



# Cardiac Magnetic Resonance Imaging Findings for Dilated Cardiomyopathy Caused by Pathogenic Disruption of Desmoplakin Gene Influences Decision for Heart Transplantation

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## Abstract

**Background:** Over the past decade, Cardiac Magnetic Resonance imaging (CMR) has come to the fore in evaluation of adults with dilated cardiomyopathy and is increasingly used for pediatric patients. This case illustrates how CMR findings contributed to the decision for heart transplantation in a child with a unique type of dilated cardiomyopathy.

**Case Presentation:** A 6-year-old girl with a long-standing history of diffuse erythroderma presented with vomiting and lethargy. Cardiomegaly on chest x-ray led to Echocardiogram, which showed severe dilated cardiomyopathy. Diffuse transmural fibrosis was noted on CMR. The patient was non-responsive to Intravenous Gamma Globulin (IVIG) (for presumed fulminant myocarditis). This patient underwent heart transplant with good result. Explant histology confirmed diffuse myocardial fibrosis. Whole exome sequencing revealed a pathogenic variant in the Desmoplakin (DSP) gene which codes for Desmoplakin, a protein involved in intercellular junctions; pathogenic disruption of this gene has been implicated as a cause of diffusely red, scaly skin (erythrokeratoderma) and severe dilated cardiomyopathy.

**Conclusion:** This case illustrates the importance of CMR for optimal management of dilated cardiomyopathy, especially when there is no clear etiology. The extent of myocardial Late Gadolinium Enhancement (LGE), due to cellular necrosis and subsequent fibrosis, may contribute to clinical decision making.

**Keywords:** Pediatric Cardiac Magnetic Resonance (CMR); Dilated cardiomyopathy; Late Gadolinium Enhancement (LGE); Cardiac transplantation

## Authorship Statements

Abhineet M Sharma, Steve Zangwill, James Southern, Kristen Holland, Gabrielle Geddes and Margaret M Samyn contributed materially to the review of the patient's case, review of relevant literature, and preparation of this manuscript.

## Introduction

Dilated cardiomyopathy has an incidence of approximately 1 case per 100,000 children in the United States [1]. Of those, approximately 27 to 40% have myocarditis [1-3]. The most common causes of pediatric dilated cardiomyopathy in the United States are idiopathic, myocarditis, and neuromuscular disorder [4]. Less likely causes include inborn errors of metabolism and familial dilated cardiomyopathy [4,5] As in this case presentation, patients often present with sudden onset fatigue and symptoms of heart failure including cough, nausea and vomiting, or cardiac anorexia, but they may even present with sudden death or aborted sudden death [4].

In this case, a child with extensive skin disease presented acutely with symptoms of heart

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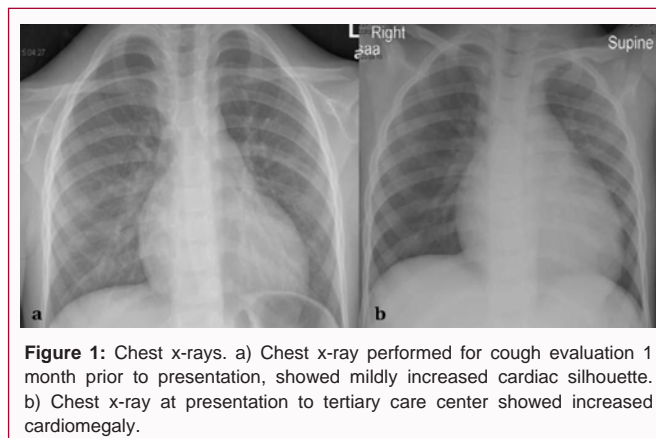
failure and was initially found by Echocardiography to have a severely dilated Left Ventricle (LV) with poor systolic function. During her initial presentation, although viral etiologies are more common, a possible association of the cardiomyopathy with her presumptive diagnosis of psoriasis was considered. Data linking chronic and severe psoriasis to dilated cardiomyopathy is sparse and limited to case reports with rare case series. Psoriatic lesions are characterized by increased T lymphocyte activity with up regulation of type 1 helper T cytokines, an immuno phenotype shared with lymphocytic myocarditis. Given this patient's negative viral studies, other etiologies for cardiomyopathy were considered-including an auto-immune mechanism of myocardial disease was postulated, supporting treatment with intravenous gamma globulin (IVIG) [6-8].

