Acute generalized exanthematous pustulosis induced by mifepristone

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Key words: acute generalized exanthematous pustulosis; drug rash; exanthematous pustulosis; mifepristone; synthetic steroidal antiprogesterone.

CASE REPORT

A 26-year-old woman of Vietnamese descent presented to the emergency department with a widespread, symmetric, erythematous, and pustular eruption (Fig 1). The outbreak initially affected the waistline, and the axillary, inguinal, and inframammary folds. It then spread to involve the neck, wrists, areolae, and the antecubital and popliteal fossae (Fig 2). The pustules were superficial, flaccid, and nonfollicular. They quickly evolved to become confluent, forming purulent lakes (Fig 1).

There was sparing of the lower aspect of the legs, palms, soles, and upper aspect of back. Nikolsky sign and mucous membrane involvement were absent. There were no target lesions or blisters. In addition, she experienced a diffuse burning sensation, facial swelling, subjective fevers, and malaise.

The patient had consumed 10 mg of mifepristone as emergency contraception 2 days before the eruption. She had not taken any other medications before her eruption and was not previously ill. The mifepristone was purchased without a prescription at a pharmacy in Vietnam. She reported using the medication once prior in a similar circumstance without incident.

On presentation, the patient was tachycardic (heart rate: 150 beats/min) with an elevated temperature (37.7°C). Laboratory studies demonstrated notable abnormalities of total lymphocyte count 18,000/mm^3 (3500-10,500/mm^3), absolute neutrophils 17,800/mm^3 (1700-7000/mm^3), albumin 2.3 g/dL (3.5-5.0 g/dL), calcium 6.5 mg/dL (8.9-10.1 mg/dL), alkaline phosphatase 31 U/L (37-98 U/L), sodium 131 mmol/L (135-145 mmol/L), potassium 3.2 mmol/L (3.6-5.2 mmol/L), bicarbonate 19 mmol/L (22-29 mmol/L), phosphorus 1.8 mg/dL (2.5-4.5 mg/dL), and glucose 179 mg/dL (70-100 mg/dL). The remainder of the renal and liver function tests revealed unremarkable findings.

Skin swab cultures and blood cultures for bacteria, and skin swab polymerase chain reaction for varicella zoster virus and herpes simplex virus were negative. The quantitative human chorionic gonadotropin was 1982.0 mIU/mL, and the patient's last reported menstrual period was approximately 5 weeks prior. She was unaware of her pregnancy. Before the human chorionic gonadotropin result, the patient was treated with 125 mg of methylprednisolone and 1 g of ceftriaxone in the emergency department. She was then admitted to the hospital and received a second 125-mg dose of methylprednisolone, and four 600-mg doses of clindamycin as a hospital inpatient, before dermatologic consultation.

Punch biopsy specimen demonstrated extensive subcorneal pustules with neutrophil spongiosis, prominent papillary dermal edema with hemorrhage, and a brisk perivascular mixed inflammatory infiltrate with many neutrophils and eosinophils (Fig 3). Focal small-vessel vasculitis was present (Fig 4).

A diagnosis of acute generalized exanthematous pustulosis (AGEP) was made, and treatment started with 25 mg of oral diphenhydramine every 4 hours and triamcinolone 0.1% cream twice daily. During day 2 of her hospitalization, she was admitted to the critical care service for hypotension and tachycardia that was not responsive to 5 L of intravenous normal

From the Department of Dermatology at Mayo Clinic.
Funding sources: None.
Conflicts of interest: None declared.
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JAAD Case Reports 2015;1:191-5.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.04.001

