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Case Report

Orthotopic Heart Transplantation in Manifesting Carrier of Duchenne Muscular Dystrophy

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DUCHENNE MUSCULAR dystrophy (DMD) is one of three dystrophinopathies associated with cardiomyopathy, including Becker muscular dystrophy (BMD) and X-linked dilated cardiomyopathy. DMD is the most common dystrophinopathy, affecting one in 3,500 male births, and it is characterized by severe, progressive muscle weakness and respiratory failure.[1] Clinical symptoms of DMD are predominantly seen in males; however, there is variable phenotypic expression among female carriers. A phenotypic expression occurs when the X chromosome with the normal dystrophin gene becomes transcriptionally inactive. The severity of manifestation varies based on the extent of X-inactivation. Some carriers only exhibit elevated creatine kinase, while others experience exercise intolerance, muscle cramps, muscle weakness, and even muscle wasting.[2] Cardiac involvement can occur irrespective of skeletal manifestation, and the frequency of cardiomyopathy increases with age.[3] The average life expectancy of DMD carriers may be reduced, especially with the progression of dilated cardiomyopathy.[3-5]

Heart transplantation may be considered for patients with drug-resistant dilated cardiomyopathy. Although DMD is a relative contraindication to heart transplantation due to the associated muscle weakness and poor pulmonary function, there are reports of transplantation in muscular dystrophy patients with preserved pulmonary function.[6] In fact, long-term outcomes in patients with BMD after cardiac transplantation are comparable with nonmuscular dystrophy patients with nonischemic cardiomyopathy.[7] Heart transplantation also has been reported in manifesting carriers of DMD. Melacini et al first described successful transplantation in a 40-year-old symptomatic DMD carrier with limb weakness, myalgias, and severe dilated cardiomyopathy.[8] Davies et al also reported successful transplantation in a 25-year-old DMD carrier who developed severe cardiac failure during the third trimester of her pregnancy.[9] Alternatively, left ventricular assist device destination therapy has been described, but information about long-term outcomes is limited.[10] While surgical intervention has been performed successfully, the possible anesthetic complications unique to this patient population should not be ignored.

Females afflicted with dystrophinopathy may be vulnerable to the same complications as patients with DMD during anesthesia. These include anesthesia-induced rhabdomyolysis with exposure to volatile anesthetics or succinylcholine, cardiac arrhythmias, prolonged neuromuscular blockade, and even coagulopathy.[11,12] Here, the authors present the anesthetic management of a manifesting carrier of DMD with dystrophin-deficient cardiomyopathy during orthotopic heart transplantation.

Case Report

A 60-year-old female carrier of DMD, with a past medical history significant for dilated cardiomyopathy, was admitted with new-onset atrial flutter, hypotension, and tachypnea. At the time of admission, she had New York Heart Association

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class IV heart failure with reduced ejection fraction, left ventricular ejection fraction 10%, grade III diastolic dysfunction, moderate mitral and tricuspid regurgitation, World Health Organization class II mild pulmonary hypertension (mean pulmonary arterial pressure 25 mmHg, pulmonary vascular resistance 3.22 Wood units), and nonsustained ventricular tachycardia. Six years prior, she was diagnosed with New York Heart Association class III heart failure with reduced ejection fraction. At the time of diagnosis, the echocardiogram demonstrated left ventricular ejection fraction less than 20%, grade III diastolic dysfunction, and severe pulmonary hypertension. Pulmonary hypertension improved with diuresis and she was managed with American College of Cardiology/American Heart Association guideline-directed medical therapy for heart failure. She was not hospitalized again until she presented with end-stage heart failure.

She had a son who died from DMD, and, thus, she was strongly suspected to be a manifesting carrier of DMD. In addition to dilated cardiomyopathy, she had a longstanding history of generalized muscle weakness, requiring assistance with tasks such as pumping gas as she lacked the grip strength to activate the pump. Her baseline creatine kinase levels were approximately 350 U/L and increased to 900 U/L with moderate exercise. Although she was not prescribed corticosteroids, she was advised to refrain from exercising due to the risk of renal failure.

