

## Two siblings with Majeed syndrome and neutropenia

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Majeed syndrome (MS) is a rare monogenic autoinflammatory disease characterized with early-onset chronic non-bacterial osteitis (CNO) and hematological features, particularly dyserythropoietic microcytic anemia.<sup>1</sup> It is associated with loss-of-function mutations of the LPIN2 gene on chromosome 18.<sup>2</sup> Neutropenia has been very rarely reported in patients with MS.<sup>1</sup> We herein report the first siblings of MS from Türkiye, both of whom had neutropenia.

A seven-year-old boy presented to the local pediatrician with recurrent joint and bone pain that started at the age of 18 months. There was no joint swelling, recurrent abdominal, chest pain, or fever in his past medical history, and there were no signs of uveitis and skin findings. His parents were first-degree cousins. Physical examination findings were normal. Acute phase reactants (APRs) were elevated at admission (erythrocyte sedimentation rate [ESR] 50 mm/h (0-20), and C-reactive protein [CRP] 3 mg/dL (0-0.5)). Neutropenia ( $1,100/\text{mm}^3$ ) was detected with mild anemia (11.1 g/dL), and normal white blood cell (WBC) count. The local pediatrician initially started him on colchicine treatment, suspecting familial Mediterranean

fever. However, MEFV gene variant analysis did not reveal any mutations. After two years of colchicine treatment, his family discontinued the drug, since there was no response. The whole-body musculoskeletal system magnetic resonance imaging (WBMSS-MRI) was normal.

The sister of Patient 1 who was 18 months old presented to our department with recurrent joint and bone pain, fatigue, and anemia during the last six months. There were no skin findings. Physical examination was unremarkable. The APRs were elevated at the time of admission (ESR 120 mm/h and CRP 14 mg/dL). Severe neutropenia ( $600/\text{mm}^3$ ) with normal WBC count, microcytic anemia (hemoglobin 8.6 mg/dL), and thrombocytosis ( $700 \times 10^3/\text{mm}^3$ ) were detected. The bone marrow assessment revealed a normocellular bone marrow with megaloblastic changes. The WBMSS-MRI demonstrated osteitis at the distal femur, proximal, and distal tibia, bilaterally (Figure 1).

A periodic fever gene panel analysis (including LPIN2, MEFV, MVK, NLRP3, PSTPIP1, and TNFRSF1Agenes) was performed with next-generation sequencing and homozygous mutation was detected in exon 4 of the LPIN2

