CASE REPORT

Sarcoidosis occuring during anti-TNF-α treatment for inflammatory rheumatic diseases: report of two cases

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ABSTRACT

Anti-TNF- α agents have been tried in cases of refractory sarcoidosis, giving favourable results. Thus, the occurrence of a granulomatous disease in a patient receiving such drug seems paradoxical. We describe 2 patients with inflammatory rheumatic disease, the first with ankylosing spondylitis, the second with rheumatoid arthritis, under anti-TNF-a treatment (infliximab and etanercept respectively) who developed non-caseating granulomas of the lungs and lymph nodes consistent with the diagnosis of sarcoidosis. Limited and various similar cases have been reported. It is generally considered that these granulomatous diseases are related to the anti-TNF- α agent.

Introduction

With the use of TNF- α blocking agents for inflammatory rheumatic diseases, various complications were described, mainly infections including granulomatous infections (1). In parallel to these granulomatous infections, certain granulomatous syndromes were also described in patients receiving anti-TNF- α therapy. TNF- α is thought to play a role in the pathogenesis of sarcoidosis, a systemic disease characterized by granulomatous lesions and therefore, TNF- α blocking agents have been tried in refractory sarcoidosis. We describe the development of noncaseating granulomatous disease in 2 patients under anti-TNF- α treatment.

Case 1

The patient, a 27-year-old white man, was seen for the first time in our department in 2001. He complained of inflammatory low back pain without peripheral arthritis, skin or eye involvement. He had a grade III bilateral sacroilitiis and was HLA-B27 positive. He was thus diagnosed to have ankylosing spondylitis (AS) and received various non-steroidal antiinflammatory drugs, without improvement. In 2002, due to the persistence of active disease (BASDAI 66/100, CRP levels: 32 mg/L) and after unsuccessful treatment with pulse prednisolone 3.5 mg/kg, infliximab therapy was begun. A tuberculin skin test and a chest x-ray

were performed before starting infliximab and the patient was not considered at high risk of developing tuberculosis (chest x-ray was normal and tuberculin skin test gave an induration of 8 mm). Between 2002 and 2003, he received 11 infusions of infliximab 5mg/kg with improvement lasting 1 year. He received his last infusion in November 2004, and he then decided to stop the treatment due to flare- up of the disease and acute axial pain. He was seen again in March 2005 for an extremely intense inflammatory back pain requiring morphine. He had no specific treatment for AS. A chest radiograph and a computed tomography (CT) of the thorax revealed bilateral hilar adenopathies and nodular infiltrates in the left lung (Fig. 1). The patient had no respiratory symptoms, fever or weight loss. A new tuberculin skin test was performed and revealed again an induration (10 mm). Sputum culture as well as polymerase chain reaction for Mycobacterium tuberculosis were negative. The angiotensin- converting enzyme was mildly elevated (31 nmol/l; reference range: 12-25), CRP levels was increased up to 37 mg/ 1 while serum calcemiae was normal. A bronchoscopy with transbronchial biopsy in a paratracheal adenopathy was performed as well as a needle lung biopsy guided by CT in a nodular lesion. The histological study showed non-caseating granulomas in both the lymph node and lung specimen (Fig. 2). Stain and culture of tissues for mycobacterium, atypical mycobacterium and fungi were negative. In September 2005, a new x-ray and CT of the chest were performed and showed the disappearance of intra-thoracic lymph nodes and nodular infiltrates and the patient did not have any signs of sarcoidosis without any specific treatment.

Case 2

The patient was a 49-year-old woman who had suffered from seropositive rheumatoid arthritis (RA) for 20 years. She had been treated with different disease modifying antirheumatic drugs (gold salts, hydroxychloroquine, sulfasalazine) without enough control of the disease. In 2002, methotrexate was introduced but stopped 2 years later

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Table I.	Cases of	developement	of sarcoidosis	during anti	TNF- α treatment.

