# Painful nodule with induration and spreading erythema

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A young woman presented with a 2-day history of a 2- to 3-cm erythematous painful papule on her right flank, which she thought was a spider bite. Initially, the lesion was a nodule that was warm, tender, and fluctuant on palpation. Clinically the lesion was most consistent with an abscess, spider bite, or inflamed cyst. The lesion was incised, drained, and cultured. Empiric therapy with cephalexin was started. Within 24 hours, the patient presented to the dermatology clinic with a low-grade fever (38.3°C, 101°F), and the lesion had become more tender. The erythema had spread to 20 cm, and the central induration had spread to 9 cm (*Figure*).

What is the most likely diagnosis? What is the most appropriate therapy at this point?
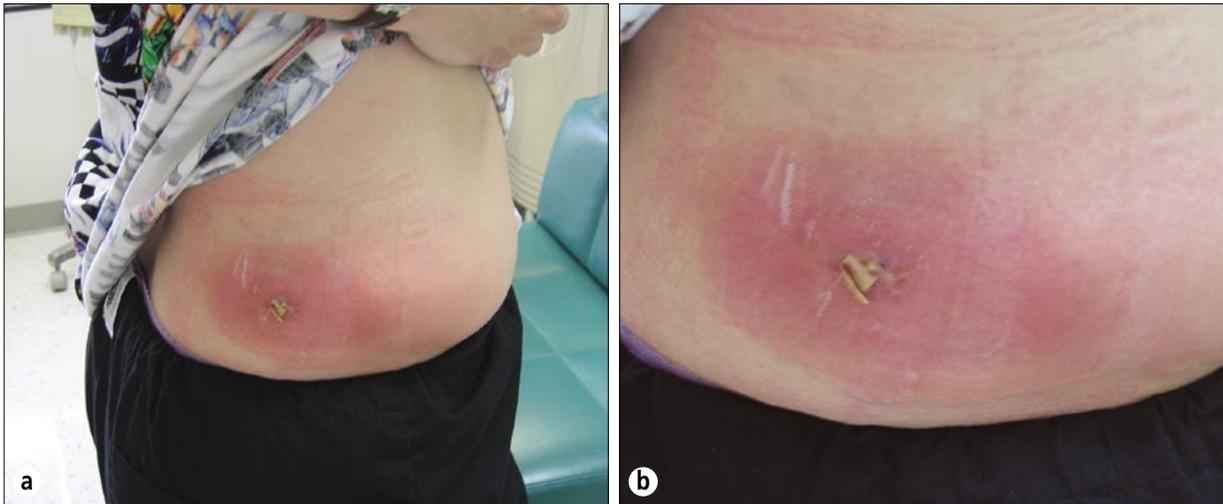
Figure. (a) Warm indurated plaque with central incision site where the culture was performed. **(b)** Close-up of the lesion.

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DIAGNOSIS: Methicillin-resistant *Staphylococcus aureus* (MRSA).

DISCUSSION

Staphylococcus aureus is responsible for the majority of skin and soft tissue infections (1). When the patient presented with evidence of extension of infection (<24 hours on cephalexin), empiric therapy with levofloxacin and linezolid was instituted. The patient was no longer febrile after 12 hours on the new regimen, and the culture and sensitivity testing confirmed MRSA sensitive to levofloxacin, tetracycline, and trimethoprim-sulfamethoxazole.

Since the inception of penicillin therapy, *S. aureus* has been adapting to maintain its stature as a cutaneous pathogen *(Table 1)*. Researchers in an urban California emergency department screened 137 adults who presented with localized cutaneous infections (i.e., cellulitis, furunculosis, or wound infections) and found that 79 had staphylococcal infections. Sixty-one (77%) of those infections were methicillin resistant (5). Currently, there is a worldwide epidemic of MRSA infections. Historically, MRSA was a hospital-acquired pathogen (HA-MRSA) with subsequent "spillover" into the community (6). However, it is now apparent that the community-acquired pathogen (CA-MRSA) is a distinctive entity (7).

