

Infliximab-Induced Nonspecific Interstitial Pneumonia

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Abstract: Infliximab has well-established complications including injection site and allergic reactions, cytopenias, induction of autoimmune and demyelinating diseases and malignancy, especially lymphoma. Pulmonary complications are well documented and include serious respiratory infections from tuberculosis, fungal and opportunistic pathogens. This has prompted a Food and Drug Administration black-box warning recommending close surveillance for these diseases. Nonspecific interstitial pneumonitis (NSIP) secondary to tumor necrosis factor- α inhibitor (TNF- α) therapy is less well described. Rarely, TNF- α inhibitor therapy has been reported to cause NSIP when used in conjunction with other immunosuppressive agents. Literature search revealed 12 independent patients with presumed infliximab-induced NSIP in 8 separate publications; all patients were on concomitant steroid sparing immunosuppressive agents, complicating cause and effect. The authors report a case in which infliximab is surmised to cause NSIP in the absence of other steroid sparing immunosuppressants in a young female with ulcerative colitis. Of importance, the patient was taking no additional steroid sparing immunomodulating agents. The diagnosis was based on clinical presentation and radiologic and histopathological data. Cessation of infliximab and high-dose steroid therapy resulted in complete resolution of the patient's presenting signs and symptoms.

Key Indexing Terms: TNF inhibitor therapy; Infliximab; Interstitial pneumonitis; Nonspecific interstitial pneumonitis. [*Am J Med Sci* 2012;344(1):75–78.]

CASE REPORT

A 29-year-old nonsmoking white female presented with progressive dyspnea, nonproductive cough, fatigue and night sweats for 1 month which did not improve with separate courses of azithromycin or moxifloxacin. Her history included mild intermittent asthma, but she denied significant asthma symptomatology before presentation. Four months before admission, she was diagnosed with ulcerative colitis (UC), requiring oral and rectal mesalamine plus prednisone to control symptoms of diarrhea, pain and rectal bleeding. Almost 3 weeks after starting therapy, she developed acute pericarditis necessitating discontinuation of mesalamine. At that time, chest radiograph and chest computed tomography (CT) were normal apart from a mild pericardial effusion. She continued on prednisone because of persistent colitis; infliximab was initiated 2 weeks later. She did well with resolution of her colitis symptoms allowing prednisone taper and discontinuation before this admission. After her second infliximab infusion, she noted onset of progressive dyspnea. She denied any symptom exacerbation of her UC including bloody di-

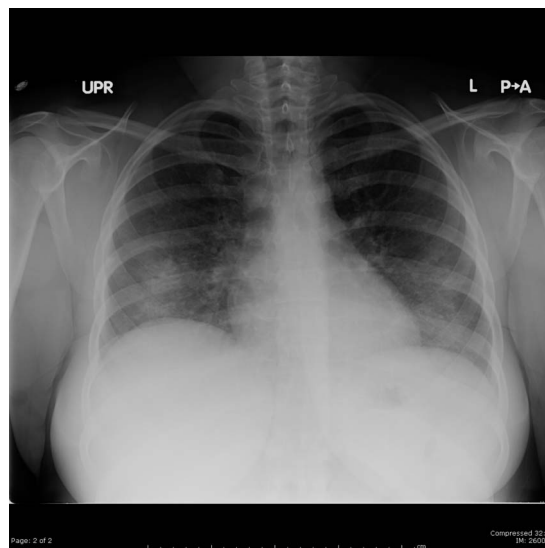


FIGURE 1. Admission chest radiograph: bilateral pulmonary infiltrates.

arrhea, abdominal pain or fever. Purified protein derivative was negative. Additional medical problems included allergic rhinitis, gastroesophageal reflux disease and depression, treated with intranasal fluticasone, cetirizine, iron supplements, lansoprazole, bupropion, ibuprofen and drospirenone/ethinyl estradiol.

