Spectrum of Pulmonary Toxicity Associated with the Use of Interferon Therapy for Hepatitis C: Case Report and Review of the Literature

John Midturi,1 Miguel Sierra-Hoffman,2 Douglas Hurley,1 Richard Winn,1 Robert Beissner,2 and John Carpenter1

1Department of Internal Medicine, Division of Infectious Disease, and 2Department of Surgical Pathology, Scott & White Memorial Hospital and Clinic, and Scott, Sherwood, and Brindley Foundation, Texas A & M University System Health Science Center College of Medicine, Temple, Texas

Hepatitis C is one of the leading causes of liver disease in the United States, and current recommendations for its treatment include the use of interferon (IFN). Pulmonary side effects, although uncommon, have been reported in association with the use of IFN. We report a case of interstitial granulomatous pneumonitis that occurred after therapy with IFN and ribavirin, and we review the literature concerning this entity and other forms of IFN-associated pulmonary toxicity in patients with hepatitis C. The purpose of the present study is to increase awareness of the unusually wide spectrum of pulmonary toxicities associated with the use of IFN and ribavirin, with the anticipation that IFN will be used more frequently in the future for the treatment of hepatitis C.

Infectious disease physicians are becoming more involved in the management of patients with hepatitis C. Most practitioners are aware of the common side effects associated with IFN-ribavirin combination therapy, including myalgias, fever, flu-like symptoms, depression, and cytopenia. There are less common side effects that can cause significant morbidity and mortality if they are not recognized expeditiously. In this report, we present a case of interstitial granulomatous pneumonitis that occurred after administration of IFN and ribavirin therapy, and we review the literature concerning this condition and other forms of IFN-associated pulmonary toxicity in patients with hepatitis C and discuss the clinical implications of pulmonary toxicity in this group of patients.

Case report. A woman, 71 years of age, who had a past medical history that was significant for hepatitis C, was admitted to the hospital because of complaints of cough, diarrhea, fatigue, and nausea of 6 weeks’ duration. She recognized these symptoms but was reluctant to voice her complaints to her primary care physician because of a desire to complete her treatment for hepatitis C. The patient had received a diagnosis of hepatitis C in 1994. Genotype analysis performed in February 2003 revealed coinfection with hepatitis C virus genotypes 2 and 4; at 5 months before admission to the hospital, medical therapy was initiated that involved administration of pegylated IFN (Peg-IFN; 180 μg once weekly) and ribavirin (800 mg once daily). The patient required supplementation with the hematopoietic growth factors erythropoietin (40,000 U weekly) and filgrastim (300 μg twice weekly), so that she could continue to receive full doses of both Peg-IFN and ribavirin.

The patient’s cough, which was described as nonproductive and progressively worsening, was debilitating enough that the patient was losing sleep; she was unable to take a deep breath because doing so might trigger coughing. The patient denied having fever, sore throat, shortness of breath, chest pain, night sweats, or rashes. She also denied that she used tobacco, had any unusual pets, had traveled recently, or had contacts with sick individuals. A chest radiograph obtained on an outpatient basis 1 week before the patient was admitted to the hospital showed no evidence of cardiopulmonary disease. The treatment that the patient was receiving included Peg-IFN, ribavirin, erythropoietin, filgrastim, conjugated estrogen (Premarin; Wyeth-Ayerst), amiloride hydrochloride, and levothyroxine sodium (Synthroid; Abbott).

The patient was admitted to the hospital and began receiving fluids intravenously for mild dehydration due to diarrhea. Treatment with Peg-IFN and ribavirin was temporarily stopped. The diarrhea quickly resolved, but the patient developed a worsening cough and shortness of breath. A chest radiograph revealed increased marking in the interstitial tissues in the middle and lower lung fields (figure 1); this was a new finding, compared with the findings that had been noted on the chest radiographs that had been obtained 1 week previously. The patient was thought to have community-acquired pneumonia, and she began receiving moxifloxacin. Her condition initially improved after antibiotics were administered and a 10-day course of therapy was completed; however, when treatment with Peg-IFN and ribavirin was reinitiated after 1 week, the...
Figure 1. Chest radiograph showing increased marking of the interstitial tissues in the bilateral middle and lower lung fields. The radiograph was obtained at the time of admission of the patient to the hospital.

The patient experienced a relapse of her condition, with worsening cough and shortness of breath. Radiography of the chest was repeated and revealed worsening interstitial infiltrates and bilateral pleural effusions, which raised the suspicion of interstitial pneumonitis due to Peg-IFN and ribavirin therapy, and Peg-IFN and ribavirin were discontinued once again.

