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STATE-OF-THE-ART REVIEW

Atlas of Regional Left Ventricular Scar in Nonischemic Cardiomyopathies

Substrates and Etiologies

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ABSTRACT

Most acquired and inherited cardiomyopathies are characterized by regional left ventricular involvement and nonischemic myocardial scars, often with a disease-specific pattern. Irrespective of the etiology and pathophysiological mechanisms, myocardial disorders are invariably associated with cardiac fibrosis, which contributes to dysfunction and electrical instability. Accordingly, cardiac magnetic resonance plays a central role in the diagnostic work-up and prognostic risk stratification of cardiomyopathies, particularly with the increasing correlation between genetic background and specific disease phenotype. Starting from pattern and distribution of myocardial fibrosis at cardiac magnetic resonance, we provide a practical regional atlas of nonischemic myocardial scar to guide the diagnostic approach to nonischemic cardiomyopathies. (JACC Adv. 2024;3:101214) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Up to 40% of patients referred to coronary angiography for chest pain, wall motion abnormalities, or evidence of structural heart disease in presence of cardiovascular risk factors have no evidence of significant coronary artery disease.[1] In a significant subset, cardiac magnetic resonance (CMR) is performed as part of the diagnostic work-up of several clinical scenarios including chest pain with normal coronary arteries, cardiomyopathies, or unexplained ventricular arrhythmias when a cardiomyopathy has not yet been suspected. The identification of a nonischemic left ventricular (LV) scar represents a significant challenge for cardiologists due to the need for differential diagnosis among a wide range of diseases, with major diagnostic, therapeutic, and prognostic implications for patients and their families. Myocardial fibrosis is a structural lesion resulting from several different damage mechanisms. Besides myocardial ischemia and necrosis, regional LV scars may be caused by direct or indirect damage affecting cardiomyocytes, the *interstitium*, and the microvasculature.[2] Indeed, the recently

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

LGE = late gadolinium enhancement

LV = left ventricular

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

SCD = sudden cardiac death

issued European Society of Cardiology guidelines for the management of cardiomyopathies [3] emphasized the importance of scar assessment by CMR in defining the phenotype of cardiomyopathies and in guiding further diagnostic tests and therapeutic strategies. Of note, a new cardiomyopathy phenotype named "nondilated left ventricular cardiomyopathy," defined as the presence of nonischemic LV scarring or fatty replacement regardless of the presence of global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring, has been introduced.

This paper reviews the pathogenesis of myocardial scar and provides an overview of value of location and distribution of LV scar patterns for diagnosis of cardiomyopathies, classified according to their distribution within the main coronary territories, ie, the 17 LV segments grouped into anterior, septal, apical, lateral, and inferior regions, and the well-known ring-like pattern remaining distinct (**Central Illustration**); moreover, a distribution of the most frequent genes involved per segment is proposed when the differential diagnosis focuses on inherited cardiomyopathies (**Figure 1**).

HIGHLIGHTS

- Presence of LV scars does not necessarily reflect coronary artery disease.
- Regional LV scars can be seen in different myocardial disorders, often with typical distribution.
- Clinical data combined with localization of LV scars is essential in raising etiological suspicion/diagnosis.
- Cardiac magnetic resonance is the new gold standard for diagnosis and risk stratification of scars.

PATHOGENESIS OF REGIONAL LEFT VENTRICULAR SCAR

Myocardial fibrosis is characterized by an excessive deposition that may occur with two different modalities, reflecting different pathophysiological mechanisms: interstitial fibrosis, which reflects abnormal superactivation of the matrix and represents diffuse process; and replacement fibrosis following tissue damage, ie, the scar, which is typically regional.[4]

Replacement fibrosis is most frequently observed after an ischemic insult in patients with coronary artery disease but may also occur as a result of pressure or volume overload, genetic cardiomyopathies (eg, hypertrophic cardiomyopathy [HCM]), or inflammatory disease (eg, cardiac sarcoidosis, myocarditis).[4] Genetic mechanisms and superimposed inflammation may often co-exist, as in the case of arrhythmogenic cardiomyopathy or Anderson-Fabry disease.

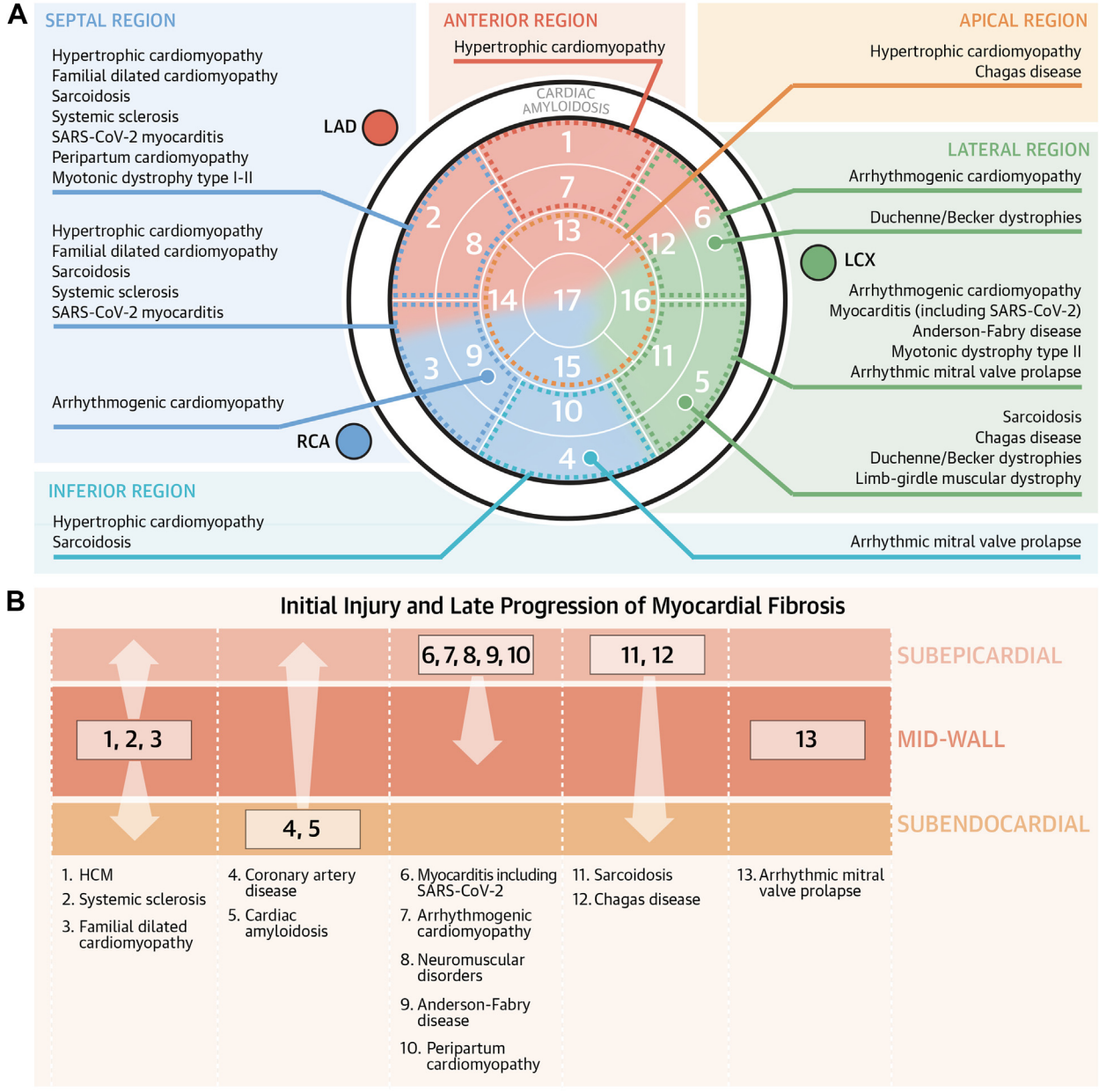
The distinction between replacement and interstitial fibrosis, however, is not clear-cut, as the two phenomena may overlap. LV scars represent the irreversible end-stage results of severe disease processes leading to cell death. Following a genetic, inflammatory, toxic, or metabolic damage mechanisms leading to myocardial cell death, the local tissue response includes a sequence of activation of inflammation, cell damage, and repair.[5] As such, the histological and imaging features are qualitatively indistinguishable in LV scars, while the regional and transmural distribution may be specific for individual diseases.

Although histological analysis remains the gold standard for confirming the presence of myocardial fibrosis, several studies have demonstrated histological validation of CMR parameters for its assessment.[6] A technique known as late gadolinium enhancement (LGE) uses the deposition of CMR contrast in the extracellular space, which is enlarged due to the loss of myocytes or deposition, to identify myocardial scar.[4] In stable chronic conditions and in the absence of edema, LGE is considered an accurate proxy of scar evaluation *in vivo* and has entered routine clinical practice to aid in differential diagnoses and assess disease progression in cardiomyopathies.