Author (Reference)	Age/sex	Underlying rheumatic disease	Anti TNF: Molecule Dosage	Time between start of anti-TNF-α treatment and onset of symptoms	Organ manifestations (clinical symptoms)	Diagnostic procedures	Treatment	Outcome of sarcoidosis symptoms	Causality assessment
Gonzalez-Lopez (6)	70/M	AS	Etanercept 25 mg twice weekly	21 months	Skin (nodular lesion) Intrathoracic lymph nodes	Skin biopsy showing non caseating granulomas Scintigraphy with 67Ga: increased uptake of hilar adenopathies Elevated ACE	Etanercept withdrawn No specific treatment for sarcoidosis symptoms	Spontaneous resolution	Probable
Phillips (7)	M/37	PsA	Etanercept twice weekly	18 months	Lung (diffuse miliary)	Transbronchial lung biopsy showing noncaseating granulomas	Etanercept Withdrawn No specific treatment for lung granuloma	Spontaneous resolution Secondary treatment by adalimumab without recurrence of sarcoidosis	Possible
Almodovar (8)	M/34	AS	Inflixmab 5 mg/kg	28 months	Intrathoracic lymph nodes	Pulmonary biopsies showing non caseating granulomas	Infiximab withdrawn No treatment for sarcoidosis	Spontaneous resolution	Probable
Verschueren (9)	F/53	RA	Etanercept 25 mg twice weekly	6 months	Intrathoracic adenopathies and reticulonodular infiltrate	Mediatinoscopy with biopsies of mediastinal adenopathies, showing non caseating granuloma	Etanercept withdrawn Corticosteroids for lung sarcoidosis	Radiological remission within 12 months	Possible
Verschuen (9)	F/46	RA	Etanercept 25 mg twice weekly	12 months	Skin (erthema nodosum) Intrathoracic adenopathies	Mediatinoscopy with biopsy of medaitinal adenopathies showing noncaseating granulomas	Etanercept withdrawn No specific treatment for sarcoidosis	Spontaneous resolution	Probable
O'Shea (10)	M/34	PsA	Infliximab 5 mg/kg	58 months	Intrathoracic adenopathies Pleural effusion	Lymph node biopsies under mediastinoscopy showing nonnecrotizing granuloma	Infliximab withdrawn Corticosteroid treatment (40 mg/day) for sarcoidosis	Resolution of pleural effusion but persistence of hilar adenopathies	Possible
Vavricka (11)	M/73	RA	Adalimumab 40 mg weekly	12 months	Lung nodular infiltrates	Lung biopsy showing necrotizing granulomas consistent with tuberculosis but culture for mycobacteria were negative	Adalimumab withdrawn Antituberculous treatment for 6 months	No regression of pulmonary lesions	Possible
Peno-Green (12)	F/50	RA	Etanercept 25 mg twice weekly	2 months	Skin (lesions located at scars and plantar soles) Lung reticulonodular infiltrates	Transbronchial lung biopsies showing noncaseating granulomas	Etanercept withdrawn Corticosteroid treatment for lung sarcoidosis	Resolution of lung lesions	Probable
Bachmeyer (13)	M/39	AS	Etanercept 25 mg twice weekly	1 month	Skin (papular skin lesion on a tatoo)	Skin biopsy: non caseating granuloma	Etanercept was maintained Treatment of skin lesions with dermocorti- costeroids	Resolution of skin lesions	Possible
Personal case 1	M/ 27	AS	Infliximab 5 mg/kg	22 months	Intrathoracic adenopathies	Transbronchial lymph node biopsy showing non caseating granulomas	Infliximab withdrawn	Resolution of hilar adenopathies	Probable
Personal case 2	F/49	RA	Etanercept	26 months	Hilar adenopathies and interstitial infiltrate	Transbronchial lung biopsies showing non caseating granulomas	Etanercept withdrawn Antituberculous treatment for 6 months	Resolution of chest abnormalities	Probable

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Fig. 1. (Case 1): computed tomography of the thorax showing bilateral hilar adenopathies (left) and nodular density in the lower zone of the left lung (right).



