

## Case report

Distinct immunologic and radiographic patterns in etanercept-induced lung injury<sup>☆</sup>Karina Serban<sup>a,\*</sup>, Michael Muzoora<sup>a</sup>, Chadi A. Hage<sup>a</sup>, Tim Lahm<sup>a,b</sup><sup>a</sup>Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Occupational Medicine, Indiana University School of Medicine, 1481 W. 10th Street, VA 111P-IU, Indianapolis, IN 46202, USA<sup>b</sup>Roudebush VA Medical Center, Indiana University School of Medicine, Indianapolis, IN, USA

## ARTICLE INFO

## Article history:

Received 16 September 2012

Received in revised form

3 December 2012

Accepted 11 December 2012

## Keywords:

TNF- $\alpha$  antagonist

Lymphocytic alveolitis

Sarcoid-like reaction

Hypersensitivity pneumonitis

Bronchoalveolar lavage

## ABSTRACT

Nonspecific clinical presentation of non-infectious, immune-mediated pulmonary complications of etanercept therapy makes the diagnosis difficult. While bronchoalveolar lavage fluid (BALF) cell analysis is frequently used in diagnosing drug-induced lung disease, BALF patterns in etanercept-induced lung injury (EILI) are not well established. Furthermore, previous reports of EILI diagnosis relied on trans-bronchial or surgical lung biopsies. Here, we report two patients who developed pulmonary toxicity after etanercept treatment. Both patients were diagnosed with EILI. While one patient presented with CD4<sup>+</sup>-predominant lymphocytic alveolitis (consistent with a sarcoid-like pattern), the other patient exhibited a CD8<sup>+</sup>-predominant pattern (consistent with hypersensitivity pneumonitis-like reaction). The different BAL patterns were accompanied by distinct radiographic findings. Both patients significantly improved after etanercept discontinuation and corticosteroid initiation. We propose that EILI can present with distinct immunologic and radiographic phenotypes. In addition, early BALF analysis with lymphocyte immunophenotyping can further define the underlying immunologic abnormalities, and thereby, avoid more invasive procedures.

© 2012 Elsevier Ltd. Open access under [CC BY-NC-ND license](http://creativecommons.org/licenses/by-nc-nd/4.0/).

## 1. Introduction

Etanercept, a dimerized protein of the extracellular portion of the human TNF- $\alpha$  receptor fused to the Fc portion of human IgG1, is considered to be less immunogenic than other TNF- $\alpha$  antagonists.<sup>1</sup> Nevertheless, with increased use of this drug in recent years, several immune-mediated adverse effects have been described. However, the mechanisms of pulmonary complications are incompletely understood.

Bronchoalveolar lavage (BAL) is widely used in the evaluation of immunosuppressed patients with respiratory abnormalities, and allows for analysis of lung injury patterns in drug-induced lung

disease.<sup>2</sup> However, very few data exist about BAL cellular analysis in etanercept-induced lung injury (EILI). Knowledge of BAL patterns in EILI may allow for a better understanding of underlying pathogenic processes in this disease. We present two cases of EILI in which BAL cellular analysis with immunophenotyping 1) helped identify distinct pathogenic mechanisms and 2) provided guidance for treatment without a need for tissue biopsy.

## 2. Case reports

## 2.1. Case 1

A 59-year-old white male with psoriasis and psoriatic arthritis presented with a one-month history of progressive dyspnea, fatigue, subjective fever, and night sweats. He was a former smoker and denied sick contacts, occupational/recreational exposure, or travel outside the Midwest. He had no history of lung disease. Prior therapy with methotrexate and oral corticosteroids was stopped due to side effects. He was switched to weekly etanercept (50 mg subcutaneously) 1.5 years prior to presentation, with good control of his rash and arthritis. Physical examination revealed hypoxemia (88–89% on 3 L O<sub>2</sub>) and bilateral fine crackles. There were no clinical features consistent with an articular or skin flare. Chest CT

**Abbreviation list:** EILI, etanercept induced lung injury; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; BAL, bronchoalveolar lavage; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; CT, computer tomography; GGO, ground glass opacities; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; COP, cryptogenic organizing pneumonia; RA, rheumatoid arthritis; VATS, video assisted thoracic surgery.

<sup>☆</sup> Case 2 presented at ATS in Denver, Colorado, on Wednesday, 05/18/2011.

\* Corresponding author. Tel.: +1 317 948 3808; fax: +1 317 948 3824.

