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Case Reports

Heart Failure as the Initial Clinical Manifestation of Becker Muscular Dystrophy in an Adult

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Congestive heart failure is an uncommon initial presentation for dystrophin-deficient muscular dystrophies. Cardiac manifestations may appear in late disease stages, although they classically present after musculoskeletal symptoms develop. This case report describes a patient who presented with heart failure and was newly diagnosed with Becker muscular dystrophy. The objective is to recognize Becker muscular dystrophy as a potential cause of dilated cardiomyopathy in young patients, even in the absence of clinically overt musculoskeletal symptoms. ***(Tex Heart Inst J. 2022;49(6):e217634)***

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Becker muscular dystrophy (BMD) is an X-linked musculoskeletal disorder that is caused by an in-frame mutation in the dystrophin gene. As with any of the dystrophin-deficient muscular dystrophies (DDMDs), myocardial involvement in BMD may manifest as electrocardiographic abnormalities or congestive heart failure.[1] Traditionally, cardiac manifestations are seen in late disease stages after musculoskeletal symptoms develop and the patient is bed-bound. However, it has been shown that cardiomyopathy onset in DDMDs is variable and is not correlated with skeletal muscle involvement.[2] Physicians approaching a young patient with new-onset heart failure often fail to include all the DDMDs as part of the differential diagnosis. This can be in part because patients deny or do not recall progressive musculoskeletal weakness in their history. This case report describes a patient who presented with heart failure and was newly diagnosed with BMD.

Case Report

A 22-year-old man presented with 4 days of worsening dyspnea on exertion, orthopnea, chest palpitations, and pleurisy. Initial vital signs were as follows: blood pressure, 100/68 mm Hg; heart rate, 96/min; and oxygen saturation, 98% on 2 L nasal canula. Physical examination revealed bibasilar crackles and lateral displacement of the point of maximal impulse. No lower-extremity edema was noted. Initial lab findings were significant for N-terminal pro b-type natriuretic peptide level of 4,800 ng/L, troponin T level of 78 ng/L, D-dimer level of 5,355 ng/mL, and lactate level of 3.4 mmol/L. Transthoracic echocardiography (Fig. 1) showed a mildly dilated left ventricle with left ventricular ejection fraction (LVEF) of 20% to 24%, end-diastolic volume index of 177 mL, mild to moderate mitral regurgitation, and a small pericardial effusion.

The patient reported a childhood history of seizures without recurrence in adulthood. He denied use of alcohol, tobacco, or illicit substances. The patient was abandoned by his parents and raised by his maternal grandparents, who reported no known family history of premature heart disease. Based on the initial assessment, the differential diagnosis included myopericarditis, idiopathic dilated cardiomyopathy (DCM), congenital heart disease, tachycardia-induced

