Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Spinelli A, Marino G, Macchiusi A, et al. **Dilated cardiomyopathy - guidelines for personalization of care.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3173

Dilated cardiomyopathy - guidelines for personalization of care

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Contributions: all the authors made a substantive intellectual contribution, have read and approved the final version of the manuscript.

Conflict of interest: the authors declare that they have no competing interests.

Ethics approval and consent to participate: institutional review board approval was not required for this study as only de-identified compliant data were used in the analysis. The Data Protection Act and the Helsinki Declaration's principles were followed in the study.

Patient consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all mentioned data in the paper are available in the medical records.

Funding: none.

Abstract

The term dilated cardiomyopathy (DCM) refers to a family of diseases characterized by complex interactions between environment and genetic predisposition. Diagnostic tools such as cardiac magnetic resonance imaging should be systematically implemented in clinical practice to define the etiological cause and undertake a specific treatment. We present the case of a young man with DCM and severe left ventricular dysfunction. The patient has a family history of sudden cardiac death (SCD). He is affected by a psychiatric pathology and has a history of alcohol and drug addiction. Many diagnostic hypotheses have been considered for etiological research. The use of a wearable defibrillator to temporarily protect the patient from SCD risk pending the completion of the diagnostic path to establish DCM etiology and the implementation of optimal medical therapy was considered. However, because of the underlying psychiatric pathology and the possibility of poor adherence to the maintenance of the wearable device, the patients would not have been sufficiently protected. Due to the young age of the patient, it was decided to make a personalized therapeutic choice, and he underwent implantation of a subcutaneous defibrillator.

Key words: heart failure, subcutaneous defibrillator.

Introduction

Cardiomyopathy is defined as a "myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease (CAD), hypertension, valvular disease, and congenital heart disease (CHD) sufficient to cause the observed myocardial abnormality" [1]. Patients with reduced ejection fraction have a high risk of sudden cardiac death (SCD), so it is imperative to protect them throughout their diagnostic examination and treatment course aimed at left ventricular function recovery. The early implantation of an implantable defibrillator (ICD) to prevent sudden cardiac death is often debated in the clinical management of these patients [1].

Case Report

We report the case of a 28-year-old with high school education patient with a family history of sudden death (maternal uncle deceased at age 39, and a sister with Rett syndrome died in her sleep at age 18). The patient practiced sports at a competitive level until the age of 12. He had a clinical history of alcohol abuse since age 14, regular intake of cannabinoids and occasional intake of cocaine, and a previous diagnosis of attention-deficit/hyperactivity disorder (ADHD). The patient was treated in a Psychiatric Diagnostic and Treatment Service with the following therapy: gabapentin, quetiapine, clonazepam, atomoxetine hydrochloride, oxcarbazepine, and trazodone hydrochloride. In September 2022, during his stay at an addiction cessation facility, he had the onset of dry cough and worsening dyspnea, and two subsequent febrile episodes in November 2022. In February 2023 he accessed the emergency room for cardio-respiratory failure after an accidental fall.

On admission, the patients had a severe left ventricular global systolic dysfunction with a left ventricular ejection fraction (EF) of 10%, in the absence of regional wall-motion abnormalities. The left ventricular telediastolic volume (LVEDV) was 251 ml/m^2, left ventricular telesystolic volume (LVESV) 197 ml/m^2. He had no significant valvulopathy and the right ventricle was enlarged but normokinetic. Blood pressure was 100/60 mmHg and oxygen saturation was 91%. The ECG showed a sinus rhythm at 110 bpm with mild nonspecific intraventricular conduction disturbance (QRS 112 msec) and nonspecific ventricular repolarization abnormalities. Procalcitonin was negative (0,24 ng/ml, n.v. 0.0 - 0.5), hemoglobin levels, white blood cells and platelet count in a normal range (Hb 12.0 g/dl, n.v. 12.0 - 16.0; WBC 9.100/uL, n.v. 4.0 – 11.0; PLT 139000/uL n.v. 130000 – 400000), peak C-reactive protein (CRP) 7.93 mg/dL, peak ultrasensitive troponin 52.50 ng/L, peak NT pro-BNP of 1297 pg/ml. Blood tests were done to study alcohol-related damage to the heart. Tests for liver function were normal. Tests for heavy alcohol use (anemia, thrombocytopenia, folate, vitamin B12 deficiency, electrolyte alterations, desialyted transferrin) were normal too. The chest radiography

