

Homozygous *LMNA* c.1579C>T mutation manifesting as mandibuloacral dysplasia type A in a pediatric patient

Dear Editor,

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder characterised by premature aging phenotypes, predominantly manifesting as skeletal abnormalities (mandibular hypoplasia and acro-osteolysis) and cutaneous manifestations (scleroderma-like skin changes, pigmentation, alopecia, and lipodystrophy).¹ Genotypically, MAD segregates into two distinct subtypes: type A (MADA), caused by pathogenic variants in *LMNA*, and type B (MADB), resulting from *ZMPSTE24* mutations. There are few studies on MADA, so relatively little is known regarding the prognosis and cause of death in these patients.² We present a case of MADA associated with the homozygous *LMNA* c.1579C>T (p.Arg527Cys) mutation and provide pathological analysis of the cause of death.

A one-year-old boy presented to the hospital with alopecia, skin sclerosis, and joint flexion deformity. The boy was delivered at 37 weeks of gestation and appeared normal at birth. In the sixth month of life, scalp and eyebrow hair loss occurred, progressing to complete alopecia [Figure 1a]. Skin on the

extremities became hard and pigmented, with subcutaneous fat loss. The fingers appeared shortened and rigid, with severe flexion at the interphalangeal joints, resulting in a characteristic claw-like deformity and significantly limited range of motion [Figure 1b]. His parents complained that the child had a poor appetite and difficulty swallowing.

Laboratory investigations demonstrated elevated creatine kinase (204 U/L; normal range: 25–200 U/L) and its isoenzyme (56 U/L; normal range: 0–25 U/L). Radiographic assessment of the hands revealed osteolysis and distal phalangeal destruction. Genetic analysis identified a homozygous *LMNA* mutation (c.1579C>T), consistent with findings in his two older sisters. The clinical phenotypes of the two sisters showed substantial overlap with the proband, but they exhibited more severe osteoarticular involvement, such as the absence of clavicular tissue and scoliosis, which might have been associated with disease progression. Both parents were asymptomatic heterozygous carriers of the same *LMNA* mutation and were non-consanguineous. The pedigree spanned three generations with 45 members, and



Figure 1a: Complete alopecia involving scalp hair, eyebrows, and eyelashes.



Figure 1b: Digital shortening with flexion contractures and joint deformities

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no phenotypic abnormalities were observed except in the affected siblings, which is consistent with an autosomal recessive inheritance pattern. Based on these findings, a diagnosis of MADA was established. Regrettably, the patient was lost to follow-up and succumbed to unknown causes at home at the age of seven years.

Pathological examination of the boy revealed organised thrombi in the coronary artery without significant atherosclerosis [Figure 2a]. Histological analysis of myocardial tissue demonstrated extensive neovascularisation, interstitial erythrocyte extravasation, and diffuse fibrosis [Figure 2b and 2c]. Similarly, fibrotic changes were evident in the lung parenchyma [Figure 3a]. Furthermore, pulmonary sections exhibited dilated and congested alveolar wall vasculature, intra-alveolar oedema, and hemosiderin-laden macrophages (heart failure cells) [Figure 3b].

To date, at least 12 distinct pathogenic *LMNA* mutations (homozygous or heterozygous) have been identified in MADA. While the c.1580G>A homozygous mutation in

LMNA exon 9 is frequently reported in MADA patients, the c.1579C>T homozygous mutation has also been confirmed as causative.²

Genetic testing revealed that all MADA cases in this pedigree resulted from a homozygous *LMNA* c.1579C>T mutation, consistent with autosomal recessive inheritance. The clinical presentation and disease progression were consistent with previously reported cases. Notably, 77.7% of documented cases originated from China, featuring juvenile-onset disease without specific age predilection and undetermined prognosis [Table 1].³⁻⁷ The observed geographical clustering in the Chinese population may suggest either a founder effect or potential environmental modifiers, which warrants further population genetic studies.

