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CASE REPORT

ANO5-related limb-girdle muscular dystrophy mimicking inflammatory myopathy: first Tunisian case report

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Objective. Limb-girdle muscular dystrophy type R12 (LGMDR12), caused by biallelic ANO5 mutations, is an autosomal recessive myopathy characterized by adult-onset asymmetric weakness and marked hyperCKemia. Its phenotypic spectrum remains incompletely defined, particularly in North African populations. This study aimed to report the first genetically confirmed Tunisian case of LGMDR12 with inflammatory myopathy-like features and early subclinical cardiac involvement.
Methods. We describe the clinical, laboratory, muscle imaging, histological, genetic, and cardiac findings of a 36-year-old Tunisian man with progressive asymmetric proximal lower-limb weakness.
Results. The patient, born to first-degree consanguineous parents, had severe hyperCKemia (60 times the upper limit of normal), negative myositis-specific antibodies, and a myopathic electromyographic pattern. Muscle MRI showed hamstring fatty infiltration and focal fascicular STIR hyperintensities of the right vastus lateralis. Muscle biopsy revealed dystrophic changes with focal pseudo-granulomatous inflammatory infiltrates, leading to an initial inflammatory myopathy suspicion. Corticosteroid therapy resulted in transient CK reduction but no sustained response. Whole-exome sequencing identified a homozygous pathogenic ANO5 variant (c.172C > T, p.Arg58Trp), confirming LGMDR12. Cardiac MRI performed for palpitations despite normal ECG and echocardiography demonstrated septal hypertrophy and diffuse myocardial oedema without late gadolinium enhancement or fibrosis, suggesting early subclinical cardiac involvement.
Conclusions. This case highlights the diagnostic challenge of ANO5-related myopathy, which may mimic inflammatory myopathy histologically and clinically. Genetic testing is essential in atypical myopathies with persistent hyperCKemia and may reveal previously unrecognized cardiac involvement.

Key words: ANO5, LGMD-R12, limb-girdle muscular dystrophy, inflammatory myopathy, cardiac MRI

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Introduction

Limb-girdle muscular dystrophy type R12 (LGMDR12) is an autosomal recessive myopathy caused by biallelic pathogenic variants in the *ANO5* gene. Mutations in *ANO5* cause a broad spectrum of muscle disorders, ranging from LGMDR12 and Miyoshi muscular dystrophy type 3 (MMD3) to distal myopathies, asymmetrical muscle involvement, and persistent asymptomatic hyperCKemia [1].

LGMDR12 is typically characterized by adult-onset, slowly progressive proximal lower-limb weakness, marked hyperCKemia, and a highly variable clinical presentation with significant intrafamilial and interfamilial phenotypic heterogeneity. ANO5 encodes anoctamin-5, a transmembrane protein involved in sarcolemmal membrane repair, and its deficiency leads to repeated myofiber injury with secondary degenerative and inflammatory changes [2].

The diagnosis of LGMDR12 may be challenging because clinical manifestations, muscle MRI, and histopathological findings can overlap with autoimmune inflammatory myopathies, occasionally resulting in inappropriate immunosuppressive treatment. In addition, while cardiac involvement is classically considered uncommon in anoctaminopathies, subclinical rhythm disturbances and structural myocardial alterations are increasingly recognized [3]. Furthermore, data regarding *ANO5*-related disease in North African populations remain extremely scarce.

Herein, we report the first genetically confirmed Tunisian patient with LGMDR12 due to a homozygous *ANO5* variant (c.172C > T; p.Arg58Trp), presenting with a pseudo-inflammatory phenotype, pseudo-granulomatous inflammatory changes on muscle biopsy, and diffuse myocardial edema on cardiac magnetic resonance imaging without myocardial fibrosis. This case suggests a possible expansion of the clinico-pathological spectrum of ANO5-related myopathy and highlights important diagnostic pitfalls.

