

Myofibrillar myopathy type 8 mimicking a Limb-Girdle Muscle Dystrophy: the first Tunisian case report

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Myofibrillar myopathy (MFM) type 8, caused by PYROXD1 gene variants, has recently been identified and has been rarely reported to date.

Our aim was to report the first case of MFM type 8 from Tunisia with delayed diagnosis due to a non-specific clinical presentation.

Results. A 36-year-old North-African male presented to our neurology department with a 15-year history of progressive muscle weakness leading to difficulty in walking and standing without dysphagia or facial weakness. His family history was unremarkable, with no similar cases reported. His medical history was insignificant, with no previous or current medication.

Neurological examination noted symmetrical proximal motor deficit in all four limbs with calf pseudohypertrophy and hyporeflexia in lower limbs. Proximal muscular dystrophy was suspected. Normal levels of blood creatine kinase (CK) and lactate dehydrogenase were noted, and the immunological work-up was negative. A muscle biopsy of the anterior tibialis was performed, revealing a histopathological pattern consistent with proximal muscle dystrophy suggestive of Limb-Girdle Muscle Dystrophy (LGMD).

Whole exome sequencing (WES) was performed, revealing a homozygous variant NM_024854.3: c.464A > G on the PYROXD1 gene. The diagnosis of MFM type 8 was retained, and physical therapy was prescribed. At 2-year follow-up, a slight worsening of motor deficit was observed, but his modified Rankin's scale remained stable at 3.

Conclusions. We reported the first Tunisian case of MFM type 8 associated with a well-known pathogenic variant in the PYROXD1 gene. This case mimics LGMD with a moderate deficit and slow progression. MFM type 8 can present with different phenotypes, making the diagnosis difficult.

Key words: myopathy, muscular diseases, congenital myopathy

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Introduction

Congenital myopathies are a heterogeneous group of genetic muscular disorders with 70 subtypes identified to date ¹. Myofibrillar myopathies (MFM) are a subgroup characterized by a specific pathological pattern of myofibrillar disorganization. This disorganization and disintegration of myofibrils result in the accumulation of several proteins, including desmin, alphaB-crystallin, dystrophin, myotilin, filamin, congophilic amyloid material, and sarcoglycans, among others ².

The common pathological and pathophysiological features contrast with phenotypical variability, which is why diagnosing MFM is challenging. MFM type 8, caused by variants in the PYROXD1 gene, was recently identified and was previously classified as limb-girdle

muscular dystrophy (LGMD) type 1A³. PYROXD1 variants causing a recessive disease, which affects the Pyridine nucleotide-disulfide oxidoreductase domain-containing protein1 and disrupts redox functions, has been rarely reported to date.

Herein, we report the first case of MFM type 8 from Tunisia with delayed diagnosis due to a misleading clinical presentation. This case broadens the geographic range of documented cases to North Africa.

Case presentation

A 36-year-old male presented to our department of neurology with a history of progressive muscle weakness, causing difficulty walking and standing since the age of 15 years. He was born to consanguineous Tunisian Arab-Berber parents. There were no similar cases reported in his family. His medical history was insignificant, with normal psychomotor development and no previous or current medication.

Neurological examination noted assisted waddling gait and marked, symmetric atrophy affecting the brachial biceps, brachial triceps, deltoid, and quadriceps muscles. A proximal and symmetric motor deficit predominantly involving the scapular girdle was observed. Furthermore, the patient exhibited right facial paresis, calf pseudo-hypertrophy, and absent deep tendon reflexes in the lower limbs. Proximal muscular dystrophy was suspected. Otherwise, he had a normal intellectual status and displayed no muscle fasciculation nor ophthalmoparesis. On general examination, cardio-pulmonary auscultation was normal; no skin lesions or osteoarticular abnormalities were found. Electromyography revealed a myogenic pattern. Biological workup showed normal levels of blood creatine kinase (125 UI/l; normal range: 22-198) (CK) and lactate dehydrogenase (228 UI/l; normal range: 140-280). The electrocardiogram and Transthoracic echocardiography did not reveal any abnormalities. Immunological screening, including Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and myositis-specific autoantibodies, was negative. An incisional biopsy from the anterior tibialis muscle showed a dystrophic fibro-adipose remodeling in striated muscle with uneven size and shape of muscle fibers, the presence of hypertrophic and atrophic fibers with circular contours. NADH staining showed well-defined vacuoles within the cytoplasm. An increase in the number of nuclei with centralization in some areas was noted, as well as some necrotic muscle fibers infiltrated with macrophages (Fig. 1). This morphological aspect was suggestive of proximal muscular dystrophy, particularly LGMD. Nevertheless, immunohistochemical studies revealed normal expression of dystrophin and sarcoglycans.

