

Clinical and Laboratory Investigations

Diffuse inflammatory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a series of 20 patients

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Summary

Background Cutaneous side-effects of treatment with interferon alfa or interferon alfa plus ribavirin in patients with hepatitis C have already been reported but they are mostly local with inflammation and, much less frequently, necrosis at the injection points. By contrast, very few data are available with regard to distant skin reactions, particularly inflammatory lesions on other parts of the body. **Objectives** To assess the clinical and histological pattern of inflammatory skin lesions outside the injection points in patients treated with interferon alfa and ribavirin for chronic hepatitis C.

Methods Twenty patients attending a University Hospital in Southern France (secondary referral centre) were evaluated regard to clinical history, type and localization of lesions, progression and histology. Skin testing was performed in some patients and the relevance of the results was evaluated.

Results Eczema-like skin lesions were mainly distributed on the extremities, sometimes associated with photosensitivity. They usually occurred between 2 and 4 months of treatment. Histology was nonspecific, with a dermal, mainly perivascular, mononuclear infiltrate. Skin testing was poorly informative and was not predictive of relapse. Treatment had to be interrupted in half the patients, of whom two of three relapsed on resuming therapy.

Conclusions The incidence of inflammatory skin lesions at a distance from injection sites in patients treated with interferon alfa and ribavirin for chronic hepatitis C is currently unknown, but this adverse event must be taken into consideration as it may lead to the transient or definitive interruption of treatment.

Key words: hepatitis C, interferon alfa, ribavirin, side-effects

The combination of interferon alfa-2a or 2b with ribavirin is currently recommended in the treatment of active hepatitis C, whose incidence is currently increasing in Western countries.^{1,2} This therapeutic combination may be responsible for a range of skin lesions including local reactions at the sites of interferon injection, and also for the onset or worsening of disorders such as psoriasis, lichen planus, vitiligo or systemic lupus erythematosus.^{3–8} By contrast, the occurrence of inflammatory lesions at a distance from the injection sites during treatment with interferon alfa

with or without ribavirin in active hepatitis C has been reported to date in only a few patients.^{9–11}

The incidence of skin reactions in the course of interferon–ribavirin treatment is not known, and could be higher than is currently estimated. The combination of ribavirin and interferon possibly leads to an increased incidence of cutaneous side-effects compared with interferon alone,¹¹ although ribavirin is only rarely reported to cause photosensitivity.¹²

We prospectively investigated the clinical and histological characteristics, results of skin testing and outcome in a series of 20 patients receiving interferon alfa and ribavirin for active chronic hepatitis C and referred to our department during 1999 and 2000 for

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the occurrence of cutaneous inflammatory lesions outside injection sites.

Patients and methods

About 90 patients treated with interferon alfa and ribavirin for active chronic hepatitis C, with inflammatory skin lesions occurring after implementation of the antiviral treatment, were prospectively referred to our Department during 1999 and 2000. From these patients, those with lesions occurring outside the injection sites and without any other obvious explanation for their onset were selected for further investigation under the assumption that the lesions were related to the antiviral treatment. Clinical data were collected from their earlier medical records and by direct or indirect follow-up (telephone contact with the patient, general practitioner and/or the hospital department of origin). A skin biopsy for histological examination was requested and interpreted by the same pathologist and direct immunofluorescence on lesional skin was performed in selected cases. Blood tests including blood count, eosinophilia and, in some cases, antinuclear antibodies, were carried out at presentation. When possible, skin testing was performed when the lesions had resolved and usually included patch tests with ribavirin (pure and diluted at 30% in petrolatum) and interferon alfa-2a and/or 2b (pure and diluted at 30% in distilled water) and/or intradermal reaction tests with interferon alfa-2a and/or 2b (pure and diluted at 1/1000, 1/100 and 1/10 in phenolated 0.09% sodium chloride solution). Phototests and photopatch tests were performed using a solar simulator Müller Electronic Optik Xenon equipped with a WG305 filter and a dichroic mirror (Mulsendorf, Germany).

Results

Twenty patients with inflammatory skin lesions located outside the injection sites of interferon were selected from the 90 or so presenting. The remaining patients had inflammation restricted to injection points ($n = 18$) or had skin lesions that were thought to be due to an unrelated cause, e.g. localized contact dermatitis.

The patients comprised 11 men and nine women, age range 36–70 years (mean 50.7). The treatment included in all cases oral ribavirin and subcutaneous injections of interferon alfa-2a (three times weekly in nine patients) or 2b (three times weekly in nine

patients or once weekly for the pegylated form in two patients). One patient had a medical record of atopic dermatitis during infancy but without any skin lesions for the past 55 years; one patient had recurrent lesions of contact dermatitis related to hypersensitivity to nickel. Eight of these patients had already received treatment with interferon alfa within the previous 5 years, without any significant skin complication.

