

CASE REPORT

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Methylprednisolone-induced anaphylaxis diagnosed by intradermal skin test: a case report

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Abstract

Background: Glucocorticoids rarely cause anaphylaxis. Common methods for the determination of allergens include in vivo skin prick test (SPT) and intradermal skin test (IDST) and the in vitro basophil activation test (BAT). However, to our knowledge, the best strategy for diagnosing glucocorticoid-induced anaphylaxis has not been elucidated.

Case presentation: A 10-year-old boy was admitted to our hospital because of 2 weeks of fever and arthralgia. He had not been treated with glucocorticoids before, including methylprednisolone (mPSL). He was suspected to have bacterial myositis and was treated with ceftriaxone. However, his symptoms persisted for > 2 weeks. Autoinflammatory arthritis was suspected, and he was treated with mPSL sodium succinate (MPS) pulse therapy (30 mg/kg). After 15 min of mPSL injection, he had wheezing and generalized wheal formation with decreased oxygen saturation. As anaphylaxis was suspected, mPSL was discontinued, and olopatadine and oxygen were administered. The symptoms improved considerably without the use of epinephrine and disappeared in 30 min. One month after discharge, SPT, IDST, and BAT were performed without discontinuing his prescribed oral prednisolone. SPTs for MPS, hydrocortisone sodium succinate (HCS), prednisolone sodium succinate (PSS), dexamethasone sodium phosphate (DSP), and betamethasone sodium phosphate (BSP) were negative. IDSTs for MPS, HCS, and PSS were positive, whereas those for DSP and BSP were negative. By contrast, BATs for MPS, HCS, and PSS were negative. Although glucocorticoid-induced hypersensitivity caused by nonmedicinal ingredients such as lactose, carboxymethylcellulose, polyethylene glycol, and hexylene glycol has been reported; the glucocorticoids tested in this patient did not contain any of these nonmedicinal ingredients. As the glucocorticoids that were positive on IDST share a succinate ester, this might have caused MPS-induced anaphylaxis.

Conclusions: We report the case of MPS-induced anaphylaxis diagnosed by IDST but not BAT. In case reports of glucocorticoid-induced anaphylaxis in the literature, most patients were diagnosed with SPT or IDST. These results suggest that BAT should be considered when IDST and SPT are negative. Further studies are necessary to clarify the best strategy for diagnosing glucocorticoid-induced anaphylaxis.

Keywords: Methylprednisolone-induced anaphylaxis, Glucocorticoids, Immediate allergy, Succinate ester, Basophil activation test, Intradermal skin test

Background

Glucocorticoids are usually used to treat anaphylaxis. However, glucocorticoids rarely cause anaphylaxis. Glucocorticoids are hydrophobic particles, and their intravenous forms have succinate ester that make them

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hydrophilic. Anaphylaxis secondary to glucocorticoids that contain succinate ester are reported to have a prevalence of about 0.3%, which is not unexpectedly rare [1].

Determination of the cause of allergy is critical for proper care. This analysis includes *in vivo* tests, such as the skin prick test (SPT) and intradermal skin test (IDST), and *in vitro* tests, such as the allergen-specific IgE test and basophil activation test (BAT). Allergen-specific immunoglobulin E (IgE) test is not a reliable test for glucocorticoid-induced allergy, as mentioned earlier [2]. BAT is a flow cytometry-based assay that measures the expression of activation markers on the surface of basophils following stimulation with an allergen [3]. The usefulness of BAT has been studied well for the determination of food allergens [3]. However, BAT has been reported in only a limited number of cases of glucocorticoid-induced anaphylaxis [4–8]. Therefore, the diagnostic strategy for glucocorticoid-induced anaphylaxis has been elucidated.

In this study, we reported the case of a boy who developed anaphylaxis secondary to intravenous methylprednisolone (mPSL) sodium succinate (MPS) during pulse therapy. The drug allergy was proven by IDST, not BAT.

Case presentation

A 10-year-old boy was admitted to our hospital because of 2 weeks of fever and arthralgia. His medical history was unremarkable, and he had not been previously treated with glucocorticoids, including mPSL. Laboratory testing showed leukocytosis of 22,400/mL with 88% segmented neutrophils and an elevated C-reactive protein of 9.21 mg/dL. Magnetic resonance imaging of the lower extremities with fat-suppressed T2-weighted images showed high intensity in the right gluteus maximus muscle. He was suspected to have bacterial myositis and was treated with ceftriaxone. However, his symptoms persisted for more than 2 weeks. Autoinflammatory arthritis was suspected, and treatment with mPSL pulse therapy (30 mg/kg) was initiated.

