ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.clinicalimagingscience.org

Journal of Clinical Imaging Science

Case Report

Chronic Anthracycline-related Myocarditis Presenting as Diffuse Myocardial Calcification

Marijan Pejic[1], Monica Shifman[2], Trevor Rose[3], Daniel Jeong[3]

[1]Department of Radiology, University of South Florida, [3]Department of Radiology, Moffitt Cancer Center and Research Institute, Tampa, [2]Department of Medicine, Ross University, Miramar, Florida, USA.

***Corresponding author:**
Marijan Pejic,
Department of Radiology,
University of South Florida,
Tampa, Florida, USA.

mpejic@health.usf.edu

Received : 08 August 19
Accepted : 02 October 19
Published : 06 November 19

DOI
10.25259/JCIS_113_2019

Quick Response Code:

ABSTRACT

In the setting of cardio-oncology, evaluation for myocarditis is a growing indication for cardiovascular magnetic resonance (CMR). Treatment-related side effects of cancer therapies comprise the majority of myocarditis cases in cardio-oncology, and these are often secondary to anthracyclines and even the newer class of immune checkpoint inhibitors. Cardiotoxicity from cancer therapy represents an increasingly recognized etiology of myocarditis and when detected, warrants prompt management changes. The conventional CMR evaluation for myocarditis includes modules for the left ventricular structure and function, early gadolinium enhancement, and late gadolinium enhancement. Newer CMR sequences including native T1 mapping and extracellular volume fraction offer improvement in diagnostic accuracy from conventional CMR methods. We present a case of subacute/chronic myocarditis related to anthracycline therapy 4 months prior that was diagnosed only after incidental diffuse myocardial calcifications on pre-treatment computed tomography raised suspicion.

Keywords: Anthracycline, Cardiac, Cardio-oncology, Myocardial calcifications, Myocarditis

INTRODUCTION

In cardio-oncology, evaluation for oncologic therapy-related myocarditis is a growing indication for cardiovascular magnetic resonance (CMR). Treatment-related side effects of cancer therapies comprise the majority of myocarditis cases in cardio-oncology, and these are often secondary to anthracyclines with a growing number of cases related to immune checkpoint inhibitors (ICIs).[1-6] In these cases, CMR can be utilized for safe and early detection which may yield prompt clinical management changes.[7] In addition, emerging CMR quantitative T1 mapping is helping to increase sensitivity and specificity in the diagnosis of treatment-related myocarditis. This case report details subacute to chronic anthracycline treatment-related myocarditis detected through diffuse myocardial calcifications on computed tomography (CT) and confirmed on CMR.

CASE HISTORY

A 78-year-old Caucasian female presented to her primary care provider with progressive fatigue. Laboratory work demonstrated pancytopenia and the patient underwent subsequent bone marrow biopsy. The bone marrow biopsy was consistent with acute myelogenous leukemia M2. Induction chemotherapy with 7+3 idarubicin (an anthracycline) was initiated 1 week later. A repeat bone marrow biopsy 2 weeks after chemotherapy initiation demonstrated

hypocellular marrow with no evidence of increased blasts. The patient subsequently underwent 2 cycles of consolidative chemotherapy with cytarabine 5 and 10 weeks after induction chemotherapy. The course of therapy was complicated by an episode of sepsis that required hospitalization 11 weeks after induction chemotherapy. The sepsis resolved with antibiotic therapy with no lasting symptoms. Eighteen weeks after the initial anthracycline administration, the patient presented to our institution to discuss low-dose total body irradiation as part of her allogeneic hematopoietic stem cell transplant. She was asymptomatic at the time (with the exception of persistent fatigue).

Three weeks after anthracycline initiation, the patient experienced intermittent episodes of palpitations and shortness of breath. A CT angiogram (CTA) pulmonary artery examination was obtained to evaluate these symptoms; however, the examination was unremarkable. Of note, the myocardium had a normal appearance on this CT examination [Figure 1a]. These symptoms were self-limiting but had been persistent with exertion. At 18-week post-anthracycline initiation, a CT thorax without IV contrast was ordered as part of the pre-transplant evaluation [Figure 1b and c]. This CT demonstrated diffuse hyperdensity within the myocardium compatible with calcifications. No other significant findings were demonstrated on the examination. Given the broad differential, a CMR was recommended for further evaluation of the atypical myocardial calcifications.

