Endogenous Invasive Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Endophthalmitis: Observations in Two Cases

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Introduction

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections remain a growing problem despite the increasing armamentarium of anti-MRSA antibiotics. The majority of reported CA-MRSA infections are skin and soft tissue infections. Recently, more invasive and life-threatening infections have been recognized.[1] Ophthalmic infections have been reported less frequently and CA-MRSA endogenous endophthalmitis has not been well described.[2] The clinical presentations, treatment, and outcome of two cases of suspected invasive CA-MRSA endogenous endophthalmitis are discussed in this report.

Case Reports

Case 1. A 26-year-old man presented to a community hospital with a right arm subcutaneous abscess. Incision and drainage was performed. The wound culture grew MRSA sensitive to all antibiotics tested except oxacillin and penicillin. He was treated with trimethoprim-sulfamethoxazole. Three days later, he developed lumbago. After two weeks of symptomatic treatment, Magnetic Resonance Imaging (MRI) appeared to demonstrate L5-S1 disk herniation. Epidural corticosteroid injection was administered. Five days later, he developed syncope and supraventricular tachycardia. He was transferred to our facility for evaluation.

Laboratory results revealed leukocytosis of 17.1 $x10^9$/L, 32% bands, and erythrocyte sedimentation rate was 53 mm/hr. He was started on vancomycin 15 mg/kg IV every 12 hours. Blood cultures grew MRSA, sensitive to fluoroquinolones and resistant to oxacillin and erythromycin (VITEK Automated Microbiology System). Repeat MRI of the spine demonstrated discitis at the L5-S1 disk space with associated epidural abscess and vertebral osteomyelitis.

Over the next three days, he developed hypoxic respiratory failure. Repeat imaging revealed paravertebral abscesses, thrombosis of the adjacent inferior vena cava, and bilateral septic pulmonary emboli. He underwent surgical drainage of the paravertebral process.

On post-operative day four, examination revealed bilaterally injected conjunctiva. Ophthalmologic evaluation revealed bilateral endophthalmitis with vitreal abscesses. A vitreous sample taken from the left eye revealed no growth (on antibiotic therapy). Due to high suspicion for MRSA endophthalmitis, he received intravitreous clindamycin and vancomycin at doses of one milligram (mg) each of a 0.1 mL solution, followed by a change in systemic IV antibiotics to linezolid, 600 mg IV every 12

hours, and moxifloxacin, 400 mg IV every 24 hours. After several days, he clinically stabilized. After multiple interventions for retinal detachments over a period of months, his visual acuity improved to 20/20 in the right eye and 20/100 in the left.

Case 2. A 53-year-old female presented to an outside facility with shoulder pain. Joint aspiration was performed and cultures grew MRSA, resistant to penicillin, erythromycin, levofloxacin, and oxacillin without inducible clindamycin resistance. Blood cultures grew MRSA and intravenous antibiotics were initiated. She also had tricuspid valve endocarditis and septic emboli to bilateral lungs with positive MRSA sputum cultures. She developed decreased visual acuity and conjunctival injection. Ophthalmologic involvement was suspected. She was transferred to our facility for treatment.

On arrival, she was tachycardic, tachypneic, and mildly hypoxic. She had conjunctival erythema and edema of the right eye. Visual acuity was 20/50 and she was diagnosed with endophthalmitis per ophthalmologic examination. Laboratory studies revealed leukocytosis of 35.2 $x10^9$/L. Chest radiograph demonstrated extensive bilateral multilobar infiltrates. MRI of the right shoulder confirmed osteomyelitis of the acromion and proximal humerus.

During the hospitalization, she had repeat (negative) cultures of blood, acromioclavicular joint, and vitreous fluid from right eye (on antibiotic therapy). She was treated with intravenous vancomycin 15 mg/kg IV every 12 hours and gentamicin 80 mg IV every 8 hours, then with rifampin 600 mg IV twice daily. She also received intravitreal vancomycin 1 mg of 0.1 mL solution to the right eye. She developed a diffuse maculopapular rash on vancomycin and rifampin and daptomycin 6 mg/kg IV every 24 hours was substituted. Sepsis improved and she was discharged to complete six weeks of daptomycin therapy. Visual acuity improved to 20/20 at the time of discharge. Work-up for an underlying immunodeficiency was negative in both cases.

Discussion

Staphylococcus aureus causes a wide array of human infection from limited skin involvement to profound septic shock.[3] While invasive *S. aureus* infection was once limited to hospital-acquired strains, CA-MRSA has been emerging as a significant pathogen.[1] There are increasing reports of invasive CA-MRSA blood stream infections and death.

A clear delineation between community and health care-associated infections (HA-MRSA) is important to understanding the spectrum of CA-MRSA infections. This delineation is made possible by acceptance of more specific definitions and molecular testing. New definitions propose HA-MRSA should include patients with positive MRSA blood cultures greater than 48 hours into hospitalization, and those with home intravenous therapy, chemotherapy, home specialized nursing care, and hospital or hemodialysis clinic attendance within 30 days before *S. aureus* bacteremia as well as those hospitalized in an acute care setting for two or more days in the preceding 90 days or residence in a long-term care facility.[4,5] Genetic testing also has helped to identify specific virulent factors associated with CA-MRSA which may explain its recently increased propensity to cause invasive infection.

