Pulmonary sarcoidosis during interferon therapy: a rare or underestimated event?

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Interferon (IFN)-α with or without ribavirin is the treatment of choice for patients with chronic HCV-related hepatitis. Cough and dyspnea during IFN therapy are often regarded as a side effect and not as a possible sign of the onset of a pulmonary interstitial disease. It may therefore be claimed that the likelihood that patients treated with IFN develop sarcoidosis is being underestimated. Although they are not conventionally classified as etiopathologic agents of sarcoidosis, the IFNs have been proven to be capable of triggering macrophages and of promoting the expression of class II HLA antigens. It is therefore possible that IFN-α treatment could trigger macrophages and promote the polarization of the immune response towards Th1 in the presence of particular susceptibility conditions, thus starting the series of events that lead to the onset of sarcoidosis. We describe a case of pulmonary sarcoidosis in a 33-year-old patient treated with IFN-α2b and ribavirin for chronic HCV-related hepatitis after 6 months of therapy. The case we report here brings forth the issue of a possible underestimation of the real incidence of sarcoidosis during IFN therapy and highlights the need for more attention to and a more careful evaluation of respiratory symptoms manifesting in treated patients.


Key words: Chronic hepatitis; Interferon; Sarcoidosis.

Introduction

Interferon (IFN)-α, with or without ribavirin, is the treatment of choice for patients suffering from chronic HCV-related hepatitis1, both primary and recurrent infection. Moreover, IFN-α and -β are nowadays used in the treatment of various diseases such as chronic myeloid leukemia, hairy-cell leukemia, Kaposi’s sarcoma, kidney carcinoma, multiple myeloma, condyloma acuminatum and multiple sclerosis2-7.

Some respiratory symptoms, such as cough and dyspnea, are often viewed during IFN-based therapy as a side effect of the drug and not as a possible sign of the onset of a pulmonary interstitial disease, some of the symptoms of sarcoidosis being similar to the pulmonary reactions originating after the use of IFN2. In addition to IFN toxicity, oral ribavirin increases the risk of cough and dyspnea8. Sarcoidosis, moreover, may also manifest a long time after the suspension of IFN therapy. It may therefore be claimed that the likelihood of this event is being underestimated9.

Recently, a dramatically high incidence of pulmonary sarcoidosis (3/60 cases, 5%) has been reported in a cohort of chronic HCV-related hepatitis patients who had participated in a controlled randomized trial with IFN-α2a in monotherapv versus IFN-α2a combined with ribavirin. With regard to these patients, sarcoidosis developed both in the combined therapy group patients and in the control group9.

The rarity with which sarcoidosis during IFN therapy is reported is all the more surprising if one considers the number of patients treated with IFN all over the world to cure the above-mentioned diseases. Indeed, very few cases of sarcoidosis (mainly lung-located) manifesting during IFN therapy, whether or not combined with ribavirin1-5,7-18, have so far been reported. Finally, there is only one reported case in whom sarcoidosis improved during IFN-α therapy19.

We here describe a case of pulmonary sarcoidosis manifesting in a patient treated with IFN-α2b and ribavirin to cure an active chronic HCV-related hepatitis.

Case report

In November 1997, a 30-year-old male with periodically increased levels of the liver transaminases (1.5-2 ULN), anti-HCV positivity and an HCV-RNA positive polymerase chain reaction (AmpliCor Roche 2.0, Branchburg, New York, USA) was submitted to liver biopsy and diagnosed as having “active chronic hepatitis, with fibrosis and moderate activity, HCV-related, HCV-RNA positive, genotype 1b”.

In January 1998, the patient was started on monotherapy with IFN-α2b (3 MU 3 times a week). During this therapy no other treatment was administered. The patient tol-
erated the therapy fairly well, and the 12-month treatment period was completed without problems. The transaminase levels returned within the normal range and the HCV-RNA serum response turned negative after 3 and 6 months and at the end of the therapy.

Treatment suspension was followed by recurrent positivity for HCV-RNA and by a new increase in the transaminase levels. After 1 year, due to persistently high transaminase levels (1.5-2 ULN) the patient was started on a new cycle of therapy including IFN-α2b 3 MU 3 times a week combined with ribavirin 1000 mg/die. The therapy was well tolerated for the first 3 months except for the common side effects of IFN such as a flu-like syndrome and a slight mood change accompanied by moderate itching, that regressed once the ribavirin dose was decreased to 800 mg/die. After 6 months of therapy the qualitative HCV-RNA response was negative and the aspartate aminotransferase/alanine aminotransferase values returned in the normal range. After 7 months the patient started suffering from mild effort dyspnea and a mild cough without catarrh. After 8-9 months of therapy the respiratory symptoms worsened, and chest pain appeared. ECG showed slight repolarization anomalies, while the creatine phosphokinase (CPK) and CPK-MB serum levels were still within normal values. Chest X-ray (Fig. 1) revealed extensive interstitial filling, more evident in the two hilar regions. A high-resolution computed tomographic scan (Fig. 2) showed dissemination of small nodular sub-centimeter parenchymal and sub-pleural formations, on both sides, and also the presence of lymph-node swellings in the Barety cavity, in the pre- and sub-carina areas and at the hilar level.