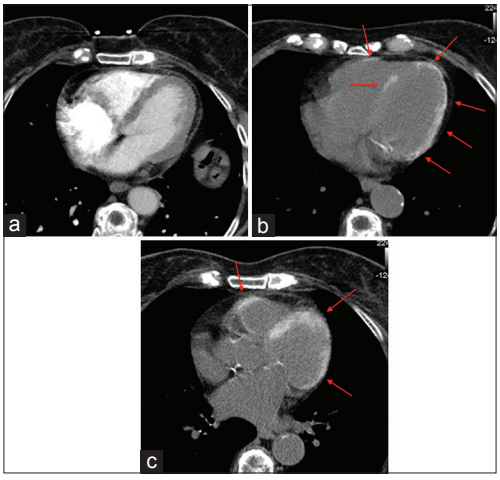

Figure 1: A 78-year-old female presenting with fatigue who was diagnosed with acute myelogenous leukemia M2 and treated with idarubicin and cytarabine. (a) Axial contrast-enhanced computed tomography (CT) image obtained 3 weeks following initiation of anthracycline therapy. The patient complained of dyspnea at this time. No abnormalities were detected. There was no pulmonary embolus. The lungs were clear and the myocardium appeared unremarkable. (b and c) Axial non-contrasted CT images obtained 18 weeks after the anthracycline induction chemotherapy. At this time, the patient had fatigue but no other symptoms. Diffuse hyperdensity is noted within the myocardium compatible with calcifications (arrows). This was new compared to the prior CT.

On CMR evaluation, cine balanced steady-state free precession CMR images demonstrated a normal wall thickness, a left ventricle size that was within normal limits, and normal left ventricular (LV) function [Figure 2a]. The dark blood T2 spectral attenuated inversion recovery images demonstrated hyperintensity of the myocardium most prominently anteriorly, laterally, and of the septal wall [Figure 2b and c]. Quantitative T2 signal ratios within the same sequence confirmed the T2 signal of the myocardium to be >1.9× of the signal of skeletal muscle. Delayed imaging demonstrated moderate, irregular, subepicardial enhancement [Figure 2d-e]. These findings met the conventional criteria for myocardial inflammation based on the Lake Louise Consensus Criteria.[7] A pre-contrast native T1 map of the mid-left ventricle demonstrated an increased T1 relaxation time which corresponded to the regions of late gadolinium enhancement (LGE) [Figure 2f]. The regions of myocardial calcification on the CT appeared more diffuse compared to the regions of abnormal LGE on the CMR; this suggested that myocarditis was not the only contributing factor for the calcifications.

DISCUSSION

The differential for diffuse myocardial calcifications is broad but has been reported in multiple cases. The previous sepsis has been shown to be a more common cause of myocardial calcifications, and this patient did have a hospitalization for sepsis at 11 weeks post-anthracycline initiation which resolved with therapy. However, many other etiologies have also been presented in literature (Table 1, adapted from Nance *et al*.[8]). Our patient had no clinical evidence of ischemia and no history of trauma. There was no evidence of a neoplastic process within the thorax on the CTA. Laboratory values did not support the diagnoses of renal failure, hyperparathyroidism, or an abnormal calcium or Vitamin D level. The patient had no prior history of sarcoidosis or rheumatic heart disease and her initial CT examination did not demonstrate valvular calcifications, lymphadenopathy, or pleural disease.

CMR showed abnormal myocardial edema and subepicardial LGE. Pre-contrast native T1 mapping quantitatively confirmed the abnormal increased T1 relaxation time of 1293 ms (normal myocardium 977 ms, MOLLI Siemens 1.5 T) (Siemens Healthcare, Erlangen, Germany).[9] With the absence of sarcoidosis risk factors, the diagnosis of myocarditis was strongly suggested.[10] However, the chronicity of the myocarditis is not always clear on CMR alone and clinical history is often helpful. The presence of new-onset palpitations and chest discomfort at 3-week post-anthracycline initiation suggests drug-related cardiac

