CASE REPORT

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Discovery of a new mutation in the desmin gene in a young patient with cardiomyopathy and muscular weakness

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Abstract

A 25-year-old woman with a five years history of syncope, mild left ventricular hypertrophy and moderately enlarged atria, was diagnosed with third degree atrioventricular heart block alternating with atrioventricular heart block 2:1, and received a dual chamber pacemaker. After three years of evolution, she developed atrial fibrillation, marked biatrial enlargement, severely depressed longitudinal myocardial velocities, associated with mild girdle weakness and slight increase in creatine kinase level. The diagnosis of restrictive cardiomyopathy with mild skeletal myopathy imposed the screening for a common etiology. Skeletal muscle biopsy revealed the morphological picture of myofibrillar myopathy with sarcoplasmic aggregates, immunoreactive for desmin and other ectopic proteins on immunohistochemistry, appearing as granulofilamentous material at ultrastructural level. Western blot analysis confirmed the desmin overexpression. Genetic testing identified a heterozygous missense variant *DES* rs869025381, c.1297C>A, p.(Pro433Thr), not previously reported. This is not only the first confirmed Romanian patient with myofibrillar myopathy with clinical features of severe restrictive cardiomyopathy associated with mild skeletal myopathy, but also a case which adds up to the known mutational spectrum in desminopathy.

Keywords: restrictive cardiomyopathy, myopathy, myofibrillar myopathy, desminopathy, atrioventricular block.

Introduction

Desmin is a member of the intermediate filament family of extra-sarcomeric cytoskeletal proteins expressed in smooth, striated and cardiac muscle, playing a crucial role in maintaining the structure of sarcomeres, interconnecting the Z-disks and forming the myofibrils, linking them not only to the sarcolemmal cytoskeleton, but also to the nucleus and mitochondria, thus providing strength for the muscle fiber during activity. The protein is much more abundant in the heart muscle (2% of total protein) than in the skeletal muscle (0.35%) and is a major component of Purkinje fibers, the specialized myocardial conduction system that enables the heart to contract in a coordinated fashion [1, 2]. The protein is especially abundant at the neuromuscular junctions in the skeletal muscle and at the myotendinous junctions. Desmin is a 53-kDa protein with a tripartite structure, comprising a central-helical coiled-coil rod domain flanked by non-α-helical head and tail domains [3, 4].

Desmin-related myopathy belongs to the broad family of myofibrillar myopathies, a genetically heterogeneous group of diseases with marked phenotypic variability, characterized by distinctive skeletal and cardiac muscle morphology of abnormal protein aggregations and myofibrillar dissolution. Myofibrillar myopathies are currently proved to be caused by different mutations in genes coding for the extra-sarcomeric cytoskeleton (desmin, plectin), for components of the myofibrillar apparatus (titin, filamin-C, myotilin, FHL1, ZASP), for cellular components involved in protein quality control (αB-crystallin, DNAJB6, BAG-3), but many other yet unknown genes and proteins are probably also responsible [5, 6].

Desmin-related myopathy is known to be caused by mutations in the desmin gene *DES* located on the chromosome 2q35, consisting mostly in point mutations, insertions, small in-frame deletions and a larger exon-skipping deletion, usually transmitted in an autosomal dominant manner, sometimes also autosomal recessive or even sporadic, and manifest as isolated skeletal myopathy, isolated cardiomyopathy, conduction disease, heart failure and combinations of these disorders. The desmin gene encompasses nine exons within an 8.4-kb region, encoding for 470 amino acids [2]. Since the first description of desmin mutations in 1998, more than 70 myopathy- or cardiomyopathy-causing desmin mutations were reported, located over the entire *DES* gene, making phenotype-genotype correlations a very complex task [7].

