

Etanercept as a Possible Trigger of Fatal Pulmonary Fibrosis

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Pulmonary fibrosis can be caused by external agents, including certain drugs. For some time now, tumor necrosis factor antagonists such as etanercept have been used to treat certain autoimmune diseases. Fibrosis caused by medication responds to withdrawal of the drug and treatment with corticosteroids. Very rarely, fibrosis is irreversible. We present the case of a patient who developed pulmonary fibrosis after initiating treatment with etanercept. The clinical course was fulminant despite withdrawal of the drug and high doses of corticosteroids.

Key words: *Etanercept. Pulmonary fibrosis. Tumor necrosis factor.*

Fibrosis pulmonar mortal, con etanercept como posible desencadenante

La fibrosis pulmonar es una enfermedad que puede estar causada por agentes externos como determinados fármacos. Desde hace un tiempo se utilizan fármacos antagonistas del factor de necrosis tumoral (TNF) para ciertas enfermedades autoinmunitarias, siendo un ejemplo de estos fármacos el etanercept. Las fibrosis secundarias a medicamentos se caracterizan por la respuesta a la retirada del fármaco y a esteroides. En muy raras ocasiones se produce una fibrosis irreversible. Presentamos el caso de un paciente que desarrolló una fibrosis pulmonar tras iniciar tratamiento con etanercept y que tuvo un curso clínico nefasto a pesar de la retirada del anti-TNF y dosis altas de esteroides.

Palabras clave: *Etanercept. Fibrosis pulmonar. Factor de necrosis tumoral.*

Introduction

Pulmonary fibrosis is a disease of the lung parenchyma that generally develops slowly and gradually. It can be associated with immune diseases, such as rheumatoid arthritis, although it bears very little relation to psoriasis or psoriatic arthritis. In some cases the disease is triggered by repeated contact with a substance that can cause extrinsic (allergic) alveolitis, and if contact persists over time, fibrosis may become established. Antagonists of tumor necrosis factor (TNF)—a proinflammatory cytokine that exists in both transmembrane and soluble forms and, like any other cytokine, is involved in host defense mechanisms¹—have proven efficacious and safe in diseases such as rheumatoid arthritis and psoriatic arthritis.^{2,3} The drugs that are currently used to treat these rheumatic diseases are etanercept, a dimeric fusion protein composed of the extracellular portion

of the human p75 TNF receptor bound to the Fc fragment of human immunoglobulin G1, and infliximab, a mouse monoclonal antibody.⁴ The safety problems of these TNF antagonists involve infection (both common and opportunistic ones), cytopenia, demyelinating disease, lupus-like syndromes, congestive heart failure, and malignant neoplasms, particularly lymphoma.⁵ They can also cause types 1 and 3 hypersensitivity pneumonitis.⁶ The literature contains few reports of lung injury associated with etanercept,^{7,8} and we were unable to find references to fatal lesions.

We report the case of a patient diagnosed with psoriatic arthritis who developed pulmonary fibrosis after starting therapy with the anti-TNF drug etanercept. The highly adverse clinical course led to death despite withdrawal of etanercept and initiation of intensive treatment for fibrosis.

Case Description

The patient was a 34-year-old man who was referred to our service with progressive dyspnea on exertion. His chest x-ray revealed a reticular interstitial pattern on the base of both lungs (Figure 1). The patient was a bricklayer

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Figure 1. Posteroanterior chest radiograph showing a mainly left-sided interstitial and reticular infiltrate at the bases of both lungs.

