Xylazine-induced acute skin necrosis in two patients who inject fentanyl

To the Editor: Xylazine is an alpha-2-agonist traditionally used in veterinary settings to sedate horses.[1] However, there are increasing reports of xylazine-laced fentanyl in the United States.[2-4] We report 2 patients with skin necrosis localized to sites of fentanyl injection. Given the increasing prevalence of xylazine in fentanyl, dermatologists need to recognize xylazine-induced skin changes in patients with active fentanyl use.

REPORT OF CASES

Case 1

A woman in her 30s, with a history of intravenous (IV) drug use and active hepatitis C (HCV), was admitted for skin breakdown on her left thigh. Toxicology screen was positive for fentanyl and cannabinoids and negative for cocaine. Patient reported injecting xylazine-laced fentanyl in the affected area 5 days prior. This was her first exposure to xylazine, although she had an extensive history of fentanyl use. She denied similar skin findings with prior fentanyl injections. Physical exam showed an oval retiform purpuric plaque with induration and a surrounding pink border on the left thigh (Fig 1, *A*). She noted severe tenderness but denied bleeding or drainage. Imaging was negative for necrotizing fasciitis or features of soft tissue infection. Punch biopsy of the skin showed epidermal necrosis with focal fibrin thrombi within superficial small vessels without vasculitis (Fig 1, *B*). Tissue cultures were negative for infection. Broad vasculitis workup was negative. Given the history of injecting xylazine-contaminated fentanyl and cutaneous necrosis showing vasculopathy on histopathology, with negative laboratory workup for a systemic coagulopathy, a diagnosis compatible with xylazine-induced skin necrosis was rendered. She received local wound care with marked improvement.

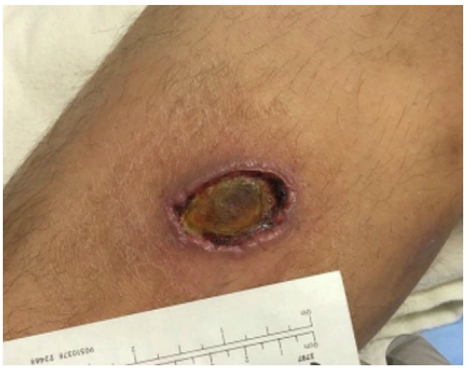

Fig 2. Clinical photo of necrotic ulceration at fentanyl injection site on right medial leg.

Case 2

A man in his 40s with a history of IV drug use and HCV presented with a spreading, painful area on his right medial thigh (Fig 2). He had a longstanding history of IV cocaine and fentanyl use and last

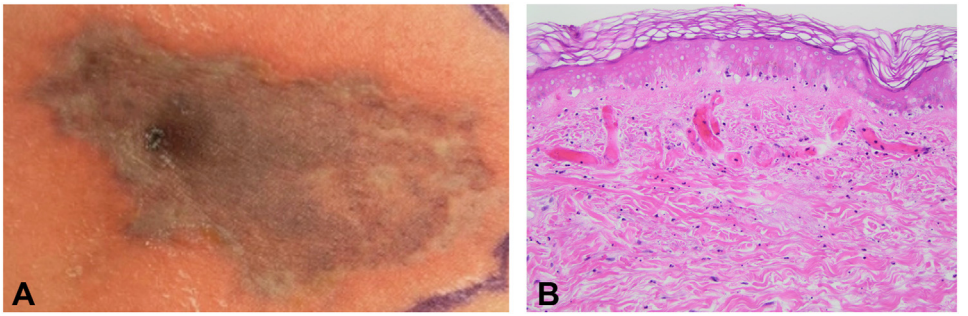

Fig 1. A, Retiform purpuric plaque on the left thigh. **B,** Vascular congestion with fibrin thrombi in the superficial dermis, consistent with vasculopathy (H&E, 200×). There is early necrosis of the overlying epidermis.