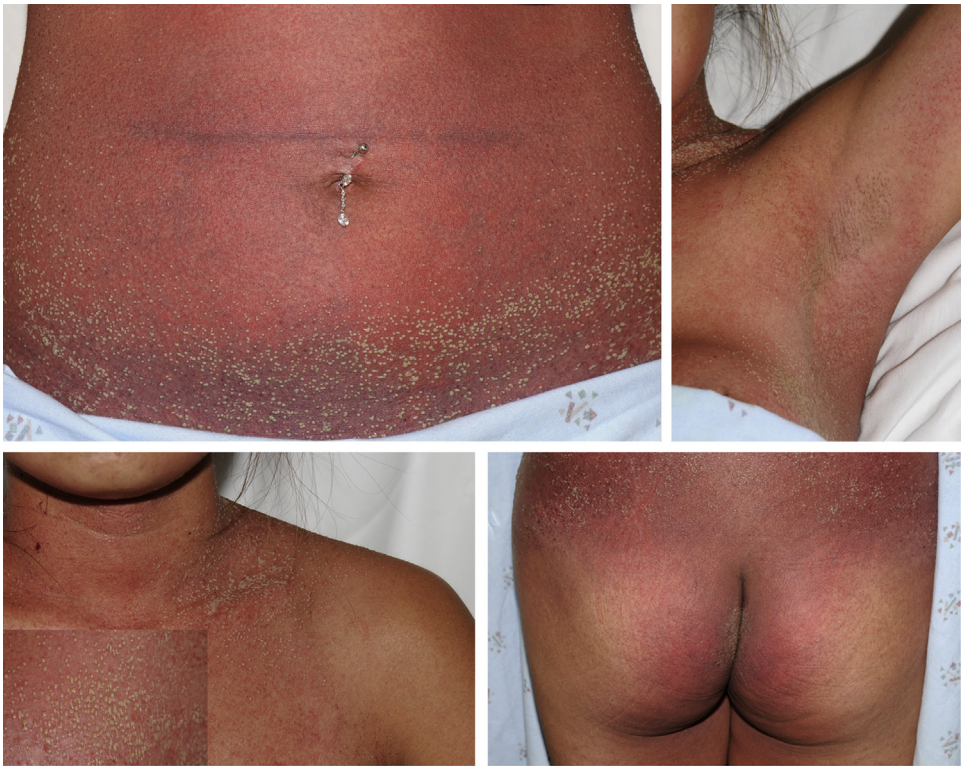

Fig 1. AGEP. Diffuse erythematous eruption covered with several hundred superficial, nonfollicular pustules. Patient reported burning of the skin. Note confluence of pustules into lakes of pus.

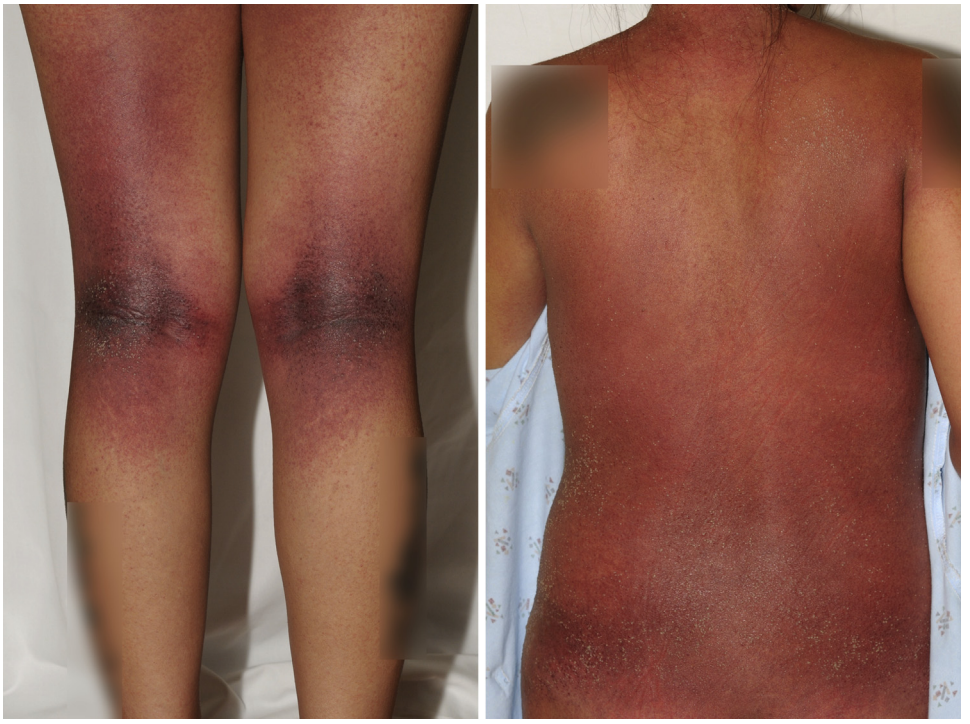

Fig 2. Accentuation in the skin folds including the waistline, intergluteal cleft, and popliteal fossae.

