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Case Report

DISSEMINATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* OSTEOMYELITIS AND ENDOCARDITIS IN A PREMATURE INFANT

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ABSTRACT

Although premature neonates are at increased risk for invasive infections, we questioned whether there were other documented cases of combined osteomyelitis, septic arthritis, and infective endocarditis (IE) due to Methicillin-resistant *Staphylococcus aureus* (MRSA) and whether adequate modalities of diagnosing osteomyelitis in neonates exist. Such severe complications of disseminated infection are rarely described in the literature before two weeks of life. To our knowledge this is the first case of disseminated MRSA with all three complications of bone and joint infections and IE described in a premature neonate. Unlike most neonates described, this patient's presentation is consistent with typical presentations of osteomyelitis in older children. This case demonstrates that dissemination of MRSA in neonates may involve multiple sites simultaneously. It also reminds us that bone and joint infections in infants have varied presentations, in this case similar to that seen in older children and adults. More studies are needed to study the varied presentations and diagnosis of disseminated MRSA infections in infants to prevent significant morbidity and mortality.

Key words: MRSA, Neonate, Osteomyelitis, Septic arthritis, Endocarditis.

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INTRODUCTION

MRSA infections in neonatal intensive care units (NICUs) have increased in prevalence throughout the world, and by 308% between 1995 and 2004 in the United States. MRSA infections may lead to osteomyelitis or septic arthritis which is rare, especially in the first month of life [1]. Osteomyelitis occurs at a rate of 1-3 cases per 1000 infants in the NICU. Neonates are at increased risk due to invasive procedures. Osteomyelitis often presents as vague symptoms in neonates such as bradycardia or poor feeding. More commonly it is clinically silent and may be missed due to poorly developed immune systems [2]. Inflammatory markers that are elevated in osteomyelitis in older children may not be elevated in neonates. In addition, imaging studies may not reveal osteomyelitis due to lack of subcutaneous fat and poor definition of fascial planes. In contrast, our patient had an elevated CRP of 207 mg/L and magnetic resonance imaging (MRI) findings of osteomyelitis.

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CASE REPORT

An 1149 gram male neonate was born at 30

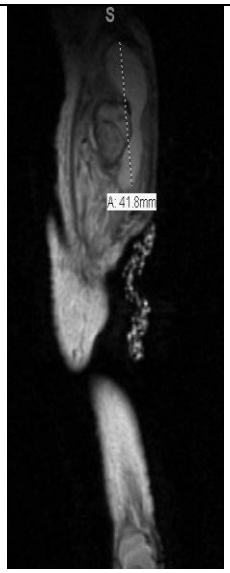
weeks gestational age by C-section due to fetal distress and breech presentation. He required continuous positive airway pressure and intubation in the delivery room. Pregnancy was complicated by placental abruption. On admission to the NICU he was negative for MRSA screening, but six days later he tested positive for MRSA in the nares. On day of life 8 he developed yellow drainage in the right foot over a previous intravenous (IV) site, initially treated with mupirocin ointment. By day 11 he developed edema and erythema of the left leg and swelling of multiple joints. X-rays revealed possible osteomyelitis and ultrasound of the knee showed significant fluid. C-reactive protein (CRP) was 207 mg/L and white blood cell count was 11.2 x 10^3/microlitres with 45% bands. The infant was started on IV piperacillin-tazobactam, vancomycin and rifampin. He had several apneic and bradycardic spells requiring reintubation. Blood cultures drawn on day 11 grew gram-positive cocci in less than 24 hours, later identified as MRSA. Echocardiogram showed a patent ductusarteriosus, patent foramen ovale, and an abnormal mass on the anterior leaflet of the mitral valve concerning for endocarditis. On day 13 MRIrevealed multiple fluid collections in the left proximal medial thigh, left buttocks, left anterior knee, right buttocks and thigh, and osteomyelitis of the left distal femur and proximal tibia (Fig 1). The next day he underwent irrigation and debridement of bilateral legs, thighs, left groin, left buttock, bilateral aspiration of knees, and aspiration of the left femur. All locations debrided yieldedpurulent material which grew MRSA. He later developed erythema and edema in the left elbow with a pustule at a prior IV site. Pus was drained from the left antecubital region. The infant underwent additional incision and drainage of the left knee on day 20 due to increasing edema and erythema, followed by another aspiration of the left knee due to increased swelling but these cultures remained negative.

