

Short report

Angioneurotic oedema and urticaria during therapy with interleukin-2 (IL-2)

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Introduction

Therapy with IL-2 may be accompanied by many side effects which have been recently reviewed [1]. Idiosyncratic reactions during IL-2 treatment are very rare. Eberlein et al. [2] reported one case of respiratory insufficiency due to severe vocal cord oedema during IL-2 therapy, making a tracheostomy and intubation necessary. The patient recovered completely. We describe one patient who experienced urticaria, and another patient who developed angioneurotic oedema while on therapy with IL-2. In addition, some of the pathogenetic mechanisms underlying these side effects will be discussed.

Patients, methods and results

Patient A, a 47-year-old woman with metastatic melanoma, received 100 µg/m²/day Interferon-gamma (IFN-γ) (Boehringer Ingelheim BV) by intramuscular injection for 5 days, followed by IL-2 (EuroCetus BV) at a dose of 6 × 10⁶ International Units (IU)/m² as a daily 15-minute infusion for 5 days. The cycle was repeated after a 10-day rest period. During IL-2 therapy, the patient experienced fever WHO grade 2, dizziness, pruritus and hypotension WHO grade 1-2. Approximately 12 to 14 h after completing the IL-2 and when the patient had returned home, she reported having skin eruptions on her legs lasting between 4 and 6 h. This phenomenon occurred regularly following subsequent cycles of IL-2 and eventually her husband took photographs of the skin abnormalities which appeared to be urticarial eruptions (Fig. 1).

Thereafter, the patient had progressive disease (14 months after the start of therapy) and the treatment was discontinued. Neither the patient nor her family members were known to have an allergic constitution. The patient had no eosinophilia and the levels of the serum immunoglobulin (Ig) classes Ig-G, Ig-A and Ig-M remained normal during the IL-2 therapy. Neither histamine nor its degradation products were determined. After cessation of IL-2 therapy, the urticaria never appeared again.

Patient B was a 63-year-old man who presented with synchronous lung metastases of renal cell cancer. Five weeks after a nephrectomy, he received 100 µg/m²/day IFN-γ (Boehringer Ingelheim BV) by subcutaneous injection for 5 days, followed by IL-2 (EuroCetus BV) as an infusion over 15 minutes at a dose of 18 × 10⁶ IU/m²/day, planned for 5 days. Fifteen minutes after the first intravenous injection, the patient developed angioneurotic oedema of the right side of the face, which disappeared within 48 h (Fig. 2).

The oedema was confined to the lips, cheek and anterior part of the tongue. He experienced a transient hypotension WHO grade 2 which followed a similar pattern as observed in other patients treated with the same protocol. In addition, he suffered from nausea, vomiting, abdominal cramps and diarrhoea for several days. After this event, the patient told us that he had experienced episodic swelling of the right side of his face over the previous 2 years, which had occurred every 3 to 6 months without any apparent predisposing factors. The patient had no history of allergic diseases. His family members were not known to have angioneurotic oedema or any other allergic symptoms. After this episode, the lung metastases showed slight regression; therefore, the patient asked for another cycle of IL-2. Although it was likely that the angioneurotic oedema had been caused by the administration of the IL-2, a mere coincidence could not be completely excluded. After 6 weeks, the patient received 18 × 10⁶ U IL-2/m²/day by subcutaneous injection under close monitoring. Twenty hours after the administration, the patient again developed angioneurotic oedema on his face, without any other constitutional symptoms or changes in blood pressure. He was treated with prednisolone and clemastine intravenously. Administration of epinephrine was not necessary. The oedema vanished rapidly within 24 h. The treatment with IL-2 was discontinued. The patient experienced a partial remission of his lung metastases and remains without disease progression 6 months later.

In patient B, blood samples were taken before and at 1, 2, 4, 6, 8 and 24 h after IL-2 administration during both cycles. All blood samples were collected in 5 ml tubes that contained EDTA (10mM) and polybrene (0.05%) to prevent activation of the complement and coagulation systems [4]. The levels of the activated third component of the complement system (C3a), factor XII antigen, functional and antigenic complement 1 esterase inhibitor (C1 inh) and kallikrein antigen were assessed as described in detail elsewhere [3-5]. The normal values for C3a are ≤5 nmol/l; the normal values of the other mentioned parameters were 100%.

The patient had normal C1 inh levels (both functional and antigenic) which did not change significantly following IL-2 treatment. The change in C3a levels was comparable to that observed in other patients treated with the same protocol, increasing from 4.6 to 11 nmol/l following the intravenous treatment and from 7.1 to 9.4 nmol/l after subcutaneous administration [6]. Factor XII and kallikrein antigen levels did not change during the treatment. The patient had no eosinophilia, no elevations in immunoglobulin (Ig) concentrations (Ig-E included) and no angio-converting enzyme deficiency. Antibodies against IL-2 were not detectable.

Discussion

There is no unifying concept to account for the occurrence of urticaria and angioneurotic oedema. Hista-



Fig. 1. Urticaria on the legs of patient A one day after IL-2 treatment.

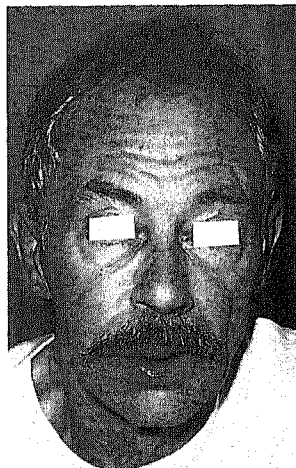


Fig. 2. Angioneurotic oedema of the face of patient B after the first administration of IL-2.

mine is considered to be a key mediator in many cases. Several mechanisms can induce the release of this mediator from mast cells and basophilic granulocytes [7]. Potential mechanisms include immediate Ig-E-dependent hypersensitivity reactions, non Ig-E-dependent degranulation, e.g., as induced by anaphylatoxins formed after activation of the classical or alternative pathways of the complement system or direct mast cell activation by pharmacological agents [7]. The plasma kinin-forming system also plays a role in the development of urticaria and in particular angioneurotic oedema, as is demonstrated by the clinical syndrome that results from a deficiency of the main inhibitor of this system, namely C1 inh [7, 8]. In these particular cases, these phenomena are not necessarily induced by histamine release [7, 8]. Bradykinin, one of the products generated during activation of the contact system, is known to increase vascular permeability and to cause vasodilatation [4, 7].

IL-2 is not known to induce direct histamine release. An Ig-E-mediated mechanism appears not to be the most likely cause of the urticaria or angioneurotic oedema in these cases. IL-2 treatment induces activation of the complement and presumably also of the contact system [4–6]. This might have contributed to the development of urticaria and angioneurotic oedema in our patients. It is likely that other unknown factors also played a role in the development of these phenomena, since activation of the complement system was observed in all patients treated with the IL-2 scheme [5, 6], whereas idiosyncratic reactions occurred only in these two patients. Activation of the contact system could not be detected in patient B. In addition, an acquired C1 inh deficiency due to malignancy was ruled out in this patient [8]. The influence of IFN- γ pretreatment on the development of these syndromes is not clear. Patient B, however, also experienced angioneurotic oedema after IL-2 administration without IFN- γ pretreatment, and this observation argues against a role of IFN- γ in the induction of this syndrome. These cases

show that patients receiving IL-2 must be closely monitored, even when the scheme is to be given in a normal oncology ward or the outpatient clinic.

References

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