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Short Communication

Methicillin-Resistant *Staphylococcus aureus* Osteomyelitis and Septic Arthritis in Neonates: Diagnosis and Management

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SUMMARY: Acute osteomyelitis (AO) in neonates, although rare, represents a diagnostic and therapeutic challenge. A high index of suspicion is necessary to make an early diagnosis, and the observation of clinical signs is crucial. The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging problem in pediatrics. In neonates, MRSA infections can cause a wide spectrum of diseases including bone and joint infections. We report two cases of AO in full-term neonates, with no risk factors, due to MRSA.

Acute osteomyelitis (AO) is a relatively rare disorder in the neonatal period, with considerable morbidity and mortality. Concomitant septic arthritis (SA) is a frequent complication of AO and is associated with long-term consequences. In the first 4 weeks of life the incidence of AO ranges from 1 to 3 per 1,000 admissions (1). Management of the condition remains a significant challenge in pediatric intensive care medicine, as early recognition and prompt institution of therapy are essential for a successful outcome (2).

AO is most often reported to be due to *Staphylococcus aureus* and, less often, to group B *Streptococcus* spp. and Gram-negative organisms such as *Escherichia coli* and *Klebsiella pneumoniae* (3). *S. aureus* is a prototypic bacterial pathogen with a long history of causing both acute and chronic infections in humans through development of many virulent or drug-resistant strains, especially methicillin-resistant *S. aureus* (MRSA) (4). In this report we are presenting two cases of AO due to MRSA complicated by SA in otherwise healthy full-term neonates, with no risk factors.

Case 1 was a 28-day-old, full-term male infant admitted to our neonatal intensive care unit (NICU) because of a 5-day history of localized swelling on the left lateral chest wall, swelling of his left knee and poor feeding during the last 12 h. Physical examination on admission revealed an area of erythematous swelling (2 to 2 cm) on the left side of the thoracic chest wall, on the anterior aschellar thoracic line, and swelling, erythema and warmth in the left knee with functional impairment. The rest of the physical examination was normal. The laboratory results revealed the following: white blood count, 33,700 $\times$ 10^3/mm^3 (with an absolute neutrofil count of 12,050$\times$$10^3$/mm^3); erythrocyte sedimentation rate, 82 mm/h; C-reactive protein, 8 mg/L; serum calcium, 10 mg/dl; phosphorus, 6.7 mg/dl; and alkaline phosphatase, 251 U/L.

X-rays revealed soft tissue swelling and osteolytic lesions in the 10th rib and in the distal metaphysis of the left femur with new bone formation (Fig. 1). Ultrasound revealed edema of the soft tissues. On the basis of the radiographic features of the lesions and multiple sites of involvement, a diagnosis of AO and SA was postulated. Antibiotic treatment with vancomycin and gentamicin was given intravenously for 10 days, after which time vancomycin alone was continued. The involved extremity was immobilized. Skeletal magnetic resonance imaging (MRI) confirmed the presence of AO and SA (Fig. 2). Surgical debridements to remove the pus and dead bone remnants were done at the age of 31 days. Biopsy findings confirmed our clinical suspicion. MRSA was isolated from both the blood and biopsy material culture. Antibiotic susceptibility testing for the isolates carried out by the broth dilution method according to Clinical and Laboratory Standards Institute (CLSI) recommendations confirmed MRSA (5).

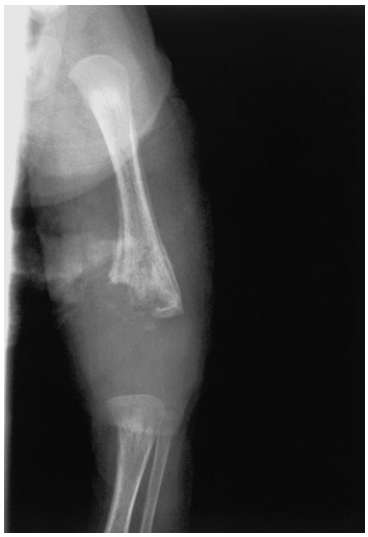

Fig. 1. Initial anterior x-ray of the left knee showing the bone destruction of the distal femoral metaphysis and the periosteal new bone formation along the metaphysis.

