Development of Sarcoidosis during Etanercept Therapy

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Abstract

This report describes a 65-year-old woman who developed granulomatous lesions consistent with sarcoidosis during etanercept therapy for rheumatoid arthritis. Hilar and mediastinal lymphadenopathy and multiple nodules in both lung fields developed 21 months after administration of etanercept. Noncaseating epithelioid cell granulomas consistent with sarcoidosis were detected in a lung biopsy specimen and in the parietal pleura obtained via thoracotomy. Diseases showing similar histologic changes were excluded, and a diagnosis of sarcoidosis was made. Etanercept was discontinued, which resulted in symptomatic relief, improvement of oxygenation and radiologic findings. There is substantial evidence of tumor necrosis factor- α involvement in the induction and maintenance of granuloma formation; however, we should keep in mind that granulomatous disease, such as sarcoidosis, can develop during treatment with a tumor necrosis factor- α blocking agent, such as etanercept.

Key words: sarcoidosis, etanercept, rheumatoid arthritis, TNF- α

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Introduction

Tumor necrosis factor- α (TNF- α) blockade with the soluble receptor fusion protein etanercept and the monoclonal antibody infliximab has recently been shown to be effective in the treatment of rheumatoid arthritis (RA). Because TNF- α is a key cytokine involved in granuloma formation, TNF- α blockade, which suppresses granuloma formation, has been suggested to be a potential treatment for sarcoidosis. Certainly, etanercept has been reported to be used successfully in some cases to treat sarcoidosis (1, 2). In this report, however, we describe a patient who developed sarcoidosis with lung involvement during etanercept therapy for RA.

Case Report

A 65-year-old woman was admitted to our hospital in

May 2007 for hilar lymphadenopathy and nodules in both lung fields. RA had been diagnosed in 2001 and was first treated with aurothiomalate sodium, methotrexate, and low-dose prednisolone (2.5 mg daily). Although the patient experienced slight improvement in morning stiffness and dactylitis with this treatment, gastrointestinal symptoms developed, which improved after the withdrawal of the methotrexate. In September 2005, chest radiography and computed tomography (CT) of the chest showed no abnormal findings, and etanercept therapy was started at 25 mg twice weekly. Within 2 months, the patient noted a marked improvement of her symptoms. However, she complained of general fatigue in April 2007. Chest radiography in May 2007 showed nodules in the bilateral lung fields with hilar lymphadenopathy (Fig. 1a). CT of the chest showed mediastinal and hilar lymphadenopathy (Fig. 1b), and nodules with perilymphatic distribution in both lung fields (Fig. 1c). The patient was admitted to our hospital for further examination. Upon admission, no skin lesions were found and chest auscultation re-

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Figure 1. Chest radiography and Computed Tomography (CT) on admission. Chest radiography on admission (a) showed bilateral and diffuse small nodular lesions with hilar lymphadenopathy. Chest computed tomography (CT) showed mediastinal and hilar lymphadenopathy (b), diffuse and small nodular lesions in the lung field and interlobar pleura, and a tuberculous lesion in the lower lobe (c).

vealed no abnormal sounds. There were no findings suggesting either ocular or neural sarcoidosis. The results of an electrocardiogram and echocardiography were normal. The reaction to a purified protein derivative skin test was negative. A blood gas analysis while the patient was breathing room air in the sitting position showed pH 7.41, a partial

pressure of oxygen (PaO_2) 62.5 Torr, carbon dioxide (PaCO_2) 40.3 Torr, and bicarbonate 25.0 mmol/l. Respiratory function tests revealed almost normal findings except for a slight decrease of vital capacity at 2.90 l (77.6%, % predicted), forced vital capacity 2.90 l (77.6%, % predicted), and diffusing capacity of carbon monoxide 15.13 ml/min/

Figure 2. a. Panoramic view showing the subpleural irregularly defined nodular lesion and many granulomas along lymphatic routes. b. The nodular lesion was composed of confluent epithelioid cell granulomas without caseous necrosis. *200. c. Epithelioid cell granulomas located the vascular wall. *200. Each was stained by Hematoxyline and Eosin Staining.

