Pulmonary complications of tumor necrosis factor-targeted therapy

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SYNOPSIS

Tumor necrosis factor (TNF)-targeted therapies are increasingly being prescribed in the management of a variety of inflammatory and autoimmune diseases. The use of this class of medications also pose risks of developing an assortment of pulmonary side effects including infections (TB, bacterial, and fungal infections), pulmonary nodules, chronic pneumonitis/fibrosis, SLE-like reactions, vasculitis, and exacerbations of underlying lung disease. In addition to surveillance for tuberculosis prior to initiation of TNF-targeted therapy, a high level of vigilance should be maintained during administration for infectious and non-infectious complications, even years into a patient’s course. The available evidence argues for caution in using these agents in patients with pre-existing lung disease and heightened suspicion of accelerated nodule formation in those with pre-existing rheumatoid nodules. Management centers on excluding infection, identifying confounders (especially methotrexate or pre-existing lung disease), and promptly discontinuing TNF-targeted therapy. In some instances, invasive procedures (e.g. bronchoscopy or VATS lung biopsy) will be necessary to establish the proper diagnosis, and the administration of steroids may be beneficial.

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Tumor necrosis factor (TNF)-targeted therapy provides disease-modifying treatment and relief to patients suffering from rheumatoid arthritis, inflammatory bowel disease, and other autoimmune conditions. A growing number of applications are being explored, including steroid-refractory asthma. The increasing frequency of use of these therapies has been accompanied by a growing number of reported side effects, with reactivation of tuberculosis as the most widely acknowledged. We set out to review the infectious and non-infectious pulmonary complications of TNF-targeted therapy by highlighting five patients seen at our institution. A MEDLINE search was conducted using the terms "anti-TNF therapy and pulmonary," and "infliximab, etanercept, or adalimumab and pulmonary."

**Case 1**

A 69-year-old female with overlap syndrome (rheumatoid arthritis, secondary Sjögren's syndrome, cutaneous discoid lupus) was admitted with several days of fever, mental status change, sore throat, history of cough and dyspnea. She was treated for community-acquired pneumonia with ceftriaxone and azithromycin but rapidly deteriorated over the next 24 h requiring transfer to the intensive care unit for hypoxic respiratory failure and shock.

She had been prescribed methotrexate for over a year and had recently started etanercept for polyarthritis. Her serologies while in the intensive care unit included a positive anti-nuclear antibody of 1:40–80 (as high as 1:1280 in the past), rheumatoid factor 39 IU/ml, and low C4 complement level. Anti-ssA/Anti-Ro, anti-cyclic citrullinated peptide (anti-CCP), Scl-70, U1RNP antibodies were negative.

A computed tomography (CT) angiogram of the chest revealed no pulmonary embolism but did show severe pulmonary edema, diffuse ground glass opacities, focal consolidation of the right upper lobe along with upper lobe emphysema and moderate bilateral pleural effusions. Her prior chest CT was noted to have upper lobe emphysema and mild basilar reticular markings consistent with fibrosis (Fig. 1A–D). Infectious workup including 2 bronchoalveolar lavages (BAL), a thoracentesis and serologic studies were unremarkable. A video-assisted thoracic surgical (VATS) biopsy revealed findings consistent with subacute interstitial lung disease. The presumptive diagnosis was etanercept-induced pulmonary toxicity vs. exacerbation of pre-existing interstitial lung disease. The patient was treated with methylprednisolone (1 g IV daily for 3 days) followed by a slow taper of prednisone over the next 2 months with dramatic improvement in her clinical picture (weaned off mechanical ventilation after 3 days) and resolution of her infiltrates over the next month. At the time of manuscript submission, she remains asymptomatic from a cardiopulmonary standpoint while on prednisone 10 mg daily and rituximab for her rheumatoid arthritis.

**Case 2**

A 57-year-old female with a history of tobacco use, asthma and psoriasis presented to pulmonary clinic with 3 months of cough and dyspnea on exertion. She had been taking etanercept for the past 6 months for psoriatic rash with good control of her symptoms. She denied sick contacts, chest discomfort, fevers, chills, or night sweats. She had not started any new medications besides etanercept in the past year and denied environmental or occupational exposures.

