

# Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases

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**Objective.** TNF blockers have been recently evaluated for treating refractory sarcoidosis and could be efficient. However, several cases of sarcoidosis have been diagnosed during anti-TNF therapy. Here, we report the largest series of sarcoid-like granulomatosis following TNF blocker treatment.

**Methods.** A call for observations of sarcoid-like granulomatosis following TNF blocker treatment was sent to the members of the French 'Club Rhumatismes et Inflammation'. Histological evidence of granulomatosis was required.

**Results.** Observations of 10 patients [seven females; median age 50.5 (range 27–72) years] with sarcoid-like granulomatosis while on anti-TNF treatment were collected: five were treated with etanercept and five with monoclonal antibodies; four patients received TNF blockers for RA and six for SpA. The median delay between anti-TNF agent introduction and granulomatosis diagnosis was 18 (range 1–51) months. Clinical symptoms were mainly pulmonary and cutaneous. Angiotensin-converting enzyme activity was increased in six cases. Lymph-node and/or lung involvement were observed by CT scan of the chest for eight patients. The median delay between drug discontinuation and remission was 6 (range 1–11) months for clinical signs and 6 (range 2–12) months for biological and radiographic findings. Improvement was observed in all patients after drug discontinuation with or without steroids.

**Conclusions.** Sarcoid-like granulomatosis is rare but not exceptional in patients treated with TNF blockers (~1/2800) and does not seem to be related to gender, rheumatic disease or in our series the type of anti-TNF drug used (monoclonal antibodies or soluble receptor). Discontinuation of anti-TNF usually leads to recovery.

**KEY WORDS:** Anti-TNF drugs, Granulomatosis, Sarcoidosis.

## Introduction

Sarcoidosis is an epithelioid-cell granulomatosis of unknown aetiology. The diagnosis is based on both clinical presentation and histopathological findings [1]. Although presentation of sarcoidosis can vary widely, the disease usually involves multiple organs and the clinical likelihood of sarcoidosis increases if more than one organ is affected. The pathological findings of sarcoidosis are granulomas, which are usually non-necrotizing, but occasionally necrosis can be observed [2]. Schaumann and asteroid bodies can be found. Sarcoidosis diagnosis requires exclusion of diagnosis of the other granulomatoses and especially tuberculosis (TB). The presence of CD4<sup>+</sup> T cells that interact with antigen-presenting cells initiates the formation and maintenance of granulomas. The triggering antigens activate selective T-cell clones that differentiate into type 1 helper T (Th1) cells. Mainly IFN- $\gamma$  and IL-2 are secreted, and production of TNF- $\alpha$  is increased through macrophage activation; the main cytokines associated with chronic disease are TNF- $\alpha$ , IL-12 and IL-8. Pulmonary fibrosis occurs after a shift in content from Th1 cytokines to Th2 cytokines (mainly IL-4, IL-10 and IL-13). TNF- $\alpha$  is central in sarcoidosis, for initiation and at the chronic stage. Consequently, TNF blockers may have a therapeutic effect on granulomatosis. The use of anti-TNF- $\alpha$  drugs, especially infliximab, has been recently investigated for treating refractory sarcoidosis and could be effective [3–5]. In contrast, cases of

sarcoidosis and granulomatosis after TNF blocker introduction have recently been described [6–17]. We report here 10 cases of sarcoid-like granulomatosis, the largest series reported to date, to better describe the adverse effect of TNF blocker treatment on sarcoidosis-like granulomatosis in terms of clinical and para-clinical characteristics and outcomes.

## Methods

### Case selection

Members of the 'Club Rhumatismes et Inflammation' (CRI), consisting of 866 French rheumatologists and internal medicine practitioners, were contacted by e-mail to collect reports of patients who presented with sarcoidosis or granulomatosis during anti-TNF therapy. The cases of granulomatosis had to occur after introduction of TNF blocker therapy. Other causes of granuloma had to be excluded, especially bacteriological causes with TB. Histological evidence of the granulomatosis was requested. Nine centres reported clinical cases and completed our questionnaire. Characteristics of patients, rheumatic disease and its treatments and sarcoidosis were collected. All observations were reported.

## Results

### Case characteristics

Observations of 10 patients [7 females; mean age 50.5 years (range 27–72 years)] corresponding to our criteria were reported (Tables 1 and 2). Four patients had RA and six had SpAs (five AS and one PsA). Five cases were treated with etanercept, three with infliximab and three with adalimumab (for one patient, adalimumab was initiated after etanercept). The median delay between anti-TNF drug onset and diagnosis of sarcoid-like granulomatosis was 18 (1–51) months: 18 (2–26) months for etanercept, 17 (14–51) months for infliximab and 11 (1–21) months for adalimumab.

