Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders ■■ (2016) ■■–■■

www.elsevier.com/locate/nmd

Suspected acute myocardial infarction in a dystrophin-deficient dog

Sarah Morar Schneider [a,1], Amanda Erickson Coleman [b,1,2], Lee-Jae Guo [c,d], Sandra Tou [b], Bruce W. Keene [b], Joe N. Kornegay [a,c,d,e,f,*]

[a] *Department of Veterinary Pathobiology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843, United States*

[b] *Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, United States*

[c] *Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843, United States*

[d] *Texas A&M Institute for Preclinical Studies, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843, United States*

[e] *Department of Pathology and Laboratory Medicine, School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC 27607, United States*

[f] *Department of Neurology, School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC 27607, United States*

Received 1 October 2015; received in revised form 1 January 2016; accepted 1 February 2016

Abstract

Golden retriever muscular dystrophy (GRMD) is a model for the genetically homologous human disease, Duchenne muscular dystrophy (DMD). Unlike the mildly affected mdx mouse, GRMD recapitulates the severe DMD phenotype. In addition to skeletal muscle involvement, DMD boys develop cardiomyopathy. While the cardiomyopathy of DMD is typically slowly progressive, rare early episodes of acute cardiac decompensation, compatible with myocardial infarction, have been described. We report here a 7-month-old GRMD dog with an apparent analogous episode of myocardial infarction. The dog presented with acute signs of cardiac disease, including tachyarrhythmia, supraventricular premature complexes, and femoral pulse deficits. Serum cardiac biomarkers, cardiac-specific troponin I (cTnI) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), were markedly increased. Echocardiography showed areas of hyperechoic myocardial enhancement, typical of GRMD cardiomyopathy. Left ventricular dyskinesis and elevated cTnI were suggestive of acute myocardial damage/infarction. Over a 3-year period, progression to a severe dilated phenotype was observed.

Keywords: Muscular dystrophy; Duchenne muscular dystrophy; Golden retriever muscular dystrophy; Cardiomyopathy; Animal model; Myocardial infarction

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked, childhood-onset disorder, with an incidence of 1 in every 4000–6000 male births, characterized by progressive muscle wasting and eventual death [1]. Affected individuals have mutations in their *DMD* gene and associated loss of the cytoskeletal protein dystrophin. In addition to severe skeletal muscle involvement, ~ 90% of DMD patients develop cardiomyopathy, now the leading cause of death [2]. While the cardiomyopathy of DMD is typically slowly progressive, rare early episodes of acute cardiac decompensation, compatible with myocardial infarction, have been described [3–6].

Genetically homologous DMD models have been well characterized in mice (mdx) and dogs (golden retriever muscular dystrophy; GRMD). The mdx phenotype is mild, with little muscular weakness and limited cardiac involvement that does not progress to failure [7]. Conversely, GRMD dogs display a more severe phenotype, resembling DMD, with analogous skeletal and cardiac muscle lesions [8,9]. Similarities in the cardiomyopathy of DMD and GRMD are well documented, including characteristic electrocardiographic (ECG) changes, lesion distribution and disease progression [9–11]. However, evidence of acute exacerbation of cardiac disease in GRMD has not been well documented.

* Corresponding author. Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, 4458 TAMU, College Station, TX 77803-4458, United States. Tel.: +979 458 4968; fax: +979 458 5912.

E-mail address: jkornegay@cvm.tamu.edu (J.N. Kornegay).

[1] Drs. Schneider and Coleman contributed equally to this paper.

[2] Present address: Amanda Erickson Coleman, Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, 501 D.W. Brooks Drive, Athens, GA 30602.

http://dx.doi.org/10.1016/j.nmd.2016.02.005
0960-8966/

Please cite this article in press as: Sarah Morar Schneider, et al., Suspected acute myocardial infarction in a dystrophin-deficient dog, Neuromuscular Disorders (2016), doi: 10.1016/j.nmd.2016.02.005

2. Case report

The dog ("Danica") of this report was a 7-month-old female golden retriever cross, homozygous for the *GRMD* mutation. She was from a colony maintained at the University of North Carolina at Chapel Hill. Animal care and use was governed by an IACUC protocol and principles outlined in the National Research Council Guide for the Care and Use of Laboratory Animals. After a routine clinical course [8], Danica developed acute generalized weakness, hyporexia, labored breathing, and ventricular ectopy. Blood work, including complete blood count and serum biochemistry panel, were unremarkable beyond mildly increased alanine aminotransferase (ALT, 541 U/L; 10–118 U/L), phosphorus (8.8 mg/dL; 2.9–6.6 mg/dL) and potassium (6.0 mmol\dL; 3.7–5.8 mmol\dL). Serum creatine kinase (CK) was not assessed.

Danica was evaluated at the North Carolina State University Veterinary Hospital. Workup included physical examination, indirect blood pressure measurement, echocardiography, 6-lead ECG, thoracic radiography, measurement of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and cardiac-specific troponin I (cTnI), arterial blood gas analysis, and 24-hour ambulatory ECG (Holter) monitoring.