Virulence of MRSA

The virulence of MRSA is dictated primarily by antibiotic resistance genes and toxin production *(Table 2)*. Some of the mechanisms of antibiotic resistance are known on a molecular level. The staphylococcal antibiotic resistance genes are found on a genomic island termed the staphylococcal cassette chromosome (SCC) (9–11). The antibiotic resistance genes have been categorized as SCC*mec* types I through V based on their antibiotic specificity. SCC*mec* types I, IV, and V are involved in beta-lactam (methicillin) resistance and primarily code for the regulatory, structural, and recombinase genes required (1, 12). SCC*mec* types II and III code for genes involved in non–beta-lactam antibiotics (trimethoprim-sulfamethoxazole, clindamycin, and tetracycline) (10–13).

Interestingly, HA-MRSA contains distinct SCC*mec* types, plasmids encoding resistance to various antibiotics, as well as heavy metal resistance elements (7). HA-MRSA characteristically lacks the toxin genes frequently associated with CA-MRSA. Increased virulence in CA-MRSA has been attributed to the presence of staphylococcal enterotoxins B and C, toxic shock syndrome toxin-1 (TSST-1) and, most importantly, Panton-Valentine leukocidin (PVL) *(Table 3)*. TSST-1 and the enterotoxins are "superantigens" that activate T cells expressing major histocompatibility complex class II molecules via the variable portion of the beta chain of the T-cell receptor. CA-MRSA cutaneous infections associated with abscess formation and tissue necrosis are increasingly associated with the presence of PVL (17, 18).

Diagnosis

Bacterial culture and sensitivity testing is required for diagnosis and appropriate therapeutic intervention for cutaneous staphylococcal infections. Clues to the diagnosis of cutaneous CA-MRSA include personal contacts with CA-MRSA (day care centers [19], assisted-living homes, college dormitories), colonization with MRSA, and a history of incarceration (20). Intriguing new data suggest that receipt of conjugate pneumococcal vaccine may induce a shift in nasal flora towards *S. aureus* colonization, including MRSA, with a risk of invasive infections (21). Risk factors for CA-MRSA necrotizing fasciitis include injection drug use, previous MRSA infection, diabetes, hepatitis C, malignancy, and HIV infection (22).

Therapy

Appropriate therapy for *S. aureus* infections varies with the age of the patient and should be dictated by local culture and sensitivity data. Cultures are imperative for adequate therapy—the days of empiric first-generation cephalosporin antibiotics for presumed staphylococcal infections are over in many major

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Table 1. History of *Staphylococcus aureus* antibiotic resistance

Date	Event
1940s	Penicillin was introduced. Within 1 year, penicillin-resistant *S. aureus* (PRSA) occurred first in the hospital and later in the community (2).
1960s	Semisynthetic penicillins were designed to overcome PRSA. Within 1 year, methicillin-resistant *S. aureus* (MRSA) was documented first in the hospital and later in the community (3).
1981	Hartman described the alteration of penicillin-binding proteins as a major resistance mechanism of MRSA (4). Penicillin-binding protein 2a has decreased affinity for beta-lactam antibiotics.
1990s	Distinct community-acquired MRSA isolates were described.

Table 2. Comparison of hospital- and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA)

Type of MRSA	Association with antibiotic overuse	Resistance genes	Toxins
Hospital-acquired (HA)	Positive association with broad-spectrum antibiotics (i.e., cephalosporins such as cefepime or quinolones, which eradicate susceptible gram-positive, gram-negative, and anaerobic flora)	Contains distinct SCC*mec* types, plasmids encoding resistance to various antibiotics, as well as heavy metal resistance elements (7)	Characteristically lacks the toxin genes
Community-acquired (CA)	No specific antibiotic usage pattern has been associated with CA-MRSA (with the possible exception of amoxicillin use in children) (8)	Contains SCC*mec* type IV	May possess staphylococcal enterotoxins B and C, toxic shock syndrome toxin-1, and Panton-Valentine leukocidin

