Etanercept-Induced Pneumonitis: Severe Complication of Tumor Necrosis Factor-Alpha Blocker Treatment

Abdulla Watad MD[1,2], Marina Perelman MD[3], Ribhi Mansour MD[2], Yehuda Shoenfeld MD FRCP MaACR[1,4] and Howard Amital MD MHA[1,2,4]

[1]Zabludowicz Center for Autoimmune Diseases, [2]Department of Medicine B, and [3]Pulmonary and Mediastinal Pathology Unit, Department of Pathology, Sheba Medical Center, Tel Hashomer, Israel

[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: etanercept, tumor necrosis factor (TNF) inhibitors, pneumonitis, interstitial lung disease (ILD), rheumatoid arthritis (RA)

IMAJ 2015; 17: 000–000

Tumor necrosis factor-alpha (TNFα) is a pleomorphic cytokine with both immune and non-immune biologic effects. The past decade has witnessed a vast increase in our understanding of TNFα biology, resulting in the widespread use of several TNF inhibitors (TNFi) for the treatment of rheumatoid arthritis (RA) and other rheumatic diseases. However, we acknowledge that TNFi may have a variety of adverse effects. Aside from infectious pulmonary complications, which have been extensively reviewed, non-infectious complications of TNFi have only recently been recognized. We report the case of a patient with RA who developed pneumonitis following treatment with etanercept.

PATIENT DESCRIPTION

A 63 year old, non-smoking, woman presented with dry cough and intermittent dyspnea that had persisted for 4 months. She had a 10 year history of RA, hypertension and diabetes mellitus type 2 and had been treated with methotrexate (MTX) at a dose of 7.5 mg weekly, prednisone 5 mg/day, atenolol 50 mg/day, aspirin 100 mg/day, insulin glargine 73 IU/day, and metphormin 850 mg twice daily. Her disease activity was not adequately controlled with this treatment and entanercept 50 mg weekly was initiated 16 weeks before presentation. Following treatment with etanercept, her arthritic symptoms abated and laboratory parameters such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) normalized. About 3 months prior to her presentation, she developed dyspnea and a dry cough.

On admission, her physical examination revealed swelling and tenderness of the metacarpophalangeal joints in her hands and knees, fine wheezes on the right lower lobe of the lung, absence of heart murmurs, bilateral moderate edema in her legs, fever of 39°C, 85% hemoglobin saturation (SPO2) in room air and 94% with oxygen supplement, respiratory rate 30, heart rate 71, and speech dyspnea associated with recruitment of the accessory respiratory muscles. Laboratory studies showed a white cell count of 8600/μl (81% of neutrophils), lactate dehydrogenase 376 IU/L and CRP 173 mg/L. Other common blood chemistries were within normal limits. Chest X-ray [Figure 1A] revealed bilateral interstitial infiltrates, enhanced on the right side. A chest computed tomography demonstrated ground-glass opacities with bilateral peripheral consolidations [Figure 1B].