Fig. 2. (Case 1): lymph node histology showing non-caseating granulomas.

Fig. 3. (Case 2): computed tomography of the

thorax showing bilateral

reticulonodular intersti-

tial pattern.



because of increased liver enzymes. At that time, the patient had active disease (Disease Activity Score 28 joints -DAS28: 4.66), rheumatoid factors and anti-cyclic citrullinated peptide antibodies were positive and joint radiographs showed erosions with advanced damage at the wrists. Due to the lack of efficacy of conventional treatments and the severity of the disease despite

corticosteroid treatment (prednisone 15 mg/day), the patient was treated with etanercept 25 mg twice weekly beginning in August 2004. Prior to the introduction of etanercept, a tuberculin skin test was negative and a chest radiograph was normal. She rapidly responded to the treatment without any adverse event (DAS28 in November 2004: 1.77) and corticosteroids were progressively tapered and stopped in June 2006. In October 2006, after 26 months of etanercept therapy, she developed respiratory symptoms with dyspnea and non-productive cough. The anti-TNF- α treatment was stopped. A CT of the chest showed bilateral reticulonodular interstitial pattern with hilar adenopathies (Fig. 3). Sputum cultures for bacteria and mycobacteria were negative. The angiotensin-converting enzyme was normal (27 U/L; reference range: 12-68) as well as serum calcemiae. A bronchoscopic examination with bronchoalveolar lavage did not reveal lymphocyte infiltrate and cultures for mycobacteria were again negative. The histological analysis of a transbronchial lung biopsy revealed a massive infiltration by non-caseating granulomas. Lung tissue cultures were also negative. In spite of negative bacteriological findings for mycobacteria, antituberculous treatment was given for 6 months. At present, and after a follow-up of one year, she is asymptomatic and shows complete resolution of chest x-ray and CT.

Discussion

We describe non-caseating granulomatous syndrome without any evidence of infection, which were located to the lungs and lymphatic system in 2 patients with inflammatory rheumatic disease. These cases were consistent with the diagnosis of sarcoidosis which occurred while on (or after) anti-TNF- α therapy and resolved without corticosteroids or any specific treatment. The hallmark of sarcoidosis is a noncaseating granuloma which infiltrates primarily the lungs and lymph nodes. The etiology of sarcoidosis is still unknown, but the disease and granuloma formation involves CD4+ T cells of Th1 phenotype and alveolar macrophages which secrete various cytokines including IFN- α and TNF- α . There are some evidences that TNF- α plays a major role in the induction and maintenance of granuloma. In addition, production of TNF- α is increased by alveolar macrophages. This gives the rationale for targeting TNF- α in sarcoidosis. Therefore, TNF- α blocking agents have been tried in cases of refractory sarcoidosis, and clinical improvement was obtained with infliximab, particularly in patients with cutaneous, neurological or eye involvement (2, 3). Results were less evident with etanercept, although isolated cases of sarcoidosis improved (4, 5). Alternatively, various granuloma syndromes were described in 9 patients receiving anti-TNF- α therapy (etanercept in 6, infliximab in 2 and adalimumab in one case) (6-13). The underlying disease was RA for 4, AS for 3 and psoriatic arthritis for 2 patients. Organ involvement of sarcoidosis corresponded mainly to lymph node and lung involvement, but also skin disease. In one case, a granulomatous skin disease developed on a tattoo (13). Sarcoidosis was diagnosed by histological examination of biopsy sample (lymph node, lung or skin) in all these cases. Spontaneous resolution of clinical symptom and organ involvement was obtained in 4 cases and corticosteroid treatment was given in 3 cases. For 2 patients, there was persistence of sarcoidosis organ involvement (hilar adenopathies or lung nodular lesions). For one patient, etanercept was withdrawn giving clinical amelioration, and adalimumab was then introduced, without recurrence of sarcoidosis symptoms (7). These patients developed symptoms which were related to the diagnosis of sarcoidosis after a mean period of 17.5 months of anti-TNF- α exposure. In our first case, sarcoidosis symptoms started 4 months after the last infliximab infusion but after 22 months of infliximab treatment. Thus, in this case, the development of sarcoidosis independently of anti-TNF- α treatment is unlikely. In an attempt to evaluate the likelihood of relationship between the drug and the development of sarcoidosis, we use the causalty assessment scale of suspected adverse drug reactions proposed by Edwards et al. (14). This scale attributes 6 levels of causality (certain, probable, possible, unlikely, unclassified and unclassifiable). Four cases were classified probable and 5 possible. Our 2 cases were evaluated probable. Of interest, some cases of Crohn's disease were reported in patients with AS taking anti-TNF- α agent, mainly etanercept (15). Finally, rare cases of rheumatoid nodules of the