Hospital Course

The patient was treated with 42 days of IV vancomycin, 10 days of rifampin, and 7 days of gentamicin. After multiple positive blood cultures, his blood cultures became sterile on days 19 and 20. CRP levels slowly normalized and he received physical therapy. X-ray of the left knee obtained on day 39 due to left leg edema revealed callus with new bone formation and some demineralization (Fig 2). Repeat echocardiogram showed continued vegetation on mitral leaflet consistent with endocarditis. By day 75 echocardiogram revealed a calcified pedunculated mass that no longer protruded into the left atrium but was adherent to the mitral valve posterior leaflet, with no change in size. On day 82 x-ray of the left lower extremity showed callus formation, healing bone, and normalizing bone density.

On follow up he had leg length discrepancy with a shorter left leg. Quantitative immunoglobulins and neutrophil oxidative burst testing were normal. At 4 months after discharge he continued to have some motor delays and leg length discrepancy.

Fig 1. Magnetic resonance imaging of the bilateral lower extremities obtained on day 13. (A) lateral left, large gluteal intramuscular fluid collection, (B) lateral right thigh intramuscular fluid collection, (C) right pretibial fluid collection.



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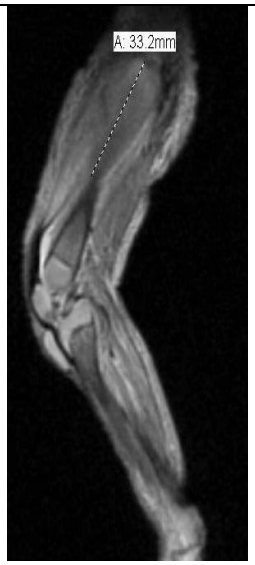

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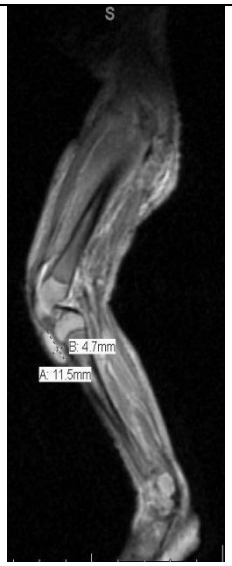

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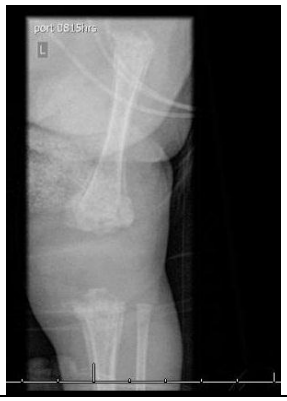
Fig 2. X-ray of the left lower extremity on day 39 shows osteomyelitis with healing: fragmentation, sclerosis, irregularity of the distal metaphysis, subperiosteal new bone formation on the femur shaft, and bone demineralization.



DISCUSSION

Staphylococcus aureus causes the majority of musculoskeletal infections in children of all ages, including neonates [3]. In a retrospective study conducted from 1982-1990 on osteomyelitis in infants less than 4 months of age, *Staphylococcus aureus* was the etiologic agent in 76% [4].In terms of osteomyelitis, MRSA is more prevalent in preterm infants.Though it is rare in neonates at a rate of 1-3 per 1000 infants, MRSA may cause up to 50% of *S. aureus* infections seen in the hospital [2-6]. MRSA causes more severe infections, more complications, multiple sites of infection, and increased need for surgical intervention [3,7-9].

The first case of MRSA was isolated in 1961 and the first case in a neonate about 20 years later. MRSA has since been increasing in prevalence [1,3,9,10]. MRSA colonization and infections in NICUs have dramatically increased worldwide, with the current rates of colonization in the USA varying between 0.6-8.4%.MRSA may be community or hospital acquired. Transmission may occur horizontally from hospital workers or siblings, but can be due to vertical transmission from the mother. Neonates may become colonized with MRSA shortly after birth, most commonly at sites such as the umbilical cord, nares, skin, and gastrointestinal tract. Once colonized, infants may become infected with MRSA anywhere in the body [1].

Neonates are at increased risk for MRSA infection due to prematurity, low birth weight, procedures performed, or devices implanted [1,2].There is a strong correlation between osteomyelitis and invasive procedures, exposure to illness, or personal illness [5]. Osteomyelitis in preterm infants is commonly associated with intravascular devices of any kind, and can even be a complication of heel sticks [4,6].These procedures are often necessary for survival of the neonate, however, such as endotracheal intubation, central or peripheral inserted catheters, surgery, and parenteral or enteral forms of feeding [1].Our patient had increased risk of infection due to invasive procedures (evident by pus at the site of previous IV catheters), prematurity, and low birth weight [1,5].