The onset of the inflammatory lesions ranged from 2 weeks to 4 months after the implementation of the antiviral therapy (mean 9.1 weeks). In 15 of 20 patients they occurred between 2 and 4 months of treatment. The clinical pattern was a pruritic, confluent, papular erythematous eruption admixed with occasional vesicles. Lesions were predominantly located on the distal limbs (legs, forearms; Fig. 1a), dorsum of the hands, face, neck and, less frequently, the trunk, axillae and buttocks. Four of 20 patients showed photosensitivity, with unusual redness of the face after limited sun exposure (Fig. 1b). Associated lesions were sometimes present: inflammatory lesions at the injec-



Figure 1. (a) Inflammatory lesions on the hands, forearms and neck; (b) photosensitivity with facial erythema.

tion site of interferon (one patient), aphthae-like lesions of the mouth (one patient), Meyerson's phenomenon (inflammatory reaction around melanocytic naevus; one patient) and erosions of the tongue (one patient).

Histological examination was performed in 19 of 20 patients, showing in all cases a nonspecific, often perivascular, infiltrate in the upper dermis with a large predominance of mononuclear cells, sometimes accompanied by sparse keratinocyte necrosis with spongiosis and vesiculation (Fig. 2a,b). Direct immunofluorescence was performed on lesional skin in the four patients with photosensitivity, but was negative in all cases. White cell count carried out in 16 of 20 patients at presentation showed a peripheral eosinophilia in two patients ($980 \times 10^6 \text{ L}^{-1}$ and $1200 \times 10^6 \text{ L}^{-1}$, respectively), but no antinuclear antibodies were present in the four patients with clinical photosensitivity.

Skin tests were carried out in six of 20 patients. All the tests were negative except in one patient who had a positive intradermal reaction with undiluted and 10% interferon alfa-2b (in use when the eruption occurred) but a negative reaction with interferon alfa-2a. Phototests were performed in one patient with photosensitivity, and showed a normal minimal erythema dose (MED) for the patient skin type (phototype II), negative phototests both with ultraviolet (UV) A (30 J cm^{-2} in two irradiations) and with polychromatic light (5 MED), and negative photopatch tests with ribavirin at 15, 30 and 100% and UVA.

Skin lesions led to the interruption of treatment in 10 patients, followed by complete clearing within 2–3 weeks. In the other 10 patients, antihistamines and topical corticosteroids led to a significant improvement of lesions, allowing continuation of therapy. Three patients for whom the treatment had been interrupted were rechallenged, either with the same (two patients) or the other type of interferon alfa (one patient); in two cases, the lesions recurred even after a change in interferon type in one patient. Intradermal tests with interferon alfa (both types of interferon and suspected interferon only, respectively) and patch tests with ribavirin were negative for both patients. The same combination was resumed in a third patient without relapse of the lesions.

Discussion

Adverse skin reactions usually occurring at the injection sites of interferon alfa have been reported previously, erythema with induration affecting up to 12% of patients,⁴ whereas the occurrence of cutaneous necro-

