Development of sarcoidosis during interferon alpha 2b and ribavirin combination therapy for chronic hepatitis C- A case report and review of the literature

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Abstract

Sarcoidosis is a chronic granulomatous multisystemic disorder of unknown aetiology. Although interferon gamma has been implicated in the pathogenesis of sarcoidosis, only a few cases of sarcoidosis associated with interferon alpha therapy have been reported. We report a case with chronic hepatitis C (CHC) who developed sarcoidosis after the treatment by interferon alpha and ribavirin.

The combination therapy of interferon alpha and ribavirin was given to a 50-year-old female with CHC who had not responded to a previous treatment by interferon alpha. She has been admitted with non-productive cough, dyspnoea and fever 11 months after the initiation of combination therapy. Chest x-ray and thorax computed tomography revealed bilateral hilar masses and nodular infiltrations in the lung parenchyma. Pulmonary function test showed a mild restriction. Biopsy of mediastinal lymphadenopathy revealed noncaseating granuloma. She was diagnosed to have pulmonary sarcoidosis at stage II, and the combination treatment was discontinued. Her symptoms regressed after inhaler steroid treatment. Six months after the diagnosis of sarcoidosis, the patient was asymptomatic and a complete sustained response to hepatitis C was achieved. During the three years of follow-up, both pulmonary sarcoidosis and hepatitis C have not recurred. We suggest that sarcoidosis may develop in chronic hepatitis C patients during interferon alpha and/or ribavirin treatment, and diagnostic tests for this adverse effect should be performed during the follow-ups (Acta gastroenterol. belg., **2005**, 68, **432-434**).

Keywords : Sarcoidosis, hepatitis C, interferon, ribavirin.

Introduction

Sarcoidosis is a chronic, multisystemic disorder of unknown aetiology (1). Specific inflammatory mediators, in particular interleukin-2 and interferon (IFN)-gamma, are involved in the pathogenesis of sarcoidosis (2-3).

Few cases of sarcoidosis that have complicated IFN alpha treatment have been reported (4-7). Because of its rarity and seriousness, we report a patient with chronic hepatitis C (CHC) that has not responded to a course of IFN alpha treatment, but has revealed a complicating sarcoidosis while on treatment with the combination of IFN alpha 2b and ribavirin.

Case report

A 50-year-old female was referred with right upper quadrant abdominal pain and elevated serum amino transferases levels (AST 120 U/L and ALT 184 U/L) against to normal limits (5-40 U/L). The physical examination, abdominal ultrasonography and chest x-ray were within normal limits. Hepatitis C virus antibody (anti-HCV) by enzyme immune assay and HCV-RNA by polymerase chain reaction were positive. The remaining biochemical, haematological, virological and immunological studies were also in normal limits. She was diagnosed to have CHC.

The liver biopsy revealed chronic active hepatitis. Recombinant IFN alpha 2b has been started at a dose of 3 MU, subcutaneously (sc), three times a week (tiw) for one year. The levels of transaminases were normal at one month and HCV-RNA became negative at the sixth month of treatment. HCV infection relapsed 6 months after the completion of interferon treatment. The transaminase levels raised (AST 46 IU/L, ALT 81 IU/L) and HCV-RNA became positive. Physical examination, chest x-ray, abdominal ultrasonography, complete blood count, erythrocyte sedimentation rate, other viral and immunologic markers were normal. The repeat liver biopsy revealed chronic hepatitis with histological activity index of 5/18. IFN alpha 2b 3 MU sc, tiw and ribavirin 1000 mg/daily per oral has been started. AST and ALT levels were within normal range after the first month of re-treatment and remained normal for the following 10 months. HCV-RNA was negative at the 6th and 11th month of treatment. The IFN dose was reduced progressively after the 7th month of treatment because of leucopoenia. During the 11th month, the patient had non-productive cough, dyspnoea and fever, erythrocyte sedimentation rate was 76 mm/hr, white blood count was 6300/mm^3, tuberculin skin test was negative, and chest x-ray revealed bilateral hilar masses and nodular infiltrations in the lung parenchyma. Pulmonary function test has shown mild restrictive type respiratory insufficiency. Serum angiotensin converting enzyme (ACE) level was 86.1 U/L (normal range 8-52 U/L), total calcium level was 10.3g/dl (normal range 8.4-9.7 g/dl) and inorganic phosphorus level was 4.7mg/dl (normal range : 2.3-4.5 mg/dl). Thorax computed tomography revealed mediastinal lymphadenopathy (LAP) and nodular infiltrations in the lung parenchyma (Fig. 1). For