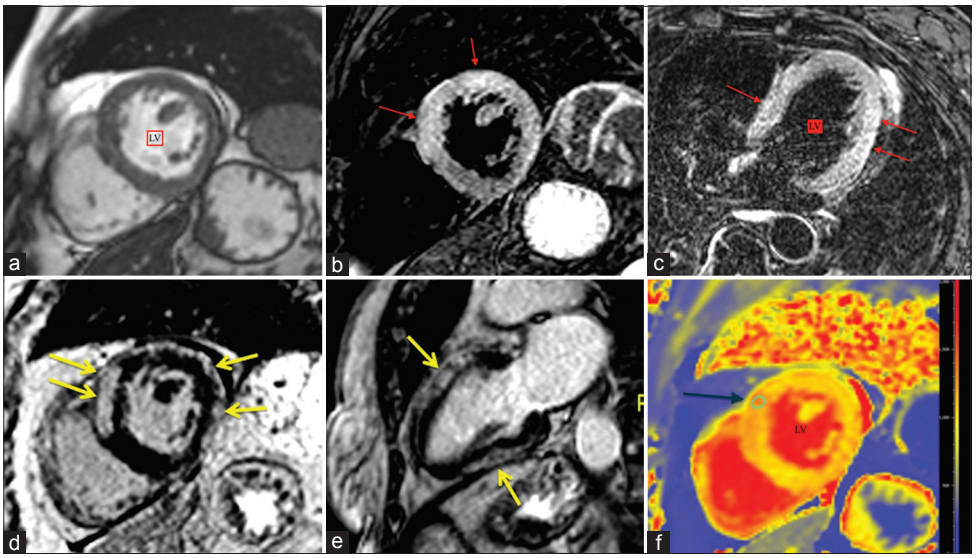

Figure 2: A 78-year-old female presenting with fatigue who was diagnosed with acute myelogenous leukemia M2 and treated with idarubicin and cytarabine. A cardiac magnetic resonance imaging cardiovascular magnetic resonance (CMR) was ordered for further evaluation of myocardial calcifications seen on the non-contrasted computed tomography. (a) Balanced short axis steady-state free precession CMR demonstrated normal left ventricular (LV) size, function, and wall thickness. (b and c) T2 spectral attenuated inversion recovery CMR short axis (b) and axial (c) images demonstrate hyperintensity of the myocardium greatest at the septum, anterior, and lateral walls (arrows). Quantitative T2 signal ratios confirmed that T2-weighted myocardium signal was >1.9× than that of the skeletal muscle signal within the same sequence. (d-e) Delayed viability phase-sensitive inversion recovery (PSIR) segmented short axis (d) and 2-chamber views (e) demonstrate moderate irregular subepicardial enhancement (arrows). (f) Mid-left ventricular short axis pre-contrast native T1 map demonstrates increased T1 relaxation time in the corresponding regions of late gadolinium enhancement (green circle denoted by the arrow). Qualitatively, the region of interest appears higher on the color map compared to the remaining myocardium (more red colored than yellow). An increased T1 relaxation time of 1293 ms is noted within the green region of interest.

Table 1: Differential diagnosis for myocardial calcifications (adapted from Nance *et al.*[8]).

Dystrophic	Metastatic	Mimics	Idiopathic
Ischemic: Myocardial infarction, ventricular aneurysm/ pseudoaneurysm	Renal failure	Pericardial calcification	Idiopathic
Traumatic: Cardioversion, cardiac surgery, hemorrhage, irradiation	Hyperparathyroidism	Valvular/annular calcification	
Infectious: Myocarditis (generally fungal or viral), myocardial abscess, tuberculosis, perimyocarditis, echinococcal disease	Oxaluria	Coronary artery calcification	
Inflammatory: Rheumatic heart disease, sepsis, sarcoidosis, endomyocardial fibrosis, hypereosinophilic endocarditis, myocarditis, cellular rejection in setting of a cardiac transplant	Aluminum intoxication (in setting of hemodialysis)	Great vessel calcification	
Neoplastic: Metastatic disease, primary cardiac tumors	Dietary calcium and/or Vitamin D deficiency	Calcified intraluminal thrombus	
Medication: Steroids, cyclosporine, calcium chloride, catecholamines	Sarcoidosis (Vitamin D hyperactivation)	Calcified intraluminal or pericardial tumors	
Other: Pulmonary hypertension, caseous calcification of the mitral annulus			

symptoms. The patient's initial symptoms which lead to the initial CT pulmonary angiography study likely represented the acute myocarditis episode which had a persistent milder subacute-chronic course. The patient had a normal LV ejection fraction (LVEF) and no acute symptoms at the time of the acquisition of the CMR. The abnormal myocardial edema and LGE demonstrated on the CMR were likely due to subacute/chronic myocarditis. In our case, the diffuse myocardial calcifications seen on CT were likely primarily a result of the patient's episode of sepsis. The patient also likely had a subacute/chronic case of myocarditis as evidenced by the time course of cardiac symptoms and the abnormal CMR

findings. The patient had anthracycline exposure in the form of idarubicine (4-demethoxydaunorubicin), an antileukemic medication. The main adverse effect from anthracyclines is cardiotoxicity, which can present as a more immediate pericarditis-myocarditis syndrome or as progressive congestive heart failure.[11] This necessitates regular cardiac LVEF monitoring in when anthracyclines are administered.[11] The patient also had cytarabine exposure, an antimetabolite, and nucleoside analog which has been reported to cause ischemia, pericarditis, CHF, and cardiogenic shock.[12,13]