Due to generalized weakness, she could not rise beyond sternal recumbency, but was otherwise alert and responsive. Consistent with the GRMD phenotype, Danica had decreased muscle mass, trismus, ptyalism, and mild inspiratory stertor. Moderate hyperpnea and tachypnea, with normal mucous membrane color and capillary refill time, were observed. Precordial palpation was normal, without jugular distension or pulsation. Thoracic auscultation revealed normal heart sounds and a regular cardiac rhythm punctuated by intermittent premature beats (average heart rate, 160 beats-per-minute [bpm]). Femoral pulses were hypokinetic, with occasional pulse deficits.

Two-dimensional, M-mode, color flow, and spectral Doppler echocardiography showed changes consistent with pre-dilatative Duchenne-type cardiomyopathy. Hyperechoic foci were detected in the apices of the left ventricular (LV) papillary muscles, basal posterior LV wall, and portions of the interventricular septum (Fig. 1). Additionally, marked LV dyskinesis was present, and indices of global LV systolic function indicated low-normal performance. LV chamber size was mildly reduced; left atrial size was normal. Mild tricuspid insufficiency, mild right ventricular (RV) dilatation, and moderate right atrial dilatation were also recorded.

ECG showed sinus tachycardia (158–176 bpm) with a competing ectopic atrial rhythm (162 bpm), occasional right-sided ventricular premature complexes and couplets, and one paroxysm of ventricular tachycardia (instantaneous rate, 200 bpm). ECG showed no ST segment abnormalities. The QT interval was at the upper limit of published reference ranges. Deep Q waves and increased Q/R ratio characteristic of DMD and GRMD [10–12] were not detected.

Thoracic radiographs suggested right atrial enlargement. The caudal vena cava was moderately distended, with mild hepatomegaly, but without the diaphragmatic abnormalities typical of GRMD.

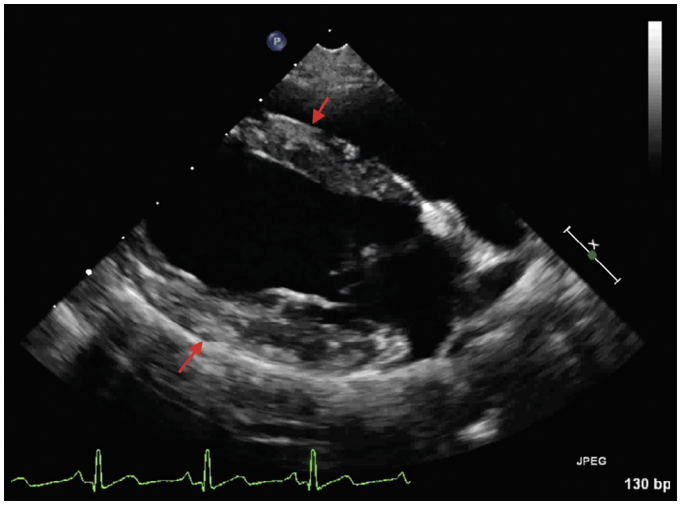

Fig. 1. Two-dimensional right parasternal long axis echocardiographic image, taken from a 7-month-old GRMD dog. Hyperechoic subendocardial foci (arrows), suggestive of fatty and/or fibrotic infiltration, are present in the basilar portion of the posterior left ventricle and interventricular septum.

Arterial blood gas analysis revealed mild hypoxemia (partial pressure of oxygen [PaO_2], 83 mmHg; 85–100 mmHg) and hypercapnia (partial pressure of carbon dioxide [$PaCO_2$], 34 mmHg; 18–32 mmHg). Arterial pH was 7.41, with low-normal bicarbonate (21.6 mmol/L; 20.7–29.2 mmol/L) and normal lactate (0.5 mmol/L; 0.4–3.0 mmol/L).

Serum biomarkers of cardiac disease, cTnI (195 ng/mL; 0–0.2 ng/mL) and NT-proBNP (>3000 pmol/L; > 1800 pmol/L evidence of myocardial stress), were severely elevated.

Holter monitoring revealed an underlying sinus rhythm with frequent ventricular ectopy (longest run, 15.7 s; fastest rate, 289 bpm). Holter monitoring also detected 14,273 supraventricular premature complexes, including 72 episodes of supraventricular tachycardia (longest run, 4.8 s). Based on these findings, the combined potassium- and beta-adrenergic receptor blocker, sotalol (2.0 mg/kg orally every 12 hours), and supportive care were initiated.

Over the following 3 weeks, Danica returned to pre-episode status, with improved appetite and ambulation within 2 days. Serum cTnI declined, showing a 64% reduction to 69.30 ng/mL after two days and to 11.50 ng/mL after 24 days. Convalescent NT-proBNP was persistently elevated (>3000 pmol/L) after 24 days.

At 3-month recheck, blood pressure, echocardiography, ECG, thoracic radiography, arterial blood gas analysis and Holter monitoring were compatible with continued improvement. Both cTnI and NT-proBNP were further decreased (cTnI 1.41 ng/mL; N-proBNP, 2,235 pmol/L). Echocardiography showed less severe changes on the right and improved contraction on the left, while Holter monitoring showed only residual atrial and ventricular ectopic beats.

Danica moved with the GRMD colony to Texas A&M University in 2012. At 34 months of age, she underwent general

Please cite this article in press as: Sarah Morar Schneider, et al., Suspected acute myocardial infarction in a dystrophin-deficient dog, Neuromuscular Disorders (2016), doi: 10.1016/j.nmd.2016.02.005