Her physical exam was remarkable for exercise desaturation, diffuse wheezing, lack of accessory muscle use, and absence of rash. Spirometry revealed severe obstruction
without significant reversibility after bronchodilator administration. Chest CT done in the month prior to presentation revealed scant areas of nodular opacities in the right and left upper lobes. The patient was prescribed oxygen and inhaled corticosteroid, long-acting beta-agonist, and anticholinergic. IgE level, α-1-antitrypsin level, quantitative immunoglobulins, sputum for acid fast bacilli were non-diagnostic.

Her cough resolved after discontinuation of etanercept but was thought to be potentially related to infection. Reintroduction of etanercept for flare of her psoriasis was followed by reoccurrence of cough and hypoxia. She was given a presumptive diagnosis of etanercept-induced bronchiolar disease. Her cough and hypoxia completely resolved after discontinuation of etanercept.

Case 3

A 43-year-old female with rheumatoid arthritis of 25 years duration complicated by subcutaneous nodules, pulmonary nodules, Sjögren’s syndrome and Raynaud’s phenomenon presented to pulmonary clinic with a minimally productive cough for 2 years and progressive dyspnea on exertion over the past year. Her arthritic symptoms involving the joints of her hands, feet, wrists, and ankles were well-controlled over this time with infliximab, methotrexate, and plaquenil. She denied tobacco use or constitutional symptoms. Her physical examination was notable for a comfortable appearing woman with prolonged expiratory phase, peripheral cyanosis, and a subcutaneous nodule over the extensor surface of her left upper extremity.

Pulmonary function tests (PFTs) were notable for a moderate fixed obstructive defect, hyperinflation and air-trapping. High resolution chest CT revealed air-trapping, bronchiolar infiltrates throughout the upper and lower lung zones with micronodules unchanged in size from a year prior.

Over the next 6 weeks her symptoms failed to improve on inhaled corticosteroid and long-acting β-agonist. Sputum for acid-fast bacilli and screen for α-1-antitrypsin

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**Figure 1** Case 1. A 69-year-old female with rheumatoid arthritis, Sjögren’s syndrome receiving methotrexate and etanercept was admitted and subsequently intubated for hypoxemic respiratory failure. Chest CT images 2 years prior to illness (A, B) and during admission (C, D) are shown for comparison. In C and D there has been interval development of patchy alveolar infiltrates (arrows), pleural effusions, and compressive atelectasis.

**Figure 2** Case 1. Lung parenchyma with reactive pneumocytes, interstitial inflammatory infiltrate and macrophages within alveolar spaces.
deficiency were negative. VATS lung biopsy revealed organizing granulomatous inflammation (Fig. 3). Tissue stains and cultures were negative. A presumptive diagnosis of infliximab-induced granulomatous inflammation was made. Her symptoms improved after discontinuation of infliximab.

Case 4

A 58-year-old female with rheumatoid arthritis, Sjögren’s syndrome and allergic rhinitis presented with 5 months of non-productive cough. She denied wheezing, dyspnea on exertion, constitutional symptoms, chest pain, reflux or post-nasal drip. She had a minimal smoking history and denied any relevant occupational or environmental exposures.

She had been treated with methotrexate for 15 years prior to its discontinuation close to 8 years ago. Over the past 9 years, she had been taking etanercept with good control of her joint pain. Her physical examination was remarkable for basilar crackles.

Her PFTs were within normal limits. However, her laboratory studies were remarkable for an elevated erythrocyte sedimentation rate, rheumatoid factor, and anti-cyclic citrullinated peptide (>60 U/ml). Chest CT showed progression of bronchiolar infiltrates and bronchiectasis most prominent in the middle and lower lung fields over the past year (Fig. 4). There were no pleural effusions, lymphadenopathy, or cystic changes. A VATS lung biopsy revealed chronic lymphocytic bronchiolitis with non-necrotizing granulomatous inflammation. All infectious and immune studies of lung tissue were negative. A presumptive diagnosis of etanercept-induced granulomatous bronchiolitis was made and etanercept was discontinued. Her symptoms, physical examination findings, and radiographic abnormalities subsequently resolved and did not recur after administration of adalimumab.