Given the patient's age at onset, along with clinical and paraclinical data, a hereditary muscular dystrophy was suspected. Screening for Becker's muscular dystrophy was performed using multiplex ligation-dependent probe amplification (MLPA) of the dystrophin gene. This diagnosis was ruled out as no deletions or duplications were detected. Screening for LGMD type R9 was conducted, showing the absence of c.1364C > A and c.1486T > A variant in the FKRP gene. Ultimately, clinical exome sequencing (CES) was performed, revealing a known pathogenic homozygous missense variant NM_024854.3: c.464A > G p.(Asn155Ser) in the PYROXD1 gene. This variant was confirmed and tested for segregation in the patient by Sanger sequencing. Therefore, based on the identified pathogenic variant, the

clinical features of LGMD-like presentation and the histopathological findings of muscle dystrophy, the diagnosis of autosomal recessive Myofibrillar myopathy type 8 was retained.

Physical therapy was started. Examination at 2-year follow-up showed a slight worsening of motor deficit, but his modified Rankin's scale remained stable at 3. From the patient's perspective, the disease had a considerable social and psychological impact due to the functional impairment and the absence of a curative treatment.

Discussion

Here, we have described the first Tunisian patient with a genetically confirmed MFM type 8. First described in 2016 by O'Grady et al., MFM type 8 is a autosomal recessive myofibrillar myopathy, usually presenting with a congenital onset, caused by PYROXD1 variants³. Pyridine nucleotide-disulfide oxidoreductase domain-containing protein1 (PYROXD1) is a 500 amino-acid enzyme that plays a role in redox reactions involving pyridine nucleotides.

Based on clinical features, three main phenotypes associated with PYROXD1 gene causative variants have been described. Polyneuropathy has been reported only once, presenting as axonal polyneuropathy in late childhood, with biopsy showing dystrophic changes⁴ while limb-girdle muscular dystrophies (LGMD). LGMD-like presentation is characterized by an age at onset between adolescence and the late fifties⁵. This phenotype features predominantly axial motor weakness with mild to moderate deficit and slow progression⁶. MFM type 8 was formerly classified as LGMD1A before the identification of the PYROXD1 gene variants⁷. MFM type 8 can also present as congenital myopathy featuring hypotonia, restrictive lung disease, dysphagia, joint laxity, and facial dysmorphism³. A case of myopathy with fatigability has been recently reported⁸.

Our patient exhibited the LGMD-like phenotype, as he developed predominantly proximal and yet moderate motor deficit at age 15 with no history of congenital hypotonia along with pathological signs of muscular dystrophy on biopsy. To date, 26 cases of PYROXD1-related MFM type 8 have been reported worldwide. Among them, 18 had the LGMD-like presentation and 20 were related to c.464A > G p.(Asn155Ser) variant. Similar to previous cases, our patient displayed progressive, predominantly proximal weakness and hyporeflexia. However, our patient did not present signs of respiratory or cardiac weakness, nor did he exhibit any joint hypermobility that was frequently observed in previous comparable cases.

Muscle biopsy findings are peculiar in this disease. First, vacuoles, a characteristic of myofibrillar myopathies, have never been reported in patients with MFM type 8. Moreover, pathological aspects of MFM type 8 do not differ according to genotype and present mostly with cores and central nuclei⁵.

In MFM type 8, more than 7 pathogenic variants have been reported in the literature. Most cases of the disease have been described in European and Turkish patients. However, an Indian and a Sudanese case have been recently published^{8,9}.

To our best knowledge, this is the first occurrence of MFM type 8 in Tunisia and North Africa. This case report expands the geographical spectrum of this disease.

