

CUTANEOUS MUCINOSIS AND SKIN NECROSIS COMPLICATES INTERFERON ALFACON-1 (CONSENSUS INTERFERON) TREATMENT OF CHRONIC HEPATITIS C

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Abstract: A 59-year-old Caucasian suffering from chronic hepatitis C started daily subcutaneous self-injections of interferon alfacon-1 (consensus interferon) according to the protocol of a randomised multicentre study. At week 10, he developed painful erythematous lesions at two injection sites. Consensus interferon dosage was reduced, and eventually, the lesions healed with small areas of scarring due to central necrosis. At week 51, again large areas of erythematous thickened skin arose at two other injection sites followed by substantial ulceration and central necrosis. Skin biopsy revealed excessive dermal mucin deposition so that cutaneous mucinosis was diagnosed. After 3-6 months, the lesions healed with central scarring. Due to a persistently negative HCV-PCR from serum (from week 12 onwards), consensus interferon treatment was not stopped but continued until week 60 according to the study protocol.

Cutaneous mucinosis has not been previously reported to complicate treatment with consensus interferon in patients with chronic hepatitis C and should therefore be added to the list of dermatological side-effects associated with interferon alfacon-1 therapy.

Key words: Consensus interferon, cutaneous mucinosis, skin ulceration, skin necrosis, hepatitis C virus

INTRODUCTION

Interferons have pleiotropic biological effects, particularly immunoregulatory, antitumor and antiviral activities [1]. Interferon alpha 2a, interferon alpha 2b, their pegylated variants and so-called consensus interferon (interferon alfacon-1) are used for the treatment of chronic hepatitis B and C virus infections [2-4, 5-6, 7-8]. Regarding treatment of chronic hepatitis C virus (HCV) infection, the combination of pegylated interferon alpha 2a (180 µg once weekly s.c.) or 2b (1.5 µg/kg body weight once weekly s.c.) with ribavirin is the most effective treatment currently available. Ribavirin was given at a dose of 1000 mg/d (body weight < 75 kg) or 1200 mg (body weight > 75 kg). As could be demonstrated in large clinical trials, sustained virological response (SVR) can be obtained in 42-51% of patients treated with such a combination therapy for 48

weeks [5, 6]. SVR rates in patients with HCV genotypes 2 or 3 approach 80% , and recent data suggest that similar effectiveness can be achieved within just 24 weeks of combination therapy using an even lower dosage of ribavirin (800 mg/d) [9]. Therapy should be discontinued if the viral load in serum has not decreased by two log steps at 12 weeks of treatment because the negative predictive value is 97-98% [6]. Detectable HCV-RNA at week 24 (assay sensitivity 50 IU/ml) reaches even higher negative predictive values (> 98%), signifying that there is no need for patients with genotype 1 to continue therapy up to week 48. No clear recommendations can be given for these patients not responding (non-responders) to combination therapy or for those showing viral relapse after finishing combination therapy. Ongoing clinical trials use daily subcutaneous injections of interferon alfacon-1 (consensus interferon) combined with ribavirin [8].

Despite these encouraging results, side-effects of interferon/ribavirin therapy are common. Approx. 25-33% of patients experience severe side-effects, and in rare instances some adverse events may be life threatening [10, 11]. Dose-reduction usually leads to resolution or at least amelioration of side-effects, so that most patients are able to complete a full course of therapy. Unfortunately, dose-reduction is quite often associated with a marked decline in SVR [6, 12].