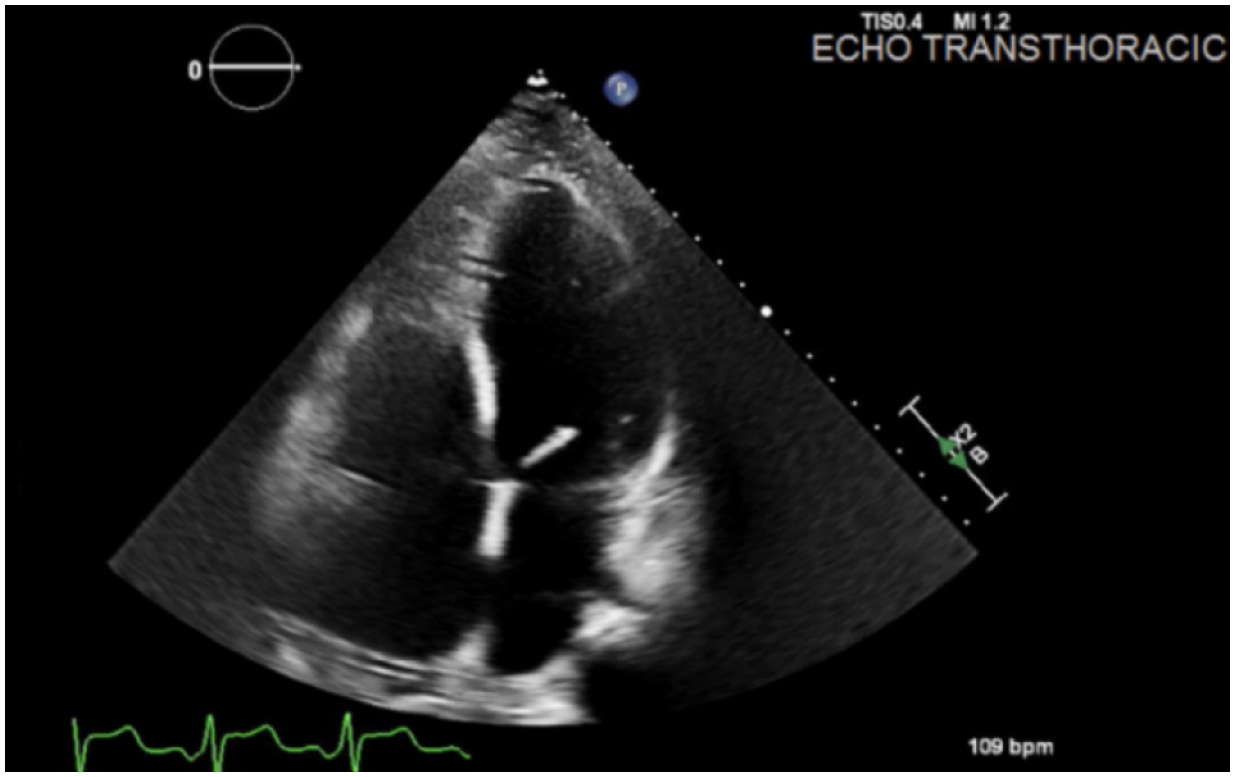

Fig. 1 *Transthoracic echocardiogram shows mildly dilated left ventricle with an ejection fraction of 20% to 24%, end-diastolic volume index of 177 mL, mild to moderate mitral regurgitation, and a small pericardial effusion.*

Supplemental motion image is available for Figure 1.

cardiomyopathy, and thyroid disease–related cardiomyopathy.

Chest x-ray demonstrated cardiomegaly with bilateral pleural effusions. Serial electrocardiograms demonstrated both an ectopic atrial rhythm and normal sinus rhythm (Fig. 2A and Fig. 2B). Coronary computed tomography angiography did not show substantial coronary artery anomalies or obstructive coronary disease. Workup for cardiomyopathies included coxsackievirus and parvovirus serologies, polymerase chain reaction for SARS-CoV-2, antinuclear antibodies, rheumatoid factor, and cyclic citrullinated peptide antibody testing, all of which had negative results. Thyroid-stimulating hormone level was 5.96 μIU/mL, but free thyroxine and triiodothyronine levels were normal. Additional testing revealed an elevated creatine kinase (CK) level of 594 U/L.

Because of the patient's abnormal CK level, he was questioned regarding muscular weakness. Although he did not report weakness, he reported taking nonsteroidal anti-inflammatory drugs to treat bilateral leg pain after prolonged physical activity. On repeat examination, dorsiflexion of the feet was found to be impaired, and he was noted to favor walking on his tip toes (Fig. 3). Mild bilateral calf hypertrophy was appreciated. Cardiovascular magnetic resonance (CMR) imaging showed lateral, mid-distal septal, and apical wall subendocardial scarring with a pericardial effusion (Fig. 4). A muscular dystrophy genetic panel revealed an in-frame deletion (exon 3-4) in the Duchenne muscular dystrophy (DMD) gene. Given this constellation of findings, the patient was diagnosed with BMD and an associated DCM.

