JAMA Dermatology Clinicopathological Challenge

# Chronic Ulceration and Fibrosis of the Forearm

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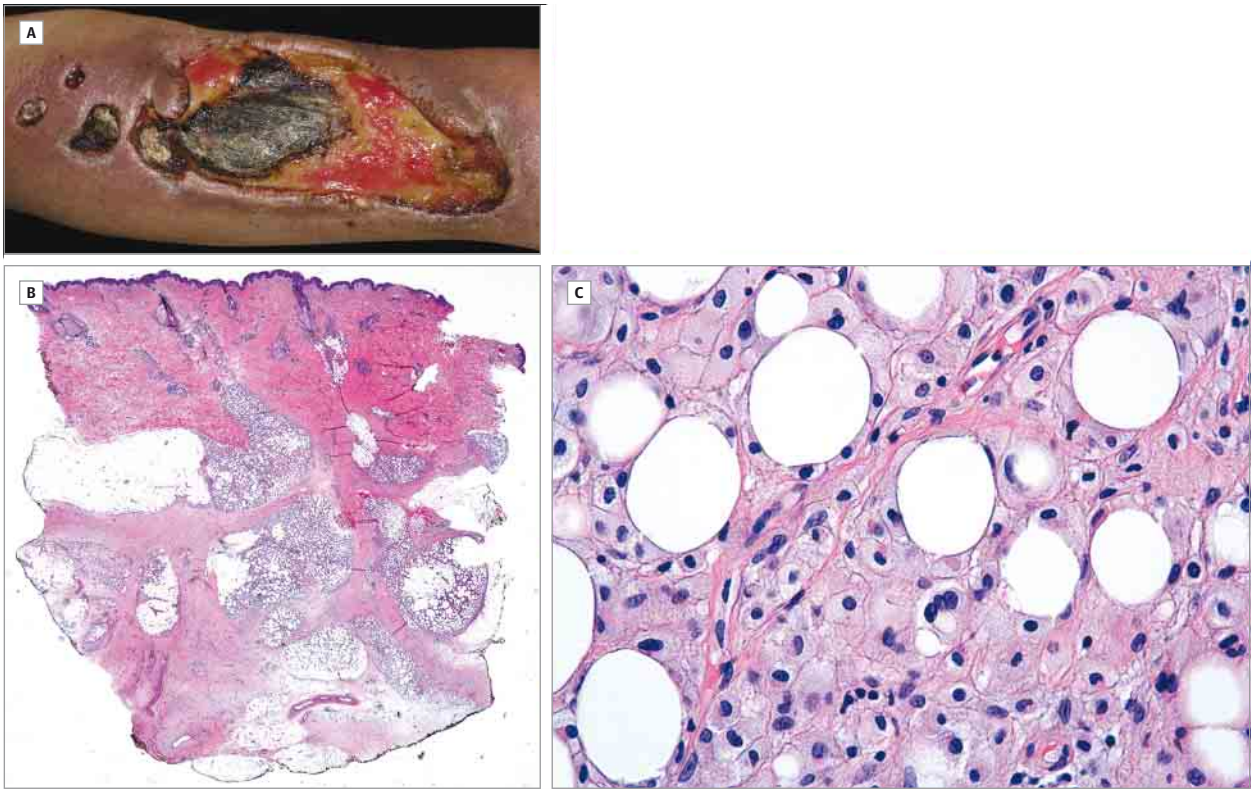


**Figure.** A, Clinical photograph of the large, deep, irregularly shaped, cutaneous ulcer on the dorsum of the right forearm. Three small ulcers are seen adjacent to the larger ulcer. B and C, Histologic images of a wedge biopsy specimen from the indurated skin of the abdominal region (hematoxylin-eosin). B, Original magnification ×10. C, Original magnification ×40.

**A white man in his 30s** with a 7-year history of severe, mechanical, low back pain and long-standing mental depression was referred to the dermatology department for evaluation of an asymptomatic cutaneous ulcer that had developed over the past year. Physical examination disclosed a large and deep, irregularly shaped, cutaneous ulcer on the dorsum of his right forearm. Necrotic tissue and muscle exposure was seen at the base of the ulcer (**Figure**, A). Woody induration of skin on both forearms and on the abdominal region was also observed. Bilateral contracture of deltoid, triceps, and biceps muscles was noted. Active and passive range of motion was restricted at the shoulders and elbows. No signs of joint inflammation were seen. At the time of consultation, the patient was taking oral treatment with duloxetine hydrochloride, clonazepam, oxcarbazepine, fentanyl, sulpiride, zopiclone, omeprazole magnesium, and baclofen. He also admitted to self-administering subcutaneous injections of meperidine, 100 mg 4 times per day, for the past 3 years, at different sites, including the deltoid areas and abdomen. Growth from culture specimens taken from the ulcer was negative for bacteria, mycobacteria, and fungal organisms. His serum creatinine kinase level was raised (192 U/L; reference range, 0-174 U/L), but test results for complete blood cell count; erythrocyte sedimentation rate; antinuclear antibody, rheumatoid factor, aspartate aminotransferase, alanine aminotransaminase, and aldolase levels; and serum electrophoresis were all within normal limits. A wedge biopsy from the indurated skin of the abdominal region was performed (Figure, B and C). (To convert creatinine kinase to microkatals per liter, multiply by 0.0167.)

