OBSERVATION

Ioversol-Induced Acute Generalized Exanthematous Pustulosis

A Case Report

Ashley A. Hammerbeck, MD; Natalie H. Daniels, MD; Jeffrey P. Callen, MD

Background: Acute generalized exanthematous pustulosis (AGEP) is a relatively rare exfoliative dermatosis consisting of a generalized eruption of sterile, nonfollicular pustules arising on widespread erythematous and edematous skin that is usually caused by drugs. It has an acute onset, and patients often have systemic manifestations, including leukocytosis, fever, and hemodynamic instability. Rarely has AGEP been associated with radiocontrast dyes.

Observations: We describe an 84-year-old man who developed AGEP on 2 separate occasions after receiving an infusion of an ioversol-containing radiocontrast dye.

Conclusion: Acute generalized exanthematous pustulosis may occur after the use of intravenous radiocontrast dye.

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A CUTE GENERALIZED EXAN- thematous pustulosis (AGEP) is an uncommon pustular skin eruption that is usually induced by medications.1 Additionally, viral infections, mercury hypersensitivity, and ingestion of “lacquer chicken” have been implicated in triggering this reaction (Table 1).1-4 (Lacquer chicken is a dish prepared by basting the chicken in teriyaki sauce, honey, sake or wine, orange juice, garlic, sesame oil, coriander, Chinese 5-spice powder, and cinnamon and then baking.) We found few reports of radiocontrast-induced AGEP in the literature.5-7

Herein, we describe a patient who developed 2 episodes of AGEP, each temporally linked to the use of an ioversol-containing, noniodinated radiocontrast dye. To our knowledge, this is the first case of ioversol-induced AGEP to be reported.

REPORT OF A CASE

FIRST PRESENTATION

An 84-year-old man with no known drug allergies presented to an oncology clinic for chemotherapy for stage IV bladder cancer. The patient also had hypertension, adult-onset diabetes mellitus, Parkinson disease, hyperlipidemia, coronary artery disease, benign prostatic hypertrophy, right-sided hydronephrosis, and chronic renal insufficiency. His daily medications included aspirin, carbidopa/levodopa combination therapy, finasteride, lisinopril, regular insulin, pramipexole dihydrochloride, furosemide, simvastatin, and terazosin. The patient complained of fever, chills, nausea, malaise, and a skin eruption that he said began 1 day after he underwent radiation therapy and received a pelvic computed tomographic scan with contrast. The most recent chemotherapy infusion was 3 weeks prior to the onset of symptoms. The patient denied beginning treatment with any new medications, recent viral illness, or a history of psoriasis.

On initial physical examination, the patient was found to have orthostatic hypotension and was admitted to the hospital. On admission he was noted to have a pruritic skin eruption mostly confined to the trunk. He was afebrile at this time. Cutaneous examination showed numerous blanchable, erythematous macules and patches scattered diffusely over his back. Papules and pustules were noted over his bilateral axillary line and midlateral abdomen (Figure 1 and Figure 2). There was no involvement of his extremities, palms, soles, or mucosa. Nikolsky sign was absent. The patient was started on treatment with topical desonide cream, 0.05%, to be applied twice daily to the affected areas as well as hydroxyzine, 25-mg tablets, for pruritis.
Laboratory results revealed a normal white blood cell count of 6000/µL. The patient’s serum urea nitrogen and creatinine values were elevated to 55 mg/dL and 1.8 mg/dL, respectively. (To convert white blood cells to number of cells /10^9/L, multiply by 0.001; to convert serum urea nitrogen to millimoles per liter, multiply by 0.357; to convert creatinine to micromoles per liter, multiply by 88.4.) The cause for the patient’s worsening renal function was believed to be multifactorial, possibly resulting from dehydration, nephrotoxic effects of the chemotherapeutic agents, recent exposure to radiocontrast dye, and progression of the patient’s known hydronephrosis. All other laboratory values were unremarkable. Chest radiograph results were also normal. A Gram stain of skin aspirate was performed, and the findings were negative.

A 4-mm punch biopsy specimen revealed inflammatory changes with a spongiform subcorneal infiltrate of neutrophils and some eosinophils. There was also a moderate perivascular, interstitial infiltrate noted. These histopathologic findings were consistent with our clinical diagnosis of AGEP.

