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Complete Recovery From Severe Anthracycline-Induced Cardiomyopathy: Unmasking a Pathogenic MYH7 Variant Through Cardiac Magnetic Resonance Imaging

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Case Report

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COMPLETE RECOVERY FROM SEVERE ANTHRACYCLINE-INDUCED CARDIOMYOPATHY: UNMASKING A PATHOGENIC *MYH7* VARIANT THROUGH CARDIAC MAGNETIC RESONANCE IMAGING

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1. Phong Le: Patient clinical management; Writing - original draft.

2. Ly Nguyen: Echocardiographic assessment and follow-up.

3. Hang Tong: Cardiac MRI analysis and interpretation.

4. Son Pham: Supervision; Guidance in writing and structuring the manuscript.

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ABSTRACT

The prevention and management of cancer therapy-related cardiac dysfunction (CTRCD) have become increasingly important. Recent studies have revealed the crucial role of genetics in determining the susceptibility to the development of CTRCD, supporting a "second-hit" hypothesis where genetic variants predispose the myocardium to injury from cardiotoxic agents. We present a case of a 31-year-old woman with breast cancer who developed severe, early-onset CTRCD following a moderate dose of anthracycline and HER2-targeted therapy. Despite her young age and the absence of conventional cardiovascular risk factors, her left ventricular ejection fraction (LVEF) plummeted to 16%. Through the use of multimodal imaging, particularly cardiac magnetic resonance with tissue characterization, we detected severe biventricular dysfunction and a mid-wall late gadolinium enhancement pattern. Further investigation with genetic testing identified a pathogenic frameshift variant in the MYH7 gene, which was also confirmed in her son and symptomatic mother through cascade screening. Notably, after six months of optimized medical therapy, the patient achieved complete functional recovery (LVEF 53%). This case underscores the potential role of genetic screening in identifying patients at risk for severe CTRCD and advocates for personalized chemotherapy and proactive cardioprotective strategies.

Keyword: ***Genetics, CMR, Anthracycline cardiotoxicity, MYH7, and Reverse Remodeling***

INTRODUCTION

Cancer therapy-related cardiac dysfunction remains a formidable challenge, affecting approximately 9% of patients treated with anthracyclines [1, 2]. While cardiotoxicity is traditionally viewed as dose-dependent, individual susceptibility varies significantly due to the "second-hit" hypothesis [1, 3]. This theory suggests that underlying genetic variants in sarcomeric genes, such as *TTN* or *MYH7*, act as a foundational vulnerability that predisposes patients to severe myocardial injury when exposed to cardiotoxic triggers like chemotherapy [1, 4]. Anthracyclines induce damage by inhibiting topoisomerase 2ß and generating reactive oxygen species, leading to mitochondrial dysfunction [5, 6]. We report a case where a moderate dose of doxorubicin unmasked a pathogenic *MYH7* variant in a young woman, resulting in severe biventricular failure followed by a remarkable recovery through early medical intervention.

CASE REPORT

A 31-year-old woman (PARA 2002) was admitted to our hospital presenting with progressive dyspnea and fatigue (New York Heart Association functional class III). She had no prior history of systemic hypertension, diabetes mellitus, or tobacco use. However, her family history was significant for her mother's premature death at age 46 due to early-onset heart and renal failure, suggesting a potential hereditary cardiovascular substrate.

The patient had recently been diagnosed with HER2-positive, hormone receptor-negative (ER-/PR-) breast cancer. At baseline, prior to any cardiotoxic exposure, her cardiac function was normal, with a LVEF of 63% and a left ventricular end-diastolic diameter (LVEDD) of 51 mm. Her chemotherapeutic regimen consisted of four cycles of AC (Doxorubicin 60 mg/m² and Cyclophosphamide 600 mg/m²), reaching a cumulative doxorubicin dose of 240 mg/m². This was followed by four cycles of Paclitaxel (175 mg/m²) combined with Trastuzumab (600 mg every 3 weeks) and radiotherapy.

Shortly after the completion of her treatment, her clinical condition deteriorated significantly. Follow-up echocardiography revealed a profound decline in systolic function, with her LVEF plummeting to 16% and her LVEDD increasing to 58 mm, the diastolic function and the right ventricular functions decreased (Figure 1).