E-mail addresses: [kserban@iupui.edu](mailto:kserban@iupui.edu) (K. Serban), [muzooram@iupui.edu](mailto:muzooram@iupui.edu) (M. Muzoora), [chage@iupui.edu](mailto:chage@iupui.edu) (C.A. Hage), [tlahm@iupui.edu](mailto:tlahm@iupui.edu) (T. Lahm).

showed diffuse nodular and reticular interstitial opacities, bibasilar tree-in-bud opacities, and mediastinal lymphadenopathy (Fig. 1). Serum, urine and BAL testing for bacterial, viral, fungal, and mycobacterial infections, and tuberculin skin testing were negative. Spirometry showed a mild obstructive ventilatory defect and moderately decreased diffusing capacity (Table 1). BAL cell analysis revealed a CD4<sup>+</sup>-predominant lymphocytic alveolitis (Table 2). A presumptive diagnosis of EILI was made. Etanercept was stopped. Short term prednisone (0.5 mg/kg/day) was started with prompt resolution of symptoms and improvement in spirometry.

## 2.2. Case 2

A 56-year-old white male with rheumatoid arthritis (RA) and associated mild pulmonary fibrosis (minimal basilar involvement stable over several years) was referred for dyspnea, dry cough, decreased exercise tolerance, and hypoxemia. Due to progression of extra-pulmonary RA symptoms on prednisone (5 mg/day), hydroxychloroquine (200 mg twice/day), and sulfasalazine (1000 mg twice/day), the latter two were stopped, and etanercept 50 mg subcutaneously weekly was added to the steroids four months before presentation. Joint symptoms rapidly resolved and the RA was under control as determined by the rheumatologist. However, the patient then developed increasing dyspnea with exertion. Spirometry demonstrated worsening restrictive defect (Table 1) since a prior study 6 months ago. Chest CT (Fig. 2) revealed increasing ground glass opacities (GGOs) and worsening interstitial infiltrates. Bacterial, viral, fungal or mycobacterial infections were ruled out. BAL revealed a CD8<sup>+</sup>-predominant lymphocytic alveolitis (Table 2), thought to represent etanercept-induced hypersensitivity pneumonitis. Etanercept was discontinued and prednisone increased to 30 mg/day.

**Table 1**  
Pulmonary function tests.

	Patient 1		Patient 2	
	At diagnosis	At follow-up (8 weeks)	At diagnosis	At follow-up (8 weeks)
FEV <sub>1</sub> L, (% predicted)	2.56 (85)	2.74 (91)	2.12(62) (L)	<b>2.40 (73)</b> (baseline)
FVC L, (% predicted)	4.31 (108)	4.42 (111)	2.75(61) (L)	<b>3.11 (77)</b> (baseline)
DLCO (% predicted)	54 (L)	<b>86 (N)</b>	n/a	n/a

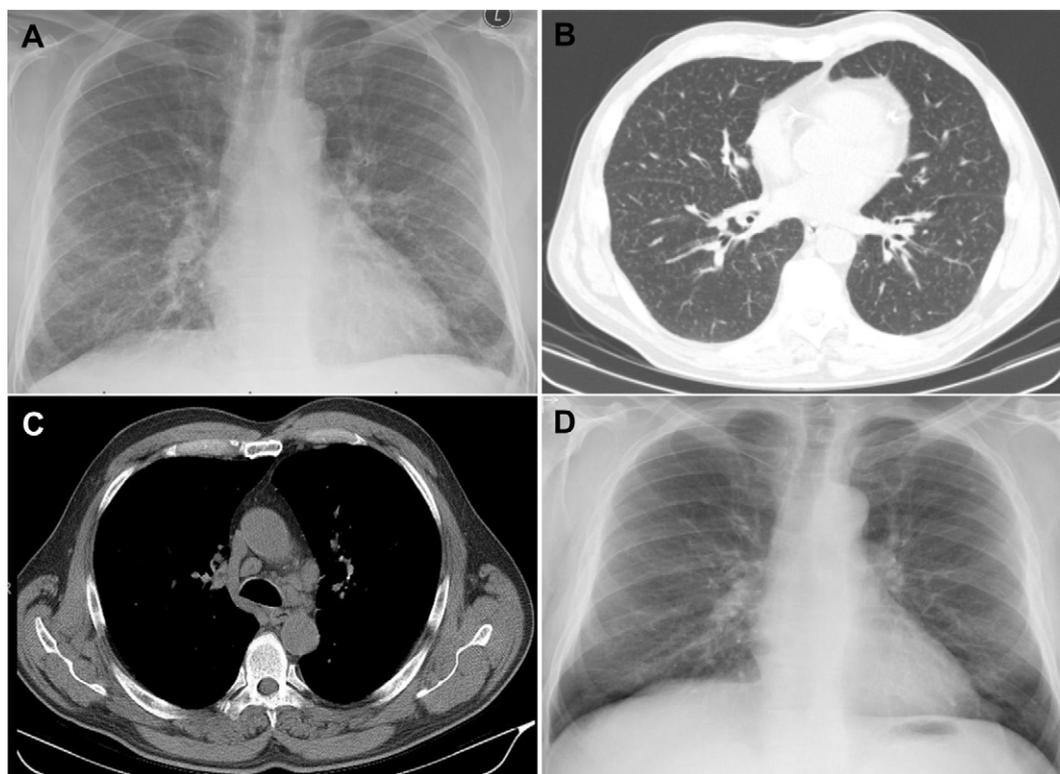
**Table 2**  
Bronchoalveolar lavage cell analysis.