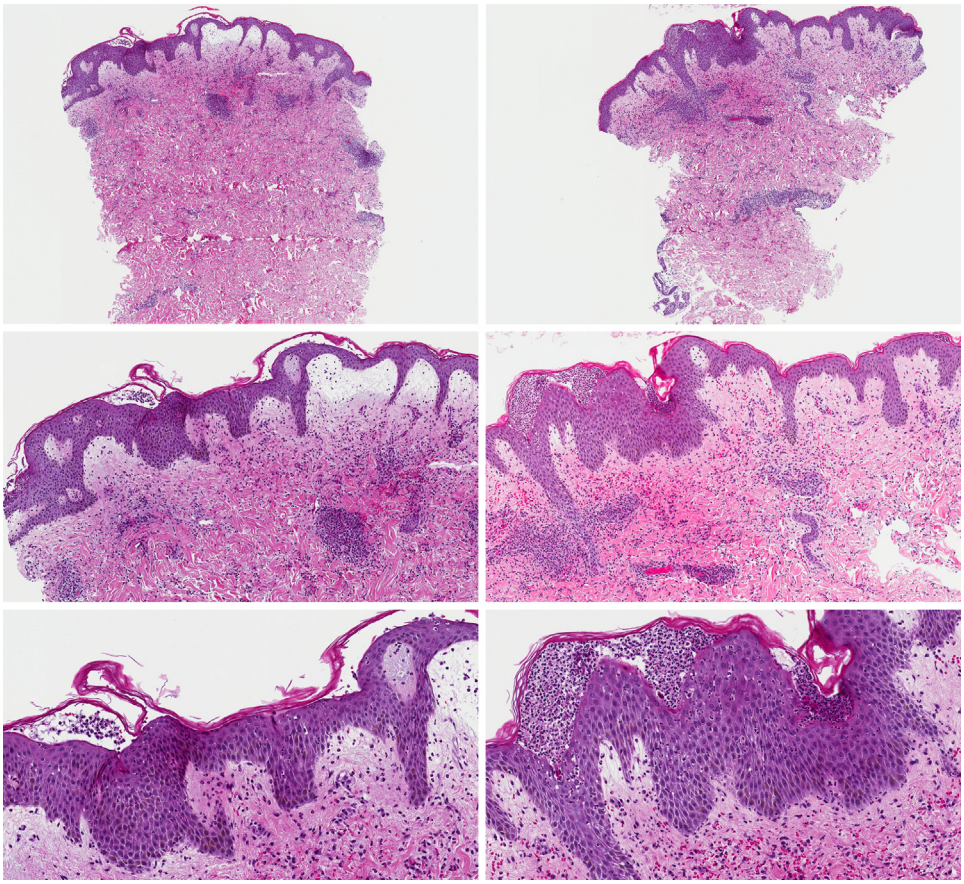

Fig 3. Biopsy specimens reveal typical histologic features of acute generalized exanthematous pustulosis. Note subcorneal pustules with neutrophils and perivascular mixed inflammatory infiltrate. (Hematoxylin-eosin stain; original magnifications: ×4 [top], ×10 [middle], ×20 [bottom].)

saline. Central and arterial lines were placed, and fluid resuscitation continued. Overnight her blood pressure recovered, and the tachycardia resolved with additional intravenous fluids. The lines were removed, and she was transferred to the care of family medicine before discharge on day 3. She made a complete recovery without any sequela. Her pregnancy was electively terminated.

DISCUSSION

AGEP, previously known as toxic pustuloderma,[1] or generalized pustular drug rash,[2] is an acute febrile eruption that is nearly indistinguishable clinically from pustular psoriasis but often has distinct histopathologic features. The following 5 criteria have been proposed for the definition of AGEP: (1) dozens of small mostly nonfollicular pustules arising on widespread edematous erythema; (2) histopathologic changes showing intraepidermal or subcorneal pustules associated with 1 or more of dermal edema, vasculitis, perivascular eosinophils, or focal necrosis of keratinocytes; (3) fever (>38°C); (4) neutrophilia; and (5) acute evolution with spontaneous resolution in less than 15 days.[3]

In nearly 90% of cases, AGEP is drug induced.[3] The remainder of cases are thought to be precipitated by acute infections with enteroviruses or by hypersensitivity to mercury.[3] Beta-lactam and macrolide antibiotics are most commonly associated with AGEP,[4] but increasing familiarity with this clinical entity has led to the implication of an extensive list of medications.

Treatment is generally conservative and includes stopping the responsible medication and treating the associated symptoms. It is important to note that the pustules are sterile, and therefore, systemic antibiotics are unnecessary. Presentation with fever, leukocytosis, and pustules is easily mistaken for infection and may lead to administration of unnecessary and potentially contraindicated antibiotics.[5] The lesions generally last 1 to 2 weeks, and their resolution is followed by superficial desquamation.