Aim

While other cases of Eastern-European desminopathy patients were already reported, we describe here the first Romanian patient diagnosed and genetically confirmed with a form of desminopathy characterized by severe restrictive cardiomyopathy and mild skeletal myopathy, caused by a novel mutation in *DES* gene [8]. Our study not only established the clinical and genetic diagnosis for the patient, enabled the genetic counseling, but also provided a new case for the study of the complex relationship between *DES* mutations and cardiomyopathies, thus expanding the known spectrum of abnormalities in the desmin gene. With our report, we also aim to improve the awareness on these rare but severe progressive diseases, considered at the moment to be dangerously under-diagnosed.

Case presentation

A 25-year-old woman was referred to our Cardiology Department, in July 2015, for progressively increased abdominal volume noted by the patient during the previous three months, accompanied by NYHA class III dyspnea and diffuse myalgia during the previous year. The medical history of the patient started at a young age: in 2010, she had presented with a history of syncope and was diagnosed with third degree atrioventricular heart block alternating with atrioventricular heart block 2:1, for which she received a dual-chamber, rate-modulated (DDDR) pacemaker. At that time, the medical file noted mild left ventricular (LV) hypertrophy (13 mm) and moderately enlarged atria, without further etiological workup. She was lost from follow-up until 2013, when the patient was diagnosed with new onset atrial fibrillation, and the echocardiography showed no progression of LV hypertrophy, severe biatrial enlargement, moderate mitral regurgitation, severe tricuspid regurgitation and mild pulmonary hypertension. Her global LV function was preserved (LV ejection fraction of 55%) but with severely depressed longitudinal myocardial velocities (Figure 1). A diagnosis of restrictive cardiomyopathy was established and an etiological workup was begun. As the patient also associated hepatomegaly, mild thrombocytopenia and high cholestasis markers, a hepatic biopsy was performed but was unremarkable. An amyloidosis workup was negative, and enzymatic and genetic testing for Fabry disease were non-diagnostic. The patient has been discharged as idiopathic restrictive cardiomyopathy.