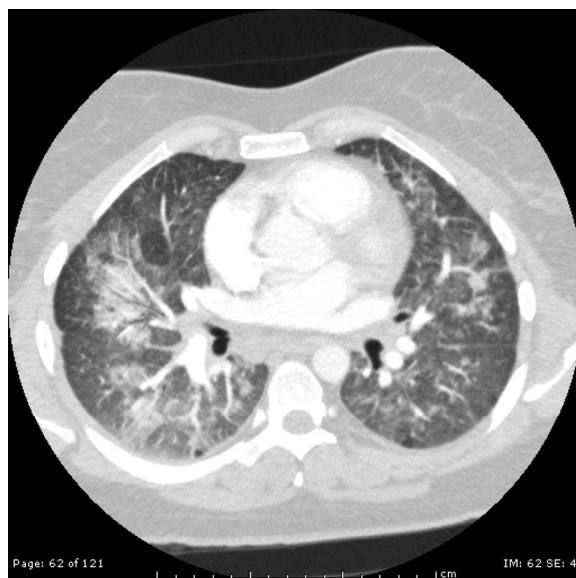


FIGURE 2. Initial chest computed tomography (CT): diffuse bilateral heterogeneous infiltrates most prominent in right middle lobe and right lower lobe.

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TABLE 1. Pulmonary function tests

Parameter	Initial (% predicted)	Follow-up (% predicted)
FVC	78	99
FEV1	69	101
FEV1/FVC	88	101
TLC	78	109
RV	70	120
VC	78	99
DLCO	49	67
DLCO/VA	84	102

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; VC, vital capacity; DLCO, carbon monoxide; diffusing capacity; VA, alveolar volume.

The patient was moderately obese in mild respiratory distress, with tachypnea and diminished bibasilar breath sounds. Abnormal laboratory studies included increased erythrocyte sedimentation rate (48 mm/hr) and C-reactive protein (40 mg/L). Urinary *Streptococcal pneumoniae*, *Legionella* and histoplasmosis antigens and blood cultures were negative. Chest radiograph demonstrated bibasilar infiltrates with decreased lung volumes, and chest CT showed bilateral patchy infiltrates in the right middle and right lower lobes (Figures 1 and 2). Bronchoalveolar lavage showed CD8 T-cell lymphocyte predominance with CD4/CD8 ratio of 0.74. The cell count differential in the bronchoalveolar lavage was 63% macrophages, 22% lymphocytes, 8% neutrophils, 7% epithelial and 0% eosinophils. Fungal, bacterial and viral cultures were negative, and transbronchial biopsy was positive for non-specific inflammation. Pulmonary function tests (Table 1) were consistent with mild restriction.

The patient's clinical status deteriorated, requiring oxygen support and prompting video-assisted thoracoscopic biopsy of the right upper and lower lobes. An acute lung injury pattern was reported with alveolar exudates, demonstrating increased

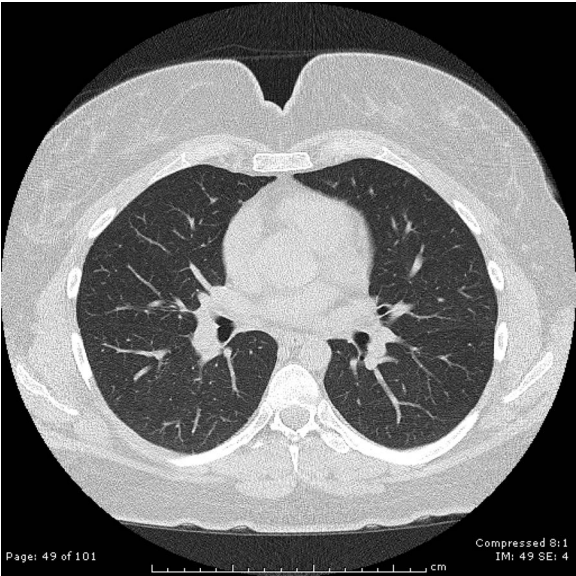


FIGURE 4. Follow-up chest computed tomography (CT): resolution of bilateral pulmonary infiltrates.

interstitial lymphocytes, pneumocyte hyperplasia, fibrinoid alveolar exudates and increased alveolar macrophages (Figure 3). In particular, the right lower lobe biopsy revealed a cellular, airway-centered interstitial pneumonia which raised possible consideration of hypersensitivity pneumonitis, but overall findings were most consistent with nonspecific interstitial pneumonitis (NSIP). Fibroblast foci, more commonly seen with usual interstitial pneumonitis, were notably absent, and a diagnosis of NSIP was made. Discontinuation of infliximab and corticosteroid initiation resulted in marked clinical improvement with complete resolution of hypoxia. Infliximab was considered the inciting agent of NSIP and was not resumed. At 3 months, her pulmonary function tests (Table 1) and chest CT scan (Figure 4) showed resolution of previous abnormalities.

