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Letter to the Editor

IgE-mediated anaphylaxis to methylprednisolone succinate in a patient with indolent systemic mastocytosis

Dear Editor,

We present the case of a 65-year-old man, with a medical history of arterial hypertension, appendicitis requiring appendectomy and transurethral resection of a transitional cell carcinoma of the bladder, who was treated with intravenous methylprednisolone succinate for an episode of idiopathic urticaria. Within 2 min of administration, the patient experienced severe angioedema of the throat, hypotension, and finally shock with loss of consciousness. He was successfully treated with epinephrine 0.3 mg twice intramuscularly and a bolus of epinephrine 50 μg intravenously. Acute serum tryptase obtained during the anaphylactic episode was 63 μg/L with a baseline of 44.8 μg/L indicative for mast cell activation (MCA).[1] During clinical examination at our center no cutaneous lesions compatible with mastocytosis in the skin were withheld. Skin prick tests (SPTs) and intradermal tests (IDTs) were performed with serial dilutions of methylprednisolone sodium succinate (Solu-Medrol® 40 mg/mL, Pfizer), hydrocortisone sodium succinate (Solu-Cortef® 50 mg/mL, Pfizer), methylprednisolone acetate (Depo-Medrol® 40 mg/mL, Pfizer), dexamethasone sodium phosphate (Aacidexam® 5 mg/mL, Aspen), triamcinolone acetonide (Kenacort A® 10 mg/mL, Bristol-Myers Squibb) and betamethasone sodium phosphate + betamethasone dipropionate (Diprophos® 5 mg/mL + 2 mg/mL, Organon). As displayed in Table 1, SPTs with methylprednisolone sodium succinate and hydrocortisone sodium succinate were positive. In contrast, SPTs and IDTs with glucocorticoids without a succinate moiety such as methylprednisolone acetate, dexamethasone sodium phosphate, triamcinolone acetonide, and betamethasone sodium phosphate + betamethasone dipropionate remained negative. Specific IgE to methylprednisolone-21-sodium succinate using a fluorescent enzyme immunoassay (FEIA ImmunoCAP, Thermo Fisher Scientific) was 0.15 kUA/L in the patient's serum sample, in contrast to <0.10 kUA/L in ten healthy controls. Basophil activation experiments were performed with the different glucocorticoids by incubating aliquots of 200 μL endotoxin-free heparinized whole blood (37 °C, 20 min) with different concentrations (0.1–100 μg/mL) of the afore-mentioned glucocorticoid compounds (Fig. 1). The patient's basophils upregulated the expression of CD63 and released histamine in response to methylprednisolone sodium succinate and hydrocortisone sodium succinate. In contrast, basophils were non-responsive to the unsuccinylated glucocorticoids. An oral challenge with methylprednisolone and an intramuscular challenge with betamethasone sodium phosphate + betamethasone dipropionate were both uneventful (Table 1). Together, these data point to an IgE-mediated hypersensitivity against the succinate moiety of the glucocorticoids.

Because of the elevated baseline tryptase, a bone marrow study was performed. Examination with tryptase staining revealed no aggregates of abnormal mast cells. However, flow cytometry of the bone marrow revealed aberrant mast cells expressing CD25 and CD2. Moreover, KIT D816V mutation analysis on bone marrow aspiration revealed a KIT D816V mutation with an allele burden of 0.071%. Together with the elevated baseline serum tryptase (>20 μg/L), these findings allowed to establish the diagnosis systemic mastocytosis.[2–4] The work-up did not reveal B- or C- findings or associated neoplasm. Therefore, the final diagnosis was Indolent Systemic Mastocytosis (ISM).