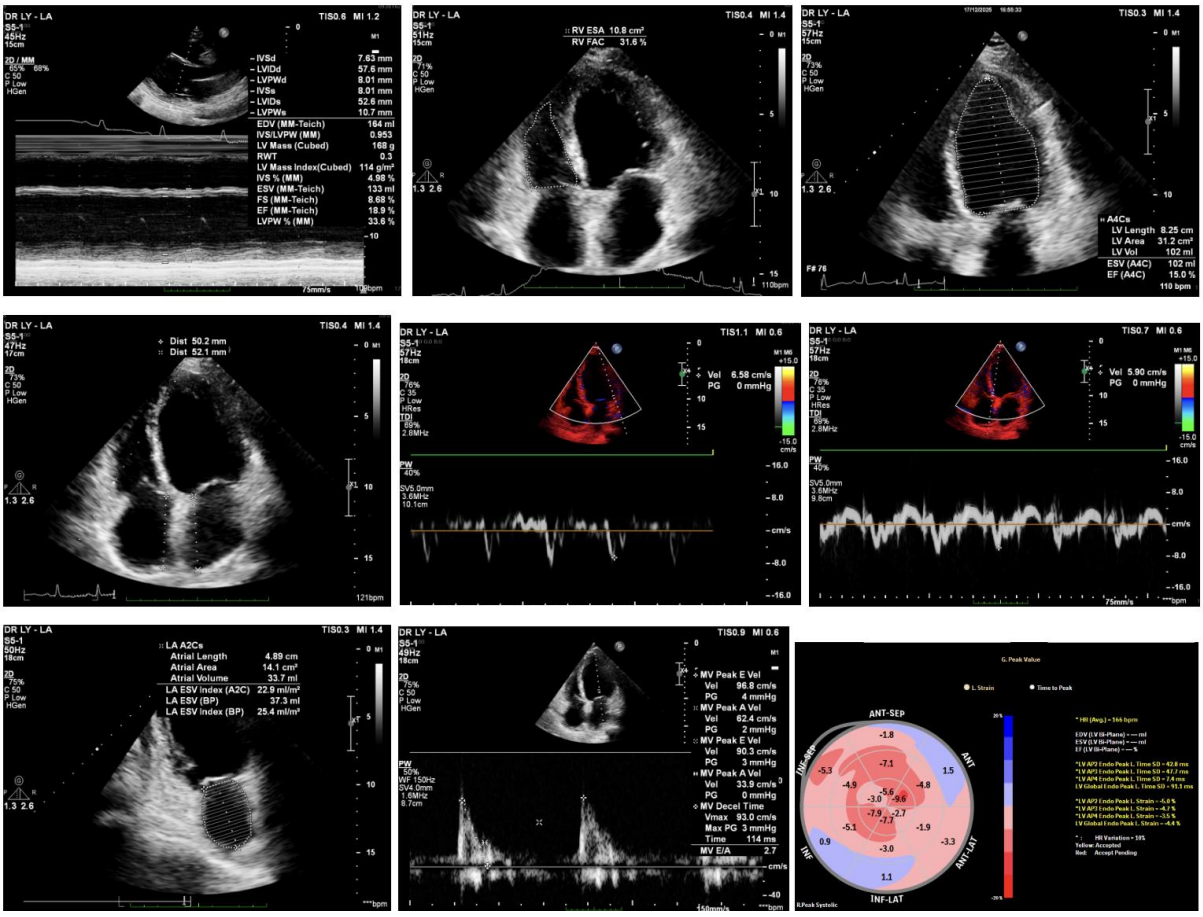


Figure 1. Findings from transthoraic echocardiography. The echocardiography shown the significant decrease of biventricular, systolic and diastolic functions. *LVEF (Simpson) was 16%, RV-FAC: 31%, LVIDd: 57.6 mm, left and right atrial diameter: 50 mm, 52 mm respectively. LV global endo peak strain: -4.4%. The septal and lateral E': 6.58 cm/s and 5.9 cm/s, respectively. The ratio of E to A: 2.7*