Case 5

A 63-year-old male with seronegative rheumatoid arthritis and myelodysplastic syndrome presented with 9 months of progressive dyspnea. His joint symptoms were well controlled on etanercept (25 mg subcutaneously twice a week) over the past 5 years. He also complained of pleuritic chest pain and infrequent dry cough. He denied fevers, chills, recent travel, or change in medication. His examination was remarkable for room air saturation of 94%, lack of crackles, wheeze, or accessory muscles of respiration use. Pulmonary function tests were notable for a moderate restrictive defect and reduced diffusion capacity. Chest CT revealed mosaic attenuation (Fig. 5). The patient underwent bronchoscopy with transbronchial biopsies revealing bronchial tissue with non-caseating granulomatous and chronic inflammation (Fig. 6A–B). Tissue stains and cultures were negative for
infection. Four weeks after discontinuation of etanercept, the patient continued to have shortness of breath. The patient’s shortness of breath and CT findings resolved with initiation of prednisone.

Role of TNF and potential mechanisms of TNF-targeted therapy

Tumor necrosis factor mediates numerous biologic effects, including fever, shock, tissue inflammation and increase in acute phase proteins. Three FDA-approved anti-TNF therapies are available in the United States (see Table 1). The different mechanisms of these drugs may lend rationale to different defects in response to infection and side effects.

Tumor necrosis factor is produced as a type 2 transmembrane protein and subsequently cleaved from the cell surface by TNF converting enzyme. Both membrane-bound and soluble TNF can bind and activate the p55 TNF receptor (TNFR1) and the p75 TNF receptor (TNFR2). In addition, the TNFRs can be released from the cell surface and bind TNF, acting either as agonists or antagonists of TNF biologic activity. TNFR1 activation is associated with cytotoxicity, cell adhesion molecule expression, cell growth inhibition, stimulation of cytokine and chemokine production, apoptosis, tissue damage and repair, and germinal center formation. TNFR2 activation is associated with skin necrosis, T cell proliferation, apoptosis and thymocyte proliferation. TNFR1 activation induces NF-κB, providing an anti-apoptotic signal.

TNF also plays a key role in response to infection. In the response to bacteria, TNFR1 mediates the activation, recruitment, and functional efficacy of immune cells and the formation of granuloma. Both TNFR1 and TNFR2 play a role in not only the control of viral and protozoal infections via apoptosis, but also the pathology associated with these infections. TNFR1 and to a lesser extent, TNFR2 control candidal infection.

Whereas the role of TNF in response to infection is well characterized, the mechanisms underlying non-infectious complications arising from TNF-targeted therapy are not established. Mouse models of TNF blockade have revealed that the p55 TNF receptor (TNFR1) is the primary receptor in vivo. What has been difficult to reconcile is the role of TNF in tumor development and anti-tumor immunity in the appropriate setting. The p75 TNF receptor (TNFR2) has more limited expression; TNFR2 knockout mice display abnormal necrosis in response to TNF. TNFR2 can enhance TNFR1 induced apoptosis and may also play a limited role in adaptive immunity. While TNF plays an important role in T cell activation via recruitment and activation of antigen-presenting cells, TNF can also down-regulate T cell receptor signaling. The absence of this latter role may explain autoantibody development in patients receiving TNF-targeted therapy.

Infectious complications

Granulomatous infections

One of the earliest recognized infectious complications of TNF inhibition was extrapulmonary tuberculosis. Since that time, testing for latent tuberculosis prior to initiation of TNF inhibition has been advocated. Reactivation tuberculosis after inhibition of TNF activity may occur secondary to impaired macrophage apoptosis (a feature of tuberculous-related granuloma formation). In vitro work has suggested that disseminated histoplasmosis in the setting of TNF inhibition is secondary to an inappropriate TH1 response. In addition, at least 4 case reports of pulmonary cryptococcosis after initiation of infliximab have been cited in the literature. Case series of Japanese patients treated with infliximab report a rate as high as 0.38% (15 in 4000) of suspected or confirmed Pneumocystis jiroveci compared to 0.33% rate of tuberculosis.