**WHAT IS THE DIAGNOSIS?**

**A.** Pyoderma gangrenosum

**B.** Fibrosis and ulceration caused by meperidine

**C.** Localized scleroderma (morphea)

**D.** *Mycobacterium haemophilum* infection

## Diagnosis

**B.** Fibrosis and ulceration caused by meperidine

## Microscopic Findings and Clinical Course

Histopathological findings demonstrated lobular panniculitis, with subcutaneous fat lobules showing necrotic adipocytes and dense inflammatory infiltrates composed mainly of foamy histiocytes. Severe fibrosis involved the deep dermis and subcutaneous septa. Foreign-body giant cells and macrophages with large, foamy cytoplasm engulfing the lipids from necrotic adipocytes were also seen. There was no evidence of thrombosis or vasculitis. No polarizable foreign material was identified. Stains for micro-organisms were negative. Results from a muscle biopsy specimen taken from the deltoid muscle ruled out muscle involvement. The history of meperidine injection and the characteristic clinical and histopathological findings led to the diagnosis.

The meperidine injections were discontinued, and the patient was referred for alternative pain management and psychiatric counseling. Topical hydrogels and films were prescribed for the ulcer, and intensive physical therapy was started for the stiffness. Three months later the ulcer had almost healed, but his mobility had improved only slightly.

## Discussion

Meperidine, also known as pethidine, is a synthetic analgesic opioid. It is prescribed as hydrochloride salt in tablets, as syrup, or as intramuscular, subcutaneous or intravenous injection. Cutaneous complications of parenteral opioid abuse are varied and include soft-tissue indurations, puffy hand syndrome, hypertrophic scars, calcifications, hyperpigmentation, and skin infections.[1,2] Diagnosis is often difficult because drug-dependent patients often deny use of the drug. Furthermore, the clinical appearance may be bizarre and not fit any known dermatosis.

The clinical features in our patient, however, are so distinctive that diagnosis can be suspected from these findings alone. Diffuse expansive fibrosis extending well beyond the injection sites and asymptomatic irregular-shaped ulcers often reaching the muscle have been described in relation to several opioids, including pentazocine,[1,3] methadone,[4] desomorphine,[5] and meperidine.[6,7] The lesions usually begin as multiple nodules, most commonly located on accessible areas, including the buttocks and thighs. Eventually, they progress to fibrosis and develop into multiple sclerodermoid plaques that extend to the underlying fascia and muscle. Large, deeply penetrating ulcers may develop on the plaques. Patients with severe dermal and muscular involvement may present with severe restriction of mobility and functional disability, sometimes simulating a neuromuscular disorder.

Histopathologically, the lesions are characterized by a lobular panniculitis associated with extensive dermal and septal fibrosis. The inflammatory infiltrate is usually granulomatous with fat necrosis and pseudocystic cavities surrounded by foamy histiocytes and giant multinucleated cells. Lipophagic granulomas and thrombi of small blood vessels may also be present. A foreign-body crystalline material is occasionally seen inside multinucleated giant cells under polarized microscopy.[8] Muscle involvement is characterized by replacement of muscle fibers with fibrous tissue and variable amounts of inflammatory infiltrate.

The exact mechanism of these cutaneous and muscular manifestations is unknown. Repetitive trauma, vascular thrombosis, endarteritis, vasoconstriction or fibrosis stimulated by the opioids themselves are some of the mechanisms that have been proposed.[1,7] A recent report[9] of successful naltrexone therapy for the treatment of chronic ulcers caused by opioid injections may support the latter hypothesis.

Differential diagnosis should be made with other sclerodermoid disorders, such as scleroderma and eosinophilic fasciitis. When muscle is involved, infiltrative or end-stage inflammatory myopathies, muscular dystrophy, and stiff-man syndrome should also be considered. A history of drug abuse, the clinical pattern of distribution, the lack of systemic involvement, and laboratory and histological findings allow the correct diagnosis to be made.

The cornerstone of treatment is to stop opioid use, but patients should also receive psychiatric counselling and alternative treatment for the chronic pain to prevent relapses of this condition.


### ARTICLE INFORMATION

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