

## Rapidly Fatal Pulmonary Fibrosis in a Patient with Psoriatic Arthritis Treated with Adalimumab

To the Editor:

Anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) drugs are used with increasing frequency for disorders involving the skin, joints, and gastrointestinal tract. A wide range of adverse effects have been identified among over one million patients treated with this class of drugs<sup>1</sup>. These include bacterial infections, mycobacterial infections, fungal infections, cutaneous malignancies, exacerbations of congestive heart failure, and autoimmune diseases<sup>1,2,3</sup>. In addition, anecdotal reports have linked interstitial lung disease (ILD) and pulmonary fibrosis to etanercept<sup>4</sup>, infliximab<sup>5</sup>, or adalimumab<sup>6,7</sup>. Recently, one study reported no clear pattern of causal relationship of treatment with infliximab and hospitalization for ILD in patients with rheumatoid arthritis (RA)<sup>8</sup>. Another investigation determined that the mortality of RA patients with ILD does not appear to increase with the use of anti-TNF therapy compared to treatment with traditional disease-modifying antirheumatic drugs<sup>9</sup>. We describe a case of pulmonary fibrosis occurring in a patient with psoriatic arthritis treated with adalimumab.

A 31-year-old man in good health and with no medical problems developed psoriatic arthritis and presented to his rheumatologist. When non-steroidal antiinflammatory drugs proved inadequate, he was treated with low-dose prednisone, and adalimumab 40 mg every other week was initiated as the disease-modifying therapy. Before starting therapy with adalimumab a PPD test and screening chest radiograph were both negative. Shortness of breath along with subjective fevers and chills accompanied the third dose and adalimumab was withheld. Suspected pneumonia appeared to resolve with moxifloxacin. Extensive skin disease and disabling pain with swelling of the hands, ankles, and feet recurred during the 2 months without adalimumab. A weekly regimen of adalimumab was resumed. Following 2 doses of adalimumab, he developed headaches, shortness of breath, cough, fevers, and blurred vision leading to hospitalization. A computerized axial tomography scan of the thorax without contrast showed multifocal bilateral patchy areas of consolidation and ground-glass opacity with underlying interstitial prominence, predominantly in the lower lobes and right middle lobe (Figure 1). A wedge resection was performed and the tissue specimen was extensively evaluated for pathogens including bacterial, fungal, and viral etiologies. Microscopic examination of the sample was positive for diffuse interstitial fibrosis



Figure 1. Peripheral and basilar predominant interstitial opacity and pneumomediastinum.

(Figure 2). Rapidly progressive pulmonary fibrosis and death ensued within 1 month while the patient was awaiting lung transplant.

Our case raises concern that adalimumab may have triggered and/or accelerated incipient pulmonary fibrosis. These observations emphasize the conundrum associated with interpreting the role of TNF- $\alpha$  in fibrotic diseases. While some studies have described TNF- $\alpha$  exhibiting profibrotic properties, the majority of *in vitro* studies show antifibrotic effects of TNF- $\alpha$ <sup>10</sup>. Therefore, inhibiting antifibrotic conditions in the lungs with a potent antagonist of TNF- $\alpha$  such as adalimumab could potentially lead to interstitial pulmonary fibrosis in susceptible patients.

Despite the considerable efficacy of TNF- $\alpha$  antagonists in treating a host of disorders, new information regarding the potential side effects associated with this class of drugs continues to emerge. In our case, it remains unclear if an infection, possibly viral, may have triggered a cascade of events leading to pulmonary fibrosis or whether inhibiting TNF- $\alpha$  directly caused the pulmonary fibrosis to develop. This case emphasizes that continuing pharmacovigilance is essential to elucidating the rare risks of a new therapy. Moreover, unpredictable outcomes underscore the need to identify risk factors for pulmonary injury and fibrosis among patients receiving this important class of drugs.

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### REFERENCES

1. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275-85.
2. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol*

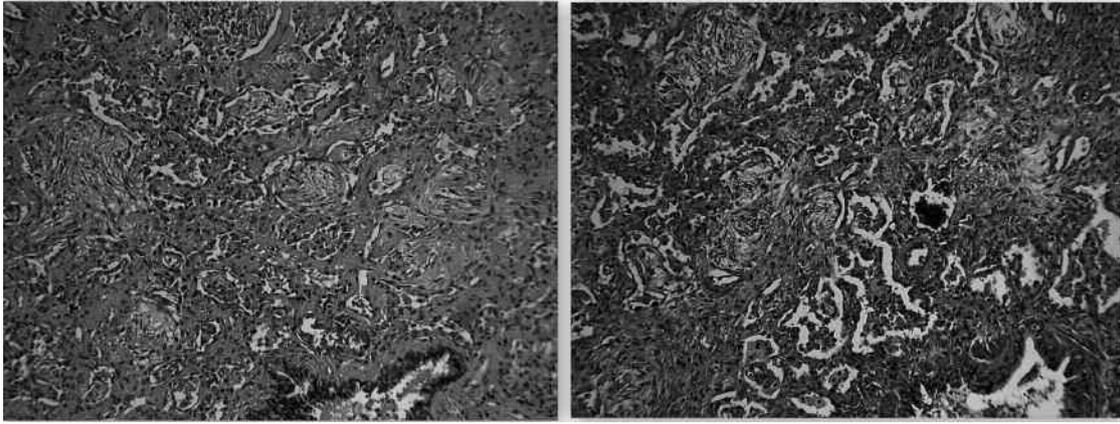


Figure 2. Lung with organizing diffuse alveolar damage with fibroblastic foci (H&E and trichrome stain).

- 2005;32:2130-5.
3. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133-40.
  4. Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. *Respir Med* 2009;103:661-9.
  5. Ostor AJ, Crisp AJ, Somerville MF, Scott DG. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 2004;329:1266.
  6. Huggett MT, Armstrong R. Adalimumab-associated pulmonary fibrosis. *Rheumatology* 2006;45:1312-3.
  7. Schoe A, van der Laan-Baalbergen NE, Huizinga TW, Breedveld FC, van Laar JM. Pulmonary fibrosis in a patient with rheumatoid arthritis treated with adalimumab. *Arthritis Rheum* 2006;55:157-9.
  8. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. *Scand J Rheumatol* 2007;36:172-8.
  9. Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2010;69:1086-91.
  10. Distler JH, Schett G, Gay S, Distler O. The controversial role of tumor necrosis factor alpha in fibrotic diseases. *Arthritis Rheum* 2008;58:2228-35.

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