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CASE REPORT

ZASP/LDB3-related atypical distal myopathy with subtle cardiac impairment unveiled after COVID-19 infection: a short report

Giulio Gadaleta[1], Stefano Pidello[2], Guido Urbano[1], Diana Carli[3], Tiziana Mongini[1]

[1] Neuromuscular Unit, Department of Neurosciences "Rita Levi Montalcini", University of Turin, Turin, Italy; [2] Division of Cardiology, Department of Cardiovascular and Thoracic Medicine, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy; [3] Department of Medical Sciences, University of Torino, Turin, Italy

Case presentation. A 34-year-old male with congenital clubfoot, post-exertional rhabdomyolysis, and a family history of sudden cardiac death in mid-life was evaluated for a severe rhabdomyolysis requiring multiple hemodialyses. Clinical evaluation showed mild distal myopathy signs, with CK levels around 3000 IU/L and muscle biopsy revealing desmin- and dystrophin-positive cytosolic protein aggregates/fibre splitting. After a minor SARS-CoV-2 infection at 55, modest signs of cardiomyopathy were observed via cardiac MRI, without patterns indicative of myocarditis. Subsequently, NGS analysis identified a variant in the LDB3 gene, potentially correlated with the clinical-histological-radiological picture, thus broadening the phenotypic spectrum of LDB3-related distal myopathies. Additionally, a possible link was suggested between the viral infection and the exacerbation of the otherwise subtle cardiomyopathy. In the context of hyperCKemia and positive family history for unexplained cardiac abnormalities, broad-spectrum NGS testing, and cardiac MRI in selected cases, should be considered for timely diagnosis and interventions.

Keywords: hyperCKemia, LDB3, distal myopathy, cardiomyopathy, genetics

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Correspondence
Tiziana E. Mongini
E- mail: tizianaenrica.mongini@unito.it

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Introduction

Myofibrillar myopathies (MFMs) are a category of neuromuscular disorders defined by their histopathologic findings, namely focal areas of myofibrillar disorganization, accumulation of myofibrillar degradation products, and ectopic expression of numerous proteins in the sarcoplasm of muscle fibers, and they are being increasingly characterized, as demonstrated by the recent description by the Italian group [1,2]. Among these, a still underdescribed subgroup is represented by MFMs caused by Z-band alternatively spliced PDZ-motif (ZASP)/Lim domain-binding 3 (LDB3) mutations, which are rare neuromuscular disorders characterized by slowly progressing late-onset distal weakness and structural cardiac abnormalities [3]. Such cardiac manifestations render affected individuals more susceptible to life-threatening arrhythmias and significant reductions in ejection fraction, particularly when exposed to specific triggers [4,5]. The objective of this study is to present an unusual case of ZASP/LDB3-related myopathy with COVID-19-exacerbated cardiomyopathy, highlighting the atypical phenotype and the potential connection between acute infection-related myocarditis and its impact on the cardiac presentation.

Methods

A cross-sectional evaluation was conducted, encompassing the patient's medical history, skeletal muscle biopsy, muscle magnetic resonance imaging (MRI), cardiac assessments (including cardiac outpatient visits, electrocardiograms, trans-thoracic echocardiograms, cardiac magnetic resonance imaging 1.5 Tesla - MRI 1.5T), and next-generation sequencing (NGS) targeting a wide range of genes associated with myopathies and cardiomyopathies. Informed consent for genetic analysis and consent-to-disclose were obtained from the patient.

Results

We first evaluated the male patient at the age of 34, when he experienced a severe episode of post-exertional rhabdomyolysis (peak CK around 300,000 IU/L), requiring six cycles of inward dialysis. His family history revealed a myocardial infarction in his maternal grandfather at the age of 59, leading to a fatal outcome within one week, despite the absence of known cardiovascular risk factors. The patient reported being born with a clubfoot and experiencing multiple episodes of pigmenturia following moderate-intensity physical activities since adolescence. Neurological examination at that time, considering the post-rhabdomyolysis, revealed ankle retractions, modest dorsal scoliosis, and bilateral symmetrical hypotrophy of the medial gastrocnemius and lateral/posterior distal thighs. A quadriceps biopsy performed after the acute phase (still age 34) revealed notable myopathic alterations, including rod-like dystrophin and desmin positive cytoplasmic bodies in approximately 5% of muscle fibres (Fig. 1) and widespread myofibrillar disruption upon ultrastructural examination. Furthermore, immunohistochemical tests revealed a diffuse cytoplasmic positivity for desmin (around 10% of fibres) even outside cytoplasmic bodies, while the others comprising dystrophin (further analyzed via western blot), alfa- and gamma-sarcoglycan, merosin, and caveolin, yielded normal results. Additionally, carnitine palmitoyltransferase, acid alpha-glucosidase, and aerobic glycolysis enzymes activity resulted within the normal ranges. Based on these findings, a general diagnosis of "congenital myopathy" was made at the time.