Comparative analysis revealed that patients with the homozygous *LMNA* c.1579C>T mutation exhibited more severe clinical manifestations than those carrying the c.1580G>A mutation, including: (1) earlier disease onset with more severe alopecia; (2) progressive joint contractures

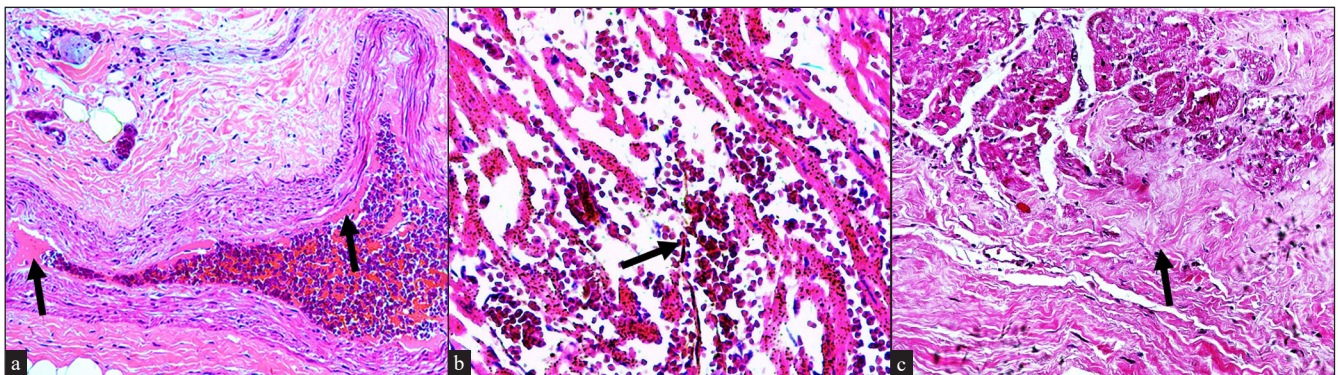


Figure 2: Histopathological examination of cardiac tissue on haematoxylin and eosin stained sections showed (a) Organised coronary thrombus (black arrows); (Haematoxylin & eosin staining, 100 \times), b) Foci of myocardial haemorrhage (black arrow; Haematoxylin & eosin staining, 200 \times) and c) Extensive myocardial fibrosis (black arrow; Haematoxylin & eosin staining, 200 \times).

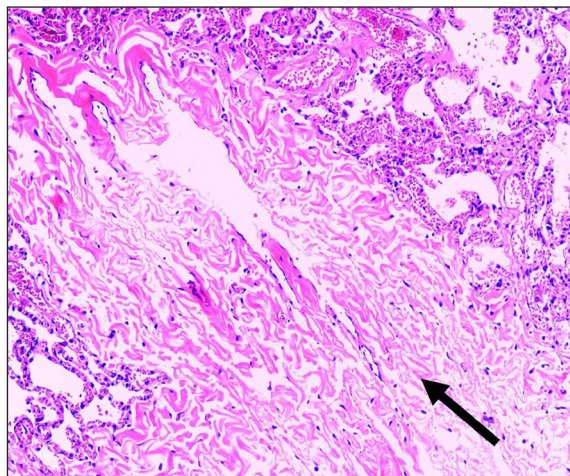


Figure 3a: Focal pulmonary fibrosis (black arrow; Haematoxylin & eosin staining, 100 \times).

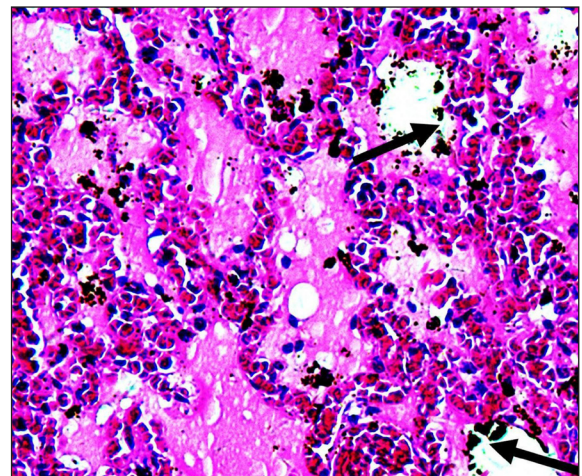


Figure 3b: Pulmonary oedema and congestion with characteristic heart failure cells: black arrow (Haematoxylin & eosin staining, 200 \times).

