Nontuberculous Mycobacterial Infections After Silicone Breast Implant Reconstruction Emphasize a Diversity of Infecting Mycobacteria

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Post-surgical skin and soft tissue infections (SSTIs) caused by nontuberculous mycobacteria (NTM) are uncommon, indolent, difficult to treat, and often mimic pyogenic bacterial infections. Here we present 3 cases of NTM infections following placement of silicone implants for reconstructive breast surgery. These cases emphasize the importance of a high index of suspicion for NTM in patients with SSI after a prosthetic reconstruction refractory to conventional antibiotic therapy and the importance of early investigation with mycobacterial-specific diagnostics.

Keywords. breast cancer; molecular identification; Nontuberculous mycobacterial infection; skin and soft tissue infection; surgical site infections.

CASE 1

A 64-year-old female with a history of stage IIA right breast invasive ductal carcinoma (ER-/PR+/Her2-) underwent a bilateral mastectomy and silicone implant reconstruction in January 1989. She was in complete remission at the time of presentation. Neoadjuvant radiation was not given. Intravenous (IV) cefazolin was administered perioperatively, and an acellular dermal matrix (ADM) was not used to assist with the breast reconstruction. Bacitracin solution with normal saline was used to irrigate her breast implant pocket. In early January 2016, she presented with an erythematous, boggy, and indurated nodule over her right breast. A wound culture revealed yellow fibrinous exudate and modest surrounding erythema × biotics, a 3 × 2 cm open wound developed. It presented with yellow fibrinous exudate and modest surrounding erythema over the medial portion of her right breast. A wound culture was obtained and was negative for both bacterial and fungal organisms. No mycobacterial culture was performed at this time. Given the lack of clinical improvement with conservative management, she was referred for surgical evaluation. At the end of January 2016, the patient underwent wide excision of the necrotic tissue and debridement of the subcutaneous tissue with primary wound closure. No involvement of the silicone implant capsule was noted during the procedure, and it was therefore left in place. Pathologic examination of excised tissue showed dense diffuse par-dermal and subcutaneous granulomatous infiltrates associated with ulceration of the overlying epidermis. Special stains for microbial agents including fungi and mycobacteria or acid-fast bacilli (AFB) were negative.

On postoperative day number 8, the patient returned with new worsening erythema over her right breast without fever and was referred for inpatient hospital admission to receive IV vancomycin (1 g q12hrs). Modest clinical improvement was noted on exam, and she was discharged home on oral linezolid (600 mg q12hrs) the following day. Five days after hospital discharge, she returned to the emergency department with worsening erythema and was taken to the operating room for a second surgical wound exploration, where more necrotic tissue was found and debrided with implant removal. Histopathologic examination of tissue obtained from the right lateral chest wall at this time showed that the thick collagenous capsule of the implant exhibited increased cellularity and thick dense bands of aligned collagen fibers in the absence of synovial-like hyperplasia, consistent with capsule contraction. An interstitial lymphocytic infiltrate in the subcapsular soft tissue aligned with ectatic blood vessels (Figure 1A). Fragmented subcutaneous tissue was infiltrated by dense sheets of histiocytes, with palisading around areas of central necrosis (Figure 1B). Overlying intra-epidermal pustular dermatitis (Figure 1C) was negative for bacterial or fungal organisms by special stains. However, repeat AFB stains revealed rare rod-like forms within areas of central necrosis (Figure 1D). Empiric treatment for mycobacterial soft tissue infection was started with IV amikacin (10 mg/kg daily), oral clarithromycin (500 mg q12hrs), and oral moxifloxacin (400 mg daily). AFB were observed on a concentrated smear of the tissue sample and were recovered 1 month after incubation from a Mycobacterium...
The AFB isolate was eventually identified as *Mycobacterium xenopi* from a subculture of the MGIT incubated for 4 weeks at 45°C and identified by partial sequencing of the 16S ribosomal RNA gene as previously described [1]. Antimicrobial susceptibility testing was not performed, and the patient remained on empiric therapy.

The use of amikacin was limited by clinical evidence of vestibular toxicity despite amikacin dose reduction to thrice-weekly and trough levels <1 mcg/mL. Amikacin was discontinued and replaced with oral rifampin (600 mg daily). The patient completed 5 months of clarithromycin, moxifloxacin, and rifampin, with complete resolution of her symptoms.

