CLINICAL NOTE

Pegylated interferon induced interstitial pneumonitis in a patient with hepatitis C infection

J. Torres-Macho¹, B. Jara-Chinarro², B. Suárez-Aliaga³, S. Gámez-Díez¹, G. García-de-Casasola¹ and B. de-Cuenca-Morón⁴

Servicios de ¹Medicina Interna, ²Neumología, ³Radiología y ⁴Medicina de Aparato Digestivo. Hospital Infanta Cristina. Parla. Madrid, Spain

ABSTRACT

Pegylated interferon and ribavirin is the treatment of choice in patients with chronic hepatitis C infection. The most common side effects of interferon therapy are flu-like symptoms and psychiatric disorders. Pneumonitis is a less frequent complication associated with non-negligible mortality. We herein report a case of interferon associated pneumonitis in a patient with non-severe clinical symptoms and a normal chest radiography. Physicians should be aware of this entity during the differential diagnosis of respiratory symptoms in patients receiving treatment with interferon due to its high morbimortality and good resolution and outcome after drug withdrawal.

Key words: Interferon. Neumonitis. Hepatitis C.

RESUMEN

El interferón pegilado asociado a ribavirina es el tratamiento de elección en los pacientes con infección por hepatitis C crónica. Los efectos secundarios más comunes son los síntomas gripales y las alteraciones psiquiátricas. La neumonitis es una complicación poco frecuente, pero se asocia con una mortalidad no despreciable. Presentamos el caso clínico de un paciente con neumonitis intersticial asociada a interferón que presentaba signos y síntomas clínicos sutiles y una radiografía de tórax sin alteraciones. Se debe de tener presente esta entidad en el diagnóstico diferencial de los síntomas respiratorios en pacientes que reciben tratamiento con interferón debido a su elevada morbi-mortalidad y a su evolución favorable tras la retirada del fármaco.

Palabras clave: Interferón. Neumonitis. Hepatitis C.

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Correspondencia: Juan Torres Macho. C/ Numancia 6, 4º-8. 28039 Madrid. e-mail: jtorresmacho@gmail.com

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection may result in liver cirrhosis and hepatocellular carcinoma (1). A combination of pegylated interferon alpha and ribavirin is the treatment of choice (2). The most frequent side effects of interferon therapy are flu-like symptoms, psychiatric disorders and hematological alterations such anemia (3). Interstitial lung disease is a known rare adverse event that often leads to discontinuation of therapy because of its significant morbidity and mortality (4).

CASE REPORT

A 57-year-old man, with a history of well-controlled intrinsic asthma treated with long acting β -2 adrenergic agonists and inhaled steroids. The patient was diagnosed of chronic hepatitis C (genotype 1b) in 1991. The infection was probably acquired by blood transfusion during childhood. In 2004, treatment with pegylated interferon and ribavirin was initiated due to a high viral load and a moderate necro-inflammation found on the liver biopsy. However, treatment was withdrawn due to side effects (anemia and neutropenia). Although there was a persistence of RNA in serum, there was a biochemical response with normalization of liver function tests. In February 2009, the presence of mildly elevated transaminase serum levels and a RNA viral load of 8.218.400 UI/ml was detected. A transient elastography (Fibroscan®) was performed showing a liver stiffness of 10.4 kPa (F3), thus treatment with pegylated

interferon 2b (100 mcgr/weekly) and ribavirin (1000 mgr twice a day) was initiated.

Twelve weeks after treatment began the patient presented to the emergency department with a history of progressive dyspnea at minimal efforts. The vital signs on admission were as follows: blood pressure 120/70 mmHg, a respiratory rate of 16 breaths per minute, a heart rate of 80 beats per minute and an axillary temperature of 36.7 °C. Physical examination was unremarkable. Basal oxygen saturation was 96%. The hemogram and biochemistry showed no abnormalities except for mild anemia (hemoglobin de 9.6 g/dL, hematocrit 31.3% and a mean corpuscular volume of 112 fL). Arterial blood gases showed: Ph 7.55, PO₂ 103 mmHg and PCO₂ 24 mmHg. A Chest X-ray showed no abnormalities (Fig 1).