confirmed the clinical suspicion of bilateral pneumonia complicated by bilateral pleural effusion. Pneumonia could be a further cause of decompensation. Antibiotic therapy was started with subsequent normalization of CRP. The research of cardiopneumotropic virus antibodies showed IgG positivity for cytomegalovirus (71 U/ml) and parvovirus B19 (4.90 U/ml), whereas specific IgM antibodies were negative. A coronarography excluded significant coronary stenosis. Cardiac magnetic resonance imaging (MRI) performed 11 days after admission confirmed a severe systolic disfunction (EF 14%, LVEDV: 320 ml/m2, LVESV: 275 ml/m2) with a reduced thickness of the midventricular antero-septal wall. Furthermore, left ventricular myocardial wall had areas of altered signal, hyperintense on T2W sequences, suggestive of myocardial oedema, associated with signal hyperintensity of the left periventricular adipose tissue, which showed marked late enhancement immediately after intravenous contrast administration (Figure 1). Symptomatic sustained monomorphic ventricular tachycardia lasting 40 seconds was observed during hospitalization in the intensive care unit (ICU). It was self-limited and no further episodes of this type were recorded. During the remaining days of hospitalization, the finding of thrombocytosis, probably because of infectious or inflammatory processes, required therapy with acetylsalicylic acid. We have observed a progressive clinical improvement, although in the absence of recovery of EF indicative of a persistent significative risk of life-threatening arrhythmias. Therefore, pending the completion of diagnostic examinations (genetic testing results) and pharmacological therapy titration, before discharge the use of wearable defibrillators (WCD) was considered. However, the psychiatric consultant pointed out the risk of poor adherence to the proper use of the device given the risk of impulsive behaviors related to the underlying psychiatric disorder, ADHD, and the history of alcohol and drug abuse. After a comprehensive interview with the patient and his family, a multidisciplinary team including clinical cardiologist, electrophysiologist, and psychiatrist, agreed with the indication of subcutaneous defibrillator implantation (S-ICD). The implantation procedure was performed in the absence of complications. The patient was discharged after 18 days of hospital stay, in satisfactory clinical-hemodynamic compensation, with the following pharmacological prescriptions: dapaglifozin 10 mg /day, sacubitril/valsartan 24/26 mg x 2/day, furosemide 25 mg /day, canrenone 100 mg /day, bisoprolol 5 mg x 2/day, acetylsalicylic acid 100 mg/day, and the psychiatric therapy previously used was confirmed. At outpatient follow-up after 1 month from discharge, the EF was unchanged (15%). Acetylsalicylic acid was suspended for normalization of platelet count. Pharmacological therapy was not up-titrated due to the finding of low arterial pressure values. At three months, EF 28% was shown and cardiac MRI, performed within the expected time frame after ICD implantation (after at least 6-8 weeks from presentation), was affected by the presence of gross artefacts due to the presence of ferromagnetic material, so

considered inconclusive (Figure 2). Genetic evaluation results did not identify variants with probable or possible pathogenic significance for major DCM-associated genes. Therefore, a pathway for the possible need for cardiac transplantation/LVAD implantation was also considered. Indeed, the patient reported complete abstention from drugs since discharge, confirmed by negativity on toxicological testing. However, important concerns remained regarding psychiatric issues related to ADHD and the relatively short period of drug abstention. It was decided to continue monthly follow-ups to intercept any changes in both the cardiological and psychiatric picture. At the follow-up performed in October 2023, EF improved and left ventricular volumes were reduced (EF 40%, LVEDV 98 ml/m^2, and LVESV 59 ml/m^2).