**CASE 2**

A 47-year-old female with a new diagnosis (March 2016) of stage IIIIB invasive ductal cancer of the right breast (estrogen receptor–positive [ER]+/progesterone receptor–positive [PR+]/human epidermal growth factor receptor–negative [Her2−]) with right axillary lymph node involvement was initially treated with neoadjuvant chemotherapy. Subsequently, she underwent a bilateral modified radical mastectomy with immediate placement of bilateral silicone implants and a right axillary lymph node dissection. Perioperative IV clindamycin was administered. An ADM was not used to assist with tissue expander placement, and bacitracin solution was used to irrigate the breast pocket. Neoadjuvant radiation therapy was planned but deferred when she developed sudden-onset erythema and significant swelling over her left breast on postoperative day 28. She was treated successfully with IV cefazolin (2 g q8hrs) while inpatient and then transitioned to a 10-day outpatient course of oral cefadroxil (1 g q12 hours). On postoperative day number 55, she developed recurrent swelling and erythema over her entire right breast (Figure 2A-B). She was initially treated with outpatient oral augmentin (875–125 mg q8hrs) without relief, prompting hospital admission. She denied any constitutional symptoms including fever. Initial laboratory work including a CBC was within normal limits. She was started on IV vancomycin (1 g q12hrs) without improvement, and she was taken
to the operative room on hospital day number 2 for removal of the right breast tissue expander. On gross exam, there was a significant amount of turbid fluid that was sent for bacterial, fungal, and mycobacterial culture; routine bacterial and fungal cultures were negative. AFB were observed on a concentrated smear of sample, and MGIT broth cultures were positive for AFB after 6 days. Four weeks later, the culture grew Mycobacterium chelonae-abscessus complex, as identified by partial sequencing of the 16S rRNA gene as described for Case 1. The clinical isolate was further speciated as M. chelonae by Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry (MALDI-TOF MS) [2]. Given spontaneous resolution of her clinical symptoms, removal of her breast implant, and the known intrinsic and acquired resistance of this organism, treatment was deferred until susceptibilities resulted. Drug susceptibility testing was performed according to standard procedures [3]. Minimal inhibitory concentrations (MICs) are noted (Supplementary Table 1). A 3-month course of doxycycline (100mg q 12hrs) and clarithromycin (500 mg q 12 hrs) was administered, with continued resolution of her symptoms.

CASE 3

Three months prior, a 56-year-old female with a history of stage IIB invasive ductal carcinoma of her left breast (ER+/PR+/Her2–), received her last dose of neoadjuvant chemotherapy with paclitaxel, doxorubicin, and cyclophosphamide, completing a total of 4 cycles; neoadjuvant radiation had yet to be given. In September 2015, she received a left modified radical mastectomy with sentinel lymph node biopsy and immediate silicone implant reconstruction. She received IV cefazolin peri-operatively, and 2 Jackson-Pratt (JP) drains were placed during her mastectomy. An ADM was not used, and bacitracin solution was given to irrigate the breast pocket. On postoperative day 12, while on prophylaxis with oral cephalexin, she presented with erythema along the insertion of 1 of the JP drains, with purulent fluid in the JP drain bulb. Systemic signs of infection including low-grade fevers and chills were present. Initial laboratory work including a CBC was unrevealing. Some improvement in erythema was noted while on empiric broad-spectrum antibiotics including IV vancomycin (1 g q 12 hrs) and IV cefepime (2g q 12 hrs) for 5 days. Her drains were removed, and the purulent fluid was sent for routine bacterial culture. A mycobacterial culture was not ordered. On day 3, significant growth of a dry, white colony on a Columbia Nalidixic agar (CNA), a selective media for gram-positive bacteria, was noted. Gram stain of the colony revealed branching, beaded, gram-positive bacilli that were acid fast by Kinyoun stain. Rapid detection of the Mycobacterium tuberculosis complex by polymerase chain reaction (PCR) was negative, and the isolate was identified as Mycobacterium fortuitum by MALDI-TOF MS. Enterococcus Faecalis also grew from the same specimen. Due to the clinical progress that was seen while on antibiotics, the growth of multiple organisms including Enterococcus, and AFB recovery on CNA, the isolated AFB was considered to be insignificant. She was discharged home on oral amoxicillin/clavulanate (875/125 mg q 12hrs) to complete a 10-day course, only to return 12 days later with worsening erythema and swelling of her left breast. She was immediately taken to the operating room for wound exploration and removal of the tissue expander. On gross examination, fibrin and fat necrosis was seen along the upper mastectomy skin flap. The tissue expander was sent to pathology for only gross inspection and appeared normal. Tissue from the left breast was also sent to microbiology to test for bacteria and fungi. After 4 days, AFB were recovered similarly on CNA and were eventually identified as Mycobacterium fortuitum 8 days later. Susceptibility testing for this organism was done (Supplementary Table 1). She was started on empiric therapy with clarithromycin (500 mg q12 hrs), ciprofloxacin (750 mg q12 hrs), and trimethoprim-sulfamethoxazole (800 mg–160 mg q12 hrs). Based on sensitivities, clarithromycin was discontinued and the patient was maintained on both ciprofloxacin and trimethoprim-sulfamethoxazole for a total of 2 months, with complete resolution of her clinical symptoms.