Coronary angiography exhibited no significant epicardial stenosis. To further characterize the myocardial injury, cardiac magnetic resonance (CMR) imaging was performed. CMR confirmed severe biventricular dilatation and dysfunction (LVEDV 135 mL/m², RVEDV 88 mL/m², LVEF 18%, RVEF 19%). Tissue characterization showed significantly elevated native T1 mapping (1361 ms), indicating diffuse interstitial changes or edema. Notably, late gadolinium enhancement (LGE) imaging identified a mid-wall enhancement pattern in the mid-lateral wall, a hallmark of an underlying non-ischemic dilated cardiomyopathy (DCM) phenotype rather than

standard diffuse toxic injury. Deformation analysis revealed severely impaired global strain (GLS -6%, GCS -7%, GRS 8%) (Figure 2).

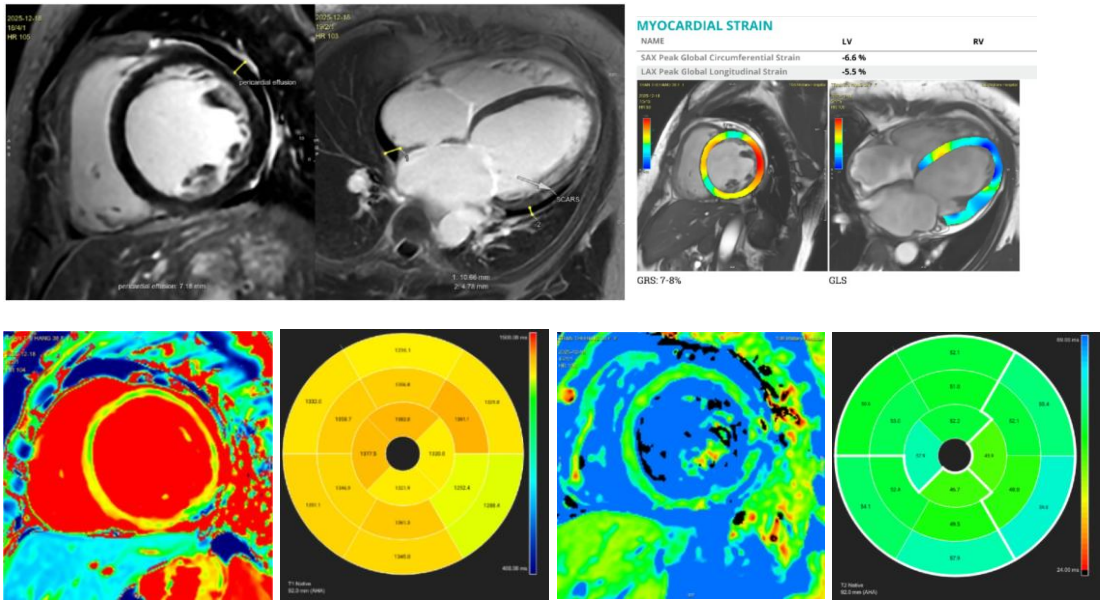


Figure 2. Cardiac magnetic resonance imaging.

To identify a potential genetic predisposition, next-generation sequencing (NGS) was performed using a comprehensive cardiomyopathy panel. The results identified a pathogenic heterozygous frameshift variant in the MYH7 gene (c.18_22del; p.Met6IlefsTer25) (Figure 3). This variant leads to a truncated protein or haploinsufficiency, compromising sarcomere integrity. Cascade screening subsequently confirmed that both her son the same variant, establishing an autosomal dominant inheritance pattern (Figure 4). This result suggests that her mother could have the same variant.

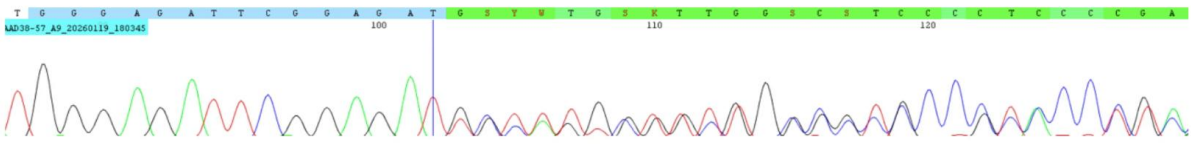


Figure 3. DNA sequencing chromatogram of the patient*. The direct sequencing confirmed a heterozygous likely pathogenic missense variant of TNNT2 , NM_000364.3:c.452G>A (p.Arg151Gln) in the patient*

