

Clinical Note

Lung Sarcoidosis Induced by TNF Antagonists in Rheumatoid Arthritis: A Case Presentation and a Literature Review

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ABSTRACT

We report the case of a 72 year-old woman with established rheumatoid arthritis diagnosed with pulmonary granulomatosis compatible with sarcoidosis after 49 months of treatment with etanercept. The symptoms and radiology remitted after the suspension of treatment against tumor necrosis factor (TNF) and with a course of steroids. To date, 27 cases of histologically-proven pulmonary sarcoidosis have been reported in relation to anti-TNF therapy, with etanercept being more frequent in comparison with the anti-TNF monoclonal antibodies infliximab and adalimumab. Probable pathogenic mechanisms of the paradoxical effect of anti-TNF treatment are discussed. It is important for clinicians to be aware of this potential and uncommon complication of biological therapy with TNF antagonists.

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Sarcoidosis pulmonar inducida por antagonistas del factor de necrosis tumoral en la artritis reumatoide: presentación de un caso y revisión de la literatura médica

RESUMEN

Se presenta una paciente de 72 años con artritis reumatoide evolucionada que fue diagnosticada de granulomatosis pulmonar compatible con sarcoidosis tras 49 meses de tratamiento con etanercept. El cuadro clínico y radiológico remitió al suspender el tratamiento contra el factor de necrosis tumoral (TNF) y con tratamiento corticoideo. Hasta la actualidad se han descrito 27 casos de sarcoidosis pulmonar, comprobados histológicamente, durante el tratamiento con antagonistas del TNF, siendo más frecuente con etanercept que con los anticuerpos monoclonales anti-TNF infliximab y adalimumab. Se discuten los probables mecanismos patogénicos de esta acción paradójica de los antagonistas del TNF. Es importante para el clínico reconocer esta infrecuente complicación del tratamiento anti-TNF.

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. An association has been described between sarcoidosis and autoimmune diseases such as Sjögren's syndrome, systemic lupus erythematosus, polymyositis, ankylosing spondylitis, inclusion body myositis and scleroderma,¹ as well as rheumatoid arthritis (RA),

although said association seems to be an exception.² In the last few years, cases of granulomatosis compatible with sarcoidosis have been documented in patients with RA and other inflammatory diseases during treatment with tumor necrosis factor (TNF) antagonists.³

We present the case of a patient with RA in whom the presence of lung sarcoidosis was detected 49 months after treatment with a soluble TNF receptor, etanercept (ETN). A review was carried out of the bibliography of the cases described with sarcoid granulomatosis with lung affection in patients treated with TNF antagonists, and physiopathological hypotheses were suggested.

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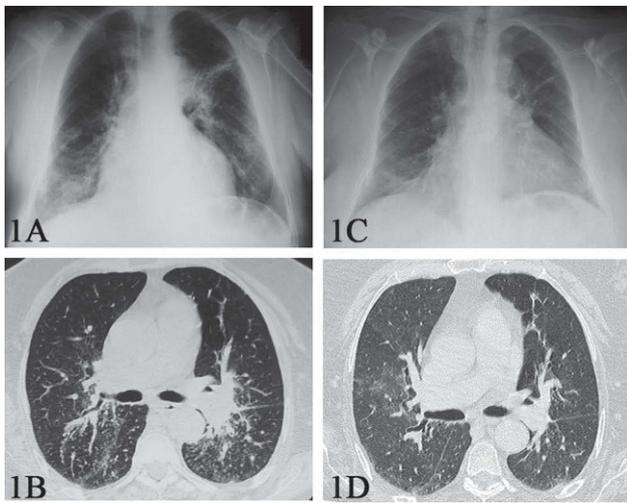


Figure 1. A) Chest radiograph at the time of diagnosis where reticular-nodular infiltrates can be observed at the left parahilar level and in the right inferior lobe; B) Computed tomography showing peri-bronchoalveolar lymph node conglomerates; C) 1-year chest radiograph; D) 1-year computed tomography, with no lymph node conglomerates.