During admission, she developed refractory heart failure requiring continuous inotropic support with milrinone and dopamine infusions. She did not receive anticoagulation therapy as an inpatient. She was listed for heart transplantation United Network for Organ Sharing status 3, and 62 days after admission, an organ became available. She had no prior anesthesia history. Volatile anesthetics and succinylcholine were avoided. The anesthesia machine was flushed, the CO_2 absorber was replaced, and the anesthesia vaporizers were removed. The avoidance of volatile anesthetics also was discussed with the perfusionist, and the vaporizer was excluded from the cardiopulmonary bypass (CPB) circuit. A radial arterial line and internal jugular venous catheter were placed before induction. General endotracheal anesthesia was induced and maintained with propofol and remifentanil. Dopamine and milrinone infusions were continued, and an epinephrine infusion was started after induction of anesthesia. Aminocaproic acid was administered before, during, and after CPB.

A median sternotomy was performed, and the aorta, superior, and inferior vena cava were cannulated for CPB. After the initiation of CPB, the native heart was excised. The donor heart was implanted with cavocaval anastomoses. The native aorta was very friable, and the donor aorta was severely atherosclerotic; hence, the aortic anastomosis was reinforced with Teflon to achieve hemostasis. The duration of CPB was 230 minutes, and the cross-clamp time was 111 minutes. The graft ischemic time was 166 minutes. After separation from CPB, there was persistent bleeding from the anastomotic sites, as well as the tissue surfaces, that was attributed to both tissue friability and coagulopathy. Bleeding was excessive, and achievement of hemostasis was prolonged. The platelet count decreased from 283,000 per microliter at baseline to 87,000 per microliter after initial resuscitation. Viscoelastography was not available during the case to assess platelet function. A total of six units packed red blood cells, ten units fresh frozen plasma, two units platelets, and one unit cryoprecipitate were transfused, in addition to 1,149 mL autologous blood from cell salvage.

At completion of the surgery, she remained sedated with propofol and was transferred to the intensive care unit on a milrinone infusion. Her postoperative course was complicated by delayed emergence from anesthesia. Nonetheless, she was extubated within eight hours of transfer to the intensive care unit. The donor heart functioned well, and milrinone was weaned off on postoperative day four. She was discharged home on postoperative day eight. Two years after transplantation, graft function remains normal, and she is able to do household chores and light yard work.

Discussion

DMD is an X-linked recessive disease caused by mutations in the dystrophin gene. Dystrophin has a vital role in skeletal and cardiac myocytes. Dystrophin links multimeric glycoprotein complexes within the cell membrane to intracellular actin filaments and transmits the force of sarcomere contraction to the extracellular matrix. Without dystrophin, the sarcolemma becomes fragile and degenerates.[13] Calcium sequestration also is affected by dystrophin deficiency. Abnormal stretch-activated calcium channels allow calcium to leak into the muscle cytosol.[14] Increased intracellular calcium stimulates the production of reactive oxygen species and eventually triggers cell death. Nitric oxide (NO) synthesis and diffusion are diminished when dystrophin is absent, vasoregulation is impaired, and susceptibility to ischemia following muscle contraction is increased.[15] Thus, dystrophin deficiency disrupts the integrity of the cellular membrane, impairs calcium sequestration, and uncouples vasoregulation, ultimately increasing myocyte susceptibility to ischemia and death.

Expression of DMD in Female Carriers

Males affected with DMD develop progressive muscle weakness, while most females with the mutation are asymptomatic carriers; although evidence of skeletal and cardiac muscle damage has been observed among female carriers.[3] Phenotypic expression is highly variable; some women are asymptomatic, while others display overt symptoms of muscle weakness.[16] Estimates of the prevalence of manifestation among DMD carriers vary widely, and approximately 8%-to-22% have some evidence of muscle weakness or cardiomyopathy.[17,18] Symptoms may manifest anytime between early childhood to late adulthood, but the majority of carriers become symptomatic during puberty.[2,19] Multiple mechanisms have been hypothesized to explain manifestation in female carriers, including chromosomal aberrations, simple inheritance, and hormonal events.[11] Chromosomal aberrancies, such as uniparental isodisomy (both X chromosomes are

inherited from one parent), and monosomies, such as Turner syndrome (X monosomy), may herald phenotypic expression in females.[11,20] Although rare, simple inheritance also may yield manifestation when a mutation is present on both X chromosomes.[11] Complete androgen insensitivity in an XY individual, combined with a DMD gene mutation, also may result in dystrophinopathy in a phenotypic female.[11,21]

However, the most likely pathologic contributor to female dystrophinopathy is skewed X-chromosome inactivation.[11,16,22] With skewed inactivation, the X-chromosome with the normal allele is preferentially inactivated, and there is a *greater expression of the X-chromosome with the abnormal dystrophin allele*. Dystrophin is expressed in a mosaic pattern—in some tissues, expression is normal, while in others, dystrophin expression is absent.[11] The prevalence of manifestation increases with the degree of skewed X-inactivation, and when inactivation of the X-chromosome with the normal allele exceeds 95%, female carriers invariably present with a DMD-like phenotype.[22] Indeed, significant morbidity has been described in females at very young ages.[23,24]

