Mandibuloacral dysplasia in a young Vietnamese girl caused by homozygous missense variant c.1579C>T in the LMNA gene with progeria and severe skin lesions

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INTRODUCTION

Mandibuloacral dysplasia (MAD) is an extremely rare disorder, distinguished by craniofacial anomalies (mandibular hypoplasia, overcrowded teeth, beaked nose, and prominent eyes), skeletal malformation (acro-osteolysis, joint stiffness, clavicular hypoplasia), cutaneous changes (hyperpigmentation, scleroderma-like, lipodystrophy), progeroid syndromes, and laminopathies.[1-4] There are 2 types of MAD: MAD type A (MADA) linked to variants in the LMNA gene, presenting with partial lipodystrophy[3] and MAD type B (MADB) caused by variants of the ZMPSTE24 gene, presenting with generalized lipodystrophy.[5] Clinical signs of MADB can appear at the age of 4 months, representing a more severe phenotype.[6] Here, we describe a MADA patient with homozygous missense variant c.1579C>T (p.Arg527Cys) in the LMNA gene, manifesting at the age of 18 months as distal phalanx changes, followed by progressed progeria and gradually severe skin lesions. This is the first case report on this issue in Vietnam.

Abbreviations used:

MAD: mandibuloacral dysplasia
MADA: mandibuloacral dysplasia type A
MADB: mandibuloacral dysplasia type B

CASE REPORT

A 7-year-old girl came to our hospital. She was the firstborn of nonconsanguineous parents. Except for skipping crawling, no other abnormality was observed until the patient was 18 months of age, when her fingertips started swelling, and she developed camptodactyly.

On examination, she had a distinctive face with prominent eyes, sparse hair, visible veins over the scalp, beaked nose, bulbous cheeks, and mandible hypoplasia associated with crowded teeth (Fig 1, *A-D*). Her voice was high-pitched, and growth was stunted with a height below the third percentile. Her intelligence quotient was corresponding to age. The patient had partial lipodystrophy, mottled pigmentation, and sclerodermatous skin in the lower part of the trunk and the lower extremities (Fig 1, *E*). The distal phalanges of all digits were short and club-shaped, and the knuckle joints were characterized by flexion deformity (Fig 2, *B*). She had skin ulcers of the bony prominence on the second and fifth of left fingers (Fig 2, *A*), which healed after 2 weeks of treatment by topical mupirocin and vaseline dressing. Severe varus deformity of the legs causing pain when standing was noticed at the age of 6 years (Fig 3, *A*). On examination, she had an ulcer with a yellow crust covering, defined border, and red-violaceous surrounding skin on the right knee (Fig 3, *B* and *C*). She had no digital ulcers or circumoral cyanosis. There was no similar anomaly in her family.

Routine blood investigations revealed values within the normal limits. X-ray films of hands and feet showed resorption of the distal phalanx with strict flexion deformity of the fingers (Fig 2, *C*). An