Clinical Notes

The patient is a 72-year-old woman with a history of erosive, seropositive RA evolving over the previous 10 years, who had received treatment with non-steroid anti-inflammatory drugs, glucocorticoid and different disease-modifying antirheumatic drugs (gold salts, methotrexate and leflunomide) that were withdrawn due to lack of efficacy. In 2002, treatment was initiated with infliximab (INF), which was withdrawn due to loss of effectiveness, and in August 2004 monotherapy was begun with ETN at a dose of 25 mg/2 times a week, with a very positive clinical response. As a consequence of her disease, the patient required total arthroplasty of both knees. The medical history also included arterial hypertension and osteoporosis with femur fracture and vertebral fracture at the level of L5.

In September 2008, the patient presented with 10 weeks of progressive dyspnea and asthenia. The patient presented tachypnea. Respiratory examination was normal and joint examination revealed tumefaction of the third metacarpophalangeal joint of the right hand. Chest radiograph showed evidence of reticular-nodular infiltrates at the left parahilar level and in the right lower lobe (fig. 1A). High-resolution computed tomography (CT) of the chest revealed a diffuse nodular pattern with perihilar conglomerates (fig. 1B). The blood analysis determined ESR 96 mm/h, PCR 4.26 mg/dl and hemoglobin 9.9 g/dl, with normal renal and hepatic function. The levels of the angiotensin-converting enzyme (ACE) were 49 IU (normal value <60 IU). Rheumatoid factor was 49 IU/l (normal value <25 IU/l) and antibodies against citrullinated peptides were 731 IU (normal value <25 IU). The tumor markers as well as the rest of the autoantibodies were negative (including antibodies: basement membrane, anti-DNA and ANCA), as well as the Mantoux skin test. Respiratory functional exploration showed restrictive ventilatory alteration (FVC 1.95 l [69% of reference values], FEV1 1.38 l [67% of reference values], FEV1/FVC 98% and decrease in carbon monoxide transfer capacity 13.9 ml/min/mmHg [65% of reference values]). Arterial gasometry found evidence of hypoxemia (PaO₂ 75 mmHg, PaCO₂ 35 mmHg and basal oxygen saturation 97%). Blood cultures and sputum analysis were negative. Bronchoscopy showed diffuse inflammation of the bronchial mucosa. The microbiological analysis of the bronchoalveolar lavage (culture for bacteria and fungi, Ziehl-Nielsen stain, silver staining, PCR mycobacteria and Lowenstein

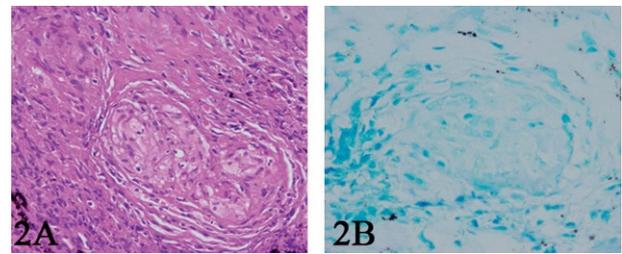


Figure 2. A) Transbronchial biopsy with hematoxylin-eosin stain (x20) showing a granuloma with histiocytic cells, multi-nuclear giant cells (with no necrosis or caseum) compatible with the diagnosis for sarcoidosis; B) Ziehl-Nielsen stain (x40) of the transbronchial biopsy, with no sign of Koch bacillus.

culture) were negative. The cytologic analysis of the bronchoalveolar lavage showed an increase in the CD4/CD8 lymphocyte ratio of 5.7 (reference values 1.6–1.8). We carried out a transbronchial biopsy that demonstrated the presence of granulomas with histiocytic cells and giant multinucleated cells, with neither necrosis nor caseum, compatible with the diagnosis of sarcoidosis (fig. 2A y B).

Treatment with ETN was withdrawn and treatment was initiated with prednisone at a dosage of 40 mg/day with progressive reduction of the dose. A month after initiating the treatment with corticoids, the patient was asymptomatic and CT showed the resolution of the lymph node conglomerates. Five months after the start of corticosteroid treatment, and despite the treatment with low doses of prednisone (5 mg), there was a moderate reactivation of the arthritis so treatment was initiated with leflunomide (10 mg/day), with good clinical response. At the 12-month follow-up, chest radiography showed an improvement in lung infiltrates (fig. 1C), and on CT (fig. 1D) no lymphadenopathies were found.