ANTERIOR REGION

Scar in the anterior region of the LV typically affecting basal and mid segments is frequently observed in patients with HCM, the most prevalent genetic cardiovascular disorder,[7] caused in 60% of cases by mutations in sarcomere protein genes (being myosin heavy chain and myosin binding protein 3 the most frequent).[8] HCM is characterized by asymmetric LV wall hypertrophy, myocardial hypercontractility, diastolic dysfunction, and dynamic left ventricular outflow tract obstruction.[9] Mitral valve morphological abnormalities are a key phenotypic manifestation of HCM; elongated mitral leaflets are a primary contributor to dynamic LV outflow tract obstruction (together with a small outflow tract dimension).[10] Although electrocardiograms (ECGs) may appear normal in 4% to 6% of HCM adult patients, several

CENTRAL ILLUSTRATION **Distribution and Localization of Myocardial Fibrosis in Different Cardiomyopathies**



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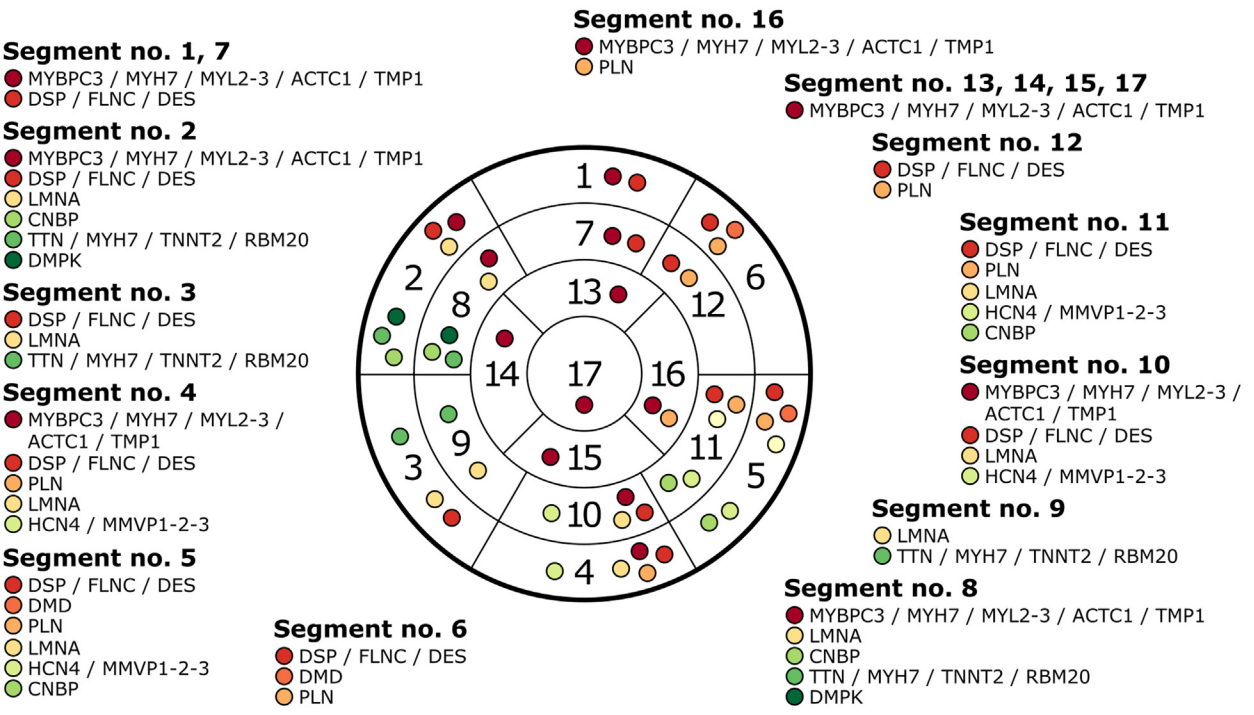
(A) List of diseases follow a hierarchical downward prevalence sequence. Cardiac amyloidosis, which has no specific distribution, is a distinctive case. Left ventricle is divided into five regions: anterior, septal, apical, lateral, and inferior. The 17 segments are: basal anterior (1), basal anteroseptal (2), inferoseptal (3), basal inferior (4), basal inferolateral (5), basal anterolateral (6), mid anterior (7), mid anteroseptal (8), mid inferoseptal (9), mid inferior (10), mid inferolateral (11), mid anterolateral (12), apical anterior (13), apical septal (14), apical inferior (15), apical lateral (16), and apex (17). (B) Location of myocardial fibrosis from the layer that is initially involved and damage progression. HCM = hypertrophic cardiomyopathy; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

FIGURE 1 Gene Map Displaying Distinct Expression Patterns for Each Left Ventricular Segments Affected by a Nonischemic Scar



ACTC1 = actin alpha cardiac muscle 1; CNBP = CCHC-type zinc finger nucleic acid binding protein; DES = desmin; DMD = dystrophin; DMPK = DM1 protein kinase; DSP = desmoplakin; FLNC = filamin C; HCN4 = hyperpolarization activated cyclic nucleotide gated potassium channel 4; LMNA = lamin A/C; MMVP1-2-3 = myxomatous mitral valve prolapse 1-2-3; MYBPC3 = myosin binding protein C3; MYH7 = myosin heavy chain 7; MYL2-3 = myosin regulatory light chain 2 to 3; PLN = phospholamban; RBM20 = RNA binding motif protein 20; TMP1 = tropomyosin 1; TNNI3 = cardiac troponin I3; TNNT2 = cardiac troponin T2; TTN = titin.

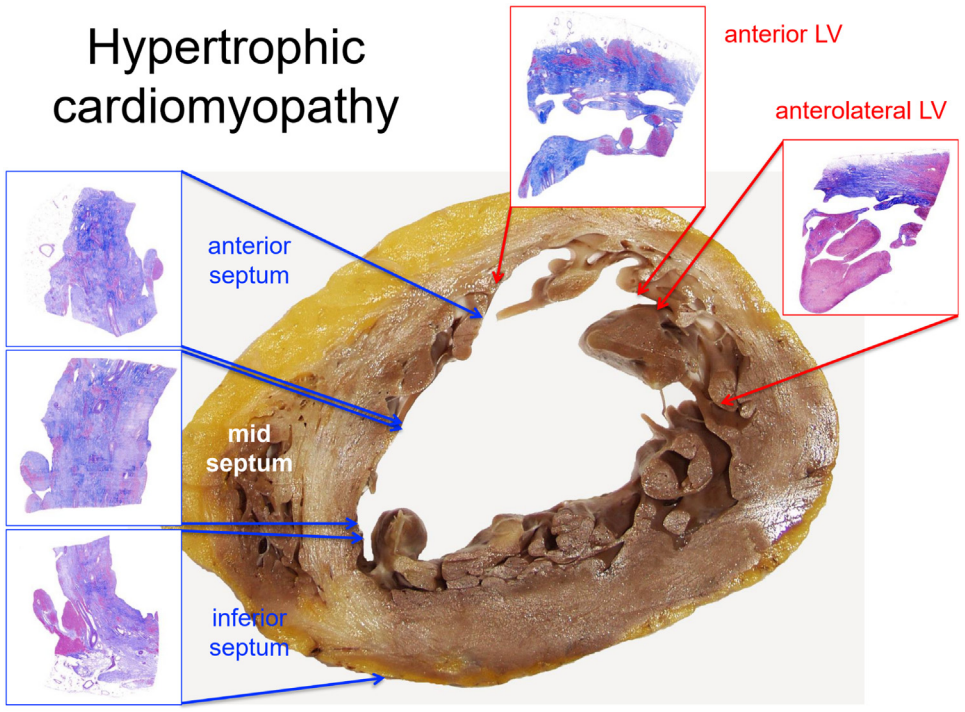
patterns are HCM distinctive, such as pathological Q waves, giant symmetric negative T waves in the precordial leads in apical HCM, and pseudo-ST-elevation myocardial infarction (pseudo-STEMI) pattern with inverted T waves in DI and aVL.[11] While generally considered a disease of the interventricular septum, anterior wall involvement is almost as constant, and the basal anterior segment is the most hypertrophied region.[12] Fibrosis is detected as LGE by CMR in over 50% of patients and most frequently occurs at the mid-wall of the hypertrophied segments but may be transmural (**Figure 2**) and involve the right ventricular intersection sites with the LV (**Table 1**). LGE is inhomogeneous and asymmetrically distributed, preferentially involving the interventricular septal wall and anterior free wall at the basal- and mid-level but may expand to the apex.[13] Further, fibrosis deposition might begin in the mid-wall and spread to the transmural distribution.[14,15] Notably, patients with a positive genotype have more myocardial fibrosis than those who are genotype-negative. Extensive areas of replacement fibrosis (>15% of the whole LV) purport adverse prognostic significance in terms of risk of sudden cardiac death (SCD) and disease progression.[14,15]

SEPTAL REGION

Septal fibrosis may result from a wide spectrum of conditions with heterogeneous etiologies and clinical manifestations including HCM,[13] dilated cardiomyopathy (DCM), sarcoidosis, systemic sclerosis, and myotonic dystrophies (**Table 2**).[16]

Septal involvement is a frequent finding also in patients with DCM phenotype,[17] particularly in individuals with familial forms linked to titin, troponin T, myosin light chain 7, and lamin A/C gene mutations,[18] the latter accounting for 10% of familial DCM. Cardiac involvement in laminopathies is characterized by a progressive form of DCM with remarkable electrical instability, often preceding structural abnormalities. Specifically, typical ECG abnormalities such as atrioventricular block, septal remodeling evidenced by Q waves in V_1-V_2, and fragmented QRS

FIGURE 2 Histological Findings in End-Stage Hypertrophic Cardiomyopathy



Transverse section at the mid-third of the native explanted heart of a 51-year-old male. Macroscopy and histology (scanned slides, Azan Mallory Trichrome) show transmural replacement fibrosis in the septum and anterolateral left ventricular wall. LV = left ventricle.

in at least two adjacent leads can be recognized.[19] Global longitudinal strain and ejection fraction apart, early alterations in septal speckle tracking longitudinal strain are associated with increased mechanical dispersion, which in turn is associated with a greater burden of ventricular arrhythmia.[20] Likewise, extensive mid-wall fibrosis in the septal region can be seen even when LV dilatation and/or dysfunction are absent (**Figure 3**).[18,20] Not surprisingly, the presence of LGE represents a strong and independent predictor of major adverse arrhythmic cardiac events occurring on an intraventricular macroreentry basis.[21,22]

Of note, mid-wall septal LGE has been observed in patients with a previous acute myocarditis[23] including severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, and is associated with a worse outcome.

