Multisystemic sarcoidosis associated with a second therapy for chronic hepatitis C

A. Froidure[1], Y. Horsmans[2], C. Lefebvre[1]

(1) Department of General Internal Medicine and (2) Gastroenterology, St Luc University Hospital, Brussels, Belgium.

Abstract

Hepatitis C virus (HCV) infection is a very common chronic infectious disease. Combined antiviral therapy including pegylated interferon and ribavirine is presently the standard treatment, with sustained viral response rate over 50%.

Interferon induces the development of several autoimmune diseases. Some cases of induced sarcoidosis have been described (affecting mostly lungs, skin and eyes), both with standard and pegylated interferon.

We report the case of an African woman, heterozygote for sickle cell anaemia mutation and for glucose-6-phosphate-deshydrogenase (G6PD) deficiency, who developed a multisystemic sarcoidosis (skin, lungs, liver, salivary and lachrymal glands, peripheral nerves), confirmed by biopsies, in the course of a second treatment with pegylated interferon and ribavirine for hepatitis C.

The antiviral treatment was discontinued and all symptoms regressed spontaneously within some weeks. (Acta gastroenterol. belg., **2009**, 72, **249-251**).

Introduction

HCV infection affects about 170 millions people worldwide (1). The present optimal treatment includes two main drugs : pegylated interferon and ribavirine. It allows up to 54-56% of patients to have a sustained viral response (2). Unfortunately, interferon has many side effects, affecting a very high proportion of patients. The common secondary effects include asthenia, influenza-like syndrome, psychological disorders or alopecia. Interferon has been also implicated in the genesis of several autoimmune diseases. A few reports of sarcoidosis, affecting mostly lungs, skin and eyes are published.

Case report

We report the case of a 58-year-old African woman, heterozygote for the sickle cells anaemia mutation and for G6PD deficiency mutations.

Hepatitis C was discovered in 2002. A first treatment, including pegylated interferon, ribavirine and amantadine was started in 2003. Viral load turned negative in 4 months, but the treatment had to be stopped 2 months later because she developed pain, paresis and dysaesthesia in both legs. A neuromuscular biopsy showed lesions of vasculitis without granulomas affecting nerves. This vasculitis was probably induced by interferon. The symptoms disappeared progressively after stopping the drug.

Two years later, viral load and liver enzymes both increased and a liver biopsy showed signs of fibrosis (Metavir F2) without granulomas. A new treatment, including subcutaneous injections of pegylated interferon (180 µg per week) and ribavirine (1000 mg per day, orally), was started. After 3 months, viral load could not be detected and the liver enzymes turned normal.

One month later the patient developed a gradual dryness in mouth and eyes, with pain, loss of taste and decline of sense of smell. She presented a transient bilateral swelling of parotid glands. The symptoms increased during another two months, along with the development of a progressive dyspnoea and exhaustion. Furthermore, she also complained about pain and weakness in both legs associated with dysaesthesia and paraesthesia.

Skin lesions appeared in the regions of the elbows and the ankles.

At physical examination, the patient presented a general asthenia and force had decreased in both legs. Non pruritic papules were present on both elbows and ankles and also on an ancient scar of hysterectomy (Fig. 1).

At auscultation, bilateral inspiratory and expiratory crackles could be heard.

Blood sample analysis showed the following relevant results : ALT 27 U/L (14-63 U/L), AST 43 U/L (6-33 U/L), gamma GT 360 U/L (7-50 U/L), alkaline phosphatase 158 U/L (28-94 U/L), serum ACE 31.9 U/L (8.0-26.9 U/L), blood lysozyme 24 mg/L (< 17 mg/L).

A thoracic scanner showed an interstitial syndrome in both lungs with fibrosis and bronchiectasias, without mediastinal adenopathy (Fig. 2).

Functional respiratory explorations confirmed the presence of a restrictive syndrome, with the following values : FEV 1.34 L (59%), FVC 1.41 L (51%). Diffusing capacity of the lung for carbon monoxide (DLCO) could not be evaluated due to the severity of the restrictive syndrome.

