

Multisystem Sarcoidosis in a Patient on Interferon- α Therapy for Chronic Hepatitis C

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ABSTRACT

Sarcoidosis is a chronic multisystemic granulomatous disease that is triggered by an autoimmune process. Nowadays, this pathology represents a well-recognized but uncommon complication for antiviral treatment in hepatitis C virus (HCV) infection. Herein, we report a remarkable case of 47-year-old woman treated for chronic HCV infection; the patient has developed interferon alfa-induced sarcoidosis involving the central nervous system. The evolution was fatal despite disrupting the antiviral therapy and initiating a high-dose corticotherapy. This complication of interferon alfa treatment was reported in the literature in only one case. Through this case and a review of the literature, we aim to underline the importance of screening for sarcoidosis before and during the follow-up of HCV patients undergoing antiviral therapy.

Key words: Chronic hepatitis C, Complication, Interferon alfa, Neurosarcoidosis, Treatment

INTRODUCTION

Sarcoidosis is a chronic multisystemic disease of unknown origin; it is characterized by an accumulation of noncaseating epithelioid granulomas. This pathology affects most commonly the lung, skin, lymph nodes, eyes, and rarely the nervous system.^[1] The relationship between the occurrence of sarcoidosis and interferon alfa (IFN- α) therapy in viral hepatitis C was suggested in earlier reports.^[1-4] This was also supported by the spontaneous resolution of sarcoidosis after cessation of IFN- α treatment for hepatitis C. Reported clinical manifestations include cutaneous sarcoidotic lesions, pulmonary nodules, and peripheral neuropathy.^[1,4]

In this paper, we report the second case in the literature of fatal central nervous system sarcoidosis secondary to IFN- α and ribavirin treatment.^[5] We aim to underline the importance of screening for sarcoidosis before and during the follow-up of hepatitis C virus (HCV) patients undergoing antiviral therapy.

CASE REPORT

Since March 2002, a 47-year-old woman without any history of sarcoidosis was regularly monitored in consultation for chronic viral hepatitis C (genotype 1). In April 2007, the alanine and aspartate aminotransferase serum levels have increased to 116 and 98 IU/l compared to normal values of 40 IU/l; the serum HCV RNA was 6.2×10^6 copies/ml. However, the physical and abdominal ultrasound examinations did not show any abnormalities. Because of the presence of biological cytolysis, a percutaneous liver biopsy was performed and revealed severe hepatic fibrosis (Metavir score A2/F3). Then, the antiviral treatment was started, and the patient received once a week the pegylated INF-2a at the rate of 180 μ g that injected subcutaneously, and ribavirin 400 mg was administrated orally twice a day. The biological response was good, and the transaminases were standardized after 2 weeks of treatment.

Six weeks after the beginning of the treatment, the patient noticed weight loss of 5 kg associated with dyspnea and progressive appearance of skin small firm nodules on both her upper and lower extremities. Chest X-ray was normal. However, thoracic computed tomography (CT) scan revealed pulmonary nodules associated with bilateral

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mediastinal lymphadenopathies, suggesting tuberculosis, lymphoma, and/or sarcoidosis. Abdominal CT scan was normal. The tuberculin skin test was negative. Afterward, bronchoalveolar lavage fluid was performed and showed an increased number of lymphocytes with a normal amount of eosinophils and neutrophils. The histological study of transbronchial lung biopsy revealed a patchy distribution of mild interstitial and perivascular fibrosis, without distinctive granulomas or significant inflammatory cell infiltrations. In addition, cultures for fungi, mycoses, and tuberculosis were all normal. Finally, a biopsy of the skin nodules was performed and found a noncaseating epithelioid granuloma formation strongly suggestive of sarcoidosis [Figure 1]. The serum angiotensin-converting enzyme was significantly elevated (130 U/l for the normal value <40 U/l); the diagnosis of sarcoidosis was retained and oral corticotherapy was started at the dose of 60 mg daily.

Four days later, the patient suddenly presented a heaviness of the right upper limb predominant distally, associated with a right central facial paralysis and aphasia; however, she was lethargic and her ophthalmologic examination was normal. The cerebral magnetic resonance imaging (MRI) showed a gyriform and nodular left frontal and parietal subcortical enhancement associated with an important perilesional edema [Figures 2a-b]. INF- α and ribavirin therapies were discontinued, and intravenous bolus methyl prednisolone was then started at the rate of 10 mg/kg/day for consecutive 3 days; this was followed by prednisone (1 mg/kg/day). Nevertheless, no clinical improvement was noticed. On the contrary, the neurological state of the patient worsened rapidly and the patient died a week later.

DISCUSSION

More than 170 million people worldwide are infected with chronic viral hepatitis C.^[6] Current antiviral treatments are effective in eradicating the virus in up to 60% of patients. Several treatment regimens have been used. Pegylated IFN- α plus ribavirin was found to be superior to all other protocols for sustained eradication of the HCV, especially in individuals with more resistant viral genotypes 1, 4, 5, and 6.^[7]

Although several reports have suggested an association between IFN therapy and sarcoidosis, this association was rarely described in the literature. In 1987, Abdi *et al.*^[3] had described the first case of pulmonary sarcoidosis in a patient who received IFN- β treatment for renal cell cancer. Since then, various cases have been published