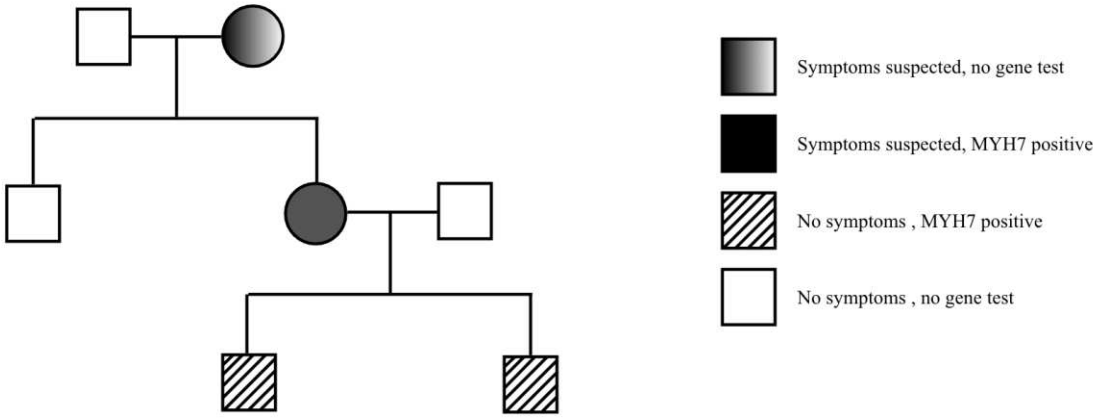


Figure 4. The genealogy chart of the patient. The diagram ilustrates the suspected F0 (patient mother) and patient (F1) and her positve but non-symptom at F2 generation. *Due to economic issue, patient's brother and her husband couldn't do generic test.*

The patient was immediately initiated on optimized guideline-directed medical therapy (GDMT), including Dapagliflozin 10mg o.d, Spironolactone 25mg o.d, Metoprolol 25mg, and ARNI (Valsartan 51mg, Sacubitril 49mg) divided twice per day. Her response was remarkable, demonstrating a "super-responder" phenotype. After 2 weeks of GDMT, her LVEF improved to 20%, increased dose of Metoprolol 25mg to 50mg; and rising to 31% by the second month. Following six months of optimized therapy (the dose at second month was the highest dose patient was initated), she achieved complete functional recovery with an LVEF of 53% without any symptoms of heart failure, indicating successful left ventricular reverse remodeling (Figure 5).