After 15 min of mPSL injection, he had wheezing and generalized wheal formation with decreased oxygen saturation. As anaphylaxis was suspected, mPSL was discontinued, and olopatadine and oxygen were administered. The symptoms improved considerably without the use of epinephrine and disappeared in 30 min. Oral prednisolone (PSL, 2 mg/kg/day) was started for the treatment of arthritis and afforded resolution of fever and arthralgia. He was discharged from the hospital 1 week after the start of oral PSL. There was no relapse and oral PSL was reduced to 5 mg/day after 1 year.

One month after discharge, SPT, IDST, and BAT were performed to assess for reaction to glucocorticoids including MPS. Of note, the patient remained on his prescribed oral PSL during this evaluation. SPTs for MPS, hydrocortisone sodium succinate (HCS), PSL sodium succinate (PSS), dexamethasone sodium phosphate (DSP), and betamethasone sodium phosphate (BSP) were negative. IDST for MPS resulted in a 7 × 7-mm wheal and a 9 × 8-mm area of erythema, whereas normal saline revealed no wheal or erythema. Therefore, IDST for MPS was positive. Moreover, IDSTs for HCS and PSS were also positive, whereas those for DSP and BSP were negative. BAT for MPS was negative compared to the positive control stimulated by a monoclonal anti-IgE antibody (1-h incubation, 1.0% vs 60.4%; 24-h incubation, 1.9% vs 18.3%). Nonmedical ingredients in the glucocorticoids tested in this patient are shown in Table 1.

Discussion and conclusions

Anaphylaxis to glucocorticoids

Nonmedicinal ingredients such as lactose, carboxymethylcellulose, polyethylene glycol, and hexylene glycol are reported causes of glucocorticoid-induced hypersensitivity [2]. The glucocorticoids tested in this patient did not contain any of these nonmedicinal ingredients (Table 1). Since the glucocorticoids that elicited positive IDSTs share a succinate ester, we diagnosed anaphylaxis secondary to the succinate ester in MPS.

Table 1 Nonmedicinal ingredients in the glucocorticoids used in skin tests

Glucocorticoid	Na ₂ HPO ₄	NaH ₂ PO ₄	NaOH	Others
Methylprednisolone sodium succinate	+	+	+	
Prednisolone sodium succinate	+	+	–	Na ₂ CO ₃
Hydrocortisone sodium succinate	+	+	+	
Dexamethasone sodium phosphate	+	–	+	NaHSO ₃ , NaCl, Sodium citrate
Betamethasone sodium phosphate	+	+	–	D-sorbitol, Na ₂ SO ₃

Succinate ester was found to be the cause in most cases of anaphylaxis secondary to systemic glucocorticoid administration [9]. Our patient had anaphylaxis induced by MPS during mPSL pulse treatment for autoinflammatory arthritis. Succinate is the common chemical structure among MPS, HCS, and PSS. Notably, IDSTs for all three drugs were positive in this patient, indicating that the anaphylaxis was attributable to succinate.

As the patient had not previously been exposed to glucocorticoid medications, he must have been exposed and sensitized to succinate ester in another form before the episode of anaphylaxis. Some food additives contain succinate ester. For example, octenyl succinic acid-modified starch is listed in the General Standard for Food Additives for use as a stabilizer, emulsifier, and thickener in several food categories [10]. Therefore, it is possible that our patient consumed these food additives and was sensitized without noticing. No study reported the cross-reactivity between succinate and phosphate ester, indicating that cross-reactivity between the two esters may not be the cause of sensitization in this patient.

SPT, IDST, and BAT

In vivo tests, such as SPT and IDST, are generally used for determining the causative drugs in patients with anaphylaxis [3], although BAT has been reported to be useful in proving anaphylaxis secondary to MPS [5]. We searched for case reports on the use of BAT for the diagnosis of glucocorticoid-induced anaphylaxis in PubMed and Ichushi-Web, which is the Japanese database of medical literature updated by the Japan Medical Abstracts Society (Table 2) [4–8]. Among the 10 patients, including ours, BAT was positive in six and negative in four. IDST was negative in one patient and SPT in five. In the four patients with a negative

BAT, IDST was positive in two and SPT in three. These facts suggest that a combination of diagnostic tests is necessary to diagnose glucocorticoid-induced anaphylaxis.