Cardiac sarcoidosis should be considered in young and middle-aged patients who present with unexplained ventricular tachycardia or high-degree atrioventricular block associated even with LV

TABLE 1 Left Ventricular Scars in the Anterior Region With Specific Disease Characteristics

LV Scar	Distribution	Phenotype	Red Flags		Etiologies	Further Investigation
Anterior Region	Mid-wall/ Transmural	HCM	CLINICAL:	• Family history of HCM or SCD	*Sarcomeric HCM*	Genetic testing
			ECG:	• "Pseudo STEMI" pattern		
			ECHO:	• Mitral valve abnormalities: elongated anterior leaflet/SAM		
				• Apical or asymmetric LVH		

HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; SAM = systolic anterior motion; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction.

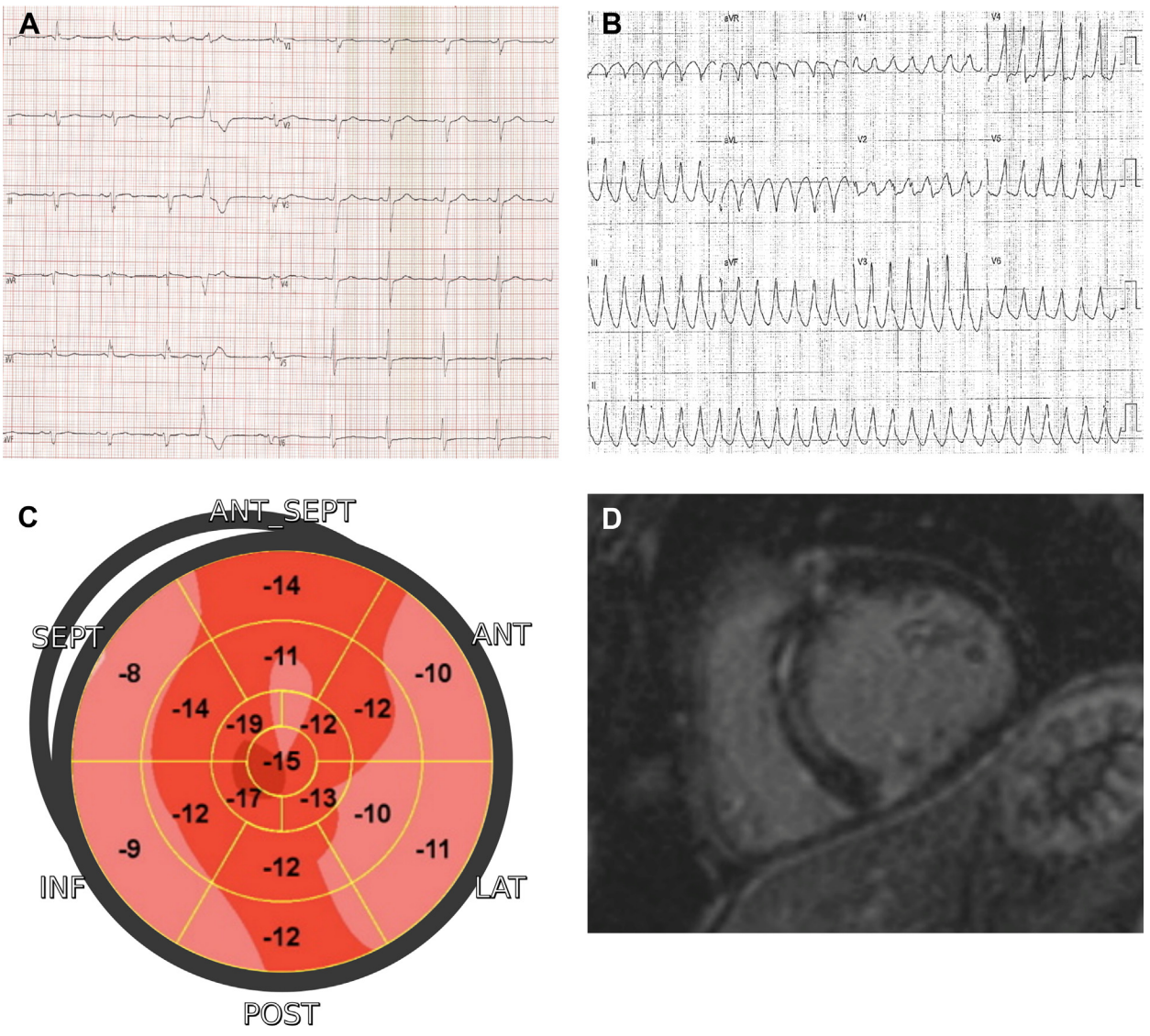
TABLE 2 Left Ventricular Scars in the Septal Region With Specific Disease Characteristics

LV Scar	Distribution	Phenotype	Red Flags		Etiologies	Further Investigation
Septal region	Mid-wall/transmural	NDLVC/DCM	CLINICAL:	• Family history of DCM or SCD • Evaluation of serum creatine kinase	*Familial DCM*	Genetic testing
			ECG:	• Early AV blocks • QS in V_1-V_2 • Fragmented QRS		
			ECHO:	• Mechanical dispersion by strain (irrespective of GLS and LVEF)		
		RCM	CLINICAL:	• Pulmonary or gastrointestinal or skin disease	*Systemic Sclerosis*	Antinuclear antibody testing
			ECG:	• Prolongation of QT interval and dispersion		
			ECHO:	• Early impaired diastolic function • Pulmonary hypertension • Pericardial effusion		
		HCM	CLINICAL:	• Family history of HCM or SCD	*Sarcomeric HCM*	Genetic testing
			ECG:	• "Pseudo STEMI" pattern • Q waves		
			ECHO:	• Mitral valve abnormalities: elongated anterior leaflet/SAM • Apical or asymmetric LVH		
	Subepicardial/ mid-wall	NDLVC/DCM/ARVC	CLINICAL:	• Family history of SCD	*Arrhythmogenic cardiomyopathy*	Genetic testing
			ECG:	• Low limb voltage • Fragmented QRS • Ventricular arrhythmias with a RBBB morphology of the ectopic QRS		
			ECHO:	• Systolic LV dysfunction related to the global extent of LGE		
		NDLVC	CLINICAL:	• Gait disturbance • Myotonia/Muscle weakness • Visual impairment	*Neuromuscular disorders*	Genetic testing Muscle biopsy[a]
			ECG:	• AV nodal and infra-nodal disease		
			ECHO:	• Regional wall motion abnormalities • Regional wall thinning or thickening		
		NDLVC/DCM	CLINICAL:	• Peripartum period	*Peripartum Cardiomyopathy*	
			ECG:	• Sinus tachycardia • Nonspecific ST-segment alterations		
			ECHO:	• Global hypokinesia		
		NDLVC/DCM	CLINICAL:	• Recent influenza-like illness	*SARS-CoV-2 myocarditis*	Molecular viral test
			ECG:	• Sinus tachycardia • Nonspecific ST-segment alterations • RBBB		
			ECHO:	• a "reverse tako-tsubo" pattern of GLS		
	Subepicardial/ transmural	DCM/HCM	CLINICAL:	• Pulmonary disease • Unexplained brady or tachyarrhythmia	*Sarcoidosis*	Thoracic FDG-PET imaging
			ECG:	• PR prolongation • Advanced AV blocks • RBBB/LBBB		
			ECHO:	• Basal septum thinning • Regional LV thickening • RV dysfunction in absence of PH • Regional wall motion abnormalities (without coronary distribution)		

[a]Indicated when genetic testing is negative and clinical suspicion remains high.

ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; DCM = dilated cardiomyopathy; FDG-PET = fluorodeoxyglucose positron emission tomography; HCM = hypertrophic cardiomyopathy; GLS = global longitudinal strain; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NDLVC = nondilated left ventricular cardiomyopathy; PH = pulmonary hypertension; RBBB = right bundle branch block; RCM = restrictive cardiomyopathy; RV = right ventricular; SAM = systolic anterior motion; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction.