BAL fluid analysis	Normal values	Patient 1	Patient 2
Total cells	13 ± 2 × 10 <sup>4</sup>	345 × 10 <sup>4</sup>	960 × 10 <sup>4</sup>
% Macrophages	85 ± 1.6	64	59
% Neutrophils	1.6 ± 0.7	1	2
% Eosinophils	0.19 ± 0.06	0	3
% Lymphocytes	1.5 ± 2.5	35	36
% CD4:CD8	2.2 ± 0.3	<b>2.56 (H)</b>	<b>0.15 (L)</b>

The patient rapidly improved, with return to baseline lung function (Table 1) and chest CT findings within 8 weeks.

## 3. Discussion

We report two cases of EILI presenting with different BAL immunologic and radiologic patterns. Patient 1 presented with a CD4<sup>+</sup>-positive lymphocytic alveolitis, interstitial opacities, and mediastinal lymphadenopathy. In the face of negative infectious work-up (BAL fluid cytological and microbiologic analysis, fungal



**Fig. 1.** Radiographs of patient 1. (A) Chest X-ray (CXR) at presentation shows diffuse bilateral micronodular disease. (B, C) Chest CT at presentation shows bilateral nodular and reticular interstitial opacities, tree-in-bud opacities, mediastinal lymphadenopathy. In conjunction with the findings of a CD4<sup>+</sup>-predominant lymphocytic alveolitis, a diagnosis of etanercept-induced sarcoid-like reaction was made, and treatment with corticosteroids was initiated. (D) CXR at follow-up (6 weeks) shows resolution of diffuse micronodular opacities.



**Fig. 2.** Radiographs of patient 2. (A) Chest CT at baseline shows bibasilar micronodular disease with patchy GGO. (B) Chest CT at presentation shows worsening bilateral GGO and reticulo-nodular opacities. In conjunction with the findings of a CD8<sup>+</sup>-predominant lymphocytic alveolitis, a diagnosis of etanercept-induced hypersensitivity pneumonitis was made, and corticosteroid dose was increased. (C) Chest CT at follow-up (8 weeks) revealed resolution of ground glass opacities, persistent subpleural micronodular opacities.

serology, tuberculin skin test), exclusion of psoriasis flare up (no skin or musculoskeletal findings), and lack of exposure to other medications with potential pulmonary side effects (discontinuation of methotrexate > 1.5 years), the clinical presentation was most suggestive of a sarcoid-like syndrome.

Patient 2 exhibited a CD8<sup>+</sup>-positive lymphocytic alveolitis with GGOs and reticulo-nodular infiltrates suggestive of a hypersensitivity pneumonitis-like reaction. We reached this diagnosis by excluding possible bacterial or granulomatous infections (BAL fluid cytological and microbiologic analysis, fungal serology); exacerbation of the pre-existing pulmonary fibrosis (clinically controlled RA; stable CT and PFTs before introduction of etanercept; BAL fluid cellular analysis not suggestive of UIP/NSIP/COP, the common presentations of RA-related pulmonary fibrosis), and medication-induced lung disease (discontinuation of sulfasalazine and hydroxychloroquine > 4 months).

