Pleural Effusion Associated with Pegylated Interferon Alpha and Ribavirin Treatment for Chronic Hepatitis C

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Disclosure: Nothing to report.

Lung toxicity related to interferon (IFN) alpha typically takes a form of interstitial pneumonitis, granulomatous inflammation, or organizing pneumonia. We report a case of a 52-year-old woman, who developed pneumonitis with exudative, lymphocytic-predominant pleural effusion following treatment with pegylated IFN alpha and ribavirin for hepatitis C. Her symptoms and lung findings resolved over 3 months of observation without corticosteroid therapy. Journal of Hospital Medicine 2009;4:E45–E46. © 2009 Society of Hospital Medicine.

KEYWORDS: hepatitis C, interferon alpha, lung toxicity, pleural effusion, ribavirin.

Case Report

A 52-year-old woman with chronic hepatitis C was admitted with complaints of dry cough, shortness of breath, and fever. Four days prior to admission, she had successfully finished a 44-week course of pegylated interferon (IFN) alpha and ribavirin with undetectable viral load on completion of treatment. At 30 weeks, she had developed a dry cough, which she initially ignored. Three weeks later, as a result of a violent coughing episode, she sustained a spontaneous uncomplicated fracture of the left sixth rib. Chest x-ray at that time did not show an infiltrate or opacity. She continued treatment, and over the next 6 weeks developed progressive dyspnea on exertion. Five days prior to admission, she had developed fever of 101°F. Repeat chest x-ray revealed a left lingular infiltrate and she was prescribed levofloxacin. Her symptoms failed to improve and she was admitted to the hospital.

On admission, she denied expectoration, sore throat, night sweats, or rashes. She also denied tobacco use, pets at home, or recent travel outside the Midwest. Examination revealed a temperature of 99.4°F and decreased breath sounds over the left lower chest. Chest x-ray revealed left-sided pleural effusion. D-dimer was negative. Computed tomography (CT) scan of the chest showed a left lingular infiltrate, right lower lobe ground-glass opacity, and a moderately-sized left pleural effusion. Azithromycin, piperacillin/tazobactam, and vancomycin were empirically started. Over the next 36 hours, she became increasingly tachypneic and short of breath. A diagnostic and therapeutic thoracentesis with aspiration of 800 mL of light-yellow-colored fluid brought symptomatic relief. Pleural fluid analysis revealed an exudative effusion with 3.8 gm/dL of protein (serum protein = 6.2 gm/dL), lactic dehydrogenase (LDH) of 998 IU/L (serum LDH = 293 IU/L), and normal adenosine deaminase. The cell count was 362 per mm³ with 37% lymphocytes, 32% macrophages, 26% neutrophils, and 1% eosinophils. There were no atypical or malignant cells. Bacterial, fungal, viral, acid-fast stains and cultures, and polymerase chain reaction (PCR) for Mycobacterium tuberculosis were all negative. An echocardiogram and plasma B-type natriuretic peptide were normal.

Serum antinuclear and antineutrophilic cytoplasmic antibodies, Bordetella pertussis PCR, serologies for Mycoplasma, Chlamydia, Coxiella, and urinary antigens for Legionella and Blastomyces were all negative. Bronchoscopy with bronchoalveolar lavage (BAL) was performed on hospital day 5. BAL stains and cultures for bacteria, fungi, acid-fast organisms, Cytomegalovirus, Herpes simplex virus, Legionella, and Pneumocystis were negative. Cytology revealed mild acute inflammation with macrophage predominance and no malignant cells.

Repeat CT scan of the chest on day 6 showed bilateral ground-glass infiltrates and persistent left pleural effusion (Figure 1). In the absence of an identifiable cause, the patient was diagnosed with interstitial pneumonitis and pleural effusion secondary to pegylated IFN alpha and ribavirin. Treatment with steroids was considered, but was not used due to recent successful suppression of hepatitis C. She was discharged with continued close follow-up. Her fever gradually subsided over the next 2 weeks and her cough continued to improve over the next 6 weeks. Follow-up CT scan of the chest 3 months after discharge showed complete resolution of the left pleural effusion and near-resolution of the bilateral basal infiltrates.

Discussion

Use of IFN alpha has been associated with multiple forms of lung toxicity, of which interstitial pneumonitis and granulomatous inflammation resembling sarcoidosis are the most common. Unusual forms include isolated nonproductive cough, exacerbation of asthma, organizing pneumonia, pleural effusion, adult respiratory distress syndrome, and...
exacerbation of vasculitis. Reports of adverse pulmonary effects of ribavirin are sparse, and it has not been implicated as a sole etiologic agent in causing lung toxicity. It is therefore likely that pulmonary toxicity observed in patients with hepatitis C virus (HCV) infection undergoing IFN alpha and ribavirin therapy is due to the IFN.

Pleural effusion may accompany the IFN-induced capillary leak syndrome.

There have been only 2 other cases of pleural effusion during treatment with IFN alpha described to date. Takeda et al. described a 54-year-old male who was accidentally detected to have a moderate-sized right pleural effusion on magnetic resonance imaging (MRI) of the abdomen, 14 days after therapy with recombinant IFN alpha was initiated. The pleural fluid was a lymphocyte-predominant exudate and resolved approximately 4 months after discontinuation of IFN treatment. Tsushima et al. reported bilateral pleural effusions and ground-glass opacities in a patient treated with IFN for metastatic renal cell cancer that resolved following a course of steroids.

IFN-related pulmonary toxicity has been reported to typically develop between 2 and 16 weeks of treatment. Our patient had a delayed onset of symptoms at 30 weeks and progressed on to develop left pleural effusion and pulmonary infiltrates by the time she finished 44 weeks of treatment. We ruled out infectious, malignant, cardiac, and autoimmune causes, which often present in a similar fashion.

BAL fluid cytology in our patient revealed predominant macrophages. Yamaguchi et al., in their analysis of BAL fluid in patients with hepatitis C, demonstrated increased macrophages (76% and 77.5%) and lymphocytes (19.8% and 18.8%) before and after treatment with IFN alpha, respectively.

The cornerstone of management of lung toxicity due to IFN is to diminish or stop use of the offending agent. Our patient demonstrated complete recovery of symptoms and radiological resolution within 3 months of completion of IFN therapy, without corticosteroid therapy. Although corticosteroid regimes of 6 to 12 months have been used to manage IFN related lung toxicity, most patients recover without them. Moreover, corticosteroids have been implicated in the recurrence of hepatitis C.

We believe that our patient’s pathology is most consistent with lung and pleural toxicity temporally related to IFN treatment. Through our case report, we bring to attention this infrequent complication, and emphasize its self-limited course upon withdrawal of the offending agent.

Acknowledgements
The authors thank Dr. Philippe Camus, Hôpital Le Bocage, Dijon, France, for his invaluable suggestions and for reviewing this case report prior to submission.

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