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Curious Crosses: Injection-Induced Lesions

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Skin biopsy provided an elusive diagnosis and evidence that the patient had likely omitted important information during medical interviews. A 43-year-old man with a history of alcohol and opioid use was admitted to the inpatient ward from the infectious disease clinic. For 2 weeks, he had experienced recurrent, painful skin nodules that expressed bloody, purulent fluid. These were associated with fever and chills but no joint pain. He reported no allergies, recent travel, tick bites, or new medications.

PRESENTATION

The patient was a groundskeeper at a golf course near the North Carolina coastline. He had intermittent episodes of similar skin eruptions over the previous several years. Multiple superficial wound cultures had been performed during this time, showing colonization with different microorganisms, including *Candida albicans* and coagulase-negative *Staphylococcus* species. Approximately 1 year earlier, a blood culture was positive for *Pantoea* species. When past skin biopsies revealed fungal yeast forms, he was treated with itraconazole without clinical improvement. Before admission, he had been on a 6-month course of alternating trimethoprim/sulfamethoxazole and doxycycline, taking each drug for 2 months at a time, with no clinical response. He denied recurrent childhood infections or chronic immunosuppressive therapy.

Twelve years before, the patient underwent spinal fusion for a golfing injury. A spinal abscess populated with methicillin-resistant *Staphylococcus aureus* complicated recovery. An extensive intravenous antibiotic course was administered in conjunction with negative pressure wound therapy and opioid analgesia. He developed a severe oral opioid dependence, progressing to a point that he spent much of his salary on illegally purchased opioids. His dependence led to the end of his marriage and his golfing career.

Five years before admission, the patient entered a drug rehabilitation program and began treatment with buprenorphine/naloxone. His therapy was subsequently transitioned to sublingual buprenorphine 8 mg 3 times daily. He denied using alcohol or illicit drugs, including intravenous substances, since that time.

ASSESSMENT

A physical examination, including a general musculoskeletal examination, showed a well-maintained man in no acute distress. His lungs were clear, and his heart sounds were normal. Multiple subcutaneous nodules were distributed on the bilateral upper and lower extremities, sparing the back, trunk, and feet (**Figure 1**). The nodules, pustular with an erythematous base, looked to be at different stages of healing. Lesions on the lower extremities were fluctuant.

After blood and wound samples were obtained for culture, the patient began empiric antibiotic therapy with piperacillin/tazobactam. Results from a complete blood count and basic metabolic panel were within normal limits. A urine toxicology screen was positive only for opioids in the setting of known buprenorphine use. Testing for human immunodeficiency virus was negative, and blood cultures showed no growth. A respiratory burst assay to evaluate for neutrophil and macrophage dysfunction produced normal results. Superficial wound cultures identified *Aspergillus flavus, Candida parapsilosis*, and *Candida dubliniensis*. Antibiotic therapy was discontinued, and fluconazole 400 mg/d was initiated.

The dermatology department was consulted, and a punch biopsy was performed on 1 of the left arm lesions. This disclosed a prominent collection of neutrophils in the deep reticular dermis. Fite, periodic acid–Schiff, and Brown-Brenn stains were negative for mycobacteria,

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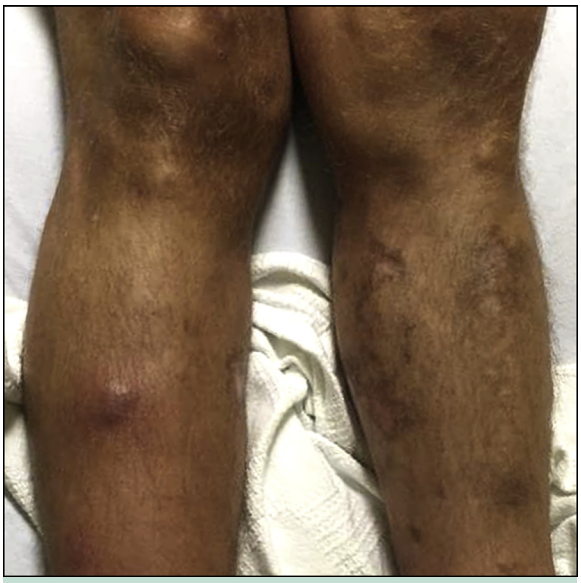

Figure 1 The patient had diffuse nodules in various stages of healing on the extensor surfaces of his legs.

fungus, and bacteria, respectively. Polarizable material was seen within the inflammatory elements of the abscess and highlighted in dark pink by the periodic acid-Schiff stain. The specimen showed small, round, birefringent entities with Maltese cross morphology.