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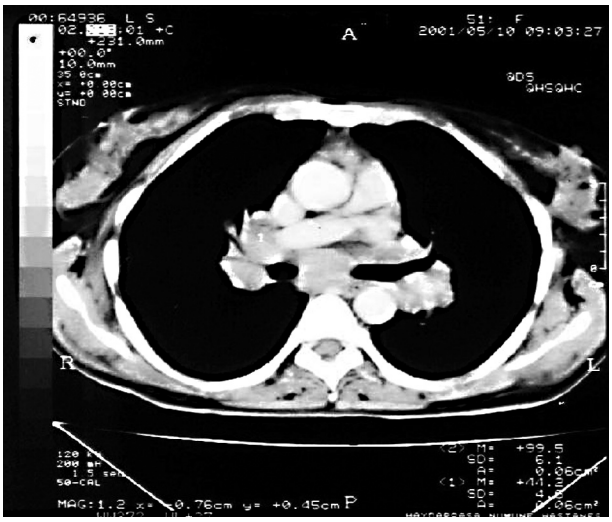

Fig. 1. — Thorax computed tomography revealed bilateral hilar and mediastinal (paratracheal and aorticopulmonary) lymphadenopathies.

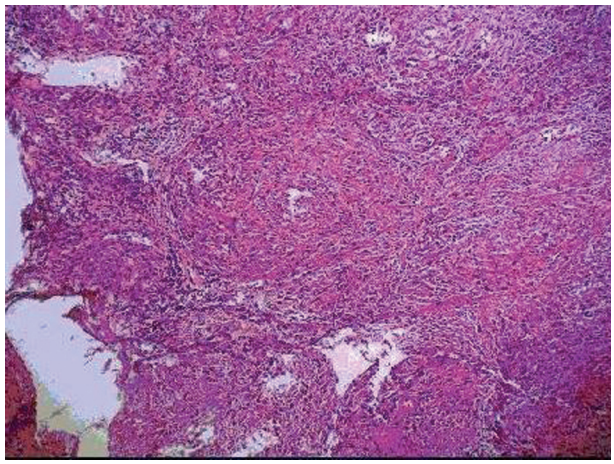

Fig. 2. — Lymph node tissue completely damaged by characteristic noncaseating granulomatous structures. (H&E, × 40).

a specific diagnosis, bronchoalveolar lavage fluid and transbronchial biopsy samples were obtained through bronchoscopy. However, non-specific results were obtained. Afterwards, biopsies were obtained from the LAP by mediastinoscopy. Histopathologic evaluation of the specimens revealed noncaseating granulomatous lymphadenitis (Fig. 2). Thus, the diagnosis of pulmonary sarcoidosis at stage II was established, and IFN and ribavirin treatment was discontinued.

After one month of follow up, no clinical and radiological remission was obtained, so an inhaler steroid (budesonide 1600 μg/day) was started. Symptoms regressed 2 weeks after inhaler steroid treatment, chest x-ray showed significant improvement, serum ACE level returned to normal (23 U/L). Inhaler steroid was discontinued after 2 months. Six months after the diagnosis of sarcoidosis, the patient was asymptomatic. Chest x-ray and thorax computed tomography, and serum ACE and transaminase levels were normal. HCV-RNA was negative.

During a follow up period of three years after admission, no recurrences of pulmonary sarcoidosis or hepatitis C was encountered.