Bacterial infections

TNF-targeted therapy may also increase the risk of newly acquired bacterial infections. In a review of 60 cases treated either with infliximab and methotrexate or with...
etanercept between 1999 and 2002, Kroesen et al.\textsuperscript{15} identified 11 patients who developed infections requiring hospitalization. A review of these 11 cases did not reveal a predilection for a specific bacteria or pre-disposing duration of therapy. Five of the 11 patients developed pneumonia. Of note, the number of serious infections after initiation of anti-TNF therapy increased.\textsuperscript{15} A retrospective study of a large US health care organization showed that patients receiving TNF-targeted therapy have a two-fold higher risk of developing a bacterial infection than those patients receiving methotrexate.\textsuperscript{16} The case series and chart review both argue for a heightened suspicion of not only granulomatous infections but also bacterial infections.

### Non-infectious complications

#### Granulomatous disease

In Cases 3, 4, and 5, our patients had evidence of granulomatous lesions on pathology after infliximab or etanercept administration. All showed improvement in signs, symptoms, and imaging after change or discontinuation of TNF-targeted therapy, supporting a causative role of TNF-targeted therapy.

There are several reports of patients developing pulmonary granulomatous inflammation after administration of etanercept. The features on imaging and pathology are non-specific. Within 4 months of etanercept therapy, patients developed ground glass infiltrates and non-caseating granulomas on transbronchial biopsy. Discontinuation of etanercept resulted in prompt improvement. Similar to our patient in Case 4, one of the patients did not have recurrence of pulmonary symptoms or findings after initiation of adalimumab for recurrent joint symptoms.\textsuperscript{17,18}

A case series of 4 women on etanercept for refractory joint symptoms developed new alveolar/ground glass infiltrates within 4 months and had biopsies showing patchy, predominantly bronchiocentric, acute fibrinous and granulomatous pneumonia on pathology.\textsuperscript{19} At sites of consolidation, T cells and histiocytes comprise loosely formed granulomas. The granulomatous lesions were believed to be different from those of sarcoidosis in that the lymphocytes were found primarily within, not surrounding, the granuloma. The infectious workup was negative. Since pre-existing lung disease was present in 3 of the 4 patients, it is also possible that these findings represent exacerbation of their pre-existing lung disease. However, the similarities in findings and temporal course (within 4 months of starting etanercept) argue in favor of a drug-induced granulomatous reaction.

The question of whether TNF-targeted therapy induces sarcoidosis, or a sarcoid-like reaction, remains unanswered. Several case reports detail development of pulmonary and extrapulmonary nodules with symmetrical mediastinal lymphadenopathy after 18 months to 5 years of infliximab or etanercept.\textsuperscript{20–22} On biopsy of skin, lymph nodes, and/or lung tissue, tightly formed granulomas with or without necrosis were seen. Infectious workup in each case, including staining and culture data, were negative.

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### Table 1: Summary of FDA-approved TNF-targeted therapies.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Mechanism of action</th>
<th>Usual dosing</th>
<th>FDA-approved indications (approved label as of 1/08)</th>
<th>Non-infectious pulmonary adverse events reported in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etanercept, Enbrel\textsuperscript{15}</strong></td>
<td>Human recombinant form of 2 of human p75 soluble TNFRs fused to the Fc fragment of human IgG1</td>
<td>Binds soluble and cell-bound TNF with high affinity (competitively inhibits binding to TNFRs)</td>
<td>25 mg SC twice weekly or 50 mg SC weekly</td>
<td>Ankylosing spondylitis, Juvenile rheumatoid arthritis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis</td>
<td>Non-caseating granuloma, Interstitial lung disease, Autoimmune disease, Accelerated nodulosis (in patients with rheumatoid arthritis)</td>
</tr>
<tr>
<td><strong>Infliximab, Remicade\textsuperscript{16}</strong></td>
<td>Human IgG1\textsubscript{κ} spliced to the murine human monoclonal anti-TNF antibody</td>
<td>Binds soluble and cell-bound TNF</td>
<td>3 mg/kg (in 0.9% normal saline) IV over 2 h every 8 weeks</td>
<td>Ankylosing spondylitis, Crohn’s disease, Psoriatic arthritis, Plaque psoriasis, Rheumatoid arthritis, Ulcerative colitis</td>
<td>Interstitial lung disease, Exacerbation of underlying lung disease, Precipitation of methotrexate pneumonitis, Diffuse alveolar hemorrhage (37), Autoimmune disease, Interstitial lung disease, Autoimmune disease, Exacerbation of underlying lung disease</td>
</tr>
<tr>
<td><strong>Adalimumab, Humira\textsuperscript{17}</strong></td>
<td>Human recombinant IgG1 monoclonal TNF antibody</td>
<td>Blocks interactions of TNF with the p55 and p75 cell surface TNFRs</td>
<td>40 mg SC every other week</td>
<td>Ankylosing spondylitis, Crohn’s disease, Psoriatic arthritis, Rheumatoid arthritis</td>
<td>Non-infectious pulmonary adverse events reported in the literature</td>
</tr>
</tbody>
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TNFR = TNF receptor.
for mycobacteria, bacteria and fungi. Symptoms and findings resolved either with discontinuation of the TNF-targeted agent and, in some cases, addition of systemic steroids.