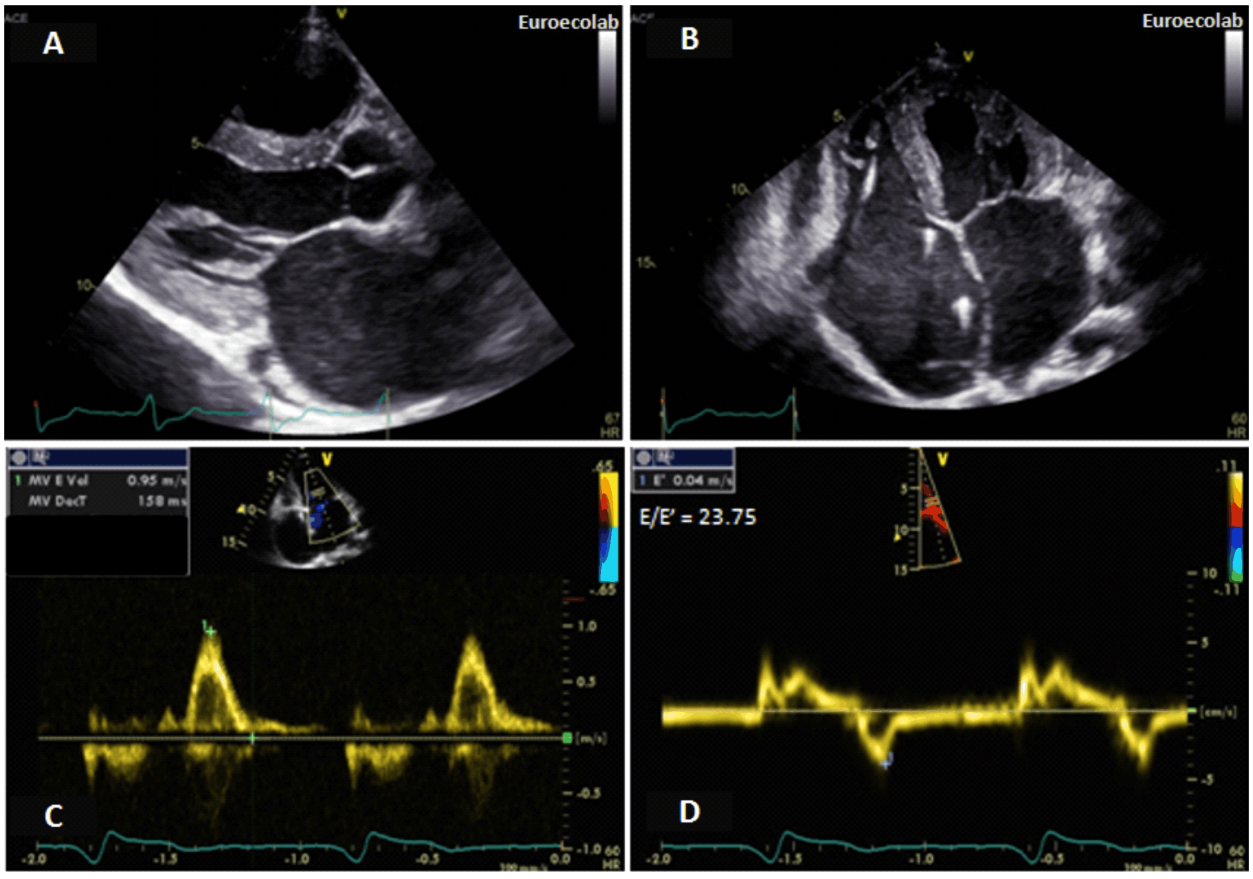

Figure 1 – ***Transthoracic echocardiography showing severe biatrial enlargement, ventricles of normal size (A and B), low myocardial velocities at the septal mitral annulus level with signs of high LV filling pressure (C and D).***

At the moment of the current admission, the clinical examination revealed a mild girdle muscular weakness, systolic murmur in tricuspid and mitral areas, a presystolic gallop rhythm, jugular veins distension, enlarged abdomen with mild ascites and hepatosplenomegaly (confirmed by abdominal ultrasound). Laboratory workup showed high brain-type natriuretic peptide (BNP) (1846 pg/mL), mild thrombocytopenia (133 000/mm^3), high serum creatine kinase (CK) (460 U/L, with CK-MB of 48 U/L), negative troponin, normal liver enzymes. Table 1 shows the progressive evolution of relevant blood tests from first evaluation in 2010 until 2015.

Table 1 – ***Evolution of laboratory values since diagnosis***

	2010	2012	2013	2014	2015
BNP [pg/mL]	592*	1146*	1182*	1705*	1846*
LDH [U/L]	278	256	256	250	303
CK [U/L]	77.7	297.2*	358*	301*	460*
CK-MB [U/L]	n/a	n/a	35	45	48
ALT [U/L]	18	12	12	7	8
AST [U/L]	24	20	27	22	25
PLT [mm^{-3}]	225 000	161 000	167 000	135 000*	133 000*

BNP: Brain-type natriuretic peptide; LDH: Lactate dehydrogenase; CK: Creatine kinase; ALT: Alanine transaminase; AST: aspartate transaminase; PLT: Platelets. *Outside of normal range; n/a: Not available.

The heart failure clinical picture responded well to intravenous diuretics with reduction of the abdominal volume and improvement of general status. Specialized evaluation in the Gastroenterology Unit suggested the presence of secondary hepatic cirrhosis, stage Child A, due to stasis.

Based on the clinical picture including mild progressive muscular weakness and myalgia, as well as the slight but progressive increase of muscular enzymes (CK), the patient was referred to a Neurology Clinic for further evaluation. Neurological examination found absence of osteotendinous reflexes in upper limbs, with preservation in the lower limbs and no pathological reflexes. No abnormality was identified in superficial or myoarthrokinetic sensation. Hippocratic fingers were noticed. Electromyography of the right deltoid muscle showed a myopathy-type of pattern with no activity at rest, a rich pattern with interference at submaximal contraction, motor unit action potentials with decreased duration and amplitude and increased polyphasic potentials. Electrophysiological studies were followed by a diagnostic open left deltoid muscle biopsy, after informed consent of the patient for the procedure was obtained.