While bedside echo provided the first glimpse of the child's dilated and poorly functioning heart, ruled out an anatomic etiology (e.g. anomalous left coronary artery from the pulmonary artery), and was easily acquired, the use of Cardiac Magnetic Resonance imaging (CMR) has emerged as standard of care in many centers. CMR provides detailed anatomic data, quantifies ventricular volumes, and valvar regurgitation, and allows for myocardial tissue characterization [9,10]. With reliable volumetric and functional measures, as well as typical patterns of Late Gadolinium Enhancement (LGE), over the past decade CMR has come to the fore in evaluation of adults with dilated cardiomyopathy with CMR having emerging utility in children [11-13]. Although there are recent data to suggest possible retention of gadolinium contrast in the brain (i.e., the dentate nucleus and globus pallidus even in subjects with normal renal function) and in other organs after repetitive magnetic resonance scans, the clinical meaning is still under investigation [14].

As there was no clear etiology for the rapid progression of this patient's clinical heart failure despite IVIG treatment, Endo Myocardial Biopsy (EMB) was considered, in accord with the joint scientific statement of the American Heart Association, American College of Cardiology, and European Society of Cardiology which advocates for EMB with new onset heart failure of greater than 2 weeks duration with dilated LV and ventricular arrhythmias or heart block or, as in this case failure to respond to usual care in 1 to 2 weeks [15]. This child did not, though, undergo EMB, as the benefit-risk ratio was not deemed favorable for her, because the risk for complications seemed high. Instead, although CMR cannot distinguish among etiologies of myocarditis per se, CMR scanning was performed to aid management [16,17] and decision-making, by assessing the extent of myocardial LGE-a marker of myocardial necrosis and fibrosis. Based on echo findings of severe LV dilation and profoundly reduced systolic function, extensive LGE was suspected and when verified by CMR, supported listing this child for heart transplant.

## Case Presentation

A 6-year-old girl presented to an outside hospital with a one-day history of vomiting and lethargy. Her past medical history was significant for persistent diffuse erythroderma, attributed presumptively to psoriasis, since the age of 2 years. For her skin disease, she had been on a combination of adalimumab and methotrexate since 3 years of age, after failing a number of immunomodulatory therapies. Over her lifetime, she had required multiple hospitalizations for painful pustular flares, which were managed with topical and occasionally systemic corticosteroids. She had a dermatologic flare 3 weeks prior to this presentation and was successfully treated with prednisone and clindamycin, returning to



her usual activities, including school. Energy level prior to admission was slightly decreased, which was attributed to recent activities (i.e. birthday party attendance and school zoo trip). The patient denied palpitations, presyncope, or syncope, but reported a brief episode of fleeting chest pain prior to presentation, which resolved without intervention. She did not have upper respiratory symptoms prior to presentation. However, she did have a positive rapid strep test and received one dose of Rocephin in the emergency department.

With a new apical systolic murmur and hepatomegaly, she was admitted to the hospital with concern for sepsis. Labs showed a white blood cell count of 44K with 68% segmented neutrophils but no bands. She had elevation in her liver enzymes (AST: 630 IU/L (normal range: 23 IU/L-65 IU/L)) and ALT: 73 IU/L (normal range: 6 IU/L-45 IU/L). At baseline in the weeks prior to admission, she had frequent mild leukocytosis with neutrophilia attributed to her prednisone exposure and her AST and ALT had been normal. She had been without hepatomegaly on several physical examinations in the weeks prior to admission. On admission, her chest X-ray showed massive cardiomegaly; in retrospect, a film performed 1 month prior to admission for "cough" demonstrated a mildly enlarged cardiac silhouette (Figure 1a and b). Subsequent echocardiogram (Echo) showed a severely dilated left ventricle with mitral insufficiency and reduced left ventricular (LV) systolic function (LV ejection fraction (EF) = 31%). She was emergently transferred to Children's Hospital of Wisconsin (CHW) for continued care.