Review

We report the case of a patient with RA who developed pulmonary sarcoidosis while receiving treatment with ETN, a biological drug that is a TNF antagonist. The respiratory symptoms and lung infiltrates improved with the withdrawal of the biological treatment and the start of treatment with glucocorticoids, so it was therefore considered that ETN could have a role in the development of the granulomatous disease in this patient.

Twenty-seven cases, including the case presented in the article, have been described with sarcoidosis and histopathological confirmation induced by treatment with TNF antagonists in patients with inflammatory rheumatic diseases. Table 1 summarizes the main data of these patients. The majority were women (78%) with a mean age of 49 (range 27–72 years). Fifteen patients had RA, 7 spondyloarthropathy, 4 psoriatic arthritis and one patient had synovitis syndrome, acne, pustulosis, hyperostosis and osteitis. The TNF antagonist most often used was ETN (in 52% of the cases), followed by INF (30%) and adalimumab (18%). The mean number of months of biological treatment before diagnosis was 23 months (range 1–60 months). Concomitant extrapulmonary affection was found in 41% of the patients, most often skin affection, followed by ocular and parotid affections. Mediastinal and paratracheal lymphadenopathies were the most frequent lung affections (85%), followed by reticulo-nodular infiltrates and lung nodules (67%). Thirty-three percent presented a Siltzbach radiological pattern in stage I, 52% a radiological pattern in stage II and 15% in stage III; no patients presented pulmonary fibrosis. The ACE values were high in 9 of the 21 patients (43%) analyzed. In all patients, biological treatment was suspended and in 52% glucocorticoid treatment was added. Twenty-six percent of the patients required biological treatment with another drug due to reactivation of arthritis, except

Table 1
Patients with pulmonary sarcoidosis induced by treatment with tumor necrosis factor antagonists¹³⁻¹⁹