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Submitted 10 September 2008; revised version accepted 6 February 2009.

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TABLE 1. Patients treated with etanercept

	Age/sex/ disease	Treatment/delay	Clinical	Paraclinical	Treatment/outcome
1	46 years/M/PsA	ETN 2 months	Three cutaneous nodules on the face	TB-st 10 mm ACE normal X-ray and CT scan normal	ETN discontinuation + 3 months of anti-TB treatment. Resolution 6 months after.
2	72 years/F/RA	ETN + MTX 15 mg/week 18 months	Inflammatory and painful scars	TB-st: negative ACE: increased X-ray and CT scan: normal	ETN discontinuation. Total resolution in 6 weeks. ADA started 2 years later, without any relapse in 3 years.
3	69 years/F/RA	ETN + 7 mg/day prednisone 27 months	Erythema nodosum Bilateral anterior uveitis	TB-st: negative ACE: normal CT scan: mediastinal lymph nodes, apex lobes infiltrate	ETN continuation. Prednisone 15 mg/day. Erythema nodosum resolution after few weeks. Uveitis relapse after steroid decrease. CT scan after 5 months: no improvement. Cutaneous and pulmonary relapse 22 months later treated by prednisone (1 mg/kg for 2.5 months). Persistence of cutaneous lesions leading to a switch with ADA. Resolution in few weeks.
4	38 years/F/AS	ETN 18 months	Dyspnoea	TB-st: ND ACE: ND X-ray and CT scan: bilateral pulmonary infiltration on bases	ETN discontinuation. Prednisone 20 mg/day. Clinical and CT scan resolution within 6 months. Initiation of ADA leading to clinical and radiological pulmonary relapse after 4 months. ADA discontinuation and prednisone 20 mg/day with resolution in 5 months.
5	49 years/F/RA	ETN 26 months	Dyspnoea, dry cough	TB-st: ND (negative before) ACE: normal CT scan: bilateral reticulonodular interstitial pattern with hilar lymph nodes	ETN discontinuation + 6 months of anti-TB therapy. Resolution of symptoms in 6 months and normalization of CT scan after 1 year.

ADA: adalimumab (40 mg/2 weeks); ETN: etanercept (50 mg/week); F: female; IFX: infliximab; M: male; ND: not done; TB-st: TB skin test.

TABLE 2. Patients treated with monoclonal antibodies

	Age/sex/ disease	Treatment/delay	Clinical	Paraclinical	Treatment/outcome
6	54 years/F/AS	IFX (5 mg/kg/8 weeks) 14 months	Brownish cutaneous nodules on arms and legs Discrete cough and dyspnoea	TB-st: negative (negative before) ACE: ND CT scan: basal infiltration and mediastinal lymph node.	IFX discontinuation. Pulmonary symptom resolution and CT scan normalization in 2 months. Cutaneous lesion resolution in 5 months. ETN given 2 months later. No relapse in 1 year.
7	50 years/M/AS	IFX (5 mg/kg/6 weeks) 51 months	Weight loss, asthenia	TB-st: negative (17 mm before) ACE: increased CT scan: mediastinal and hilar lymph nodes.	IFX discontinuation. Improvement of general symptoms in 3 months. CT scan after 4 months unchanged.
8	27 years/M/AS	IFX (5 mg/kg/6 weeks) 17 months + 4 months without treatment because of therapeutic escape	No symptom	TB-st: 10 mm ACE: increased X-ray and CT scan: bilateral mediastinal lymph nodes and nodular infiltrates	IFX discontinuation. Resolution on CT scan 6 months later.
9	53 years/F/RA	ADA 21 months	Weight loss, asthenia, Erythema nodosum, cutaneous nodules on lower limbs	TB-st: negative (ND before) ACE: increased CT scan: mediastinal lymph nodes and infiltrate	ADA discontinuation. Weight normalization and resolution of cutaneous lesions within 3 months, but persistence of mediastinal lymph nodes at 3 months.
10	51 years/F/SAPHO	ADA 4 weeks	Isolated fever	TB-st: negative (5 mm before) ACE: increased Hypercalcaemia CT scan: mediastinal and hilar lymph nodes + infiltrate	ADA discontinuation. Fever regression after 1 month. Improvement of CT scan lesions at 6 months.

ADA: adalimumab (40 mg/2 week); ETN: etanercept (50 mg/week); F: female; IFX: infliximab; M: male; ND: not done; SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis; TB-st: TB skin test.

In Case 8, infliximab was stopped 4 months before the granulomas were found.