Hypersensitivity reactions to glucocorticoids mainly present as delayed type IV hypersensitivity skin reactions to topically applied agents and occur with a frequency of 0.5–5%.[5] Immediate type hypersensitivity reactions to systemically administered compounds are rarer, occurring with a prevalence of approximately 0.1–0.3%.[6] IgE-mediated reactions to glucocorticoids can occur to the glucocorticoid itself, or secondary to the excipients in the systemic glucocorticoid preparation.[7] Glucocorticoids are poorly soluble in saline solution and are therefore combined with esters at the C21 position.[8] For intravenous therapy sodium succinate is the most commonly used ester, for intra-articular of soft tissue administration sodium phosphate and acetate esters are used. It is

Table 1
Positive skin test results are expressed as wheal and flare reactions in mm together with the applied dilution.

Allergological work-up: results				
Compound	SPT	IDT	BAT	Challenge
methylprednisolone succinate 40 mg/mL	1:1000 5/27 mm	NP	+	NP
hydrocortisone succinate 50 mg/mL	1:10 5/25 mm	NP	+	NP
methylprednisolone acetate 40 mg/mL	–	–	–	NP
methylprednisolone	NP	NP	NP	–
dexamethasone sodium phosphate 5 mg/mL	–	–	–	NP
triamcinolone acetonide 10 mg/mL	–	–	–	NP
betamethasone sodium phosphate 2 mg/mL + betamethasone dipropionate 5 mg/mL	–	–	–	–

Skin tests were considered negative when no response was observed up to the undiluted formulation.
SPT, skin prick test; IDT, intradermal test; BAT, basophil activation test; NP, not performed.

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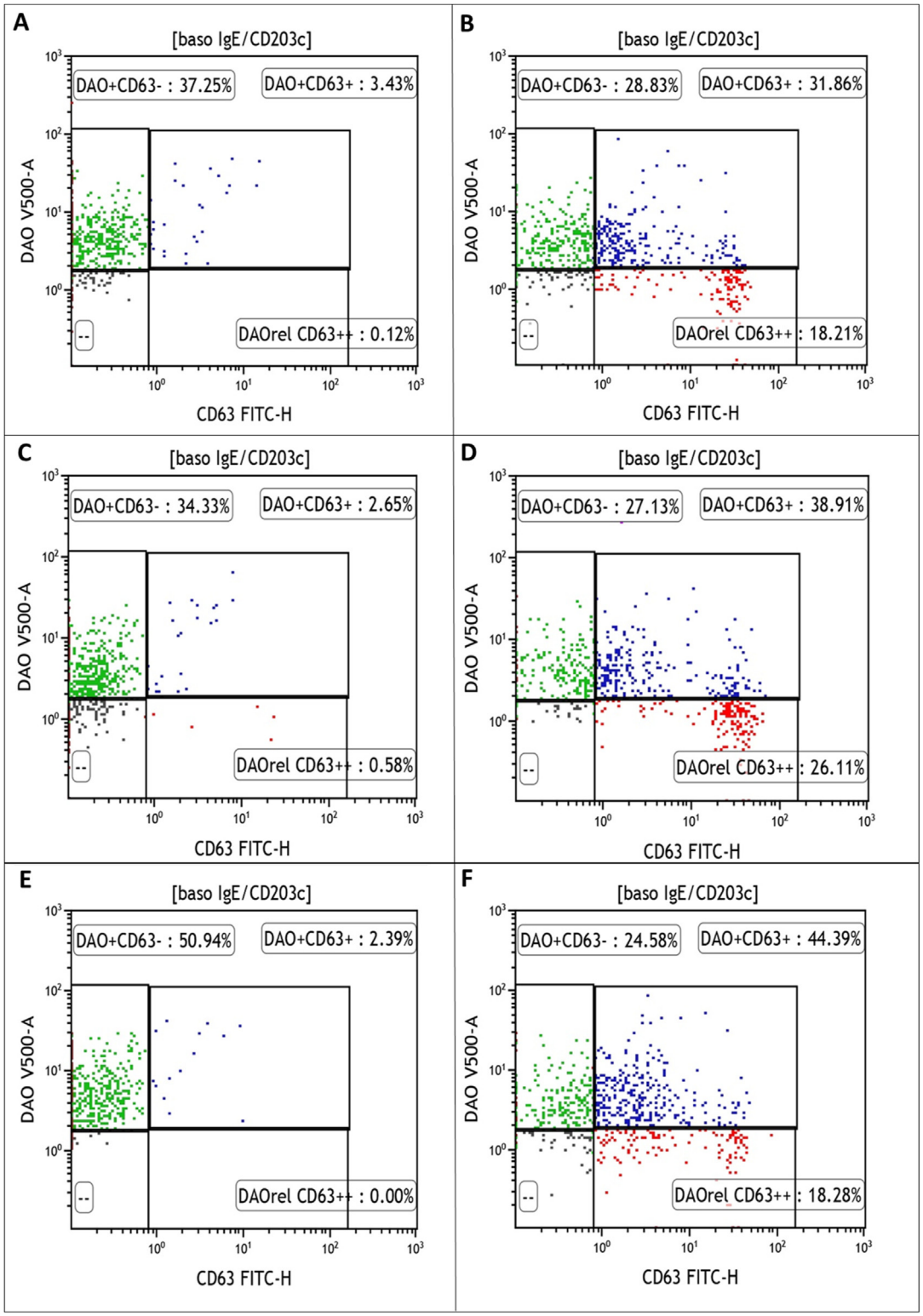