Apart from a chronic high elevation of creatine kinase values (10-times the upper normal level, around 2500-3000 IU/L), regular annual instrumental (*i.e.*, electrocardiograms and trans-thoracic echocardiograms) did not identify any significant abnormalities until the age of 55, when the patient complained of persistent cough and chest pain, occurring one month after a mild SARS-CoV-2 infection with minimal upper respiratory trait symptoms. Subsequent to a mild increase in troponin T levels, a cardiac MRI (1.5T Siemens) was performed three months from symptoms onset revealing moderate reduction in left ventricular ejection fraction (LVEF 39%). While subacute COVID-19-related myocarditis was suspected, no myocardial oedema was identified, likely due to the delay from the initial complaints. Treatment with a beta-blocker (nadolol 40 mg bid) and an angiotensin-receptor blocker (valsartan 160 mg bid) led to stabilization of LVEF values within the range of 42-47% during echocardiographic monitoring, with the most recent assessment performed 24 months after the COVID-19 infection. Concurrently, a subsequent cardiac MRI confirmed the mild reduction in LVEF and demonstrated persistent midwall fibrosis in the basal septum and inferior wall, a location atypical for myocarditis but consistent with cardiomyopathy.

During the patient's last neuromuscular evaluation at age 57, CK was still ten times the upper normal value, and lower-limb muscle MRI revealed symmetrical bilateral alterations in T1-weighted images in the distal portion of the vastus lateralis, vastus intermedius, vastus medialis, as well as the entire medial gastrocnemius and soleus (Fig. 2). Short-TI Inversion Recovery (STIR) imaging exhibited positivity in the same regions. Neurological examination confirmed previously reported signs of distal myopathy and scoliosis, without evidence of significant focal weakness.

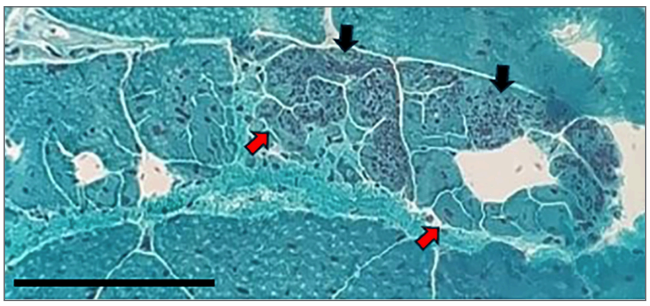


Figure 1. Trichromic staining of quadriceps muscle biopsy showing fibre splitting (red arrows) and rod-like cytoplasmic bodies (black arrows) (scale bar 100 µm).



Figure 2. T1-weighted MRI images of legs showing symmetrical fatty infiltration of both medial gastrocnemi.

To further investigate the phenotype, an extended NGS panel targeting genes associated with myopathies and cardiomyopathies was performed (genes listed in Tab. I), revealing a variant in the LDB3 gene. Given the gene's complexity and its pleiotropic expression in various tissues, including skeletal and cardiac muscles, the canonical transcript NM_007078.3 was considered. The identified variant, c.985G > A (p.Asp261Asn), was classified as a variant of uncertain significance based on a comprehensive genetic assessment; however, it remains highly relevant to the patient's clinical, histological, and radiologic features. According to ACMG criteria [6], the variant was considered clinically relevant, as BP4 was deemed inconsistent due to conflicting results from multiple in silico predictors, while PP4 and PM2 supported the classification.

Table I. Genes included in the NGS study. If not specified, both coverages > 10x and > 20x are assumed to be 100.00%. For the following genes: HSPG2 (coverage > 20x 99.83%); SELENON (coverage > 10x 89.96%, > 20x 87.87%); TSFM (coverage > 10x 93.95%, > 20x 93.95%).