In our patient, BAT was negative for glucocorticoids that contained succinate ester regardless of incubation time, whereas IDST was positive. This may be explained by the use of an oral glucocorticoid during blood sampling for BAT. Individuals being tested on BAT should stop treatment with oral steroids 3 weeks before the test [11], although no significant reduction of basophil reactivity was observed at the concentration of the therapeutic range of prednisolone [12]. PSL may reduce basophil reactivity to succinate ester by different mechanisms in 1-h and 24-h incubations. The rapid inhibitory effect of glucocorticoids through a nongenomic pathway induces decreased basophil activity [13], which may be the cause of a negative BAT at 1 h. On the other hand, glucocorticoids are reported to induce DNA fragmentation and apoptosis of basophils for several hours through modulation of gene expression [14], which may be the cause of the negative BAT 24 h after incubation. Although BAT is known to be safe [3], its diagnostic value in patients with MPS-induced anaphylaxis should be elucidated, especially when the patient is taking glucocorticoids. Another possible explanation for the negative BAT in this patient is a non-IgE-mediated hypersensitivity to MPS. Hypersensitivity reactions to drugs are often type I, but they can be type II, III, or IV [15]. If the result of BAT is accurate, then the possibility of an IgE-mediated allergy is unlikely. However, considering the time between drug administration and the onset of anaphylaxis, type 1 allergy is the most likely cause of anaphylaxis in this case.

In conclusion, IDST was useful in establishing the diagnosis of MPS-induced anaphylaxis in this case,

Table 2 Case reports of BAT for steroid-induced anaphylaxis in the literature

No.	Authors	Year	Age	Sex	Primary disease	Steroids	BAT	SPT	IDST	Challenge test
1	Ben Said [5]	2007	18	F	General anesthesia	MPS	Positive	Positive	Positive	ND
2	Lehmann [8]	2008	2	M	Bronchial asthma	PSS	Positive	Negative	Positive	ND
3	Aranda [4]	2010	22	F	Dental infection	MPS	Positive	Positive	ND	ND
4			32	M	Parotitis	MPS	Negative	Positive	ND	ND
5			46	F	Dental infection	MPS	Positive	Negative	Negative	Positive
6			65	F	Dental surgery	MPS	Positive	Negative	Positive	ND
7	Walker [7]	2011	26	M	Bee bite	PSS, MPS	Negative	Positive	ND	Positive
8			70	M	Sudden deafness	PSS, HCS	Positive	Negative	Positive	ND
9	Nucera [6]	2011	45	F	Dialysis surgery	HCS	Negative	Positive	Positive	ND
10	Amano (this study)	2020	10	M	Autoinflammatory arthritis	MPS	Negative	Negative	Positive	ND

M male, F female, MPS methylprednisolone sodium succinate, PSS prednisolone sodium succinate, HCS hydrocortisone sodium succinate, SPT skin prick test, IDST intradermal skin test, ND not described

whereas BAT was not probably due to the prednisolone use before testing. This highlights the need to choose the appropriate procedure to diagnose glucocorticoid-induced anaphylaxis. The results in our patient suggest that BAT may be considered when IDST and SPT are negative. Further studies are necessary to clarify the best strategy for diagnosing glucocorticoid-induced anaphylaxis.

Abbreviations

BAT: Basophil activation test; BSP: Betamethasone sodium phosphate; DSP: Dexamethasone sodium phosphate; HCS: Hydrocortisone sodium succinate; IDST: Intradermal skin test; IgE: Immunoglobulin E; MPS: Methylprednisolone sodium succinate; mPSL: Methylprednisolone; PSS: Prednisolone sodium succinate; SPT: Skin prick test.

Authors' contributions

HI contributed to the design of the research, the interpretation of data for the patient, and was a major contributor in writing the manuscript. HA, YK, TH, and TM contributed to the acquisition and analysis of data from the patient. HI and AO revised the manuscript critically for important intellectual content. HI contributed to the final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the study are available from the corresponding author by request.

Declarations

Ethics approval and consent to participate

This case report was approved by the ethical committee at Aichi Medical University (2020-H075).

Consent for publication

Written consent to participate and for publication was obtained from the parents.

Competing interests

The authors declare that they have no conflict of interest.

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