The patient was diuresed to optivolemia using intravenous furosemide and transitioned to oral diuretics before discharge. He was started on lisinopril and spironolactone for guideline-directed medical therapy. β-Blockade with carvedilol was attempted but was not tolerated as a result of hypotension. He was enrolled in outpatient cardiac rehabilitation with a focus on increasing baseline aerobic and physical capabilities. The patient completed a total of 8 sessions over the course of 8 weeks and was ultimately lost to follow-up because of transportation issues. As a result of heel cord contracture and calf hypertrophy, he largely avoided upright total weight–bearing exercises such as the treadmill and lap-walking. He tolerated increases in total aerobic exercise time and upper-extremity ergometer exercises, progressing in both duration and intensity.

The patient was hospitalized with community-acquired pneumonia 4 months after his initial presentation. During this admission, he experi-

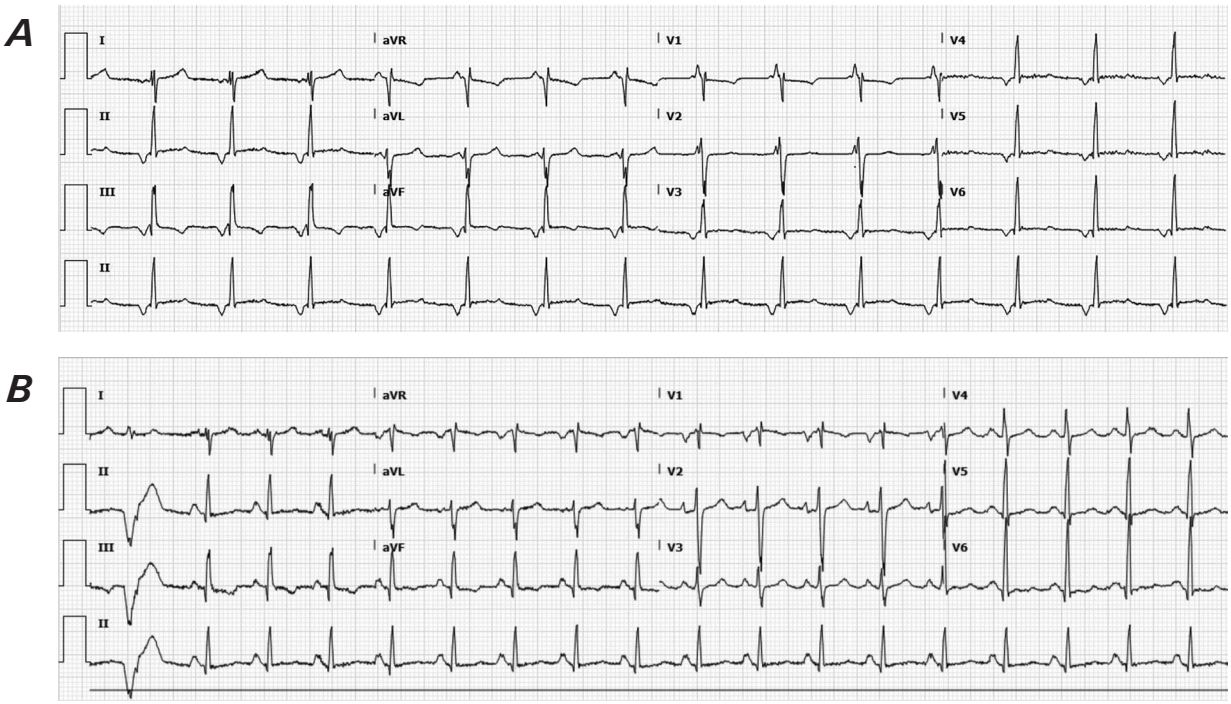

Fig. 2 *Electrocardiogram is significant for* ***A****) an ectopic atrial rhythm, which would alternate with* ***B****) sinus rhythm.*

enced cardiogenic shock and intravenous inotropes were started. He was discharged on intravenous milrinone for 3 months, which had to be discontinued because of a tunneled line infection. Lisinopril and spironolactone in addition to torsemide as a loop diuretic were continued, and advanced therapy options were subsequently considered.

Fig. 3 *Image of the patient's gait shows abnormal gait favoring support on his left toes.*

Supplemental motion image is available for Figure 3.