Case observation

A 36-year-old Tunisian man, born to first-degree consanguineous Tunisian parents, with no significant medical history, was referred for a progressively worsening proximal motor weakness of the lower limbs evolving over few years. He reported no myalgia or systemic manifestations. There was no history of toxic exposure, or family history of neuromuscular disease. Neurological examination revealed asymmetric proximal lower limb weakness, predominantly affecting hip flexors and knee extensors.

Laboratory investigations showed marked hypercreatine phosphokinase (CK) elevation, reaching 60 times the upper limit of normal. Thyroid function tests and myositis-specific and myositis-associated autoantibodies were negative. Electromyography demonstrated a myopathic pattern. Muscle MRI revealed fatty infiltration and bilateral atrophy of the hamstring muscles, associated with signs of active muscle involvement characterized by fascicular STIR hyperintensities, particularly involving the right vastus lateralis muscle (Fig. 1).

Muscle biopsy showed dystrophic changes, including fiber size variability and repeated cycles of degeneration and regeneration, associated with a focal inflammatory infiltrate organized in pseudo-granulomatous structures (Fig. 2). Based on the initial suspicion of seronegative inflammatory myopathy, corticosteroid therapy was initiated at a dose of 1 mg/kg/day. This resulted in partial improvement of muscle strength and a decrease in CK levels (to 20 times the upper limit of normal); however, this response was transient, with secondary enzyme elevation despite maintenance therapy.

Given this atypical profile, Whole-exome sequencing identified a homozygous pathogenic variant, c.172C > T (p.Arg58Trp), in the ANO5 gene, confirming the diagnosis of limb-girdle muscular dystrophy recessive type 12 (LGMDR12).

Cardiac evaluation, performed because of rare episodes of palpitations in an otherwise cardiovascularly asymptomatic patient, showed a normal electrocardiogram and transthoracic echocardiography. However, cardiac magnetic resonance imaging revealed mild septal hypertrophy associated with diffuse myocardial edema, evidenced by increased T2 mapping signal, without late gadolinium enhancement or evidence of established fibrosis, suggesting early subclinical myocardial involvement.

Corticosteroids were progressively tapered and discontinued. Current management is supportive, including functional rehabilitation, avoidance of intense eccentric muscle exercise, and close cardiac surveillance.