Discussion

We report the case of a patient with non-ischemic DCM and severe left ventricular contractile dysfunction. Previous studies have confirmed that there are many known and unknown causes of DCM, the known causes are mainly infection, genetic, and immune factors. Studies have confirmed that viral myocarditis (VMC) is one of the possible causes for DCM. The molecular mechanisms underlying the progression from VMC to DCM remain unclear and require further investigation. It is likely that acute inflammation may progress to subacute and chronic stages and finally to tissue remodeling, fibrosis, and loss of myocardium architecture and contractile function. The latter chronic damages lead to development of DCM [1,2]. According to literature data, the estimated prevalence of DCM is about 1:2500 individuals in the general population, slightly higher in men, with a female-to-male ratio between 1:1.3 and 1:1.5 [3,4]. In our patient the presumptive etiological hypothesis is that DCM may be secondary to viral myocarditis, which probably occurred in November 2022 during febrile episodes. Overall, between 0 and 52% of patients with acute myocarditis develop DCM [4,5]. Retrospective studies report that 9–16% of unexplained non ischemic DCM cases have histological evidence of myocarditis. Other studies estimate a wider range of 10–50% of DCM cases having evidence of myocarditis as could be determined by endomyocardial biopsy [5,6]. Cardiac MRI findings, showing features typical of myocardial fibrosis, supported the hypothesis and provided valuable diagnostic and arrhythmic risk stratification information, in agreement with recent European Society of Cardiology (ESC) guidelines (recommendation class I - level of evidence B). Indeed, the presence of late gadolinium enhancement, observed in 25-30% of patients with DCM, is a strong predictor of ventricular arrhythmias and all-cause mortality [1,7]. We performed genetic evaluation, which is recommended as Class I by the 2022 ESC guidelines on heart failure management and was confirmed as Class I in the most recent 2023 ESC

guidelines on cardiomyopathies [1,7,8]. A panel of genes associated with DCM was subjected to analysis:
MYBPC3,MYH7,TNNT2,TNNI3,TPM1,ACTC1,MYL2,MYL3,CSRP3,TNNC1,PNL,LAMP2,GLA,TTR,PRKAG2,TNNT2,TNNI3,SCN5A,LMNA. Genetic evaluation results did not identify variants with probable or possible pathogenic significance for major DCM-associated genes. The genetic test for Rett syndrome was not considered useful by the geneticist for several reasons: it was negative in both screened parents; Rett syndrome is almost exclusive to females and in males it is lethal in the first few years of life or during fetal life; The definitive diagnosis of viral myocarditis requires an endomyocardial biopsy, but in clinical practice biopsy is rarely used. In our case, the anamnestic reference (recent flu), the finding of IgG for CMV and Parvovirus B19 made the hypothesis of viral origin very probable. Cardiac MRI also showed myocardial oedema and fibrosis. According to the most recent guidelines, endomyocardial biopsy is recommended when other methods are insufficient [9]. Other etiological hypotheses, that we have considered, included DCM from alcohol abuse, accounting for up to 32% of cases of DCM, or from toxic substance abuse (cocaine and/or antipsychotic drugs) [3,10,11]. Alcohol-induced cardiomyopathy (AC) is a type of heart disease caused by long-term alcohol use. The amount of alcohol needed to cause AC is usually thought to be more than 80 grams a day over five years, but this is still debated. AC develops in different ways. Alcohol and a metabolite of alcohol called acetaldehyde can cause it. Genes also play a part. Not all heavy drinkers have DCM. AC doesn't have any specific cardiac signs or symptoms. However, the natural history of AC is different from that of DCM. Recovery in abstainers is associated with an excellent prognosis. For this reason, we recommended complete abstinence from alcohol to our patient, and we have seen an improvement in the ejection fraction over the follow-up period [12]. However, the identification of an acquired cause does not rule out an underlying genetic variant, while the latter, if present, may be triggered earlier when an acquired cause intervenes [2,8]. Drugs that are used for ADHD treatment may have potential adverse cardiovascular effects. These agents exert stimulant effects on the central nervous system, increase norepinephrine and dopamine levels in the prefrontal cortex and stimulate adrenergic receptors in the heart and blood. Sympathetic nervous system stimulation can lead to an increased risk of cardiovascular mortality [13]. Some of the drugs taken by the patient could be a further cause of heart failure, such as gabapentin. Other drugs may have exposed the patient to an increased risk of life-threatening arrhythmias or other cardiovascular events (myocardial infarction, Takotsubo syndrome, SCD) as in the case of quetiapine, trazodone and atomoxetine [3,13]. It has been reported that adults with DCM have an annual incidence of SCD between 2 and 4 percent [1,3]. According to recent ESC guidelines on cardiomyopathies, ICD implantation in primary prevention is indicated in patients symptomatic for heart failure