The presence of pulmonary granulomas raises suspicion of mycobacterial or fungal infection, sarcoidosis, hypersensitivity pneumonitis or rheumatoid nodules (in patients with rheumatoid arthritis). While the workup (short of surgical lung biopsy) does not entirely exclude infection, the continued resolution of symptoms despite new regimens of immunsuppression argues against infection.

Pulmonary nodules

Rheumatoid nodules have been reported to occur in up to 25% of patients with rheumatoid arthritis. The typical rheumatoid nodule consists of a necrotic center enclosed by macrophages and fibroblasts and an outer layer of mononuclear cells. Patients with low disease activity can still develop rheumatoid nodules, suggesting that the development of nodules is based on a different mechanism than the mechanism responsible for joint inflammation. Cunnane et al. reported on 3 patients who had resolution of joint symptoms but developed accelerated nodule formation while receiving etanercept. The finding that the nodules resolved or stabilized on reduced dosing or discontinuation of etanercept supports a causative role of etanercept therapy. Similar reports of etanercept-related nodule development have been described. Although the distinction between etanercept-induced granulomatous inflammation and sarcoidosis or hypersensitivity pneumonitis can be difficult, the former is suggested in the presence of well-formed granulomas, some of which may have necrosis, as well as if there is prompt resolution once etanercept is discontinued.

Interstitial pneumonitis/fibrosis

There is some evidence that anti-TNF therapy can induce chronic pneumonitis/fibrosis. One report described 4 patients with rheumatoid arthritis who either suffered from progression of usual interstitial pneumonitis (3 patients) or developed bronchiolitis obliterans with organizing pneumonia (BOOP) within 3 weeks of the 3rd dose of infliximab. The joint symptoms of all 4 patients responded favorably to infliximab. Infectious workup in all 4 patients was unrevealing. The 3 patients with underlying lung disease were either asymptomatic or had stable symptoms over the year prior to infliximab initiation and progressed to respiratory failure and death. The pathologic features were inconsistent with diffuse alveolar damage typically found in acute exacerbations of usual interstitial pneumonitis. None of the patients had received methotrexate, but 2 had received azathioprine in an attempt to reduce formation of anti-chimeric antibodies.

Hagiwara et al. included these 4 cases in a review of 24 cases of reported acute exacerbations of interstitial lung disease in patients with rheumatoid arthritis receiving anti-TNF therapy (etanercept n = 7; infliximab n = 17; adalimumab n = 1). While it is difficult to draw firm conclusions from this small series, the factors that associated with increased risk of development of interstitial pneumonitis after initiation of anti-TNF therapy were increased age and underlying lung disease. Over half of the patients had underlying interstitial lung disease. The range of onset of pulmonary symptoms after initiation of anti-TNF therapy was 3 weeks to 51 months, with most occurring within 3 months.