While the patient was on milrinone, 6-Minute Walk Distance (6MWD) and bilateral hand grip strength (HGS) tests were assessed approximately 6 to 8 months apart. There was an increase in 6MWD and maintenance in total HGS; these findings were dissimilar to the declines seen in previous studies.[3,4] The patient was finally listed for heart transplantation as United Network of Organ Sharing status 3 and underwent transplant.

Discussion

Becker muscular dystrophy and DMD are X-linked recessive neuromuscular disorders resulting from mutations in the dystrophin gene. These disorders are characterized by mechanical weakness in skeletal and cardiac myocytes, which leads to a loss of cell membrane integrity and ultimately myocyte death. Although patients with DMD have complete absence of dystrophin and typically are diagnosed in childhood, BMD is characterized by in-frame mutations in the DMD gene leading to reduced dystrophin protein expression and relatively delayed disease progression.[1]

Age at symptom onset in BMD is variable, ranging from 2 to 20 years. Proximal muscle groups and lower extremities are the first involved, leading to initial symptoms of muscle cramps with strenuous physical activity. Although BMD-related cardiomyopathy is classically thought to present years after the start of musculoskel-

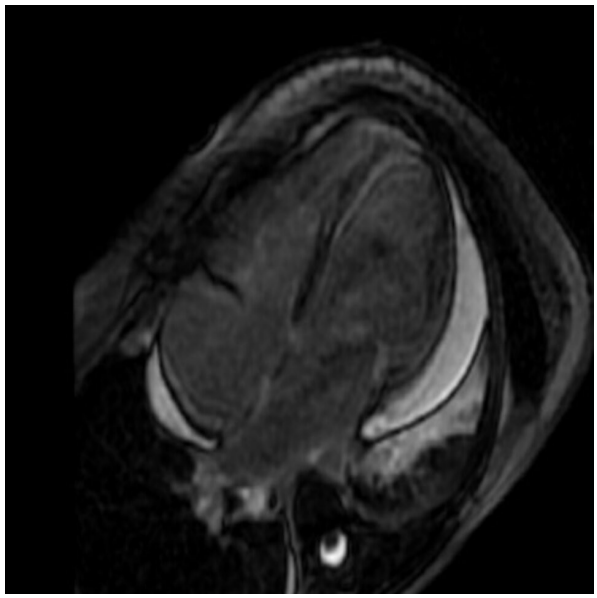

Fig. 4 *Cardiovascular magnetic resonance imaging shows lateral, mid-distal septal, and apical wall subendocardial scarring with a pericardial effusion.*

etal symptoms, cardiomyopathy onset is variable and is not correlated with skeletal muscle involvement.[2]

Dilated cardiomyopathy is present in more than 70% of the population with BMD. Patients typically present in their 30s or 40s with symptoms of heart failure, and manifestations of DCM are rare in patients younger than 20 years.[5] Although age at presentation is variable, specific deletions in the DMD gene have been correlated with age at DCM onset. The locus of the dystrophin deletion in this patient (exon 3-4) has been associated with early-onset DCM even in patients without an obvious decline in muscle function.[6] It is possible that some patients are falsely diagnosed with idiopathic DCM despite underlying abnormal DMD gene expression because of minimal musculoskeletal symptoms.

A screening electrocardiogram and echocardiogram are recommended at the time of BMD diagnosis and every 5 years thereafter. Cardiovascular magnetic resonance imaging is gaining acceptance as a more sensitive modality than echocardiography for detecting early regional myocardial fibrosis in BMD, and some groups have recommended that screening CMR imaging be conducted every 2 years.[7] Previous CMR imaging studies have demonstrated subepicardial gadolinium enhancement in BMD and DMD.[1] Interestingly, the patient in this case report presented with subendocardial scarring.