A high-resolution CT scan revealed mixed interstitial and airspace opacities in all lobes, with interstitial thickening and ground-glass opacity within the right upper lobe and the superior aspect of the right lower lobe, respectively (figure 2). A transthoracic echocardiogram and detection of a normal plasma concentration of B-type natriuretic peptide excluded any cardiac pathologic abnormalities. Pulmonary function tests were performed and revealed moderate volume restriction and a severely reduced diffusion capacity of the lung for carbon monoxide of 10.3 mL/mm Hg/min (43% of the predicted capacity). A bronchoscopy with transbronchial biopsy and bronchoalveolar lavage was performed. The results of cultures and stains of the bronchoalveolar lavage specimens were negative for bacteria, fungus, acid-fast bacteria, cytomegalovirus, herpes simplex virus, and Legionella organisms. Lung biopsy specimens (figure 3) revealed a granulomatous process with some organizing pneumonitis with fibroblastic plugs. Interstitial pneumonitis associated with Peg-IFN and ribavirin therapy was diagnosed, and Peg-IFN and ribavirin were permanently discontinued.

The patient was discharged from the hospital with a schedule of follow-up appointments for serial chest radiography and clinical examinations. Her symptoms showed significant improvement within 2 weeks of discontinuation of treatment with Peg-IFN and ribavirin, she was able to discontinue treatment with filgrastim and erythropoietin as her hematologic counts improved, and marked improvement in her radiographic findings was noted 1 month after discharge of the patient from the hospital (figure 4).

Discussion. Several pathophysiological mechanisms have been proposed to explain the lung damage produced by IFN. These mechanisms center around the known immunomodulatory activity of IFN [1–3]. Proposed mechanisms for the activity and pulmonary toxicity associated with IFN include inhibition of suppressor T cells, enhancement of cytotoxic T cells, induction of proinflammatory cytokines, and exaggerated release of fibrinogenic cytokines, such as platelet-derived growth factor and transforming growth factor-β, leading to lung tissue...
Figure 2. CT scan showing interstitial thickening and ground-glass opacity within the right upper lobe and the superior aspect of the right lower lobe. The scan was obtained ∼2 weeks after admission of the patient to the hospital.

fibrosis [4, 5]. Bini et al. [6] have also proposed that IFNs can contribute to exacerbations of asthma through the activation of Th1 lymphocytes, which results in increased production of IFN-γ and cytokines.

Therapeutic IFN is a recombinant α-IFN associated with higher blood levels and a prolonged half-life that results from attachment of a polyethylene glycol chain (pegylation) to the parent compound. Commercially available pegylated products are pegylated IFN-α2a (Pegasys; Hoffmann-La Roche) and pegylated IFN-α2b (PEG-Intron; Schering-Plough) [7]. Ribavirin is given in conjunction with IFN for the treatment of hepatitis C. The mechanism of action of ribavirin against hepatitis C is unknown. Although ribavirin can cause dry cough and dyspnea, there are no documented cases of pathologic pulmonary toxicity due to ribavirin therapy alone.

The spectrum of lung tissue damage associated with the use of IFN for treatment of hepatitis C is very diverse. All cases involving patients with hepatitis C reported in the English-language literature, to the best of our knowledge, are summarized in table 1 [6, 8–24]. Information on the clinical, virological, and histological characteristics of the patients’ underlying cases of hepatitis C was limited, because fewer than one-half of the reports contained this information. Only 1 patient had a documented case of cirrhosis. Of the 10 cases of hepatitis C for which the genotype was documented, 5 cases were due to hepatitis C virus genotype 1. Genotype 1 may be the predominant genotype associated with pulmonary toxicities because of the longer duration of IFN therapy required for treatment of hepatitis C due to genotype 1, compared with that required for hepatitis C due to genotypes 2 and 3.

It should be noted that there are other cases of IFN-associated pulmonary pathologic findings in patients without hepatitis C, primarily among patients who have a malignancy [5, 25–29]. The associated pathologic findings can range from mild interstitial pneumonitis to a severe acute respiratory distress–like syndrome that leads to death. On the basis of our review of

Figure 3. Lung biopsy specimen revealing parabronchial granuloma (arrow) (hematoxylin-eosin stain; original magnification, ×40)
Figure 4. Chest radiograph showing interval clearing of infiltrates. The radiograph was obtained 1 month after discharge of the patient from the hospital.