## Admission and Workup

On CHW admission, the patient was a febrile with normal HR and BP for age (110 bpm and 83/49). She was dyspneic (respiratory rate 26/min) although with her oxygen saturation was 100% in room air. She had a normoactive precordium with a regular rhythm and normal heart sounds with no murmurs or gallops. Her lungs were clear to auscultation with no retractions or nasal flaring. Her liver was 2 cm to 3 cm below the costal margin. She had good distal pulses but delayed capillary refill (3 to 4 seconds).

Her lab work up on presentation was significant for an elevated BNP (1240 pg/ml with normal < 300 pg/ml), CK-MB (1178 ng/ml with normal range 33 IU/L- 45 IU/L), and Troponin-I (284 ng/ml, with normal range 0.012 ng/ml- 0.034 ng/ml). Extensive workup (including viral, immunologic, rheumatologic, and metabolic studies) was negative (Table 1). A repeat Echo, performed on admission, showed dilated cardiomyopathy with moderate to severe LV dilation with severely reduced systolic function ( LV EF = 18%). Milrinone and furosemide drips were initiated.

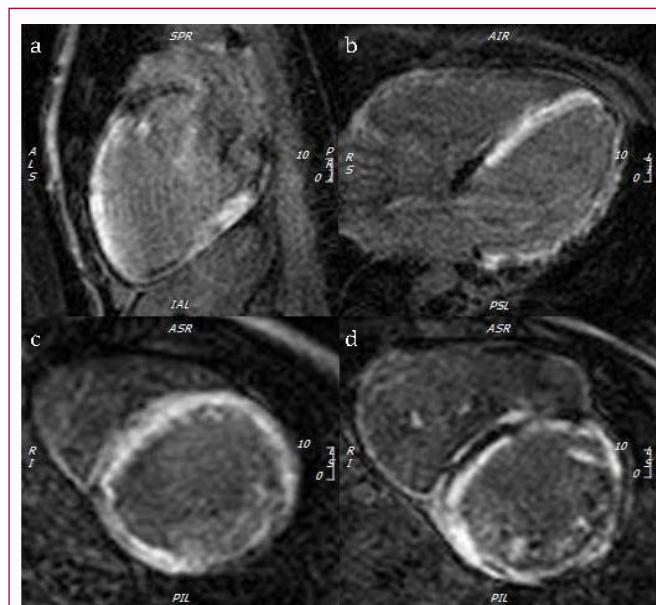
**Table 1:** Laboratory work up.

		Test	Result
Infectious	Adenovirus	PCR	Negative
	Parainfluenza 1, 2, 3	PCR	Negative
	HIV	Rapid	Negative
	Toxoplasmosis	Ab	Negative
	HSV	Ab	Negative
	Hepatitis C	Ab	Negative
	Hepatitis B	Ab	Negative
	EBV	Ab	Seroconverted
	CMV	Ab	Recent seroconversion
	Enterovirus	PCR	Negative
	Lyme	Western Blot	Negative
	Antistreptolysin	Ab	Negative
	Anti Dnase B	Ab	Negative
Immune	Immunoglobulin	Quant	Normal
	IgE	Quant	Borderline
Rheumatologic	ENA	Quant	Negative
	ANA	Quant	Negative
	Polymyositis	Ab	Negative

