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Severe Cutaneous Reactions Following Interferon Injections

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ALTHOUGH TRANSIENT mild cutaneous reactions are frequent with interferon (IFN) treatment (10% of patients) [1], to our knowledge, there have been 9 reported cases of severe local toxicity with ulceration and necrosis of the skin [2–9]. These adverse effects have been described with different types of IFN alpha (recombinant as well as natural) and very recently with IFN beta-1b [8]. The doses varied between 6 and 20 million units. Incidents occurred after at least 2 months, but in 2 cases after more than a year [4, 5] of daily or alternate days subcutaneous injections. Patients were treated for chronic myelogenous leukaemia (CML) [4, 6, 7], Kaposi's sarcoma [2, 3, 5] or multiple sclerosis [8, 9]. We report a new case of atypical local reaction caused by IFN alpha at the injection site.

The patient, a 61-year-old man, was initially diagnosed as having a Philadelphia (Ph) positive CML. After a short period of cytoreductive therapy with hydroxyurea, treatment with recombinant IFN alpha 2a (ROFERON, Roche Pharmaceutical Company) was initiated at a daily dose of 3 MU and rapidly increased to 9 MU daily. All the injections were subcutaneous and delivered by a qualified nurse. Because of an initially low cytogenetic response and excellent tolerance, the treatment was continued with a progressive disappearance of the Ph chromosome in mitoses. Approximately 2 years after the initiation of treatment, the patient presented some hours after an injection with intense pain of the external surface of his right arm. There were no other clinical signs until the appearance, a week later, of a deep and extensive 3 cm by 8 cm induration. A surgical biopsy revealed a hyalin sclerosis of the deep dermal, hypodermal and subcutaneous tissue. This sclerosis was associated with adiponecrosis, mainly located at the vicinity of a clear space, which probably corresponds to the site of injection. Furthermore, the tissue was slightly infiltrated by lymphocytes and eosinophils, but there was no evidence of vasculitis or venous thrombosis. Unlike other cases, we did not find epidermal or superficial dermal necrosis, probably because of a deeper injection in this patient. Bacteriological cultures of the lesion were negative. Blood chemistry and coagulation factors, including antithrombin III, protein C, protein S and the resistance to activated protein C, were normal. The administration of antibiotics and topical care with a corticosteroid-based cream ameliorated the pain and reduced the size of the induration after one month.

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The pathogenesis of this toxicity is unknown. Several mechanisms have been proposed. Rasokat and colleagues [2], who first described this effect, proposed an unintentional intra-arterial injection (Nicolau's syndrome), usually described after intramuscular injections. Cnudde and colleagues [3] suggested a local procoagulant activity of IFN, possibly potentiated by a deficiency in the antithrombin III or other anticoagulant proteins. Oeda and Shinohara [5] postulated a local immune-mediated inflammatory process, but the delay in the appearance of the lesions which can happen more than a year after the beginning of the treatment is then surprising. Finally, Chritian and colleagues [6] and Vives and colleagues [7] proposed a direct toxic effect of the IFN on the skin. Because our case does not support the other hypotheses, we think, as others [6, 7], that a direct toxic effect of IFN is responsible for this adverse effect. Further studies are necessary for a better comprehension of the pathogenesis of this effect, but we believe it is important to advise patients to carefully rotate the site of injections.

Note added in proof: After acceptance of our letter in this journal, an interesting report [10] was published concerning significant cutaneous reactions in 8 patients of a large series of approximately 400 patients treated for multiple sclerosis with high doses of recombinant IFN beta injections. Furthermore, we have omitted to name, despite an intensive research, Miles [11] who seems to be the first to have noted these adverse effects with the IFN beta in 8 other patients treated for AIDS-related Kaposi's sarcoma. IFN beta seems then to be responsible for a larger number of cases of cutaneous ulcerations than other interferons. However, it should be noted that the doses of IFN beta usually injected were very high, reaching in some cases 96 MU/day.

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