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Majeed Syndrome: Five Cases With Novel Mutations From Unrelated Families in India With a Review of Literature

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ABSTRACT. ***Objective.*** Majeed syndrome (MJS) is an autosomal recessive, systemic autoinflammatory disease (SAID) caused by biallelic loss-of-function variants in the *LPIN2* gene. It is characterized by early-onset chronic recurrent multifocal osteomyelitis (CRMO), dyserythropoietic anemia, and neutrophilic dermatosis. We analyzed a cohort of uncharacterized Indian patients for pathogenic variants in *LPIN2* and other genes associated with SAIDs.

Methods. We performed whole-exome sequencing (WES) for 1 patient and next-generation sequencing (NGS) targeted gene panel for SAIDs in 3 patients. One patient was a referral from neurology after clinical exome sequencing identified a novel variant in *LPIN2*. We reviewed the literature for all published studies of mutation-positive MJS patients and have summarized their clinical features and disease-causing variants.

Results. We describe the largest series of patients with MJS outside of the Middle East. All 5 patients are homozygous for novel, possibly pathogenic variants in the *LPIN2* gene. Two of these variants are missense substitutions, and 3 are predicted to alter transcript splicing and create a truncated protein. In addition to the classical features of CRMO and anemia, patients exhibited previously unreported features, including abdominal pain, recurrent diarrhea/ear discharge, and erythema nodosum.

Conclusion. Patients with MJS may present initially to different specialists, and thus it is important to create awareness in the medical community. In India, consanguinity is a common sociocultural factor in many ethnic communities and an abbreviated NGS gene panel for autoinflammatory diseases should include MJS. The unavailability of interleukin 1 inhibitors in some countries poses a treatment challenge.

Key Indexing Terms: CRMO, dyserythropoietic anemia, *LPIN2* mutation, Majeed syndrome, neutrophilic dermatosis

Chronic recurrent multifocal osteomyelitis (CRMO; Online Mendelian Inheritance in Man [OMIM]: 259680) is a common genetically heterogenous autoinflammatory disease of the bone, first described in 1972[1] with the typical mean age at diagnosis being 9 years.[2] Syndromic CRMO presents early in life and includes 3 monogenic recessively inherited conditions: Majeed syndrome (MJS), deficiency of interleukin (IL)-1 receptor antagonist, and CRMO related to the *FBLIM1* gene.[2]

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MJS (OMIM: 609628) was first described in 1989 as a rare, recessively inherited autoinflammatory disease.[3] It is characterized by CRMO, dyserythropoietic anemia in all, and neutrophilic dermatosis in < 25% of patients.[4] The anemia in MJS is microcytic, hypochromic, and can present at birth or during the first year of life with variable severity ranging from mild to severe, sometimes requiring blood transfusions.[4]

MJS is caused by homozygous or compound heterozygous loss-of-function (LoF) pathogenic variants in *LPIN2*, which encodes the lipin-2 protein, a phosphatidic acid phosphatase that has an important function in the control of lipid metabolism.[5] Lipin-2 is highly expressed in myeloid cells and plays a role in the regulation of innate immune responses as it downregulates proinflammatory signaling induced by saturated fatty acids in macrophages.[6,7,8] The *LPIN2* gene (GenBank NM_014646) is composed of 20 exons and is translated into the protein of 896 amino acid residues with several known domains (Figure 1). Disease-causal mutations are located over the entire protein with some predilection for clustering in a carboxyl terminal lipin (CLIP) domain. *LPIN2*-deficient monocyte-derived M2 macrophages promote osteoclastogenesis, shedding light on the mechanism for bony lesions.[9] The molecular mechanism of anemia is still unclear.