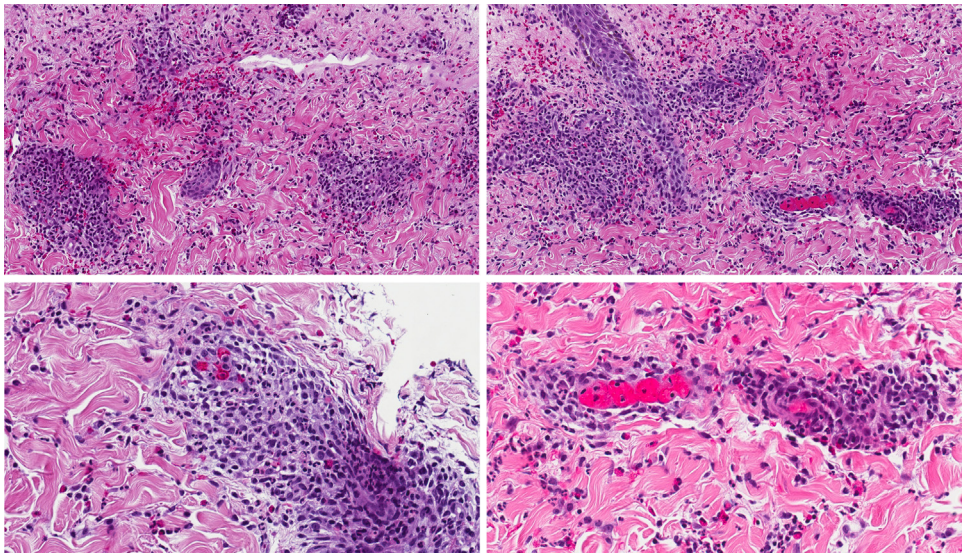

Fig 4. Brisk perivascular infiltrate with many eosinophils and focal small-vessel vasculitis. (Hematoxylin-eosin stain; original magnifications: ×20 [top], ×40 [bottom].)

It is difficult to distinguish AGEP from pustular psoriasis. Some controversy exists about whether these are distinct entities. In most cases, AGEP has a more acute course of fever and pustulosis with rapid spontaneous healing.[6] The histopathology of AGEP typically shows spongiform subcorneal and/or intraepidermal pustules, marked edema of the papillary dermis, possible vasculitis, eosinophils, and/or focal necrosis of keratinocytes.[5] In contrast, pustular psoriasis more frequently has papillomatosis and acanthosis.[5] Not surprisingly, both demonstrate subcorneal and/or intraepidermal pustules. In this case, a brisk perivascular dermal infiltrate with numerous eosinophils helped to distinguish AGEP from pustular psoriasis.

Drug reaction with eosinophilia and systemic symptoms may also show papular and pustular lesions. This case was differentiated from drug reaction with eosinophilia and systemic symptoms by lack of eosinophilia and lack of visceral involvement (eg, hepatitis, nephritis, myocarditis, or pneumonitis), and the rapidity of rash onset and subsequent resolution.[7] Additional consideration was given to impetigo herpetiformis or pustular psoriasis of pregnancy. In 1872, von Hebra[8] introduced the term "impetigo herpetiformis" to describe 5 cases of acute pustular eruptions in pregnant or puerperal women. Although there is debate surrounding its classification, this entity is usually characterized by an eruption in the third trimester, and is histologically consistent with pustular psoriasis.[9] Of interest, pustular psoriasis of pregnancy may be accompanied by major complications such as sepsis, placental insufficiency, and fetal morbidity and mortality.[10]

We believe that the acute pustular eruption in this patient developed from the use of mifepristone. Mifepristone, also known as RU-486 and marketed under the trade names Korlym and Mifeprex, is synthetic steroidal antiprogesterone. It is used as an abortifacient in the first months of pregnancy and as emergency contraceptive in lower doses. A prior sensitization to mifepristone in our patient, suggesting immunologic recall phenomenon, likely explains the short interval between drug administration and the onset of her eruption. The Naranjo Scale is a questionnaire designed by Naranjo et al[11] for determining whether a suspected adverse drug reaction is a result of the drug or other factors. Application of the Naranjo Scale to determine the likelihood of adverse drug reaction revealed that mifepristone yields a score of 5, suggesting a probable association. As a consequence, we propose that mifepristone be added to the list of drugs that may cause AGEP.

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