Interferon (INF) α, a naturally occurring glycoprotein, inhibits intracellular replication of many viruses. It is the cornerstone of treatment for chronic hepatitis C virus (HCV) infection. Pegylated interferon (PEGINF) α-2b (PEG-Intron; Schering–Plough, Ireland) reduces the frequency of administration and increases the efficacy of INF α-2b by delaying its clearance and reducing its immunogenicity (1). Various side effects are well known for INF α treatment (2–10). We report a case of severe interstitial pneumonitis in a patient treated with a combination therapy of PEGINF α-2b and ribavirin for chronic HCV infection.

CASE REPORT

A 51-year-old man of Asian origin with an elevated serum alanine aminotransferase (ALT) level (77 U/L) and serum aspartate aminotransferase (AST) level (13.35 G/L) and C-reactive protein level (11.2 mg/dL), a platelet count of 316 G/L, a total bilirubin level of 1.03 mg/dL, an AST level of 63 U/L, an ALT level of 93 U/L, and serum creatinine of 0.53 U/L. Arterial blood gas analysis showed severe hypoxemia while breathing room air (P\textsubscript{a}O\textsubscript{2}, 7 mm Hg; P\textsubscript{a}CO\textsubscript{2}, 30 mm Hg). Congestive heart failure was excluded by echocardiography. Chest x-ray and high-resolution computed tomography (HRCT) of the lung revealed bilateral interstitial infiltrates and areas of ground-glass opacity (Figure 1A). Extensive serological analysis and blood and urine cultures were unremarkable for infection. Bronchoalveolar lavage was negative for bacteria, fungi, acid-fast organisms, and malignant cells. Open-lung-biopsy revealed diffuse alveolar damage in organization with beginning interstitial fibrosis (Figure 2). No granulomas or eosinophils were seen. Interstitial pneumonitis secondary to PEGINF α-2b and ribavirin was suspected. PEGINF α-2b and ribavirin were discontinued and therapy with 125 mg of prednisolone intravenously per day was initiated. The patient required noninvasive ventilation due to progressive respiratory failure. A second HRCT 1 week later revealed deterioration in both lungs (Figure 1B). Intubation and aggressive mechanical ventilation were necessary despite upgrading the immunosuppressive therapy using sirolimus and mycophenolat–mofetil. Liver biopsy revealed typical signs of hepatitis C infection and septal fibrosis (META VIR scoring system A0, F3) (11). Therefore the patient was considered ineligible for lung transplantation. Nine weeks after hospital admission he developed signs of cerebrospinal herniation (dilated fixed pupils, absent brain stem reflexes) due to chronic hypoxia (Figure 3)-induced cerebral edema. The

**Severe Interstitial Pneumonitis Secondary to Pegylated Interferon α-2b and Ribavirin Treatment of Hepatitis C Infection**

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**KEY WORDS:** peginterferon α; ribavirin; hepatitis C; interstitial pneumonitis; pulmonary toxicity; side effect.
Fig 1. (A) High-resolution computed tomography (HRCT) of the lung, performed after hospital admission, shows bilateral ground-glass opacities with lobular recesses. (B) Follow-up HRCT, performed 1 week later, demonstrates deterioration in terms of expansion of the ground-glass opacities and an increasing peribronchovascular interstitium.
patient died 20 weeks after initiation of PEGINF α-2b/ribavirin treatment.

DISCUSSION

Combination PEGINF α-2b and ribavirin therapy is increasingly used in chronic HCV infection due to its higher sustained virological response rate compared with standard INF α-2b plus ribavirin (2). Treatment can be associated with adverse effects such as influenza-like symptoms, anorexia, nausea, diarrhea, injection-site reaction, alopecia, pruritus rash, psychiatric symptoms, anemia, neutropenia, and respiratory symptoms like coughing and dyspnea (2). Moreover, development and exacerbation of autoimmune diseases, cardiotoxicity, and even sudden death have been associated with INF α therapy (3, 4). There are reports of severe pulmonary toxicity during therapy with INF α alone, INF α/ribavirin, or PEGINF α/ribavirin such as interstitial pneumonitis (5–7), bronchiolitis obliterans organizing pneumonia (8), sarcoidosis (9), and severe exacerbation of asthma (10).

The impact of ribavirin in these side effects during combination therapy is unclear. Ribavirin’s known adverse symptoms of dyspnea and cough may suggest the possibility of independent pulmonary toxicity (12). However, as no case of interstitial pneumonitis caused by ribavirin alone has been reported so far, PEGINF α-2b seems to be the main agent for pulmonary toxicity.

Interstitial pneumonitis usually developed from 2 weeks (5) to 12 weeks (6) after starting INF α/ribavirin therapy for HCV infection. Diagnosis was commonly based on clinical findings like dyspnea, dry cough, hypoxemia, and a restrictive pattern in pulmonary function testing, bilateral diffuse lung infiltrations, histopathological findings of interstitial pneumonitis, a temporal relationship between interstitial pneumonitis and INF α application, and exclusion of any other causative agent. Symptoms were reversible in most of the reported cases after discontinuation of the drug or after additional treatment with corticosteroids. There are only two reports of sustained interstitial pneumonitis despite withdrawal of INF α/ribavirin and subsequent immunosuppressive therapy in the English literature. Chin et al. presented a case of a woman who required intermittent prednisolone pulse therapy to control the symptoms (5). Abi-Nassif et al. recently reported severe interstitial pneumonitis in a man who finally died due to ARDS and septic multiorgan failure (7).

Our patient died despite cessation of PEGINF α-2b/ribavirin and additional application of immunosuppressive therapy due to interstitial pneumonitis induced progressive hypoxemia.
PNEUMONITIS DURING PEGINTERFERON α AND RIBAVIRIN

Fig 3. The chest x-ray performed a few days before the patient died shows bilateral diffuse reticular opacities of the lung.

The pathway of lung injury following treatment with PEGINF α-2b/ribavirin remains unclear. INF α increases the lytic potential of natural killer cells, increases the expression of class 1 major histocompatibility complex molecules on virus-infected cells, and stimulates the development of TH-1 cells (13). INF α toxicity seems to increase with higher doses and longer treatment duration. PEGINF α-2b provides higher levels of INF α-2b due to its prolonged half-life and increased area under the curve (1). However, it is unknown if pegylation of INF α increases the rate of interstitial pneumonitis.

Ueda et al. found a surprisingly high seroprevalence rate of HCV antibodies in patients with idiopathic pulmonary fibrosis (14). Although Irving et al. were not able to reproduce these findings (15), we cannot exclude the potentiality of HCV infection as a predisposing irritant to the lung.

In conclusion, we report a case of interstitial pneumonitis secondary to PEGINF α-2b/ribavirin. Although this rare side effect is reversible in most of the reported cases, our patient died despite discontinuation of PEGINF α-2b/ribavirin and initiation of immunosuppressive therapy. PEGINF α and ribavirin are the mainstay of therapy for chronic HCV infection. However, persistent respiratory symptoms during treatment must lead to careful clinical surveillance, pulmonary function testing, and chest x-ray/HRCT. Prompt withdrawal of the drugs and/or application of immunosuppressive medication is required if signs of significant pulmonary toxicity occur, to minimize the risk of fatal pulmonary damage.

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