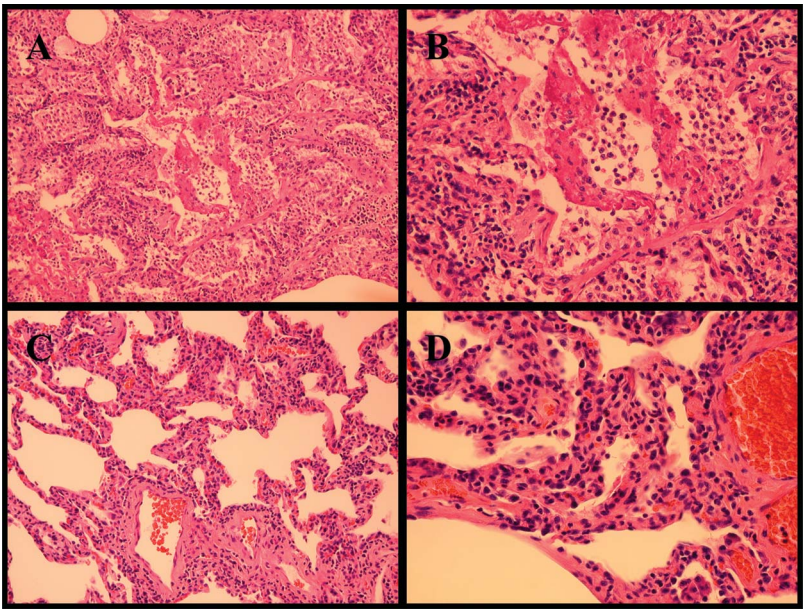


FIGURE 3. (A) Acute lung injury with alveolar exudates (low magnification). (B) Acute lung injury showing hyaline membranes and alveoli filled with neutrophils (high magnification). (C) Nonspecific interstitial pneumonitis (NSIP) pattern with cellular alveolar septae and no alveolar exudates (low magnification). (D) NSIP with increased lymphocytes in the alveolar septae (high magnification).

TABLE 2. List of medications implicated in NSIP⁶

Abacavir
Anagrelide
TNF-alpha inhibitors
Beta-blockers
Bortezomib
Bromocriptine
Carbamazepine
Ciprofloxacin
Trimethoprim/sulfamethoxazole
Cladribine
Cyarabine
Docetaxel
Erlotinib
Everolimus
Fenfluramine
Fludarabine
Imatinib
Interferon-alpha
Leflunomide
Lenalidomide
Methotrexate
Nilutamide
Nitrofurantoin
Procarbazine
Rituximab
Sirolimus
Statins
Tacrolimus
Temozolomide
Thalidomide
Trastuzumab
Venlafaxine

TNF, tumor necrosis factor.

DISCUSSION

NSIP diagnosis requires a compatible clinical history, with characteristic radiographic and histopathologic findings. Presenting symptoms include subacute onset of dyspnea and

nonproductive cough which do not improve with antibiotic therapy. Bilateral pulmonary infiltrates with basilar predominance, absence of honeycombing and diminished lung volumes can be seen on high-resolution chest CT. Histopathologic findings include alveolar septal thickening with varying degrees of inflammatory cell involvement, but the absence of fibroblast foci typical of usual interstitial pneumonitis.¹

Glucocorticoids are used for severe symptoms, although azathioprine, cyclosporine or cyclophosphamide may be indicated for refractory symptoms. Identification and treatment of underlying cause remains important in management, although an inciting cause is found in only 50% of patients. NSIP occurs in association with connective tissue disorders, human immunodeficiency virus/AIDS and inflammatory bowel disease. In addition, multiple medications have been implicated (Table 2). Eight prior publications have reported NSIP as a complication of tumor necrosis factor (TNF)-alpha inhibitor therapy (Table 3); however, in all reported cases, patients were taking concomitant steroid sparing immunosuppressive agents complicating determination of cause and effect. In contrast to previously cited cases, our patient was not on any other steroid sparing immunosuppressive agents.

