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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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 x 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-

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**Table 1. Partial List of Agents Causing AGEP**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Antituberculosis agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Antipyretics</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Acetaminophen</td>
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<tr>
<td>Penicillin</td>
<td>Anticonvulsants</td>
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<td>Cefaclor</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Phenobarbital sodium</td>
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<tr>
<td>Erythromycin</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>Diltiazem hydrochloride</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Antithrombotics</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Triclopride</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Resprim</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Other</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Antifungal agents</td>
<td>PUVA</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Viral infection</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Mercury</td>
</tr>
</tbody>
</table>

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

*a Table reprinted from Mashiah and Brenner.²

*b 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 che-
motherapy infusion with 5-fluorouracil and cisplatin was
1 month prior to onset of the eruption.

On physical examination, the patient was afebrile. Cu-
taneous examination revealed numerous pustules within
erythematous plaques on the abdomen, back, and bilat-
eral 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 vi-
ral cytopathic effect or psoriatic changes. These histo-
pathologic findings were again consistent with a diag-
nosis of AGEP. Results of viral, bacterial, and fungal
cultures were all negative. The patient’s laboratory val-
ues were all within normal limits, and he remained afe-
brile. The medical history was consistent with AGEP due
to radiographic contrast dye exposure. Treatment with
triamcinolone acetonide ointment, 0.1%, and hydroxy-
zine was started, and within 1 week the eruption had
markedly improved.

**COMMENT**

While outlining 104 cases of pustular psoriasis in 1968,
Baker and Ryan\(^8\) 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 al\(^9\) introduced the term *pustuloses exan-
thematiques aigues generalises* (in English, AGEP) into
the French literature in describing the cases previously re-
ported by Baker and Ryan\(^8\) and set clinical and histo-
logic criteria to establish the diagnosis.

In 1991, Roujeau et al\(^1\) described AGEP as an acute
pustular dermatosis distinct from pustular psoriasis and
emphasized systemic drugs as its main cause. In most pa-
tients, the eruption develops on the face or intertrig-
nous areas within 24 to 48 hours of drug exposure, dis-
seminates 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 involve-
ment, if it occurs, is generally mild and limited to 1 lo-
cation. Patients often describe a burning or itching
sensation, and the skin symptoms are frequently accom-
panied 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.\(^1,11\)

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 des-
quamation.\(^11\) The EuroSCAR project, a multinational epi-
demiologic case-control study on cutaneous adverse re-
actions, 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 particu-
lar drugs that are most strongly associated with the re-

Figure 3. Resolving eruption; faded erythema without pustules.

Figure 4. Histopathologic examination reveals a subcorneal pustule with an
associated infiltrate composed of neutrophils with subadjacent epidermal
spongiosis and a patchy bandlike infiltrate within the superficial dermis
(hematoxylin-eosin, original magnification \(\times200\)).

Figure 5. Pustule cavity revealing infiltrate composed of neutrophils and
scattered eosinophils, eosinophilic spongiosis at the pustule base, and
scattered eosinophils in the superficial dermis (hematoxylin-eosin, original
magnification \(\times600\)).
AGEP over pustular psoriasis. Histopathologic examination of the skin is crucial in distinguishing AGEP from other conditions, especially in cases where a history of recent drug exposure is known. Although differences in disease features and progression exist, distinction is often difficult because the 2 conditions may share similar clinical presentations. However, no psoriasis history, a predominance of the eruption on intertriginous surfaces, and a history of recent drug exposure to drugs other than corticosteroids favor a diagnosis of AGEP. The histopathologic characteristics of early AGEP lesions are 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.

Several disease processes produce the generalized, non-follicular pustules found in AGEP. Included in the differential is Sneddon-Wilkinson disease, pustular psoriasis (von Zumbusch type), and pustular vasculitis. Of these, the major differential diagnosis is acute pustular vasculitis. Although differences in disease features and progression exist, distinction is often difficult because the 2 conditions may share similar clinical presentations. However, no psoriasis history, a predominance of the eruption on intertriginous surfaces, and a history of recent drug exposure to drugs other than corticosteroids favor a diagnosis of AGEP over pustular psoriasis. Histopathologic examination is recommended to help distinguish the entities. However, histologic pattern alone is not determinative in all cases. Overall, the diagnosis of AGEP is good; the disease is self-limited once the causative drug therapy is stopped. Treatment is symptomatic and rarely requires the use of systemic corticosteroids.

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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 ioxaglate. The second eruption, which developed more rapidly than the first, occurred after the patient was injected again with ioxaglate. In another case report published by Belgodère et al, a man who received iopamidol for pelvic imaging developed a reaction consistent with AGEP. Atasoy et al similarly report on a case of iopamidol-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, and 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>
<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>Atasoy et al⁷</td>
<td>F/52</td>
<td>Abdominal CT</td>
<td>Iohexol</td>
<td>3 d</td>
</tr>
<tr>
<td>Peterson et al⁶</td>
<td>F/44 (3 episodes)</td>
<td>CTA</td>
<td>Iodixanol</td>
<td>60 h</td>
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<tr>
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<td>Iodixanol</td>
<td>14 h</td>
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<tr>
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<td>Iodixanol</td>
<td>6 h</td>
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<td>Belgodère et al⁵</td>
<td>F/30</td>
<td>Pelvic CT</td>
<td>Iopamidol</td>
<td>20 h</td>
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<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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<tr>
<td>Present case</td>
<td>M/84 (2 episodes)</td>
<td>Pelvic CT</td>
<td>Ioversol</td>
<td>1 d</td>
</tr>
</tbody>
</table>

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

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REFERENCES