In this article, we describe the clinical, genetic, and radiological findings from 5 new unrelated Indian patients with

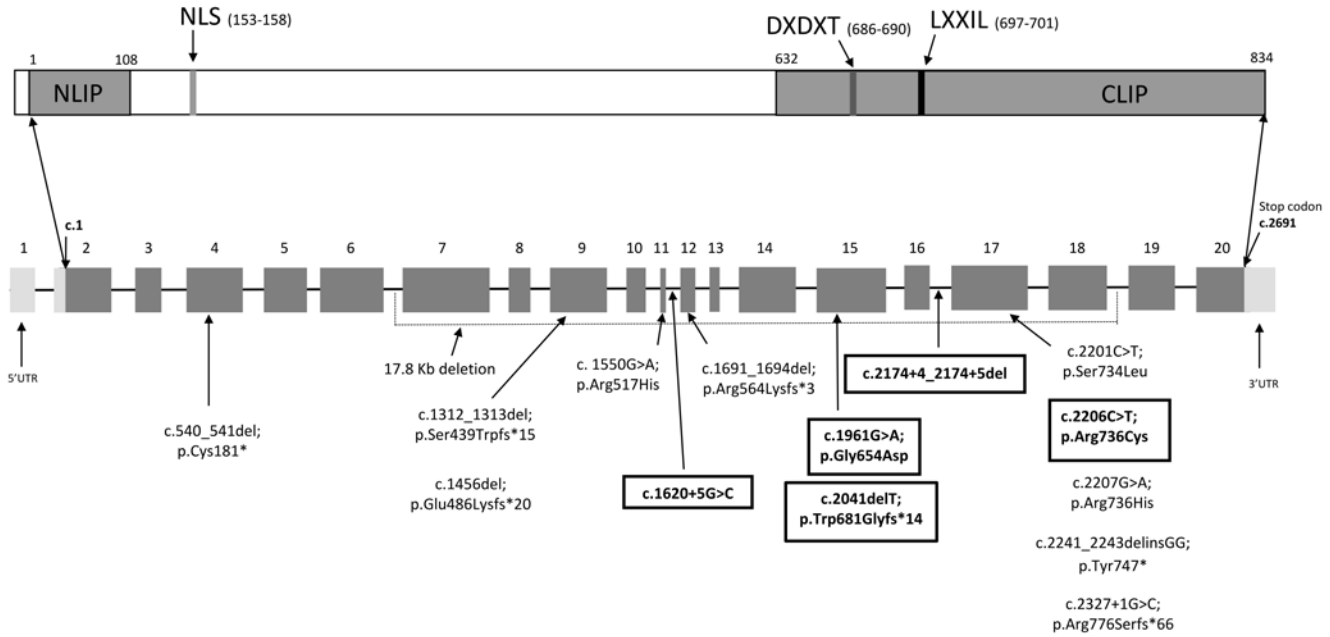

Figure 1. Domain structure and functional motifs of the lipin-2 protein and summary of pathogenic variants in the *LPIN2* gene. Mutations reported in literature are depicted; mutations identified in 5 patients with Majeed syndrome from India are in bold. CLIP: carboxyl terminal of lipin domain; DXDXT motif: required for phosphatidate phosphatase enzyme activity; LXXIL motif: transcriptional coactivator; NLIP: amino terminal of lipin domain; NLS: nuclear localization signal.

unreported, possibly pathogenic variants in *LPIN2,* and extend the MJS phenotypes. We also review literature for clinical features and disease-causing variants in all reported mutation-positive patients with MJS.

METHODS

Patient 1 was seen by a neurologist for delayed motor milestone and skin rash, and was referred to us after his clinical exome sequencing identified a homozygous, possibly pathogenic variant in *LPIN2*. Patient 2 was referred by a pediatrician, whereas the other 3 patients were part of our cohort of long-standing patients with undiagnosed systemic autoinflammatory diseases (SAIDs). Relevant ethics approval (number: 201901) and informed patient consent were obtained. We performed whole-exome sequencing (WES) in Patient 2 and next-generation sequencing (NGS) panel consisting of 53 genes associated with SAIDs in the other 3 patients.