and FE 35%, despite three months of optimized medical therapy (OMT) and in patients with FE 35% and additional risk factors for example: high arrhythmic risk genotype, arrhythmias and late gadolinium enhancement on cardiac MRI (documented in our patient, Figure 1) (Table 1). The choice of implantable defibrillator type depends on clinical setting [7,14]. In the case of our patient, who underwent a diagnostic definition and was at risk of SCD, a WCD (class II-B) was suggested [14,15]. WCD allows to manage the transient risk of arrhythmic death pending SCD risk reduction or permanent protection or definitive indication to ICD implantation [16]. Although WCD use does not have a class I recommend in the most recent guidelines, its use in clinical practice is growing [15-17]. Indeed, even if the guidelines provide a valuable reference for treatment choices, it is necessary to consider that the decision at the individual level may be influenced by several factors such as age, psychosocial conditions, and the patient's will, factors that are not always taken sufficiently into account by the guidelines. We planned to improve medication for three months and then re-examine the patient protected by the wearable defibrillator (WCD). In our case, the psychiatric condition made our management decision challenging. According to the psychiatrist who followed the patient during his hospital stay, adherence to treatment was considered a serious problem, both about taking medication at home and, in particular, about WCD. For this reason, the choice, shared with other specialists, fell on the definitive ICD [1,14,16]. The indication to S-ICD implantation [1,17] was established based on the patient age, and possible long-term complications secondary to the implantation of intravascular leads in case of ICD (Table 1).The S-ICD has been proven to be a valuable alternative to transvenous defibrillators in all patients who do not require bradycardia pacing, resynchronization, or anti-tachycardia pacing (class II-B) [17,18]. As a matter of fact, an S-ICD is considered the best treatment option before the age of 50 [18,19]. We chose the S-ICD also because our patient could be at risk of endocarditis (history of drug addiction), and we did not know if he could undergo a transplantation or ventricular assist device (VAD) implantation that requires the protection of the vascular access site to limit the risk of systemic infection. Furthermore, the potential for explantation and the possibility of complications associated with the procedure must be considered. Therefore, in our patient, the use of a WCD would have allowed us to have cardiac MRI not hindered by artefacts which limited examination interpretation (Figure 2) [15,20].

Conclusions

This case report emphasizes that in clinical practice, though the guidelines provide a valuable reference for treatment choices, it is necessary to consider that the decision at the individual level may be influenced by several factors including age, psychosocial conditions, and the patient's will, that are not always taken into sufficient account by guidelines.

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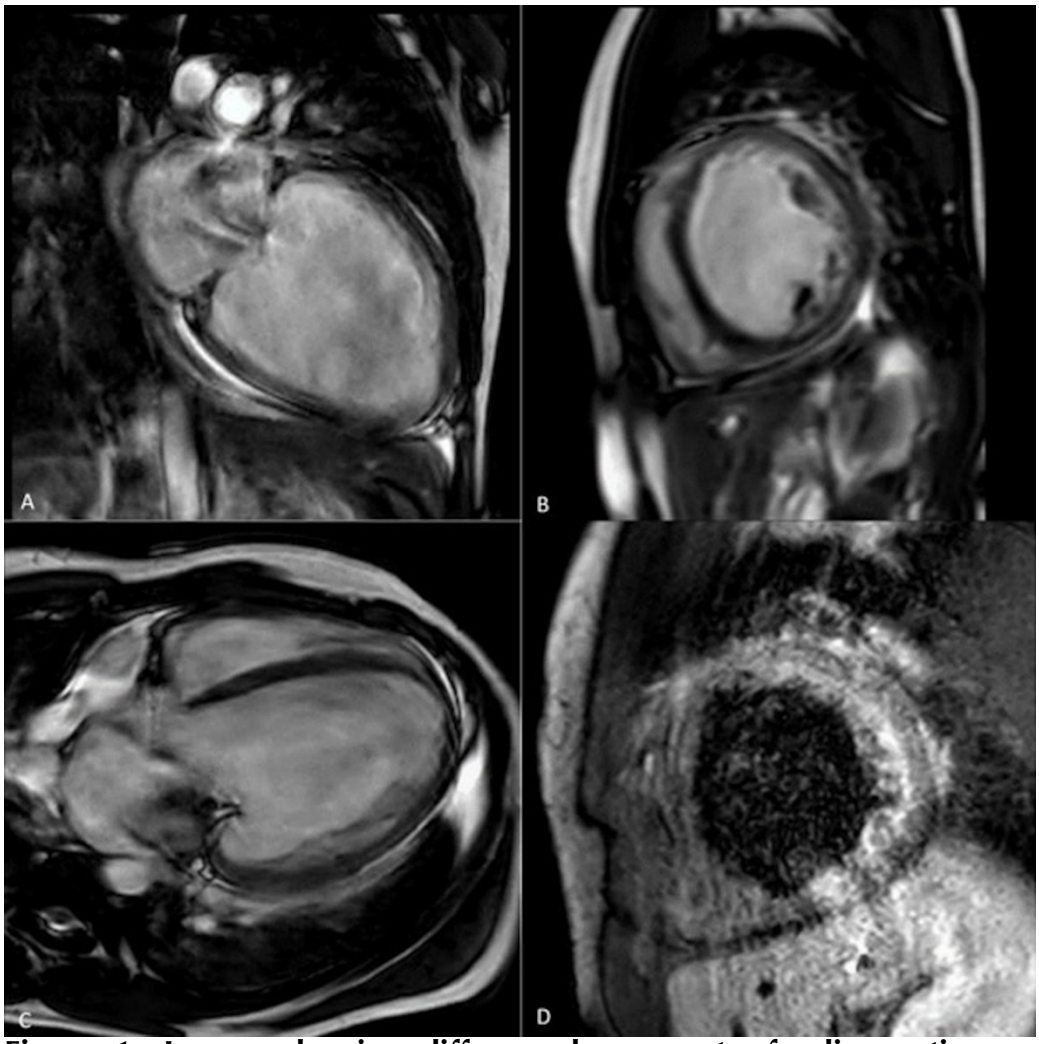