The most common side-effects of alpha interferons include flu-like symptoms (fever, sore-throat, headache, arthralgia, myalgia), gastrointestinal complaints (e.g. abdominal pain, nausea, diarrhoea, anorexia and weight loss), noncardiac chest-pain, neuropsychiatric side-effects (e.g. irritability, insomnia, depression, neuropathy), the triggering of autoimmune disorders (e.g. rheumatoid arthritis, systemic vasculitis, hypo-/hyperthyroidism), haematological toxicity (neutropenia, thrombocytopenia) and dermatological disorders [10, 11]. Dermatological toxicity frequently occurs and ranges from pruritic or painful erythema at the injection sites to local necrosis and ulceration, generalised rashes, alopecia and dermatological immune-mediated manifestations such as vitiligo, psoriasis, lichen planus, leukoclastic vasculitis and lupus erythematosus [10, 11]. Here, we describe cutaneous mucinosis complicating interferon alfacon-1 (consensus

interferon) treatment in a patient with chronic hepatitis C, which to our knowledge has not been previously reported as a dermatological side-effect of interferon alfacon-1 therapy.

CASE-REPORT

A 59-year-old, otherwise healthy Caucasian with chronic hepatitis C virus infection diagnosed a year ago (genotype 1b, viral load 3×10^6 IU/ml serum) showed elevated liver enzymes: AST 79 U/l (normal range < 18 U/l), ALT 96 U/l (normal range < 24 U/l), gamma-GT 119 U/l (normal range < 29 U/l) and GLDH 39 U/l (normal range < 5 U/l). Liver biopsy revealed chronically active intralobular inflammation with focal necrosis and substantial periportal fibrosis. Therefore, pegylated interferon alpha 2b (1.5 µg/kg body weight) and ribavirin (1200 mg/d) were given for 48 weeks. Apart from the initial flu-like symptoms, the patient complained about tiredness, headaches, chest-pain and hyperesthesia of his legs, but no severe side-effects occurred. Despite undetectable hepatitis C virus from treatment week 12 onwards, viral relapse was diagnosed already 3 months after cessation of treatment. Therefore, the patient was considered for participation in a randomised multicentre study: interferon alfacon-1 (consensus interferon) was given at a dosage of 27 µg/d subcutaneously for the first 4 weeks, followed by 18 µg/d for 8 weeks and 9 µg/d thereafter. From week 12 onwards, ribavirin was added (1200 mg/d p.o.). The same side-effects as described for the treatment course with pegylated interferon alpha 2b occurred, but they were more pronounced. Particularly general fatigue, muscle pain and flu-like symptoms were much more severe. During week 10, painful erythematous patches developed at two injection sites on the lower abdomen. Therefore, consensus interferon dosage was reduced to 18 µg/d one to two weeks earlier than suggested in the study protocol, and eventually, the lesions healed with small areas of scarring due to central necrosis. At week 51, again large areas of erythematous, thickened skin arose at two lateral abdominal injection sites (Fig. 1A) followed by substantial ulceration and central black necrosis (Fig. 1B). Besides perivascular lymphocytic infiltrates in the upper dermis, skin biopsy revealed excessive mucin deposition in the dermal Stratum reticulare (Fig. 2) so that cutaneous mucinosis was diagnosed. No other underlying pathology could be confirmed by laboratory testing: negative autoantibodies to nuclei (ANA), dsDNA, c and p antineutrophil cytoplasm (ANCA), Ro and La. Normal serum TSH levels were measured, and there was no indication of monoclonal gammopathy or thrombophilia (normal prothrombin and thrombocytes, normal partial thromboplastin time, protein C and S, antithrombin III, homocysteine, fibrinogen and negative antiphospholipid antibodies and lupus anticoagulant, no resistance to activated protein C, no cryoglobulinaemia). After 3-6 months, the lesions healed with central scarring (Fig. 1C). Due to a persistently negative HCV-PCR from serum (from week 12 onwards), consensus interferon treatment was not stopped but could be continued until week 60 according to the study protocol. Nevertheless, three months after having finished the treatment,

viral relapse was noted with a high viral load of 3×10^7 IU/ml serum.

DISCUSSION

We described a case of recurrent necrotising skin lesions and, particularly, cutaneous mucinosis complicating interferon alfacon-1 (consensus interferon) treatment in a patient with chronic hepatitis C, which apparently has not yet been reported as a dermatological side-effect of interferon alfacon-1 therapy. Although the patient was able to complete a full course of therapy, he nevertheless complained about substantial reduction in his quality of life. More importantly, the inevitable dose reduction of consensus interferon may have been responsible for the viral relapse occurring as early as three months post-therapy.