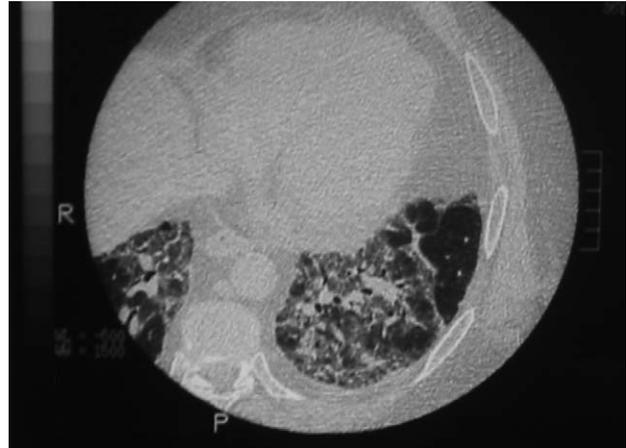


Figure 2. Computed tomography scan of the thorax showing a ground-glass pattern and patchy infiltrates in both lower lobes.

who had been a smoker of 40 cigarettes/d (30 pack-years) but who had quit smoking 8 months earlier. Relevant aspects of his clinical history included psoriasis, psoriatic arthritis, rhinoconjunctivitis, and extrinsic (allergic) asthma with a skin prick test that was positive for grass pollen (for which he had taken immunotherapy over several years, until 12 years previously). He had also had meningitis (no microbiological diagnosis) without sequelae that required admission to the intensive care unit. His symptoms were dry cough and a 1-year history of dyspnea on strenuous exertion (rating of 1 on the Medical Research Council dyspnea scale that had progressed to a rating of 2 during the last 8 months and 3 during the last month). At the time of his visit, he was taking extended-release indomethacin (1 tablet/d) and deflazacort (15 mg/d), which

had been prescribed by the rheumatology service. He had taken methotrexate for more than a year, but had stopped on his own initiative 2 years earlier, and etanercept during the last year, until 15 days before consulting us.

Computed tomography (CT) of the thorax revealed bilateral patches in all lobes, with volume loss, and ground glass patterns in the lung bases (Figure 2). The results of the basic laboratory workup were as follows: 7450 leukocytes/ μ L (46% polymorphonuclear cells, 37.7% lymphocytes, 7% eosinophils); hemoglobin 16.6 g/dL; hematocrit 48.2%; platelets $261 \times 10^3/\mu$ L; erythrocyte sedimentation rate in the first hour 41 mm/h; lactate dehydrogenase 622 U/L; triglycerides 157 mg/dL; cholesterol 202 mg/dL; and C-reactive protein 0.7 mg/dL. The remaining parameters were normal. Baseline arterial gas values were PaO₂ of 78 mm Hg, PaCO₂ of 35.2 mm Hg, pH of 7.43, and HCO₃ of 23.4 mmol/L. The results of lung function tests are shown in the Table. The electrocardiogram showed a sinus rhythm of 90 beats/min, with no signs of overload or repolarization abnormalities. The patient underwent fiberoptic bronchoscopy, which revealed no relevant endoscopic findings, and bronchoalveolar lavage of the middle lobe. Transbronchial biopsy was attempted but had to be interrupted due to patient intolerance and an episode of vomiting. The lavage fluid was negative for malignant cells, but analysis revealed a mixed lymphocyte-predominant inflammatory cell profile (differential cell count: 79% histiocytes, 15% lymphocytes, 4% neutrophils, and 2% eosinophils).

The patient agreed to an open biopsy procedure, and thoracotomy was performed. The diagnosis was advanced chronic interstitial pneumonia. The presence of foamy histiocytes in the septal interstitium indicated that an initial insult could have led to hypersensitivity pneumonitis. The dose of deflazacort was increased to 30 mg/d and he was started on tiotropium (1 inhaled capsule/d) and salbutamol as needed.

