Urticaria, Angioedema and Dyspnoea in Adjuvant Therapy of Melanoma with Interferon α-2b

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Adjuvant therapy with interferon (IFN) α-2b has been shown to increase disease-free survival in patients with stage II (3 million IU, 3 times/week, subcutaneous: low-dose) or stage III melanoma (20 million IU/m^2 body surface area, intravenous 5 times/week: high-dose) without improving overall survival (1). The most frequently reported cutaneous adverse drug reactions (ADR) reported in a group of 33 patients on adjuvant low-dose IFNα-2b therapy because of malignant melanoma were alopecia (48%), hair discoloration (18%), eczematous reactions (39%) and pruritus (30%) (2). Urticaria was reported in only one of these patients (3%) (2). In most reported cases, cutaneous ADR to IFNα-2b do not necessitate cessation of therapy. There are no reports in the literature of urticaria during high-dose IFNα-2b.

CASE REPORT

We report here the case of a 48-year-old man with no history of allergy, who was started on adjuvant high-dose therapy with IFNα-2b because of stage IIIb melanoma. On day one, he was treated with IFNα-2b (40 million IU) intravenously, after premedication with 1 g oral paracetamol 1 h previously. Approximately 1 h after the first infusion, he developed slight oedema of the face, which resolved without any further therapy. As an intolerance reaction to paracetamol was suspected, the premedication was changed to ibuprofen on day two. However, within 20 min of the second infusion (after only approximately 10% of the amount had been applied) the patient developed urticarial exanthema and angioedema of both hands, which disappeared within one hour after stopping the infusion and oral antihistamines. Polyvalent intolerance to analgesics was suspected.

Three weeks later, skin-prick tests were negative for a series of analgesics (including paracetamol, diclofenac and ibuprofen), latex and for IFNα-2b. Total IgE, specific IgE for latex and serum tryptase were within normal ranges. Oral provocation testing with ibuprofen was well tolerated, as was paracetamol on another occasion.

On week 4, 1 million IU IFNα-2b was applied subcutaneously after premedication with ibuprofen, which was well tolerated. The following day, 10 min after application of 3 million IU IFNα-2b subcutaneously, the patient again developed generalized urticaria with dyspnoea. Premedication had not been changed. The immediate type symptoms required application of methylprednisolone and dimetindene intraveneously. Therapy with IFNα-2b has not been restarted since.

DISCUSSION

We attributed the patient's immediate type symptoms to application of INFα. The differential diagnosis included intolerance to analgesics or latex allergy, which could be excluded by *in vitro* and *in vivo* testing, including oral provocation test to analgesics. There were no signs of underlying mastocytosis.

The pathogenesis of the reaction in our patient is not clear. Interestingly, the patient showed a spontaneously resolving facial oedema after 40 million IU IFN α-2b intravenous, but urticarial exanthema and angioedema after the second infusion and after administration of only 3 million IU IFN α-2b subcutaneously. One might speculate that this was due to an immunological sensitization, which was, however, not shown by skin prick test, although non-immunological hypersensitivity might also be suspected.

IFNs are anti-viral and immunoregulatory agents that may increase the activity of macrophages, B- and T cells, as well as of mast cells (3–5). The response of mast cells to IFN might be differentially regulated intra- and inter-individually. This is emphasized by the fact that high concentrations of IFNα-2b were shown to give rise to an IgE-mediated histamine release from basophil granulocytes from patients without formerly known urticaria, but not in a group with pre-existing urticaria (6).

Immediate-type reactions to IFNα have been reported occasionally, i.e. in a patient with hepatitis C who developed angioedema after 22 weeks of IFNα-2b 6 million IU/week (7, 8). In this case, the pathogenesis of IFN-related angioedema was suggested to be similar to that of angioedema induced by angiotensin-converting enzyme (ACE) inhibitors, because there was an increase in the plasma bradykinin level and the onset was delayed after the start of IFN therapy. *In vitro* investigations demonstrated a release of IFNγ and macrophage migration inhibition factor by peripheral blood lymphocytes of patients with drug-induced urticaria, indicating immune sensitization (9). Furthermore, IL1-induced IL8 production was dramatically suppressed by the administration of IFNα-2b (10).

Specific desensitization, as reported with IFN-β in a patient with multiple sclerosis (11), was also considered, but finally not realized in our patient because of

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unknown pathogenesis of reaction and lack of compliance.

In summary, we report here a rare case of immediate-type reaction to IFNα-2b in a patient with melanoma, which led to discontinuation of adjuvant therapy with IFNα-2b.

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