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A Rare Case of Morphine-Induced Bullous Sweet Syndrome

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Abstract:

Drug-induced Sweet syndrome is a rare clinical entity defined by sudden-onset skin lesions with histology showing dense neutrophilic infiltrate without vasculitis associated with the administration of a medication. Reported drug causes of Sweet syndrome span many classes, including immunomodulatory agents, chemotherapeutics, antibiotics, and antihypertensives; however, there are no published cases of opioid-induced Sweet syndrome. This report discusses a case of presumed morphine-induced Sweet syndrome. An 86-year-old female admitted for acute cholecystitis developed a rash five days after admission. Her medications notably included hydralazine, morphine, and acetaminophen. Physical examination revealed periocular edema with scattered vesicles and bullae on the face, neck, and chest, along with erythematous plaques on the right upper extremity. Punch biopsy revealed neutrophilic dermatosis with edema and subepidermal bullae formation, and autoimmune and infectious testing returned negative. While bullous Sweet syndrome caused by hydralazine was initially favored from the results, the rash recurred over a week later without additional doses. Medications were reviewed, and although no additional doses of hydralazine had been administered after it was discontinued, there were two doses of morphine given shortly before the rash reemerged. No additional doses of morphine were administered between the initial eruption and its recurrence. Given the timing in relation to morphine, it was determined to be the cause and was discontinued. The patient was restarted on methylprednisolone for 3 days and experienced remission of the lesions without further recurrence, supporting the diagnosis of morphine-induced Sweet syndrome. This report is the first to discuss this potentially rare adverse drug reaction related to morphine.

Keywords:

Sweet Syndrome, Bullous, Drug-induced, morphine, opioid, case report

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Introduction

Sweet syndrome is defined by sudden onset, painful, erythematous skin lesions with histology showing dense neutrophilic infiltrate without vasculitis **[1]**. While most commonly idiopathic, it can present with underlying conditions including malignancies, infections, autoimmune disorders, and, very rarely, as a drug-induced disease **[2]**. There are few drugs known to be associated with Sweet syndrome, and there are no published reports of an association with morphine. In this report, we describe a case of

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bullous Sweet syndrome, a rare and aggressive clinical entity, associated with morphine.

Case Presentation

An 86-year-old female with a history of hypertension, admitted for acute gangrenous cholecystitis status post cholecystectomy, developed a rash five days after admission. Her scheduled inpatient medications included piperacillin-tazobactam, pantoprazole, simvastatin, and hydralazine. Prior to the rash, the patient was given a course of morphine and acetaminophen. Physical examination revealed periocular edema with scattered vesicles and bullae on the face, neck, and chest, along with erythematous plaques on the right upper extremity **(Figure 1A)**. Punch biopsy of the lesion was taken, as well as viral and bacterial swabs. Infectious workup returned negative, and in the interim, the patient's lesions worsened and became more painful **(Figure 1B)**.

There was suspicion of a drug-induced reaction; thus, hydralazine was put on hold, and the patient was once again started on systemic methylprednisolone and topical hydrocortisone. Antinuclear and SSA/SSB antibodies returned negative. Hematoxylin & eosin (H&E) stain on the biopsy specimen revealed neutrophilic dermatosis with edema and broad subepidermal bullae formation **(Figure 2A & 2B)**. Direct immunofluorescence studies showed no specific antibody deposition. Bullous Sweet syndrome caused by hydralazine was favored from the results, and hydralazine was discontinued. The patient finished 5 doses of methylprednisolone with gradual improvement of the lesions.

Over a week later, dermatology was reconsulted for recurrence of the rash. Physical exam revealed shallow erosions on the neck and face at sites of previous bullae, as well as new bullae appearing on the right neck and face. The patient was also febrile around the time of re-consultation. The patient's medications were reviewed, and while no doses of hydralazine were given since the hold, there were two doses of morphine given a few hours before the rash reemerged. No doses of morphine were given in between the first appearance of the rash and the recurrence. Given the timing of the rash in relation to morphine doses both at initial presentation and this second occurrence, morphine was determined to be a causative drug and was discontinued. The patient was restarted on methylprednisolone for 3 days and experienced remission of the lesions. The patient's rash did not recur after finishing the second course of steroids.

Discussion

While rare, drug-induced Sweet syndrome has been documented for a few classes of medications **[2]**. In 1996, Walker et al. published specific drug-induced Sweet syndrome criteria adapted from original Sweet syndrome criteria, requiring (1) abrupt onset of rash, (2) histopathologic evidence of neutrophilic infiltrate, (3 & 4) a temporal relationship after initiation of an offending medication and resolution after its cessation or use of steroids, and (5) fever **[3]**. In addition to the patient meeting all 5 criteria for morphine-induced Sweet syndrome, the Naranjo Adverse Drug Reaction (ADR) Probability Scale for morphine administration in this patient is a 6, reflecting probable ADR. All other medications were reviewed and scored < 4, reflecting less probable cause. While there are other diagnoses to be considered in this case, including idiopathic Sweet syndrome or hydralazine-induced Sweet syndrome, which has been documented in literature before, the recurrence of the rash over 7 days after initial resolution with steroids without any additional doses of hydralazine, along with a close temporal relationship with the re-administration of morphine for pain, makes morphine the more likely culprit.