Exogenous endophthalmitis, including *S. aureus* endophthalmitis, has been described extensively in post-operative ophthalmologic surgery.[2,6,7] Endogenous endophthalmitis is much rarer, however, comprising only 5-10% of cases.[8] *S. aureus* represents a minority of these cases and,

until recently, differentiation between HA-MRSA and CA-MRSA was not made.

In a review of MRSA infections of the eye in an urban healthcare system, 3640 patients had a positive culture of MRSA and 70% were suspected CA-MRSA.[2] Of these, only four (8%) had endogenous endophthalmitis. Two of these patients would not have had CA-MRSA based on Friedman's definition.[5] A 2005 review of necrotizing fasciitis cases in a large US medical center identified one patient who had co-existing endopthalmitis related to MRSA bacteremia.[9] A 2006 review examined cases of MRSA culture positive patients at a US university and county hospital and found nine patients with the USA300 clone; three had endogenous endopthalmitis.[10] A retrospective study of treatment of endophthalmitis identified 14 cases of endogenous endophthalmitis over a four-year span.[11] Only one patient had *S. aureus*, however, the strain was not identified as MRSA. Another 7-year review of cases of endogenous endophthalmitis from a US university medical facility found 21 cases; five were *S. aureus* and two were MRSA. The strains were not identified further and based on information provided, only one remained as possible CA-MRSA.[8]

While *S. aureus* represents a small percentage of reported pathogens in cases of endogenous endophthalmitis, additional reports of MRSA and CA-MRSA infections are being identified and more may be missed. The true prevalence of MRSA endophthalmitis is unclear as availability of, and indications for, full ophthalmologic evaluation in MRSA bacteremia are unknown. It is unclear if specific toxic production or protein expression increases the likelihood of endophthalmitis. Colonization with MRSA also has not been found universally in subjects with endogenous endopthalmitis.[12] The aforementioned cases demonstrated need for vigilance in identifying endophthalmitis in patients with invasive MRSA infection. Reported cases, including our own, showed complications may be severe. Endogenous MRSA endophthalmitis can result in significant visual loss. In one series of 32 patients with MRSA endophthalmitis, only 36% of those with MRSA infections achieved visual acuity greater than 20/400 at three-month follow-up.[13] Retinal detachment is also common.[14] Goals should include early ophthalmologic evaluation and directed antibiotic treatment.

Standard therapy of MRSA endophthalmitis has not been defined. While the most clinical experience with MRSA endophthalmitis lies with intravitreal vancomycin, acceptable intravitreal concentrations have been demonstrated with systemic vancomycin, fluoroquinolones, daptomycin, and linezolid making these potential treatment options.[15,16] It is unclear if intravitreal antibiotics of these classes provide additional benefit to systemic therapy. Appropriate number and interval between intravitreal injections is undefined. Retinal toxicity also may limit antibiotic usage. Further studies are required.

Table 1. Reported cases of CA-MRSA endogenous endophthalmitis.

	Case	Age/ Sex	Proven CA-MRSA*	Suspected CA-MRSA**	Possible CA-MRSA***	IV Treatment	Vitreal Treatment	Visual Acuity
Our series	1	26/M		x		Vancomycin	Vancomycin/Clindamycin	20/100
	2	53/F		x		Vancomycin, then Daptomycin and Rifampin	Vancomycin	20/20
Blomquist[2]	1	40/M		x		Not Reported	Vancomycin/Ceftazidime	Not Reported
	2	43/M		x		Vancomycin /Gentamicin	Enucleation	Not Reported
Miller et al.[9]	1	45/M	x			Not Reported	Not Reported	Not Reported
Ruter et al.[10]	1	39/M	x			Vancomycin, Rifampin, Gentamicin	Vancomycin	20/40
	2	43/M	x			Vancomycin	Vancomycin	20/30
	3	39/M	x			Vancomycin	Vancomycin	20/30
	4	61/M	x			Vancomycin	Vancomycin, then Enucleation	No LP
Schiedler et al.[8]	1	75/F			x	Vancomycin	Vancomycin/Ceftazidime	20/25
Ho et al.[14]	1	66/M			x	Vancomycin	Vancomycin/Ceftazidime	20/150
	2	38/F			x	Vancomycin	Vitrectomy	HM 2 Feet
	3	74/M		x		Vancomycin	None	CF 2 Feet
	4	77/M			x	Vancomycin	Vancomycin/Ceftazidime	20/100
	5	49/F			x	Vancomycin	Vitrectomy	Enucleation
	6	18/M		x		Vancomycin	Vancomycin/Ceftazidime	Left - HM 2 Feet; Right - LP
	7	85/M			x	Vancomycin	Vancomycin/Ceftazidime	20/40
Leibovitch et al.[17]	1	37/F			x	Not Reported	Not Reported	No LP
Ness et al.[12]	1	F			x	Not Reported	Not Reported	Not Reported
	2	M			x	Not Reported	Not Reported	Not Reported

*Genetic testing performed. **No genetic testing available, however, absence of HA-MRSA risk factors, community-acquired infection known. ***Not enough provided information to exclude possibility of CA-MRSA.
LP = light perception, HM = hand motion, CF= count fingers.

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