Acute generalized exanthematous pustulosis caused by iopamidol with recurrence on rechallenge with iopromide

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INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe pustular cutaneous adverse reaction caused by drugs in the majority of cases. However, it has been rarely reported after the use of iodinated contrast media, especially iopamidol and iopromide.[1] Delayed hypersensitivity reactions to iodinated contrast media, which uncommonly manifest as AGEP and are T-cell mediated, are presumably underdiagnosed and thus underreported. The reaction may be mistaken as caused by oral medications, particularly in patients receiving multiple drugs simultaneously.[2] Generally, patch testing can be used for the diagnosis of delayed hypersensitivity reactions to iodinated contrast media, and it is useful in determining the causative agent of AGEP.[2,3] Here, we present a case of iopamidol-induced AGEP confirmed by patch testing, with recurrence after iopromide rechallenge.

Abbreviation used:

AGEP: acute generalized exanthematous pustulosis

CASE REPORT

A 56-year-old Japanese woman underwent 3 radiologic examinations with intravenous iopamidol infusion for the management of inferior thyroid artery aneurysm, which was assumed to be the cause of her repeated minor hemoptysis. Seven days after the third injection, the patient was referred to our department for evaluation of rapidly spreading systemic erythematous eruptions. She had not previously received any iodinated contrast media and had no history of psoriasis or cutaneous drug reactions, and with the exception of an inferior thyroid artery aneurysm, her medical history was unremarkable. She received no regular medications, over-the-counter medications, or nutritional supplements.

During examination, her vital signs were normal. A physical examination revealed multiple scattered erythematous eruptions, mainly on the abdomen. The laboratory evaluation revealed leukocytosis (13,400/μL; reference 3900-9000/μL) and increased C-reactive protein level (0.37 mg/dL; reference $\leq$0.3 mg/dL). Renal and liver involvements were absent. The patient was administered topical steroid and antihistamine treatment.

Five days later, when she visited our department for follow-up, a skin examination revealed new erythematous rashes studded with numerous small, nonfollicular pustules localized to the intertriginous areas, including the axillae and groin (Fig 1). The Nikolsky sign was negative, and mucosal lesions, bullae, erosions, and generalized peripheral lymphadenopathy were not observed. Apart from a low-grade fever (37.5°C or 99.5°F), all other vital signs were normal. Her blood tests revealed leukocytosis (12,400/μL), neutrophilia (75%; reference range 30%-70%), and increased C-reactive protein level (5.22 mg/dL). Results for renal and liver involvement were unremarkable.

A skin biopsy revealed subcorneal neutrophilic pustules and marked edema of the papillary dermis with mixed inflammatory cell infiltration, including

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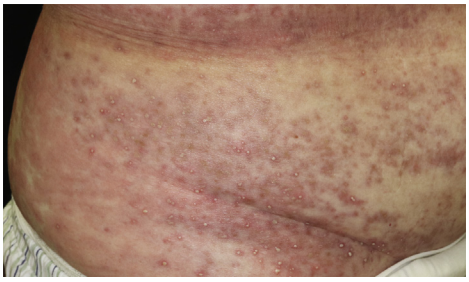

Fig 1. Acute generalized exanthematous pustulosis. Erythematous eruption with numerous pinpoint nonfollicular pustules on the inguinal region.

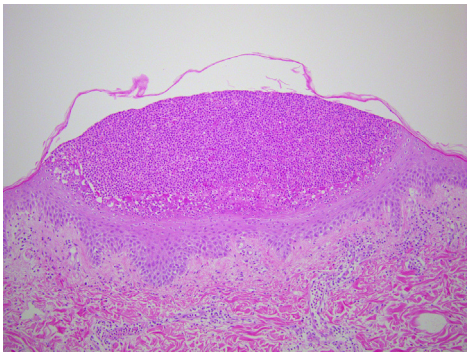

Fig 2. Histologic picture. Subcorneal neutrophilic pustules and marked papillary edema with a mixed inflammatory infiltrate including lymphocytes, neutrophils, and eosinophils. (Hematoxylin-eosin stain; original magnification: ×100.)

lymphocytes, neutrophils, and eosinophils, consistent with AGEP (Fig 2). Moreover, bacterial culture tests of the pustule content showed negative results. Her cutaneous lesions resolved in 5 days with continued topical steroid therapy.