Consensus interferon is a synthetic, recombinant type I interferon derived by assigning the most commonly observed amino acid in each position of several alpha interferon subtypes to generate a consensus sequence (89% homology with interferon alpha, 30% homology with interferon beta) [8]. It binds with 10-fold higher affinity to type-I interferon receptors than other alpha interferons and has greater biological activity. Its use seems to be most advantageous when treating relapsers or nonresponders to prior interferon therapy [7, 8]. As stated above, interferons quite frequently cause manifold side-effects, and dermatological complications are among the commonest to be registered [10, 11]: besides generalised rashes, alopecia and immune-mediated manifestations like vitiligo, psoriasis, lichen planus, leukoclastic vasculitis and lupus erythematosus [13], local reactions at the injection sites with pruritic or painful erythema are most frequently observed (21% - 58%; [5, 6]). Although ulceration and necrosis at the injection sites are rare events the number of cases described in the literature increases, both for interferon alpha and beta (compilation e.g. in [14]) and pegylated interferon alpha [15, 16]. Yet, we were not able to find data on cutaneous necrosis resulting from treatment with interferon alfacon-1 (consensus interferon) like in the case presented here. Despite several hypotheses the pathogenesis of skin ulceration and necrosis secondary to interferon treatment is unknown: platelet-dependent thrombosis with abnormalities of platelet activation or focal deficiencies in protein C is discussed [17] but vasospastic effects triggered by interferon [16], unintentional peri- or intraarterial injection with resulting embolia cutis medicamentosa [15, 18] and immune-mediated vasculitic processes in the skin due to the release of inflammatory cytokines like TNF-alpha, IL-1 and IL-6 by interferons are also taken into consideration [14, 19].

In our patient, excess mucin deposition was additionally observed leading to the diagnosis of secondary cutaneous mucinosis. Cutaneous or dermal mucinoses are a heterogeneous group of connective tissue disorders in which there is an accumulation of mucin, a glycoprotein, which is normally produced by fibroblasts in the skin or within the hair follicle [20]. Morphology and microscopic appearance are manifold [21]. Primary and secondary forms can be distinguished. Primary mucinoses are subdivided into degenerative-inflamma-

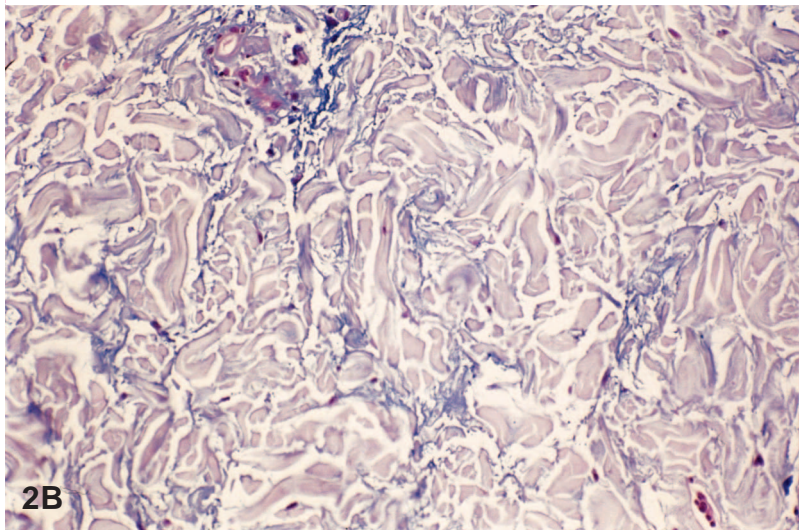
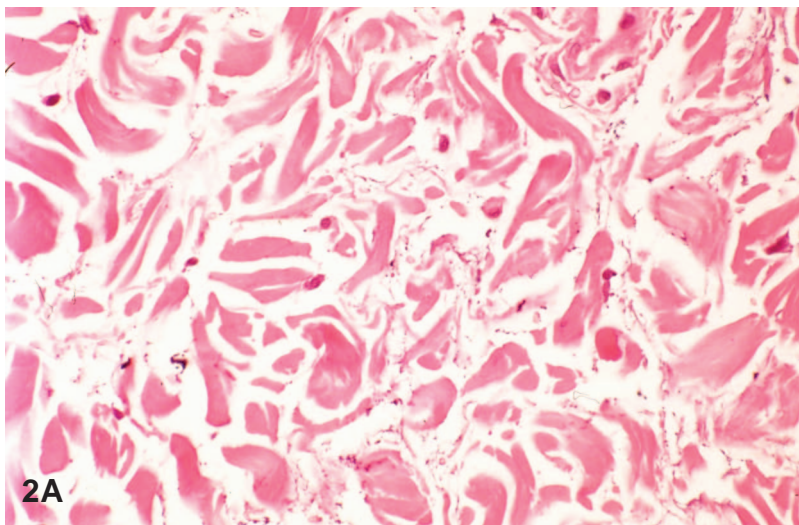