DIAGNOSIS

The broad initial differential diagnosis principally focused on infectious causes. Sporotrichosis was considered, given that the patient worked as a groundskeeper and his lesions were principally distributed on the distal extremities. The fluctuance discovered on examination led us to include fungal abscess, as well as infection with methicillin-resistant *Staphylococcus aureus*, atypical mycobacteria species, or *Nocardia* species. However, all were excluded by pathologic examination. Last, extensive neutrophils in the deep dermis suggested the potential for neutrophilic dermatoses, including pyoderma gangrenosum, Behçet's disease, and Sweet's syndrome, but the presence of birefringent material is not characteristic of any of these.[1]

Over time, the patient had been treated with multiple antibiotics and antifungals without any resolution in his lesions, further supporting a noninfectious cause. However, the identification of *Pantoea* species in a culture obtained during a previous outbreak was peculiar. A report in the medical literature documented the association of contaminated intravenous materials with an acute febrile illness known as "cotton fever," a syndrome that resembled the fevers and chills our patient described.[2] Symptoms of cotton fever, named for the practice of filtering illicit drugs with cotton, are spurred when *Pantoea agglomerans* unleashes an endotoxin. The information directed our attention to the possibility that our patient was injecting a foreign substance subcutaneously.

Closer examination verified that lesions were isolated to the volar aspect of his arms and the anterior aspect of his legs, areas easily accessible for self-injection. He had no lesions on his back or trunk where self-injection would be more difficult. In addition, no new lesions appeared during hospitalization while the patient's privacy and access to illicit substances were restricted. Review of his medication list further raised our clinical suspicion, because he was on sublingual buprenorphine alone, not traditional buprenorphine-naloxone therapy. The patient stated that the combination caused nausea and vomiting. If the sublingual combination is crushed and injected illicitly, the opioid effects of buprenorphine are attenuated by the naloxone component, producing a withdrawal syndrome not seen when the drug is administered correctly or when buprenorphine is injected alone.[3,4]

The skin biopsy was essential in diagnosis. Negative Fite, periodic acid-Schiff, and Brown-Brenn stains ruled out many of the common infectious processes first considered. Consultations with the dermatology and pathology departments confirmed that the degree of tissue necrosis seen was inconsistent with neutrophilic dermatoses. The birefringent material bearing Maltese cross morphology on punch biopsy was highly indicative of skin injections of a foreign substance. Thus, we were led to a diagnosis of exclusion: subcutaneous injection of buprenorphine.[5-7] Amidon, an excipient in the buprenorphine formulation, can be identified under polarized light as a Maltese cross-shaped foreign body (**Figure 2**).[6,8]

Cutaneous complications of buprenorphine injection include ulceration and infection; the latter can be devastating, advancing to necrotizing fasciitis.[6] Treatment consists of antibiotic or surgical therapy to drain lesions and eliminate bacteria.[8] Lesions stop forming once patients discontinue self-injecting. Rare case reports detail

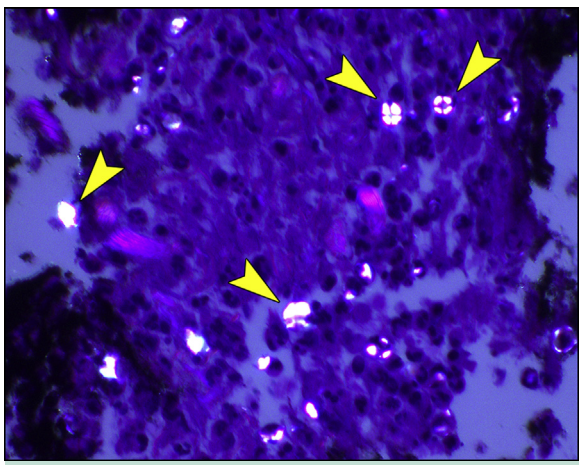

Figure 2 Refractile material (*yellow arrows*) within the patient's dermal abscess showed Maltese cross morphology under polarized light.

livedoid, necrotic skin lesions due to intra-arterial and subcutaneous injections of buprenorphine.[6-8] We were unable to determine the patient's route of injection, although we believe it was likely to be subcutaneous because the infection was local, and blood cultures were negative.[6]

MANAGEMENT

On further questioning, the patient denied misuse of buprenorphine despite presentation of the histopathologic facts. Instead, he revised his reason for use of buprenorphine alone, stating his preference for the single drug was related to cost not to intolerance.

The patient was discharged on oral fluconazole for positive wound cultures. At 1-month follow-up, he had improvement in some lesions but persistent inflammation in others. His prescribing physician, notified of the team's suspicions, planned to develop a strategy for discontinuing buprenorphine and addressing psychosocial stressors.

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