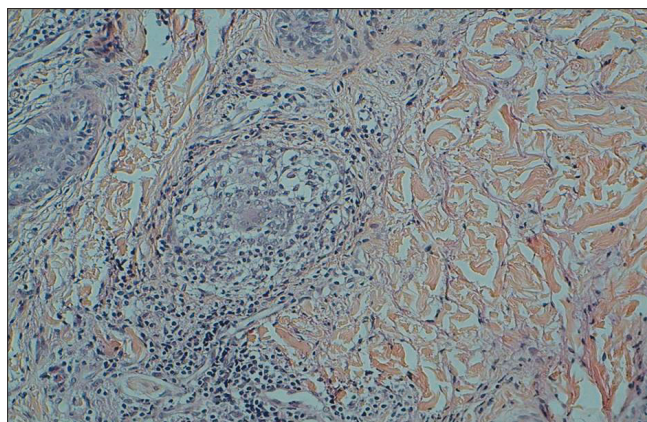


Figure 1: No caseating epithelioid granuloma formation composed of macrophages, lymphocytes, and fibroblasts

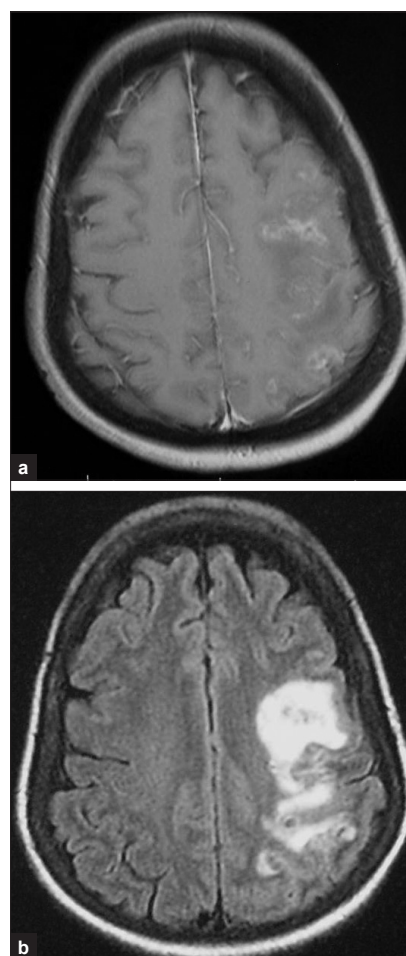


Figure 2: Cerebral MRI in postgadolinium axial T1-weighted image (a) and FLAIR image (b), showing a gyriform and nodular left frontal and parietal subcortical enhancement associated with an important perilesional edema

suggesting a relationship between sarcoidosis and IFN treatment in patients with a variety of diseases, including renal cell carcinoma, hematological malignancies, and viral hepatitis. So far, more than 30 cases of sarcoidosis occurring in the context of chronic hepatitis C treated by

INF- α have been reported in the literature.^[2-4] Reported clinical manifestations include cutaneous sarcoidotic lesions, pulmonary nodules, and peripheral neuropathy. In this paper, we report the second case in the literature of severe central nervous system sarcoidosis secondary to INF- α treatment. To the best of our knowledge, only one case of neurosarcoidosis associated with INF therapy has been reported in the literature.^[5]

Most of the cases described in the literature occurred in patients who have received a treatment combining INF- α or pegylated INF- α and ribavirin.^[4] Indeed, it is well recognized that INF- α is an immunomodulator that has not only direct antiviral activity but also powerful stimulation of the immune activities, especially on T-helper (Th1) immune response,^[8-10] which is strongly involved in the pathogenesis of sarcoidosis.^[11,12] Furthermore, granulomas in sarcoidosis are associated with an abundance of CD4⁺ T lymphocytes and mononuclear phagocytes, which are being considered a result of cytokine stimulation and immunologic dysregulation.^[13]

Importantly, in cases of chronic hepatitis C, INF could induce^[2] and reactivate sarcoidosis,^[14] and INF-based combination antiviral regimens cannot eliminate the occurrence of sarcoidosis.^[15] In contrast, ribavirin, an antiviral agent that increases the anti-HCV effect of INF in chronic hepatitis C, would also enhance Th1 cytokine response while inhibiting Th2 cytokine response.^[11,12]

All patients previously solely treated with INF- α did show any manifestation of sarcoidosis. Furthermore, there was no case report of sarcoidosis in patients treated using ribavirin only. This suggests that the combination of INF- α and ribavirin enhances the immune response, consequently predisposing the patient to sarcoidosis.

The mean time to the onset of the disease after starting INF- α therapy is 4 months.^[1] In our case, manifestations of sarcoidosis occurred earlier, associating rapid deterioration of clinical symptoms, which lead to death in 10 weeks.

Most patients with INF- α associated sarcoidosis had spontaneous resolution of the disease without immunosuppressive treatment. Indeed, INF- α treatment was discontinued in several cases and subsequent resolution of sarcoidosis within months has followed. In contrast, the treatment protocol was not modified in other cases, and the sarcoidosis resolved several months later, either during or after the achievement of treatment. However, some patients were treated with oral corticosteroids with rapid resolution of sarcoidosis. Indeed, steroids that are the

main treatment for systemic sarcoidosis increase the HCV load in both *in vitro* and *in vivo*.^[16] Thus, physicians should exert caution while treating INF- α associated sarcoidosis with systemic corticosteroids.

The prognosis of peripheral neurosarcoidosis is better as compared to the central nervous system involvement, which leads to higher disability and mortality.^[16,17] In addition, neurosarcoidosis of the CNS usually occur in the early stages of the disease, while peripheral nervous system and skeletal muscle sarcoidosis are typically seen in the chronic stages of the disease.^[17] This would suggest that our patient has recent neurosarcoidosis after introducing INF- α and ribavirin therapy.

CONCLUSION

Based on this case report, INF- α associated sarcoidosis might also include CNS involvement and might lead to death. Considering earlier reports of heterogeneous spectra of sarcoidosis manifestations, clinicians should be aware of associated potential complication while evaluating the benefit/risk ratio of the treatment in patients with chronic hepatitis C infection. Therefore, patients suggested such treatments are recommended to be monitored for sarcoidosis before and during INF therapy.

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