Broncho-alveolar liquid was collected by bronchoscopy and analysed : the cell concentration was 248 millions per mL, with 61% of lymphocytes and an increased

Correspondence to : Antoine Froidure, Rue des Déportés, 92, 6700 Arlon, Belgium. E-mail : a_froidure@hotmail.com

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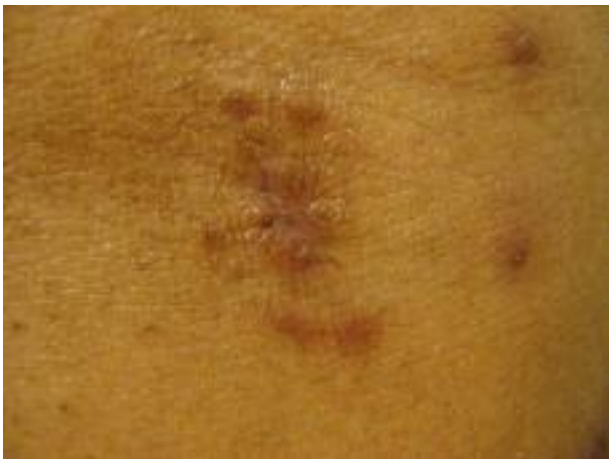

Fig. 1. — Cutaneous papules (elbow)

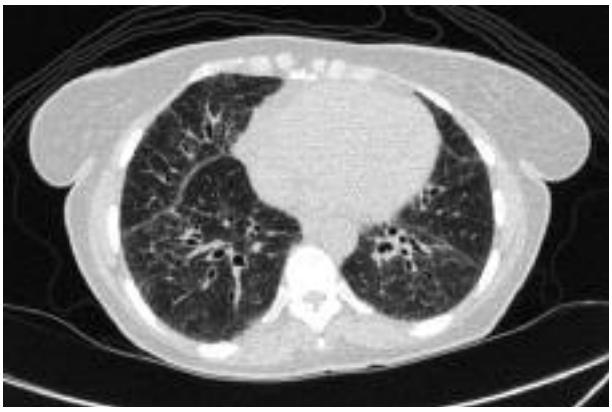

Fig. 2. — Thoracic scanner image showing bilateral lung fibrosis with bronchectiasias.

ratio between T4 and 78 lymphocytes at 3.16. Histological examination of epithelial cells showed the presence of multiple granulomas without caseous necrosis.

Electromyography of the lower limbs showed a bilateral acute mononeuritis (L4, L5 and S1 myotomes).

Finally, biopsies were performed in salivary gland, liver and skin. All of them showed multiple noncaseating granulomas, suggesting a sarcoidosis (Fig. 3).

Both drugs were discontinued, leading to a decrease of symptoms. Three weeks later, dry syndrome and dyspnoea improved.

One month later, a control of the blood test showed a regression of cholestasis : ALT 18 U/L (14-63 U/L), AST 33 U/L (6-33 U/L), gamma GT 196 U/L (7-50 U/L), alkaline phosphatase 149 U/L (28-94 U/L). The viral load was still negative.

Skin lesions were smaller and less numerous ; dysaesthesia and paraesthesia improved too.

Two months after stopping pegylated interferon and ribavirine, no corticotherapy was administered yet.

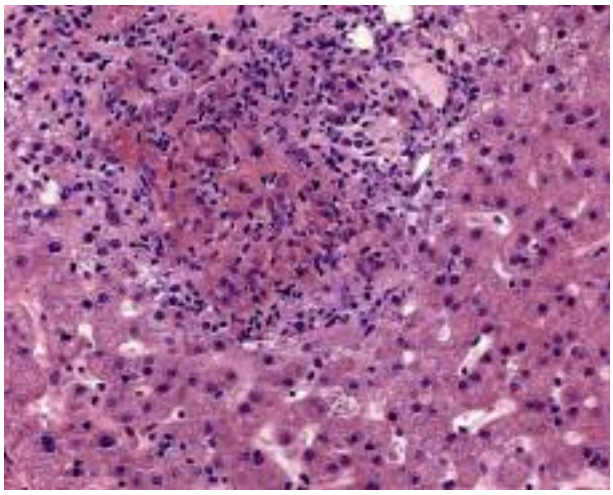

Fig. 3. — Liver biopsy showing non-caseiting granuloma (H&E, magnification 640 ×20).

Discussion

The patient had a multisystemic sarcoidosis, demonstrated by biopsies, with skin, lungs (stage III), liver, glands and nervous lesions, probably due to her treatment with pegylated interferon and ribavirine.

Sarcoidosis is an auto-immune systemic disease characterized by an inappropriate immune response to one or several antigen of unknown origin, involving Th1 mediated response. Interleukine-2 and interferon-γ activate macrophages, leading to the formation of granulomas (3, 4). The disease affects mostly middle-aged women, but both sex and all ages can be affected.