Lung function tests were performed again after 2 months. The results are shown in the Table. Oxygen saturation at rest was 94% and the clinical situation

Changes in Lung Function Parameters

	2001 ^a	February 2004 ^b	June 2004 ^b	October 2004 ^c	January 2005 ^c
FVC, mL	3460	2790	2820	2290	1990
FVC, %	74	63	59	47.4	41.3
FEV ₁ , mL	3340	3620	2220	2010	1400
FEV ₁ , %	88	67	59	52.7	36.7
FEV ₁ /FVC, %	96.5	77.07	78.7	87.67	70.12
DLCO					
(mL/min/)				4080	3540
mm Hg					
DLCO, %				39.5	34.3
KCO					
(mL/min/),				1190	1130
mm Hg/L					
KCO, %				73	69.5
TLC, mL				2720	2530
TLC, %				43	39.9
RV, mL				460	670
RV, %				26.5	38.2

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; RV, residual volume; TLC, total lung capacity.

^aNo treatment.

^bTreatment with etanercept.

^cTreatment with indomethacin and deflazacort.

remained unchanged. Pretransplant evaluation (follow-up CT, ultrasound imaging, walk test, serology for the human immunodeficiency and hepatitis viruses, and Mantoux test) was requested at this time. Over a 3-month period, while these tests were being carried out, the patient's dyspnea and general status deteriorated considerably, with the result that he was admitted to hospital, where the remaining tests were performed. The CT scan of the thorax revealed traction bronchiectases in the upper and lower lobes, in addition to signs of activity, especially in the lower lobes. The echocardiogram revealed good contractility with no dilation of the chambers or pulmonary hypertension. Treatment was started with azathioprine at 50 mg/12 h and prednisone at 30 mg/d. Tolerance was good. The patient nevertheless required oxygen at increasingly high flow rates to maintain arterial oxygen saturation above 90%. The doses of azathioprine and intravenous corticosteroids were increased, but respiratory insufficiency became extreme despite oxygen at 100%. He was admitted to the intensive care unit for mechanical ventilation. Treatment was started with boluses of methotrexate, but there was no response. Liver failure developed and the patient died.

Discussion

Pulmonary fibrosis is marked by the presence of cough, dyspnea on exertion, a restrictive pattern in lung function tests, and honeycombing in high-resolution CT (the most characteristic finding). It usually progresses slowly but inexorably, and most patients die of respiratory failure between 3 and 8 years after diagnosis.

Several theories on the origin of pulmonary fibrosis have been posited, including hereditary susceptibility to the disease, fibrosis as a response to viral infection or other lung injury, and immune-mediated inflammation. The last theory might explain the origin of our patient's disease, given that he was diagnosed with diseases involving an immune disorder (psoriatic arthritis and atopy).

Some authors have reported the rare association of plaque psoriasis and common interstitial pneumonia.^{9,10} The clinical course was not fulminant in those cases, however, as it was in the one we report.

The most common side effects described for etanercept are reported to be local skin reactions, headache, and upper respiratory tract infections.⁵ Though very few reports demonstrate a relationship between lung injury and etanercept, frequent upper respiratory tract infections have been reported in clinical trials comparing etanercept with placebo.⁵ Pre-approval clinical trials also detected cases

involving opportunistic infections such as tuberculosis, histoplasmosis, infection by *Pneumocystis jiroveci*, listeriosis, and aspergillosis, thus reflecting the drug's ability to affect the immune system.⁵

Peno-Green et al⁷ report a case in which noncaseating granulomas were observed in a patient diagnosed with rheumatoid arthritis who started treatment with etanercept. The patient showed clear improvement when etanercept was replaced by prednisone. In this case, there was a causal relationship between the drug and the onset of symptoms. The same was true for our patient, who complained of symptoms (dry cough and dyspnea on exertion) almost as soon as he started taking etanercept. However, unlike the case described by the aforementioned authors, when our patient's treatment was suspended there was no clinical, radiographic, or functional improvement whatsoever. On the contrary, his condition worsened rapidly and suddenly.

In the literature we found a single case of pneumonitis that did not respond to withdrawal of the causative agent (gefitinib) or to high doses of corticosteroids.¹¹ Therefore, we think that etanercept could have triggered fibrosis, even though we cannot demonstrate that the patient's condition improved when it was withdrawn, as usually occurs in other cases of pneumonitis due to medication.

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