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Multifocal Osteolysis, Nodulosis, and Arthropathy in a Saudi Boy with Osteoporosis and Short Stature

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Abstract
MONA syndrome, characterized by multifocal osteolysis, nodulosis, and arthropathy, is a rare autosomal recessive disease, with only 44 cases reported worldwide. Clinically, MONA syndrome presents as a progressive deformity of the hands and feet, with soft nodules developing in the palm of the hands and foot pad, with osteolysis of the carpal and tarsal bones. As such, MONA syndrome is frequently diagnosed incorrectly as polyarticular juvenile idiopathic arthritis, leading to late diagnosis and the potential for the development of severe complications. We describe the case of a 7-year-old boy who was misdiagnosed with juvenile idiopathic arthritis rather than MONA syndrome. The child initially presented with progressive arthropathy, with negative inflammatory markers, leading to the diagnosis of juvenile idiopathic arthritis and initiation of anti-human necrotic factor and anti-inflammatory treatment. MONA syndrome was diagnosed based on radiological and genetic assessments performed when treatment provided no benefit. Ultimately, the course of MONA syndrome in this child was complicated by osteoporosis and short stature. Careful evaluation to a child presenting with MONA syndrome will lead to accurate diagnoses while avoiding unnecessary management.

Keywords: osteolysis, nodulosis, arthropathy, osteoporosis, deformity

1. Introduction
Multifocal osteolysis, nodulosis and arthropathy (MONA) syndrome is a very a rare autosomal recessive disease. Although various names have been used in the literature to describe this syndrome, including NAO syndrome, Torg-Winchester syndrome and Al-Aqeel Sewairir syndrome, MONA was adopted as the appropriate nosology term in 2006 [1]. Due to the its rarity, the incidence rate of MONA cannot be determined, with only 44 cases of genetically confirmed MONA syndrome having been reported to date [2].
Clinically, the MONA syndrome presents as a triad of progressive deformity of the hands and feet, the development of soft nodules in the palm of the hands and foot pad and osteolysis of the carpal and tarsal bones. Other features of the syndrome include osteopenia, brachycephaly and dysmorphic features, such as hypertelorism, gingival hyperplasia and hirsutism [3, 4]. Although there is no definitive treatment for MONA syndrome, studies have shown that bisphosphate administration can increase bone mineral density, decrease pain and slow the progression of the disease, but without providing a curative effect [5]. Osteoporosis and short stature are considered to be late presenting complications of the disease, and have only been mentioned in few case reports [6].
We describe the case of a 7-year-old boy, misdiagnosed with juvenile idiopathic arthritis rather than MONA syndrome, whose clinical course was complicated by osteoporosis and short stature.

2. Case Report
A 7-year-old male, of Saudi ethnicity, with a prior diagnosis of juvenile idiopathic arthritis, underwent further diagnostics due to the clinical presentation of osteoporosis and short stature. His relevant past clinical history was as follows.
He was born preterm, from a twin pregnancy, with no birth complication. However, he was admitted to the neonatal intensive care for 1 week for the treatment of neonatal jaundice, requiring phototherapy and blood transfusion.
His monozygotic twin died at age 4 months due to liver and congenital heart disease. At that time, the patient developed jaundice, with high serum levels of bilirubinemia. A liver biopsy was performed, confirming a diagnosis of neonatal giant cell hepatitis, treated using ursodeoxycholic acid.
With regard to physical development, independent walking developed late at 2 years of age, with an abnormal gait pattern reported by the family. He developed swelling of the hands and feet, with bilateral involvement of the 4th digit initially, with eventual appearance of nodules on the right foot, bilateral swelling of the feet and involvement of all digits of the hand, including a flexion deformity. Joint stiffness was greater in the morning and following rest periods. The child had no history of rash or fever associated with these manifestations, and no visual impairments. There was no prior history of infection. At the age of 4 years, he developed a non-traumatic greenstick fracture, as well as night bone pain, more pronounced in the knees and lower limbs in general.
With regard to family history, parents were first cousins, with a positive family history of MONA in the third maternal grandfather, but with no family history of short stature or osteoporosis presenting at a young age.
At the age of 4 years, the patient was evaluated by a

rheumatologist who provided treatment for polyarticular juvenile idiopathic arthritis, including non-steroidal anti-inflammatory drugs, in combination with anti-human necrotic factor and anti-inflammatory drugs. The treatment was ineffective and all drugs were discontinued. The family was lost to follow up until the child was 7 years old.

He was referred to the endocrine clinic for evaluation of both short stature and suspected osteoporosis. His weight and height were <25th percentile for age, with a mid-parental height of 168 cm and a predicted adult height of 163 (Figure 1). Neither a rash nor hirsutism were observed, and the patient did not present with dysmorphic features. Eye examination results were normal but he did have hypertrophy of the gingiva with delayed dentition.

