Acute Generalized Exanthematous Pustulosis Simulating Toxic Epidermal Necrolysis

A Case Report and Review of the Literature

Shaquil Peermohamed, BSc; Richard M. Haber, MD, FRCPC

Background: Both acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis (TEN) are adverse cutaneous reactions. Despite the fact that these 2 cutaneous reactions differ in presentation, prognosis, pathologic features, and treatment, overlap can exist between them, creating a diagnostic challenge.

Observations: We describe a patient who presented with clinical features of both AGEP and TEN, and we summarize overlapping cases of AGEP-TEN that have been reported in the literature. It is essential to be able to differentiate between AGEP and TEN, as these conditions are clinically and morphologically distinct entities. They also differ considerably in their prognosis and treatment.

Conclusions: Because overlap exists, AGEP should be considered in the differential diagnosis of widespread blistering and erosive conditions. A greater understanding of how to differentiate AGEP and TEN can lead to quicker diagnosis as well as more effective case management and treatment.

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is usually characterized by sterile pinhead-sized nonfollicular pustules, erythema, edema, fever, and leukocytosis with neutrophilia. This immunologically mediated reactive process is most commonly caused by the use of drugs such as antimicrobial agents, most frequently β-lactams (including penicillins and cephalosporins). The onset of AGEP is rapid, often occurring hours to days after drug exposure.

Acute generalized exanthematous pustulosis usually resolves once the causative drug is no longer used. One case report, however, describes how AGEP can evolve into a TEN-like picture, illustrating how AGEP is not al-
Acute generalized exanthematous pustulosis is characterized by the following histopathologic features: spongiform subcorneal and/or intraepidermal pustules, perivascular inflammation (mainly lymphocytes) and skin sloughing. Secondary infections, ocular complications, and sepsis are significant concerns in patients with TEN. The differences between AGEP and TEN are further summarized in Table 1.

While the distinctions between AGEP and TEN have been described, clinical pictures often can be complicated and can display the features of both AGEP and TEN. This blurring of distinctions creates diagnostic challenges, as in the present case. Acute generalized exanthematous pustulosis can present with morphological features that are similar to those of TEN, including diffuse erythema, edema, oral mucous membrane involvement, and a positive Nikolsky sign. While mucous membrane involvement in TEN can include the mouth, vagina, and conjunctiva, mucous membrane involvement in AGEP, if present, is usually limited to the mouth. Biopsy specimens should be obtained to make a definitive diagnosis in cases with overlapping morphological features. Histopathologic findings can help to differentiate between AGEP and TEN; however, 1 case has been described in which the biopsy specimens showed histologic features of both AGEP and TEN. Therefore, it is possible that there can be both clinical and histologic overlap with these 2 cutaneous reactions. The particular exanthema that emerges in a patient may depend on a variety of factors, such as the type and duration of stimulus exposure and that individual’s specific T-cell subset population. A summary of case reports describing overlapping features of AGEP and TEN is provided in Table 2.

Acute generalized exanthematous pustulosis is characterized by the following histopathologic features: spongiform subcorneal or intraepidermal pustules, perivascular leukocytosis with mostly neutrophils and some eosinophils, and edema of the papillary dermis. In contrast, TEN is commonly characterized by necrotic keratinocytes, scarce cell infiltration with mainly lymphocytes, and full-thickness epidermal necrosis with separation from the dermis. The histologic features will usually provide evidence in support of either AGEP or TEN, but there is 1 reported case in which histopathologic analysis showed features of both reactions.

Both AGEP and TEN are thought to be type IV hypersensitivity reactions that are mediated by T cells but with important distinctions. Preferential activation of different types of T cells can lead to different delayed drug hypersensitivity reactions. According to the revised Coombs and Gell classification, AGEP is characterized largely as a type IVd T-cell reaction, involving the recruitment and activation of neutrophils by interleukin 8. In contrast, TEN is a type IVc T-cell reaction, in which keratinocyte apoptosis is dependent on cytotoxic CD8+ T cells that produce perforin and granzyme B. While overlap of such immune-mediated reactions can occur, 1 type is usually most prominent.