One part of the skeletal muscle tissue was snap frozen in liquid nitrogen cooled isopentane for histological, histochemical and enzyme histochemical preparation: Hematoxylin and Eosin (HE), Van Gieson, modified Gömöri's trichrome (MGT), Periodic Acid–Schiff (PAS), Oil red O, reduced nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), lactate dehydrogenase (LDH), adenosine triphosphatase (ATPase) at pH 9.4, 4.63 and 4.35, cytochrome c oxidase (COX). Immunohistochemistry for desmin (mouse anti-human, Novocastra, Medist Life Science, Bucharest, Romania, 1:200), dystrophin (mouse anti-human Novocastra, 1:40), dystrophin-related protein 2 (mouse anti-human, Novocastra, 1:20), dysferlin (mouse anti-human, Novocastra, 1:20), major histocompatibility complex class I (MHC I) (mouse anti-human, Santa Cruz, Santa Cruz Biotechnology, Texas, USA, 1:100) was performed on muscle serial cryosections. Calpain-3 (mouse anti-human, Novocastra, 1:100) and desmin (Novocastra, 1:100), were analyzed by Western blotting (WB). For immunohistochemistry, after overnight incubation with the primary antibodies, the sections were incubated with Novolink Polymer Detection Systems kit (Novocastra) and visualized with 3,3'-diaminobenzidine (DAB, Novocastra). For WB, after tissue homogenization and protein extraction, tissue lysates were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) in 10% acrylamide gels (Bio-Rad, California, USA), blotted on polyvinylidene difluoride (PVDF) membranes in a wet transfer system (Mini-Protean Tetra, Bio-Rad), incubated overnight with the primary antibody, amplified the next day for one hour with a goat anti-mouse horseradish peroxidase (HRP) secondary (Santa Cruz, 1:45 000), detected with an enhanced chemiluminescent (ECL) kit (Thermo Scientific), and visualized under a ChemiDoc-It2 515 Imager (Analytik Jena, Upland, CA, USA). Another portion of the tissue was fixed in buffered glutaraldehyde, embedded in Epon after osmication; semi-thin and ultrathin sections were obtained and contrasted with uranyl acetate and lead citrate for electron microscopy. One piece of muscle tissue was formalin-fixed, paraffin embedded and the sections were stained with HE.

The muscle biopsy revealed a considerable fiber size variation with numerous atrophic and hypertrophic/hyper-contracted fibers, many internally located nuclei, but the most important findings were few focal sarcoplasmic amorphous inclusions within muscle fibers and also under the sarcolemma and in the perinuclear regions, colored in dark blue on the modified Gömöri trichrome staining and devoid of oxidative enzyme activities on enzymatic stainings (NADH-TR, SDH and COX). Other fibers, mainly grouped, contained inclusion body-like rimmed vacuoles. On Gömöri trichrome staining, rare fibers had a "ragged red" appearance, a finding further confirmed by the oxidative enzyme stainings. These fibers were cytochrome c oxidase-negative. Necrosis, phagocytosis, regeneration or inflammatory infiltrates were not identified on the biopsy. Type I and type II fibers were distributed in chessboard normal pattern on ATPases. On immuno-histochemistry, the sarcoplasmic inclusions revealed little scattered desmin deposits in some fibers, alongside with accumulation of dystrophin. No up-regulation of MHC I was observed on the muscle sarcolemma. The findings were further confirmed by desmin overexpression on Western blotting. Electron microscopy examination highlighted aggregates of granulofilamentous material beneath the sarcolemma and within the fibers, features considered to be the ultrastructural hallmark of desminopathies, disrupting the internal architecture, producing myofibrillar dissolution, Z-disks streaming in connection with these deposits, demonstrating the origin of the dense material, desmin, in Z-bands, alongside with autophagy vacuoles containing aggregates of myelin-like structures (Figure 2).