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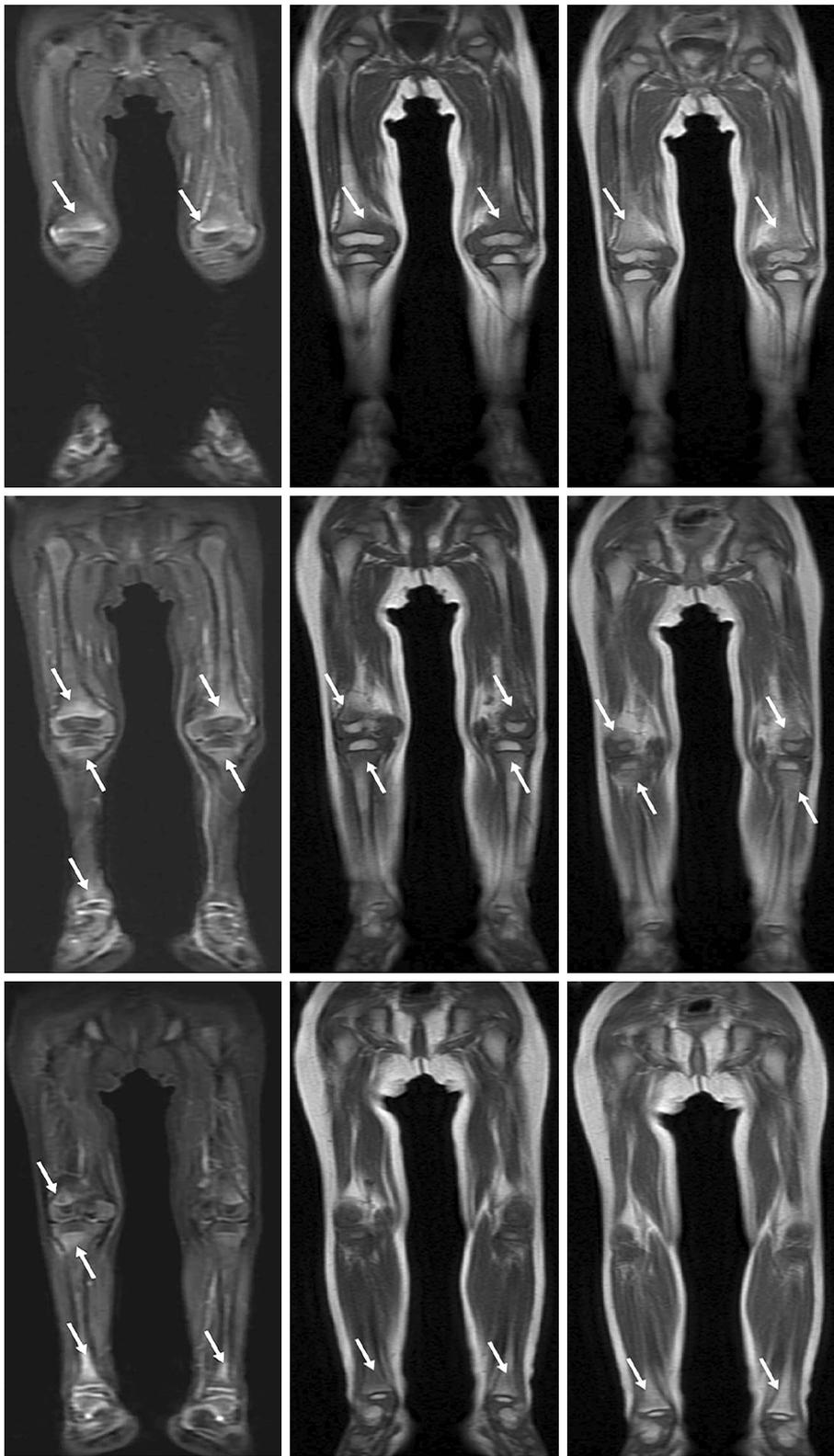
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**Figure 1.** (a-c) The whole-body magnetic resonance imaging showing bone marrow inflammation at both distal femur, proximal and distal tibia metaphysis (arrows) that are hyperintense on STIR, (d-f) hypointense on pre-contrast T1-weighted and (g-i) enhanced diffusely on post-contrast T1-weighted images consistent with osteitis.

(NM\_014646.2) gene; c.589C>T (p. Arg197Ter) in both patients. The homozygous c.589C>T (p.Arg197Ter) stop codon variant was submitted to ClinVar and interpreted as “pathogenic” on November 20<sup>th</sup>, 2017 with the accession number VCV000567272.1. Besides, this genetic alteration is observed in gnomAD database with an allele count of 4 (allele frequency:  $1.59 \times 10^{-5}$ ). Both their parents were carriers for this variant. The presence of the variant was confirmed with Sanger sequencing both in the siblings and their parents.

After the diagnosis of MS, anakinra was initiated at a dose of 2 mg/kg/day at the same time to siblings. They were remained free of symptoms with normal APRs on anakinra treatment. However, they still have neutropenia ( $900/\text{mm}^3$ ) four months after the diagnosis.

In a recent comprehensive review, there were only 24 genetically confirmed patients with MS reported to date.<sup>3</sup> Microcytic anemia was present in most of these patients ( $n=22$ ; 92%), while there was neutropenia in only three of them.<sup>3</sup> The LPIN2 mutation (R776Sfs\*66) was present in these three patients with neutropenia.<sup>4</sup> However, the mechanism for anemia or neutropenia remains unknown. Interleukin-1 receptor antagonists (IL-1RA) are also used in the treatment.<sup>5</sup> Although our patients responded to anakinra treatment with regards to bone and joint pain, neutropenia persisted. Our index patient (Patient 1) had elevated APRs and bone pain, despite absence of osteitis in his WB-MRI. It is an interesting findings, since most of the reported Majeed patients had CNO causing bone pain. In MS, the aberrant activation of NLRP3 inflammasome was demonstrated as a result of LPIN2 mutations although the link between NLRP3 overactivity and osteitis remains unknown.<sup>3</sup> This may be the reason of elevated APRs in our patient. Having said that, it is difficult to explain the presence of bone pain in this patient in the absence of MRI lesions in his bones.

In conclusion, we herein present the first cases with neutropenia who were homozygous for

p. Arg197\* mutation in LPIN2 gene. Anti-IL-1 drugs seems to be effective in treatment with MS regards to bone pain; however, neutropenia may persist. Increased data about the rare phenotypic variations of MS can improve our knowledge about the extent and course of the disease.

**Patient Consent for Publication:** A written informed consent was obtained from the parent of patients.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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