The patient’s renal function improved under treatment with intravenous hydration, and his serum creatinine level decreased to 1.4 mg/dL, a value close to the patient’s baseline. With the exception of 1 fever on the third night of admission (temperature measured by mouth, 38.7°C), he remained afebrile. On the fourth day of admission, worsening erythema was noted along the posterior axillary lines. The eruption had disseminated as a large crop of pustules with background erythema noted in the left popliteal region.

Within 5 days of admission, the patient’s truncal eruption had markedly improved, with notably less erythema and resolving pustules. At this time, it was unclear to us and the primary medicine caregivers what the cause of the eruption was. Oncologists believed that the eruption might have been caused by an adverse reaction to taxol and planned to change his chemotherapy to 5-fluorouracil and cisplatin.

Eight days later, his cutaneous examination revealed faded erythematous patches without pustules on his back and bilateral flanks (Figure 3).

SECOND PRESENTATION

The patient presented again 2 months later to the emergency department complaining of a painful and pruritic skin eruption over his chest, back, and legs as well as subjective fever and chills. The rash had been present for approximately 3 days, developing 1 day after administra-

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Antituberculosis agents</th>
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<tr>
<td>β-Lactams</td>
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<td>Viral infection</td>
</tr>
<tr>
<td>Terbinafine&lt;sub&gt;b&lt;/sub&gt;</td>
<td>Mercury</td>
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</table>

Abbreviations: AGEP, acute generalized exanthematous pustulosis; PUVA, psoralen UV-A.

<sup>a</sup> Table reprinted from Mashiah and Brenner.<sup>2</sup>

<sup>b</sup> Drugs eliciting positive patch test results.

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tion of ioversol-containing contrast media for a computed tomographic scan. The patient denied any changes in medications or recent viral illness. His most recent chemotherapy infusion with 5-fluorouracil and cisplatin was 1 month prior to onset of the eruption.

On physical examination, the patient was afebrile. Cutaneous examination revealed numerous pustules within erythematous plaques on the abdomen, back, and bilateral lower extremities. There was no involvement of the palms, soles, mucosa, or nails.

Two punch biopsy specimens were obtained. Both specimens showed subcorneal pustules, epidermal edema, and superficial neutrophilic infiltrate with eosinophils (Figure 4 and Figure 5). There was no evidence of viral cytopathic effect or psoriatic changes. These histopathologic findings were again consistent with a diagnosis of AGEP. Results of viral, bacterial, and fungal cultures were all negative. The patient's laboratory values were all within normal limits, and he remained afebrile. The medical history was consistent with AGEP due to radiographic contrast dye exposure. Treatment with triamcinolone acetonide ointment, 0.1%, and hydroxyzine was started, and within 1 week the eruption had markedly improved.

**COMMENT**

While outlining 104 cases of pustular psoriasis in 1968, Baker and Ryan8 noted a subset of 5 patients without a history of psoriasis and in whom the pustular eruption appeared acutely, resolved quickly, and did not recur. In 1980, Beylot et al9 introduced the term *pustuloses exanthematives aigues generalises* (in English, AGEP) into the French literature in describing the cases previously reported by Baker and Ryan8 and set clinical and histologic criteria to establish the diagnosis.

In 1991, Roujeau et al1 introduced AGEP as an acute pustular dermatosis distinct from pustular psoriasis and emphasized systemic drugs as its main cause. In most patients, the eruption develops on the face or intertriginous areas within 24 to 48 hours of drug exposure, disseminates rapidly, and resolves after discontinuation of the causative drug treatment. Systemic symptoms are not uncommon.

Acute generalized exanthematous pustulosis often develops acutely and is characterized by the appearance of nonfollicular, amicrobial pustules on erythematous and edematous plaques. Mucous membrane involvement, if it occurs, is generally mild and limited to 1 location. Patients often describe a burning or itching sensation, and the skin symptoms are frequently accompanied by a fever (temperature above 38°C).10 Blood neutrophil count is usually elevated, and mild renal impairment occurs in approximately 30% of cases; both of these abnormalities disappear with improvement of the eruption.11

The eruption is self-limited once the causative drug treatment is discontinued, generally resolving within 4 to 10 days, and is often followed by postpustular desquamation.11 The EuroSCAR project, a multinational epidemiologic case-control study on cutaneous adverse reactions, developed a validation score based on rash morphologic and histologic characteristics and disease course for retrospective assessment of cases.11 Recently, this ongoing study showed that systemic drugs are the most important causes of AGEP and identified particular drugs that are most strongly associated with the re-
AGEP over pustular psoriasis. Histopathologic examination of early AGEP lesions is papillary edema, neutrophilic clusters in the dermal papilla, and perivascular eosinophils, whereas advanced lesions show intraepidermal or subcorneal spongiform pustules. Notably, psoriatic changes are usually absent.