With the combined clinical and morphological high suspicion of a myofibrillar myopathy mainly involving the heart, we tested the patient for genetic confirmation. After written informed consent of the patient, blood for total genomic DNA was drawn and sent to Helsinki for genetic analysis (Blueprint Genetics, Helsinki, Finland). Sequence analysis using a commercially available pan-cardiomyopathy panel including 103 genes [Blueprint Genetics (BpG) Pan Cardiomyopathy Panel] using a proprietary oligonucleotide-selective sequencing (OS-Seq) method performed using an Illumina sequencing device (Illumina, Inc., San Diego, CA, USA), identified a heterozygous missense variant *DES* rs869025381, c.1297C>A, p.(Pro433Thr) in the desmin gene. To our knowledge,

this variant has not been reported in the literature or on currently available databases [9, 10]. Of note, there was no family history of neuromuscular or cardiac disorders, suggesting a *de novo* mutation in our cases. Mutation nomenclature is based on GenBank accession NM_001927.3 (*DES*) with nucleotide one being the first nucleotide of the translation initiation codon ATG. ClinVar submission accession number is SCV000263831.1.

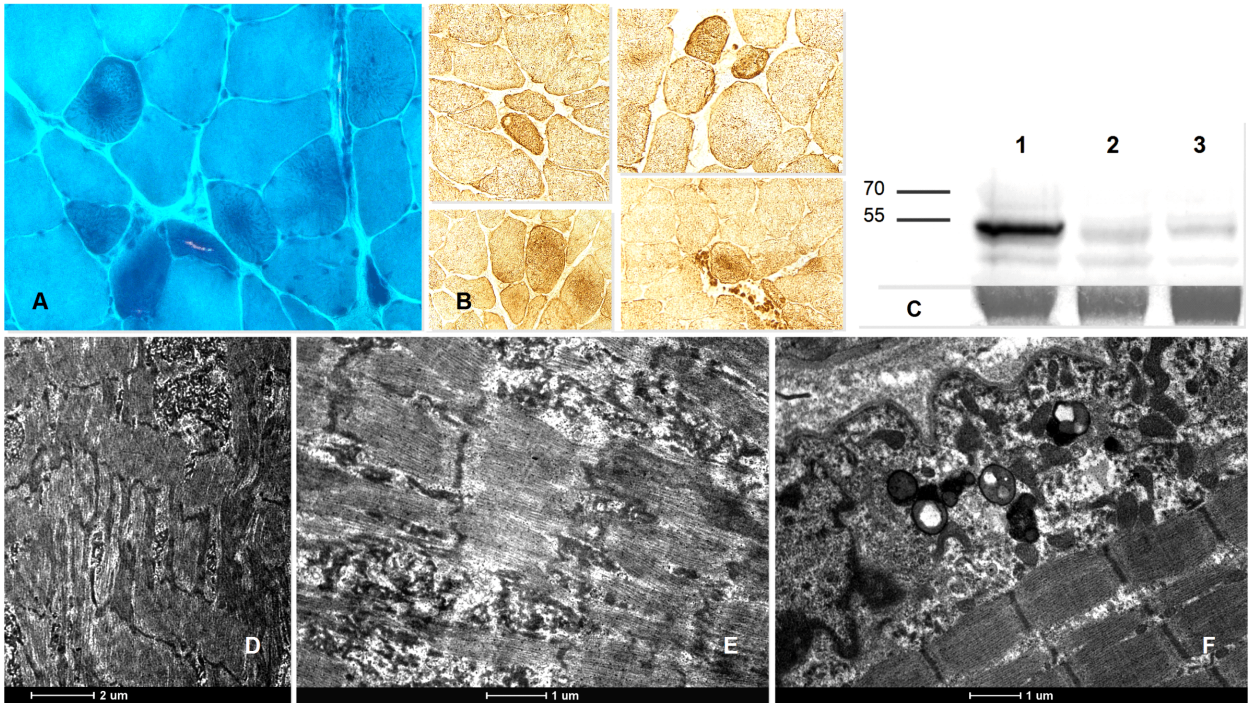

Figure 2 – ***Histopathological analysis: (A) Muscle fibers with dark bluish cytoplasmic masses and some rimmed vacuoles (cross-cryosections stained by modified Gömöri trichrome method), ×400; (B) Immunohistochemistry reveals scattered desmin deposits in some fibers (mouse monoclonal anti-desmin antibody), ×200; (C) Western blot analysis of the muscle shows desmin expression in the patient (lane 1), compared with normal muscle (control – lane 2) and with a case of limb girdle muscular dystrophy 2A (lane 3). Myosin bands (at the bottom) on the post-transfer SDS-PAGE gel stained with Coomassie blue were used as loading control. Immunoblotting showed a 53-kDa desmin band in all cases with stronger signal intensity in lane 1, indicating an increased amount of desmin; Transmission electron micrographs showing multiple deposits of granulofilamentous material with intermyofibrillary localization, many areas with Z-disks streaming (D), some being replaced by deposits of dense material (D and E) with focal disruption of myofibrils (D). Few dense bodies, degenerating membranous organelles, mitochondria and myelin-like structures near a nucleus (F).***

Discussion