There currently are no established guidelines for the management of female dystrophinopathy patients; thus, management largely is extrapolated from treatment guidelines for males with DMD or BMD.[3] While males affected with DMD demonstrate a decrease in heart failure-associated mortality, with angiotensin-converting enzyme inhibitors, beta-blockers, and corticosteroid therapy, the benefit in female carriers remains to be established.[3,11]

Dilated Cardiomyopathy

Cardiomyopathy has emerged as a major contributor to morbidity and mortality, as deaths related to respiratory failure have declined among adults with dystrophinopathy. The risk of dilated cardiomyopathy increases with age, and by 18 years of age, more than 90% of males will have evidence of myocardial dysfunction.[12] Female carriers also are susceptible to cardiomyopathy; often, cardiac dysfunction remains subclinical until provoked by triggers, such as pregnancy.[9] The prevalence of cardiomyopathy among female carriers is estimated to be 7.3%-to-16.7%, and after age 40, the frequency may be as high as 53%.[11,16] Early detection is paramount because the initiation of heart failure therapy can delay progression and may even reverse remodeling.[25-27] Clinical guidelines in Europe and the United States recommend female carriers have surveillance with echocardiography every five years.[28,29] However, myocardial damage may be present even when echocardiography findings are normal (Fig 1). Cardiovascular magnetic resonance imaging with late gadolinium-enhancement is highly sensitive and demonstrates a similar pattern of myocardial fibrosis in DMD patients as well as carriers—subepicardial fibrosis in the inferolateral wall.[15]

Dystrophin dysfunction produces muscle pathology through two main mechanisms: increased sarcolemma permeability and altered NO diffusion.[12,30] Increased membrane permeability allows extracellular calcium to leak into the cytosol, leading to the degradation of contractile proteins, generation of reactive oxygen species, and protease activation.[12] Neuronal NO synthase is the muscle-specific isoform associated with dystrophin. When dystrophin is absent, neuronal NO synthase is displaced from the sarcolemma into the cytosol, and NO production is greatly reduced.[31] NO normally is released during muscle contraction to increase blood flow, and when NO release is impaired, microvascular constriction is unopposed, and myocytes are vulnerable to ischemia.[15] Both mechanisms contribute to cell death and apoptosis, resulting in inflammation, fibrosis, stretching, and thinning of myocytes. Contractility is impaired, end-diastolic volume increases, and lusitropy decreases, ultimately leading to the development of dilated cardiomyopathy and heart failure.[30]

Therapies aimed at increasing the availability of NO have indeed demonstrated improved myocyte function and reduced inflammation and fibrosis in *mdx knockout* mice models of DMD. Unfortunately, NO therapy has failed to improve clinical outcomes in the DMD population.[32,33]

Anesthesia Management

Recognition of this population is important because manifesting carriers may develop skeletal muscle weakness and cardiomyopathy and also may be susceptible to cardiac arrhythmia, rhabdomyolysis, respiratory compromise, difficult airway, and coagulopathy.[15,34,35] Female dystrophinopathy is rare, and the anesthetic management of manifesting carriers has been extrapolated primarily from males afflicted with DMD or BMD (Fig 2). Nonetheless, the heterogeneity of phenotypic expression among female carriers warrants significant caution; hyperkalemic cardiac arrest after exposure to volatile anesthetics and succinylcholine have been described.[36] Therefore, the authors here suggest avoiding volatile anesthetics and succinylcholine.

Arrhythmia

Fibrosis and inflammation alter conduction pathways and increase susceptibility to cardiac arrhythmias. Dystrophin-deficient cardiomyopathy classically is associated with subepicardial fibrosis of the inferolateral wall, and, consequently, conduction abnormalities are best observed in the lateral leads of the electrocardiogram. Atrioventricular conduction abnormalities are evident by the prolongation of the PR interval. Complex ventricular arrhythmia and sudden death are rare, typically seen with late-stage dystrophin-deficient cardiomyopathy.[37] Most commonly, dystrophinopathy is associated with persistent labile sinus tachycardia. Atrial arrhythmias also may be observed, especially with concomitant respiratory insufficiency and right heart failure. A thorough cardiac evaluation, including electrocardiogram and echocardiography, is warranted for all adults with dystrophinopathy, including manifesting carriers, as cardiomyopathy is common and likely underappreciated. Anesthesia providers should maintain vigilance for arrhythmias and be prepared to manage associated hemodynamic compromise.[2,15,30]

