Prolonged Treatment with Interferon Alpha and Peginterferon Induces Rheumatoid Artrhitis Syndrome and Erythema Nodosum

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Abstract

The antiviral treatment of chronic C hepatitis has improved significantly over the past decade with the introduction of interferons (IFNs), and more recently, pegylated IFNs. Up to two-thirds of all patients treated with pegylated IFN combined with ribavirin can now achieve viral eradication if treated according to current guidelines. Despite this success rate, hematological, immunological, rheumatological and dermatological side effects have been reported in chronic hepatitis C patients treated with IFN-alpha. The subjects of this report are two young females with chronic hepatitis C, who developed rheumatoid syndrome and/or erithema nodosum during antiviral treatment with IFN-alpha or pegylated IFN combined with ribavirine.

Key words

Interferon alpha – peginterferon – chronic hepatitis C – rheumatoid arthritis syndrome – erythema nodosum.

Introduction

Interferons (INF) are a family of natural cytokines that share a common ability to interfere with viral replication, cell proliferation, immunoregulation, tumour cells growth [1]. Various side effects have been reported in chronic hepatitis C (CH-HCV) patients treated with IFN-alpha, including hematological, immunological, rheumatological and dermatological disorders. We report the cases of two young Caucasian females with chronic hepatitis C, who developed rheumatoid syndrome and/or erithema nodosum during antiviral treatment.

J Gastrointestin Liver Dis
June 2008 Vol.17 No 2, 211-212
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Case report 1

We present the case of a 40-year-old Caucasian female patient with chronic hepatitis C (Ishak score: necroinflammation - grade 9, fibrosis - stage 2), genotype 1b treated with IFN alpha-2b, 5 MU x 3/week and Ribavirine 1000 mg/day, for 48 weeks. In the 45th week of antiviral therapy, she developed symmetric peripheral inflammatory arthritis, associated with pain, oedema, and sensibility. Blood tests results defined nonspecific inflammatory syndrome (ESR=48mm/1h, fibrinogenemia=580mg/dl, moderate polyclonal hypergammaglobulinemia, IgG prevalent) and the presence of rheumatoid factor (RF) in a titre of 1/84. The HLA map, in this case restricted only to DR and B27 antigens showed the presence of DR3 and DR4 and the absence of B27. The rheumatoid syndrome disappeared after interruption of IFN therapy with analgesic and non-steroidal anti-inflammatory drugs. By that time, RF was in normal range.

Two years after the initial IFN treatment, the patient started a re-treatment with Peg IFN alpha-2a 180µg/week and Ribavirine 1000 mg/day, due to the relapse of CH. After 10 months of treatment she developed a similar rheumatoid syndrome associated with tender red nodules in the tibial region of both lower limbs, diagnosed as erythema nodosum (Fig.1). Blood tests revealed elevated titres of RF. The treatment consisted of analgetic and non-steroidal anti-inflammatory drugs until antiviral therapy was completed. After cessation of IFN therapy, the symptoms rapidly regressed.

Case report 2

A 45 year-old Caucasian female with chronic hepatitis C (Metavir score: 8; A2F2), treated with Peg Interferon alpha-2a 180µg/week and Ribavirine 1000 mg/day developed bilateral tender red nodules in the tibial region during the 32 weeks of treatment. A bilateral hilar adenopathy was diagnosed by a screening chest X-ray. The nodules gradually changed from pink to bluish to brown, resembling a bruise. Fever and arthralgia, the most common features associated

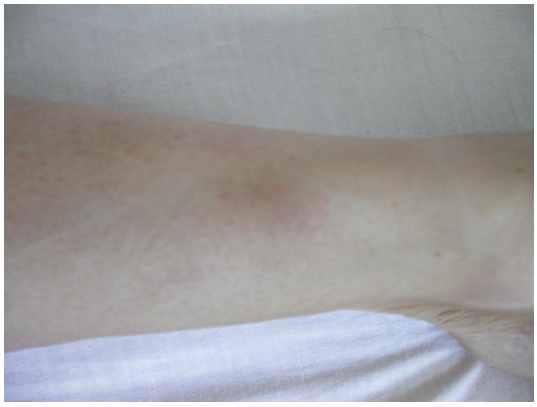

Fig 1. Erythema nodosum in the pre-tibial region (Patient 1)

