Salmonella Osteomyelitis Due to *IRAK-4* Deficiency

To the Editor:

Interleukin-1 receptor (IL-1R)-associated kinase-4 (*IRAK-4*) plays an important role in immunity. *IRAK-4* deficiency is an autosomal recessive abnormality and is associated with systemic and peripheral pyogenic bacterial disorders.[1] It is shown in animal models that *IRAK-4* -deficient animals are more sensitive to viral and bacterial infections.[2] *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* are the most common infectious agents.[3,4]

Acute osteomyelitis is uncommon in pediatric age. *Staphylococcus aureus* is isolated for more than 50% of cases. *Escherichia coli*, *Streptococcus*, *Klebsiella*, and *Proteus* are other pathogens.[5] Generally, salmonella rarely causes osteomyelitis in pediatric age.[6] We report an extremely rare *IRAK-4* deficient case of osteomyelitis caused by *Salmonella*.

An 11-month-old male patient, who was brought to our outpatient clinic due to recurrent infections and whose parents were found to be first-degree relatives, had a history of death due to a resistant lung infection of his brother. Immunoglobulins were at an agammaglobulinemia level and the amount of CD19 and CD20 was $<3\%$. Homozygous p.K115E (c.343A > G) missense variant was detected in the *IRAK-4* gene in the whole exome sequence analysis and IVIG treatment was started every 3 weeks. The patient was admitted to our clinic again at the age of 3.5 years old with complaints of swelling and pain in the right ankle. It was found out in his anamnesis that he fell from a height about 3 months ago. Physical examination revealed swelling and increased heat in the ankle. Infectious markers were found to be very slightly elevated on examination (WBC: 11.800 mm^3/L, sedimentation rate: 22 mm/h, CRP: 6.4 mg/L, PRC: 0.39 ng/mL, IL-6: 9.36 pg/mL). The radiograph showed a lytic lesion on the lower-end epiphysis of the right tibia. Bone biopsy was performed in terms of differential diagnoses of infection and other neoplasms from the patient whose hyperintense signal increases were detected in the knowledge that there was a lytic lesion on MRI. Myofibroblastic cell proliferation accompanied by polymorphonuclear cells, lymphocytes, macrophages, and plasmocytes intertwined with sequestered bone fragments was observed in the biopsy of the distal metaphyseal bone of the right tibia. There was a growth of Salmonella Group B bacteria in the tissue biopsy material. The patient started antibiotic therapy with a preliminary diagnosis of chronic osteomyelitis. After 8 weeks of intravenous antibiotic therapy, there was no significant regression of the lesion, the abscess material was surgically drained, and the Salmonella Group B bacterium was reproduced in the tissue biopsy culture. According to the results of the culture antibiogram, broad-spectrum antibiotics were started. No pathologic involvement in other bone structures was observed in whole-body bone scintigraphy.

Interleukin-1 receptor-associated kinase-4 (*IRAK-4*), a member of the IRAK family, plays an important role during toll-like receptor and IL-1 receptor-mediated signaling. And has a pivotal role in the pathway that is involved in the early recognition of pathogens and the initiation of the cascade of the inflammatory response together with myeloid differentiation factor 88 (MyD88, a key cytosolic adapter molecule).[7]

IRAK-4 deficiency was first described in 2003 by Dr Picard on 3 children[1] then, the clinical characteristics and follow-up of 48 patients were documented by the same author in 2011.[3] The pathogens that cause invasive bacterial infection, which is most often isolated in *IRAK-4* deficiency are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*. *Staphylococcus aureus* is the most common infectious agent encountered in noninvasive bacterial infections.[7]

IRAK-4 -deficient cells may produce small amounts of IL-6. IL-6 is important for CRP induction and IL-1 and TLR agonists activate IL-6. Even in severe cases of infection, clinical and laboratory signs of inflammation do not appear rapidly, leading to a later and more difficult diagnosis.[8] In our patient with invasive bacterial infection, there was a slight increase in acute phase reactants and no fever.

While the prognosis of *IRAK-4* deficiency is quite poor in early childhood, significant improvement is observed in adolescence. In diagnosed patients, death after 8 years of age and invasive infection after 14 years of age have not yet been reported. The improvement in patients with age is thought to be related to the improvement in T-cell and B-cell responses, and it is predicted that antibody responses to bacterial antigens may progressively compensate for the defect in TIR immunity.[8] While our patient was examined for recurrent pulmonary infection at the age of 11 months, *IRAK-4* deficiency was detected in the whole exome analysis (*IRAK-4* homozygous variant c.343A > G [p. Lys115Glu]) performed with suspicion of primary immunodeficiency.

