member.

At present, after a follow-up of 1 year, the patient is asymptomatic and shows complete resolution in control chest CT.

Discussion

We present the first case found in the literature of a patient with ankylosing spondylitis that developed Stage II thoracic sarcoidosis during treatment with infliximab.

Coexistence of sarcoidosis and seronegative spondylarthropathy is rare, and to date only 14 cases have been reported; it seems to be more a coincidence than an association as genetic predisposing factors have not been found and few cases have been described (10).

Sarcoidosis is a systemic inflammatory disease. The clinical spectrum of the disease is wide-ranging and can vary from an abnormal chest x-ray in an asymptomatic patient to severe multiorganic diseases (11). Symptoms of pulmonary sarcoidosis include dry cough (30%), dyspnea (28%) and chest pain (15%) (1).

The etiology of sarcoidosis is not clear, but it appears that a specific genetic polymorphism of the major histocom-

patible complex (MHC) and several cytokines, notably tumoral necrosis factor (TNF) alpha play a significant role in the physiopathology of the granulomatous inflammation (2, 3). Numerous microorganisms, such as *mycobacterium tuberculosis, propionibacterium acnes* and *p. granulosum* have been identified as possible etiological agents (12, 13).

At present, two biological agents are used as treatment for AS, infliximab and etanercept (14). Several cases have been published reporting infliximab treatment as producing clinical improvement and reduction in the need for corticosteroids in patients with sarcoidosis refractory to conventional therapy (4-9). Considering the potential adverse effects of biological agent, it is important to rule out diagnoses of infectious diseases (microbacterial and fungic infections, beryliosis) and neoplastic diseases, as was done in the case we present, in order to establish an adequate therapeutic procedure (15).

In the case we present, attention should be drawn to the development of thoracic sarcoidosis in a patient with AS that received treatment with infliximab, and is contradictory to previous published studies that report improvement in sarcoid manifestation particularly with infliximab therapy (4-9). A case to highlight is that of sarcoid-related uveitis in a 7 year-old child with juvenile idiopathic arthritis treated with etanercept (16). The result of the case is that anti-TNF therapy can cause sarcoidosis. The pathogenic mechanism is not known, and a hypothesis is that the immunosuppresant effect of biological therapies could favor the mediation of infectious agents in the development of sarcoidosis, though more studies and long-term experience with these treatments are needed.

Therefore, sarcoidosis development must not be ruled out in patients that receive anti-TNF treatment.

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