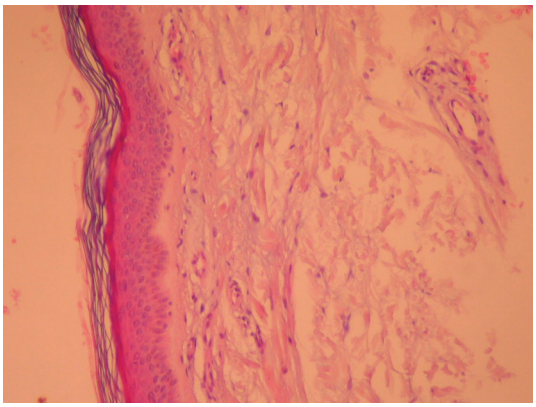

Fig 2. Skin biopsy showing histological aspect of erythema nodosum (Patient 2) (H&E, 4x).

with skin lesions in erythema nodosum, were not present in this case. A biopsy specimen of skin and subcutaneous tissue diagnosed erythema nodosum of the lower limbs (Fig. 2).

Discussion

Few case reports have described the onset of polyarthritis after the administration of alpha-IFN for HCV-related chronic hepatitis [2]. Moreover, HCV-related arthritis has been recognized as an autonomous rheumatic disorder [3]. It is essential to individualize the causal role of treatment with IFN-alpha in HCV patients with rheumatological symptoms.

In our patients rheumatoid arthritis appeared during treatment with IFN-alpha. Moreover, when patient 1 was retreated with Peg IFN-alpha for the relapse of liver disease the symptoms reappeared. Therefore it is more probable to accept the idea of IFN-alpha related rheumatoid arthritis in an HCV infected female patient with an HLA profile favorable for autoimmune diseases.

The rheumatoid arthritis seems not to be related with the type of interferon since both types, IFN alpha-2b and pegylated form of IFN alpha-2a were used in this case.

Chronic HCV infection has been described in association with various skin disorders. Certain dermatological conditions are associated with HCV infection and some skin lesions have been reported as side effects to IFN [4-6]. The most commonly reported association is the triad of leukocytoclastic vasculitis, cryoglobulinemia and HCV infection. Other cutaneous disorders associated with HCV infection are: porphyria cutanea tarda, lichen planus, erythema nodosum, urticaria, erythema multiform, and polyarteritis nodosa. In the cases presented, erythema nodosum seemed to be related with Peg IFN alpha therapy more than with HCV infection alone. The inflammatory skin disorder appeared during antiviral treatment and the skin lesions disappeared after cessation of IFN therapy. In both cases, other potential causes of erythema nodosum (sarcoidosis, streptococcal infections, tuberculosis, coccidiodomycosis, histoplasmosis, psittacosis) were excluded. No sulfamides, iodides, bromides or contraceptives were used as concomitant medication by our two patients.

In the first case presented, retreatment with PegIFN alpha, for the relapse of CH-HCV, induced the reappearance of more pronounced immune disorders. In the second case, primary treatment with PegIFN-alpha induced erythema nodosum after 2/3 of the duration of treatment.

In conclusion, in our patients IFN alpha and Peg-IFN alpha induced immune changes such as rheumatoid arthritis syndrome and erythema nodosum. The presence of a HLA DR3 and DR4 profile, is a favorable circumstance for occurrence of IFN-alpha induced autoimmunity. Retreatment with Peg-IFN in patients with autoimmune disorders induced by IFN-alpha might cause more severe immune disease.

Conflicts of interest

None to declare.

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