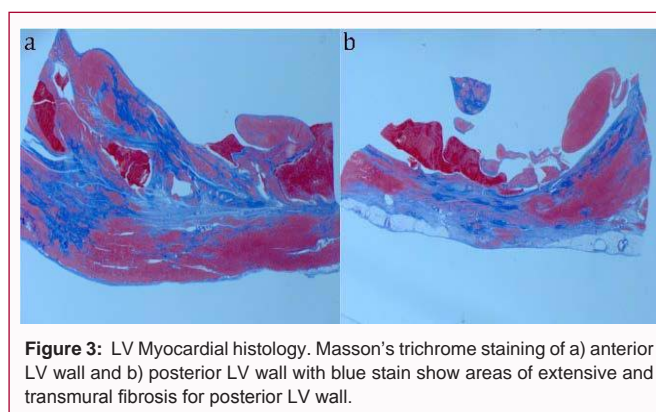
Given the elevated troponin and clinical symptoms, Cardiac Magnetic Resonance (CMR) was performed to assess for myocarditis and Late Gadolinium Enhancement (LGE). Endo myocardial Biopsy (EMB) was considered for this case, but rejected due to concerns for complications for this acutely ill child. EMB, while still the “gold standard” for myocarditis diagnosis, carries an increased risk for complications (including possible catastrophic Right Ventricular (RV) perforation), which are increased by presence of inflamed myocardium and by the hemodynamic instability of the patient [18,19]. In addition, EMB also presents problems with sampling error and sub optimal inter-observer variability [20,21]. While once common place for myocarditis, EMB, therefore, has become less popular and is no longer standard of care at many institutions. Thus, in practice, history, test results, and clinical course are all integrated to make the diagnosis [16].

The CMR scan showed severe dilation of the LV (LV end-diastolic volume (EDV) index = 134 ml/m<sup>2</sup> (normal range 58 ml/m<sup>2</sup>– 87 ml/m<sup>2</sup>) with severely reduced LV systolic function (LV EF ~19%) [22]. The RV was also severely dilated (RVEDV index = 141 ml/m<sup>2</sup>, where normal range 61 ml/m<sup>2</sup>–103 ml/m<sup>2</sup>) and had reduced systolic function (RV EF = 20%). Cardiac anatomy was otherwise normal, with normal coronary origins. Interestingly, there was diffuse myocardial edema on T2 weighted imaging. Additionally, global LGE was seen throughout the right and left ventricles with many areas having transmural LGE (Figure 2).

This patient was presumptively treated with IVIG for presumed fulminant myocarditis. Cardiac support continued during her intensive care stay, but her cardiac function failed to improve, and she was listed for cardiac transplant – a decision corroborated by the extensive LGE seen on CMR. Despite supportive care, she developed progressive respiratory insufficiency with worsening cardiac output and bilateral pleural effusions, leading to a need for ventilator support. Eight weeks after admission, the patient underwent heart transplant



**Figure 2:** Cardiac magnetic resonance images. a) LV 2 chamber, b) biventricular 4 chamber, c) LV apical short axis and d) LV mid short axis planes of the patient's heart which has dilated cardiomyopathy with extensive myocardial LGE for a child with erythrodermic and pustular psoriasis (Siemens 1.5T Symphony using FLASH PSIR LGE sequence with FOV 208 x 256, slice thickness 4.5 mm, TE 3.4 msec, TR 389 msec).

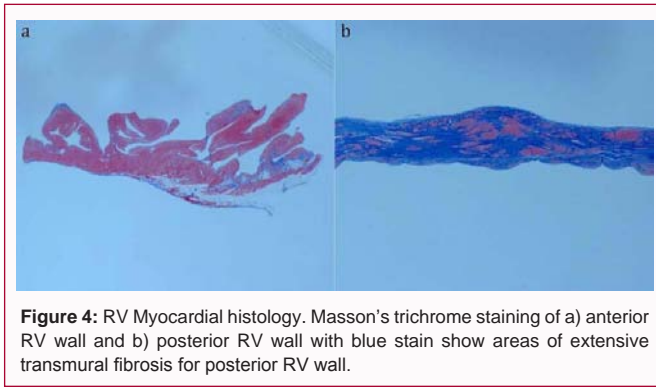


**Figure 3:** LV Myocardial histology. Masson's trichrome staining of a) anterior LV wall and b) posterior LV wall with blue stain show areas of extensive and transmural fibrosis for posterior LV wall.

and has done well thereafter.

On histological examination of the cardiac explant, the left atrial wall showed typical thick, vein-like endocardium and uniformly thick muscular wall with mild hypertrophy and pale sarcoplasm, consistent with typically glycogenated cardiac myocytes. Both anterior and posterior left ventricular sections were thinned with inter trabecular spaces filled by mural thrombus. The myocardium of the anterior wall had loose fibrosis, fibroblast-rich scar, consistent with healed laminar necrosis in the inner third of the wall. The posterior LV wall had extensive fibrous scar interdigitating with hypertrophic cardiac muscle bundles and fibrous tissue extending irregularly and transmurally (Figure 3). Gross focal lesions within the coronary arteries were not seen, and no focal inflammation was seen for the epicardial and intramyocardial vessels sectioned.