Rare cases of sarcoidosis occurring during a treatment with interferon and ribavirine have been reported since 1987 (3), both with standard and pegylated interferon (3, 4, 5). These cases have been reported with interferon alone or with interferon and ribavirine but never with ribavirine alone (5).

The incidence of interferon-induced sarcoidosis is unknown as sarcoidosis can be clinically silent. This rare side effect usually occurs in the first 6 months of treatment (6).

The current hypothesis concerning interferon-related sarcoidosis is that interferon induces the differentiation of lymphocytes to CD4 rather than CD8 (7). In vitro, ribavirine seems also to have an action on lymphocytes differentiation (8). This leads to an elevated activation of macrophages and to the formation of granulomas. The triggering antigen for this immune response could be the hepatitis C virus itself (4).

Interferon-induced sarcoidosis involves lungs in 70% of cases and skin in 60%, versus 90% and 25%, respectively, in idiopathic sarcoidosis (4). All other organs can be also affected.

The difficulty of the diagnosis comes from the fact that systemic symptoms in a patient with hepatitis C can be explained by the disease itself (polyarteritis nodosa,

mixed cryoglobulinemia), or by more classical side effects of pegylated interferon, such as influenza-like syndrome or vasculitis. The clinician must then be careful to consider sarcoidosis in the differential diagnosis. Biological findings (high ACE level, high T4/T8 ratio or high lysozyme), radiological exams (thoracic imaging) and histological analysis (noncaseiting granulomas) are useful to lead to the diagnosis.

The first particularity of this case lies in the fact that the patient suffered from induced sarcoidosis after a second cure with pegylated interferon. The first cure had been interrupted because of a vasculitis induced by the drug (biopsy performed at that time showed vascular lesions without granulomas). This indicates that the treatment itself and the hepatitis C virus do not seem to be sufficient to induce a sarcoidosis and that other environmental aspects must play a role in the physiopathology of induced sarcoidosis.

The second notable characteristic of this case is the multisystemic pattern of the disease, which affected lungs, skin, salivary and lachrymal glands, liver and peripheral nerves. So far, it is the first case of such an extended sarcoidosis occurring during a treatment with pegylated interferon. This could be explained by the African origin of the patient while the other cases reported concern Caucasians. It is known that Africans suffer from more severe forms of sarcoidosis (9).

Another explanation could be the heterozygote genotype of the patient for G6PD deficiency. This enzyme plays an important role against oxidative stress. A more severe case of idiopathic sarcoidosis has already been described in a patient heterozygote for G6PD deficiency (10) and more recently, a study has shown that antioxidative defences are reduced among patients who suffer from sarcoidosis (11). Those elements indicate that oxidative stress pathways might have a role in the pathogenesis of the disease.

It is well established that interferon-alpha may induce many autoimmune diseases (12, 13). Interferon-alpha seems to over-activate B lymphocytes and to inhibit lymphocytes apoptosis through an up-regulation ofBCl-2 and a modulation of the Fas system. Beside that, interferon induces an over-expression of type I and II major histocompatibility complexes (13). This increases the occurrence of autoimmune diseases. Our patient suffered from two distinct autoimmune syndromes while treated with pegylated-interferon at different periods (neuromuscular vasculitis and sarcoidosis). It is likely that she presents a very high sensitivity to immunomodulating treatments, maybe due to her particular phenotype.

The treatment of interferon-induced sarcoidosis consists in stopping the drug. Most cases regress within some weeks or some months without corticosteroids administrated. Some cases required topic steroids, and general steroids were necessary only for a few patients (4). It was remarkable that the case we describe did not require corticosteroids despite the severity of the affection.

In conclusion, the occurrence of a sarcoidosis is a very rare side effect of the treatment of hepatitis C with interferon and ribavirine. It can be revealed by multisystemic symptoms. The differential diagnosis includes systemic manifestations of hepatitis C and other side effects of the treatment. The diagnosis is based on clinical, biological, radiological and histological features.

We describe an original case of induced sarcoidosis, which occurred after the second cure with pegylated interferon and presenting with a multisystemic pattern.

The induction of a sarcoidosis by interferon and ribavirine helps to understand the physiopathology of this granulomatous disease, characterised by an over activation of CD4 lymphocytes. It also illustrates the polypathogenic nature of sarcoidosis.

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