Cardiovascular impairment, common during the evolution of different neuromuscular diseases in both children and adults, can precede the onset of myopathy signs or even dominate the clinical picture and manifests as dilated or hypertrophic cardiomyopathy, heart rhythm and conduction disturbances. The list of muscular diseases with cardiac involvement is very long and comprises various types of muscular dystrophies: Duchenne and Becker forms of dystrophinopathies, α-, β-, γ- and δ-sarcoglycanopathies, Emery-Dreifuss muscular dystrophies and laminopathies, FKRP-related limb-girdle muscular dystrophy type 2I and Steinert myotonic dystrophy. Other myopathies with heart impairment are metabolic diseases: mitochondrial diseases, glycogenosis, disorders of carnitine, periodic paralysis, congenital and inflammatory myopathies and myofibrillar myopathies: desminopathies, αB crystallinopathies and myotilinopathies.

The diagnostic workup of cardiomyopathies can be a challenging road, and the current recommendations of the *European Society of Cardiology Working Group of Myocardial and Pericardial Diseases* insist on an approach based on the systematic search for diagnostic clues or "red flags", which can guide a rational selection of diagnostic tests [11]. Genetic testing is appropriate for the precise diagnosis of a rare or particular cardiomyopathy, especially in the presence of atypical phenotypic features, in the setting of expert teams, after detailed clinical and family assessment [12]. Our case represents an excellent proof of concept.

The best-described cardiac manifestations of desmin mutations include restrictive or dilated cardiomyopathy, arrhythmias, heart failure, and sudden cardiac death. The age of disease onset and rate of progression is highly variable, but most common starts in the second to fourth decade of life, depending on the type of inheritance and type of causative mutation; in cases presenting with cardiomyopathy the onset tends to be earlier and the illness more severe. The youngest reported case was of a 6-month-old infant with recurrent syncope [13]. Some patients develop tachyarrhythmia, requiring implantation of a cardioverter defibrillator, and desminopathies appear to be one of the neuromuscular diseases most frequently associated with sudden cardiac death [14, 15]. This is the main reason why it is crucial to identify such patients early, as this would ensure prevention of sudden cardiac death or other severe complications. While in some reported families, cardiac conduction abnormalities usually appeared later than skeletal myopathy, in our patient the

muscular symptoms remained mild and were described succeeding the moment of cardiac diagnosis [16]. Atrioventricular conduction abnormalities requiring urgent implantation of a permanent pacemaker are a frequent feature of desminopathy. Therefore, the most common "red flags" of restrictive cardiomyopathy due to desminopathy are muscle weakness, increased CK and atrioventricular block, all present in this case.