The strain was resistant to penicillin (MIC > 32 μg/ml) and oxacillin (MIC = 24 μg/ml) but sensitive to vancomycin (MIC = 1 μg/ml). Antibiotic therapy was continued for 6 weeks. No evidence of immunological abnormalities was found. A radiograph taken at the age of 6 months showed

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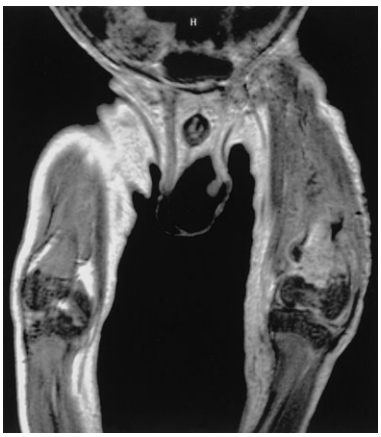

Fig. 2. Anterior T2 weighted image in the MRI examination of both limbs of the first neonate showing a diffuse abnormal bone marrow sign in the distal left femoral metaphysis with parostal abscess.

periosteal new bone formation, partial cortical bone remodeling and a remaining osteolytic lesion in the distal femoral metaphysis. At the 2 years follow-up, the child had a limp due to a 2-cm discrepancy in the left lower limb, flexion deformity of the left knee joint and ankylosis.

Case 2 was a 15-day-old, full-term female neonate admitted to our department because of swelling of the left lower limb. Physical examination showed a well-appearing, afebrile infant with swelling and limited motion of the left knee joint without any signs of systemic illness. Initial laboratory studies were normal. An X-ray of the left lower limb appeared normal. Ultrasound examination demonstrated edema of the soft tissue of the knee joint. Intravenous administration of vancomycin and gentamicin was initiated. Immobilization of the involved extremity was also performed. MRI examination was consistent with AO of the left tibia and concomitant SA of the knee joint. No other lesions were noted. The patient underwent surgery at the age of 21 days. Biopsy results were positive for AO. Blood and tissue cultures grew MRSA. Susceptibility to antimicrobial agents by the determination of the MICs using the broth dilution method advocated by CLSI showed that the strain was resistant to penicillin (MIC = 4 μg/ml) and oxacillin (MIC = 8 μg/ml) but sensitive to vancomycin (MIC = 0.5 μg/ml). Intravenous therapy at 10 days was changed to vancomycin alone and continued for 6 weeks. At 12 months of age, the infant has a full range of knee motion and shows no radiological evidence of growth disturbance.

AO and SA in neonates, although extremely rare, present a serious diagnostic and therapeutic challenge. Successful treatment depends on early recognition of the infection and rapid initiation of therapy in order to prevent permanent sequelae (6). However, the establishment of appropriate diagnostic and therapeutic strategies remains elusive, as only a few cases of AO in neonates have been reported.

In neonatal AO and SA, the clinical presentation differs when compared to presentation in older children and is usually unspecific, resulting in delayed diagnosis. There is a benign clinical onset in the majority of neonates with little or no evidence of infection. Presenting symptoms may be as vague as increased irritability or poor feeding. Local swelling and erythema on the region of infection may be the only useful clinical signs. Systemic manifestations of sepsis are rarely present (2,3). Multifocal involvement is commonly found in neonates with AO, as in the first of our cases.

The dissemination of neonatal osteomyelitis can be in the majority of cases primarily hematogenous due to slow blood flow in the capillary bed of ossifying tissue, or secondarily by extension from an adjacent focal infection, or direct inoculation of the bone following penetrating trauma or surgery. Risk factors for neonatal AO are related to the risk of bacteremia. Invasive procedures such as umbilical artery catheterization, prematurity and respiratory distress syndrome have been found to be predisposing risk factors (2,3). In neither of our reported cases was there any history of medical or surgical procedures or other risk factors predisposing the patients to AO and SA. We suspect that hematogenous spreading of infection may have been the mechanism that led to AO in our cases.

