

Dear Editor

Hypersensitivity to Fludrocortisone Acetate in a Recipient of Bone Marrow Transplantation

Fludrocortisone acetate, a 9 α -fluorinated derivative of hydrocortisone, is a synthetic steroid possessing a predominantly high level of mineralocorticoid activity.¹ It is generally used in replacement therapy for adrenocortical insufficiency, such as Addison's disease, as well as in the treatment of salt-losing adrenogenital syndrome and less frequently for orthostatic hypotension. Since fludrocortisone acetate is a steroid, it is plausible that it has little potential to cause a hypersensitivity reaction. Indeed, to the best of our knowledge, there are no reported cases of hypersensitivity to fludrocortisone acetate in the English-language literature. We herein present the first case of hypersensitivity to fludrocortisone acetate.

A 23-year-old man with acute myeloid leukaemia underwent bone marrow transplantation from an unrelated donor after being conditioned with total body irradiation and high-dose cytarabine. Around post-transplant day 180, he developed orthostatic hypotension, which seriously impaired his daily life activities. Treatment with midodrine hydrochloride and amezinium metilsulfate yielded no improvement of his hypotension symptoms. Fludrocortisone acetate was then administered orally at a daily dose of 0.1 mg. Two days after he commenced fludrocortisone acetate treatment, he developed a high-grade fever and sharply margined, infiltrative, erythematous skin eruptions. These eruptions distributed on the face, trunk, and all extremities, but not involved mucous membranes. The laboratory findings were remarkable: a white blood cell count of $5.5 \times 10^9/\text{L}$ with 23% eosinophils and an elevated C-reactive protein value (2.69 mg/dl). A drug-induced lymphocyte stimulation test (DLST) for fludrocortisone acetate was performed by the ³H-thymidine absorption method.² DLST was positive for fludrocortisone acetate with a stimulating index of 281%. Neither patch test nor provocation test was performed. Based on these findings, the diagnosis of drug hypersensitivity caused by fludrocortisone acetate was made. Fludrocortisone acetate treatment was discontinued. Defervescence was then obtained within 2 days, and the erythema completely disappeared within 10 days. Fludrocortisone acetate was not readministered thereafter, and any other types of steroid preparations were not given for the treatment of orthostatic hypotension.

In the present case, fludrocortisone acetate caused a severe hypersensitivity reaction, presenting as generalized erythema. In general, it is difficult to definitely determine which drug causes a hypersensitivity

reaction unless only a single agent is given. In fact, our case received several drugs at the onset of generalized erythema. However, all the drugs except fludrocortisone acetate had been initiated at least one month before and were continued even after the patient had developed generalized erythema. Based on such a clinical course together with the positive results of DLST, we conclude that fludrocortisone acetate caused the hypersensitivity reaction in our case.

While the prominent characteristic of fludrocortisone acetate is a high mineralocorticoid activity (125 times the potency of cortisol), it also possesses moderate glucocorticoid activity (10 times the potency of cortisol).³ Therefore, during the administration of fludrocortisone acetate, warnings are necessary for hypertension, hypernatremia, hypokalemia, and water retention due to mineralocorticoid activity; and for impaired glucose tolerance and psychiatric reaction due to glucocorticoid activity. We believe that the present case is the first report documenting hypersensitivity to fludrocortisone acetate, while there have been reported cases of hypersensitivity to other types of steroid preparations such as hydrocortisone and methylprednisolone.⁴ Although most of the reported cases of hypersensitivity to steroid were due to immediate-type hypersensitivity, it is notable that the present case manifested as delayed-type hypersensitivity. Our findings strongly suggest that fludrocortisone acetate, a synthetic steroid, may be antigenic and cause hypersensitivity in spite of its pharmacologic activity not only as a mineralocorticoid but also as a glucocorticoid. However, impaired immunity due immune reconstitution after allogeneic bone marrow transplantation might have also played some role in the development of hypersensitivity to the drug.

We conclude that physicians should be aware of hypersensitivity as an adverse effect of fludrocortisone acetate. An accumulation of such cases is needed to further elucidate the characteristics and epidemiology of this rare adverse effect.

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Conflict of Interest: No potential conflict of interest was disclosed.

Authors' contributions: JK and TM managed the treatment of the patients and wrote the paper. MK and AT managed the care of toxicoderma and edited the paper. OI gave pharmacological advices and edited the paper. SO managed the treatment of the pa-

tient and gave an approval of this paper.

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