

First case report of acute generalized exanthematous pustulosis (AGEP) caused by gadolinium confirmed by patch testing

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Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction that is most often attributed to antibiotics. Typically, AGEP occurs soon after drug intake, and resolves spontaneously and rapidly after the causative drug is discontinued. Gadolinium-based magnetic resonance contrast media have been used for approximately three decades. Severe adverse reactions include immediate hypersensitivity reactions (urticaria and anaphylaxis) and nephrogenic systemic fibrosis (1,2). AGEP induced by contrast media, however, is very rare (3). According to our investigation, gadolinium-induced AGEP has not been previously reported. We present a case confirmed by skin biopsy and patch testing.

Case Report

A 53-year-old woman presented with a generalized eruption of pustules and erythema on intertriginous areas. She had no family or personal history of psoriasis. Her medical history included Cushing's syndrome resulting from a pituitary gland adrenocorticotrophic hormone-secreting tumour, type 2 diabetes mellitus, arterial hypertension, cerebrovascular accident, and osteoporosis. Her long-term medications had not been changed within the last 3 months, and consisted of olmesartan, amlodipine and hydrochlorothiazide in combination, pantoprazole, acetylsalicylic acid, metformin, and daily supplementation with calcium carbonate and vitamin D3.

Physical examination showed numerous small, sterile (upon culture), non-follicular pustules on a diffuse erythematous base with minimal mucosal involvement. The rash was pruritic and more prominent in the flexural areas, and showed active borders (Fig. 1a, b). Serology was negative for acute viral infections, including hepatitis A, B, and C, Epstein–Barr virus, cytomegalovirus, human herpesvirus-6, and parvovirus B19. Other systemic and laboratory examinations showed leukocytosis, elevation of serum creatinine, and an increase in the level of C-reactive protein. A skin biopsy from a lesion on the trunk showed the histological features of a drug-induced pustular eruption, such as subcorneal blistering with neutrophils and eosinophils, mild spongiosis, and a sparse infiltrate of neutrophils and eosinophils in the papillary dermis (Fig. 1c).

Three days before AGEP onset, the patient had undergone magnetic resonance imaging with a gadolinium-based contrast medium. Moreover, she reported two previous episodes of a pruritic and pustular eruption in 2011 and 2012, both following application of gadolinium-based contrast media. During hospitalization, the clinical course was favourable, even though exacerbations were noted up to 5 weeks after gadolinium administration. The eruption eventually resolved after 6 weeks, and there has been no relapse during follow-up.

Skin tests were performed 4 months after the last reaction. Patch tests were performed with aqueous gadoteric acid (Dotarem®) and aqueous gadobutrol (Gadovist®) 'as is'. The contrast media were applied on the forearm with Leukotest (Beiersdorf, Hamburg, Germany). The reactions were read on day (D) 2 and D4, and scored according to ESCD guidelines (4). Patch tests showed positive reactions on D2 and D4 to gadobutrol, and negative results with gadoteric acid (Fig. 1d). The positive reactions in the patch test clinically mimicked the clinical lesions. Patch tests were performed on 12 control subjects (6 healthy

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Fig. 1. (a, b) Typical acute generalized exanthematous pustulosis with accentuation on flexural areas. (c) Histopathological examination shows a subcorneal pustule with associated infiltration by neutrophils with epidermal spongiosis (haematoxylin and eosin; magnification: $\times 100$). (d) Positive patch test reactions to gadolinium on day (D) 2 (left) and D4 (right).

subjects and 6 atopic patients), and all of them had negative results.

Discussion

On the basis of the patient's history, classic clinical and histological presentations and positive patch reactions, our patient was diagnosed with AGEP caused by gadolinium-containing contrast media. AGEP is an uncommon cutaneous eruption characterized by acute, extensive, non-follicular, sterile pustules accompanied by widespread erythema, fever, and leukocytosis (4–6).

Our patient also showed some systemic symptoms characteristic of AGEP, including mild renal impairment, malaise, fever, and leukocytosis, during her hospital treatment. Although the diagnosis of AGEP is mainly based on history and clinical examination, patch tests may be necessary to identify the offending drugs; however, positive results have been reported in only a minority of

patients (6). In our patient, the positive patch test reaction to gadolinium confirmed the clinical diagnosis.

AGEP symptoms most often develop 1–12 days after patients start taking the new drug, and, typically, resolution occurs < 15 days after drug cessation (5). In contrast, our patient showed a prolonged clinical course with active pustular borders and annular desquamation for 6 weeks, despite application of topical corticosteroids. Such long persistence of skin lesions may be related to decreased gadolinium elimination, owing to (i) iatrogenic deterioration of renal function following intravascular contrast administration, estimated glomerular filtration rate values being < 59 ml/min, and (ii) a high level of gadolinium deposition in the bone tissue of patients with osteoporosis (7). The persistence of skin lesions may be related to decreased release of gadolinium, which has been detected in the tissues of several end-stage renal disease patients as long as 2 years after they have received a contrast medium. Data from animal models are supportive of this (8). Pietsch et al. (9) recently showed that gadolinium

could be detected in the skin of partially nephrectomized rats several months after injection.

To the best of our knowledge, we present the first report of AGEF induced by gadolinium with a prolonged course,

confirmed by biopsy and patch tests. It is important to recognize that, although AGEF induced by gadolinium may be relatively rare, it should be added to the list of agents recognized as causing AGEF.

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