Author	Age,sex	Baseline disease	Anti-TNF and duration (months)	Pulmonary and extra-pulmonary affectation:	ACE	Withdrawal of anti-TNF	Resolution
González López, 2006	70, M	AS	ETN (21 m)	Hilar and paratracheal lymphadenopathies + skin nodules	↑	Yes	Total
Verschueren, 2007	53, F	RA	ETN (6 m)+MTX	Mediastinal lymphadenopathies + reticulonodular infiltrates	↑	Yes	Total
Verschueren, 2007	46, F	RA	ETN (12 m)	Hilar lymphadenopathies + skin lesions	NA	Yes	Total
Farah, 2007	40, F	PsA	ETN (10 m)	Mediastinal lymphadenopathies + pulmonary nodules	↑	Yes	Total
Kudrin, 2007	52, F	RA	ETN (18 m)	Mediastinal lymphadenopathies + lung nodules + parotid tumefaction	N	Yes	Total
Louie, 2007	35, F	AS	ETN (1 m)	Hilar and mediastinal lymphadenopathies + pulmonary infiltrates + uveitis	NA	Yes	Total
Toussiro, 2008	49, F	RA	ETN (26 m)	Hilar lymphadenopathies + reticulonodular infiltrates	N	Yes	Total
Peno-Green, 2002	50, F	RA	ETN (2 m)	Reticulonodular infiltrates + skin lesions	N	Yes	Total
Phillips, 2005	37, M	PsA	ETN (19 m)	Bilateral reticulonodular infiltrates	N	Yes. ADA begun.	Total
Daijen, 2009	69, F	RA	ETN (27 m)+CC	Mediastinal and apical lymphadenopathies + erythema nodosum + bilateral anterior uveitis	N	Yes. ADA begun.	Total
Ishiguro, 2008	65, F	RA	ETN (21 m)	Hilar adenopathies + pulmonary nodules	N	Yes	Total
Daijen, 2009	38, F	AS	ETN (18 m)	Bi-basal pulmonary infiltrates	NA	Yes. ADA begun.	Total
Skoie, 2010	48, F	RA	ETN (36 m)+MTX	Hilar lymphadenopathies	N	Yes	Total
Josse, 2009	64, F	RA	INF (38 m)	Bilateral paratracheal lymphadenopathies + pulmonary nodules + skin lesions	N	Yes. Rituximab begun.	Partial
O'Shea, 2006	34, M	PsA	INF (60 m)	Hilar lymphadenopathies + pleural effusion	NA	Yes	Partial
Toussiro, 2008	27, M	AS	INF (17 m)	Hilar lymphadenopathies + pulmonary infiltrates	↑	Yes	Total
Almodovar, 2007	34, F	AS	INF (24 m)	Hilar lymphadenopathies + pulmonary infiltrates	NA	Yes	Total
Massara, 2009	45, M	PsA	INF (25 m)	Hilar lymphadenopathies + reticulonodular infiltrate	N	Yes	Total
Daijen, 2009	54, F	AS	INF (14 m)	Mediastinal lymphadenopathies + basilar infiltrate	NA	Yes. ETN begun.	Total
Daijen, 2009	50, M	AS	INF (51 m)	Hilar and mediastinal lymphadenopathies	↑	Yes	Total
Van der Stoep, 2009	51, F	RA	INF (48 m)+MTX	Hilar lymphadenopathies + parotid tumefaction	N	Yes. ETN begun	Total
Massara, 2009	30, F	RA	ADA (27 m)+MTX	Bilateral pulmonary infiltrates	↑	Yes	Total
Daijen, 2009	53, F	RA	ADA (21 m)	Mediastinal lymphadenopathies + pulmonary infiltrates + erythema nodosum	↑	Yes	Partial (pulmonary) Total
Daijen, 2009	51, F	SAPHO	ADA (1 m)	Hilar and mediastinal lymphadenopathies + pulmonary infiltrates	↑	Yes	Total
Metvys, 2007	62, F	RA	ADA (24 m)+MTX+LFN	Subcarinal and paratracheal lymphadenopathies + granulomas in bone marrow	↑	Yes. HCQ begun.	Total
Van der Stoep, 2009	55, F	RA	ADA (8 m)	Hilar and mediastinal lymphadenopathies + erythema nodosum	N	Yes. ADA re-started.	Total
Caso presentado	72, F	RA	ETN (49 m)	Hilar lymphadenopathies + pulmonary nodules	N	Yes	Total

↑: high; ADA: adalimumab; PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; ACE: angiotensin-converting enzyme; ETN: etanercept; M: male; HCQ: hydroxychloroquine; INF: infliximab; LFN: leflunomide; F: female; MTX: methotrexate; N: normal; NA: not available; SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis; TNF: tumor necrosis factor.

Table 2
Patients with extrapulmonary sarcoidosis induced by treatment with tumor necrosis factor antagonists^{5,14-16,20}

Author	Age, Sex	Baseline disease	Anti-TNF and duration (months)	Extrapulmonary affectation:	ACE	Suspension of anti-TNF	Resolution
Hashkes, 2003	7, M	JIA	ETN (2 m)	Uveitis + hepatitis	↑	Yes	Partial
Baughman, 2003	46, M	PsA	ETN (2 m)	Skin nodules	N	Yes	Total
Popper, 1999	72, F	RA	ETN (18 m)+ MTX	Painful inflammatory reaction in scarring skin lesions	↑	Yes. ETN re-started.	Total
Skoie, 2010	42, M	AS	ETN (12 m)	Parotid tumefaction + cervical, para-aortic and mesenteric lymph adenopathies + hepatic affectation	↑	Yes. ADA + MTX started	Total
Sturfelt, 2008	41, F	AR	INF (69 m)+MTX	Meningoencephalitis + iridocyclitis + mediastinal lymphadenopathies + parotid affectation	N	Yes	Ventriculoperitoneal derivation
Dhaille, 2010	56, F	JIA	ADA (3 m)	Skin nodules + inflammatory reaction in scarring skin lesions	N	Yes	Total

↑: high; ADA: adalimumab; JIA: juvenile idiopathic arthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; ACE: angiotensin-converting enzyme; ETN: etanercept; M: male; INF: infliximab; F: female; MTX: methotrexate; N: normal; TNF: tumor necrosis factor.

in one case that was indicated due to sarcoid lung affectation. The evolution of the sarcoidosis was satisfactory with complete resolution in most cases (89%), except in 3 patients in whom it was partial.