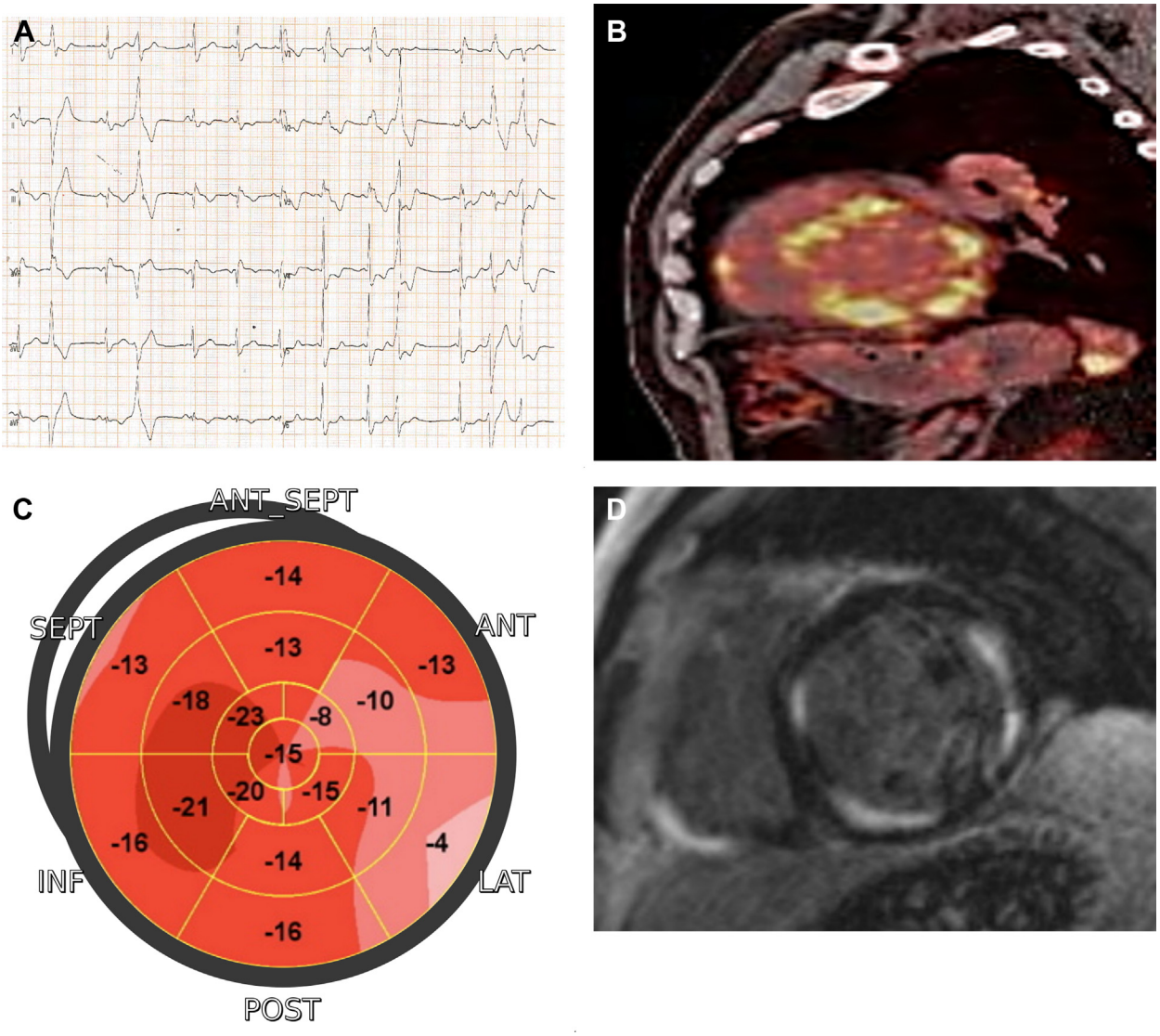
FIGURE 3 **Laminopathy**



(A) A 12-lead electrocardiogram showing a slight intraventricular conduction disturbance and an occasional premature ventricular beat. (B) Ventricular tachycardia with basal septum exit demonstrated by right bundle morphology in V1 with positive concordance. (C) Two-dimensional echocardiography speckle tracking analysis highlighting the septal impairment. (D) Short-axis CMR image showing mid-wall and linear enhancement of the basal septum. CMR = cardiac magnetic resonance.

hypertrophy.[24] Postmortem and imaging studies have demonstrated unrecognized myocardial involvement in up to 54% of patients with systemic sarcoidosis, with differences related to different imaging techniques and ethnicity.[25] Common ECG abnormalities include PR prolongation, advanced atrioventricular blocks, and bundle branch blocks. Although echocardiography is not sensitive enough to identify mild or minor localized abnormalities, the most common observation is basal septal thinning with hyperechogenicity. Additional anomalies include abnormal wall motions, right ventricular dysfunction in absence of pulmonary hypertension, aneurysm formation, and LV wall thickening.[26] Myocardial scar involvement usually presents as subepicardial to transmural fibrosis, mainly located in the interventricular septum and the inferior/inferolateral wall with a patchy distribution[27] (**Figures 4 and 5**). Given that detection of LGE is unable to distinguish between acute and chronic processes, T1 mapping

FIGURE 4 Cardiac Sarcoidosis



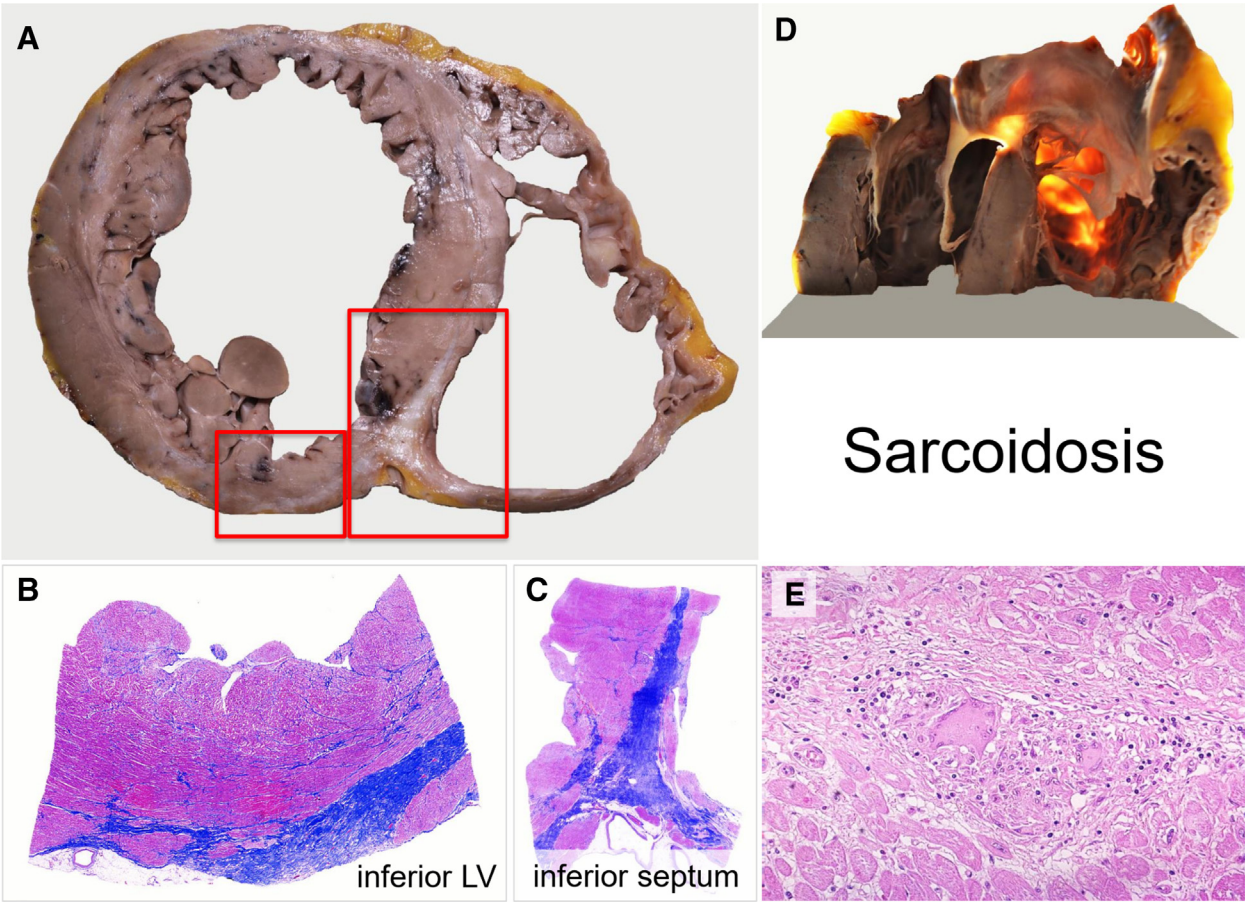
(A) A 12-lead electrocardiogram showing an intraventricular conduction disturbance and polymorphic ventricular ectopic beats. (B) The 18-FDG myocardial PET demonstrating patchy/diffuse hypermetabolic activity. (C) Two-dimensional echocardiography speckle tracking analysis highlighting the impairment of the lateral wall. (D) Short-axis CMR image showing multifocal patchy enhancement in the inferoseptum and anterolateral and inferior LV walls. Notice how the enhancement correlates to segments with high metabolic activity. CMR = cardiac magnetic resonance; FDG = fluorodeoxyglucose; PET = positron emission tomography.