Table 3. Functions of staphylococcal toxins

Toxin	Function
Staphylococcal enterotoxins (A through O)	Potent emetic activity
Exfoliative toxin A and B	Bind to keratohyalin granules. Toxin A is chromosomally encoded, while toxin B is plasmid encoded.
Toxic shock syndrome toxin-1	Former names: staphylococcal pyrogenic toxin C and staphylococcal enterotoxin F. Involved in cytokine release. Unique ability to cross mucosal surfaces.
Panton-Valentine leukocidin	Comprises two elements that are secreted separately and then recombine to create an active toxin that induces pore formation in cell membranes of monocytes, macrophages, and polymorphonuclear neutrophils. The result is cellular cytolysis (leukopenia) and the release of interleukin-8 and leukotriene B4, as well as other cytokines (14–17).

geographic areas. For cutaneous and soft tissue CA-MRSA infections, surgical incision and drainage are critical (23, 24). Recently, investigators at Children's Medical Center in Dallas, Texas, determined that for pediatric patients with CA-MRSA abscesses <5 cm in diameter, incision and drainage constituted effective therapy even when patients received antibiotics to which the isolate was not susceptible (25).

Outpatient staphylococcal infections of the skin can be treated with a variety of agents. Recently, MRSA infections reported by sentinel hospitals and reference laboratories in three US cities from 2001 through 2002 were categorized by researchers at the Centers for Disease Control and Prevention (26). CA-MRSA accounted for 8% to 20% of the total; >75% of these infections involved skin or soft tissue. Of CA-MRSA isolates, 97% were sensitive to trimethoprim-sulfamethoxazole, 87% to clindamycin, 88% to tetracycline, and 65% to ciprofloxacin (26). Trimethoprim-sulfamethoxazole is one of the most common antibiotics utilized for outpatient MRSA infections; however, resistance has been noted in up to 29.5% of CA-MRSA isolates in parts of Europe (27, 28). In the pediatric population, clindamycin is commonly used; however, the incidence of inducible resistance may be 20% or higher, especially when it is used as monotherapy (29). CA-MRSA appears to be most susceptible in vitro to minocycline as compared with doxycycline (30). Finally, the "respiratory" fluoroquinolones such as levofloxacin, gatifloxacin, and moxifloxacin have been successfully used for CA-MRSA (1). Ciprofloxacin use should be avoided in CA-MRSA because of its inferior activity against gram-positive bacteria and the propensity for rapid development of resistance (31).

In general, vancomycin is the drug of choice for moderate to severe methicillin-resistant staphylococcal infections (3). Historically, in methicillin-sensitive staphylococcal infections, however, the beta-lactam antibiotics are associated with faster clinical responses as well as more rapid clearing of bacteremia when compared with vancomycin (32). In keeping with history, vancomycin-resistant MRSA has been documented, especially in MRSA-colonized patients with prolonged exposure to vancomycin and indwelling devices ("hardware" infections) (33). For such patients, linezolid is indicated for the treatment of adults and children with MRSA and vancomycin-resistant enterococcal infections involving skin, soft tissue, or lungs. Unlike vancomycin, linezolid is 100% bioavailable, allowing for easy oral dosing (34).

Prevention

Since colonization with CA-MRSA is a risk factor for the development of invasive disease (35), patients must be evaluated and treated for this as well. While CA-MRSA may reside in the nose, axilla, groin, and navel, eradication of nasal colonization is key to successful decolonization (36). One local protocol for decolonization includes topical mupirocin to the nares twice daily; chlorhexidine body scrubs daily; and trimethoprim-sulfamethoxazole (double strength) twice daily for 5 days. Additionally, since direct contact is the primary mode of transmission for staphylococcal infections, alcohol-based hand sanitizers may be helpful, as they have been shown to decrease colonization and transmission of pathogens within the household setting (37).

Dedication

This report is dedicated to the founder of *BUMC Proceedings*, George J. Race, MD, PhD, who has provided inspiration and motivation to generations of physicians at Baylor University Medical Center, Dallas, Texas.

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