### Clinical symptoms

Clinical symptoms were mainly pulmonary and cutaneous. Three patients had cough and/or dyspnoea, and five patients had cutaneous symptoms including nodules, erythema nodosum, hypodermatitis and scar inflammation. One case of bilateral anterior uveitis with etanercept therapy was seen. Three patients presented general signs such as weight loss and fatigue or fever.

### TB skin test

In two cases, test results were positive before infliximab and negative after granulomatosis diagnosis. In six cases, test results were

negative on diagnosis (previous test results were not available for two patients). In two cases, TB skin testing was not performed at the time of diagnosis.

### Biological findings

Lymphopenia was found in one patient with adalimumab treatment. One case showed hypercalcaemia with adalimumab treatment, and six cases (two with each anti-TNF therapy) showed increased angiotensin-converting enzyme (ACE) activity.

### Radiological findings

Mediastinal and/or hilar adenopathies were found in seven cases and lung infiltrates in seven other cases, bilateral most of the time and either on lower or upper lobes. Two patients had normal

pulmonary CT scan. Chest X-ray previous to anti-TNF treatment was normal for all cases.

### Histology

For all patients, the pathological area was biopsied: five skin and six bronchial and transbronchial lymph nodes and pulmonary tissue (Case 3 with both). Two patients underwent salivary gland biopsy with one revealing granulomas and one that was normal. All biopsies presented non-caseating granulomas, except one showing rare necrotizing areas. All cultures were negative for mycobacteria. Two biopsies presented aspects preferentially observed in sarcoidosis: asteroid bodies and Schaumann bodies. In one biopsy, foreign bodies were described and in one *Propionibacterium acnes* were isolated. In three of the five skin biopsies, granulomas were exclusively in the dermis; in the fourth biopsy, they were in both the dermis and hypodermis; and in the last biopsy, only in hypodermis. The epidermis always remained normal.

### Treatment and outcomes

All anti-TNF agents were discontinued, except in Case 3. Two patients received anti-TB treatment. Because of symptom persistence, one patient (Case 4) received prednisone (20 mg/day) after adalimumab discontinuation. All patients showed clinical recovery after anti-TNF drug discontinuation with or without prednisone. The median delay to recovery was 6 (range 1–11) months. In six of the eight patients with radiographic signs (Cases 3 to 10), the condition improved or resolved; the median delay was 6 (range 2–12) months for patients who stopped anti-TNF drugs and was 11 months for the patient who did not stop TNF blocker therapy. For Cases 7 and 9, CT scans at 4 and 3 months, respectively, showed stable disease.

In Case 3, etanercept was not interrupted. Clinical improvement was seen with prednisone treatment (15 mg/day) but when steroid dosage was decreased, sarcoid uveitis reappeared. Generally, pulmonary and cutaneous symptoms were noticed 22 months after clinical improvement. Most signs disappeared with high-dose steroid therapy (1 mg/kg) during 11 months. Persistence of scar inflammation finally led to a switch to adalimumab with fast remission. Two patients switched therapy from etanercept to adalimumab (Cases 2 and 3) and one from infliximab to etanercept (Case 6) without any relapse in condition. One patient experienced relapse after switching from etanercept to adalimumab (Case 4).

### Discussion

We collected 10 cases of sarcoid-like granulomatosis after TNF blocker initiation, which represents the largest nation-wide series. Since this association with AS and RA is very rare, it suggests that these sarcoid-like granulomatoses are likely related to anti-TNF therapy [18, 19]. In our series, much other evidence supports the causal link between anti-TNF therapy and granulomatosis. First, the chronology between anti-TNF therapy and disease is always compatible. Indeed, patients have previously received anti-TNF therapy with an exposure delay varying from 1 to 51 months. Also, the disease progression was reversed after anti-TNF discontinuation and when TNF blocker therapy was not interrupted, improvement was partial and did not last, despite steroid treatment. Finally, recurrence of symptoms and pathology could be observed when an anti-TNF drug (the same or a different one) was restarted. Nevertheless, for three patients, there was no relapse after the switch for another anti-TNF therapy, indicating that the granulomatosis occurrence is however not predictable. By the time this study was completed, 16 other cases of sarcoid-like granulomatosis had been published [6–17].