In 2018, Göktürk et al[9] it has been reported that they detected *Salmonella enteritis* in a patient they followed up with the diagnosis of *IRAK-4* deficiency. While *Salmonella* infection is rare in *IRAK-4* deficiency cases, enteritis is a common presentation in this infection.

In the childhood age group, salmonella osteomyelitis accounts for 0.45% of all cases of osteomyelitis. Infection is usually associated with immune deficiencies such as sickle cell disease, malignancies, and chronic granulomatous disease.[10] Although Salmonella osteomyelitis typically involves the diaphysis of the long bones and predominantly the femur and humerus, it can also occur in other bones, such as the lumbar spine, tibia, radius, and ulna. Adjusting antibiotic treatment according to culture results It is very important to regulate antibiotic treatment according to culture results in Salmonella osteomyelitis.[6] Salmonella osteomyelitis was detected at the distal tip of the tibia in our patient and cure was achieved at the end of 8 weeks with antibiotherapy according to the culture antibiogram result.

In *IRAK-4* deficiency, treatment of pyogenic bacteria includes prophylactic antibiotics and vaccination, and immunoglobulin replacement for

The authors declare no conflict of interest.
DOI: 10.1097/MPH.0000000000002887

supportive therapy is required for early life up to adolescence.[6] Patients should be administered conjugated and unconjugated *S. pneumoniae* and *Haemophilus influenzae* conjugated Neisseria meningitides vaccines for immunization 7. We are still performing immunoglobulin replacement every 3 weeks for our 4-year-old patient. Vaccines are administered according to the vaccination schedule and we are monitoring him for antibody positivity.

In conclusion, *IRAK-4* deficiency should be considered in the differential diagnosis of children with recurrent pyogenic infection, consanguineous marriage, and especially sibling death, even if the immunologic evaluations are not clear and there is no increase in inflammatory parameters. Although sinopulmonary infections and gram-positive bacteria are more common in these patients, salmonella can also be seen as a causative agent. *IRAK-4* deficiency is very rare in the community. While our patient was being followed up with this diagnosis, he presented with osteomyelitis, and salmonella was isolated as the causative agent. With this aspect, our case is the first case report in the literature, it is important and quite remarkable.

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Transforming Childhood AML Care in India

To the Editor:

According to a recent study using the 2011 census data in India, an estimated 52,366 children develop cancer annually, with leukemia contributing to 33% of cases.[1] Considering that ~15% of patients with leukemia have acute myeloid leukemia (AML), the annual incidence of childhood AML in India would be 2592, making it one of the most prevalent childhood cancers. However, there is substantial underreporting of the incidence and outcomes of childhood AML in India. Treatment of AML often requires prolonged hospitalizations and imposes a significant financial burden on families and health care institutions.[2] Given the constraints of resources, several government and private hospitals prioritize allocating scarce resources towards the treatment of more prevalent and treatable childhood cancers such as acute lymphoblastic leukemia (ALL).

In childhood AML treatment, a major concern is sepsis and its associated mortality. A recent systematic review of childhood AML in India highlighted the overall treatment-related mortality (TRM) to be as high as 23.2% (95% CI: 10.3%-35.9%) with induction mortality of 12% (95% CI: 6.4%-17.8%), in comparison to $<5\%$ observed in high-income countries (HICs).[3] The only prospective study on childhood AML from India reported an induction mortality rate of 17%.[4] A combination of host-dependent factors, including malnutrition and delayed presentation to hospital, along with environmental factors such as high incidence of multidrug resistant bacterial sepsis and invasive mold infections often contribute to high TRM. Although some aspects of AML care in India, such as trained medical personnel, critical care facilities and access to newer broad-spectrum antibiotics have improved over the past decade, certain challenges continue to persist, including lack of immediate access to beds for initiation of therapy, unmet requirements for blood products, inadequate pediatric transplant services in the public sectors and ongoing concerns regarding sepsis and malnutrition, as previously mentioned. These factors necessitate a unique approach to childhood AML treatment in contrast to strategies used in HICs. The SIOP Pediatric Oncology in Developing Countries (PODC) also recognizes this issue and suggests commencing AML therapy with low-dose, low-intensity therapy before proceeding to more intensive therapy.[5] In the realm of adult AML patients deemed unsuitable for intensive therapies, notable advancements have been achieved through the application of low-intensity chemotherapy, particularly when combined with novel agents. While it is presumed that children are better suited for intensive chemotherapy, this may not hold in the context of India and other LMICs, for reasons previously described.

The authors declare no conflict of interest.
DOI: 10.1097/MPH.0000000000002876