To evaluate the pathogenicity of novel *LPIN2* variants we used Variant Effect Predictor (VEP GRCh37) tool and VarSome (www.varsome.com) for American College of Medical Genetics and Genomics (ACMG) criteria.[10] *In silico*, prediction tools including SIFT, PolyPhen, Mutation taster, Combined Annotation Dependent Depletion (CADD), and SpliceAI were used to predict pathogenicity in addition to the ACMG criteria.

A detailed literature search was performed in PubMed, using the following terms: "Majeed syndrome," "CRMO and dyserythropoietic anemia," and "CRMO, dyserythropoietic anemia/microcytic anemia and Sweet syndrome," along with an additional language filter of "English," which yielded 54 articles published from 1986 to December 2020. All pathogenic variants shown in Figure 1 of this article were obtained from these 54 articles.

RESULTS

The clinical features and laboratory findings of 5 Indian patients are summarized in Table 1. The summary of radiological findings and treatment of the 5 patients are described in Supplementary Table 1 (available with the online version of this article).

Four out of 5 patients were born of first-cousin marriages. Patient 3 was found to have a homozygous, possibly pathogenic, variant in *LPIN2* despite no known consanguinity. Disease onset was during the neonatal period in Patients 1 and 2, and the first year of life in the remaining 3 patients. All 5 children presented with bone pains and arthritis, whereas recurrent fever was reported in only 3 patients. Two patients (Patients 1 and 4) had skin lesions (Figures 2A,B). All 5 patients continue to have early-onset microcytic, hypochromic anemia; however, none of them required transfusions. Bone biopsy, skin biopsy, and bone marrow aspiration were not performed in any of these patients. Four children presented with irritability in the first year of life and were suspected to have abdominal colic by their primary care practitioner. There was no history of rheumatic illness in any of these families, and siblings of Patients 2–5 were unaffected.

In this cohort, we observed clinical features that expand the MJS phenotype to include recurrent diarrhea (Patient 1), recurrent ear discharge (Patient 3), erythema nodosum (Patient 4), and abdominal pain (Patient 5). Patient 1 had watery stools, which started at 2 months of age with each episode lasting for 3–6 days and recurring every 6–8 weeks. The stool frequency has gradually reduced after starting treatment. Patient 3 has isolated, recurrent, unilateral, serous ear discharge, which started at 6 years of age. She continues to have intermittent ear discharge and involvement of the mastoid bone was ruled out on imaging. Patient 4 has skin involvement in the form of erythema nodosum (Figure 2B); Patient 5 has recurrent episodes of abdominal pain

Table 1. Salient features of our patient cohort with Majeed syndrome.

Patients	1	2	3	4	5
Sex	M	M	F	M	M
Consanguinity	Yes	Yes	No	Yes	Yes
Genotype	Homozygous c.2206C>T; p.Arg736Cys	Homozygous c.2041delT; p.Trp681Glyfs*14	Homozygous c.2174+4_2174+5del	Homozygous c.1961G>A;p.Gly654Asp	Homozygous c.1620+5G>C
Parental genotype					
Father	NA	Carrier c.2041delT	Carrier c.2174+4_2174+5del	Father deceased	Carrier c.1620+5G>C
Mother	NA	Carrier c.2041delT	Carrier c.2174+4_2174+5del	Carrier c.1961G>A	Carrier c.1620+5G>C
Age at onset	8 d	7 d	8 m	8 m	2 m
Age at diagnosis	3 y	11 y 6 m	13 y 10 m	12 y 10 m	14 y 4 m
Clinical features					
Failure to thrive	+	+	+	+	+
Irritability	+	+	–	+	+
Motor delay	+	+	–	–	+
CRMO					
Bone pain/swelling	+	+	+	+	+
Arthritis	+	+	+	+	+
Recurrent fever	+	+	–	–	+
Anemia	+	+	+	+	+
Skin[a]	+ (pustular)	–	–	+ (EN)	–
Other features	Recurrent diarrhea	Hepatomegaly, massive splenomegaly	Recurrent unilateral ear discharge	–	Recurrent abdominal pain
Laboratory findings (range from onset to diagnosis)					
Hemoglobin, g/L	83–112	56–61	61–107	90–126	70–108
MCV, fL (ref: 83–101)	63.9–75.7	56.6 –59	45.6–62.82	60.2 –78.4	55–82
MCH, pg (ref: 27–32)	20.3–25.8	19.8[b]	15.1–20.74	21 –27.9	16–26
Peripheral smear	Microcytic hypochromic with target cells	Microcytic hypochromic anisocytic	Microcytic hypochromic anisocytic	Microcytic hypochromic anisocytic	Microcytic hypochromic anisocytic with target cells
WBC, × 10^9/L	4.7–12.5	3.0–5.2	6.2–17	5.1–24.2	6.2–16.4
Platelet, × 10^9/L	290–443	230–520	340–860	240–580	490–1020
CRP, mg/L	310–980	Positive[c]	ND	24.6–67	810–1340
ESR, mm/h	25–105	36–105	30–145	10 –108	16–96
Iron studies					
Serum iron, µmol/L	ND	2.33	ND	6.62	3.94
TIBC, µmol/L	ND	28.11	ND	53.89	57.46
TS, %	ND	8.28	ND	12.2	6.85
Serum ferritin, µg/L	ND	ND	56.6	93	114