MECHANISM OF INJURY

The exact mechanism of infliximab-induced NSIP is unclear. Of note, the lower lobe biopsy in this patient revealed an airway-centered distribution of cellular infiltration that is sometimes seen with hypersensitivity reactions. Indeed, cutaneous delayed-type hypersensitivity reaction to infliximab has been reported. Torres et al² described a perivascular lymphocytic infiltrate composed predominantly of CD8 T cells with a paucity of eosinophils similar to hypersensitivity reactions induced by other drugs; however, a similar mechanism causing pulmonary toxicity has not been described in prior published cases of infliximab-associated pulmonary toxicity. In addition, histopathologic findings in hypersensitivity pneumonitis generally reveal aggregates of lymphocytes, plasma cells, macrophages and multinucleated giant cells resembling non-necrotizing granulomas (not present on this patient's histopathology). The majority of investigators have proposed the following mechanism of injury for infliximab-induced pulmonary toxicity. TNF-alpha acts as a proinflammatory cytokine that initiates apoptosis of inflammatory cells in the lungs, thereby mediating tissue healing. In the presence of TNF-alpha inhibitor therapy, apoptosis does not occur and

TABLE 3. Summary of reported cases of infliximab-associated NSIP

Publication	Indication for infliximab therapy	Concomitant immunosuppressant therapy	Number of infliximab infusions before onset of symptoms	Steroid therapy initiated?	Clinical improvement?
Kramer et al ⁷ (3 cases)	1. RA 2. RA, psoriasis 3. RA	1. MTX and Pred 2. MTX and Pred 3. MTX, Pred and Sulfasalazine	3 (all cases)	Yes (all cases)	Yes (all cases)
Courtney et al ⁸ (3 cases)	RA all cases	MTX all cases	3 (all cases)	Yes (all cases)	Cases 1 and 2: yes Case 3: death
Chatterjee ⁹	RA	Leflunomide	2	No	No
Villeneuve et al ¹⁰	RA	MTX and Pred	3	Yes	Yes
Mori et al ¹¹	RA	MTX and Pred	2	Yes	Yes
Weatherhead et al ¹²	Crohn's disease	Azathioprine	1	Yes	Yes
Weiner et al ¹³	UC	Azathioprine balsalazide	5	Yes	Yes
Taki et al ¹⁴	RA	Azathioprine	2	Yes	Yes

MTX, methotrexate; Pred, prednisone; RA, rheumatoid arthritis; UC, ulcerative colitis.

inflammatory cells remain in the lung parenchyma, with resultant histopathologic changes characteristic of NSIP. Support for this hypothesis originates from experiments in TNF-alpha homozygous knockout mice, where intratracheal administration of bleomycin resulted in an accelerated form of pneumonitis. Moreover, challenging these mice with recombinant TNF-alpha effectively reduced inflammation and promoted lung tissue healing.³

In this case, infliximab therapy was initiated for symptomatic UC. Extraintestinal manifestations are reported in up to 40% of patients with UC; however, symptomatic pulmonary disease from UC is uncommon. Examples of pulmonary involvement include vasculitis, thromboembolic disease, pleuritis, tracheobronchitis, bronchiectasis and interstitial lung disease, including NSIP. In general, NSIP occurs as a complication of medication used to treat UC rather than a true extraintestinal manifestation.⁴ Mesalamine, sulfasalazine, leflunomide, methotrexate and balsalazide have all been implicated. In contrast, a case series review published by Black et al⁵ reported only 1 case of NSIP attributed to UC alone. We do not believe that NSIP occurred secondary to UC in this case; the temporal relationship of symptom onset to infliximab initiation, along with complete resolution following infliximab discontinuation, strongly supports infliximab as causative of NSIP. This case adds to the existing literature regarding pulmonary complications of infliximab, prompting physicians to consider this less known but potentially serious entity.

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