Left Ventricular Noncompaction Cardiomyopathy and Aortopathy in a Patient With Recessive Dystrophic Epidermolysis Bullosa

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Both epidermolysis bullosa (EB) and nonischemic cardiomyopathy (CM) are rare clinical entities. An association between EB and dilated CM (DCM) has been appreciated for at least 25 years, but a common mechanism of disease has not emerged. In this report, we present a patient with EB and left ventricular noncompaction (LVNC), a newly recognized type of CM.

EB is a broad group of diseases characterized by skin fragility and blistering. Dystrophic EB occurs as either a dominantly or recessively inherited (RDEB) type, with scarring and blistering in the sublamina densa layer of the skin. DCM has been described in several patients with RDEB, but the relationship between these conditions has not been understood. For this reason, RDEB patients at our EB Center are screened yearly with echocardiograms. Outcomes for patients with RDEB are generally determined by comorbidities, and treatment currently focuses on symptomatic management; however, active areas of research include gene, protein, and stem cell therapies.

There are 7 subtypes of LVNC, including isolated that accounts for 25% of cases, isolated with arrhythmias, dilated, hypertrophic, hypertrophic and dilated, restrictive, and LVNC with congenital heart disease. The most commonly used diagnostic criteria focus on the ratio of the thickness of noncompacted to compacted left ventricular wall at the midpapillary level as measured by echocardiography or magnetic resonance imaging. Overall, outcomes in patients with LVNC are poor because of early death from heart failure or sudden death related to arrhythmias or stroke.

Herein, we describe an 8-year-old boy with RDEB. Direct immunofluorescence showed absent collagen 7, and electron microscopy revealed a split in the lamina densa, consistent with the disease. Pedigree analysis was consistent with autosomal recessive inheritance. He suffers several comorbidities common to RDEB, including esophageal stricture, joint contractures, and failure to thrive, requiring a feeding gastrostomy and enteral supplementation. A routine screening echocardiogram at 5 years of age demonstrated a spongiform myocardium, with 4 segments of the left ventricle affected showing deep trabeculations and a thin compacted layer with a noncompacted-to-compacted ratio >2:1 (Figure, online-only Data Supplement Movie 1). Blood flow within the deep trabeculations was demonstrated (online-only Data Supplement Movie 2). The left ventricular end-diastolic dimension was normal (3.9 cm; z score, +1.4), as were left ventricular systolic function (ejection fraction, 65%) and diastolic function (isovolumetric relaxation time, 49 ms), precluding a diagnosis of DCM. Interestingly, there was also dilation of the aortic root (2.6 cm; z score, +4.3) without aortic insufficiency or mitral valve prolapse; the degree of dilation has not progressed during 3 years of serial observation.

The current case is novel because a patient with RDEB has LVNC without overt DCM. LVNC can result from sarcomeric gene mutations or arise in conjunction with genetic syndromes, mitochondrial disorders, or inborn errors of metabolism. To our knowledge, this is the first report of an association between LVNC and RDEB. It is important to note that in some cases LVNC evolves into a DCM phenotype, suggesting LVNC may precede DCM in RDEB. CM is a complex genetic disease with a multifactorial cause. In considering a possible link between EB and LVNC, the extracellular matrix is a compelling area of overlap. The absence of type VII collagen is responsible for all cases of RDEB, and disruption of extracellular matrix is known to lead to CM in both animal models and patients. Although type VII collagen has not been shown to have a role in the heart, its normal function may serve as a major modifier of factors that regulate cardiovascular remodeling and function. Aortopathy in our patient adds another layer of complexity. A relationship between LVNC and aortopathy has previously been described in patients with mitochondrial disease, and connective tissue disorders often involve both skin and heart. Other conditions affecting both skin and heart, such as LEOPARD [Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal...
genitalia, Retardation of growth, and sensorineural Deafness syndrome, have been identified and may provide insight. Taken together, the unusual association of these 3 conditions suggests dysregulation of a broadly functioning regulator of extracellular matrix. Future efforts to study CM in patients with EB are underway, and an increased awareness of the need to screen this patient group will result in improved care and a better understanding of the underlying pathogenesis.

Disclosures
Dr Towbin is on the advisory board of the Children’s Cardiomyopathy Foundation.

References
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Circ Heart Fail. 2012;5:e81-e82
doi: 10.1161/CIRCHEARTFAILURE.112.969675

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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SUPPLEMENTAL MATERIAL

Movie 1: Two-dimensional echocardiogram in the parasternal short-axis plane showing a sweep through the left ventricle from the level of the mitral valve to the apex. Deep trabeculations can be appreciated along the posterior aspect of the free wall, from approximately 3 o’clock to 9 o’clock.

Movie 2: Two-dimensional echocardiogram in the apical four chamber plane showing simultaneous color imaging. Color signal is demonstrated between deep trabeculations representing blood flow in this area, consistent with diagnostic criteria for LVNC.