lungs (accelerated nodulosis or new onset of nodules) were observed in patients with RA treated by anti-TNF- α agents (16). Taken together, a wide range of granuloma reactions were described in patients with inflammatory diseases requiring TNF- α blocking agent. These granuloma reactions were primarily located to the lungs and the lymphatic system and also to the skin. They were observed mainly but not exclusively with etanercept. With the interruption of the treatment, these reactions generally improved or resolved. The observance of granulomatous lesions in patients taking anti-TNF-a agents seems paradoxical. However, the temporal relationship between drug administration and the pathogenic process, and the regression of the lesions after suspension of treatment as well, suggests that the TNF- α blocking agent is probably related to granuloma formation. As seen above, these reactions occurred mainly with etanercept and it has been suggested that these granulomatous syndromes may result from the biological properties of etanercept (6, 7). Indeed, there is a number of differences between etanercept and infliximab (and adalimumab as well): they have different binding avidities, different clearances; infliximab causes in vitro antibody and complement mediated cell lysis while etanercept does not; infliximab induces apoptosis in monocytes and T cell from certain tissue (gastrointestinal mucosa); etanercept is a soluble receptor that neutralizes soluble TNF- α and binds to membrane TNF- α with reduced avidity compared to infliximab; etanercept binds lymphotoxin- α while infliximab does not; infliximab inhibits both TNF- α receptors (p55 and p75) signalling pathways while etanercept leaves p75 partially intact; infliximab inhibits IFN-y expression and etanercept does not (and IFNy participated to granuloma formation) (17, 18). It has been thus suggested that etanercept could preserve in part the mechanisms leading to granuloma formation, explaining the lack of efficacy of this agent in Crohn's disease and refractory sarcoidosis. However, our first case and other previously reported (8, 10, 11) do not completely support this hypothesis since these granulomatous diseases developed under infliximab or adalimumab. Another hypothesis could be that these granulomatous syndromes occurred in predisposing patients: the association of sarcoidosis with AS has been reported as well as, more rarely, with RA (19, 20). In the same way, Crohn's disease may be unmasked by anti-TNF- α therapy given for AS. In this context, the TNF- α blockers act as a precipitating agent and induce granulomatous reaction. It may also be hypothesized that our patients had undiagnosed and latent sarcoidosis (associated to AS or RA) and that the interruption of infliximab and corticosteroids (for the first and second case, respectively) revealed the granulomatous disease. An infectious cause has been suspected for sarcoidosis for a long time. Thus, it may also hypothesized that anti-TNF- α therapy may favour the development or reactivate an infectious agent that is linked to sarcoidosis pathophysiology, leading to the development of clinical symptoms. In this sense, it has been observed in patients receiving anti-TNF- α agents the development of psoriasis or psoriasis-like lesions. Recent data suggest that the skin lesions are associated to chlamydial infection which was activated or reactivated by anti-TNF- α treatment (21). Such a mechanism could also be an explanation for the cases of sarcoidosis under these agents. So far, we do not know the exact mechanisms, but all these cases of non-infectious granulomatous diseases are instructive and we have certainly to learn again from other similar cases occurring under anti-TNF- α therapy. Finally, the clinician must be aware of this potential problem and will initiate diagnostic procedures at the earliest possible time.

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