In both AGEP and TEN, initial keratinolysis may be mediated by keratolytic cytokines. Immunophenotyping in the early stages of AGEP reveals more perforin,

Table 1. Comparison of Acute Generalized Exanthematous Pustulosis (AGEP) and Toxic Epidermal Necrolysis (TEN)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AGEP</th>
<th>TEN</th>
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</thead>
<tbody>
<tr>
<td>Incidence, cases/million/y</td>
<td>1-5</td>
<td>0.4-1.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>Rare</td>
<td>30%</td>
</tr>
<tr>
<td>Distribution</td>
<td>Intertiginous but can extend to face and become generalized</td>
<td>Generalized</td>
</tr>
<tr>
<td>Mucous membrane involvement</td>
<td>20%, Usually oral</td>
<td>96.5%-100%, At least 2 membranes are typically involved</td>
</tr>
<tr>
<td>Presence of pustules</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Atypical target lesions</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Positive Nikolsky sign</td>
<td>Rare</td>
<td>Usual</td>
</tr>
<tr>
<td>Presence of fever</td>
<td>Usual</td>
<td>Usual</td>
</tr>
<tr>
<td>Time of onset after initiation of drug therapy</td>
<td>Hours to days</td>
<td>2-3 wk</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Spongiform subcorneal and/or intraepidermal pustules, dermal edema, perivascular leukocytosis</td>
<td>Full-thickness epidermal necrosis with little dermal inflammation (mainly lymphocytes)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Discontinue drug therapy</td>
<td>Discontinue drug therapy; consider treatment with cyclosporin, infliximab, oral or intravenous corticosteroids, or intravenous immunoglobulin</td>
</tr>
</tbody>
</table>
granzyme B, and Fas ligand staining of T cells than it does in the later stages. In the later stages of AGEP, more interleukin 8 is produced by T cells, attracting neutrophils, which fill the intraepidermal vesicles, producing pustules. The TEN-like appearance of AGEP is attributed to coalescent intraepidermal pustulation producing bullae and resulting in denudation. This histopathologic finding was demonstrated in the biopsy specimen from a bulla in our case that showed widespread intraepidermal bulla formation with neutrophils (Figure 5).

<table>
<thead>
<tr>
<th>Source</th>
<th>Brief Description of Patient</th>
<th>Suspected Causative Agent</th>
<th>Clinical and Laboratory Findings</th>
<th>Site of Biopsy</th>
<th>Histologic Findings</th>
<th>Time of Onset</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al, 2001</td>
<td>91-y-old patient</td>
<td>Cefuroxime, paracetamol</td>
<td>Diffuse erythematous eruption with nonfollicular pustules; bullae containing clear fluid; skin detachment involving 41% BSA; positive Nikolsky sign; nonfebrile; leukocytosis</td>
<td>Pustule</td>
<td>Spongiform pustules; papillary edema; perivascular mononuclear infiltrate; leukocytic vasculitis</td>
<td>After 10 d of drug therapy</td>
<td>Cessation of all systemic drugs, wet dressings</td>
<td>Resolution after 10 d</td>
</tr>
<tr>
<td>Scheinfeld et al, 2003</td>
<td>60-y-old Hispanic woman with ampicillin allergy</td>
<td>Famotidine</td>
<td>Diffuse erythema; erosions on torso and 2- to 3-mm pustules on chin, neck, and forarms; positive Nikolsky sign; leukocytosis; neutrophilia</td>
<td>Not specified</td>
<td>Subcorneal blistering</td>
<td>After 2 d of drug therapy</td>
<td>Cessation of drug, dexamethasone propionate</td>
<td>Resolution within 3 d</td>
</tr>
<tr>
<td>Byerly et al, 2005</td>
<td>45-y-old white woman with no known drug allergies</td>
<td>Valdecoxib</td>
<td>Generalized erythematous eruption with nonfollicular papules and plaques; involvement of 80% BSA; negative Nikolsky sign; febrile; hypotensive; leukocytosis</td>
<td>Pustule</td>
<td>Neutrophilic and eosinophilic infiltrate; spongiform pustules.</td>
<td>Within 24 h of initiation of drug therapy</td>
<td>Cessation of drug, wound dressings with bacitracin, IV fluids</td>
<td>Resolution during hospital stay.</td>
</tr>
<tr>
<td>Meiss et al, 2007</td>
<td>34-y-old patient</td>
<td>Amoxicillin, sulbactam</td>
<td>Edematous erythema with many pinhead-sized pustules; positive Nikolsky sign Progression of pustular exanthema; persistent malaise; bullae formation and widespread exfoliation (observed in all 3 cases)</td>
<td>Not specified</td>
<td>Not available</td>
<td>Not documented</td>
<td>Cessation of suspected drugs, systemic corticosteroids, infliximab in all 3 cases</td>
<td>Complete resolution in 6-14 d with postinflammatory hyperpigmentation</td>
</tr>
<tr>
<td>Goh et al, 2008</td>
<td>28-y-old Chinese woman with a history of drug exanthem</td>
<td>Carbamazepine</td>
<td>Generalized erythematous macular rash that evolved into nonfollicular pustules and clear bullae; involvement of 55% BSA; positive Nikolsky sign; involvement of multiple mucous membranes; febrile; elevated liver enzyme levels</td>
<td>Subcorneal pustule; necrosis of the epidermis; mild spongiosis; perivascular lymphocytic infiltrate</td>
<td>After 14 d of drug therapy</td>
<td>Cessation of drug, IV hydrocortisone, IV Ig</td>
<td>Skin reepithelialization after 9 d, with minimal scarring; discharged 4 d later</td>
<td></td>
</tr>
<tr>
<td>Lateef et al, 2009</td>
<td>67-y-old Chinese woman with SLE</td>
<td>Hydroxychloroquine sulfate</td>
<td>Diffuse erythematous, papulopustular, pruritic rash involving entire BSA; febrile; leukocytosis; multiple mucous membrane involvement developed later, with targetoid erythematous macular patches</td>
<td>Pustule</td>
<td>Epidermal spongiosis; intraepidermal infiltrate of neutrophils; perivascular infiltrate of neutrophils and lymphocytes</td>
<td>After 3 wk of drug therapy</td>
<td>Cessation of drug, IV fluids, antihistamines, analgesics, IV hydrocortisone, IV Ig</td>
<td>Complete resolution of rash gradually over time, with minimal scarring</td>
</tr>
<tr>
<td>Present case</td>
<td>25-y-old male with abdominal trauma</td>
<td>Piperacillin and tazobactam</td>
<td>Diffuse erythema on chest, abdomen, and arms, with superimposed nonfollicular pustules and diffuse, sloughing vesicles and bullae; positive Nikolsky sign; no mucous membrane involvement</td>
<td>Pustule and bulla</td>
<td>Intraepidermal pustules containing neutrophils but no eosinophils; widespread intraepidermal bulla formation; no epidermal necrosis</td>
<td>After 24 h of drug therapy</td>
<td>Cessation of piperacillin and tazobactam, IV Ig, IV hydrocortisone</td>
<td>Resolution over 2 wk, with postinflammatory hyperpigmentation but no scarring</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; IV, intravenous; IV Ig, IV immunoglobulin; SLE, systemic lupus erythematosus.