Discussion

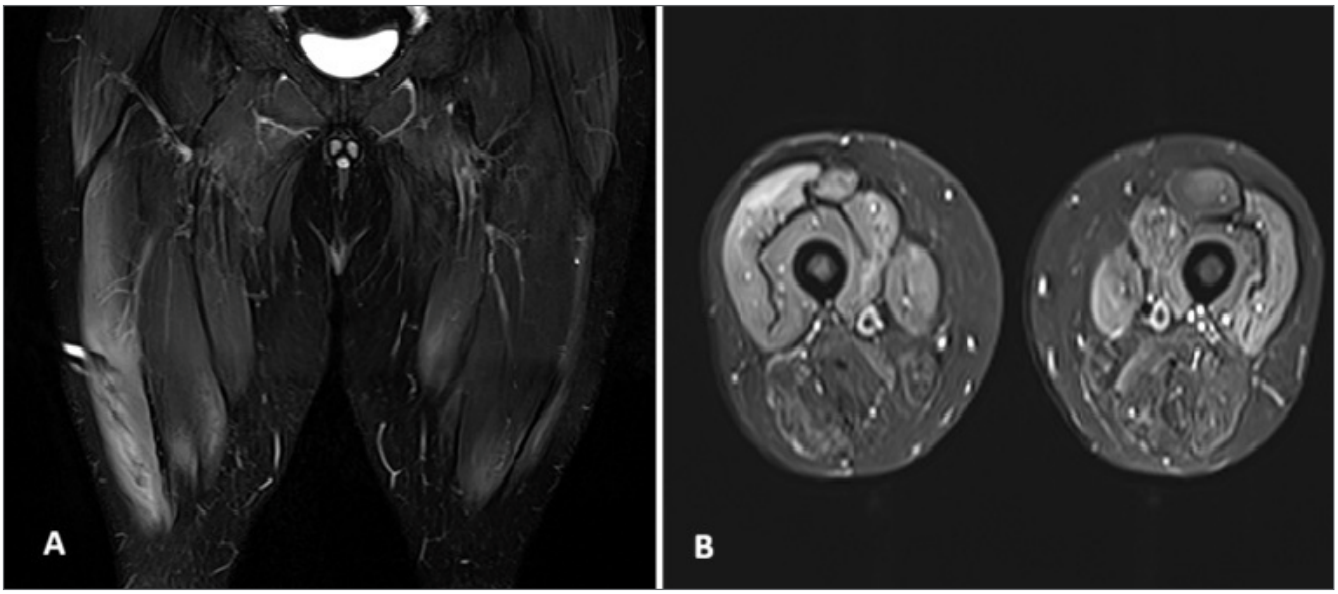


Figure 1. Muscle MRI findings. (A) Coronal STIR image of both thighs showing fascicular STIR hyperintensity in the bilateral vastus lateralis muscles, more pronounced on the right. (B) Axial STIR image of the mid-thighs showing superficial STIR hyperintensity in the right vastus lateralis muscle, with bilateral atrophy and diffuse fatty infiltration of the hamstring muscles.

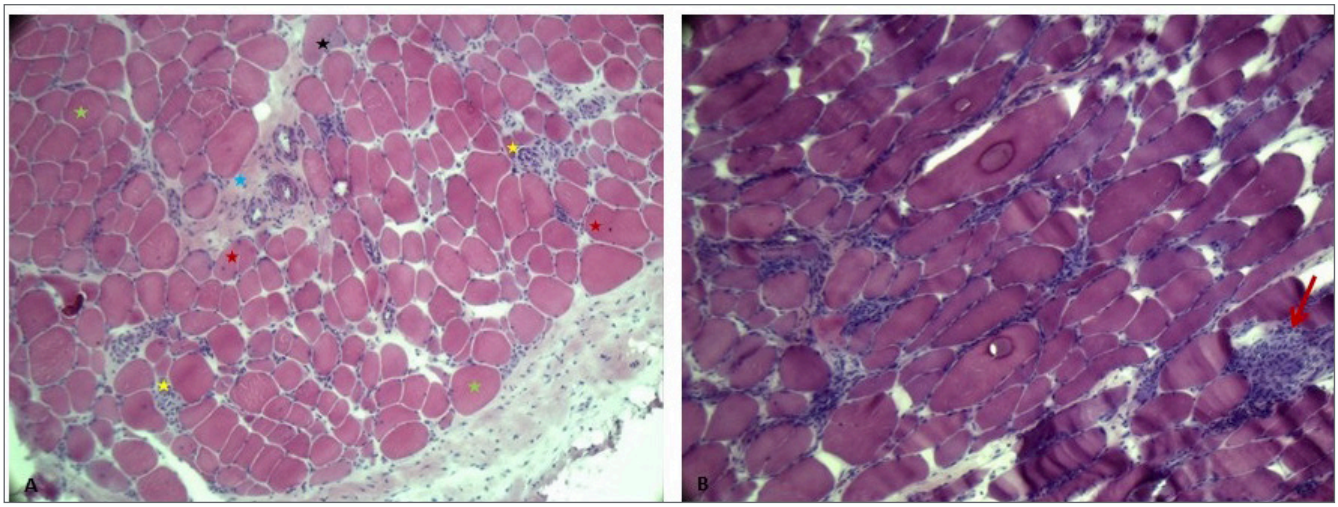


Figure 2. Muscle biopsy findings. Hematoxylin and eosin staining of the quadriceps muscle in transverse sections (A, B), showing marked variation in muscle fiber size with necrotic fibers (yellow asterisk), basophilic regenerating fibers (black asterisk), internal nuclei (red asterisk), rounded hypertrophic fibers (green asterisk), increased endomysial connective tissue (blue asterisk), and inflammatory infiltrates with pseudogranulomatous aggregates (red arrow).