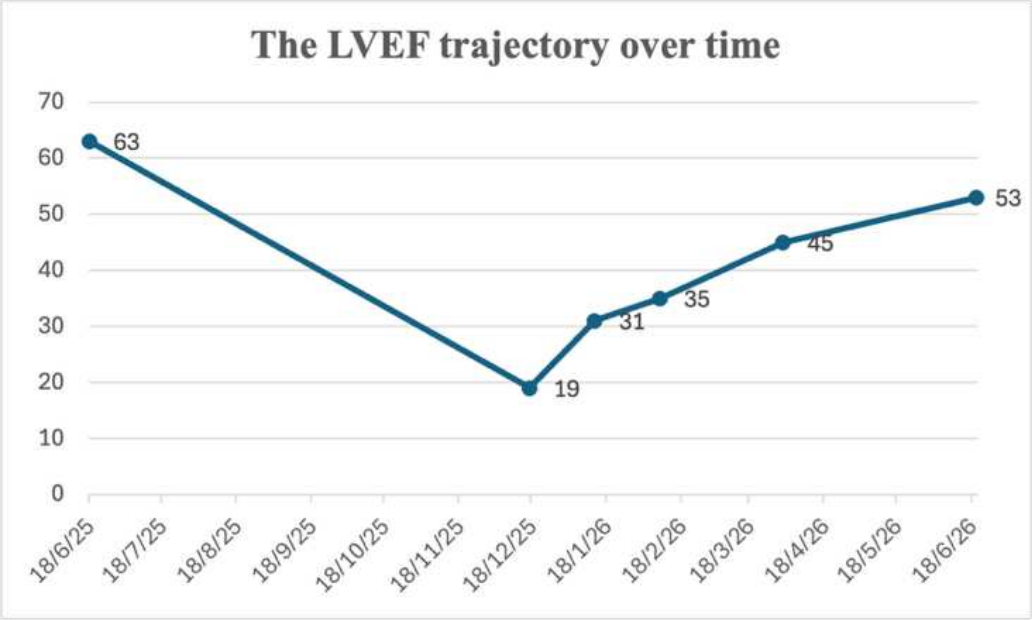


Figure 5. The LVEF trajectory over time. *The graph illustrates a significant decline in the patient's LVEF following Doxorubicin administration, with a gradual recovery following the initiation of GDMT. After approximately 6 months of treatment, the EF had recovered to reach 53%.*

DISCUSSION

The present case illustrates a severe, early-onset presentation of cancer therapy-related cardiac dysfunction (CTRCD) triggered by a moderate cumulative dose of doxorubicin (240 mg/m²) in a patient with a previously undiagnosed genetic predisposition. While anthracycline-induced cardiotoxicity is traditionally considered dose-dependent—with significant risks typically rising above 250–300 mg/m²—this patient's profound decline in LVEF to 16% underscores the "second-hit" hypothesis [7, 8]. In this paradigm, an underlying pathogenic genetic variant (the "first hit") creates a foundational structural vulnerability in the myocardium, which then suffers acute, disproportionate failure when exposed to cardiotoxic agents like anthracyclines (the "second hit") [9, 10].

The role of CMR was pivotal in differentiating standard toxic injury from an unmasked genetic substrate [11]. While echocardiography is the first-line screening tool, it is often limited by acoustic windows and geometric assumptions [11-13]. CMR provided three critical diagnostic layers:

- Quantitative Volumetry: CMR confirmed biventricular involvement (LVEF 18%, RVEF 19%), which is often a marker of global cardiomyopathic processes rather than localized injury [14, 15].
- Tissue Mapping: The native T1 mapping was markedly elevated at 1361 ms. Elevated native T1 and extracellular volume (ECV) are highly sensitive markers for diffuse interstitial fibrosis and edema, which often predate an LVEF decline [16, 17]. In this patient, the T1 elevation reflected a profound degree of myocardial remodeling [18].
- The "Hallmark" LGE Pattern: Most importantly, the identification of a mid-wall LGE pattern in the lateral wall provided a definitive clue [18]. While direct anthracycline cardiotoxicity usually presents as diffuse injury without focal LGE, the mid-wall dstriation is a hallmark of non-ischemic DCM [19, 20]. This finding confirmed that the chemotherapy had unmasked a pre-existing genetic DCM phenotype.

Furthermore, deformation analysis via CMR-feature tracking revealed a GLS of -6%, which is a powerful predictor of mortality and MACE in both ischemic and non-ischemic cardiomyopathy [19].

The patient’s "super-responder" status achieving a recovery from 16% to 53% LVEF - highlights the potential for complete functional recovery even in high-risk genetic carriers [21]. Prompt initiation of GDMT (ARNI, MRA, beta-blockers, SGLT2 inhibitors) following the detection of the LVEF drop is essential [6]. Previous studies suggest that carriers of sarcomeric variants (such as TTN or MYH7) can be highly responsive to early heart failure therapy, leading to significant left ventricular reverse remodeling [22, 23]. This case reinforces that intensive cardiac surveillance and early aggressive medical management can shift the prognosis of CTRCD from permanent damage to a reversible condition.

CONCLUSION

This case underscores that genetic susceptibility can transform standard-dose chemotherapy into a life-threatening "second hit." The integration of CMR with tissue characterization and genetic screening is vital for identifying high-risk patients and their family members. Early detection, combined with optimized GDMT, can lead to full functional recovery, advocating for a personalized approach in the field of cardio-oncology.