Discussion

Pulmonary toxicity from IFNs is rare, with clinical evidence of pneumonia occurring in <1% of patients (8). Deregulated IFN-gamma production plays a role in the enhanced pulmonary macrophage activity that is observed in sarcoidosis (3, 9, 10). There is evidence that exogenously administered IFN alpha can activate macrophages in vitro (11). Increased lymphocyte, neutrophil and eosinophil counts and CD4/CD8 ratio were demonstrated in bronchoalveolar lavage fluids of HCV positive patients and it was stated that HCV may trigger alveolitis and pulmonary fibrosis (12, 13). Additionally, reports of increased percentage of anti-HCV positivity in idiopathic pulmonary fibrosis patients may point to a connection between the two diseases (14, 15).

Shiomi S et al (16) showed that in patients treated with IFN alpha for hepatitis C and examined with ^{67}Ga-citrate scanning, there was a significant increase in radionuclide uptake in the lungs after therapy, suggesting a subclinical inflammatory process in asymptomatic individuals. Ribavirin, like IFN, changes Th1/Th2 response (17), but there is no reported case of sarcoidosis during ribavirin treatment alone. The effect of ribavirin in combination treatments on the development of sarcoidosis needs further evaluation.

In our case, the patient had no symptoms and physical signs of sarcoidosis either before or after one year of IFN alpha 2b treatment in monotherapy. Sarcoidosis developed after combination treatment, during regression of CHC with negative HCV-RNA. All these findings suggest that long term IFN alpha and/or ribavirin treatment rather than HCV triggered development of sarcoidosis. While IFN gamma has been repeatedly cited, IFN alpha has not been implicated in the pathogenesis of sarcoidosis and less is known about the potential role of IFN alpha in the immunopathogenesis of sarcoidosis (2, 3, 5). There are case reports of sarcoidosis or idiopathic pulmonary fibrosis caused by IFN alpha treatment in CHC patients (4-7, 18). When we searched the literature in the main database (PubMed, MEDLINE) using the words “hepatitis C,” “interferon alpha,” “ribavirin,” and “sarcoidosis”, we have found a total of 11 matched references with 17 cases (4, 7, 18, 19-26). In these reports, 55% of the cases that developed sarcoidosis while on combination therapy were non-responders to interferon alpha alone. Combination therapy was interferon alpha plus ribavirin therapy in 15 cases and pegylated interferon plus ribavirin in the rest. One case in these reports had an exacerbation of previously diagnosed skin sarcoidosis (4). None of the authors have described subclinical pulmonary sarcoidosis in their

cases that had initially been treated with IFN alone. Following the combination therapy, lung, skin, and systemic involvement of sarcoidosis appeared in 50%, 43.75%, and 6.25% of these cases, respectively (4, 7, 18, 19-26). In our patient, we do not know whether a subclinic pulmonary inflammatory process occurred during the first IFN treatment (16). Although it is difficult to state if IFN alone, or combination treatment or cumulative dose of IFN has caused sarcoidosis in our case, in conjunction with other reports in which also sarcoidosis occurred during a second course of treatment, we may mostly accuse of cumulative dose of INF or combination therapy. On the other hand, it would have been possible to answer this question if non-invasive methods such as serum ACE levels or scintigraphic examinations had been routinely performed in patients under IFN treatment. Because of the rarity of the case reports and unknown cost effectiveness of systematically screening for sarcoidosis in all treated patients with CHC, sarcoidosis must be remembered and searched in the treatment course of CHC patients developing unexplained dyspnoea, cough, fatigue and other signs such as skin lesions.

Conclusion

Sarcoidosis can occur as a complication in CHC patients during IFN alpha and/or ribavirin treatment. Depending on symptoms and signs, sarcoidosis also should be remembered and searched in the IFN alone or combination treatment course of CHC patients.

Abbreviations

ACE = angiotensin converting enzyme ;
CHC = chronic hepatitis C ;
HCV = hepatitis C virus ;
IFN = interferon ;
LAP = lymphadenopathy.

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