Torr (91.6%, % predicted). Laboratory values including peripheral blood cell counts and biochemistry were within normal limits. The erythrocyte sedimentation rate was 30 mm/hr. The serum C-reactive protein concentration was 0.38 mg/dL. Serum angiotensin converting enzyme (ACE) was not elevated (21.3 U/L, normal range, 7.0-25.0 U/L) and serum lysozyme concentration was slightly elevated (8.3 µg/mL, normal range, 2.7-7.5 µg/mL). The soluble interleukin (IL)-2 receptor concentration was 998 U/mL, and the serum IL-6 concentration was below 8 pg/mL. The serum interferon-γ concentration was below 0.4 IU/mL. Gallium 67 scintigraphy showed an increased uptake in the paratracheal and hilar lymph nodes and both lung fields. Bronchoalveolar lavage of the right middle lobe (B4b) was performed. The total cell count was 10.3×10^5 cells/mL, with 74.2% macrophages, 0.2% neutrophils, 0.4% eosinophils, and 25.2% lymphocytes. The CD4/CD8 ratio was elevated at 6.6. No granulomas or specific changes were found in a transbronchial lung

biopsy specimen; therefore, lung biopsy via video-assisted thoracic surgery was performed for the differential diagnosis of pulmonary disease. Histopathologic study of the superior segment of the right lower lobe, in which a large nodule was detected with CT, showed numerous confluent non-caseating epithelioid cell granulomas (ECGs) and tiny non-caseating ECGs in the lung and parietal pleura (Fig. 2a, b). The ECGs were mainly distributed along the lymphatic pathways. The results of tissue staining and a culture for bacteria, fungus, and mycobacterium, as well as a polymerase chain reaction analysis for *Mycobacterium tuberculosis* and *Mycobacterium avium* complex were all negative. The diagnosis of sarcoidosis was made on the basis of the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders criteria (3). Because of a possible relation between the development of sarcoidosis and treatment with etanercept, and because of the existence of case reports de-

Table 1. Sarcoid-Like Granulomatous Reactions Associated with TNF-Blockade

Author (year)	Ref	Age, Sex	TNF-blockade	Time to reaction	Pathological features
Peno-Green et al (2002)	8	50, F	RA Etanercept	2	Noncaseating granulomas in lungs and skin
Hashkes et al (2003)	9	7, M	JRA Etanercept	1	Noncaseating granulomas in the liver
Hubscher et al (2003)	10	41, F	RA Etanercept	19	Necrotizing area surrounded by a palisade of histiocytes and chronic inflammatory cells
Vavricka et al (2003)	14	73, M	RA Adalimumab	12	Necrotizing granulomatous inflammation with multinucleated giant cells
Gonzalez-Lopez et al(2006)	11	70, M	AS Etanercept	21	Noncaseating granulomas in skins
O'Shea et al (2006)	16	34, M	AS infliximab	60	Nonnecrotizing granulomas in lungs, lymph nodes
Vershueren et al (2007)	12	53, F	RA Etanercept	6	Noncaseating granulomas in mediastinal lymph nodes
Vershueren et al (2007)	12	46, F	RA Etanercept	12	Noncaseating granulomas in mediastinal lymph nodes
Almodovar et al (2007)	15	34, M	AS infliximab	12	Noncaseating granulomas in lungs
Kudrin A et al (2007)	13	52, F	RA Etanercept	18	Noncaseating granulomas in the lung
The present case	-	57, F	RA Etanercept	25	Noncaseating granulomas in the lung

Author (year)	Treatment/Outcome
Peno-Green et al (2002)	Stabilization after etanercept withdrawal/Resolution with prednisone
Hashkes et al (2003)	Etanercept withdrawal/Slight improvement with methotrexate
Hubscher et al (2003)	Etanercept withdrawal/Outcome not specified
Vavricka et al (2003)	Adalimumab withdrawal/persistence despite antituberculous therapy
Gonzalez-Lopez et al(2006)	Etanercept withdrawal/Resolution 2 months after withdrawal
O'Shea et al (2006)	Symptomatic and radiological improvement with prednisolone
Vershueren et al (2007)	Etanercept withdrawal/Complete remission with methylprednisolone
Vershueren et al (2007)	Etanercept withdrawal/Complete remission with no additional therapy
Almodovar et al (2007)	Infliximab withdrawal/Complete remission with no additional therapy
Kudrin A et al (2007)	Symptomatic and radiological improvement with prednisolone
The present case	Etanercept withdrawal/Improvement