As soon as the lesions resolved, a radiologic examination was performed by administration of iopromide as an alternative to iopamidol to assess the bleeding source and indication for transcatheter arterial embolization, after oral administration of prednisolone 50 mg at 13 and 7 hours before the injection. Within 24 hours, there was a mild recurrence of her skin lesions, with widespread pruritic erythema on the abdomen and limbs and several small pustules in the intertriginous folds of the abdomen, without a fever. The rash rapidly improved during the next 3 days with topical steroid and antihistamine use.

Patch tests conducted approximately 4 weeks later with iopamidol and scored according to the International Contact Dermatitis Research Group criteria[4] revealed a positive result after 48 and 72 hours. A test with iopromide revealed a negative result after 48 hours, 72 hours, and 7 days.

DISCUSSION

AGEP is diagnosed with the validation score developed by the EuroSCAR study group.[5] According to the score, our patient represented definitive AGEP with 10 points (range for definite AGEP 8-12 points).

In a previous study, a patch test was conducted for 8 of 16 patients with AGEP to determine the causative agent, and for 7 patients, it was caused by iodinated contrast media.[1] Conversely, neither of the 2 previously reported cases of iopamidol-associated AGEP was confirmed with patch tests.[1,6] In our patient, the positive patch test result for iopamidol strongly suggested that AGEP was induced by this agent.

Cross-reactions among different types of iodinated contrast media are occasionally confirmed by patch testing, and thus patch testing may contribute to the selection of an appropriate alternative iodinated contrast medium for patients with a previous delayed hypersensitivity reaction to iodinated contrast media.[7] However, our patient needed immediate radiologic examination with iodinated contrast medium administration to assess the bleeding source. Therefore, we used intravenous iopromide immediately after the skin lesions had adequately improved. We selected iopromide for the following reasons. First, the findings of a previous study had indicated that iopamidol, iomeprol, and iohexol, which are used in our hospital, frequently cause cross-reactions because they belong to the same group of iodinated contrast media agents.[8] Second, cross-reactions between iopamidol and iopromide have been reported in only a single patient with AGEP caused by iopromide.[9] We also used oral prednisolone as a premedication, considering the possibility of AGEP recurrence after rechallenge. This procedure facilitated an assessment of the bleeding source; however, we noted a recurrence of AGEP with milder reactions. Although the patch test results for iopromide were negative and indicated undetermined cross-reactivity between iopamidol and iopromide, a clinical examination of our patient suggested a cross-reaction between these 2 agents. These findings indicated that delayed hypersensitivity reactions tend to manifest more rapidly in patients with a previous iodinated contrast media reaction.[2] Further systematic patch testing with other iodinated contrast media may be helpful to understand cross-reactions among iodinated contrast media.

We suspect that the discrepancy between the clinical course and patch test results for iopromide

could be attributed to various factors, including a metabolite of the agent as the actual source for the cutaneous reaction and the anti-inflammatory activity of steroid treatment, although patch testing performed at 4 weeks after systemic steroid discontinuation seems to be generally acceptable.[10]

Our findings highlight that iopamidol can act as a potential trigger for AGEP, and that a patch test could be beneficial in the diagnosis of a delayed hypersensitivity reaction to iodinated contrast media. However, the patch test does not help in the selection of an alternative iodinated contrast medium. Furthermore, our case study reveals that cross-reactions between iopamidol and iopromide might be underestimated because of the small number of reported cases of AGEP associated with these 2 agents.

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