DISCUSSION

NTM are common environmental organisms that cause wide-ranging clinical manifestations including SSTIs [4], especially when a prosthesis is involved. Most cases of NTM infections have been documented in people traveling to developing countries to receive cosmetic surgeries [5]. In such cases, the infection usually has an insidious onset—often not presenting with signs and symptoms of a systemic infection—and it appears to persist when antibiotics are given that target normal skin flora. A delayed hypersensitivity reaction also should be considered when postoperative erythema is present as a result of an offending antigen such as an ADM [6].

The rapidly growing mycobacteria (RGM) that have emerged as pathogens that cause SSTIs are M. fortuitum [7–9], M. abscessus [10], and M. chelonae [11]. Skin infections from RGM related to body modification procedures [12] and cosmetic surgeries [13] are now being widely recognized. Clinical presentation of SSTIs from RGM usually manifest as a localized cellulitis, a draining abscess or sinus tract, an individual nodule, or chronic ulcers [14, 15]. M. marinum, M. ulcerans, and other species of NTM have slower growth rates but also have a propensity to cause cutaneous NTM infections [16, 17].

M. xenopi is an NTM that mainly causes pulmonary disease [18] and has been recognized as both an opportunistic and a nosocomial pathogen found primarily in Southeastern England, Italy, and France [19, 20]. This species of NTM usually contaminates hot water distribution systems, and biofilms likely serve as the environmental reservoir [21–23]. Extrapulmonary infections caused by M. xenopi have been reported to affect spinal and other osteoarticular sites following surgical procedures [24, 25]. However, to our knowledge, no cases of M. xenopi causing an
SSTI after surgical breast reconstruction have been described in the literature as in Case 1. The addition of *M. xenopi* to the list of NTMs that can cause prosthetic implant infection has several implications for the evaluation of these infections. As noted above, the most common NTM pathogens isolated in SSTI or prosthetic device infections are rapid-growing mycobacteria. *M. xenopi*, as a slow-growing mycobacterium, with specific in vitro optimal culture conditions, may escape detection unless suspicion is high and appropriate culture techniques are applied. The slow growth may also mandate initiation of empiric treatment for mycobacterial infection (eg, if seen on AFB smears) before cultures are positive, and this report emphasizes the need to include *M. xenopi* as a possible infecting pathogen when choosing this empiric regimen.

Multilocus analysis and 16S rRNA gene sequencing allowed the identification of *Mycobacterium chelonae-abscessus* complex in Case 2. Species that make up this complex are biochemically inert, and their genetic profiles by partial 16S rRNA gene sequencing are often similar, making identification problematic [26]. MALDI-TOF MS has emerged as a rapid, simple, and accurate method for identification of bacteria, mycobacteria, and fungi, and a recent study shows the ability of MALDI-TOF MS to differentiate between *M. chelonae* and *M. abscessus* [2]. Infections caused by members of the *M. chelonae-abscessus* complex have been more frequently described in the literature [15, 27–29] as causing infections in both immunocompetent and immunocompromised hosts [30–33]. It has also been implicated in infections complicating surgical procedures, including a case of osteomyelitis of the foot [34]. Development of multidrug resistance has been shown to occur with *M. chelonae-abscessus* complex infections [35], but Case 2 demonstrated a more favorable antibiotic sensitivity profile.