The right atrial wall was quite muscular with moderately hypertrophic cardiac myocytes and a thick fibrotic epicardium. The anterior RV free wall had areas of fatty replacement and moderate hypertrophy. In contrast, the posterior right ventricular free wall was markedly thinned with zones that were completely fibrous scar



**Figure 4:** RV Myocardial histology. Masson's trichrome staining of a) anterior RV wall and b) posterior RV wall with blue stain show areas of extensive transmural fibrosis for posterior RV wall.

(Figure 4). Immune histology was not performed, as not deemed necessary for this heart transplant recipient.

Four years after her transplant, the patient underwent clinical whole exome sequencing and was found to have a *de novo* heterozygous variant in DSP gene resulting in a p.L583P alteration. Based on American College of Medical Genetic Variant assessment guidelines, this variant is clinically classified as pathogenic [23]. Mutation in the Desmoplakin (DSP) gene has been associated with impaired binding of keratins to the desmosomes in the epidermis, alteration of hard keratins in hair, and disruption in desmin fibers in the myocardium, leading to dilated cardiomyopathy [24].

The patient is now ten years old and continues to do well from a cardiovascular standpoint. Her recent transplant biopsies have not shown rejection, and her cardiac systolic function is normal.

## Discussion

CMR allows for myocardial tissue characterization especially when gadolinium (Gd) contrast is used. Given Intravenously (IV), Gd enters the coronaries and can be used to assess myocardial perfusion. As Gd contrast does not enter intact myocardial cells, but distributes in the interstitial/extracellular spaces of the heart within a few minutes after IV injection, its present late (~5 min to 15 min) post infusion can be indicative of myocardial fibrosis due to any number of etiologies. This late presence of Gd is known as Late Gadolinium Enhancement (LGE) or Myocardial Delayed Enhancement (MDE). Areas with retained Gd will appear brighter than normal myocardium. Histologic studies have validated the meaning of LGE [9,25]. Different patterns of LGE exist with different disease states. For example, ischemia typically has sub endocardial or transmural LGE in regions of the myocardium corresponding with the distribution of a coronary artery. Non ischemic heart disease, such as cardiomyopathy, often present with different patterns of LGE, not corresponding to any coronary territory and often not involving the sub endocardium, but rather affecting the mid-wall or the epicardium [26]. For example, hypertrophic cardiomyopathy has patchy infiltrates and myocarditis has sub epicardial LGE.

The accuracy of CMR for myocarditis may vary with the population studied and CMR techniques employed, but sensitivities and specificities approach 76% and 96% when at least 2 of 3 CMR criteria (T2, T1, and LGE) are met [17]. While CMR cannot distinguish among the various etiologies of myocarditis (viral, bacterial, fungal, toxin, auto-immune), CMR can show the extent of myocardial involvement better than a right ventricular biopsy, which due to the often patchy nature of disease, may lead to misdiagnosis. In this child's case, viral etiologies for her myocarditis (i.e., enterovirus,

adenovirus, human herpes virus 6, and parvo virus among the most frequent) were eliminated by PCR, so other possibilities were considered including toxins (i.e. chronic adalimumab and methotrexate use) and auto-immune phenomenon related to her dermatologic disease. Interestingly, the literature suggests that immunomodulatory therapies, like methotrexate, though, may be protective for cardiovascular disease by complex and multi-factorial means [27].

The pattern of myocardial LGE seen on our patient's CMR scan was most consistent with diffuse fibrosis/scar. The unusual, extensive transmural LGE seen in this patient pointed towards fulminant myocarditis or another fibrosing cardiac pathology [11]. LGE has been associated with poor prognosis, with only variable response to IVIG. Myocardial LGE has been shown to correlate well with biopsy or autopsy findings as in this case [28-30]. The extent of myocardial LGE, due to cellular necrosis and subsequent fibrosis, has been shown in the literature to contribute to clinical decision making, as in this unique pediatric case. CMR has been used for risk stratification, allowing identification of those patients more likely to have a benign course versus those with extensive LGE, who are more likely to have a significant course [31,32].