The patient was submitted to spirometry, which revealed a mild ventilation deficit (forced vital capacity-FVC 96% of the expected value; forced expiratory volume in 1 second-FEV1 88% of the expected value; FEV1/FVC 72), with a slight decrease in carbon monoxide alveolar-capillary diffusion (85% of the expected value). Blood gas analysis was suggestive of mild hypoxemia (PaO2 80.1 mmHg; PaCO2 36.7 mmHg; pH 7.430 U). The Mantoux skin test was negative after 72 hours; the angiotensin-converting enzyme serum values were normal (99 U, normal values 40-120 U). Peripheral blood lymphocyte phenotype analysis revealed a substantial reduction in CD4+ lymphocytes (429/mm3, 19%, normal values 40-55%), with a normal CD8+ count (943/mm3, 41%, normal values 20-45%). The patient underwent fiberoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage. Examination of the bronchoalveolar lavage fluid was suggestive of the presence of lymphocytic alveolitis with a CD4/CD8 ratio 3.7 [(cellularity 3.0 • 105 (0.5-1.5 • 105); macrophages 62% (75-85%); neutrophils 2% (1-2%); lymphocytes 35% (8-12%); CD4+ 67% (40-60%); CD8+ 18% (30-50%); CD4+/CD8+ 3.7 (0.8-2)]. Transbronchial biopsy was not diagnostic. The patient was then offered pulmonary video-thoracoscopic biopsy, that he refused. Whole body scintigraphy with 67Ga-citrate documented evident uptake in both lungs [2+ (range 0-3)], with uptake also at the eyeballs and the parotids. Ophthalmic evaluation did not highlight any ocular lesion. Finally, there was no peripheral adenopathy, nor any evident cutaneous lesions.

Due to the lack of histobioptical data (because of the patients’ refusal to undergo pulmonary video-thoracoscopic biopsy) the diagnosis of sarcoidosis was made using a probability rank20 based on the evidence of a
lymphocytic alveolitis with a CD4/CD8 ratio > 3.5 (3.7 in our case) provided by the bronchoalveolar lavage together with the uptake of the $^{67}$Ga-citrate in the pulmonary hilar, parotid and ocular areas (the so called “Panda + Lambda” sign).

At dismissal, the patient was prescribed prednisone treatment (37.5 mg/day). At the first follow-up visit, 1 month after dismissal, the clinical symptoms had apparently improved. The cough had significantly decreased both in frequency and intensity and the effort dyspnea had almost disappeared.

Four months after the initiation of the corticosteroid therapy the patient underwent a chest high-resolution computed tomography (Fig. 3) that showed a substantial improvement of the “emery glass” areas and of the widespread micro-nodular-based interstitial thickening evident at the onset of the disease. The respiratory function (spirometry, arterial blood gas analysis) had also improved and the carbon monoxide alveolar-capillary diffusion was within normal limits.

At present, after an 18-month follow-up, the patient refers a continual and steady improvement with complete regression of the cough, dyspnea and asthenia and a normal respiratory function.

**Discussion**

Sarcoidosis is a chronic, granulomatous multisystemic disease of unknown origin, histologically characterized by granulomatous non-curdling infiltrations. Many are the hypotheses regarding the etiology of this disorder: environmental factors, infective agents and autoantigens. However, so far a specific agent has not yet been identified$^{21}$. Genetic factors have to be regarded as important, since sarcoidosis is more frequent among Northern Europeans and African Americans. Moreover, some studies suggest that certain inflammatory mediators, namely interleukin (IL)-2 and IFN-$\gamma$, are involved in the pathogenesis of the disease$^{22-24}$. On the other hand, sarcoidosis is a typical example of an immuno-induced disease and it is not surprising that IFNs, characterized by a strong stimulatory and regulatory effect on the immune response, could play a leading role in the pathogenesis of this disease$^{23,25-28}$.

In fact, although they are not regarded as true etiopathogenetic factors for sarcoidosis, *in vitro* IFNs may trigger the alveolar macrophages of patients suffering from sarcoidosis, an event that is characteristic of this pathology$^{2,29}$ as far as immuno-pathology is concerned, and also start the polarization of the immune response towards the Th1-type granulomatous inflammation reported in sarcoidosis$^9$.

Such a polarization, in turn, steers cytokine production towards an IFN-$\gamma$/IL-2-type pattern. In sarcoidosis, moreover, a remarkable increase in the production of IL-12, an immune-regulatory cytokine that produces a strong Th1-oriented promoting action, has been reported$^{30-32}$. On the other hand, the alveolar macrophages of patients with pulmonary sarcoidosis as well as those of patients with non-active disease if exposed to IFN-$\gamma$ spontaneously.