Methotrexate pneumonitis

Our patient in Case 1 raised the concern of potential interaction between etanercept and methotrexate causing interstitial lung disease. In most therapeutic trials of rheumatoid arthritis, the effect of methotrexate alone and methotrexate with a TNF-targeted agent is compared. Although one report suggests that co-administration of methotrexate and infliximab reduces formation of human anti-chimeric antibodies, other studies suggest that co-administration of infliximab and methotrexate can potentiate methotrexate pneumonitis. Methotrexate pneumonitis most commonly presents within 32 weeks of initiating the drug and has pathologic features that include 1) acute and organizing diffuse alveolar damage and/or 2) cellular interstitial infiltrates with or without granulomas on pathology (usually non-caseating). Eight patients developed pneumonitis after administration of infliximab despite the fact that seven had been on a stable dose of methotrexate. Most patients develop symptoms within weeks of the 3rd infliximab infusion. Findings on pathology consisted of type II pneumocyte proliferation with fibrin deposition with or without a nodular infiltrate of lymphocytes, histiocytes, plasma cells, and rare multinucleated giant cells. Further studies are required to better define the distinguishing features of pneumonitis/fibrosis caused by methotrexate as compared to TNFα-targeted therapy as well as to determine whether there is an interactive effect between these two agents.

Autoimmune disease

A growing body of literature suggests that TNF-targeted therapies may cause autoimmune disease. The formation of new autoantibodies during therapy with anti-TNF agents is not clearly understood. Anti-nuclear antibody formation rate varies between 34–95% with infliximab, 11–26% with adalimumab, and 11–54% with etanercept in rheumatoid arthritis patients. Proposed mechanisms include non-specific B cell activation, alteration of apoptosis with subsequent increased exposure of antigens to the immune system, and downregulation of C-reactive protein leading to reduction in clearance of apoptotic debris. Ninety-four percent of patients with suspected lupus developed positive autoantibodies. While the majority of patients who develop autoantibodies on TNF-targeted therapy are asymptomatic, Ramos-Casals et al. reported on 226 patients who developed autoimmune disease manifestations in the setting of anti-TNFα therapy that included vasculitis (n = 113), lupus (n = 92), and interstitial lung disease (n = 24). Reports of interstitial lung disease are more difficult to attribute to autoimmune disease as positive serology was not required and patients who had been receiving methotrexate or had a prior history of interstitial lung disease were also classified as having autoimmune disease. The occurrence of anti-TNF-induced systemic lupus syndrome has been reported after etanercept, infliximab, and adalimumab. Diri et al. recently
described 3 patients with infliximab-induced lupus-like syndrome involving the lung and pleura. All three patients developed positive serology, lymphocytic pleural effusions and dyspnea with or without pulmonary infiltrates. Symptoms and findings resolved with discontinuation of infliximab and initiation of prednisone in 2 of the patients. It appears that while there is a possibility developing manifestations of a new autoimmune disease after initiation of TNF-targeted therapy, there is a larger subset of patients that will develop positive serology without manifestations of autoimmune disease.

Summary
TNF-targeted therapies are increasingly being used in the management of a variety of inflammatory and autoimmune diseases. The beneficial effects may come at the risk of developing an assortment of pulmonary side effects including infections (TB, bacterial, and fungal infections), pulmonary nodules, chronic pneumonitis/fibrosis, SLE-like reactions, vasculitis, and exacerbations of underlying lung disease. The presentation is often not straightforward with management focused on excluding infection, identifying confounders (especially methotrexate or pre-existing lung disease), and promptly discontinuing TNF-targeted therapy. In some instances, invasive procedures (e.g. bronchoscopy or VATS lung biopsy) will be necessary to establish the proper diagnosis, and the administration of steroids may be beneficial. The mechanisms of these side effects are unclear. However, TNF appears not only to play a role in response to infection, but also to have a regulatory role in autoimmunity. In addition to surveillance for tuberculosis prior to initiation of TNF-targeted therapy, a high level of vigilance should be maintained during administration for infectious and non-infectious complications, even years into a patient’s course. The available evidence argues for caution in using these agents in patients with pre-existing lung disease and heightened suspicion of accelerated nodule formation in those with pre-existing rheumatoid nodules. Further studies are required to better understand the varied clinical manifestations, pre-disposing risk factors, and treatment.

Conflict of interest statement
The authors have no conflict of interest.

References


