Blisters in a Comatose Elderly Woman

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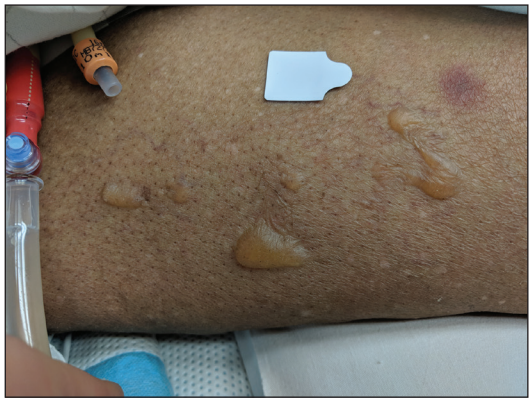

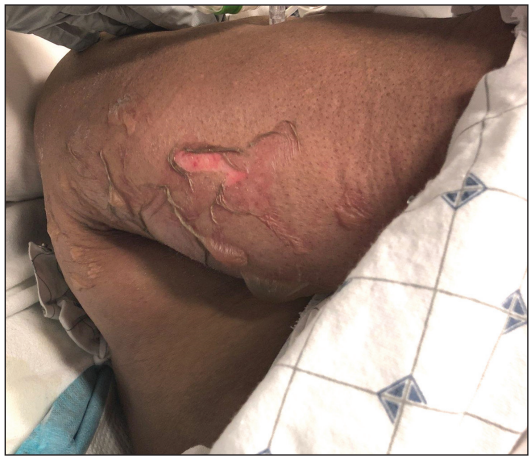

An 82-year-old woman presented to the emergency department after her daughter found her unconscious in the bathroom laying on her right side. Her medical history was notable for hypertension and asthma for which she was on losartan, furosemide, diltiazem, and albuterol. She recently had been prescribed lorazepam for insomnia and had started taking the medication 2 days prior. She underwent intubation and was noted to have flaccid, fluid-filled bullae on the right thigh (top) along with large areas of desquamation on the right lateral arm (bottom) with minimal surrounding erythema. There was no mucous membrane involvement. Urine toxicology was positive for benzodiazepines and negative for all other drugs, including barbiturates.

WHAT'S YOUR **DIAGNOSIS?**

a. bullous pemphigoid
b. coma blisters
c. edema blisters
d. friction blisters
e. toxic epidermal necrolysis

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The authors report no conflict of interest.
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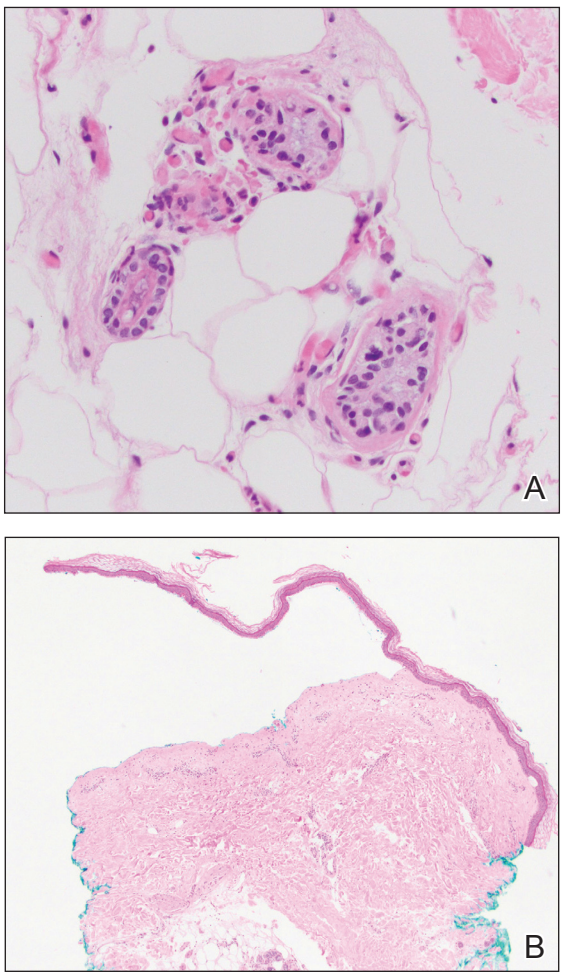
doi:10.12788/cutis.0441