At present, the diagnosis of myocarditis cannot be confirmed with a single clinical or imaging finding with absolute certainty.[7] Diagnosis and treatment should be guided with an integrated approach including history, clinical assessment, and non-invasive testing. CMR offers a unique combination of safety, clarity of anatomical visualization, quantitative accuracy, and interobserver consistency.[7] The combination of utilizing T2-weighted images and early and LGE has proven to be an accurate tool for the evaluation of myocarditis.[14] In addition, native T1 mapping and extracellular volume fraction are playing an increasing role in diagnosing myocarditis [Figure 2f].[15] Patients with acute myocarditis have higher T1 relaxation times compared to healthy volunteers.[15] Ferreira *et al*. reported that a T1>990 ms (sensitivity 90% and specificity 88%) detected larger areas of acute myocarditis involvement than T2W and LGE imaging.[15] Luetkens *et al*. showed that native T1 relaxation time had higher diagnostic accuracy (0.94) compared to LGE (0.90), T2 signal ratio (0.79), and extracellular volume fraction (0.71).[16]

Myocardial calcifications on CT can present secondary to a wide range of differential considerations. In our case, careful correlation with the patient's clinical history was helpful to determine prior sepsis as the primary cause for the calcifications. In addition, the superimposed subacute/chronic anthracycline-related myocarditis seen on CMR could have served as a secondary contributor to the myocardial calcifications.

CONCLUSION

We present a rare case of diffuse myocardial calcifications that were best explained by the patient's clinical history of sepsis and by myocarditis revealed on CMR. By understanding the conventional and emerging techniques of diagnosing myocarditis on CMR, the cardiac imager can yield timely accurate diagnosis and facilitate prompt clinical management changes to improve patient outcomes.

Declaration of patient consent

Patient information is de-identified and HIPPA compliant and as per our institutional policy it does not require the patient's consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, *et al.* Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer 2016;4:13.
2. Mehta A, Gupta A, Hannallah F, Koshy T, Reimold S. Myocarditis as an immune-related adverse event with ipilimumab/nivolumab combination therapy for metastatic melanoma. Melanoma Res 2016;26:319-20.
3. Gibson R, Delaune J, Szady A, Markham M. Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. BMJ Case Rep 2016;2016:bcr2016216228.
4. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, *et al.* Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 2016;4:50.
5. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohé C. Drug-induced myocarditis after nivolumab treatment in a patient with PDL1 negative squamous cell carcinoma of the lung. Lung Cancer 2016;99:117-9.
6. Tadokoro T, Keshino E, Makiyama A, Sasaguri T, Ohshima K, Katano H, *et al.* Acute lymphocytic myocarditis with anti-PD-1 antibody nivolumab. Circ Heart Fail 2016;9:e003514.
7. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, *et al.* Cardiovascular magnetic resonance in myocarditis: A JACC white paper. J Am Coll Cardiol 2009;53:1475-87.
8. Nance JW Jr. Crane GM, Halushka MK, Fishman EK, Zimmerman SL. Myocardial calcifications: Pathophysiology, etiologies, differential diagnoses, and imaging findings. J Cardiovasc Comput Tomogr 2015;9:58-67.
9. Gottbrecht M, Kramer CM, Salerno M. Native T1 and extracellular volume measurements by cardiac MRI in healthy adults: A meta-analysis. Radiology 2019;290:317-26.
10. Cummings KW, Bhalla S, Javidan-Nejad C, Bierhals AJ, Gutierrez FR, Woodard PK, *et al.* A pattern-based approach to assessment of delayed enhancement in nonischemic cardiomyopathy at MR imaging. Radiographics 2009;29:89-103.
11. Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Expert Opin Drug Saf 2006;5:791-809.
12. Conrad ME. Cytarabine and cardiac failure. Am J Hematol 1992;41:143-4.
13. Vaickus L, Letendre L. Pericarditis induced by high-dose cytarabine therapy. Arch Intern Med 1984;144:1868-9.
14. Chu GC, Flewitt JA, Mikami Y, Vermes E, Friedrich MG. Assessment of acute myocarditis by cardiovascular MR: Diagnostic performance of shortened protocols. Int J Cardiovasc Imaging 2013;29:1077-83.

15. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Ntusi N, *et al.* Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. J Cardiovasc Magn Reson 2014;16:36.
16. Luetkens JA, Doerner J, Thomas DK, Dabir D, Gieseke J, Sprinkart AM, *et al.* Acute myocarditis: Multiparametric cardiac MR imaging. Radiology 2014;273:383-92.

How to cite this article: Pejic M, Shifman M, Rose T, Jeong D. Chronic anthracycline-related myocarditis presenting as diffuse myocardial calcification. J Clin Imaging Sci 2019;9:47.