proved to be a more effective method of monitoring disease activity and response to immunosuppressive drugs than LGE alone.[28]

In patients with systemic sclerosis, myocardial fibrosis is an early warning sign of cardiac involvement, may be seen in up to 80% of cases[29] and is mainly detected in the septal region at the basal and mid-segments with a mid-wall linear or nodular patchy pattern.[30] In this context, fibrosis is thought to result from ischemia-reperfusion damage, microvascular dysfunction, and myocardial inflammation.[31] Despite preserved LV systolic function or only minor signs (like prolongation of QT interval/dispersion and increased LV filling pressure), an extensive quota of myocardial fibrosis has a detrimental impact on prognosis.[32]

Peripartum cardiomyopathy is a rare and potentially life-threatening condition. It is defined as the

FIGURE 5 Histological Findings in Cardiac Sarcoidosis



(A to C) Native explanted heart of a 35-year-old male showing marked biventricular dilatation and thinning of anterior/inferior ventricular walls and septum. Both macroscopic transverse and histologic sections show extensive epicardial-mid-wall replacement fibrosis in LV inferior wall and inferoseptum (scanned slides, Azan Mallory Trichrome). In D, transillumination highlights the ectasia of the right ventricular outflow with almost no myocardium. E shows a typical compact noncaseating granuloma with giant cells (hematoxylin-eosin, 400x). LV = left ventricle

development of new-onset cardiomyopathy (LV ejection fraction <45% and without an identifiable cause of heart failure) during the peripartum episode, with an incidence ranging from 1/1,000 to 1/4,000 deliveries.[33] Several studies reported different prevalence rates for chronic LGE in these patients, with recent data asserting a prevalence of about 10%.[33] Its distribution with subepicardial or mid-wall pattern is usually linked to regional wall motion abnormalities and predominantly affects the anteroseptal and basal to midventricular regions. Detection of LGE at CMR could be often correlated with extensive disease involving both ventricles and a poor prognosis.[34] Therefore, monitoring LGE is essential for the long-term management of peripartum cardiomyopathy and the prevention of detrimental consequences.

APICAL REGION

Causes of nonischemic apical scarring include apical HCM and Chagas disease, both associated with a pattern that may be confined or preferentially involve the apical region (**Table 3**). In apical or mid-apical HCM, particularly when mid-ventricular obstruction is present, an extensive apical scar with transmural distribution may evolve into an apical aneurysm[35] (**Figure 6**). The latter has important prognostic implications as a substrate for sustained ventricular arrhythmias.[35]

Chagas disease is caused by the protozoan *Trypanosoma Cruzi*, affecting millions in endemic areas in South America and increasingly seen in the western world following migratory fluxes. The cardiac

TABLE 3 Left Ventricular Scars in the Apical Region With Specific Disease Characteristics

LV Scar	Distribution	Phenotype	Red Flags	Etiologies	Further Investigation
Apical region	Mid-wall/ transmural	HCM	CLINICAL: • Family history of HCM or SCD ECG: • "Pseudo STEMI" pattern ECHO: • Mitral valve abnormalities: elongated anterior leaflet/SAM • Apical or asymmetric LVH	*Sarcomeric HCM*	Genetic testing
	Subepicardial/ transmural	DCM	CLINICAL: • Origin from endemic countries • Previous flulike illness (chagoma) ECG: • Normal ECG (2/3 of patients) • Infra-nodal disease ECHO: • Regional wall-motion abnormalities • Apical aneurysms • Mural thrombi	*Chagas Disease*	Testing for parasite specific antibodies

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; SAM = systolic anterior motion; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction.

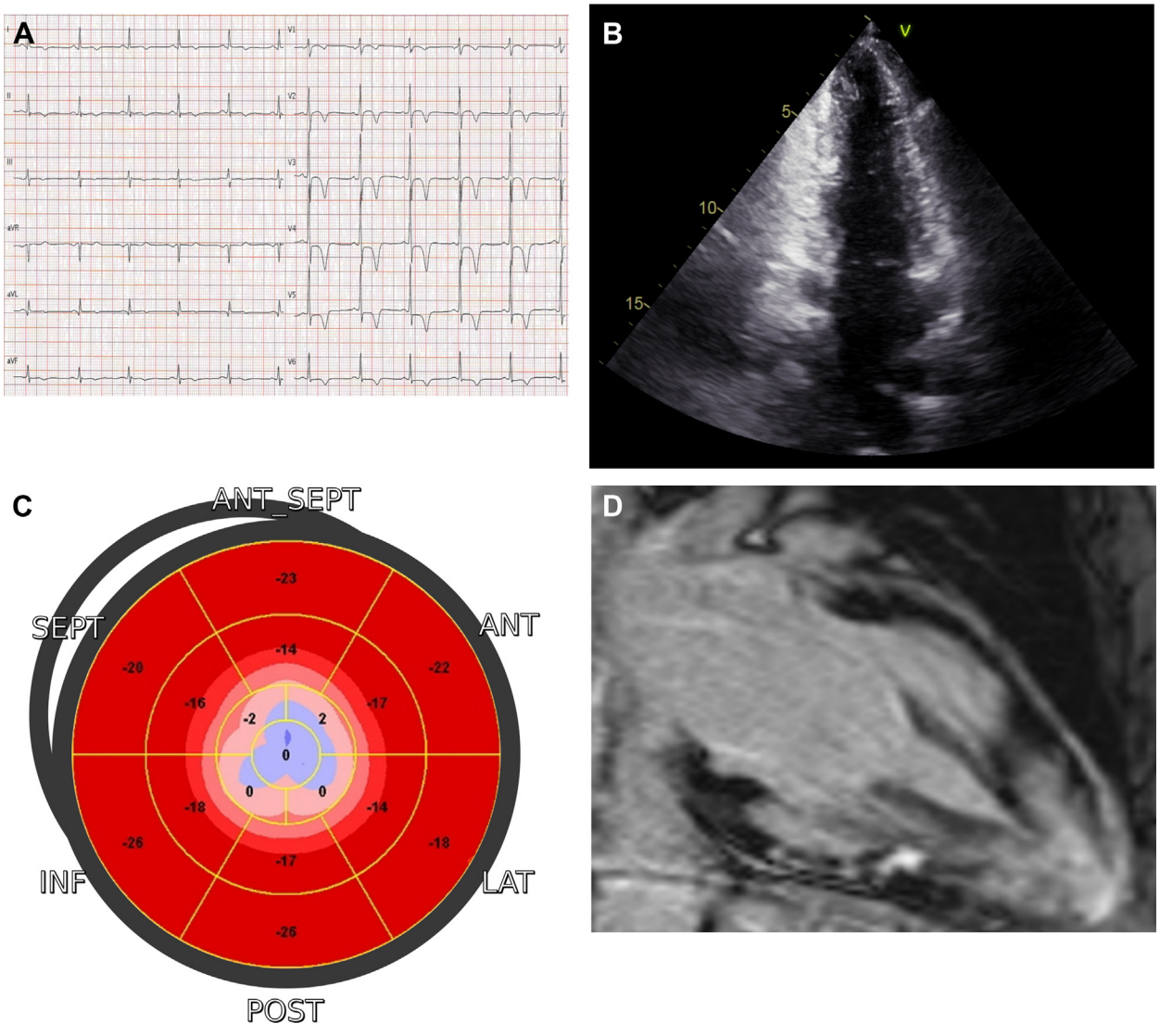
involvement is identified in 20% to 40% of patients who may present in the 2nd to 5th decade of life with DCM, conduction blocks and tachyarrhythmias, biventricular aneurysms, heart failure, thromboembolism, and SCD.[36] While acute Chagas disease may show cardiac involvement in the form of a nonspecific myocarditis, chronic disease is characterized by diffuse mononuclear cell infiltration and granulomata, suggesting an exaggerated delayed immune response akin to that of tuberculosis in the lung.[37] The upregulation of pro-inflammatory pathways modifies the expression of cardiac genes and proteins, causing hypertrophy, ventricular dilatation, and fibrosis that affect muscle and conduction system.[38] Since Chagas disease typically affects the apical and inferolateral levels, LGE is commonly detected in these regions, with patterns ranging from subendocardial and mid-wall to subepicardial or transmural. As a result, wall motion abnormalities ranging from mild hypokinetic segments to dyskinetic ones reflect the degree of myocardial fibrosis. But a small level of LGE has also been identified in walls with normal function, supporting the utility of CMR as a screening test in individuals who have had a negative echocardiogram and even normal ECG. Finally, while extensive LGE has been associated with fatal arrhythmias, a relationship between its pattern of distribution and cardiovascular outcomes has not been clearly assessed.[39]