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However, although the role of IFN-$\gamma$ in the immuno-pathogenesis of this disease has been thoroughly investigated, that of IFN-$\alpha$ still merits further attention.

The triggering capacity of IFN-$\alpha$ at the onset of autoimmune diseases such as thyroid diseases, insulin-dependent diabetes, rheumatoid arthritis, lupic syndromes and idiopathic thrombocytopenic purpura is known$^{26,33}$. This effect is probably mediated by the upsetting of the tolerance/autoimmunity balance. Indeed, although the biological characteristics of IFN-$\alpha$ and $\beta$ (class I IFNs) are different from those of IFN-$\gamma$ (the localization of genes on different chromosomes, different receptors and molecular structures), and although only the latter is credited with being capable of triggering macrophages and promoting the expression of class II HLA antigens$^{27}$, experimental evidences prove that class I IFNs can perform similar biologic activities$^{34}$. In particular, IFN-$\alpha$ seems capable of adjusting the T response at different levels and promotes Th1-oriented polarization, inhibits Th2 triggering, stimulates the production of IFN-$\gamma$ and the emergence of receptors for IL-12 and, lastly, it counters the effects of IL-4 and the production of IL-5$^{35-39}$.
It is therefore possible, as suggested by previous reports, to claim that the therapeutic administration of IFN-α may, in the presence of particular susceptibility conditions (for example the emergence of increased values of IL-12-mRNA), trigger the cascade of immunological events that in turn lead to the onset of sarcoidosis.

Finally, as an alternative, it is possible that the administration of IFN-α is capable per se of initiating the cascade of immunopathologic events that are at the basis of sarcoidosis, while in other cases it only helps to reveal a latent (sub-clinical) sarcoidosis.

We think that the case described above poses – from a clinical point of view – the problem of a possible underestimation of the actual incidence of sarcoidosis during IFN therapy and highlights the need for more attention to and a more careful evaluation of the respiratory symptoms manifesting in treated patients.

Even in the absence of histobiopitical data these patients could benefit from the application of the screening protocol recently proposed for cases of suspected or ascertained sarcoidosis (Table I). Further information could be obtained by monitoring the serum levels of angiotensin-converting enzyme and of β2-microglobulin and the 24-hour calcium excretion, as even these are markers of disease activity.

**Table I. Screening for patients with suspected or ascertained sarcoidosis**

<table>
<thead>
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<th>Test</th>
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<tr>
<td>X-ray, antero-posterior and latero-lateral</td>
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<tr>
<td>Spirometry, DLCO and KCO</td>
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<tr>
<td>Blood cell count</td>
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<tr>
<td>Blood calcium, transaminases, alkaline phosphatase, azotemia, creatinine level</td>
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<tr>
<td>Urine testing</td>
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<td>Electrocardiography</td>
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<td>Mantoux skin testing</td>
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<td>Ophthalmic evaluation</td>
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Riassunto

La terapia con interferone (IFN)-α con o senza ribavirina, è il trattamento di elezione dei pazienti con epatite cronica da HCV. Le manifestazioni cliniche polmonari, quali tosse e dispnea, in corso di terapia con IFN vengono spesso considerate effetti collaterali del farmaco e non possibili manifestazioni dell’insorgenza di un’interstizialpatia polmonare. Si può quindi ipotizzare che la possibilità che pazienti trattati con IFN sviluppino una sarcoidosi sia attualmente sottostimata. Pur non essendo convenzionalmente classificati come agenti eziologici nella patogenesi della sarcoidosi, gli IFNs si sono rivelati in grado di attivare i macrofagi e di promuovere l’espressione di antigeni HLA di classe II. È possibile pertanto che la somministrazione a scopo terapeutico di IFN-α, in particolari condizioni di suscettibilità, determinando attivazione macrofagica e promuovendo la polarizzazione in senso Th1 della risposta immune, possa innescare la cascata di eventi che conduce alla sarcoidosi. Le segnalazioni in letteratura di sarcoidosi polmonare, insorta in corso di terapia con IFN con o senza ribavirina, sono a tutt’oggi infrequenti. Riportiamo il caso di una sarcoidosi polmonare insorta in un paziente di 33 anni in terapia con IFN-α e ribavirina per il trattamento di un’epatite cronica attiva HCV-correlata, che al sesto mese di terapia manifestava sintomatologia polmonare con tosse e dispnea da sforzo. Il caso da noi segnalato ripropone il problema della possibile sottostima dell’incidenza reale del fenomeno sarcoidosi in corso di terapia con IFN e ripropone, quindi, la necessità di un maggior controllo e di una più attenta valutazione della sintomatologia respiratoria insorta nei pazienti trattati.

**Parole chiave:** Epatite cronica; Interferone; Sarcoidosi.

**References**