S. aureus is a major cause of AO in neonates. Methicillin resistance among *S. aureus* isolates has become an emerging problem in pediatrics. The prevalence of MRSA varies among countries as well as among hospitals. In Greece, the methicillin-resistance rate gradually increased from 32% in 1986 to 41% in 1997 and remained at 39.3% in 2001 (7). However, studies of the prevalence of MRSA among neonates in Greece are rare. In our NICU, over a period of 5 years, from 2000 to 2005, nine neonates with positive blood cultures for *S. aureus* were identified, of which four had MRSA strains (44.4%), including the two reported cases. MRSA strains are typically viewed as hospital pathogens, but this image is now changing. Outbreaks of community-acquired MRSA infections have recently been described worldwide, mainly in previously healthy children with no recognizable risk factors (4).

In neonates, MRSA can cause potentially serious infections including AO and SA (8). Data for MRSA transmission among neonates are limited. Recent reports have shown that MRSA can spread via nosocomial, familial and mother-to-infant transmission. The main mode of nosocomial transmission of MRSA in the NICU is by its spreading from one colonized neonate to another on the hands of hospital personnel. Along with healthcare workers who carry MRSA, the environment may be a primary reservoir for infection. Studies have also shown that infants may acquire MRSA from their mother's contaminated breast milk or by skin-to-skin contact (8). However, there is little in the literature describing the transmission from MRSA culture-positive breast milk in infants. None of the mothers of the infants reported here showed signs of mastitis or skin lesions.

The diagnosis of AO in neonates is confirmed by clinical presentation of signs and symptoms suggestive of a bone infection, by the presence of a positive blood or bone aspirate culture and by radiographical evidence (3). White blood cell counts, C-reactive protein and erythrocyte sedimentation rate are poor parameters (2). Also, early signs of bone destruction may not be evident by x-ray until 7 to 14 days after the onset of symptoms; so roentgenographic studies may be insufficient to reveal abnormalities at initial evaluation (3). Radionuclide or radioisotopic bone scanning is more sensitive than plain radiography in detecting early bone involvement. However, false negative and false positive cases of AO in neonates have been documented from bone scans (3,9). Ultrasonography may be helpful in cases of neonatal AO by identifying the presence of purulent fluid collection or an abscess overlying the affected bone (6). However, findings may not be specific, and there are only a few reports supporting its use in the early detection of OA. Computed tomography and MRI seem to be equally successful in revealing AO early. MRI examina-

tions have been shown to be more sensitive and specific, delineating the extent of bone and soft tissue involvement (9).

Our patients' MRI images were indicative of AO and concomitant SA. Our reported cases support the need of additional imaging workup in relation to suspicious clinical symptoms. In the first of our cases, the parents failed to seek medical attention until signs of skeletal infection in the second involved site occurred, due to the insidiousness of the initial symptoms. In the second case, x-rays on admission failed to detect the bone lesion, which was revealed by MRI.

The goal of treatment of neonatal AO and SA is eradication of bone and intraarticular infection, and treatment should be initiated as soon as possible. Treatment involves broad spectrum and specific antimicrobial therapy, immobilization of the involved extremity, pain management and possibly surgical intervention. The optimal antibiotic regimen and duration of therapy has not been defined and should be individualized for each case. Initial antibiotic therapy should cover the most common causative pathogens and can be altered later based on microbiological test results. MRSA should be considered when empirical antibiotic therapy is selected for such infections, especially in areas with a high incidence of MRSA strains. MRSA strains tend to be resistant to all beta-lactam agents (e.g., penicillins and cephalosporins). Therefore, vancomycin remains a first-line therapy for severe infections potentially caused by MRSA (10). It may require as long as 6 weeks of antibiotic treatment for infection to resolve (3). Surgical intervention may become necessary if there is evidence of abscess formation as well as in the cases of inadequate clinical response after 48 h of antimicrobial therapy (3).

In conclusion, primary osteomyelitis and SA in full-term infants, although rare, is an emergency situation and should be included in the differential diagnosis of neonates with localized soft tissue swelling, as well as of neonates with non-specific signs and symptoms of bacteremia. Once a diagnosis is suspected, findings from imaging studies, accompanied by blood and tissue cultures are the most useful diagnostic tests and are necessary for appropriate diagnosis. To avoid treatment delays, MRSA should be kept in mind even in cases of AO involving otherwise healthy, full-term newborns.

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