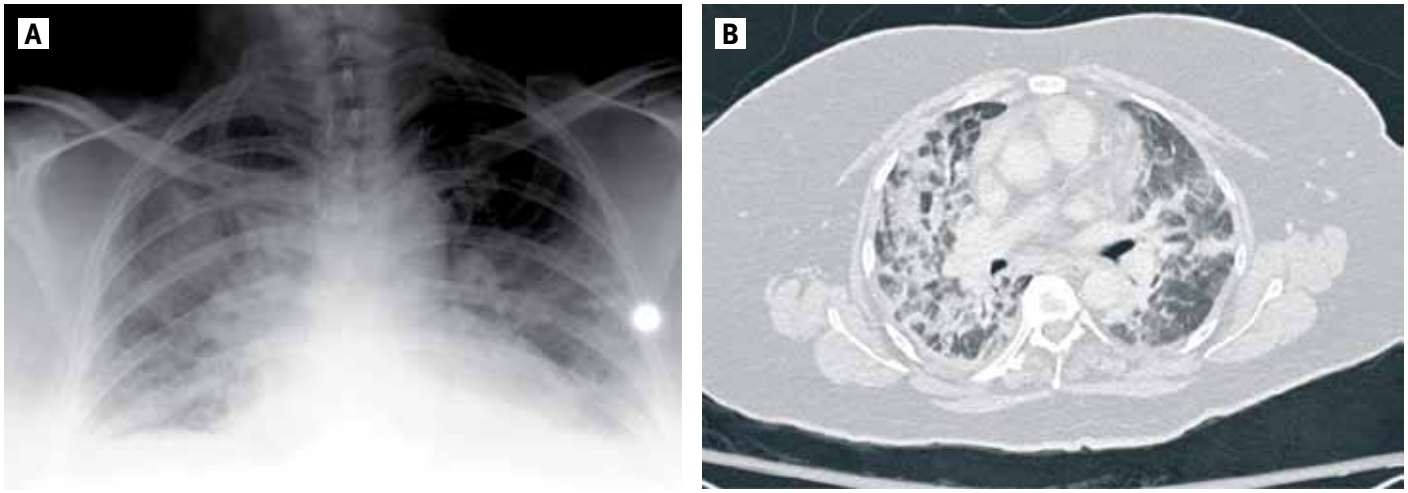
Serology tests for human immunodeficiency virus and cytomegalovirus were also negative. Bronchoscopy with bronchoalveolar lavage was performed and was negative for *Pneumocystis jiroveci*. Echocardiogram did not reveal significant pathological findings. Video-assisted thoracoscopic surgery biopsy of lung [Figure 2] demonstrated diffuse homogenous thickening of the alveolar septae with chronic inflammatory infiltrate, associated with reactive hyperplasia of type II pneumocytes. Some of the alveolar spaces contained fibrin, partially with organizing fibrin. Occasional hyaline membranes were seen. No microorganisms were identified on periodic acid-Schiff, Grocott methenamine-silver, Gram or Ziehl-Neelsen stains. Immunohistochemical stains for Pneumocystis and cytomegalovirus were negative. The above morphological findings were compatible with a cellular-type non-specific interstitial pneumonia pattern, associated with features of acute and organizing diffuse alveolar damage. These morphological patterns of lung injury can be seen in autoimmune diseases, lung drug toxicities, and infections.

Treatment with ceftriaxone and azithromycin was initiated, and cotrimoxazole was later added for *Pneumocystis jiroveci* pneumonia. Since there was no improvement with the antibiotic regimen, the dosage of steroid treatment was increased. Despite the high dose of steroids, the patient continued to deteriorate and become hypoxic despite oxygen supplement, without any improvement using an oxygen reservoir mask or BIPAP. The patient was intubated and transferred to the intensive care unit.

COMMENT

Drug-induced interstitial lung disease (ILD) has been reported in the past as a rare but severe adverse effect of disease-modifying antirheumatic drugs (DMARDs) such as gold and MTX. A meta-analysis of 21 studies with 8276 RA patients conducted by

Figure 1. [A] Enlarged cardiac silhouette with bilateral pulmonary interstitial infiltrates, enhanced primarily on the right side. **[B]** Chest computed tomography demonstrating ground-glass opacities with multiple bilateral peripheral consolidations