While the radiographic features of our patients are in agreement with the published literature,<sup>3–5</sup> BAL patterns in EILI are not well defined. In fact, only one case of CD8<sup>+</sup> alveolitis associated with EILI is reported.<sup>3</sup> Interestingly, we did find two reports of CD4<sup>+</sup>-positive lymphocytic alveolitis in EILI. However, both patients underwent further invasive diagnostic biopsies (transbronchial or VATS) before treatment with systemic steroids was started.<sup>6,7</sup>

Our report emphasizes that EILI can present with distinct BAL immunologic patterns. We speculate that a sarcoid-like reaction (patient 1) and a hypersensitivity pneumonitis-like reaction (patient 2) represent two different, but steroid-sensitive, manifestations of EILI. Interestingly, paradoxical granulomatous reactions have been described before in patients receiving etanercept. These reactions appear to be more common in patients with underlying RA or psoriasis (as seen in our patients). A potential explanation is less robust TNF binding and quicker TNF release<sup>8</sup> by etanercept than with other anti-TNF- $\alpha$  monoclonal antibodies. Subsequently the residual TNF- $\alpha$  activity induces CD4<sup>+</sup> Th1-cells activation and increases production of IFN- $\alpha$ . The elevated IFN- $\alpha$  unopposed by an optimal TNF- $\alpha$  activity enhances the survival and proliferation of CD8<sup>+</sup> blasts<sup>9</sup> and IFN- $\gamma$  secretion from NK cells.<sup>10</sup> In the presence of Th1 environment IFN- $\gamma$  is a key event in granuloma formation.<sup>11</sup> An excess of various interferon ( $\alpha$  and  $\gamma$ ) activity, a TNF- $\alpha$ -induced Th1 environment combined with increased susceptibility to airborne antigens may explain paradoxical pulmonary CD4<sup>+</sup> or CD8<sup>+</sup> granulomatous reaction seen in EILI.<sup>12</sup>

In previously reported EILI cases, the diagnosis was established via open lung or transbronchial biopsies; BAL fluid analysis was used only to exclude infectious causes. Our report suggests that analysis of BAL cell differential and lymphocyte subtyping may obviate the need for tissue biopsy in EILI, and thereby, allows for targeted therapy while avoiding the potential complications of a more invasive procedure.

In conclusion, EILI can present with CD4<sup>+</sup>- or CD8<sup>+</sup>-positive lymphocytic alveolitis and distinct radiographic patterns, possibly representing a sarcoid or a hypersensitivity reaction phenotype. In either case, BAL cellular analysis may allow for correct diagnosis and initiation of steroid therapy without a need for tissue biopsy.

#### Financial/non financial disclosure

None.

#### Conflict of interest statement

I hereby disclose all of my conflicts of interest and other potentially conflicting interests, including specific financial interests and relationships and affiliations relevant to Respiratory Medicine Case Reports Journal (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or stock options, expert testimony, royalties, or patents filed, received, or pending) as well as other forms of conflict of interest, including personal, academic and intellectual issues.

I also agree that I will promptly notify the Editor in Chief in writing about any additional potential conflicts of interests that occur.

#### References

- Anderson PJ. Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005;**34**:19–22.
- Costabel U, Uzaslan E, Guzman J. Bronchoalveolar lavage in drug-induced lung disease. *Clin Chest Med* 2004;**25**:25–35.
- Oggenovski VM, Ojo TC, Fox DA. Etanercept-associated pulmonary granulomatous inflammation in patients with rheumatoid arthritis. *J Rheumatol* 2008;**35**:2279–82.
- Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011;**41**:256–64.
- Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. *Respir Med* 2009;**103**:661–9.
- Farah RE, Shay MD. Pulmonary sarcoidosis associated with etanercept therapy. *Pharmacotherapy* 2007;**27**:1446–8.
- Ishiguro T, Takayanagi N, Kurashima K, Matsushita A, Harasawa K, Yoneda K, et al. Development of sarcoidosis during etanercept therapy. *Intern Med* 2008;**47**:1021–5.
- Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002;**301**:418–26.
- Marrack P, Kappler J. Control of T cell viability. *Annu Rev Immunol* 2004;**22**:765–87.
- Gough DJ, Messina NL, Clarke CJ, Johnstone RW, Levy DE. Constitutive type I interferon modulates homeostatic balance through tonic signaling. *Immunity* 2012;**36**:166–74.
- Fiorentino DF. The Yin and Yang of TNF- $\alpha$  inhibition. *Arch Dermatol* 2007;**143**:233–6.
- Pink AE, Fonia A, Smith CH, Barker JN. The development of sarcoidosis on antitumor necrosis factor therapy: a paradox. *Br J Dermatol* 2011;**163**:648–9.