LATERAL REGION

Myocarditis is one of the most common causes of scar in LV lateral wall, particularly in younger patients with acute coronary syndrome-like clinical presentation and normal coronary arteries (**Figure 7**, **Table 4**). Since no ECG or echocardiographic abnormalities are specific of myocarditis, CMR is required for a prompt diagnosis of myocardial inflammation.[40] While the acute phase is characterized by myocardial edema, subepicardial/transmural LGE and thickening of involved segments, once the inflammatory process has healed, are often associated with a residual subepicardial scar. Inferolateral segments are usually involved, although localization in other segments does not rule out such diagnosis. Acute myocarditis may also evolve into inflammatory cardiomyopathy, even after a mild or clinically silent acute phase. In these cases, subepicardial scar is accompanied by persisting low-grade myocardial inflammation only detectable by T2 mapping CMR sequences or cardiac 18F-fluorodeoxyglucose positron emission tomography-computed tomography. In fact, in selected cases, endomyocardial biopsy can be indicated to guide further immunosuppressive or antiviral treatment.[41]

SARS-CoV-2 infection can induce a specific type of myocarditis as a result of immune and hypercoagulability responses, with a chronic myocardial scar in up to 30% of patients who had been previously hospitalized [42] or 50% of patients who have been recovered.[43] LV scars, in most cases associated with preserved biventricular systolic function, showed a unique distribution with a more involvement of the septal segments than non-SARS-CoV-2 myocarditis, beyond the basal or mid-cavity inferolateral segments.[43,44] The involvement of various segments at the basal level allows the identification of a pattern

FIGURE 6 Apical Hypertrophic Cardiomyopathy

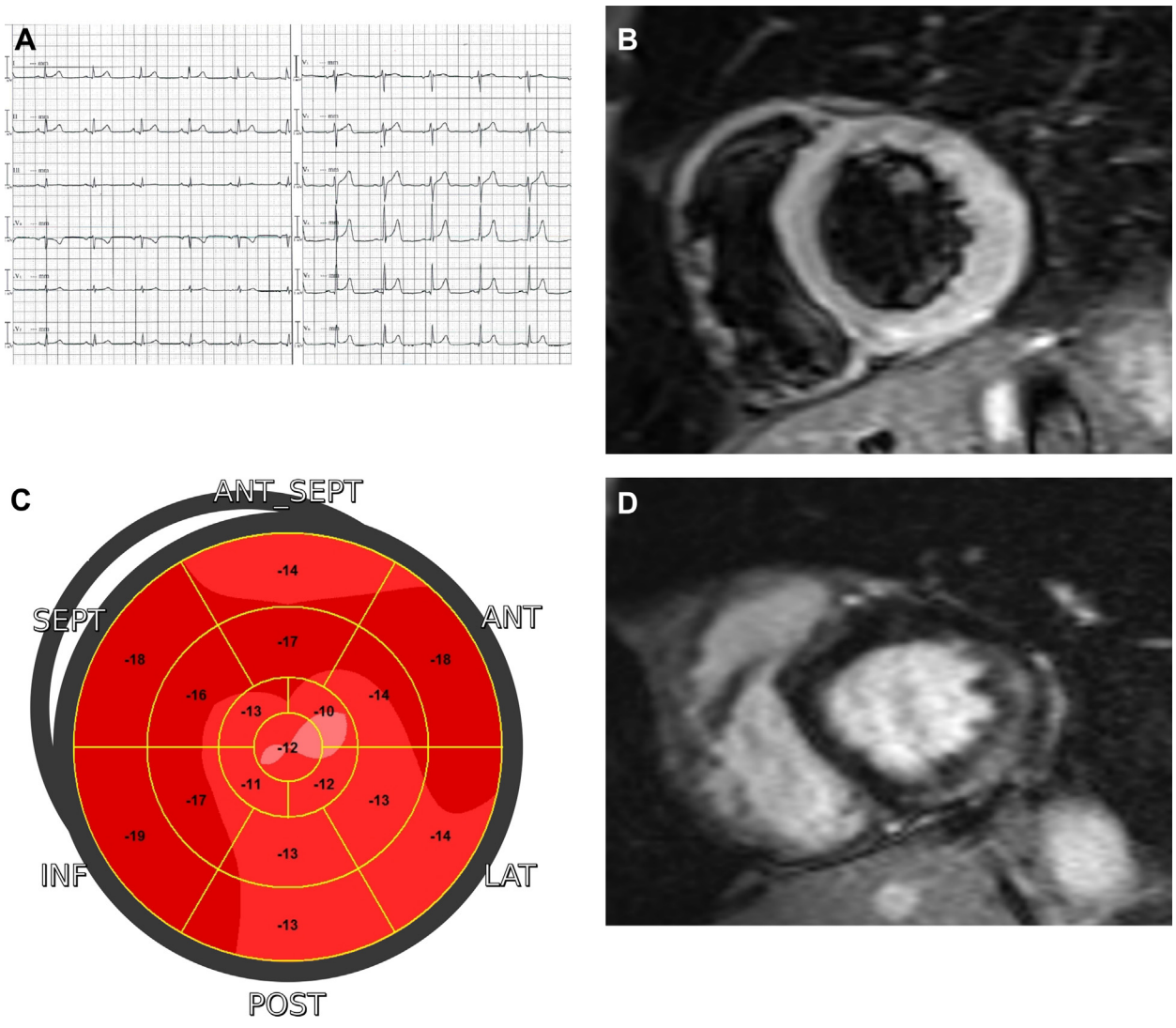


(A) A 12-lead electrocardiogram showing left ventricular hypertrophy and giant negative T-waves in precordial and inferolateral leads. (B) At 2D-echocardiography, the apical aneurysm becomes clearly evident in end-systolic apical 2-chamber view. (C) Speckle tracking analysis highlights the contractile impairment of the apex. (D) CMR image showing late gadolinium enhancement in the apical aneurysm. CMR = cardiac magnetic resonance.

named "reverse tako-tsubo" in speckle tracking.[45] Moreover, it is likely that the septal involvement is the cause of LV dyssynchrony or arrhythmia.

In cases of recurrent or familial myocarditis, CMR can detect the progressive expansion of subepicardial LGE. In these patients, particularly when the clinical picture is characterized also by ventricular arrhythmias, an arrhythmogenic cardiomyopathy progressing through inflammatory hot phases should be suspected.[46] Indeed, some forms of arrhythmogenic cardiomyopathy, while being caused by genetic variants affecting both desmosomal genes and others—psuch as desmoplakin, desmin, phospholamban and filamin C—may have a pathophysiology that heavily entails inflammatory pathways overlapping classic myocarditis.[47,48] Arrhythmogenic cardiomyopathy affecting the left ventricle is a rare disorder with a prevalence of 1:2,000-1:5,000;[48] although its true prevalence may be underestimated, it is increasing due to the widespread use of CMR. Electrical

FIGURE 7 Acute Myocarditis



(A) A 12-lead electrocardiogram showing inferolateral ST-segment elevation, mimicking myocardial infarction. (B) Short-axis T2-weighted CMR image showing myocardial edema in the lateral wall. (C) Two-dimensional echocardiography speckle tracking analysis highlighting reduced contractility in the same segments. (D) Short-axis CMR image showing matching fibrosis with an epi- and mid-wall distribution. CMR = cardiac magnetic resonance.

instability with ventricular arrhythmias is the most typical sign of the disease, which has been recognized as one of the leading causes of SCD in young athletes. At the onset and during its "hot phases," arrhythmogenic cardiomyopathy may mimic acute myocarditis, presenting with episodes of chest pain, troponin release, and acute ECG modifications.[49]

As disease progresses with a wavefront of myocardial loss and fibrofatty replacement from the epicardium to endocardium, LGE is localized at the epicardial level,[50] localizing preferentially to the lateral wall (**Figure 8 and 9**). Although the endocardium is often spared, justifying the absence of wall motion abnormalities at echocardiography, transmural extension may occur in advanced cases. ECG abnormalities such as low-amplitude QRS complexes in the limb leads, fragmented QRS, and T-wave inversion or flattening in the lateral leads are suggestive findings. Additional features include ventricular arrhythmias with right bundle branch block