The c.464A > G p.(Asn155Ser) variant, identified in our patient, is

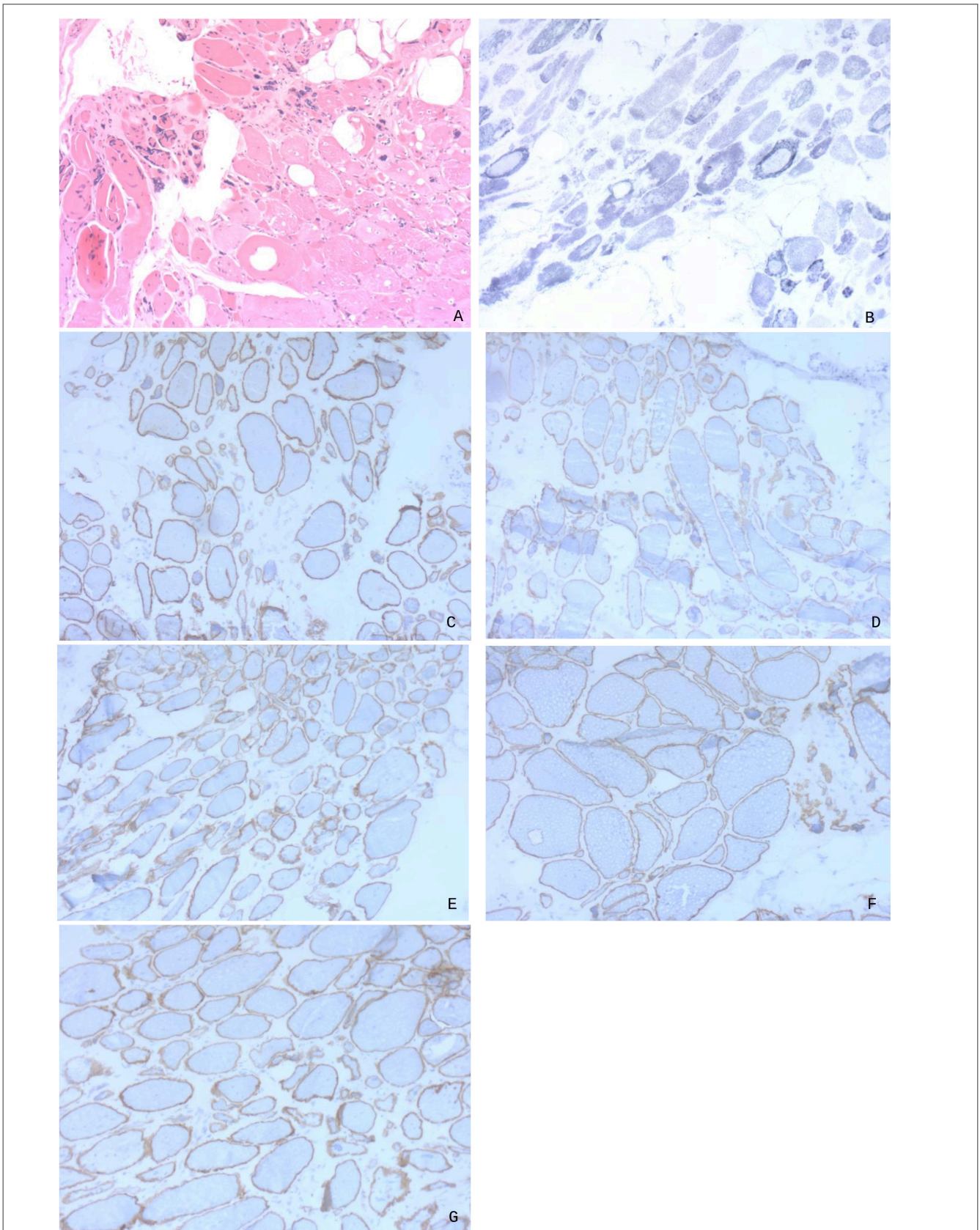


Figure 1. Muscle biopsy of our patient consistent with limb-girdle muscle dystrophy

(A): on hematoxylin eosin staining, dystrophic fibro-adipose remodeling in striated muscle with uneven size and shape of muscle fibers. (B): NADH staining showing well-defined vacuoles within the cytoplasm. An increase in the number of nuclei with centralization in some areas was noted, as well as some necrotic muscle fibers infiltrated with macrophages. (C): Normal Dystrophin staining immunofluorescence. (D): Normal alpha - sarcoglycan staining immunofluorescence. (E): Normal beta - sarcoglycan staining immunofluorescence. (F): Normal gamma - sarcoglycan staining immunofluorescence. (G): Normal delta - sarcoglycan staining immunofluorescence.

Table 1. Clinical features of previously reported cases of myofibrillar myopathy type 8 related to PYROXD1 gene variants.

