

CLINICAL CASE OF A PATIENT WITH MITOCHONDRIAL MYOPATHY – DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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Abstract. Mitochondrial myopathies are a heterogeneous group of hereditary neuromuscular disorders in which pathogenic alterations in mitochondrial or nuclear DNA impair oxidative phosphorylation. The clinical spectrum is broad and frequently includes multisystem involvement, such as muscle weakness, sensorineural hearing loss, cardiac manifestations, and neurological symptoms. Due to the overlap of these features with autoimmune myositis, establishing the correct diagnosis presents a significant challenge in rheumatologic practice. We report the case of a 54-year-old woman with progressive proximal muscle weakness, myalgia, and sudden bilateral sensorineural hearing loss, initially suggestive of autoimmune myositis. Paraclinical investigations demonstrated elevated muscle enzymes, a myopathic pattern on electromyography, and a chronic inflammatory infiltrate on muscle biopsy. Molecular-genetic testing revealed a heteroplasmic MT-TK m.8344A>G mutation, confirming the diagnosis of mitochondrial myopathy. This case highlights the role of genetic evaluation in patients with multisystem symptoms and its importance in avoiding unnecessary immunosuppressive therapy.

Key words: mitochondrial myopathy, m.8344A>G, sensorineural hearing loss, myopathic damage, differential diagnosis

INTRODUCTION

Mitochondrial myopathies are a heterogeneous group of inherited disorders caused by pathogenic changes in mitochondrial DNA (mtDNA), as well as nuclear genes encoding essential components of mitochondrial energy metabolism [1, 2]. Defects in oxidative phosphorylation result in insufficient production of adenosine triphosphate and in increased generation of oxygen radicals, which secondarily damage cellular structures, disrupt calcium homeostasis, and enhance apoptotic processes [4]. Clinical presentation is highly variable and may include proximal muscle weakness, myalgia, cardiomyopathy, endocrine abnormalities, sensorineural hearing loss, or diverse neurological symptoms [1, 2]. This heterogeneity often mimics autoimmune myositis and can lead to diagnostic delay, especially in patients with multisystem involvement [1, 2, 13]. The m.8344A>G mutation in the MT-TK gene, encoding mitochondrial tRNA^{Lys}, is classically associated with MERRF syndrome, but subsequent studies have revealed a much broader phenotype including myopathy, sensorineural deafness, peripheral neuropathy, and other systemic manifestations [3, 9, 10]. This phenotypic diversity is explained by variable levels of heteroplasmy and unequal tissue distribution of the mutation [2, 11].

The diagnostic approach in patients with progressive muscle weakness and multisystem features requires an integrated, multimodal strategy, including assessment of serum muscle enzymes, electromyography, histopathological examination of muscle tissue, and molecular-genetic testing. Although muscle biopsy remains an important diagnostic tool, the implementation of expanded genetic panels and next-generation sequencing has significantly improved early detection of pathogenic variants and often reduces the need for invasive procedures [1, 6]. Consensus documents of the Mitochondrial Medicine Society (2015-2023) emphasize the importance of a standardized diagnostic algorithm and identify molecular-genetic analysis as a key element in patients with heterogeneous or incomplete clinical phenotypes, particularly in early disease stages [6].

The aim of this publication is to present a clinical case of mitochondrial myopathy confirmed by the identification of a heteroplasmic m.8344A>G mutation, demonstrating typical diagnostic challenges and underscoring the importance of a multidisciplinary approach.

CASE PRESENTATION

We report the case of a 54-year-old woman admitted for diagnostic evaluation due to progressive proximal muscle weakness accompanied by myalgia and

sudden bilateral sensorineural hearing loss. Her initial symptoms appeared in 2020, with subsequent progression during 2023-2024. The patient reported a significant family history: a mother with muscle weakness and deafness who died at 67 from acute heart failure, and a brother diagnosed clinically with “polymyositis,” with symptom onset at the age of 37 and death at 49. Comorbidities included arterial hypertension, ischemic heart disease, dilated cardiomyopathy, chronic heart failure (NYHA III), and type 2 diabetes mellitus.

The family history, combined with the systemic nature of her clinical manifestations, raised suspicion for a hereditary – specifically mitochondrial – disorder. Neurological examination revealed a pronounced myopathic syndrome with symmetric proximal muscle weakness, lower limb hypotrophy, a myopathic gait, and reduced to absent knee reflexes. Achilles tendon reflexes were absent bilaterally. Findings were also consistent with a polyneuropathic syndrome, including peroneal and marked tibial paresis.

Laboratory tests showed moderate elevation of creatine phosphokinase and transaminases, low inflammatory activity, and a positive ANA titer of 1:320 with negative myositis-specific antibodies (Table 1). Electromyography demonstrated a myopathic pattern. Muscle biopsy revealed isolated dystrophic fibers and chronic inflammatory infiltrates – findings that may be misleading, as they occur in both inflammatory and mitochondrial myopathies.