Concerning the genetic results, it is the first report of a desminopathy with cardiac and skeletal muscle involvement, genetically confirmed in Romania. The nucleotide substitution c.1297C>A may have consequences on mRNA sequencing, and thus on protein structure. Most of the mutations described in the literature affect the highly conserved α-helical regions (rod domain) of the desmin protein. Most of the mutations result in changing one original amino acid into proline, known to be a helix breaker. In the recent years, many mutations in the desmin tail were added and involve interactions with other cytoskeletal proteins in the build-up of intermediate filament cytoplasmic network. Most of these mutations are related to a severe phenotype dominated by cardiomyopathy, as in our case [17, 18]. In our patient, *DES* rs869025381, c.1297C>A, p.(Pro433Thr) being a heterozygous mutation, it suggests autosomal-dominant transmission. Previous studies underlined that autosomal dominant and sporadic cases of desminopathies are caused by heterozygous mutations, but homozygous as well as compound heterozygous desmin mutations have been reported in rare autosomal recessive cases [4].

On the other hand, the presence of certain features of myopathy (myofibrillar dissolution with accumulation of amorphous, granular or dense cytoplasmic bodies originating in the Z-disks and ectopic expression of various proteins) shows that desmin mutation in our patient affects also the skeletal muscle, as the desmin is a Z-disc component. In this regard, it would be possible also to have a concomitant smooth muscle impairment. A systematic search for mutations in the genes related to the Z-disk-associated proteins, other than desmin, would be required: myotilin, ZASP, αB-crystallin, filamin-C and BAG-3 [19]. The severity of the myopathological changes observed on the muscle biopsy in light microscopy is highly variable, depending on the stage of disease progression. Some biopsies show only subtle myopathic changes with or without amorphous protein aggregates as pathological hallmark of the disease, or may have the picture of a vacuolar myopathy [5]. Other morphological aspects like the "rimmed vacuoles" are more nonspecific, being observed in other myopathies (especially inclusion body myositis and myopathies, distal muscular dystrophies), while the presence of rare "ragged red" fibers can be interpreted as a morphological sign of mitochondrial dysfunction, previously described in cases of myofibrillar myopathy and predictable due to the close functional interactions of intermediate filaments and mitochondria in the muscle fiber architecture [20–24].

At the ultrastructural level, identification of granulofilamentous material denser than the Z-disc in the subsarcolemmal region and/or between myofibrils is highly indicative of desminopathy, but is still a non-specific finding, such pattern of aggregation being observed in other forms of myofibrillar myopathies, especially in αB crystallinopathies. Similar deposits are identifiable in cardiomyocytes in a higher percentage of fibers, probably because desmin is much more abundant in the heart. Some authors report distinct ultrastructural patterns in different subtypes of myofibrillar myopathies and recommend electron microscopy to be included in the diagnostic workup of all these disorders [25]. Other findings like autophagy vacuoles are considered to represent an underappreciated pathology present in desminopathy patient muscle and were described in 2015 in two families with autosomal dominantly inherited myopathies with autophagy vacuolar pathology and tail domain mutation in *DES* gene. A proposed explanation is that the protein aggregates, alongside with the myofibrillar dissolution, may activate the autophagic system [26]. Finally, we consider that each novel mutation identified in *DES* gene hold an undeniable value for genotype-phenotype correlations, since currently, it is widely accepted that in the majority of myofibrillar myopathy patients the disease gene awaits discovery [27].

Conclusions

The absence of any pathology in the familial history of the patient pleads for a sporadic mutation in this case. The clinical association of severe cardiomyopathy followed by mild skeletal myopathy was caused by a novel mutation in the desmin gene. Establishing a fast and accurate diagnosis in such cases is essential for the efficient management of patient complications and for appropriate genetic counseling. Further studies on other cases from all over the world in the next years are required to get more insight into how each different mutation in desmin reflects in a specific pattern of muscular and cardiac involvement.

Conflict of interests

The authors report no relationships that could be construed as a conflict of interests.

Author contribution

Ruxandra Oana Jurcuţ and Alexandra Eugenia Bastian shared first authorship.

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