

## CASE REPORT

# Immunological profile of neonatal osteomyelitis cases

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## Abstract

Osteomyelitis in childhood is often hematogenous and neonates are generally prone to bacteremia because of immature immunity. Neonatal osteomyelitis occurs even in the absence of apparent immunological or perinatal abnormalities.

## KEYWORDS

immunology, necrotic bone, neonate, osteomyelitis, *Staphylococcus aureus*

## 1 | INTRODUCTION

Osteomyelitis in the neonatal period is a rare invasive infection and often causes permanent skeletal deformities or growth disturbance. Previous studies have shown that prematurity, pregnancy complications, and antecedent infections are risk factors for neonatal osteomyelitis.<sup>1</sup> However, little is known about immunological profiles in neonatal patients with osteomyelitis. We report neonatal cases of osteomyelitis without apparent immunological abnormalities.

## 2 | CASE PRESENTATION

A 24-day-old female neonate was referred to our hospital with swelling in the left leg. She was born by spontaneous

vaginal delivery at 40 weeks of gestation with a birth weight of 3392 g. The maternal vaginal culture was positive for group B *Streptococcus* (GBS; *Streptococcus agalactiae*) in the third trimester, and her mother had received a prophylactic antibiotic at delivery. There were no perinatal complications, including birth trauma or antecedent infections. She did not receive any invasive medical interventions, such as catheterization or parenteral nutrition. Her umbilical cord fell off on day 15 after birth. She had no significant family history of recurrent or intractable infections. On day 21 after birth, her parents noticed that she cried during diaper change. On day 23 after birth, her left leg was swollen and she was referred to our hospital. On admission, she had mild fever with left leg swelling and erythema. She had no history of trauma. Laboratory data showed an elevation of inflammatory markers, including blood leukocyte count 22 140/ $\mu$ L, absolute

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neutrophil count 15 276/ $\mu$ L, C-reactive protein 4.5 mg/dL, and erythrocyte sedimentation rate 31 mm/h. A lower leg plain radiograph revealed osteolytic cortex and hyperlucency at the left proximal tibia. Osteomyelitis in the left proximal tibia was diagnosed, and intravenous cefotaxime was initiated. On hospital day 4, magnetic resonance imaging (MRI) indicated an intramedullary ring-enhanced lesion in her left tibia. On day 5, surgical debridement of necrotic bone and pus drainage were performed. The pus culture was positive for methicillin-susceptible *Staphylococcus aureus*, whereas three sets of blood cultures on admission were all negative. Cefotaxime was switched to cefazolin based on the culture result. Her clinical symptoms and inflammation markers improved gradually. On day 52, follow-up MRI showed no enhanced intramedullary lesions, and she was discharged on day 57 of admission without complications. Antibiotic treatment was completed with 6 weeks of cefazolin, followed by 5 months of oral cephalexin. No adverse event, including neutropenia, renal, or liver dysfunction, was observed during the treatment. The time from onset to detection of osteomyelitis was short in this case; however, we clinically diagnosed chronic osteomyelitis because sequestrum was observed intraoperatively and the pathological findings of the scraped tissues showed necrotic bone trabeculae. We decided to administer a 6-month treatment for chronic osteomyelitis. Permanent disabilities, such as growth arrest or limb length discrepancy, have not been observed during 1.5 years of observation.

Immunological studies exhibited no abnormal findings in lymphocyte subsets, neutrophil reactive oxygen species, immunoglobulin levels, or complement components. Normal thymus and spleen were confirmed by chest radiograph and abdominal ultrasonogram. We retrospectively reviewed neonatal patients with osteomyelitis at our institution between 2002 and 2019 and found two additional cases. All three patients received immunological assessments, but no apparent immunological abnormality was detected (Table 1).