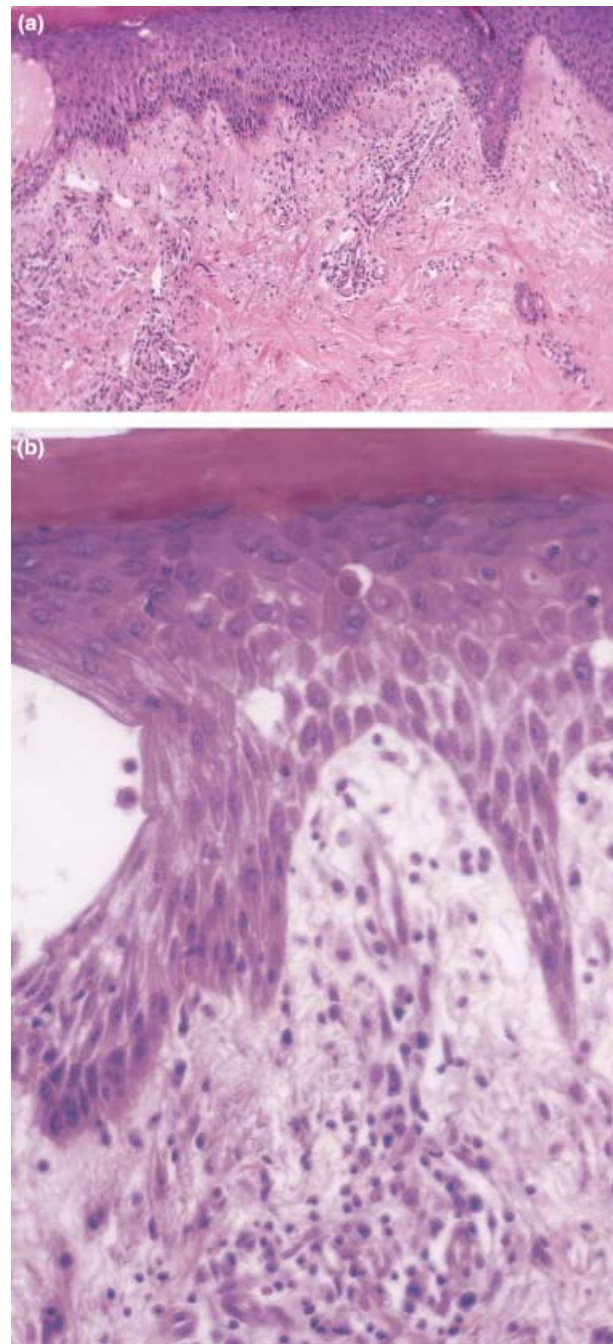


Figure 2. (a) Photomicrograph showing a nonspecific, predominantly mononuclear, perivascular inflammatory infiltrate of the upper dermis; (b) sparse keratinocyte necrosis with spongiosis and vesiculation (haematoxylin and eosin; original magnification: a, $\times 100$; b, $\times 250$).

sis has been reported in only 20 patients.¹³ Inflammatory reactions, localized alopecia or injection-site perivascular inflammatory infiltrates or vasculitis have only occasionally been seen.^{9,10,14,15} Cutaneous side-

effects at a distance from injection points are also possible, with reports of the occurrence or worsening of psoriasis, lichen planus, vitiligo, alopecia areata, lupus erythematosus, aphthae and livedo, sometimes associated with antiphospholipid antibodies or Raynaud's phenomenon seldom complicated with distal finger necrosis.^{3-8,16}

Our series of 20 patients provides new data on the occurrence of distant cutaneous reactions. The incidence of such reactions is not known, but it appears to be low because the number of patients starting this therapy for hepatitis C virus infection in our centre is between 20 and 30 new patients per month even if not all patients affected with this complication were referred to our Department. There does not seem to be any trend for a particular type of interferon alfa, either 2a, 2b standard or pegylated, to induce skin lesions. The main results from our series are the following: there is no clinical predictive factor such as a previous history of skin inflammatory lesions; there is a predilection for the distal limbs and the head and neck region, which means perhaps a predominance on sun-exposed areas; there is a delay between implementation of the treatment and the occurrence of skin lesions, with a peak of frequency during the third and the fourth months of treatment, consistent with reports in interferon-induced psoriasis, lichen planus or lupus erythematosus;³⁻⁶ photosensitivity and mucous lesions were present in six of 20 patients; inflammation at the sites of interferon injections was noticed in only one patient.

Berger *et al.*¹⁰ reported one patient treated with interferon alfa alone and three patients receiving interferon alfa and ribavirin for chronic hepatitis C, all of them with an atopic background, who developed inflammatory reactions at the site of injections and more remote similar lesions in two cases, occurring 3 weeks to 6 months after the treatment was started. Treatment was not interrupted and one patient tested negative in patch tests, prick tests and intradermal reaction with interferon. Sookoian *et al.*¹¹ published a prospective series of 33 patients treated with interferon alfa and ribavirin for chronic hepatitis C: three of them developed inflammatory lesions on limbs, outside the sites of injections, after 6 weeks to 4 months of treatment. Six Japanese patients experienced remote early transient erythematous lesions during intravenous administration of interferon alfa for chronic active hepatitis, with a nonspecific lymphocytic perivascular infiltrate.⁸ Skin testing was mostly unhelpful in our series, data in line with the results obtained by Berger *et al.*¹⁰

The underlying mechanisms are only speculative. Worsening of atopic eczema has been reported in patients treated by interferon alfa alone,¹⁷ although this treatment may lead to improvement in other patients.¹⁸⁻²⁰ Contact dermatitis has been observed in one patient with hairy cell leukaemia treated by interferon alfa.²¹ The immunomodulatory effects of interferon alfa themselves might be responsible for an aberrant behaviour of T lymphocytes, inappropriately stimulated and leading to abnormal reactions to usual stimulations such as limited sun exposure, slight trauma or cutaneous irritation. Ribavirin alone can cause photosensitivity, especially with UVB.¹² If this side-effect were exacerbated by interferon alfa, this could account for the predominance of lesions on photoexposed areas.

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