We report the first genetically confirmed Tunisian case of LGMDR12 caused by a homozygous *ANO5* variant (c.172C > T; p.Arg58Trp). This case is distinguished by pseudo-granulomatous inflammatory lesions on muscle biopsy, an unusual histopathological finding, and diffuse myocardial edema without late gadolinium enhancement on cardiac MRI, suggesting a possible expansion of the recognized clinico-pathological spectrum of ANO5-related myopathy. It also highlights important diagnostic pitfalls and suggests that ANO5-related disease may be underrecognized in North African populations.

Pseudo-granulomatous inflammatory lesions: a diagnostic pitfall

The inflammatory component observed on muscle biopsy represented the main diagnostic challenge in our patient. Histological examination showed unequivocal dystrophic changes associated with prominent endomysial inflammatory infiltrates and focal pseudo-granulomatous aggregates. While inflammatory infiltrates have been reported in 13-31% of ANO5-related myopathies and may mimic inflammatory myopathy [4,5], pseudo-granulomatous lesions have not, to our knowledge, been previously described.

This unusual histological pattern broadened the differential diagnosis to include granulomatous myositis, seronegative immune-mediated necrotizing myopathy, and, less likely, inclusion body myositis [6]. However, unlike autoimmune myopathies, inflammation in ANO5-related disease is considered a secondary consequence of defective sarcolemmal repair and ongoing myofiber degeneration rather than a primary immune process [4].

In our patient, the combination of marked hyperCKemia, STIR muscle edema, inflammatory biopsy findings, and an initial biochemical response to corticosteroids strongly favored an inflammatory myopathy. The identification of a homozygous pathogenic *ANO5* variant ultimately established the diagnosis of LGMDR12, demonstrating that even prominent inflammatory infiltrates with pseudo-granulomatous features should not be regarded as evidence of autoimmune myositis. This case highlights the importance of integrating clinical, imaging, histopathological, and genetic findings before initiating long-term immunosuppressive therapy.

Cardiac MRI: diffuse myocardial edema without fibrosis

Cardiac involvement in ANO5-related myopathy is considered uncommon but increasingly recognized, ranging from subclinical rhythm abnormalities to cardiomyopathy. However, myocardial tissue characterization remains poorly documented. In the largest cardiac MRI phenotyping study of genetically confirmed ANO5-related disease, subtle abnormalities were identified, including late gadolinium enhancement (LGE) in a subset of patients, whereas myocardial edema or inflammatory changes were not reported [7].

Our patient exhibited diffuse myocardial edema on T2 mapping (54 ms) associated with mild septal hypertrophy, despite normal ECG, preserved ventricular function, and absence of LGE or evidence of myocardial fibrosis. This pattern may represent an early stage of myocardial involvement preceding irreversible structural remodeling. Given the role of ANO5 in membrane repair mechanisms, a primary myocardial involvement related to impaired membrane integrity represents a plausible hypothesis [2].

To our knowledge, diffuse myocardial edema without established fibrosis has not previously been described in genetically confirmed LGMDR12. This finding may expand the cardiac phenotype of ANO5-related myopathy and suggests that advanced cardiac MRI techniques may reveal subclinical myocardial abnormalities not detected by conventional cardiac assessment. Further longitudinal studies are required to determine the prevalence, prognostic significance, and clinical implications of these findings.

Corticosteroid therapy: a transient and misleading response

The initial decline in creatine kinase (CK) levels following high-dose corticosteroid therapy represented an additional diagnostic challenge in our patient. Treated initially for presumed inflammatory myopathy,

he showed partial clinical improvement with a marked CK reduction; however, persistent weakness and subsequent CK elevation despite maintenance therapy argued against a sustained effect.

Although corticosteroid responsiveness is uncommon in genetic myopathies, transient biochemical improvements have been reported in some muscular dystrophies with inflammatory features. The pilot Weekly Steroids in Muscular Dystrophy (WSiMD) study [8] also suggested that glucocorticoids may modulate secondary inflammatory pathways in LGMD and Becker muscular dystrophy, with trends toward reduced CK levels and functional improvement, without proving a disease-modifying effect.