Table I. Clinical characteristics of reported cases

Patient age, sex	Past medical history	Urine drug screen	Xylazine confirmation	Laboratory work-up	Histopathological results	Treatment course
F in 30s	IV drug use, infective endocarditis, hepatitis C	Fentanyl	Not collected	ANA, ANCA, C3/C4, cryoglobulins, cryofibrinogen, fungitell assay, HIV, RF (all negative)	Epidermal necrosis with focal fibrin thrombi within superficial small vessels without vasculitis.	Antibiotics, local wound care with full resolution
M in 40s		Fentanyl, cocaine	Yes		Nonspecific inflammation and subcutaneous necrosis, without vasculopathy	

ANA, Antinuclear antibody; *ANCA*, antineutrophilic cytoplasmic antibody; *HIV*, human immunodeficiency virus; *RF*, rheumatoid factor; *SPEP*, serum protein electrophoresis.

injected fentanyl 1 week prior. He believed the fentanyl contained xylazine, as the last dose of fentanyl was "more potent" than prior doses. Toxicology screen was positive for cocaine and fentanyl. Urine xylazine analysis was positive at 40,000 mg/mL. Necrotic ulcerations at previous injection sites were observed on bilateral arms, hands, legs, and feet. A broad vasculitis workup was negative. Punch biopsy showed nonspecific inflammation and subcutaneous necrosis, without vasculopathy. Tissue cultures were positive for 1 colony of streptococcus and cultibacterium, which were deemed contaminants. His clinical presentation was most suggestive of xylazine-induced skin necrosis. He received local wound care with significant improvement.

DISCUSSION

As xylazine use rises, adverse effects are being seen in clinical settings. Xylazine-associated skin ulcers have been newly reported in the literature.[5] Though it is unclear how xylazine induces necrosis, 1 proposed mechanism is local vasoconstriction secondary to alpha-2-agonist properties, resulting in poor perfusion and increased susceptibility to inflammation and secondary infection.[6]

Physicians should maintain a high level of suspicion of xylazine exposure in patients with fentanyl use, particularly when acute skin necrosis is localized to injection sites. Diagnosis can be challenging, as xylazine is not included on routine toxicology testing, but specialized testing for xylazine levels is available, as in our second case. Ruling out underlying vasculitis and infection with broad serologic workup is imperative (Table I). If there is recent cocaine ingestion, levamisole-induced vasculopathy/vasculitis should be considered.

There are limited data characterizing histolopathologic features of xylazine-induced cutaneous necrosis. We hypothesize that small vessel vasculopathy may be a contributing feature, given the drug's mechanism and resultant skin necrosis, but this was only seen in 1 case, so it remains unclear. Since the mechanism is uncertain, current treatment options are limited. With vasculopathy, a trial of anticoagulation may mitigate cutaneous damage, but further data are needed to substantiate this proposed treatment modality. Prompt local wound care is recommended for recovery of affected skin.

Lucy Rose, MA,[a] Rachel Kirven, MD,[b] Kelly Tyler, MD,[b] Catherine Chung, MD,[b,c] and Abraham M. Korman, MD[b]

From The Ohio State University College of Medicine, Columbus, Ohio[a]; Department of Dermatology, The Ohio State University Wexner Medical Center, Columbus, Ohio[b]; and Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio.[c]

Funding sources: None.

IRB status approval: Not applicable.

Key words: adverse reactions; consultative dermatology; injection site reactions; necrosis; ulcer xylazine.

Correspondence to: Abraham M. Korman, MD, OSU Dermatology, 540 Officenter Pl, Suite 240, Columbus, OH 43230

E-mail: Abraham.korman@osumc.edu

Conflicts of interest

None disclosed.

REFERENCES

1. Nunez J, DeJoseph ME, Gill JR. Xylazine, a veterinary tranquilizer, detected in 42 accidental fentanyl intoxication deaths. *Am J Forensic Med Pathol*. 2021;42:9-11.
2. Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine overdose deaths in the US by sex and race and ethnicity. *JAMA Psychiatry*. 2021;78:564-567.
3. Rodríguez N, Vargas Vidot J, Panelli J, Colón H, Ritchie B, Yamamura Y. GC-MS confirmation of xylazine (Rompun), a veterinary sedative, in exchanged needles. *Drug Alcohol Depend*. 2008;96:290-293.
4. Johnson J, Pizzicato L, Johnson C, Viner K. Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010-2019. *Inj Prev*. 2021;27:395-398.
5. Malayala SV, Papudesi BN, Bobb R, Wimbush A. Xylazine-induced skin ulcers in a person who injects drugs in Philadelphia, Pennsylvania, USA. *Cureus*. 2022;14(8):e28160. https://doi.org/10.7759/cureus
6. Liu CM, Chiu MJ, Fang CC, Chen WJ. Xylazine abuse: a rare cause of syncope. *Clin Toxicol (Phila)*. 2007;45:309-311.

https://doi.org/10.1016/j.jdcr.2023.04.010