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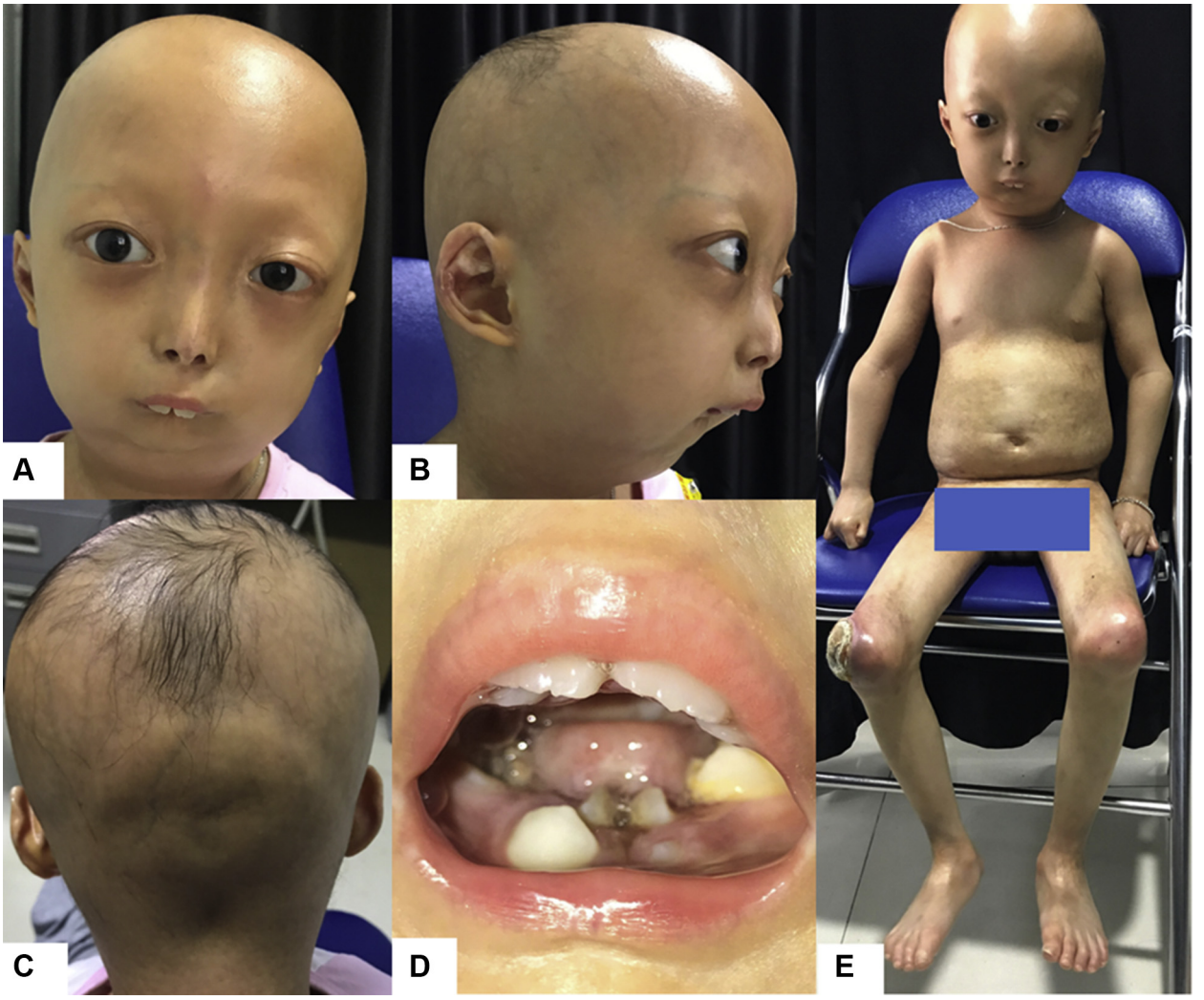

Fig 1. The patient had a distinctive face with prominent eyes, beaked nose, fullness of cheeks (**A**), sparse hair with visible veins over the scalp (**C**), and mandible hypoplasia with crowded teeth (**B**, **D**); partial lipodystrophy with thin extremities, central distribution of fat in the face, neck, and trunk; mottled pigmentation, and sclerodermatous skin over the lower trunk and lower extremities (**E**).

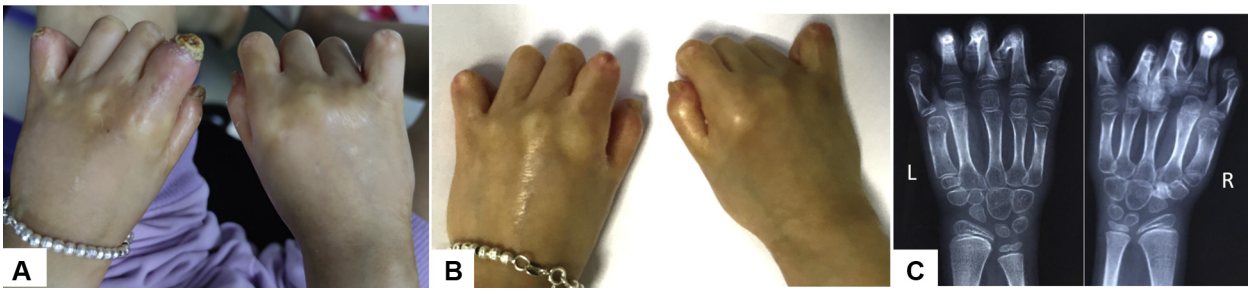

Fig 2. Ulcers of the bony prominence on the second and fifth of left fingers (**A**) healed after 2 weeks (**B**). **C**, X-ray films revealed acro-osteolysis with strict flexion deformity of the fingers.

X-ray of the right knee did not reveal any calcinosis or bone destruction. The anteroposterior X-ray of the chest showed a bell-shaped thorax and absence of clavicles (Fig 4). Electrocardiography and echocardiography were normal. A homozygous NM 170707.4:c.1579C>T (p.Arg527Cys) variant in the