ABHD5	DNM2	LMOD3	SDHA
ACAD9	DOK7	LPIN1	SDHAF1
ACADM	DPAGT1	LRP4	SDHB
ACADS	DPM1	MAP3K20	SDHD
ACADVL	DPM2	MATR3	SELENON
ACTA1	DPM3	MEGF10	SGCA
ACTN2	DYSF	MGME1	SGCB
ADSS1	ECEL1	MSTO1	SGCD
AGL	EMD	MTM1	SGCG
AGRN	ENO3	MTTP	SIL1
ALDOA	ETFA	MUSK	SLC12A3
ALG14	ETFB	MYF6	SLC16A1
ALG2	ETFDH	MYH14	SLC18A3
AMPD1	FHL1	MYH2	SLC22A5
AMPD3	FKRP	MYH3	SLC25A20
ANO5	FKTN	MYH7	SLC25A32
ATP2A1	FLAD1	MYH8	SLC5A7
B3GALNT2	FLNC	MYO18B	SMCHD1
B4GAT1	GAA	MYO9A	SNAP25
BAG3	GBE1	MYOT	SPEG
BIN1	GFER	MYPN	SQSTM1
BVES	GFPT1	NEB	STAC3
CACNA1S	GMPPB	NEFL	STIM1
CAPN3	GNE	ORAI1	SUCLA2
CAV3	GOSR2	PFKM	SYNE1
CCDC78	GYG1	PGAM2	SYNE2
CFL2	GYS1	1,00 PGK	SYT2
CHAT	HACD1	PGM1	TAFAZZIN
CHCHD10	HADHA	PHKA1	TANGO2
CHKB	HADHB	PHKB	TCAP
CHRNA1	HNRNPA1	PIEZO2	TIA1
CHRNB1	HNRNPA2B1	PLEC	TK2
CHRND	HNRNPDL	PNPLA2	TMEM43
CHRNE	HSPB1	POGLUT1	TNNT1
CHRNG	HSPB8	POLG	TNPO3
CLCN1	HSPG2	POLG2	TOR1AIP1
CNTN1	ISCU	POMGNT1	TPM2
COL12A1	ITGA7	POMGNT2	TPM3
COL13A1	KBTBD13	POMK	TRAPPC11
COL6A1	KCNJ12	POMT1	TRIM32
COL6A2	KCNJ2	POMT2	TRIP4
COL6A3	KCNJ5	PREPL	TSFM
COLQ	KLHL40	PRKAG2	TTN
COQ8A	KLHL41	PUS1	TWNK
CPT2	KLHL9	PYGM	TYMP
CRPPA	LAMA2	PYROXD1	UNC45B
CRYAB	LAMB2	RAPSN	VAMP1
DAG1	LAMP2	RBCK1	VCP
DES	LARGE1	RNASEH1	VMA21
DGUOK	LDB3	RRM2B	VWA1
DMD	LDHA	RXYLT1	YARS2
DNA2	LIMS2	RYR1	
DNAJB6	LMNA	SCN4A	

Discussion

ZASPopathies typically present with late-onset, distal-predominant weakness, initially affecting the intrinsic muscles of the hands and/or feet, with subsequent progression to proximal muscles, and cardiac involvement [3,7]. Skeletal muscle biopsies often reveal cytosolic protein accumulations, and early muscle MRI findings demonstrate alterations in the medial gastrocnemius muscles [7,8]. In our case, we observed a unique manifestation characterized by neonatal foot abnormalities and recurrent episodes of exertional rhabdomyolysis, along with an MRI pattern compatible with ZASP/LDB3-myopathy, potentially expanding the phenotypic spectrum of ZASPopathies.

Notably, cardiac involvement in our patient was only identified following SARS-CoV-2 infection. While establishing a definitive diagnosis of myocarditis may be challenging, such presumptive diagnosis may be plausible according to previous studies that have reported a direct association between SARS-CoV-2 infection and myocardial inflammation [5]. In our case, the cardiac MRI revealed an abnormal distribution of endomyocardial fibrosis, suggesting the presence of a subtle pre-existing ZASP/LDB3-related cardiomyopathy that was not detected through routine transthoracic echocardiography and worsened after COVID-19-associated myocarditis.

Conclusion

Our case highlights a distinct presentation of ZASP/LDB3-related myopathy with atypical neonatal foot abnormalities and recurrent exertional rhabdomyolysis from early life, together with lower limbs distal hypotrophy. During his disease course, a viral infection unveiled a pre-existing mild cardiac involvement mimicking myocarditis. In order to timely identify such cases, cardiac and muscular MRI can be helpful in distinguishing disease-specific patterns and timely reveal signs of even subtle cardiomyopathy, especially when chronic hyperCKemia and remarkable personal or familial medical histories are present. Alongside, relevant hyperCKemias should be comprehensively assessed using wide genetic panels, such as NGS panels for myopathies, including genes linked to cardiomyopathy to aid in the early identification of variants that may lead to severe complications.

Acknowledgement

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Conflict of interest statament

The authors state that they have no Conflict of Interest (COI).

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Authors contribution

GG and SP manuscript preparation; GG, SP, GU data collection; GG, SP, DC interpretation and discussion of results; GG, SP, TM supervision and revision.

Ethical consideration

The present study was approved for publication in a scientific journal by the institutional ethical committee (Prot. n° 0027994, 03 Mar 2023). The local ethical committee also reviewed the written informed consent form (ICF) which was presented to the patient and collected for the same purpose.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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