### 3 | DISCUSSION

Previous studies have described risk factors for neonatal osteomyelitis.<sup>1</sup> Pregnancy complications occurred in half of the neonatal osteomyelitis patients. Prematurity, invasive medical procedures, prolonged nosocomial exposures, and antecedent infections were associated with this disease.<sup>1</sup> Although immunological abnormalities are well-known causes of invasive bacterial infections, little information is available on the relationship between immunological abnormalities and neonatal osteomyelitis. To our knowledge, among immunodeficiency diseases, only chronic granulomatous disease has been reported in a case of neonatal

**TABLE 1** Clinical characteristics and laboratory data of neonatal patients with osteomyelitis in our institution

Case	1 (this case)	2	3
Age (d)	21	18	27
Sex	Female	Male	Male
Location	Tibia	Humerus	Radius
Bacterial culture	MSSA	GBS	MSSA
Blood culture	Negative	Positive	Positive
Surgery	Yes	Yes	No
Gestational age	40 wk 4 d	40 wk 4 d	39 wk 1 d
Birth weight (g)	3392	3375	2500
Pregnancy or perinatal complications	No	No	No
Thymus	Normal	Normal	Normal
Spleen	Normal	Normal	Normal
IgG (mg/dL)	682	1327	561
IgA (mg/dL)	23	48	<23
IgE (IU/mL)	3.0	NA	NA
IgM (mg/dL)	64	94	25
C3 (mg/dL)	68	NA	126
C4 (mg/dL)	9	NA	26
CH50 (mg/dL)	49.2	56.2	45.9
DHR-123-positive neutrophils (%)	93	95	95
WBC ( $\mu$ L)	13 320	8670	7850
Neutrophils ( $\mu$ L)	2944	1864	1727
Lymphocytes ( $\mu$ L)	8964	5150	5809
T cells (%)	77	61	70
CD4 <sup>+</sup> T cells (%)	60	67	53
CD8 <sup>+</sup> T cells (%)	35	33	44
B cells (%)	17	28	19

Abbreviations: DHR, dihydrorhodamine; GBS, group B *streptococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NA, not available; WBC, white blood cells.

osteomyelitis.<sup>2,3</sup> In this study, all three patients with neonatal osteomyelitis had no obvious immunological abnormalities, family history of immunodeficiency, or known risk factors. In case 3, the IgA value at 29 days old was low (<23 mg/dL), but increased to the normal range (39 mg/dL) at 4 months old. Several immunodeficiency conditions, such as interleukin-1 receptor-associated kinase-4 and myeloid differentiation factor 88 deficiencies, often cause invasive gram-positive bacterial infections.<sup>4</sup> Although genetic analysis was not performed and it is difficult to deny the existence of these conditions, we believe the possibility is low because all three cases had no recurrences during months to years of observation. Newborns have fetal vessels that penetrate the

cartilaginous epiphyseal plate and an extremely rich blood supply in the epiphysis. Rich and sluggish blood flow in the metaphysis provides favorable conditions for the growth of pathogens,<sup>1,5</sup> suggesting that they are structurally prone to osteomyelitis regardless of immunological abnormalities. In addition, high risk of bacteremia is known during the neonatal period because of immature immune systems, including low neutrophil functions and low immunoglobulin concentrations.<sup>6</sup> To our knowledge, there is no review to suggest that specific primary immunodeficiencies, except chronic granulomatous disease, are risk factors for osteomyelitis. Considering the fact that most neonatal osteomyelitis develops by hematogenous dissemination,<sup>1</sup> osteomyelitis might develop during the neonatal period without specific primary immunodeficiency.

## 4 | CONCLUSIONS

In all three neonatal cases of osteomyelitis at our institution between 2002 and 2019, no apparent immunological abnormality was detected. Further studies are required to clarify the association between neonatal osteomyelitis and immunodeficiency.

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## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

IS and HI: contributed to the conception and wrote the manuscript; TM, TI, KS, and AI: reviewed the manuscript and supervised the whole study process. All authors reviewed and approved the final manuscript.

## ETHICAL APPROVAL

Written informed consent in accordance with the Declaration of Helsinki was obtained from the patient's parents, in addition to consent for publication.

## DATA AVAILABILITY STATEMENT

All data that support the findings of this study are available from the corresponding author upon reasonable request.

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