Lupus syndrome, hypothyroidism and bullous skin lesions after interferon alfa therapy for hepatitis C in a haemodialysis patient

Sir,

Interferon alfa (IFN-α) is a cytokine available for the treatment of malignant diseases and hepatitis B and C. Major complications of this drug include the occurrence of autoimmune disease [1].

Case. A 37-year-old woman undergoing haemodialysis (HD) in August 1983 following focal segmental glomerulosclerosis received a kidney donated by her father in July 1985. In 1994, hepatitis C (HCV), genotype 1a, was discovered during a routine follow-up. In August 1997, liver biopsy demonstrated a stage 2, grade 2 hepatitis by the Metavir score. In September 1998, HD was recommended due to chronic rejection. In October 1998, HCV-RNA was positive with 500,000 copies/ml. ANA with indirect IF were negative and thyroid tests were normal. Recombinant IFN-α 2a therapy (Roferon Roche) 3 MU three times weekly following dialysis was commenced. During the first 2 months of treatment, the patient presented with flu-like symptoms treated with paracetamol. Following 3 months of treatment, the viral blood count was negative. In September 1999, the patient presented with tiredness, arthralgia, myalgia, pruritic bullous skin lesions and suicidal thoughts. Blood results demonstrated the following: ANA 1/2560 (normal 1/40), anti-DNA-antibodies (AB) in Elisa 100 U (normal < 30 U), antinucleosomic AB in Elisa 33 U (normal < 10 U), complement in RIA 4.1 U/ml (normal > 23 U/ml), free T3 in RIA 1.45 pg/ml (normal 1.8–4.6 pg/ml), free T4 in RIA 0.16 ng/ml (normal 0.97–1.72 ng/ml), TSH in RIA 23.6 μU/ml (normal 0.27–4 μU/ml), anti-TPO AB 605 IU/ml (normal 100 IU/ml), anti-thyroglobulin AB 740 IU/ml (normal < 300 IU/ml) and anti-intercellular-substance AB with indirect IF. IFN-α was discontinued. The malaise and pain disappeared after 1 month and the skin lesions and depression after 3 months. In January 2000, blood tests were negative except for ANA 1/1280 and anti-DNA AB 80 U. In February 2001, lupic markers had disappeared. HCV-RNA remained negative.

Comment. The occurrence of autoimmune disorders such as lupus syndrome, thyroid disorders and bullous skin lesions has been described after IFN-α therapy but only in immuno-competent subjects.

Lupus syndrome has been reported in 14 cases [2–3]. In 13 of these, symptoms gradually disappeared over several months after cessation of treatment. The fourteenth patient required corticosteroid therapy despite cessation of treatment. In one case, lupus syndrome was associated with autoimmune thyroid disease [3]. This was a 33-year-old patient who had been treated for chronic myeloid leukaemia with IFN-α 2a, 9 MU per day during 12 months. Following cessation of treatment, ANA diminished and thyroid function returned to normal.

Thyroid disorders are frequently associated with IFN-α therapy [1] either hyperthyroidism with an onset 2–6 months after the onset of treatment, or more frequently hypothyroidism, appearing within 6–12 months of treatment, or biphasic thyroiditis. In 60% of cases, thyroid function returns to normal within 6 months cessation of treatment.

The occurrence of bullous skin lesions has been reported in only three patients undergoing IFN-α therapy. Two patients were being treated for Kaposi’s sarcoma [4] with 3 MU weekly. The lesions appeared during the eighth week of treatment. In one of them, direct IF revealed IgG and C3 deposits in the epidermal intercellular substance and C3 deposits at the dermo-epidermal junction consistent with pemphigus/pemphigoid features. The third patient [5], treated with IFN-α 2a, 9 MU 3 times weekly, for hepatitis C, developed bullous lesions consistent with pemphigus foliaceus with IgG and C3 deposition on the surface of keratinocytes under direct IF. Indirect IF performed on human skin revealed circulating IgG AB that bound to the epithelial cell surface. A skin biopsy was not performed in our patient but the occurrence in the blood of anti-intercellular-substance AB suggests an autoimmune process.

The mechanisms by which such autoimmune disorders appear are complex and poorly understood [1]. Observations in humans have shown that IFN-α therapy activates a multiple cytokine cascade effect within the immune system, thus explaining the diversity of autoimmune side effects presenting in such patients. In most cases, as with our patient, autoimmune symptoms disappear after cessation of cytokine treatment. This suggests a cause–effect link between cytokine therapy and autoimmune disorders. As already described, our patient had no evidence of autoimmune disorders prior to treatment. Vial and Descotes [1] have proposed that the autoimmune mechanism originates from the abnormal expression of MHC molecules activated from cells targeted by T-lymphocytes resulting from a B-cell dysfunction.

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