Patients 1, 2, 4 and 5 are born of first-cousin marriage. [a] See Figure 2. [b] 1 value available. [c] Qualitative. CRMO: chronic recurrent multifocal osteomyelitis; CRP: C-reactive protein; d: days; EN: erythema nodosum; ESR: erythrocyte sedimentation rate; m: months; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; NA: not available; ND: not done; TIBC: total iron binding capacity; TS: transferrin saturation; WBC: white blood cell; y: years.

that started at 7 years of age, although the frequency of abdominal pain has reduced over time. Patients 1 and 3 had received multiple courses of antibiotics for recurrent diarrhea and ear discharge episodes, respectively. Due to chronic pain, there was a history of motor delay in 3 children (Patients 1, 2, and 5), and hence Patient 1 was first seen by a neurologist.

Four patients (Patients 1, 3–5) demonstrated typical imaging features of CRMO (Supplementary Table 1, available with the online version of this article), which were more evident on magnetic resonance imaging (MRI) and bone scans, and in keeping with established current literature. Patient 2 did not have an MRI, his bone scan was normal, and skeletal survey showed reduced bone density with ankylosis of the elbows and subchondral sclerosis.

On genetic testing, except for a few variants with high minor allele frequencies, no other biallelic, homozygous, compound heterozygous, pathogenic, or likely pathogenic variants were detected in these 5 patients. Four of the 5 identified *LPIN2* variants are not reported in any public databases; however, they might be population-specific and be present at a low allele