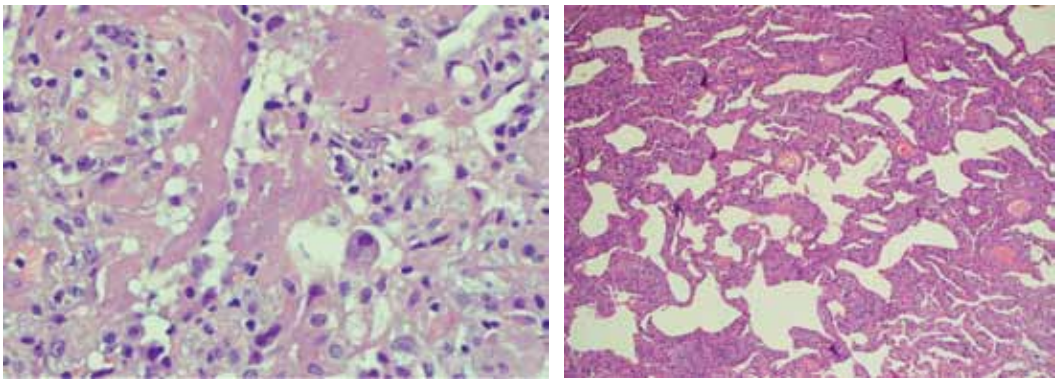


Figure 2. [A] Diffuse thickening of interstitium by chronic inflammatory infiltrate (Hematoxylin & eosin x 100). **[B]** Higher magnification showing hyaline membranes (H&E x 400)

Conway et al. [1] for the period 1990–2011 showed that MTX was not associated with an increased risk of total adverse respiratory events and there was no difference in the risk of pulmonary death among MTX-treated RA patients. However, they found an increased risk of pneumonitis among MTX-treated patients (relative risk 7.0, 95% confidence interval 1.57–31.05). Treatment of such events consisted of drug cessation and sometimes the addition of corticosteroids especially in patients who remain symptomatic following MTX withdrawal.

The general prognosis of MTX-induced acute and subacute lung toxicity is usually favorable. Some patients present with subsequent respiratory failure. A review of 123 published cases of MTX-induced pneumonitis, including 62 RA cases, demonstrated a mortality rate of 13% secondary to respiratory disease [1]. A total of 122 cases of new onset (62%) or exacerbation (38%) of ILD secondary to treatment of systemic autoimmune diseases with biological drugs were collected and analyzed by the BIOGEAS registry project [2]. The underlying disease was RA in 89% of the patients, but cases also occurred in patients with inflammatory bowel disease, ankylosing spondylitis, psoriatic arthritis and other rheumatic diseases [2]. Except for five cases that emerged during rituximab treatment, all the patients were treated with anti-TNF, with etanercept and infliximab each accounting for almost 50% of cases while only 3 cases were associated with adalimumab. Interestingly, two-thirds of the patients had used MTX in the past but only 16% were current users. Only a few ILD cases among patients undergoing therapy with adalimumab have been described [3]. In addition, a patient with RA who had received tocilizumab for 8 months experienced a fatal acute exacerbation of ILD [4].

Post-marketing surveillance studies in Japan indicated that the frequencies of drug-related ILD in Japanese RA patients treated with infliximab or etanercept were 0.5% and 0.6%, respectively [5]. In accordance with findings in TNF antagonist-naïve RA patients, men were affected by ILD twice as frequently as women. ILD is also a frequent extraarticular complication

of RA, and it is unclear whether treatment with TNF antagonists truly raises the risk of such occurrences developing. Very few cases of ILD have been reported in anti-TNF-treated patients with ankylosing spondylitis, which is less often associated with ILD. Several reports underlined the occurrence of ILD in the first months following initiation of anti-TNF therapy, which strongly suggests a causal link [2,3,5].

In this report we describe a patient with RA without known extra-articular involvement who presented with an acute pulmonary disease following initiation of therapy with etanercept. Given the increasing use of biological therapy, we believe that clinicians should be alert to this association and learn to recognize it early in the disease. The literature stresses that early intervention results in better chances of survival.

Correspondence

Dr. A. Watad

Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-2435

Fax: (972-3) 535-4796

email: watad.abdulla@gmail.com

References

1. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis – a meta-analysis of randomized controlled trials. *Arthritis Rheum* 2014; 66: 803-12.
2. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011; 41: 256-64.
3. Komiya K, Ishii H, Fujita N, et al. Adalimumab-induced interstitial pneumonia with an improvement of pre-existing rheumatoid arthritis-associated lung involvement. *Intern Med* 2011; 50: 749-51.
4. Kawashiri SY, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheumatol Int* 2012; 32: 4023-6.
5. Takeuchi T, Tatsuki Y, Nogami Y, et al. Post-marketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 189-94.