In the literature, the most common pathologic finding is interstitial pneumonitis, which is followed in frequency by a sarcoidlike reaction with noncaseating granuloma formation. Other, less frequent, processes are asthma exacerbation, pleural effusion, and bronchiolitis obliterans with organizing pneumonia. All except 1 individual survived after the cessation of IFN therapy. The clinical implication of not recognizing IFN-associated pulmonary toxicity is the continued occurrence of pulmonary damage that leads to fibrosis. The development of pulmonary fibrosis leads to progressive loss of lung volume, abnormal gas exchange, and a median survival period of <5 years [30]. Therefore, it is of paramount importance to recognize the development of this fatal disease and to intervene expeditiously.

Table 1. Summary of case reports in the English-language literature of lung tissue damage associated with the use of IFN for the treatment of hepatitis C.

<table>
<thead>
<tr>
<th>Lung tissue damage</th>
<th>Therapy received</th>
<th>Condition proved by biopsy</th>
<th>Steroids received</th>
<th>Duration of treatment</th>
<th>Outcome</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN Peg-IFN Ribavirin</td>
<td>Yes No NR</td>
<td>0–4 Weeks 5–8 Weeks 9–12 Weeks &gt;12 Weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP (n = 15)</td>
<td>14 1 1</td>
<td>8 5 9 1</td>
<td>3 5 5 2</td>
<td>All survived</td>
<td>[8–15]</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdlike reaction (n = 10)</td>
<td>9 1 6</td>
<td>8 3 7 0</td>
<td>0 0 2 8</td>
<td>All survived</td>
<td>[16–21]</td>
<td></td>
</tr>
<tr>
<td>BOOP (n = 3)</td>
<td>3 0 2</td>
<td>3 0 0</td>
<td>1 0 0 2</td>
<td>All survived</td>
<td>[15, 22]</td>
<td></td>
</tr>
<tr>
<td>Asthma exacerbation (n = 2)</td>
<td>2 0 0</td>
<td>NA 2 0 0</td>
<td>0 0 2 0</td>
<td>All survived</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion (n = 1)</td>
<td>1 0 0</td>
<td>NA 0 1 0</td>
<td>1 0 0 0</td>
<td>Survived</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>ARDS (n = 1)</td>
<td>0 1 1</td>
<td>1 1 0 0</td>
<td>1 0 0 0</td>
<td>Died</td>
<td>[24]</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are the no. of case patients, unless indicated otherwise. ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; IP, interstitial pneumonitis; NA, not available; NR, not reported; Peg-IFN, pegylated IFN.

a Before diagnosis of pulmonary pathologic findings.

b Including the case report presented here.
The clinical presentation of interstitial pneumonitis is usually insidious in onset, and, initially, it can be difficult to differentiate its clinical presentation from that of a transient viral respiratory process, congestive heart failure, atypical pneumonia, or ribavirin-induced cough and dyspnea. Interstitial pneumonitis usually is characterized by dry cough, dyspnea, and fine inspiratory crackles noted on examination. Hemoptysis, wheezing, and signs of consolidation are rare. Chest radiographs usually show bilateral patchy infiltrates or opacifications, and thin-section CT scans show bilateral patchy consolidation as well as ground-glass attenuation [31].

The cornerstone of the management of interstitial pneumonitis associated with IFN therapy is to stop use of the offending agent. Some investigators have tried to manage the condition for their patients by administering steroids for 6 months to 1 year, although this approach is controversial. Our review of cases documented that all patients who did not receive steroids recovered. The 1 patient who died received steroids, but this death was due to nosocomial complications and was not related to IFN therapy [24].

Our case patient demonstrated most of the characteristics and principles previously reported in the literature. She was treated with high-dose Peg-IFN and ribavirin, and she developed pulmonary symptoms after receiving treatment for ~4 months. Most patients develop pulmonary toxicity several months after the initiation of therapy. In addition, some authors believe that treatment with high-dose IFN is more likely to lead to pulmonary toxicity than is standard-dose IFN [15]. Because Peg-IFN has been used for a relatively short time, it is unclear whether it is more likely than standard IFN to cause pulmonary toxicity. The case patient in the current report presented with dry cough and dyspnea, and she had new infiltrates that were noted on a chest radiograph. Although it is possible that she had a case of bacterial pneumonia or a “respiratory virus,” we believe that the course of her disease is more consistent with disease associated with IFN therapy. The patient recovered without the use of corticosteroids.

We are presenting this case report because infectious disease physicians are becoming more involved in the treatment of hepatitis C, and it is important for them to be aware not only of the common toxicities associated with the use of IFN for the treatment of hepatitis C but, also, of the wide spectrum of more-unusual pulmonary toxicities associated with these medications. It is anticipated that the use of IFN for the treatment of hepatitis C will continue to increase and that pulmonary complications, although unusual, will be seen with increasing frequency.

Acknowledgment

Potential conflicts of interest. All authors: no conflicts.

References