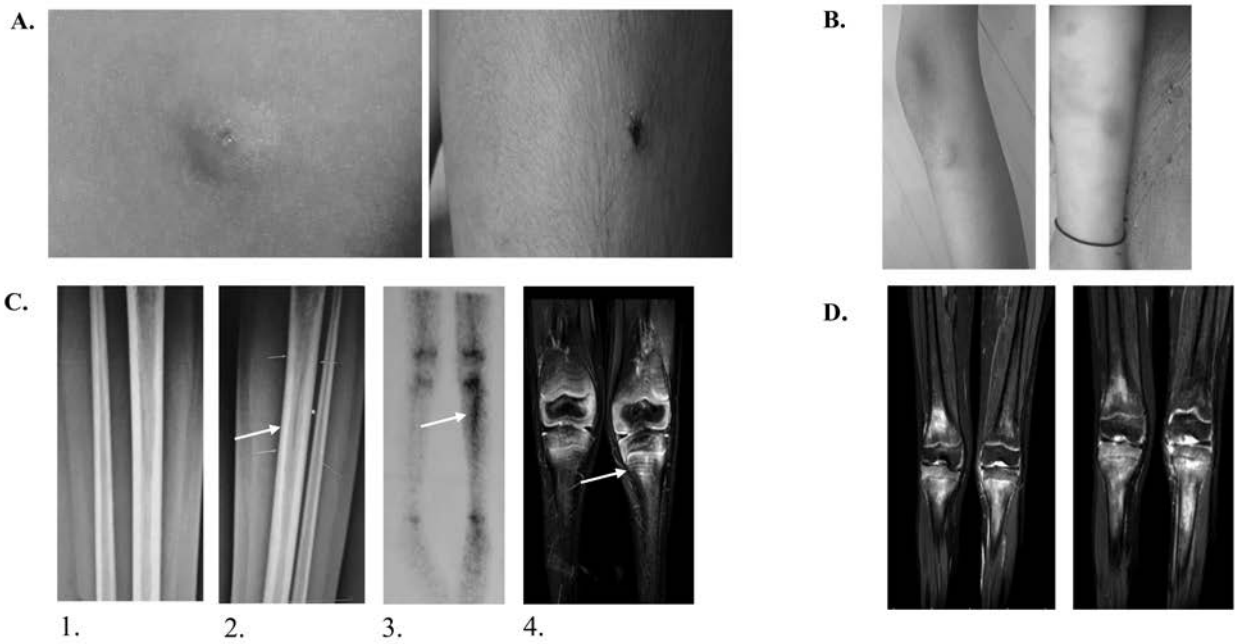

Figure 2. Skin manifestations and radiological images demonstrating importance of different imaging techniques in patients with CRMO. (A) Pustular skin lesions on right leg and back (Patient 1). (B) Erythema nodosum in bilateral lower limbs (Patient 4). (C) 1. Normal comparative right tibial radiograph; 2. Subtle periosteal thickening on the left tibia (can be easily missed); 3. Delayed phase bone scan demonstrating discrete increased uptake along left proximal tibial metadiaphysis; and 4. Coronal STIR MRI image demonstrating left proximal tibial signal hyperintensity (Patient 1). (D) Coronal STIR MRI images of bilateral knee demonstrating right distal femoral and bilateral proximal tibial edema. There is transphyseal edema in the proximal tibia (note: this is not seen in distal femur) and this could predispose to growth disturbances (Patient 3). CRMO: chronic recurrent multifocal osteomyelitis; MRI: magnetic resonance imaging; STIR: short-tau inversion recovery.

frequency in the Indian population. The *in silico* algorithm predictions for the effect of these variants on the protein function are summarized in Supplementary Table 2 (available with the online version of this article). According to ACMG classification, 1 variant is classified as pathogenic and 4 are classified as variants of unknown significance (VUS). The c.2041delT variant creates truncated protein at the position p.Trp681Glyfs*14, which lacks the last 201 amino acid residues, including most of a C-terminal CLIP, haloacid dehalogenase-like (HAD domain; amino acids [aa] 635–837). Of 4 VUS variants, the c.1961G>A (p.Gly654Asp; CADD 29.9) substitution affects an evolutionarily conserved residue in the vicinity of a highly conserved DXDXT catalytic motif (aa 689–693), known to be essential for phosphatide phosphatase activity. The second missense variant, c.2206C>T (p.Arg736Cys; CADD 32), affects the evolutionarily conserved residue Arg736, which was previously associated with another disease variant, p.Arg736His, in a consanguineous Pakistani family.[11] In this family, the proband and 2 male siblings presented with the severe form of CRMO and microcytic anemia, whereas both their parents and elder female sibling were found to be homozygous for this pathogenic variant; however, they presented with a milder phenotype of nonspecific knee/limb pain and mild anemia. The pathogenicity of 2 homozygous intronic variants is less clear. The c.2174+4_2174+5del variant is a 2bp deletion that could affect the splicing of intron 16, whereas the c.1620+5G>C variant could alter the splicing of intron 11; both are predicted to be a donor loss by SpliceAI. The probability that these 2 variants disrupt splicing at their respective chromosomal positions are 0.97 and 0.7. Parental Sanger sequencing confirmed heterozygosity for the intronic variants (Table 1). Functional validations of these variants have not been performed due to the nonavailability of patients' RNA samples.