*Increased serum concentration of tumor necrosis factor in 2 of the 3 cases.*
It is possible for AGEP to simulate TEN, although these cases are rare. Acute generalized exanthematous pustulosis can display both clinical and histologic features of TEN. These diagnostic similarities pose a challenge for dermatologists and other physicians when they are determining diagnosis, treatment, and prognosis. When there are overlapping morphological features and the clinical presentation is unclear, biopsies should be performed to help make a definitive diagnosis. It is important for dermatologists to be aware that, unlike TEN, most cases of AGEP have an excellent prognosis once treatment with the precipitating agent is discontinued.

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Comparative Effectiveness Research

Comparative effectiveness research expands the scope of clinical research to compare different therapies against one another as a means to improve delivery of value-based health care. Typically, outcomes analysis of quality of life, disability, and death are used to compare the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor dermatologic conditions. Traditional efficacy research, used for approval of pharmaceuticals or devices, compares 1 or more treatment alternatives with placebo in a carefully selected population cared for in an ideal setting, thus answering the question of whether the intervention is effective and safe for human use.

In contrast, comparative effectiveness research seeks to answer a different set of questions including: (1) when to use the treatment (appropriate time), and (2) who should receive the intervention (proper patient selection). This research also considers patients from populations that are under less than ideal conditions. Thus, comparative effectiveness research seeks to replace the physician’s informed intuition of case management with data-driven, scientifically derived, “best-treatment” protocols. We at the Archives are interested in comparative effectiveness research using observational and clinical trial methods comparing different strategies provided by dermatologists in heterogeneous patient populations and heterogeneous health care settings.

The Archives of Dermatology, along with JAMA and other Archives Journals, will publish a theme issue devoted to comparative effectiveness research in early 2012. Priority will be given to studies using rigorous methodological designs that are generalizable beyond a single institution. Authors should consult the Instructions for Authors at http://www.archdermatol.com for guidelines on manuscript preparation and submission. Manuscripts must be received before October 1, 2011, to allow for appropriate consideration.

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