There are several theories regarding the pathogenesis of AGEP. Britschgi et al suggest a T-cell-mediated mechanism, which is evidenced by positive findings on patch tests and lymphocyte transformation tests. In this model, infiltrating T cells release amplified amounts of CXCL8, a neutrophil attracting chemokine, resulting in neutrophilic inflammation. In addition to the CXCL8, T cells also generate other cytokines, including interferon γ, interleukin 4, interleukin 5, and granulocyte-macrophage colony-stimulating factor, provoking eosinophilic and neutrophilic aggregation. Helper T cells are believed to form vesicles; cytotoxic T cells are involved in local tissue destruction; and neutrophils create the sterile pustules. In this view, drug-specific T cells expressing CXCL8 play a critical role in the development of AGEP, and there may be an initial sensitization period.

Moreau et al propose that AGEP is a delayed type of hypersensitivity reaction. Another possible mechanism is the production of antigen-antibody complexes induced by an infection or drug that activate the complement system, which in turn leads to neutrophil chemotaxis.

While drug-induced AGEP accounts for most reported cases, AGEP has also been linked to other causes, including contrast media. Several reports have described cases of delayed adverse reactions to iodinated contrast media (Table 2). Peterson et al reported 2 cases of patients who developed delayed cutaneous eruptions consistent with AGEP after the administration of iodinated nonionic contrast media. One of the patients developed AGEP on 2 separate occasions. The first eruption appeared after receiving both iohexol as well as ioxidal. The second eruption, which developed more rapidly than the first, occurred after the patient was injected again with ioxidal. In another case report published by Belgodère et al, a man who received iopamidol for pelvic imaging developed a reaction consistent with AGEP. Atosoy et al similarly report on a case of iohexol-induced AGEP. In addition, several studies from Japan and Europe have described delayed adverse cutaneous reactions following administration of iodinated contrast media, further suggesting the clinical significance of these events.

Our patient displayed the classic features of AGEP with characteristic morphologic and histologic characteristics and course. He developed a pruritic, pustular eruption on 2 separate occasions following administration of ioversol, a nonionic contrast medium commonly used in radiographic imaging studies. The eruption resolved within 10 days and required only symptomatic treatment. He also showed some systemic symptoms characteristic of AGEP, including mild renal impairment, nausea, malaise, and 1 recorded fever during his first hospital course. Though our patient did not exhibit leukocytosis, which is commonly found in AGEP, it is possible that the concurrent chemotherapy resulted in a blunted immune response.

It is important to recognize that although AGEP induced by nonionic contrast media is relatively rare, it represents a clinically significant event. Nonionic contrast dye should therefore be added to the list of agents recognized as causing AGEP.

Table 2. Cases of Radiocontrast-Induced AGEP

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Sex/Age, y</th>
<th>Type of Imaging</th>
<th>Type of Radiocontrast</th>
<th>Time to Onset of AGEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atosoy et al</td>
<td>F/52</td>
<td>Abdominal CT</td>
<td>Iohexol</td>
<td>3 d</td>
</tr>
<tr>
<td>Peterson et al</td>
<td>F/44 (3 episodes)</td>
<td>CTA</td>
<td>Iodixanol</td>
<td>60 h</td>
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<tr>
<td>Belgodère et al</td>
<td>F/30</td>
<td>Pelvic CT</td>
<td>Iopamidol</td>
<td>20 h</td>
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<tr>
<td>Present case</td>
<td>M/84 (2 episodes)</td>
<td>Pelvic CT</td>
<td>Ioversol</td>
<td>1 d</td>
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</table>

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CT, computed tomography; CTA, computed tomographic angiography.
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REFERENCES