Nine patients were treated for RA, three for AS, two for PsA and two for juvenile arthritis. The characteristics of these patients

are very similar to those observed in our series. Indeed, initial clinical events were mainly pulmonary ( $n=11$ ) and cutaneous ( $n=5$ ; erythema nodosum, nodules and tattoo inflammation). Some of the features usually described in sarcoidosis were infrequent: TB skin-test turned negative in three cases and ACE activity was increased in three others. Like in our series, chest radiographs were abnormal in most cases with affected mediastinal or hilar lymph nodes ( $n=5$ ) and lung infiltrates ( $n=8$ ). Biopsies usually showed a granulomatosis that had negative culture results. The delay between diagnosis of granulomatosis and initiation of anti-TNF therapy is comparable with our series (12 months), with a period of time ranging between 1 and 67 months. Patients were more often treated with etanercept ( $n=12$ ), than monoclonal anti-TNF antibodies (three infliximab and one adalimumab). This last point contrasts with our series, since in our patients there was a comparable distribution between the two types of TNF antagonists. We could put in parallel occurrence of TB and sarcoid-like granulomatosis. Indeed, tuberculous granulomas are more frequent in patients treated with monoclonal anti-TNF antibodies but can be observed with etanercept [20]. Inversely, sarcoid like granulomatoses have been more frequently reported with TNF soluble receptor although they were also described with monoclonal anti-TNF antibodies. In addition, it is interesting to note that clinical trials failed to demonstrate the efficacy of etanercept in granulomatous diseases such as Crohn's disease and WG [21, 22]. Granuloma formation has also been described with anti-TNF therapy and mainly etanercept for Crohn's disease [23], rheumatoid nodules [24–26], interstitial granulomatous dermatitis [27] and GCA [28]. Moreover, in progressive pulmonary sarcoidosis, etanercept was used in an open-label study, but worsening of the disease was observed in 11 of 16 patients [29]. In contrast, >30 cases of successful results with infliximab have been reported [4, 30]. Therefore, if TNF blockers have a common effect allowing the development of granulomatous diseases, etanercept would preserve, at least to some degree, the mechanisms leading to granuloma formation whereas monoclonal anti-TNF antibodies would antagonize its formation and even enhance its destruction. These opposing effects between TNF blockers might be explained by the different way of TNF neutralization. Soluble TNF receptor might leave sufficient TNF activity to support granuloma formation [20, 31]. Nevertheless, since sarcoid-like granuloma has also been described in some patients with monoclonal anti-TNF antibodies, other mechanisms could be implicated. Thus, anti-TNF therapies can modulate the cytokine environment and may restore a Th1 response. Indeed, etanercept can enhance T-cell production of IFN- $\gamma$  [32, 33] and monoclonal anti-TNF- $\alpha$  antibodies raise the Th1:Th2 ratio in the peripheral blood [34, 35]. Therefore, restoration of IFN- $\gamma$ , a key player in granuloma formation might contribute in particular conditions to occurrence of sarcoid-like granulomatosis. It is interesting to note that sarcoid-like granuloma preferentially developed in the skin and lungs, which are in direct contact with exogenous antigen. The development of sarcoidosis requires exposure to an antigen and among the triggering agents suspected there are *Mycobacterium tuberculosis* and *P. acnes* [36, 37]. Anti-TNF drugs are known to decrease antigenic clearance and increase infections. Triggering infectious antigens from *M. tuberculosis* [38] or less frequently *P. acnes* [39, 40] infection was reported in patients under anti-TNF treatment. *Propionibacterium acnes* was found in the granuloma in one of our cases. Then, the mechanisms involved in granulomatosis development during anti-TNF therapy could include increased susceptibility to infection and changes in cytokine and cellular environment.

Sarcoid-like granulomatosis is rare but not exceptional and is an adverse effect of anti-TNF therapy. Since 28 000 patients were treated in France with TNF blockers in 2008, we can roughly estimate the frequency of this adverse event to at least 0.04% (1/2800). The prevalence of sarcoidosis is about 6/100 000 per



year [41]. The development of disease seems to be independent of sex and rheumatic disease. The occurrence of granulomatosis appears to be directly dependent on the TNF blocker therapy, and in our series regardless of the type of drug (monoclonal antibodies or soluble receptor). The diagnosis can be decided only after excluding a diagnosis of TB. Discontinuation leads to granulomatosis resolution in most cases. Corticosteroids can be required in cases of severe symptoms as in usual sarcoidosis. When anti-TNF therapy is required to control rheumatic disease, a switch from a soluble receptor format to monoclonal antibodies and the converse could be recommended. However, relapse could occur even after a switch. Anti-TNF- $\alpha$  therapy could promote sarcoid-like granulomatosis by enhancing the level of triggering infectious antigens and/or modification of the cytokine environment and cellular recruitment within the tissues.

### Rheumatology key messages

- Sarcoid-like granulomatosis should be known as an adverse effect of TNF blockers.
- Anti-TNF treatment discontinuation leads to recovery with or without corticosteroids.

### Acknowledgements

The authors would like to thank S. Barete, Hôpital Tenon Paris.

**Disclosure statement:** The authors have declared no conflicts of interest.

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