Fig. 1. Macroscopic aspects of interferon alfacon-1-induced necrotising skin lesions - time course of appearance and healing: (A) initial diffuse erythema, (B) ulceration and necrosis with thickened, deep-red surrounding skin area, (C) healed lesions with small central area of scarring.

Fig. 2. Histological appearance of dermal mucinosis: A biopsy specimen of the skin lesion (magnification x400) showing granular material, i.e. mucin, between collagenous fibres of the dermal Stratum reticulare using hematoxylin and eosin staining (panel A) and Alcian Blue staining (panel B). The amount of mucinous depositions is reduced because mucopolysaccharides are washed out of the specimen due to the fixation process.

tory mucinoses (either dermal or follicular) and neoplastic-hamartomatous mucinoses. [20-22]. Secondary mucinoses occur in patients with various systemic disorders: endocrinopathies, such as hypo- and hyperthyroidism; malignancy, such as mycosis fungoides and other lymphomas; infectious diseases, e.g. HIV and upper respiratory tract infections [23]. Localised cutaneous mucinosis as a side-effect of interferon therapy has to the best of our knowledge only been reported in association with the application of interferon beta 1b in one patient suffering from multiple sclerosis one month after treatment initiation [24]; therapy was stopped two months later. Another group observed even severe generalized scleromyxoedema in another patient with multiple sclerosis three years after starting an interferon beta 1a treatment [25] which certainly demanded discontinuation of interferon injections. The mechanisms underlying mucin accumulation are unknown. The authors suggested an interferon-induced increase in transforming growth factor beta (TGF- β) which could stimulate fibroblasts to produce more mucin than normally [24]. Interestingly, interferon is known to act antifibrogenic at the liver by antagonising TGF-beta/Smad3-stimulated transcription of the alpha2(I) collagen gene in activated hepatic stellate cells [26]. As regards the case described here, the time course of skin complications is remarkable: The preceding treatment course with 48 weekly injections of pegylated interferon alpha 2b was well-tolerated without any major dermatological side-effects. Despite daily injections of consensus interferon only four injections were complicated by mucinosis and necrosis, and an uneventful interval of 41 weeks lay between the initial skin manifestations and their reappearance in another skin area.

In summary, interferon therapy is frequently accompanied by dermatological side-effects. As already described for other alpha and beta interferons, interferon alfacon-1 is also able to elicit skin ulceration and necrosis. Moreover, cutaneous mucinosis should be kept in mind as a rare side-effect associated with interferon therapy. The pathogenesis of such lesions is not understood. Interferon treatment can in most cases be continued but dose reduction is necessary, which can ultimately result in reduced viral elimination rates.

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