On literature review, we identified 25 patients with pathogenic or likely pathogenic variants in *LPIN2*, and 6 other patients[12] were reported to have a homozygous mutation in *LPIN2*, but these variants were not described. Of these 31 patients, most are from Middle Eastern ancestry families and accompanied by single reports from India, Pakistan, China, and America.[3,9,11–23] The summary of salient features and disease variants identified in these patients are depicted in Figure 1, and in Supplementary Table 3 and Supplementary Figure 1 (available with the online version of this article).

Of the 31 patients described in literature, clinical features were reported in 24 patients.[3,9,11,13–22] Twenty out of 24 patients (83%) had bone lesions of varying severity and one presented with predominantly nocturnal pain. Twenty-one out of 24 (87.5%) patients had microcytic, hypochromic anemia; 2 were transfusion dependent.[17] A minority of patients are known to present with neutrophilic dermatosis in the form of pustulosis, plaques, nodules, or ulceration, and heterozygous family members may have psoriasis.[11] Skin lesions in the form of Sweet syndrome are described in 2 children, whereas pustulosis is described in 1 child.[15]

DISCUSSION

In 2005, Ferguson and colleagues identified a homozygous mutation in the *LPIN2* gene in 6 children who presented with CRMO, microcytic hypochromic anemia, and skin lesions; this disease was termed *Majeed syndrome*.[15] It was noted that heterozygous carriers of MJS-associated variants have no clinical manifestations consistent with MJS, but they can have psoriasis or other inflammatory dermatosis.[15] In this cohort of patients, parents' heterozygous carriers for respective likely causal variants have no features of inflammation.

Our literature review revealed that almost all the 31 patients with MJS were born of a consanguineous marriage, except for 2 patients described by Liu, *et al*[13] and Bhuyan, *et al*[9] from China and America, respectively. In our cohort, only Patient 3 was born of a nonconsanguineous marriage but was found to have a homozygous splice-site variant in *LPIN2*. All 5 patients reported here have features of CRMO and anemia, whereas skin lesions were seen in 2 patients (Patients 1 and 4; Figures 2A,B). Nocturnal bone pain was predominant in Patient 3, who was homozygous for the splice variant classified VUS. All 5 patients had failure to thrive and only 2 presented with delayed puberty (Patients 3 and 5), consistent with other reports in literature.[17,19] In patients with MJS, hepatosplenomegaly was reported in 6 children, accompanied by cholestatic jaundice in 1 child (Supplementary Table 3, available with the online version of this article). Splenomegaly was observed in 1 child who later underwent splenectomy, which resolved the need for blood transfusions.[17] In our cohort, only Patient 2 had severe hepatosplenomegaly mimicking a storage disorder.

Motor delay was observed in 3 patients (Patients 1, 2, and 5), which may be secondary to chronic osteomyelitis similar to findings reported by Majeed, *et al*.[17] Patient 2 has severe contractures affecting daily activities, whereas Patients 1, 3, and 5 have only minimal contractures that improved after initiation of treatment and physiotherapy. Of note, features such as maxillary hyperplasia or prominent forehead can be seen in patients with MJS due to hyperplasia of the marrow secondary to long-standing anemia.[17] The radiographic findings in our patients (Supplementary Table 1, available with the online version of this article) showed that in early stages the findings can be subtle and could be easily missed, as seen in Patient 1 (Figure 2C). A whole-body MRI in T1 and fluid-sensitive, fat-suppressed sequences are useful and may help to assess the extent of multifocal disease at diagnosis and follow-up. As seen in Patient 3 (Figure 2D), MRI with increased spatial resolution also helps in identifying the transphyseal spread of the disease, which can potentially progress to growth deformity due to formation of physeal bars.