REFERENCES

1. Boen, H.M., et al., *Variants in structural cardiac genes in patients with cancer therapy-related cardiac dysfunction after anthracycline chemotherapy: a case control study.* Cardiooncology, 2024. **10**(1): p. 26.
2. Linschoten, M., et al., *Truncating Titin (TTN) Variants in Chemotherapy-Induced Cardiomyopathy.* J Card Fail, 2017. **23**(6): p. 476–479.
3. Lee, S.Y., et al., *Genetic predisposition in chemotherapy-induced cardiomyopathy in a 65-year-old female with metastatic breast cancer.* ESC Heart Fail, 2024. **11**(4): p. 2410–2414.
4. Zhang, Y.W., et al., *Cardiomyocyte death in doxorubicin-induced cardiotoxicity.* Arch Immunol Ther Exp (Warsz), 2009. **57**(6): p. 435–45.
5. Lenneman, C.G. and D.B. Sawyer, *Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment.* Circ Res, 2016. **118**(6): p. 1008–20.
6. Kundnani, N.R., et al., *Revisiting Secondary Dilative Cardiomyopathy.* Int J Mol Sci, 2025. **26**(9).
7. *Erratum to: 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC).* Eur Heart J, 2023. **44**(18): p. 1621.
8. Zamorano, J.L., et al., *2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC).* Eur J Heart Fail, 2017. **19**(1): p. 9–42.
9. Rickham, P.P., *Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki.* Br Med J, 1964. **2**(5402): p. 177.
10. Proost, D., et al., *Targeted Next-Generation Sequencing of 51 Genes Involved in Primary Electrical Disease.* J Mol Diagn, 2017. **19**(3): p. 445–459.
11. Wei, X., et al., *Cardiovascular Magnetic Resonance Imaging in the Early Detection of Cardiotoxicity Induced by Cancer Therapies.* Diagnostics (Basel), 2022. **12**(8).
12. Armstrong, G.T., et al., *Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging.* J Clin Oncol, 2012. **30**(23): p. 2876–84.
13. Baldassarre, L.A., et al., *Advances in Multimodality Imaging in Cardio-Oncology: JACC State-of-the-Art Review.* J Am Coll Cardiol, 2022. **80**(16): p. 1560–1578.

14. Anghel, N., et al., *Acute cardiotoxicity induced by doxorubicin in right ventricle is associated with increase of oxidative stress and apoptosis in rats.* Histol Histopathol, 2018. **33**(4): p. 365–378.
15. Shen, Y., et al., *Right Ventricular Ejection Fraction Assessed by Three-Dimensional Echocardiography Is Associated with Long-Term Adverse Clinical Cardiac Events in Patients with Anthracycline-Induced Cardiotoxicity.* J Am Soc Echocardiogr, 2022. **35**(6): p. 600–608 e3.
16. Mabudian, L., et al., *Cardiac MRI assessment of anthracycline-induced cardiotoxicity.* Front Cardiovasc Med, 2022. **9**: p. 903719.
17. O'Quinn, R., et al., *Cardiac Magnetic Resonance in Cardio-Oncology: Advantages, Importance of Expediency, and Considerations to Navigate Pre-Authorization.* JACC CardioOncol, 2021. **3**(2): p. 191–200.
18. Cannizzaro, M.T., et al., *Role of advanced cardiovascular imaging in chemotherapy-induced cardiotoxicity.* Heliyon, 2023. **9**(4): p. e15226.
19. Johnson, J.N., et al., *Cardiac magnetic resonance imaging in the assessment of cardiac injury and toxicity from cancer-related chemotherapy.* Pediatr Radiol, 2025. **55**(11): p. 2381–2399.
20. Kim, R.J., et al., *Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function.* Circulation, 1999. **100**(19): p. 1992–2002.
21. Yu, C., et al., *Cardiac magnetic relaxometry versus ejection fraction in anthracycline-related cardiac changes: a systematic review and meta-analysis.* Open Heart, 2023. **10**(2).
22. Merlo, M., et al., *Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment.* J Am Coll Cardiol, 2011. **57**(13): p. 1468–76.
23. Lorca, R., et al., *Concealed Inherited Cardiomyopathies Detected in Cardio-Oncology Screening.* J Clin Med, 2023. **13**(1).

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Ethics Approval: Ethics approval was not required for this single case report in accordance with local institutional guidelines. Written informed consent was obtained from the patient to participate in this study.

Clinical trial number: not applicable.