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Cutaneous Sarcoidosis: An Uncommon Side Effect of Pegylated Interferon and Ribavirin Use for Chronic Hepatitis C

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Key Words
Sarcoidosis · Hepatitis C · Interferon · Pegylated interferon alpha · Granulomatous dermatitis · Tattoo

Abstract
The treatment of chronic hepatitis C (CHC) has evolved in the past 15 years and combination of pegylated interferon plus ribavirin is its current standard therapy. However, several side effects are commonly observed and frequently lead to transient or definitive interruption of treatment. Although sarcoidosis in its systemic or cutaneous form is a very rare side effect in such circumstances, some cases have been reported even with conventional interferon. This brief review of the literature and description of a case of sarcoidosis occurring in a tattoo and a scar patient's face, during treatment with pegylated interferon alpha-2b plus ribavirin, is an educative report directed in special to dermatologists. The lesion improved after drug interruption and recurred after retreatment with pegylated interferon alpha-2a. We conclude that this side effect must call the attention of doctors to seek for the diagnosis and therapy as soon as possible in such circumstances. No differences were noticed neither with alpha-2a nor alpha-2b pegylated interferon employment.

Introduction

The treatment of chronic hepatitis C (CHC) has evolved in the last 15 years from monotherapy with interferon alpha (IFNalpha) to the combination treatment with

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pegylated IFN (peg-IFN) plus ribavirin for 24–48 weeks [1, 2]. Up to now, several viral, host and drug-related reactions in response to IFNalpha-based therapy have been identified [1, 3]. Recent studies suggest that liver inflammation in CHC is controlled by several mechanisms, including host regulatory immune responses and viral polypeptides interacting with cells involved in innate and adaptive immunity [4]. It is well known that cutaneous side effects of treatment with IFNalpha alone or IFNalpha plus ribavirin in patients with CHC have been widely reported, beyond the fact that the virus itself can cause skin lesions. However, the cutaneous side effects during therapy of CHC are of inflammatory type with local erythema, edema and, much less frequently, necrosis at the injection skin sites. By contrast, skin side effects of such drugs have few data available in the literature [5], although the number of reports has been increasing in the last years, including cosmetic filler site injections [6–11].

Sarcoidosis is a multisystem granulomatous disorder of unclear etiology. There are almost 30 cases of IFN-induced sarcoidosis reported in the literature [12, 13]. Roughly one half of these patients had cutaneous findings, either alone or with systemic involvement. More recently there have been reported dermatological diseases in patients receiving the combination of IFN/ribavirin or IFN/ribavirin/amantadine for the treatment of CHC [12, 13].

Case Report

A 44-year-old man with CHC genotype 1a and a viral load of HCV >800,000 IU/ml, A2-F1 on liver biopsy according to METAVIR criteria, was treated for the hepatic disease. He had a seahorse tattoo in left deltoid region. Peg-IFNalpha-2b 1.5 μg/kg weekly and 1,000 mg of ribavirin daily was introduced. In the 40th week the patient reported sudden intense pain, pruritus, erythema and skin hypertrophy in the left deltoid area over the seahorse tattoo and in a scar on his face (**fig. 1**). A skin biopsy on the scar and tattoo showed granulomatous dermatitis (**fig. 2**). All tests for fungi and mycobacterium were negative. Chest X-ray was normal and the level of angiotensin enzyme converter was 50 IU/ml (range 18–55 IU/ml). Hydrocortisone butyrate 1% cream was prescribed for topical use four times daily. A moderate relief occurred and the treatment could be completed until the 48th week. We intend to call attention especially to dermatologists to the possibility of a granulomatous tattoo reaction as a side effect during CHC treatment with peg-IFNalpha-2b plus ribavirin. Until now, eight cases of sarcoidosis as a complication of IFN therapy in CHC have been reported in the English language literature [14–18]. The most relevant topic in this case is the occurrence of disease on a tattoo area.

Six months later retreatment using peg-IFNalpha-2a 180 μg once a week plus ribavirin 1,000 mg daily was tried. In the 6th week, cutaneous symptoms relapsed in an unbearable way. The patient did not accept to continue therapy, since hydrocortisone cream was prescribed again but no satisfactory pruritus and pain improvement was noticed. A prompt regression of skin reaction occurred after stopping therapy.