Figure 1. Images showing diffuse enhancement of adipose tissue and subepicardial myocardium throughout the left ventricle wall (A, B, C). The hyperintense signal on T2w of the left ventricular myocardial wall is suggestive of oedema, associated with hyperintense signal of the left periventricular adipose tissue (D).

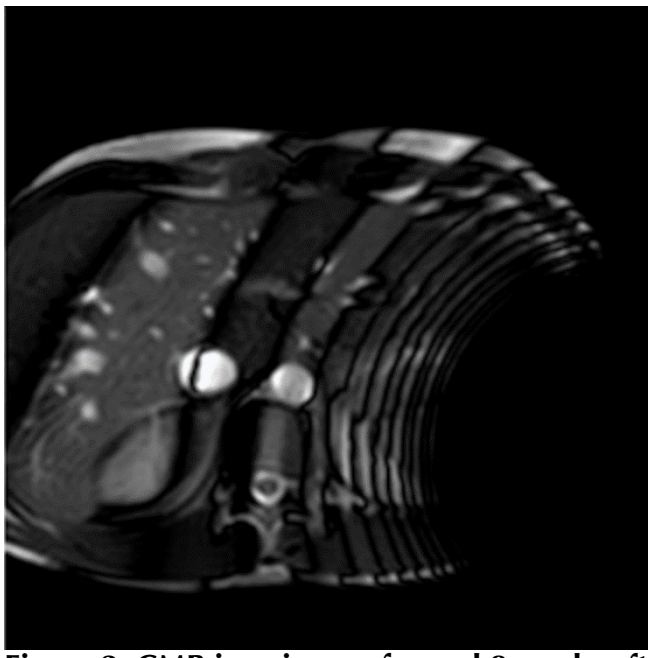

Figure 2. CMR imaging performed 8 weeks after S-ICD implantation.

Table 1. Recommendations for an implantable or wearable cardioverter defibrillator in primary prevention for patients with Dilated Cardiomyopathy (DCM) in agreement with 2023 ESC Guidelines for the management of cardiomyopathies [1], and 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [16].

Recommendations	Class	Level
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with DCM, symptomatic heart failure, and LVEF 35% despite >3 months of OMT.	**IIa**	**A**
An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors*	**IIa**	**C**
An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors	**IIb**	**C**
An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors*	**IIb**	**C**
Subcutaneous defibrillator should be considered as an alternative to transvenous defibrillator in patients with an indication for an ICD when pacing therapy for bradycardia, cardiac resynchronization, or ATP is not needed.	**IIa**	**B**
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	**IIb**	**B**

ICD, implantable cardiac defibrillator; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death; ATP, anti tachi pacing; HF, heart failure; *additional risk factors include syncope, LGE presence on CMR.