Though neonates are at increased risk of osteomyelitis due to procedures, it is still rare and can be difficult to diagnose, as it presents differently than in older children [4,5,11]. Osteomyelitis in infants is challenging to diagnose due to generalized symptoms and since laboratory results may be normal [4,5,8,11]. Older children usually present focally as there is a separate blood supply between the epiphyses and metaphyses [4,11]. Typical presentation in neonates is either localized signs such as tenderness, swelling, and decreased movement of a limb, or generalized symptoms such as irritability, feeding intolerance, lethargy, episodes of bradycardia, apnea, and desaturation. Fever is an unreliable sign for osteomyelitis [4,5].The immaturity of the immune system in neonates, especially those born at less than 35 weeks gestation, compared to older children contributes to lack of obvious signs [6,11].This can contribute to varying lab values. White blood cell counts and other inflammatory markers are often not elevated in neonates with osteomyelitis [4,5,11].Similar to the literature our patient had generalized symptoms and required reintubation, but did not have fever. He also had focal findings of pus at the site of an IV catheter and erythema and edema of the extremities. In contrast to the literature our patient did have an elevated CRP.

Since infants typically have a vague presentation and unreliable labs, imaging studies are helpful. Radiography is one of the first investigative tools when osteomyelitis or septic arthritis is suspected, but can also be unreliable as it may be

difficult to detect soft tissue swelling and radiographs have low sensitivity [4,8,11]. Soft tissue swelling can be seen about 48 hours after the onset of osteomyelitis but bony destruction may not be seen until one-third of the bony matrix is involved.Ultrasound can be helpful in determining joint effusions and subperiosteal collections, but is operator dependent and may look normal [11].MRI is usually more sensitive for diagnosing osteomyelitis and determining the extent of disease [8,11]. In our case the infant had signs of infection on x-ray concerning for osteomyelitis, multiple joint effusions on ultrasound, and MRI revealed osteomyelitis of multiple sites in the lower extremities.

In neonates the most common location of involvement of osteomyelitis are the metaphyses and epiphyseal plates due to being highly vascular and having slow blood flow. This is due to the vascularization of the neonate and the hematogenous spread of MRSA [4,5,10,11]. It is common for blood culture and joint culture to correlate, confirming the hematogenous spread [4,6-8]. Hematogenous spread leads to increased risk for other body parts to be involved. For example, in one study of osteomyelitis as a primary diagnosis, 76% had septic arthritis, and in another study with septic arthritis as the primary diagnosis, 30% had osteomyelitis [10,11]. In a study of children with *S. aureus* bacteremia the majority of children identified with deep focus of infection had osteomyelitis. Other deep-seated infections identified were abscesses and endocarditis. Endocarditis was rare and associated with congenital heart disease [12]. In our patient it is likely that hematogenous spread led to multiple different locations of infection within one patient, confirmed via positive blood cultures, wound cultures, and imaging studies. In a review of OVID and PUBMED from 1974-2016 using the words neonate and MRSA combined with septic arthritis, osteomyelitis, and endocarditis, no studies or case reports were found with the above three infectious complications. There were no results with the elimination of MRSA from the search either. This case is atypical due to the severity and multifocal nature of bone and joint infections and widespread dissemination of MRSA in a neonate.

Due to the vague presentation and unreliable diagnostic tools for osteomyelitis and septic arthritis in neonates, they often require surgical intervention for treatment [9].In septic arthritis this involves aspiration guided by ultrasound [11].In osteomyelitis treatment consists of antibiotics and possible surgical intervention, sometimes more than once when accompanied by septic arthritis as seen in this case [8,11].

CONCLUSION

MRSA infection in neonates may involve many different infectious sites in the body, resulting in serious complications [2,4,9]. Neonates are at greater risk of infection due to size, prematurity, and procedures performed [2,3,12]. To our knowledge this is the only reported case of disseminated MRSA infection in an infant with all three presentations of septic arthritis, osteomyelitis, and endocarditis. Unlike most of the neonates described in the literature, this patient's presentation is consistent with typical presentations of osteomyelitis seen in older children. This case demonstrates that dissemination of MRSA in neonates may involve multiple sites at the same time, such as the heart, bones and joints simultaneously. It also reminds us that bone and joint infections in infants may have varied presentations, in this case similar to that seen in older children and adults. More studies are needed to study the varied presentations and diagnosis of disseminated MRSA infections in infants to prevent significant morbidity and mortality.

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None

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human subjects or animals performed by any of the authors.

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