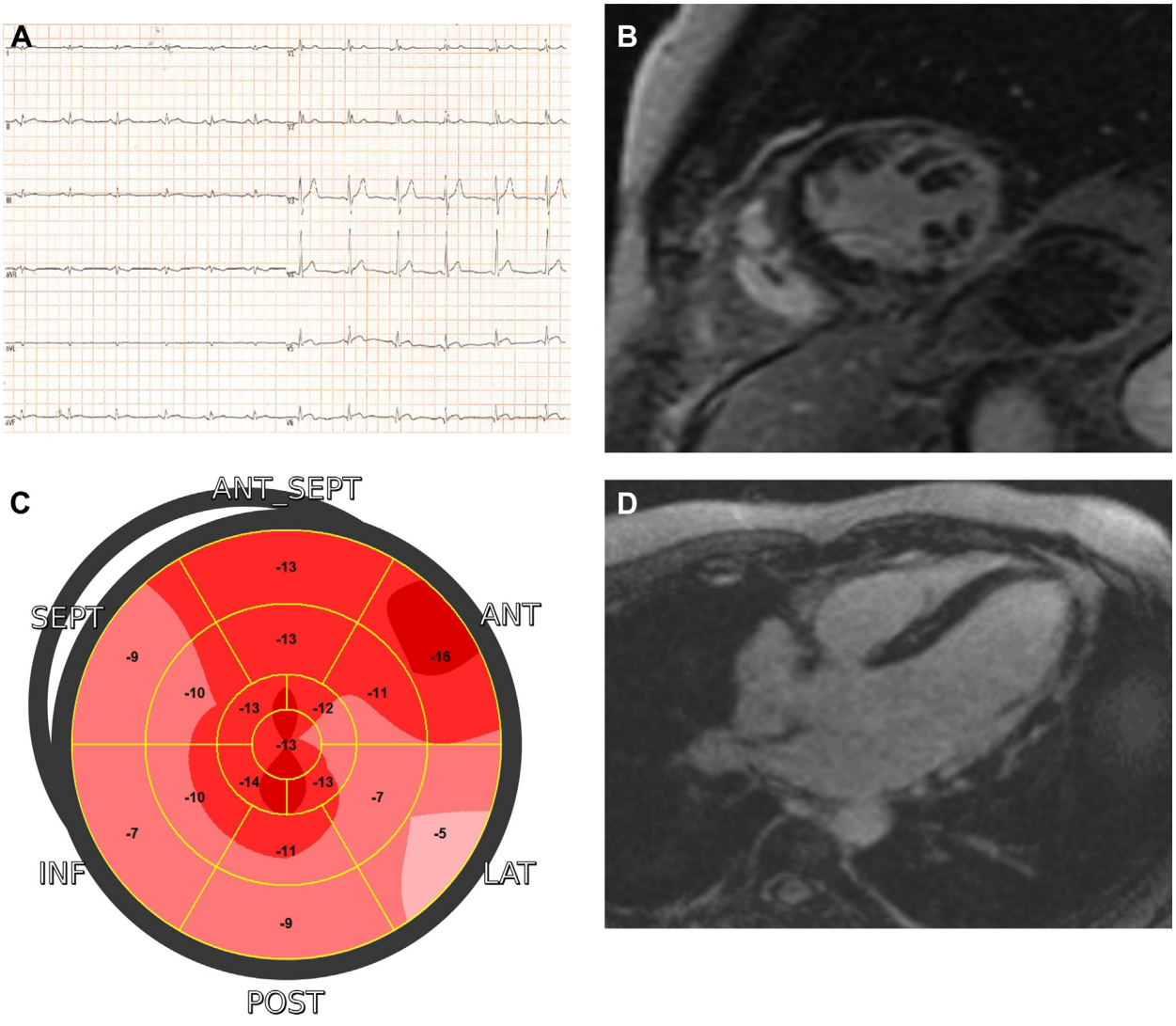
TABLE 4 Left Ventricular Scars in the Lateral Region With Specific Disease Characteristics

LV Scar	Distribution	Phenotype	Red Flags		Etiologies	Further Investigation
Lateral region	Subepicardial/ mid-wall	NDLVC/DCM/ ARVC	CLINICAL:	• Family history of SCD	*Arrhythmogenic cardiomyopathy*	Genetic testing
			ECG:	• Low limb voltage • Fragmented QRS		
				• Ventricular arrhythmias with a RBBB morphology of the ectopic QRS		
			ECHO:	• Systolic LV dysfunction related to the global extent of LGE		
		NDLVC/DCM	CLINICAL:	• Recent influenza-like illness	*Myocarditis (including SARS-CoV-2, see above)*	Laboratory tests[b] Endomyocardial biopsy[c]
			ECG:	• Sinus tachycardia • Nonspecific ST alterations		
			ECHO:	• Regional thickening of LV wall (without coronary distribution)		
		NDLVC/DCM/ HCM	CLINICAL:	• Gait disturbance • Myotonia/muscle weakness • Visual impairment	*Neuromuscular disorders*	Genetic testing Muscle biopsy[a]
			ECG:	• AV nodal and infra-nodal disease		
			ECHO:	• Regional wall motion abnormalities		
				• Regional wall thinning or thickening		
		HCM	CLINICAL:	• X-linked transmission • Juvenile stroke • Angiokeratomas	*Anderson-Fabry disease*	Genetic testing for glycosphingolipid metabolism
				• Visual impairment • Neuropathic pain • Renal failure		
			ECG:	• Progression of ECG: alterations together with persisting LVH signs		
				• Short PR interval • RBBB • Chronotropic incompetence		
				• Inferolateral TWI		
			ECHO:	• Symmetric LVH • RVH • Thickening of mitral valve		
	Subepicardial/ transmural	DCM	CLINICAL:	• Origin from endemic countries • Previous flulike illness (chagoma)	*Chagas Disease*	Testing for parasite specific antibodies
			ECG:	• Normal ECG (2/3 of patients) • Infra-nodal disease		
			ECHO:	• Regional wall-motion abnormalities • Apical aneurysms • Mural thrombi		
		DCM/HCM	CLINICAL:	• Pulmonary disease • Unexplained brady or tachyarrhythmia	*Sarcoidosis*	Thoracic FDG-PET imaging
			ECG:	• PR prolongation • Advanced AV blocks • RBBB/LBBB		
			ECHO:	• Basal septum thinning • Regional LV thickening		
				• RV dysfunction in absence of PH		
				• Regional wall motion abnormalities (without coronary distribution)		

[a]Indicated when genetic testing is negative and clinical suspicion remains high. [b]Including inflammatory and cardiac markers and rheumatologic screening. [c]In case of suspected fulminant myocarditis or acute myocarditis with acute heart failure, left ventricular dysfunction, and/or rhythm disorders; setting of immune checkpoint inhibitor therapy; acute myocarditis associated with peripheral eosinophilia.

ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; DCM = dilated cardiomyopathy; ECG = electrocardiogram; FDG-PET = fluorodeoxyglucose positron emission tomography; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NDLVC = nondilated left ventricular cardiomyopathy; PH = pulmonary hypertension; RBBB = right bundle branch block; RV = right ventricular; RVH = right ventricular hypertrophy; SAM = systolic anterior motion; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; TWI = T-wave inversion.

FIGURE 8 Desmoplakin-Related Arrhythmogenic Cardiomyopathy

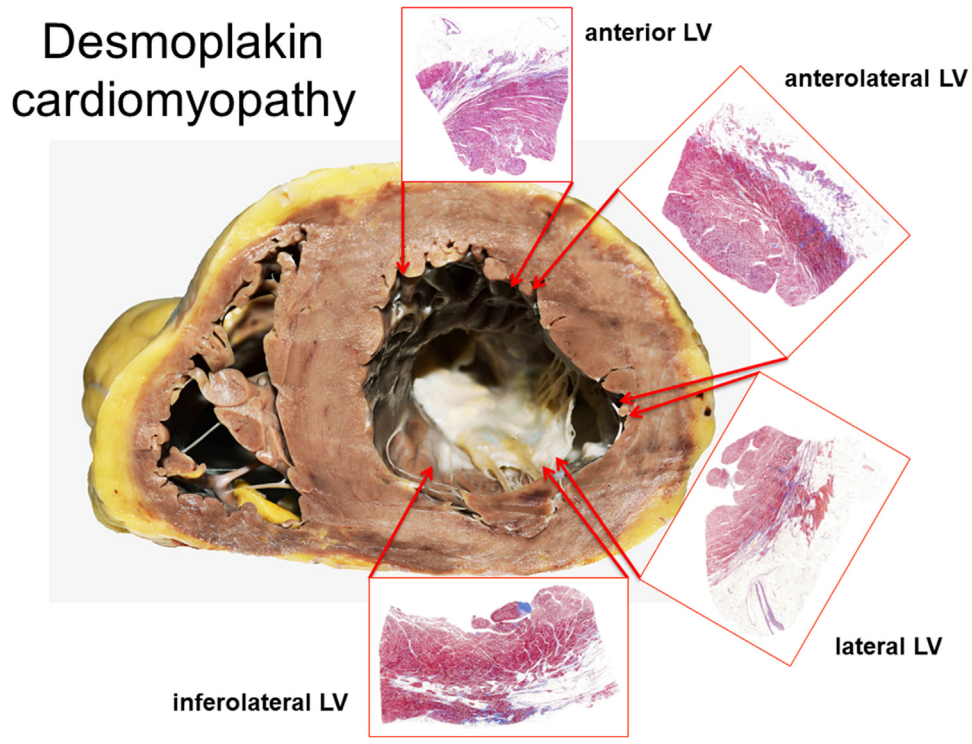


(A) A 12-lead electrocardiogram showing low QRS voltages in limb leads and diphasic T-waves in the lateral leads. (B) Short-axis T2-weighted CMR image showing myocardial edema in the lateral wall. Short-axis (B) and 4-chamber (D) CMR images showing extensive late gadolinium enhancement as a stria proceeding from epicardium toward endocardium in the lateral wall with partial apical involvement. (C) Two-dimensional echocardiography speckle tracking analysis highlighting concordant regional impairment. CMR = cardiac magnetic resonance.