Echocardiography demonstrated left ventricular hypertrophy, mild aortic and mitral regurgitation (grade 0-1), and moderate tricuspid regurgitation (grade 2). Audiometry confirmed severe bilateral sensorineural hearing loss. Additional imaging studies showed diffuse hepatic parenchymal changes and bilateral renal abnormalities (calcifications, microlithiasis, right kidney cyst). Given the clinical picture, family history, and discordance with classical inflammatory myopathies, molecular-genetic testing was performed, revealing a heteroplasmic pathogenic MT-TK m.8344A>G mutation (tRNA^{Lys}), confirming mitochondrial myopathy.

Table 1

Parameter	Result
CPK	up to 689 U/L
ASAT	53 U/L
ALAT	45.9 U/L
ESR	20 mm/h
CRP	2.60 mg/L
ANA-screen	1:320
Myositis-specific antibodies	negative

Note: Moderate elevation of muscle enzymes is present, with absent significant inflammatory activity and negative myositis-specific autoantibody profile

DISCUSSION

Mitochondrial myopathies often mimic autoimmune myositis, especially when muscle enzymes are elevated and non-specific histological abnormalities are present. The differential diagnosis includes polymyositis, dermatomyositis, immune-mediated necrotizing myopathy, and inclusion body myositis [13]. In the present case, a positive ANA (1:320), negative ANA immunoblot, and inflammatory infiltrates on biopsy further complicated the diagnostic process. However, the absence of myositis-specific antibodies, positive family history, and multisystem involvement favored a mitochondrial etiology, consistent with contemporary diagnostic algorithms. Muscle biopsy can be misleading, as inflammatory features may also occur in mitochondrial disorders [3, 5, 7, 13].

Table 2. Key distinguishing features between mitochondrial myopathy and autoimmune myositis

Characteristics	Mitochondrial Myopathy	Autoimmune Myositis (AIM)
Family history	Often maternal inheritance	Usually absent
Serology	ANA ±, no myositis-specific antibodies	Frequently positive for myositis-specific antibodies
Muscle biopsy	Dystrophic fibers, ragged-red fibers	Inflammatory infiltrates, necrosis
Multisystem involvement	Common (heart, hearing, CNS)	Less common
Therapeutic response	Ineffective response to immunosuppression	Responds to immunosuppressive therapy

Currently, no etiological treatment exists for most mitochondrial myopathies. However, ongoing clinical studies are actively exploring novel therapeutic strategies [16]. In the United States, elamipretide received FDA approval as the first registered therapy for Barth syndrome [24]. This approval was based on clinical trial data, including the TAZPOWER study. Although limited to this rare disorder, it represents a major step toward targeted treatment options for mitochondrial diseases and stimulates further research in the field [19, 20, 22].

Additional clinical trials are underway in patients with mitochondrial myopathies. Among them is the phase III randomized, double-blind MMPOWER-3 study evaluating the efficacy and safety of elamipretide in primary mitochondrial myopathy. Despite good tolerability, the study did not demonstrate statistically significant improvement in key clinical endpoints, such as the six-minute walk test and fatigue indices [21].

One of the promising therapeutic approaches includes supplementation with pyrimidine deoxynucleosides in TK2 deficiency, where clinical series have reported substantial improvements in survival and motor function, especially in early-onset disease [17, 18]. Other explored compounds aim to enhance mitochondrial biogenesis (e.g., niacin, bezafibrate, epicatechin) or exert antioxidant effects, including EPI-743 (vatiquinone), vitamin E, vitamin C, and α -lipoic acid [16]. Additional interest has been directed toward agents stabilizing cardiolipin, such as elamipretide, whose role is being investigated in various mitochondrial dysfunctions [22].

Genetic therapies for mitochondrial diseases are rapidly evolving and include several experimental strategies. One approach is allotopic expression, in which nucleus-encoded versions of defective mitochondrial genes are synthesized and imported into mitochondria. Technologies for mitochondrial DNA editing, such as mtZFNs (mitochondria-targeted zinc-finger nucleases) and mtTALENs (mitochondria-targeted transcription activator-like effector nucleases), aim to selectively reduce mutant mtDNA copies. Mitochondrial replacement therapy (spindle or pronuclear transfer) is being investigated primarily to prevent maternal transmission of pathogenic mtDNA variants. All of these techniques remain in preclinical or early clinical stages and are not part of routine medical practice [23].

In everyday clinical care, nutritional supplements, such as coenzyme Q10, L-carnitine, and various vitamin cofactors, are frequently used to support mitochondrial function. Their efficacy, however, is primarily supported by small observational studies and uncontrolled case series. The heterogeneity of available data reflects genetic diversity among mitochondrial diseases and the lack of randomized controlled trials. Contemporary expert reviews also emphasize that these supplements are widely used but supported by limited evidence [14, 15]. Future developments are expected to involve advances in gene and cell therapy, mitochondrial genome editing, and metabolic reprogramming, but these approaches remain experimental.

CONCLUSION

This case illustrates the significant diagnostic challenges in distinguishing mitochondrial myopathy from autoimmune myositis. Multisystem involvement, characteristic family history, and the absence of specific myositis antibodies pointed toward a mitochondrial disorder, which was ultimately confirmed

by detecting the MT-TK m.8344A>G mutation. Timely diagnosis prevents ineffective and unnecessary immunosuppressive therapy and enables improved patient management through coordinated multidisciplinary follow-up.

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