On review of existing literature, there are no published reports of opiates causing drug-induced SS. However, review of unpublished data from a large study analyzing the causative drugs behind 136 cases of drug-induced Sweet syndrome in France revealed two instances of opiates, nalbuphine and dextropropoxyphene, being the suspected drugs behind cases of Sweet syndrome **[4]**. This suggests that while rare, morphine and other opioids cannot be ruled out as a cause of drug-induced Sweet syndrome. In addition, the bullous variant of Sweet syndrome is a rare presentation seen in this case. A study examining the pathogenesis of Sweet syndrome found that inflammatory markers such as tumor necrosis factor-alpha and interleukins-8/17 were more

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aggressively upregulated in the bullous variant of Sweet syndrome compared to classical Sweet syndrome **[5]**. However, while the bullous variant can be incredibly debilitating, there is no change in management compared to standard drug-induced Sweet syndrome. Identification of the causal drug is crucial, as Sweet syndrome, particularly the bullous variant, progresses rapidly **[6]**. Rapid comprehensive testing should be done to rule out all other causes, and histopathological analysis of lesions can help to confirm the diagnosis.

Declarations

Author Contributions: NC: Conceptualization, Data Curation, Literature Review, Writing - Original Draft, Writing - Review & Editing; NS: Literature Review, Writing - Review & Editing, Supervision; SK: Validation, Writing - Review & Editing, Supervision; WSC: Writing - Original Draft, Writing - Review & Editing; PRW: Writing - Original Draft, Writing - Review & Editing; AL: Conceptualization, Writing - Review & Editing, Supervision.

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Patient Consent: The authors obtained written consent from patients for their photographs and medical information to be published in print and online, and with the understanding that this information may be publicly available. Patient consent forms are retained by the authors.

Declaration of Competing Interests: Authors have no conflicts of interest or financial ties to disclose.

Data Availability: Not applicable.

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Figure Legends

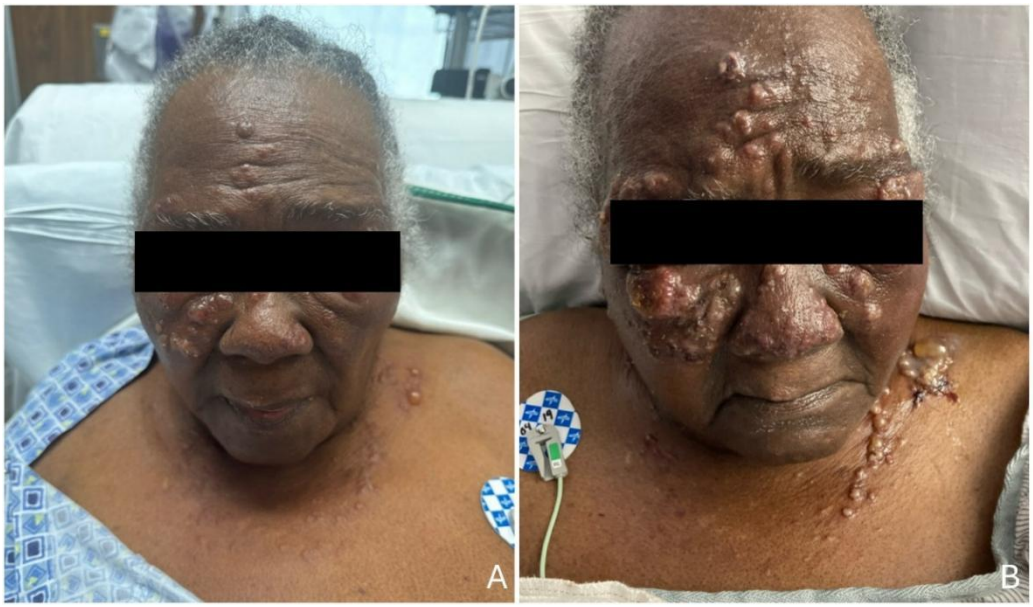

Figure 1. Clinical image showing periocular swelling and dispersed vesicles/bullae on the forehead, cheeks, and nose (1A). After a few days, significant progression of lesions was observed, with many new vesicles on the left upper chest (1B).

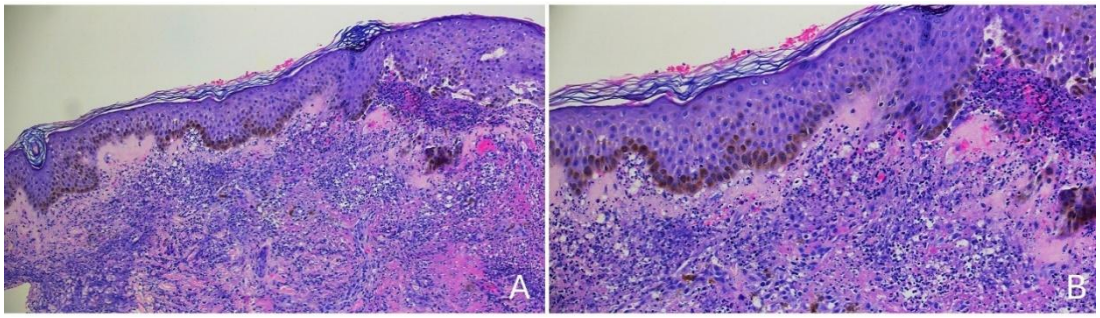

Figure 2. H&E sections show dense dermal neutrophilic infiltrate with subepidermal vesicle formation (2A, Magnification 100X). Higher magnification (200X) allows for better appreciation of the scattered subepidermal vesicles present (2B).