Ultimately, this patient's CMR finding of diffuse LGE supported listing her for cardiac transplantation. As expected, the explanted heart's histology showed areas of fibrosis that mirrored the location of LGE on the CMR. Whole exome sequencing for this patient showed a pathogenic variant in the Desmoplakin (DSP) gene (coding for Desmoplakin 2). Desmosomes, comprised of proteins especially Desmoplakin, are major cell adhesion junctions, highly prevalent in the epidermis and cardiac tissue; desmosomes are important for the cell rigidity and strength. Mutation in the DSP gene altered Desmoplakin, leading to this patient's phenotype - erythrokeratoderma with cardiomyopathy spectrum [24,33]. She shares clinical features previously described in patients with similar DSP variants [33,34]. Additionally, gross histologic and microscopic examination of explanted hearts from patients with pathogenic DSP gene often shows diffuse fibrosis (as seen in this patient) and sometimes may also show fibro-fatty replacement of the myocardium [35].

## Conclusion

This case illustrates the importance of CMR scanning for optimal management of pediatric dilated cardiomyopathy, especially when there is no clear etiology. The extent of LGE seen for this patient contributed to the clinical decision to list her for cardiac transplantation.

In addition, this case highlights the importance of genetic testing to discern the association of systemic disease with cardiomyopathy, especially when the pattern of LGE is more extensive than usually seen with myocarditis and when a patient fails to respond to conventional therapy (IVIG). Furthermore, this case suggests that for children with DSP mutation, screening for cardiomyopathy with Echo and CMR throughout childhood may allow earlier identification of the extent of cardiac disease. Finally, with a team of clinician-scientists, optimal care can be delivered to pediatric patients with rare diseases.

## Ethics Approval and Consent to Participate

IRB approval was not required at our institution for a single case; patient assent and parental consent to publish was granted.