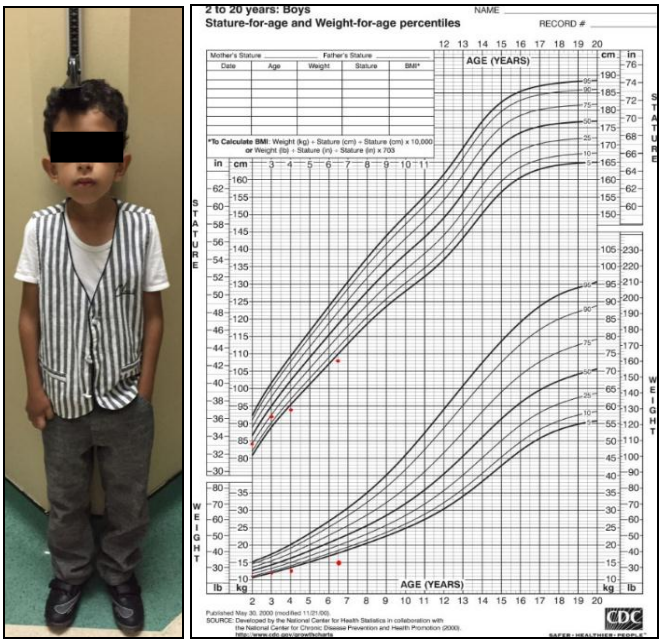

Fig 1: Height is plotted from age 2 to 7 years, confirming a short stature.

Flexion contractures were present at all interphalangeal and metacarpophalangeal joints, with bilateral swelling of the hands but no nodules or tenderness (Figure 2). Flexion contractures were also observed in his feet, with bilateral swelling and a soft nodule within the foot pads (5 × 5 cm area for the right foot and 3 × 3 cm for the left). Both nodules were mobile and soft (Figure 3). Eversion and inversion range was limited bilaterally. Other joints of the foot were normal.

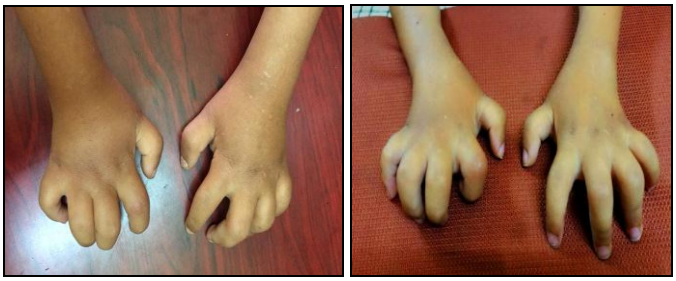

Fig 2: Sequence of progression of contractures of the metacarpophalangeal and interphalangeal joints of the hands. (A) 5 years of age and (B) 6 years of age.

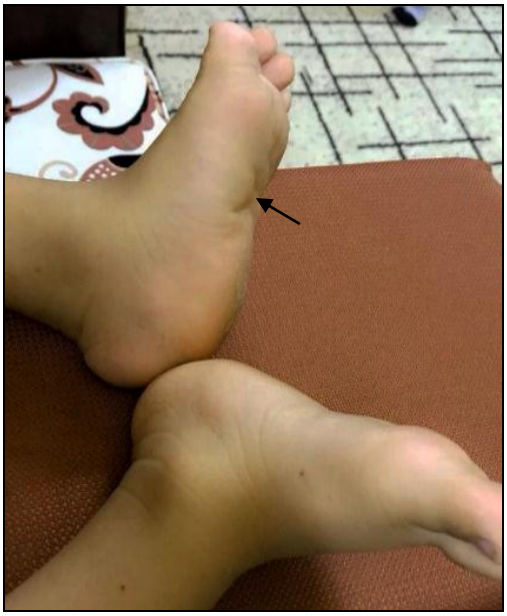

Fig 3: Bilateral swelling of the feet, with plantar subcutaneous nodules indicted by arrows.

DNA sequencing for matrix metalloproteinase-2 (MMP2) revealed a homoallelic mutation in nucleotide c.732C> A, specifically in codon 244 of exon 5. This mutation is known to cause an alteration of tyrosine (TAC) to a termination codon (TAA), resulting in a nonsense mutation. The genetic study confirmed the clinical diagnosis of MONA syndrome (Table 1), and excluding the diagnosis of juvenile idiopathic arthritis.

Table 1: Blood works excluding juvenile idiopathic arthritis with high alkaline phosphatase

Test	Results	Normal Range
Rheumatology marker		
C-Reactive protein	3.44	0-3
Erythrocyte sedimentation rate	9	1-20
Antinuclear antibody	Negative	-
Anti-mutated citrullinated vimentin	6.1	0-20
Rheumatoid factor	Negative	-
Bone Function Profile		
Alkaline phosphatase	258	40-150
Calcium	2.33	2.12-2.52
Albumin	40	40.2-47.6
Magnesium	0.91	0.70-1
Phosphate	1.30	0.81-1.58
Parathyroid hormone	5	1.18-8.43

Radiological estimation of bone age placed the child at 4.5 years (Figure 4). In comparison to the hand radiograph obtained at 4 years of age, the present findings indicated development of osteopenia, with osteolysis and digital contracture (Figure 5). Brachycephaly is shown in Figure 6. The bone mineral density scores, shown in Figure 7 (Z-score of -4 for the total body and -2.4 for the lumbar spine), confirmed generalized osteoporosis. The echocardiogram findings were normal.