THE **DIAGNOSIS:** Coma Blisters

Histologic examination revealed pauci-inflammatory subepidermal blisters with swelling of eccrine cells, signaling impending gland necrosis (Figure). Direct immunofluorescence testing on perilesional skin was negative. These findings would be inconsistent for diagnoses of edema blisters (most commonly seen in patients with an acute exacerbation of chronic lower extremity edema), friction blisters (intraepidermal blisters seen on histopathology), and bullous pemphigoid (linear IgG and/or C3 staining along the basement membrane zone on direct immunofluorescence testing is characteristic). Although eccrine gland alterations have been seen in toxic epidermal necrolysis,[1] the mucous membranes are involved in more than 90% of cases, making the diagnosis less likely. Furthermore, interface changes including prominent keratinocyte necrosis were not seen on histology.



A, Degenerative eccrine gland changes in the subcutis with early necrosis (H&E, original magnification ×400). B, Pauci-inflammatory subepidermal blister (H&E, original magnification ×40).

Given the localized nature of the lesions in our patient and negative direct immunofluorescence studies, a diagnosis of coma blisters was made. Gentle wound care practices to the areas of denuded skin were implemented with complete resolution. The patient's condition gradually improved, and she was extubated and discharged home.

Coma blisters are self-limited bullous lesions that have been reported in comatose patients as early as 1812 when Napoleon's surgeon first noticed cutaneous blisters in comatose French soldiers being treated for carbon monoxide intoxication.[2] Since then, barbiturate overdose has remained the most common association, but coma blisters have occurred in the absence of specific drug exposures. Clinically, erythematous or violaceous plaques typically appear within 24 hours of drug ingestion, and progression to large tense bullae usually occurs within 48 to 72 hours of unconsciousness.[3] They characteristically occur in pressure-dependent areas, but reports have shown lesions in non–pressure-dependent areas, including the penis and mouth.[1,4] Spontaneous resolution within 1 to 2 weeks is typical.[5]

The underlying pathogenesis remains controversial, as multiple mechanisms have been suggested, but clear causal evidence is lacking. The original proposition that direct effects of drug toxicity caused the cutaneous observations was later refuted after similar bullous lesions with eccrine gland necrosis were reported in comatose patients with neurologic conditions.[6] It is largely accepted that pressure-induced local ischemia—proportional to the duration and amount of pressure—leads to tissue injury and is critical to the pathogenesis. During periods of ischemia, the most metabolically active tissues will undergo necrosis first; however, in eccrine glands, the earliest and most severe damage does not seem to occur in the most metabolically active cells.[7] Additionally, this would not provide a viable explanation for coma blisters with eccrine gland necrosis developing in variable non–pressure-dependent areas.

Moreover, drug- and non–drug-induced coma blisters can appear identically, but specific histopathologic differences have been reported. The most notable markers of non–drug-induced coma blisters are the absence of an inflammatory infiltrate in the epidermis and the presence of thrombosis in dermal vessels.[8] Demonstration of necrotic changes in the secretory portion of the eccrine gland is considered the histopathologic hallmark for drug-induced coma blisters, but other findings can include subepidermal or intraepidermal bullae; perivascular infiltrates; and focal necrosis of the epidermis, dermis, subcutis, or epidermal appendages.[6] Arteriolar wall

necrosis and dermal inflammatory infiltrates also have been observed.[7]

Benzodiazepines have been widely prescribed and abused since their development, and overdose is much more common today than with barbiturates.[9] Coma blisters rarely have been documented in the setting of isolated benzodiazepine overdose, and of the few cases, only one report implicated lorazepam as the causative agent.[4,7] The characteristic finding of eccrine gland necrosis consistently was seen in our patient. This case not only emphasizes the need for greater awareness of the association between benzodiazepine overdose and coma blisters but also the importance of clinical context when considering diagnoses. It is essential to note that coma blisters themselves are nonspecific, and the diagnosis of drug-induced coma blisters warrants confirmatory toxicologic analysis.

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