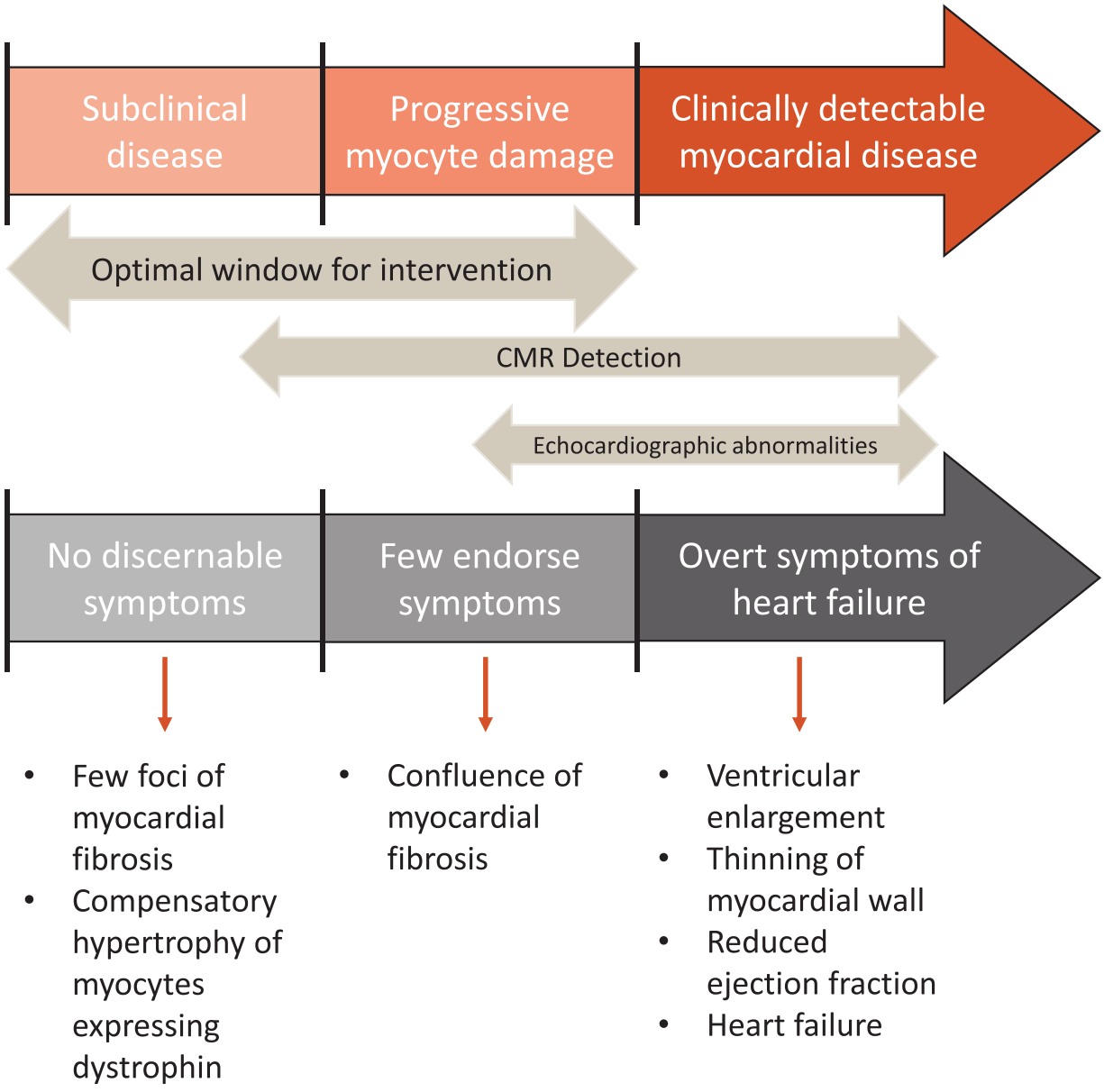

Fig 1. Dystrophin-deficient cardiomyopathy. Dystrophinopathy-associated cardiomyopathy progresses in a stepwise fashion. During the presymptomatic phase, myocardial fibrosis is limited to a few foci, and there is compensatory hypertrophy of the myocardium that still expresses dystrophin. Eventually, the confluence of myocardial fibrosis leads to ventricular enlargement, thinning of ventricular walls, reduced ejection fraction, and heart failure. Although initially responsive to pharmacologic treatment, dystrophinopathy-associated cardiomyopathy ultimately may be refractory to medical therapy and warrant heart transplantation.[6]