There are no specific guidelines for pharmacotherapy in patients with BMD and associated DCM, although guideline-directed medical therapy should be initiated if LVEF is reduced. Some groups have suggested that earlier initiation of angiotensin-converting enzyme inhibitors in patients with DMD may delay the progression of cardiac dysfunction before LVEF is reduced.[8] In addition, eplerenone has been demonstrated to attenuate left ventricular systolic function decline in patients with DMD who have preserved LVEF and evidence of myocardial disease on CMR imaging.[9] Glucocorticoids are indicated in patients with DMD and declining motor function; observational studies have shown a potential role for steroids in preserving cardiac function in these patients.[10] However, no prospective trials have been completed, and steroids are not currently indicated in the setting of isolated dystrophin-deficient cardiomyopathy.

Previously, orthotopic heart transplantation (OHT) was relatively contraindicated in patients with inherited myopathies because of concerns regarding severe musculoskeletal weakness limiting rehabilitation potential and respiratory muscle dysfunction impairing the ability to wean from mechanical ventilation postoperatively.[11] Despite these concerns, Wu et al[12] demonstrated similar outcomes after OHT between patients with idiopathic DCM and selected patients with muscular dystrophy (ie, patients with mild muscular disability and no respiratory muscle involvement). Notably, left ventricular assist devices have been shown to be effective as destination therapy in patients with inherited muscular dystrophies.[13] The major contribution of this case report to the existing medical literature is an increase in physician awareness that patients with BMD can present with decompensated heart failure because of DCM before experiencing musculoskeletal symptoms. Dystrophin-deficient cardiomyopathies should be included in the differential diagnosis of young adult male patients with DCM and an elevated CK level.

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References

1. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. *J Am Coll Cardiol*. 2016;67(21):2533-2546. doi:10.1016/j.jacc.2016.02.081
2. Nigro G, Comi LI, Politano L, Bain RJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. *Int J Cardiol.* 1990;26(3):271-277. doi:10.1016/0167-5273(90)90082-g
3. Henricson E, Abresch R, Han JJ, et al. The 6-Minute Walk Test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. *PLoS Curr.* 2013;5:ecurrents.md.9e17658b007eb79fcd6f723089f79e06. doi:10.1371/currents.md.9e17658b007eb79fcd6f723089f79e06
4. McDonald CM, Henricson EK, Han JJ, et al. The 6-Minute Walk Test in Duchenne/Becker muscular dystrophy: longitudinal observations. *Muscle Nerve.* 2010;42(6):966-974. doi:10.1002/mus.21808
5. Rajdev A, Groh WJ. Arrhythmias in the muscular dystrophies. *Card Electrophysiol Clin.* 2015;7(2):303-308. doi:10.1016/j.ccep.2015.03.011
6. Kaspar RW, Allen HD, Ray WC, et al. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker muscular dystrophy. *Circ Cardiovasc Genet.* 2009;2(6):544-551. doi:10.1161/CIRCGENETICS.109.867242
7. Lamacie MM, Warman-Chardon J, Crean AM, Florian A, Wahbi K. The added value of cardiac magnetic resonance in muscular dystrophies. *J Neuromuscul Dis*. 2019;6(4):389-399. doi:10.3233/JND-190415
8. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksmann G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol*. 2005;45(6):855-857. doi:10.1016/j.jacc.2004.09.078
9. Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2015;14(2):153-161. doi:10.1016/S1474-4422(14)70318-7
10. Dec GW. Steroid therapy effectively delays Duchenne's cardiomyopathy. *J Am Coll Cardiol.* 2013;61(9):955-956. doi:10.1016/j.jacc.2012.12.011
11. Ho R, Nguyen ML, Mather P. Cardiomyopathy in Becker muscular dystrophy: overview. *World J Cardiol.* 2016;8(6):356-361. doi:10.4330/wjc.v8.i6.356
12. Wu RS, Gupta S, Brown RN, et al. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. *J Heart Lung Transplant.* 2010;29(4):432-438. doi:10.1016/j.healun.2009.08.030
13. Adorisio R, Mencarelli E, Cantarutti N, et al. Duchenne dilated cardiomyopathy: cardiac management from prevention to advanced cardiovascular therapies. *J Clin Med.* 2020;9(10):3186. doi:10.3390/jcm9103186