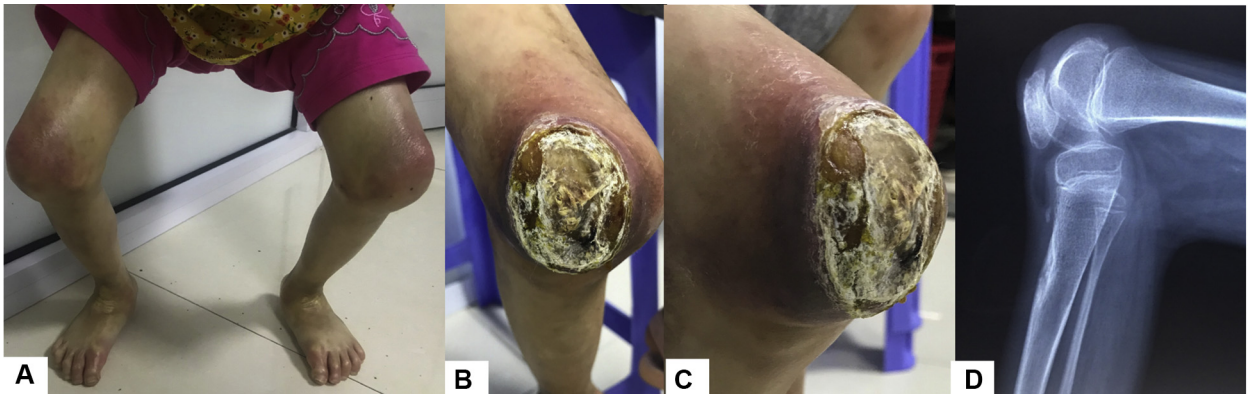

Fig 3. **A**, Picture at the age of 6 years revealing severe varus deformity causing pain when standing. **B** and **C**, The ulcer on the right knee had a yellow crust covering, defined border, and red-violaceous surrounding skin. **D**, X-ray of the right knee revealed neither skin calcinosis nor bone destruction.

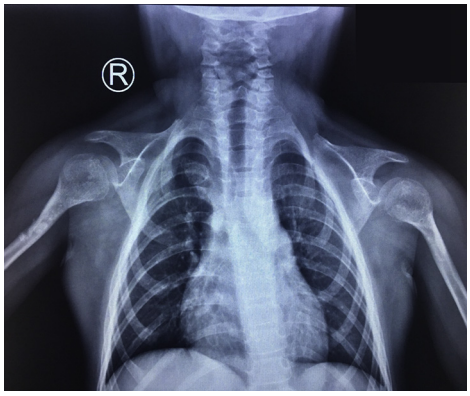

Fig 4. X-ray of the chest showed a bell-shaped thorax and absence of clavicles.

LMNA gene was detected, whereas no variant of the ZMPSTE24 gene was found.

DISCUSSION

Mandibuloacral dysplasia is an immensely rare syndrome that was first reported by Young et al in 1971.[3] After 30 years, Novelli et al[3] discovered a c.1580G>A LMNA variant causing alteration of arginine at codon 527 to histidine (p.Arg527His) in lamin A/C in MADA patients, and then at least 13 different variants of LMNA were found in MADA.[7] In 2003, Agarwal et al[5] found a variant on the ZMPSTE24 gene encoding a zinc metalloproteinase involved in post-synthetic processing of prelamin A to mature lamin A in MADB patients. When compared with patients with MADB, MADA patients are less severely affected by developing clinical manifestations later in life (7 years versus 4 months).[6] However, 5 severe MADA cases (3 girls and 2 boys) with the c.1579C>T (p.Arg527Cys) LMNA variant were reported who had an early age of onset associated with progeria and severe skeletal abnormalities.[2,4,8] Our patient is the first MADA patient with severe disease associated with homozygous missense variant c.1579C>T in the LMNA gene in Vietnam.

The patient exhibited typical signs of MADA, with the earliest sign being finger abnormality with acral osteolysis at the age of 18 months, similarly to the case reported by Shen et al[2] and the first case of the series reported by Luo et al.[8] The difference in this case presentation was the ulcers of the bony prominence. In this patient, severe joint contracture and flexion deformity led to the bone being close to the joint skin, and consequently these skin areas would be more vulnerable to trauma. This type of ulcer is different from the digital ulcer, which resulted from the abnormality of small vessels in scleroderma. To our knowledge, this is the first case to have skin ulcer lesions to be reported.

Different variants in the LMNA gene can cause various laminopathies.[9] The variant c.1579C>T in the LMNA gene leads to the replacement of a basic amino acid (arginine) with a neutral one (cysteine) in the C-terminal tail domain of lamin A/C, provoking disruption of the surface structure of lamins in nuclear cells. This LMNA variant associated with atypical Hutchinson-Gilford progeria syndrome was reported in 4 children from 2 Chinese families, and all of them shared characteristics of MAD, including acral osteolysis and mandible and clavicle hypoplasia, while no cardiovascular abnormality was described.[9,10] The question of whether the c.1579C>T LMNA variant in the LMNA gene causes severe MAD or phenotype overlap with MAD and Hutchinson-Gilford progeria syndrome warrants further studies.

Conflicts of interest

None disclosed.

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