In addition to the patients with pulmonary sarcoidosis induced by the biological treatment, cases have been reported of sarcoid granulomatosis, confirmed by histology, without lung affectation during the treatment with TNF antagonists (table 2). Six cases (50% women) have been published with a mean age of 44 (age range 7-72), and in 50% of the cases the concentration of ACE was high. The drug mainly implicated was also ETN and the mean number of months of treatment before the appearance of sarcoidosis was 18 months. One patient with psoriatic arthritis treated with the three anti-TNF drugs currently available presented skin nodules compatible with sarcoidosis.⁴

As in the case of TNF antagonists, cases have also been described of sarcoidosis during treatment with interferon α ,³ a drug used in the treatment of neoplasia, multiple sclerosis and infections by the hepatitis C virus.⁵ It has been suggested that interferon α , due to its immunomodulatory action, could induce the activation of macrophages and the formation of granulomas, producing sarcoidosis-type lesions.⁵

Discussion

The pathogenic mechanisms involved in the appearance of sarcoid granulomatosis in patients treated with TNF antagonists are unknown. In fact, TNF- α intervenes in the formation and the maintenance of the granuloma,^{6,7} therefore it has been postulated that TNF antagonists could be useful for the treatment of granulomatous diseases like sarcoidosis.⁸ In a series of 9 patients with pulmonary sarcoidosis, treatment with INF was effective in all the cases.⁹ In a later double-blind study in 138 patients, the efficacy of INF was confirmed in this disease.¹⁰ Thus, the induction of sarcoid granulomatosis in the course of treatment with TNF antagonists should be considered a difficult-to-explain paradoxical effect. In addition, there could be notable differences regarding the risk of this complication, which is higher in the course of treatment with ETN. This increase in risk would have been supported by the prospective study in phase II including 17 patients with pulmonary sarcoidosis who were treated with ETN, which was cancelled before its completion as the condition of the majority of the patients treated did not improve or even worsened.¹¹

Although all the anti-TNF drugs exert their action blocking the TNF- α proinflammatory cytokine, they have important differences in their structure as well as in their pharmacokinetic and pharmacodynamic characteristics, which could explain, in part, the differences that can be observed in clinical efficacy in the same

patient and the different frequency or characteristics of the possible side effects, including the induction of granulomatous lesions.^{6,12}

This fact could partially explain the greater incidence of sarcoidosis with ETN compared with monoclonal antibodies. ETN, unlike INF, only partially binds with transmembrane TNF, also leaving free the monomeric soluble form, and it does not produce cell lysis, therefore the inhibition of TNF would not be enough to preserve the formation of the granuloma.^{6,12} On the other hand, it must be considered that there are other cytokines that are also involved in the formation and the maintenance of the granuloma, such as IL-2, IL-18 and gammainterferon.⁸ It has been suggested that the antagonists of TNF could modulate the expression of these cytokines, reestablishing a TH1 response. Thus, ETN has been demonstrated to induce an increase of the lymphocytic synthesis of gamma-interferon. It has also been suggested that, due to the particular binding kinetics between the soluble receptor and the TNF molecule, there could be a redistribution of TNF- α from the places where the inflammation is produced to other tissues.^{6,12} Furthermore, although less frequently, sarcoidosis can be induced by monoclonal anti-TNF antibodies, that, at the same time, increase the TH1/TH2 rate in peripheral blood.⁶

In summary, 27 cases have been reported of pulmonary sarcoidosis during anti-TNF treatment, most with ETN, which, due to its characteristics and relation in time, seems to be a direct consequence of the biological treatment. It is important for the specialist to recognize this possible complication, which should be contemplated in the differential diagnosis of the different forms of lung affectation that can be observed in patients with inflammatory rheumatic diseases, especially RA.

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