Fig. 1. Chest X ray showing no abnormalities.

Cutaneous oxygen saturation was assessed after a moderate effort (walking on a level surface) showing a significant desaturation (down to 90%). Pegylated interferon and ribavirin were withdrawn and a chest high resolution CT was performed the next day demonstrating bilateral, multifocal, patchy ground-glass opacities of peripheral location (Fig 2). Pulmonary function tests showed no restriction or obstruction with a diminished diffusion capacity. Bronchoalveolar lavage was performed to rule out an infectious origin. The results of strains were negative for bacteria, fungi, acid-fast bacteria, virus and malignant cells. After interferon and ribavirin was withdrawn the patient presented a slow amelioration of dyspnea and after eight weeks, symptoms disappeared completely with a normalization of pulmonary function tests.

Fig. 2. Chest CT showing bilateral, patchy ground-glass opacities of peripheral location.

DISCUSSION

Hepatitis C infections become chronic in up to 85% of patients. Pegylated interferon and ribavirin are the mainstay of treatment (5). Pegylation is the attachment of an inactive, polyethylene glycol moiety to the conventional interferon molecule. The resulting compound has a sustained absorption, high blood levels and a prolonged half-life (6, 7). Sustained virological response (SVR) is defined as the presence of HCV RNA negative 24 weeks after cessation of treatment which usually leads to resolution of hepatic inflammation and regression of fibrosis. SVR can be achieved in up to 36 to 75 % of patients, depending on many factors like age, genotype, viral load, grade of fibrosis, etc. (2,8). Pulmonary side effects like asthma exacerbation, pleural effusion, sarcoid-like reaction, bronchiolitis obliterans organizing pneumonia and interstitial pneumonitis have been described (6,9).

The mechanism of this side effect remains unclear but it is supposed to be idiosyncratic and it is probably related to interferon immunomodulatory activity that includes induction of enzymes, suppression of cell proliferation, enhancement of macrophage phagocytic activity, inhibition of suppressor T cells and liberation of proinflammatory cytokines (10-12). It remains unclear if pharmacokinetic properties of peginterferon compared to conventional interferon are linked to an increased toxicity (4,6). Although ribavirin can cause dry cough and dyspnea, there are no documented cases of pathologic pulmonary toxicity due to ribavirin therapy alone.

The clinical presentation of interstitial pneumonitis is usually insidious at the onset. The most common symptoms associated with pneumonitis are cough, fever, dysp-

nea and fine dry crackles in pulmonary auscultation. It is not a frequent side effect. The incidence of pneumonitis is not a frequent side effect and is experienced in less than 1% (13,14). To date, about 60 cases have been reported in the literature (4). Differential diagnosis includes infections like viral respiratory processes, atypical pneumonia or mycobacterial infection and congestive heart failure. Chest radiographs may be normal, but usually show bilateral interstitial infiltrates. High resolution CT scan may show bilateral patchy consolidation as well as ground glass attenuation (15).

There is no consensus regarding treatment although the cornerstone of management is to stop using the offending drug. Different options have been described ranging from drug withdrawal to steroid addition or treatment with azathioprine in steroid resistant patients (6,16). A high mortality rate (7%) have been found and most patients did not have relevant pulmonary or other previous severe disease (4).

In our case study, clinical exploration and chest X-ray showed no alterations; however, symptoms and physical signs suggested a lung diffusion alteration (oxygen desaturation while walking) and led us to the diagnosis. Given the clinical stability, we decided not to treat with steroids.

Clinicians should be aware of pneumonitis development in patients treated with pegylated interferon who develop pulmonary symptoms like cough or dyspnea, even with an unremarkable exploration and a normal chest X-ray. It is a severe complication and it needs to be recognized in order to prevent lung damage and/or progression to pulmonary fibrosis and death.

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