In ANO5-related myopathy, inflammatory infiltrates are considered secondary to chronic myofiber injury and defective membrane repair rather than a primary autoimmune proces [4]. Corticosteroids may therefore suppress this secondary inflammatory response, explaining the transient biochemical improvement observed in our patient, while failing to modify the underlying dystrophic process. This highlights the risk of misdiagnosis and prolonged unnecessary immunosuppression in ANO5-related disease.

Genetic and epidemiological specificities in North Africa

Although ANO5-related myopathies are well characterized in European populations [9], their epidemiological and genetic spectrum remains poorly documented in North Africa. In this region, autosomal recessive muscular dystrophies have historically been dominated by sarcoglycanopathies [10], while the prevalence and mutational landscape of ANO5-related disease remain largely unknown. Unlike Northern Europe, where the founder variant c.191dupA is prevalent, no specific recurrent ANO5 variant has been established in Maghrebian populations.

The homozygous pathogenic variant identified in our patient, c.172C > T (p.Arg58Trp), represents the first genetically confirmed report of LGMDR12 in Tunisia. Previously classified as pathogenic in international databases (ClinVar ID:VCV000197402) [11] and associated with different ANO5-related phenotypes, this variant further illustrates the marked clinical heterogeneity of anoctaminopathies, presenting in our case with an inflammatory-like phenotype, severe hyperCKemia, and myocardial involvement. This classification is further supported by expert curation from the ClinGen Limb Girdle Muscular Dystrophy Variant Curation Expert Panel, using disease-specific ACMG/AMP criteria [12]. The supporting evidence includes segregation in affected families, with individuals carrying either homozygous c.172C > T or compound heterozygous (c.172C > T in trans) with pathogenic ANO5 variants, demonstrating phenotype concordance and consistent segregation patterns. The variant also has an extremely low frequency in population databases [11].

Whole-exome sequencing (WES) was performed and did not identify any additional clinically significant variant that could readily explain the patient's phenotype. However, WES cannot completely exclude pathogenic variants in deep intronic or regulatory regions, certain structural variants, low-level mosaic variants, or other alterations beyond the technical scope of the assay [13]. Therefore, although the homozygous pathogenic ANO5 variant provides a compelling explanation for the muscular phenotype, the contribution of an additional genetic factor, particularly a variant in a cardiomyopathy-associated gene, cannot be entirely excluded.

This observation suggests that ANO5-related myopathies may be underrecognized in Tunisia and possibly in North African populations. The overlap with seronegative inflammatory myopathies, combined with limited access to molecular diagnosis, may contribute to delayed or incorrect classification. Wider use of next-generation sequencing, including targeted neuromuscular panels or exome sequencing when appropriate, may improve diagnosis of adult-onset myopathies with persistent hyperCKemia, particularly in populations with high rates of consanguinity.

Conclusion

We report the first genetically confirmed Tunisian case of LGMDR12 due to a homozygous *ANO5* variant (c.172C > T; p.Arg58Trp), characterized by two unusual features: pseudo-granulomatous inflammatory changes on muscle biopsy and diffuse myocardial edema without fibrosis on cardiac MRI. These findings broaden the phenotypic spectrum of ANO5-related disease and emphasize the potential diagnostic overlap with autoimmune inflammatory myopathies. The transient response to corticosteroids further illustrates the secondary nature of inflammation in this genetic myopathy and the importance of integrating clinical, histological, and molecular data for accurate diagnosis.

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Conflict of interest statement

The authors declare that they have no competing interests.

Authors contributions

Mariem Essouri: Writing – review & editing; Walid Tiouiri: Writing – original draft; Emna Farhati: histopathological analysis – Provision of biopsy images– Critical revision; Imen Mariem Abbassi: Data curation; Naziha Khammassi: Validation.

Ethical consideration

This case report was conducted in accordance with the principles of the Declaration of Helsinki. All personal data and identifying information of the patient were anonymized.

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 the 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. All relevant clinical information is included within the manuscript.

Declaration of generative AI and AI-assisted technologies:

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing and improve the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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