RA: rheumatoid arthritis; AS: ankylosing spondylitis; JRA: juvenile idiopathic arthritis

Time to reaction indicates when epithelioid cell granulomatous reaction developed after initiation of TNF blockade.

scribing that sarcoidosis developed during etanercept therapy with an improvement after the withdrawal of the drug (4, 5), etanercept therapy was therefore stopped. This resulted in a symptomatic relief and radiologic improvement within 2 months. Blood gas analysis improved (pH 7.419, a partial pressure of oxygen (PaO₂) 71.2 Torr, carbon dioxide (PaCO₂) 40.1 Torr, and bicarbonate 25.5 mmol/l). The patient was discharged and has been in good health without any symptoms. She has been followed-up regularly on an outpatient basis.

Discussion

The recent progress in the therapy for RA has been remarkable, and some novel biological agents have helped us to improve the control of RA which had previously been refractory to the usual treatment. Simultaneously, it has been reported that various diseases or side effects, including respiratory tract infections, sometimes develop during the administration of these agents.

To date, there are three TNF- α -blocking agents currently available: etanercept (a soluble TNF- α receptor fusion protein), infliximab (a humanized mouse monoclonal antibody), and adalimumab (a fully human monoclonal antibody). It has been reported that respiratory tract infections, especially mycobacterial and fungal infections which can induce granuloma formation, develop during the administration of

TNF- α blockade. In the present case, however, the results of a culture as well as polymerase chain reaction analysis for infection were all negative, and the evident infectious agents were excluded.

Sarcoidosis is considered to be a systemic, granulomatous, and immune-mediated inflammatory disorder. There is evidence that inflammation and granuloma formation occur in a genetically susceptible host as a result of a Th1-type immune response. This is characterized by large numbers of activated macrophages and CD4+ T lymphocytes. Although a large variety of cytokines are produced under these conditions, TNF- α as well as interferon- γ (IFN- γ), IL-12, and IL-18 play critical roles in driving the Th1 commitment in the course of the granulomatous process (6, 7). Therefore, the development of granulomatous reactions during a TNF- α -blockade in this case seems paradoxical. However, there have been some reports of sarcoid-like granuloma/sarcoidosis development during TNF- α -blockade for RA and for ankylosing spondylitis (8-16) (Table 1).

In this case, sarcoidosis improved after the withdrawal of etanercept, thus suggesting a relation between the development of sarcoidosis and etanercept administration. It is not known whether etanercept can cause sarcoidosis, but two hypotheses of pathogenic mechanism can be raised. One is the immunosuppressant effect of biological therapies that could favor the mediation of infectious agents in the development of sarcoidosis because some microorganisms such as

Propionibacterium acnes and *Propionibacterium granulosum* have been identified as possible etiologic agents (17). The other is the involvement of other cytokines that could play a crucial role in granuloma formation under treatment with TNF- α -blockade. There are some reports supporting the latter hypothesis. It is known that patients treated with etanercept show a significant increase in the percentage of T cells expressing IFN- γ (18), which is one of the lymphokines most relevant to the generation of granulomas and is known to be significantly increased in the serum of patients with sarcoidosis compared controls (19). In addition, some investigators reported that pulmonary sarcoidosis worsened in 11 of 16 cases after etanercept administration (4).

The relation between infliximab and granulomatous formation remains controversial. As shown in Table 1, 2 cases who developed sarcoid-like granulomas/sarcoidosis during

the infliximab therapy have been reported (14, 15), but these cases were contradictory to previous published studies that report an improvement in sarcoid manifestation by infliximab therapy (20, 21). There are differences in the kinetics, the binding avidities for soluble versus transmembrane TNF- α (12), and the ability to inhibit IFN- γ production (18) between etanercept and other types of TNF- α blockade. These observations may explain the different efficacy of these agents for sarcoidosis, or the frequency of the development of sarcoidosis under TNF- α blockade; however, data are limited, and further studies are needed to clarify these matters.

In summary, this report describes a patient with RA who developed sarcoidosis during etanercept therapy. We should keep in mind that a granulomatous disease, such as sarcoidosis, can develop during TNF- α -blockade therapy.

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