LPIN2 gene is considered a LoF-tolerant gene based on the ratio of observed and expected (o/e) predicted LoF (pLoF) mutations reported in the Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/gene/ENSG00000101577?dataset=gnomad_r2_1), adjusted for sequence context, coverage, and methylation, with a pLoF o/e = 0.34 and probability of being loss-of-function intolerant (pLI) = 0. There are 17 LoF genetic variants reported in gnomAD, and they include nonsense, frameshift, and splice mutations. However, there are no individuals in gnomAD who are homozygous for any of these LoF variants. Consequently, heterozygous LoF variants in *LPIN2* are likely to be identified by WES or targeted NGS gene panels in patients suspected to have a monogenic autoinflammatory disease. In such patients, unless they have a clinical history consistent with CRMO, searching for a second pathogenic variant in *LPIN2* is not warranted. Recently, Bhuyan, *et al*[9] described a structural mutation, a 17.8-Kb deletion in *LPIN2*, suggesting that in patients diagnosed with CRMO/MJS and carriers for 1 deleterious variant, screening for a second mutation may require different technology. The major limitation of the current report and previous reports is that most MJS-associated *LPIN2* variants are not functionally validated.

Studies in lipin-2–deficient mice revealed that mice developed anemia but there was no evidence of osteomyelitis, suggesting the contribution of additional environmental or genetic factors.[24] Lipin-2 has been shown to regulate the activation of the NLRP3 inflammasome by modulating P2X7 receptor activation. Lordén, *et al* demonstrated that lipin-2 ameliorates Toll-like receptor 4 signaling and maintains proper cellular lipid homeostasis, which is necessary for inhibition of purinergic receptor P2X7.[8] Lipin-2 function is regulated by posttranslational modification including ubiquitination. A recent study showed that lipin-2 interacts with β–transducin repeat-containing protein (TRCP), a substrate receptor subunit of the $SCF^{\beta\text{-}TRCP}$ E3 ligase, to undergo proteasomal degradation. A β-TRCP knockout in the murine cell line increased lipin-2 protein expression and decreased expression of IL-1β and other proinflammatory genes.[25] Herlin, *et al*[14] reported elevated levels of proinflammatory cytokines IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α in 2 patients with MJS during active disease. Bhuyan, *et al*[9] described accelerated osteoclastogenesis in M2-like macrophages of a patient with MJS, resulting from enhanced activation of c-Jun N-terminal kinase/mitogen-activated protein kinase and reduced Src kinase activation. Together, these data suggest that MJS is predominantly an IL-1–mediated autoinflammatory disease. Recombinant IL-1 receptor antagonist (anakinra) and human anti–IL-1β monoclonal antibody (canakinumab) have been used successfully in patients with MJS and resulted in drastic clinical and laboratory improvement, especially after failure of TNF inhibitors.[9,11,14,20,21,22] Other treatments such as bone marrow transplant or gene therapy have not yet been tried in MJS.

Due to current lack of availability of IL-1 inhibitors in India and many other countries, treating these patients is a major challenge. All 5 patients received injectable bisphosphonates, whereas Patients 1, 3, and 5 required the addition of other disease-modifying antirheumatic drugs such as methotrexate (Patient 1), and methotrexate, azathioprine, and sulfasalazine (Patients 3 and 5). In addition, Patient 5 also received TNF inhibitors etanercept and adalimumab biosimilar molecules (Supplementary Table 1, available with the online version of this article). Patient 1 has reduced frequency of bone pain and skin rash, whereas Patients 3 and 5 experience frequent flares on this treatment. Patients 2 and 4 are well controlled on injectable

bisphosphonates alone, with reduced need for PRN diclofenac or naproxen, respectively.

In conclusion, patients with MJS may present to varied specialists such as neonatologists or pediatricians for fevers or irritability, neurologists for motor delay due to chronic pain, hematologists for anemia, or dermatologists for skin lesions. Thus, it is important to create awareness about MJS in the medical community. Due to limited genetic testing, the prevalence of MJS in India is probably underestimated. Consanguinity is a common sociocultural factor in many ethnic communities in India, and an abbreviated NGS gene panel for autoinflammatory diseases should include MJS. Targeted therapy for SAIDs remains a problem in India due to challenges such as nonavailability, unaffordability, and nonlicensure of IL-1 antagonists.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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