Fig. 1. Basophil activation experiments with different glucocorticoids (**C:** methylprednisolone acetate; **D:** methylprednisolone succinate; **E:** betamethasone sodium phosphate + betamethasone dipropionate; **F:** hydrocortisone succinate). Dilution buffer and anti-IgE served as a negative **(A)** and positive control **(B)** respectively. Basophil activation and histamine release at a single cell level were flow-cytometrically evaluated by measuring up-regulation of CD63, CD203c and diamine oxidase (DAO) staining.

reported that up to one-tenth of all reported reactions to intravenous corticosteroids can be attributed to the succinate ester moiety.[6] In our case, diagnosis of sodium succinate hypersensitivity is documented by *in vivo* and *in vitro*/ex vivo tests, i.e. skin testing, quantification of sIgE antibodies, and basophil activation experiments. The selectivity of the anti-succinate response was endorsed by negative provocation tests with unsuccinylated methylprednisolone and betamethasone sodium phosphate + betamethasone

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dipropionate. Based on our findings, we recommend that succinylated glucocorticoids should absolutely be avoided in this patient. Of special interest in this case, is that supplementary to the *in vivo* skin tests, ex vivo tests such as BAT were also performed. The negative BAT results also corresponded with the *in vivo* skin tests and provocation tests. The advantage hereof is the possibility of performing multiple evaluation studies simultaneously without the risk of endangering the patient's health. Several authors already suggested that ex vivo tests such as BAT could be of interest in excipient testing for glucocorticoid allergy.[7,8] Our case is a prime example of the utility of BAT in excipient testing. The second particularity in this case was the presence of an underlying indolent systemic mastocytosis in this patient. This case illustrates that the diagnosis of an underlying clonal mast cell disorder in severe anaphylaxis can be challenging, especially in the absence of skin lesions, which is often associated with a negative KIT D816V mutation in peripheral blood.[9]. In this patient, based on bone marrow examination alone, the diagnosis of ISM could have been missed due to the absence of mast cell infiltrates on light microscopy. Techniques with a higher sensitivity such as flow cytometry for CD25 and CD2-expression or PCR-based mutation analysis for KIT D816V are paramount to prevent underdiagnosis and therefore possible recurrence of severe anaphylactic reactions.

In conclusion, sodium succinate hypersensitivity is rare but should not be overlooked as it might entail a severe risk for drug-induced anaphylaxis. In the presence of severe, mast cell-triggered anaphylaxis measurement of baseline serum tryptase is of help in identifying patients with possible concomitant (clonal) mast cell disorder. Diagnosis of ISM was made on basis of 4 minor criteria in the absence of mast cell infiltrates on bone marrow examination, highlighting the need for highly sensitive techniques in the diagnostic workup.

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Conflict of interest

The authors have no conflict of interest to declare.

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