## References

- Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med*. 2003;348(17):1647-55.
- Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela A, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: a nationwide study in Finland. *American Journal of Epidemiology*. 1997;146(5):385-93.
- Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med*. 2003;348(17):1639-46.
- Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. 2006;296(15):1867-76.
- Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10(9):531-47.
- Eliakim-Raz N, Shuvy M, Lotan C, Planer D. Psoriasis and dilated cardiomyopathy: coincidence or associated diseases? *Cardiology*. 2008;111(3):202-6.
- McNamara DM, Rosenblum WD, Janosko KM, Trost MK, Villaneuva FS, Demetris AJ, et al. Intravenous Immune Globulin in the Therapy of Myocarditis and Acute Cardiomyopathy. *Circulation*. 1997;95(11):2476-8.
- McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, et al. Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy. *Circulation*. 2001;103:2254-9.
- Sohrab Fratz, Taylor Chung, Gerald F Greil, Margaret M Samyn, Andrew M Taylor, Emanuela R Valsangiacomo Buechel, et al. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. *J Cardiovasc Magn Reson*. 2013;15(1):51.
- Cummings KW, Bhalla S, Javidan-Nejad C, Bierhals AJ, Gutierrez FR, Woodard PK. A Pattern-based Approach to Assessment of Delayed Enhancement in Nonischemic Cardiomyopathy at MR Imaging. *Radiographics*. 2009;29(1):89-103.
- Wu KC, Weiss RG, Thieman DR, Kitagawa K, Schmidt A, Dalal D, et al. Late Gadolinium Enhancement by Cardiovascular Magnetic Resonance Heralds an Adverse Prognosis in Nonischemic Cardiomyopathy. *J Am Coll Cardiol*. 2008;51(125):2414-21.
- Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, et al. Cardiovascular Magnetic Resonance, Fibrosis, and Prognosis in Dilated Cardiomyopathy. *J Am Coll Cardiol*. 2006;48(10):1977-1985.
- Latus H, Gummel K, Klingel K, Moysich A, Khalil M, Mazhari N, et al. Focal myocardial fibrosis assessed by late gadolinium enhancement cardiovascular magnetic resonance in children and adolescents with dilated cardiomyopathy. *J Cardiovasc Magn Reson*. 2015;17:34.
- Huckle JE, Altun E, Jay M, Semelka RC. Gadolinium Deposition in Humans: When Did We Learn That Gadolinium Was Deposited In Vivo? *Invest Radiol*. 2016;51:236-40.
- Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2007;28:3076-93.
- Agliardi MG, Bevilacqua M, Di Renzi P, Picardo S, Passariello R, Marcelletti C. Usefulness of magnetic resonance imaging for diagnosis of acute myocarditis in infants and children, and comparison with endomyocardial biopsy. *Am J Cardiol*. 1991;68:1089-91.
- Banka P, Robinson J, Uppu S, Harris M, Hasbani K, Lai W, et al. Cardiovascular magnetic resonance techniques and findings in children with myocarditis: a multicenter retrospective study. *J Cardiovasc Magn Reson*. 2015;17:96.
- Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol*. 1992;19:43-78.
- Pophal SG, Sigfusson G, Booth KL, Bacanu SA, Webber SA, Etedgui JA, et al. Complications of endomyocardial biopsy in children. *J Am Coll Cardiol*. 1999;34:2105-10.
- Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. *J Am Coll Cardiol*. 1989;14:915-20.
- Shanes JG, Ghali J, Billingham ME, Ferrans VJ, Fenoglio JJ, Edwards WD, et al. Inter observer variability in the pathologic interpretation of endomyocardial biopsy results. *Circulation*. 1987;75:401-5.
- Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. *J Magn Reson Imaging*. 2009;29:552-9.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-423.
- Norgett EE, Hatsell SJ, Carvajal-Huerta L, Ruiz Cabezas J, Common J, Purkis PE, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Human Molecular Genetics*. 2000;9:2761-6.
- Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100(19):1992-2002.
- Doltra A, Amundsen BH, Gebker R, Fleck E, Kelle S. Emerging concepts for myocardial late gadolinium enhancement MRI. *Curr Cardiol Rev*. 2013;9(3):185-90.
- Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology*. 2010;49:295-307.
- Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, et al. Cardiovascular Magnetic Resonance Assessment of Human Myocarditis. *Circulation*. 2004;109:1250-58.
- Etesami M, Gilkeson RC, Rajiah P. Utility of late gadolinium enhancement in pediatric cardiac MRI. *Pediatr Radiol*. 2016;46(8):1096-113.
- Muller KAL, Muller I, Kramer U, Kandolf R, Gawaz M, Bauer A, et al. Prognostic Value of Contrast-enhanced Cardiac Magnetic Resonance Imaging in Patients with Newly Diagnosed Non-Ischemic Cardiomyopathy: Cohort Study. *PLOS ONE*. 2013;8:e57077.
- Schumm J, Greulich S, Wagner A, Grun S, Ong P, Bentz K, et al. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. *J Cardiovasc Magn Reson*. 2014;16:14.
- Scott PA, Rosengarten JA, Curzen NP, Morgan JM. Late gadolinium enhancement cardiac magnetic resonance imaging for the prediction of ventricular tachyarrhythmic events: a meta-analysis. *European Journal of Heart Failure*. 2013;15:1019-27.
- Boyden LM, Kam CY, Hernández-Martín A, Zhou J, Craiglow BG, Sidbury R, et al. Dominant de novo DSP mutations cause erythrokeratoderma-cardiomyopathy syndrome. *Human Molecular Genetics*. 2016;25:348-57.

34. Carvajal-Huerta L. Epidermolyticpalmoplantarkeratoderma with woolly hair and dilated cardiomyopathy. *J Am Acad Dermatol.* 1998;39:418-421.
35. Chalabreysse L, Senni F, Bruyère P, Aime B, Ollagnier C, Bozio A, et al. A new hypo/oligodontia syndrome: Carvajal/Naxos syndrome secondary to desmoplakin-dominant mutations. *J Dent Res.* 2011;90:58-64.