morphology and superior axis not suppressed or elicited by exercise, normal or mildly depressed LV systolic function, and no or mild LV dilatation.[48]

In patients with Anderson-Fabry disease, HCM associated with myocardial fibrosis involving the lateral region represents a classic feature.[51,52] This lysosomal storage disease is marked by phenotypic variability that is both intra- and inter-family due to its multisystemic involvement, with the most affected organs being the neurological, cardiovascular, cochleovestibular, and cutaneous systems. Early signs of cardiac involvement in Anderson-Fabry disease include short PR intervals, alterations in tissue Doppler and speckle tracking imaging, and decreased native T1. Over time, these signs can progress to LV hypertrophy and fibrosis with corresponding changes

FIGURE 9 Histological Findings in Desmoplakin-Related Arrhythmogenic Cardiomyopathy



Extensive/diffuse fibro-fatty replacement of the LV myocardium spreading from the epicardial toward the mid-wall layer in section from a 49-year-old man (scanned slides, Azan Mallory Trichrome). LV = left ventricle.

in the ECG (chronotropic incompetence, bundle branch block), as well as changes in echocardiography (symmetric LV hypertrophy, right/biventricular hypertrophy, and valve thickening).[53]

Although LGE and inflammation appear mainly in the basal inferolateral wall, LV scars can occasionally be seen at the septal and/or apical regions; they usually have a mid-wall localization, with transmural lesions being observed in advanced stages.[53] Although the disease has X-linked inheritance, female patients usually present cardiac involvement with lateral wall scar in some cases preceding the development of LV hypertrophy.[53]

Neuromuscular disorders should be considered as a possible alternative diagnosis, despite their rarity.[54] Both in Duchenne and Becker muscular dystrophy, cardiac involvement is common and occurs even before the onset of other symptoms.[55] Similarly, patients with limb girdle muscular dystrophy or myotonic dystrophies may experience severe cardiac symptoms and an increased risk of SCD.[56] Cardiac dysfunction originates from an abnormal and unstable nucleotide repetition in the dystrophia myotonica protein kinase and cellular nucleic acid binding protein genes, which leads to a DCM phenotype with wall thinning and/or altered wall motions and LGE in the lateral wall, sometimes mistaken for the *sequelae* of myocarditis in patients with milder neurological manifestations.[57] Furthermore, atrioventricular nodal or infra-nodal disease has been often documented. Myocardial fibrosis may indeed appear years before clinical signs of cardiac involvement or muscular weakness, both in carriers and patients.

Conversely, Friedreich's ataxia presents as a HCM phenotype with LGE involving the septum and inferolateral wall,[56] progressing toward systolic impairment after the 4th decade.

RING-LIKE PATTERN. A unique scenario with LGE involving at least 3 consecutive segments in the short-axis view, resulting in a ring-like pattern usually with an epicardial and mid-wall distribution, has been recently reported.[58,59] This pattern has been

TABLE 5 Left Ventricular Scars in the Inferior Region With Specific Disease Characteristics

LV Scar	Distribution	Phenotype	Red Flags		Etiologies	Further Investigation
Inferior region	Mid-wall/ transmural	HCM	CLINICAL:	• Family history of HCM or SCD	*Sarcomeric HCM*	Genetic testing
			ECG:	• "Pseudo STEMI" pattern		
			ECHO:	• Mitral valve abnormalities: elongated anterior leaflet/SAM		
				• Apical or asymmetric LVH		
	Mid-wall	NDLVC/ DCM	CLINICAL:	• Young female • Bi-leaflet involvement	*Arrhythmic mitral valve prolapse*	Rhythm monitoring
			ECG:	• Inverted/biphasic T waves in the inferior leads		
				• PVC morphologies compatible with papillary muscle or mitral annular origins		
			ECHO:	• Presence of Pickelhaube sign • MAD • Systolic curling		
	Subepicardial/ transmural	DCM/HCM	CLINICAL:	• Pulmonary disease • Unexplained brady or tachyarrhythmia	*Sarcoidosis*	Thoracic FDG-PET imaging
			ECG:	• PR prolongation • Advanced AV blocks • RBBB/LBBB		
			ECHO:	• Basal septum thinning • Regional LV thickening		
				• RV dysfunction in absence of PH		
				• Regional wall motion abnormalities (without coronary distribution)		

AV = atrioventricular; DCM = dilated cardiomyopathy; FDG-PET = fluorodeoxyglucose positron emission tomography; HCM = hypertrophic cardiomyopathy; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MAD = mitral annular disjunction; NDLVC = nondilated left ventricular cardiomyopathy; PH = pulmonary hypertension; PVC = premature ventricular complex; RBBB = right bundle branch block; RV = right ventricular; SAM = systolic anterior motion; SCD = sudden cardiac death; STEMI = ST fluorodeoxyglucose positron emission tomography elevation myocardial infarction.

clinically associated with recurrent or familial myocarditis and a high burden of ventricular arrhythmias,[47] but not with an impairment of LV ejection fraction. The latter suggests that this pattern, despite the extension and the distribution of the scar, may represent a major arrhythmogenic substrate without impairing LV function.[60]

Due to its association with arrhythmogenic cardiomyopathy, which affects the left ventricle,[61,62] and the arrhythmogenic subtypes of DCM,[63] the true incidence of this pattern is yet unclear. As a result, these individuals may exhibit a wide spectrum of phenotypic expression, from dilated to nondilated LV cardiomyopathy, and because of the increased risk of malignant arrhythmic events, they should always get appropriate therapeutic care and tailored decisions, particularly regarding primary prevention of SCD. Finally, further research is required to ascertain if a "cascade" CMR screening of the proband's family members is beneficial, even in absence of an arrhythmic profile.

INFERIOR REGION

Nonischemic myocardial fibrosis in this region may be a result of sarcoidosis[27] or arrhythmogenic mitral valve prolapse (Table 5). The latter can be associated with mitral annular disjunction, the Pickelhaube sign—the high-velocity systolic signal with tissue Doppler imaging—and systolic curling.[63] Although the genetic etiology of mitral valve prolapse remains largely unknown, some genes have been identified in familial aggregation, including hyperpolarization activated cyclic nucleotide-gated potassium channel 4. Inverted/biphasic T waves in the inferior leads are a common evidence, and premature ventricular complexes originate from the papillary muscle or mitral annular regions.[64]

Patients with arrhythmogenic mitral valve prolapse may typically present localized fibrosis at the inferior and inferolateral regions,[63] and in some cases involving the base of the posteromedial papillary muscle. Mitral valve prolapse has an estimated annual risk of SCD ranging from 0.2% to 1.9%,[64] higher in young women and in presence of bi-leaflet involvement. Although risk stratification is challenging, the presence of LGE together with complex ventricular ectopy, concomitant mitral annular disjunction, severe mitral regurgitation, and ECG repolarization abnormalities identifies the high-risk patients requiring further evaluation and closer monitoring.

DIFFUSE PATTERN. A distinct case that does not recognize any specific regionality is cardiac amyloidosis. Due to the deposition of different misfolded proteins in an extracellular space of the myocardium, cardiac amyloidosis usually results in heart failure, conduction system disease, and SCD. LGE proved to be a useful way to identify cardiac amyloidosis qualitatively and quantitatively and to provide prognostic information.[65] In addition to echocardiographic abnormalities (LV hypertrophy, diastolic dysfunction, and pericardial effusion), a diffuse circumferential subendocardial LGE is present in at least one-third of patients [65] and represents a highly specific marker for the diagnosis of cardiac amyloidosis, with a specificity of nearly 95%. While subendocardial LGE is typical of patients with light-chain amyloidosis, the pattern of LGE in transthyretin-related cardiac amyloidosis is more extensive, with right ventricular involvement and a higher prevalence of transmural distribution.[66] Moreover, given the potential challenges of LGE imaging due to the diffuse amyloid deposition throughout the heart, which may result in incorrect nulling, high values of native T1 and extracellular volume provide an additional accurate tool for diagnosis and quantitative measurement of disease burden.[67]

RIGHT VENTRICLE

The present review focuses primarily on LV injury, as qualitative and quantitative assessment by CMR of myocardial fibrosis in the right ventricle is challenging due to the thin-walled and trabeculated myocardium. Nevertheless, right ventricular involvement may be relevant in several cardiomyopathies. For instance, it is important to distinguish LGE confined to the right ventricular insertion sites, associated with a low risk of adverse events in patients with HCM [68] or DCM,[69] from LGE extending to the right free wall, which is associated instead with a pronounced arrhythmic burden in cardiac sarcoidosis [70] or in myocarditis.[71]

CONCLUSIONS

Several causes other than ischemic heart disease may cause segmental myocardial fibrosis of the left ventricle with a disease-specific scar distribution that can guide differential diagnosis. Despite clinical and morphological variability of myocardial disease, the proposed atlas may serve as a reference to interpret CMR scar patterns in the context of clinical presentation, family history, and electrocardiographic and physical findings.

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