Rhabdomyolysis

DMD is associated with anesthesia-induced rhabdomyolysis (AIR), which may occur when exposure to volatile anesthetics and succinylcholine precipitates acute rhabdomyolysis and hyperkalemia. AIR primarily is seen with myopathy. The pathophysiology is distinct and unrelated to malignant hyperthermia. AIR is hallmarked by hyperkalemia, peaked T waves, and arrhythmia, and is not associated with hyperthermia or muscle rigidity.[38] Although rare, AIR may precipitate hyperkalemic cardiac arrest and death.[39] Without dystrophin, the muscle cell membrane is unstable, and sarcolemma permeability is increased. Volatile anesthetics and succinylcholine exacerbate the membrane instability and permeability; potassium and creatine kinase are released from necrotic cells into the serum, and intracellular calcium increases.[40] Succinylcholine further potentiates myocyte damage and hyperkalemia because of the upregulation of extrajunctional acetylcholine receptors that occur with muscular dystrophies, burns, and muscle atrophy. Lethal hyperkalemic cardiac arrest has been reported after volatile anesthetic administration in patients with DMD, as well as manifesting carriers.[36] Therefore, the avoidance of volatile anesthetics is recommended.[40] During cardiac surgery, it is important to communicate with the perfusionist and convey the risk of AIR with exposure to volatile anesthetics during CPB.

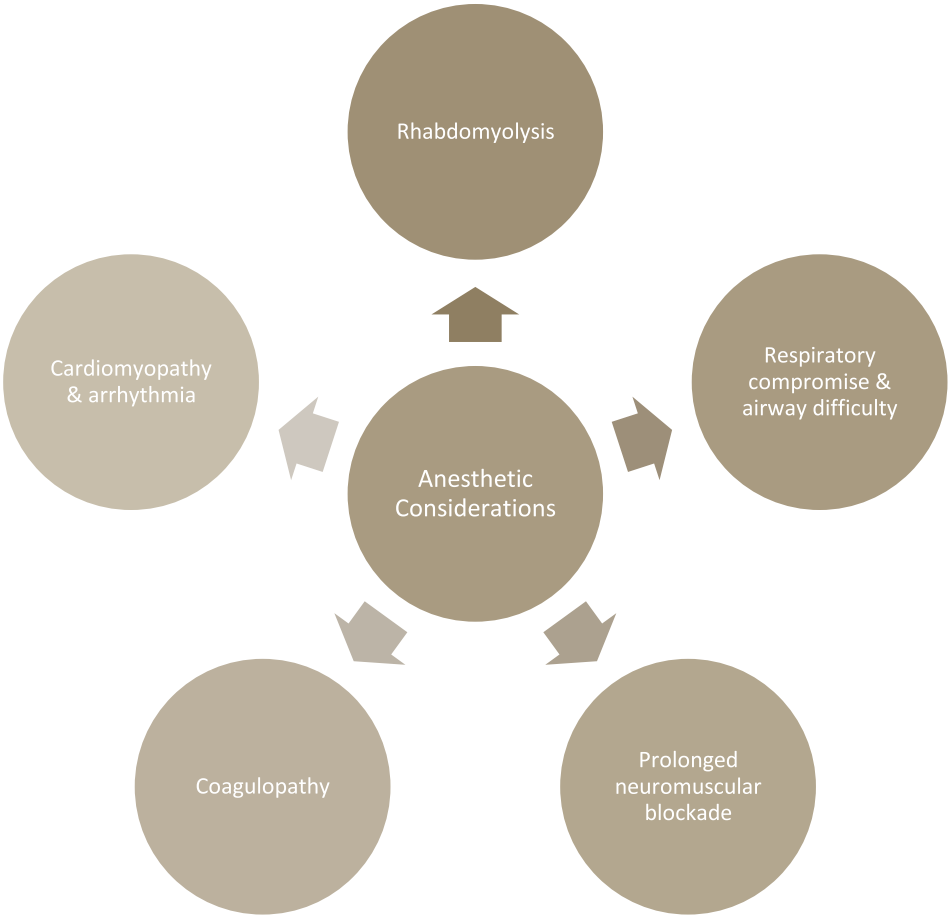

Fig 2. Anesthetic considerations for adults with dystrophinopathy. Adults with dystrophinopathy may present with dilated cardiomyopathy, heart failure, and arrhythmias. Dystrophinopathy patients are susceptible to anesthesia-induced rhabdomyolysis and hyperkalemic cardiac arrest with exposure to volatile anesthetics or succinylcholine. Recovery from neuromuscular blockade may be prolonged and exacerbate underlying respiratory compromise. Additionally, hemostasis may be impaired by disruption of platelet activation.[15,34,35]