Table 1: Reported cases with homozygous *LMNA* c.1579C>T pathogenic variant in the medical literature.

Ref	Country	Number of cases	Sex/Age	Characteristics	Accumulation of prelamin A	Mode of inheritance
Agarwal <i>et al.</i> ³	German-Irish origin	1	Female/7 years	Severe mandibuloacral dysplasia-associated lipodystrophy and progeria	No	-
Liang <i>et al.</i> ⁴	China	2	Male/11 years Female/3 years	Atypical Hutchinson–Gilford progeria syndrome	-	Autosomal recessive
Xiong <i>et al.</i> ⁵	China	2	Female/10 years Male/18 months	Hutchinson–Gilford progeria syndrome with severe skeletal abnormalities	-	Autosomal recessive
Luo <i>et al.</i> ⁶	China	3	Female/7 years Female/3 years 3 months Male/10 months	Mandibuloacral dysplasia type A with progeroid features	-	Autosomal recessive
Doanh <i>et al.</i> ⁷	Vietnam	1	Female/7 years	Mandibuloacral dysplasia with progeroid features and severe cutaneous manifestations	-	-

leading to significant mobility impairment; and (3) prominent osteolytic changes, particularly evident in clavicular and costal bone resorption.

Currently, neither prognosis nor causes of death in MADA have been systematically documented. To address this gap, we characterised the histopathological features of key organs to elucidate potential causes of death. Histopathological examination at autopsy revealed severe cardiopulmonary pathology, including: (1) organised coronary thrombus, (2) diffuse myocardial fibrosis, (3) myocardial haemorrhage, (4) pulmonary congestion and oedema, and (5) heart failure cells. These findings suggest that myocardial infarction could have been the immediate cause of death in the background of compensated heart failure.

In the setting of compensated heart failure, the cardiovascular system operates under persistent haemodynamic stress. Multiple pathophysiological factors may precipitate myocardial infarction in this state, including: progression of coronary artery disease, myocardial oxygen supply-demand mismatch, neuroendocrine system activation, and superimposed complications (e.g., infection or anemia). The precise interplay of these factors warrants further investigation.

MADA is a lethal progeroid syndrome with a poor prognosis and no established therapy. We demonstrate that myocardial infarction may be the primary cause of death in MADA patients harboring the *LMNA* c.1579C>T homozygous mutation.

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References:

1. Simha V, Agarwal AK, Oral EA, Fryns JP, Garg A. Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. *J Clin Endocrinol Metab* 2003;88:2821-4.
2. Cenni V, D'Apice MR, Garagnani P, Columbaro M, Novelli G, Franceschi C, *et al.* Mandibuloacral dysplasia: A premature ageing disease with aspects of physiological ageing. *Ageing Res Rev* 2018;42:1-13.
3. Agarwal AK, Kazachkova I, Ten S, Garg A. Severe mandibuloacral dysplasia-associated lipodystrophy and progeria in a young girl with a novel homozygous Arg527Cys *LMNA* mutation. *J Clin Endocrinol Metab* 2008;93:4617-23.
4. Liang L, Zhang H, Gu X. Homozygous *LMNA* mutation R527C in atypical Hutchinson–Gilford progeria syndrome: evidence for autosomal recessive inheritance. *Acta Paediatr* 2009;98:1365-8.
5. Xiong Z, Lu Y, Xue J, Luo S, Xu X, Zhang L, *et al.* Hutchinson–Gilford progeria syndrome accompanied by severe skeletal abnormalities in two Chinese siblings: two case reports. *J Med Case Rep* 2013;7:63.
6. Luo DQ, Wang XZ, Meng Y, He DY, Chen YM, Ke ZY, *et al.* Mandibuloacral dysplasia type A-associated progeria caused by homozygous *LMNA* mutation in a family from Southern China. *BMC Pediatr* 2014;14:256.
7. Doanh LH, Phuong HT, Phuong NTT, Thu LTH, Thuong NV. Mandibuloacral dysplasia in a young Vietnamese girl caused by homozygous missense variant c.1579C>T in the *LMNA* with progeria and severe skin lesions. *JAAD Case Rep* 2021;16:5-8.