Cases of *M. fortuitum* infection occurring after prosthetic breast reconstruction performed with and without an ADM have been reported [9, 36]. Like other species of mycobacteria, *M. fortuitum* is an RGM found in cold water systems and associated with nosocomial outbreaks. Also, RGM species including *M. fortuitum* have been associated with prosthetic joint infections involving the knee and hip [37]. Unlike the other species of RGM, *M. fortuitum* is generally more drug susceptible than other RGM species [28], and the cutaneous and soft tissue infections in which it is implicated predominantly affect younger patients [38].

Improved culture techniques and widespread use of molecular techniques such as gene sequencing and MALDI-TOF MS in pathogen identification have led to an increased recognition of this infection, corresponding to the rise in reports of cutaneous NTM infections over the recent decades [19, 39, 40]. Before the 1990s, initial culture for mycobacteria was frequently performed using solid media, but this has been supplemented by the use of continually monitored broth culture systems to enhance the recovery of mycobacteria. This has increased the sensitivity of mycobacterial cultures and resulted in large increases in the number of NTM identified [19]. Molecular methods have also decreased the time from culture positivity to pathogen identification. Molecular probes can identify select species (*M. tuberculosis*, *M. avium* complex, *M. gordonae*, and *M. kansasi*) within 1 hour of broth culture positivity. 16S rRNA gene sequencing can identify other mycobacterial species within a few hours of culture positivity, much more rapidly than traditional techniques [1]. The use of MALDI-TOF mass spectrometry, used for routine identification of bacteria and yeasts, is now extended to the identification of mycobacteria, primarily in reference laboratories, further decreasing the time required for identification to minutes [2].

Despite the availability of molecular techniques for microbial identification, the initial diagnosis of the infection in Case 1 was based on the recognition of suspicious histologic features (palisaded granulomas with central necrosis) and appropriate use of special stains for AFB. While the capsule in this case was deemed unaffected at initial surgical exploration, clinical evidence of late capsule contraction as seen on histology from this patient could serve as a clue to nearby infection and encourage submission of periprosthetic soft tissue for surgical pathology or cytology analysis to expedite diagnosis in similar cases of slow-growing micro-organisms.

Beyond being able to make a prompt diagnosis of NTM infections, a highly resistant phenotype carried by some of these organisms also makes treatment challenging. Clinical guidelines from well-defined mycobacterial infections (*M. avium-intracellulare*) emphasize the need to avoid monotherapy [14, 41] and encourage the use of a multidrug regimen. Effective antibiotics are limited, and support from the literature is scarce. Based on in vitro studies and descriptive clinical reports, *M. xenopi* is known to be susceptible to antituberculous drugs including isoniazid, rifampin, ethambutol, and moxifloxacin, which in combination with macrolides may enhance clinical response. Optimal duration of therapy is unknown, but clinical consensus indicates that removal of the foreign body is likely crucial for a microbiologic cure [14, 38].

Although detection systems for mycobacteria have developed, such advancements are not helpful if clinicians do not consider NTM in the realm of possibilities as the cause of infection. It is not uncommon for NTM infections only to be considered after multiple courses of antimicrobials directed at more common pyogenic bacteria are trialed. NTM are ubiquitous in the environment; in the appropriate clinical context, NTM should be considered by evaluation with appropriate histopathology and microbiological testing, including isolation from skin and wound specimens.

Based on the patient cases highlighted in this series, along with many of those cited in literature, there seems to be an association between the use of silicone implants in cosmetic and reconstructive surgery and NTM infections. Many mycobacteria, including RGM, can form biofilms on prosthetic surfaces [42–44], making eradication of this infection very difficult. It is reassuring that treatment success was achieved in the 3 cases highlighted...
above that were facilitated by prosthetic removal, which is highly encouraged. Treatment of NTM infections in the setting of a prosthesis with antibiotics alone would likely not have achieved similar results. However, in some instances, including Case 2, spontaneous resolution can be achieved with prosthetic removal alone.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References
15. Atkins BL, Gottlieb T. Skin and soft tissue infections caused by nontuberculous mycobacteria: predisposing conditions and clinical characteristics of six cases and a review of 63 cases in the literature. Infect Dis (Lond) 2016; 48:509–16.