Discussion

Sarcoidosis is a granulomatous disorder of unknown etiology and whose epidemiology suggest a genetic tendency face to infectious agents being supposed to result of immune system deregulation leading to non-caseating granulomas as an immune reaction to an unknown persistent antigenic stimulus [19]. Inflammatory mediators such as IFN and interleukin 2 are involved in granuloma formation. IFN has been linked to pulmonary macrophage activation, a characteristic feature of sarcoidosis which has been assumed an exaggerated T helper 1 (Th-1) immune response to a variety of exogenous antigens. It seems very likely that a potent immunoregulatory protein for Th-1 response such as IFN may induce the disease [19]. In January 2003 the eighth case of IFN-related sarcoidosis was reported with a review of the literature [19]. Chest X-ray revealed hilar

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lymphadenopathy in three patients, with reticulonodular shadows in another three, while the patient with only cutaneous involvement had a normal chest X-ray [19].

The case we report presented with cutaneous sarcoidosis during CHC therapy and spontaneous regression of the lesions was noted with treatment discontinuation. An immune cell reaction triggers a greater granulomatous reaction in such patients [12]. Sarcoidosis during IFN therapy may present as systemic, cutaneous or combined disease. The disease has already been reported in tattoos after use of IFN [20].

We intend to emphasize, especially to dermatologists, the risks of a granulomatous tattoo and other cutaneous sites during CHC treatment with peg-IFNalpha-2b plus ribavirin. Other similar cases have been reported in the English language literature [14–18]. Thalidomide has been also shown to have specific activity to the inflammatory mediators of sarcoidosis and to be an alternative beneficial therapy [21].

Fig. 1. Sarcoid reaction in a seahorse tatoo on the deltoid skin.

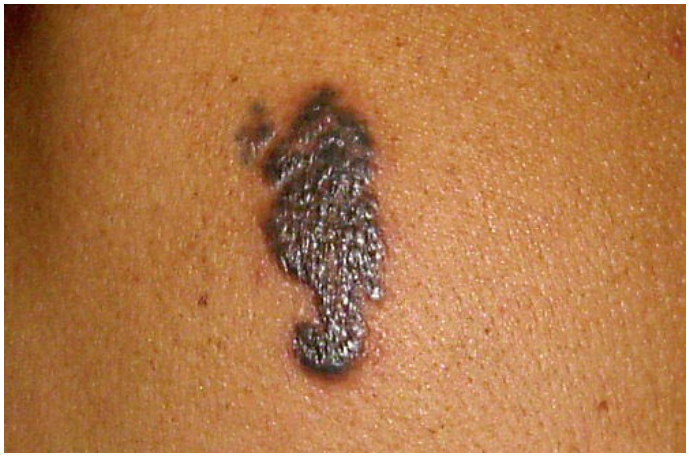

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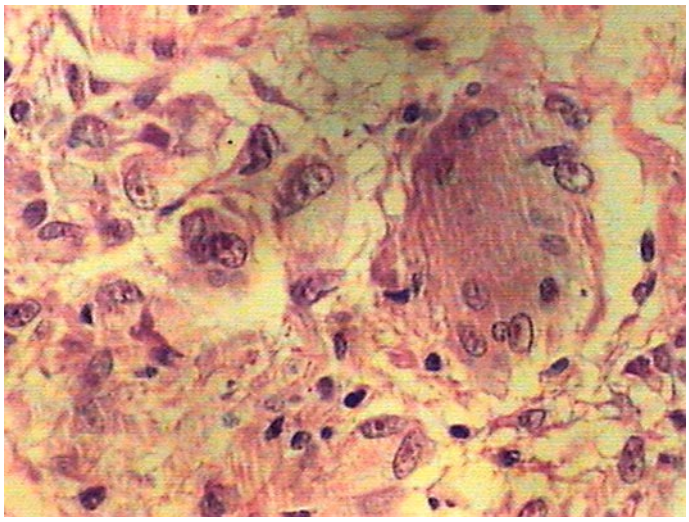
Fig. 2. Skin biopsy (HE, 400×) with granulomatous reaction from sarcoidosis.



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