Respiratory Compromise and Airway Difficulty

Although nocturnal ventilation and spinal stabilization have decreased the morbidity and mortality associated with respiratory failure, the respiratory reserve is reduced with DMD.[41] While less severe, manifesting carriers also are vulnerable to respiratory compromise.[42] Perioperative sedation must be balanced with the need to maintain the respiratory drive. Recovery from neuromuscular blockade is delayed in DMD. When paralysis is necessary, nondepolarizing neuromuscular blockers should be used and judiciously titrated using an acceleromyograph or train-of-four assessment. Depolarizing neuromuscular blockade with succinylcholine is contraindicated because of the risk for rhabdomyolysis. It is important to recognize that the onset of blockade with nondepolarizing neuromuscular blockers also is delayed. Although the mechanism has not been established, it has been hypothesized that the total number of neuromuscular junctions and receptors decreases with the progressive degradation of muscle fibers.[43] Complete reversal of neuromuscular blockade is imperative. Reversal with Sugammadex has been reported in the dystrophinopathy population, but experience is limited.[44]

A higher incidence of difficult airway has been described among the DMD population.[42] Adults with dystrophinopathy often present with obesity, large tongue, restricted mouth opening, and limited cervical spine mobility that contribute to difficulties with airway management. Delayed-onset of paralysis with nondepolarizing neuromuscular blockers may further complicate airway management. Although airway difficulty has not yet been described in manifesting carriers, anesthesia providers should be prepared for the management of a difficult airway when caring for adults with dystrophinopathy.

Coagulopathy

While dystrophin is predominantly found in myocytes, its absence also impacts hemostasis, as dystrophin has a role in platelet function. Greater blood loss has been observed in patients with DMD during scoliosis surgery as compared with healthy individuals.[42] The patient described here also demonstrated persistent coagulopathy and higher-than-anticipated blood loss postbypass despite adequate protamine reversal. The observed bleeding diathesis likely was multifactorial,

attributable to a prolonged duration of bypass as well as inherent coagulation abnormalities.

The hemostatic process is divided into two major steps: primary and secondary hemostasis. Secondary hemostasis involves plasma clotting factors and has not been found to be affected in dystrophinopathy. However, primary hemostasis, which involves platelet adhesion and vessel wall contraction, may be altered.[45] Dystrophin is present in vascular smooth muscle and is important for NO signaling in the microvasculature. Therefore, dystrophin deficiency alters vessel reactivity, and the vessel wall contraction that normally occurs after vessel injury may be impaired.[46] Additionally, the dp71 dystrophin isoform is present within the platelet cytoskeleton and is vital for the linkage of glycoproteins involved in platelet signaling.[46,47] Without dystrophin, platelet activation is impaired. In vitro studies also have demonstrated delayed collagen reactivity and decreased platelet adhesion to collagen in DMD patients.[45,46] Platelet transfusion prior to major surgery may reduce blood loss in this population,[45-47] and viscoelastography may be useful for guiding platelet transfusion.

Conclusion

Anesthesia considerations for manifesting carriers largely are extrapolated from experience with DMD and BMD patients. This discussion highlights the pathophysiology and manifestations of adult dystrophinopathy in female carriers. Phenotypic expression is highly variable in DMD carriers, and the absence of symptoms does not preclude the potential for adverse events with anesthesia, as manifestation may remain subclinical until provoked. Manifesting carriers may present with skeletal muscle weakness and/or cardiomyopathy, and may be predisposed to cardiac arrhythmia, anesthesia-induced rhabdomyolysis, respiratory compromise, difficult airway, and coagulopathy. The authors suggest anesthetic management that avoids volatile anesthetics and succinylcholine and recommend quantitative assessment of neuromuscular blockade in all carriers of DMD and BMD. Viscoelastography may also be useful for managing coagulopathy during surgical procedures in which blood loss is anticipated or hemostasis is crucial.

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Conflict of Interest

Victoria Vo is related to the patient presented in the case report. There are no competing financial interests to disclose.

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