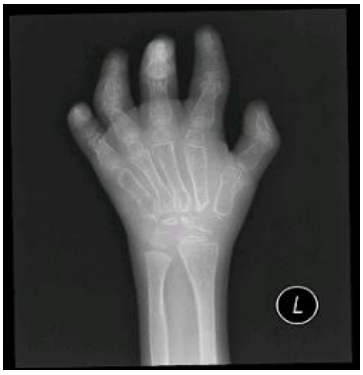

Fig 4: Radiograph of the left hand obtained at age 7 years, with bone maturity estimated at 4.5 years. Multiple abnormalities of bone are evident, including: generalized osteopenia, osteolysis of the carpal bones and distal phalanges, arthritic changes in the 4th and 5th distal phalanges, widening of the phalanges, digital contracture, and irregular epiphysis.

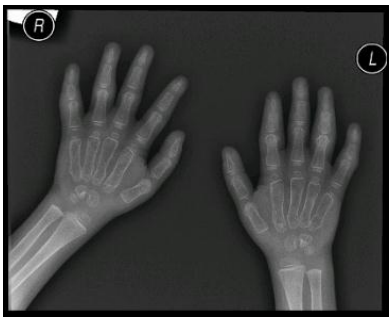

Fig 5: Radiograph at age 4 years, showing generalized osteopenia and cortical thinning.

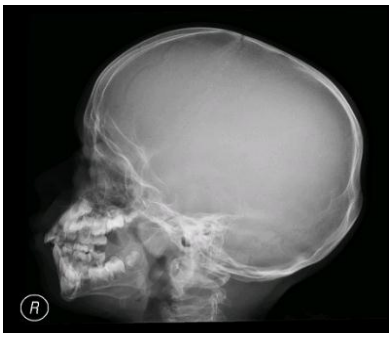

Fig 6: Radiograph of the skull, showing brachycephaly, osteopenia and normal skull sutures.

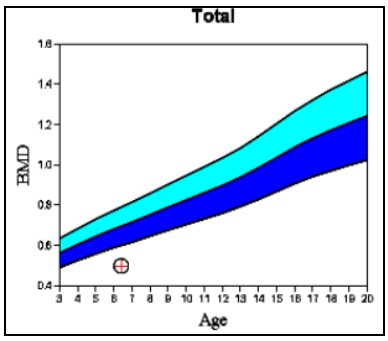

Fig 7: Bone mineral density evaluated at the age of 6.5 years, showing severe osteoporosis, with a Z score of -4 standard deviations.

Bisphosphonate therapy was initiated during hospital admission. Zoledronic acid was given in combination with calcium gluconate and normal saline. Mild side effects were noticed in the first session including fever and vomiting, the second session is planned after three months.

3. Discussion

MONA was clinically diagnosed based on the presence of the characteristic triad, namely osteolysis, nodulosis and arthropathy, with the diagnosis confirmed by detection of the MMP2 mutation and radiological findings [7]. MONA is caused by a mutation of the gene MMP2 that is located on chromosome 16q12.2. The genetic basis of MONA was first described in 2001 by Martignetti *et al*., [8] with 13 mutations of the MPP2 gene having been reported to date with the potential to lead to MONA syndrome [9].

Our patient was first diagnosed with polyarticular juvenile idiopathic arthritis, with early misdiagnosis being a common problem for patients with MONA syndrome [10]. Unlike arthritis, however, blood work for familial arthropathy and radiological findings are usually nonspecific, with no evidence of either systemic or synovial inflammation [11]. Therefore, the use of anti-inflammatory medication is of no clinical benefit [11]. The use of bisphosphonates for the treatment of osteoporosis increases bone mineral density, while decreasing pain and slowing the progression of the disease, but is not curative [12]. The response of MONA patients to bisphosphonates is variable and the extent of their effectiveness is an area of future study [13].

Consanguinity is an important risk factor for MONA syndrome, which is of interest in Saudi Arabia due to the high rate of consanguineous marriage [4, 6]. Many clinical features of MONA syndrome were present in our patient at the time of the initial assessment in our endocrine clinic, including brachycephaly, gingival hyperplasia, short stature, and osteoporosis as reported in previously published cases [3, 4, 6]. However, the patient did not present dysmorphic features, hirsutism, eye abnormalities, or congenital heart disease, which also have been previously reported [14, 15]. However, we did identify a possible new association between MANO syndrome development and neonatal giant cell hepatitis, with no previous association with any hepatic diseases having been reported. This association in our case may be due to a family history of chronic liver disease.

4. Conclusion

The presence of osteolysis, nodulosis and arthropathy should alert physicians to the possibility of MONA syndrome, rather than polyarticular juvenile idiopathic arthritis. We recommend early screening of osteoporosis for these patients MONA to allow early intervention to improve bone health.

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