Main author	Year of publication	Ethnicity (number of cases)	Age at onset (number of cases)	Motor deficit (number of cases)	Associated signs (number of cases)	Causative variant (number of cases)
O' Grady et al.	2016	Turkish (5)	Infantile-onset (5)	LGMD-like (5)	Hyporeflexia (5), Achilles contractures (1), bulbar involvement (5), ptosis (1)	c.464A>G p.(Asn155Ser)* (7)
		Persian-Jewish (2)	Congenital onset (1) Infantile onset (1)	-Congenital myopathy (1) -LGMD-like (1)	Hyporeflexia (2), Achilles contractures (1), joint hypermobility (2), bulbar involvement (2), ptosis (2), high-arched palate (2)	
		European (2)	Infantile onset (2)	LGMD-like (2)	Bulbar involvement (2),	c.285 p1G>A (chr12: g.21598401G>A), c.116G>C (p.Gln372His, chr12: g.21615796G>C) (2)
Sainio et al.	2019	Finnish (4)	Adult-onset (3) Infantile onset (1)	LGMD-like (4)	Bulbar involvement (1), ptosis (1)	c.464A>G p.(Asn155Ser)* (4)
Saha et al.	2018	Sudanese (1)	Infantile onset (1)	LGMD-like (1)	Not available	c.464A>G p.(Asn155Ser)* (1)
Lornage et al	2019	French (3)	Neonatal onset (2),	Congenital myopathy (2),	Joint hypermobility (1), high-arched palate (1)	c.285 +1G > A (intron 3), c.464A > G p.(Asn155Ser)* (1) c.415-979A > G (non coding), c.1116G > C p.Gln372Hi (1)
			Infantile onset (1),	LGMD-like (1)	Not available	c.464A>G p.(Asn155Ser)* (1)
Daimagüler et al.	2021	Turkish (3)	Infantile onset (2) Not available (1)	LGMD-like (3)	Bulbar involvement (2), ptosis (1), polyneuropathy (1)	c.464A>G p.(Asn155Ser)* (3)
Woods et al.	2020	Persian-Jewish (3)	Adult onset (3)	LGMD-like (3)	Achilles contractures (1), bulbar involvement (1),	c.464A>G p.(Asn155Ser)* (3)
Evesson et al	2023	European (2)	Congenital onset (2)	Congenital myopathy (2)	Bulbar involvement (2)	c.464A>G p.(Asn155Ser)* (1) c.892_895del p.V298Mfs*4 (1)
Baskar et al	2025	Indian (1)	Infantile onset	Fatigability, proximal myopathy	Hyporeflexia (1), polyneuropathy, (1), joint hypermobility (1), high-arched palate (1)	c.394C > T (p. Arg132Cys) (1)

*NM_024854.3 – genome reference : chr12:21452130 A>G (hg38)

LGMD: Limb-girdle muscular dystrophy.

the most frequent variant in MFM type 8, accounting for 20 among the 26 cases worldwide (Tab. 1). It is the Turkish founder variant that has also been identified in other ethnic groups ⁴. Regarding genotype-phenotype correlations, carriers of this missense mutation at the homozygous or compound heterozygous states exhibit almost always with infantile onset or adult onset LGMD-like phenotype (Tab. 1). Our patient was no exception to this rule. It worth noting that two further cases having this variant presented with the congenital myopathy phenotype ^{3,10}. Associated signs such as bulbar involvement, hyporeflexia and joint hypermobility are most-likely a part of the clinical spectrum of MFM type 8 ¹⁰. Hyporeflexia was observed in our patient as well as almost all reported cases.

Conclusions

Herein, we expanded the ethnic groups affected by PYROXD1-associated MFM type 8. We reported the first North-African case of this disease presenting with LGMD-like symptoms and hyporeflexia. This case highlights the importance of suspecting PYROXD1-associated MFM type 8 in patients developing slowly progressive LGMD-like presentation during adolescence or adulthood with normal CK.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors contributions

Mohamed Slim Majoul: Writing – original draft; Rania Zouari: Writing – review & editing; Anis Hassine: Conceptualization; Moncef Mokni: Data curation; Samia Ben Sassi: Validation

Ethical consideration

Ethics approval and consent to participate: This paper was written according to Helsinki Declaration. All personal data and identity of the patient were anonymized.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the reviewers and the Editor-in-Chief of this journal.

Availability of data and material: Data sharing does not apply to this article, as no datasets were generated or analysed during the current study.

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