Journal of Rare Cardiovascular Diseases 2017; 3 (5): 176–179
www.jrcd.eu

CASE REPORT
Diseases of the heart

Doxorubicin cardiomyopathy – case report and review of histopathologic findings (RCD code: III-1B.5a)

Hamza Tariq*, Urooj Zahra

Department of pathology and laboratory medicine, University of Texas Health Science Center at San Antonio, Texas, USA

Abstract

The anthracycline anticancer drug Doxorubicin (Adriamycin) is an effective and frequently used chemotherapeutic agent for various malignancies. The use of doxorubicin is limited by its major adverse effect, cardiotoxicity. Doxorubicin cardiomyopathy, once developed, carries a poor prognosis with a mortality rate of over 50%. Although invasive, histopathologic analysis of myocardial tissue remains the most sensitive and specific method of diagnosing doxorubicin cardiomyopathy. Histopathologic analysis reveals not only the characteristic diagnostic features of the disease but also aids in grading the severity of doxorubicin cardiomyopathy, which guides further therapy. We report the autopsy findings of a 31-year-old man with a history of T-cell Acute Lymphoblastic Leukemia (ALL) who died of severe doxorubicin induced dilated cardiomyopathy after he was given multiple rounds of hyperfractionated Cyclophosphamide, Vincristine, Adriamycin (doxorubicin) and Dexamethasone (hyper-CVAD) over a period of six years. JRCD 2017; 3 (5): 176–179

Key words: Doxorubicin, Adriamycin, cardiomyopathy, leukemia, rare disease

Introduction

The anthracycline anticancer drug Doxorubicin (Adriamycin) is one of the most effective anticancer agents and is used as a first line agent in the treatment of many malignancies including acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, and breast cancer. Due to its promising results, doxorubicin is not only being used with increasing frequency, it is being given in higher dosages in an attempt to improve treatment outcomes [1]. Unfortunately, the use of doxorubicin is limited by its major adverse effect, cardiotoxicity. Doxorubicin exerts both acute and chronic effects on the cardiovascular system. The acute manifestations include arrhythmias (supraventricular tachycardia, ventricular premature beats), hypotension, and various electrocardiographic changes (nonspecific ST-T change, left axial deviation, low voltage). The incidence of acute doxorubicin cardiotoxicity is approximately 11% [2,3]. The chronic effects of doxorubicin, on the other hand, are dose-dependent and include irreversible cardiomyopathic changes leading to congestive heart failure. The incidence of doxorubicin-induced cardiomyopathy is 1.7%, and the mortality rate in established cases of congestive heart failure is more than 50% within the first year of onset [4,5]. We report the autopsy findings in a 31-year-old man with a history of T-cell Acute Lymphoblastic Leukemia (ALL) who developed severe dilated cardiomyopathy following multiple rounds of hyperfractionated Cyclophosphamide, Vincristine, Adriamycin (doxorubicin) and Dexamethasone (hyper- CVAD) given over a period of six years.

Please cite this article: Tariq H, Zahra U. Doxorubicin cardiomyopathy – case report and review of histopathologic findings. J Rare Cardiovasc Dis. 2017; 3(5): 176-179; doi: https://doi.org/10.20418/jrcd.vol3no5.301

Conflict of interest: The authors whose names are listed above certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Submitted: December 14, 2017. Accepted: December 10, 2017.

* Corresponding author: Department of pathology and laboratory medicine, University of Texas Health Science Center at San Antonio, Mail Code 7750, 7703 Floyd Curl Drive, San Antonio, Texas, 78 229–3900; phone: (210) 567–4000, fax: (210) 567–6729; e-mail: TariqH@uthscsa.edu.

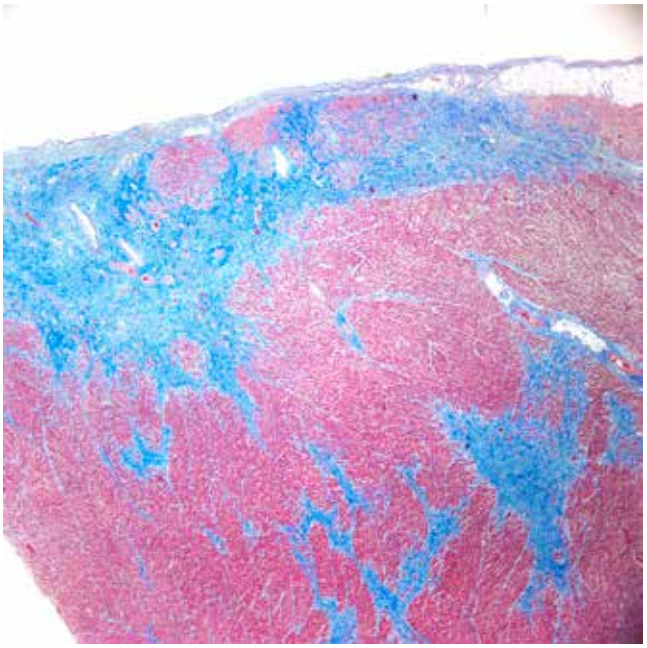

Figure 1. Trichrome stain on a section of the left ventricle showing extensive subepicardial and myocardial fibrosis

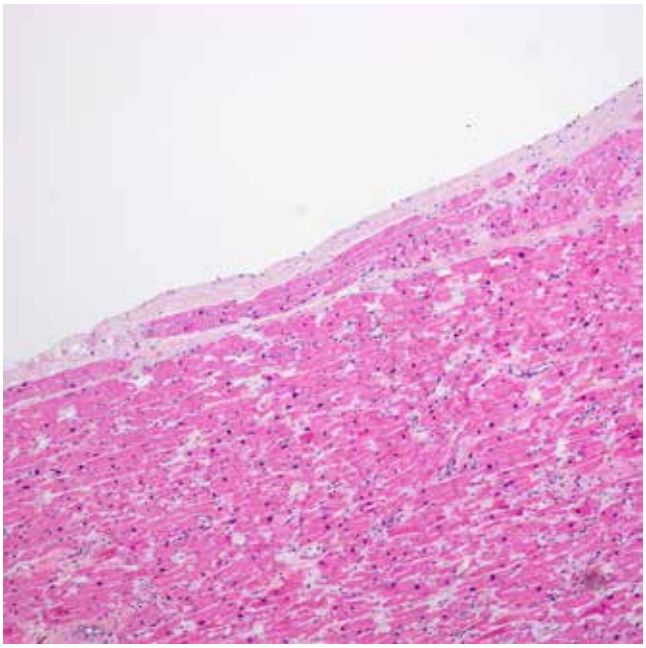

Figure 2. Subendocardial tissue showing minimal fibrosis

Case presentation

The patient was a 31-year-old man with a history of T-cell Acute Lymphoblastic Leukemia diagnosed six years antemortem. He was started on Hyper-CVAD and was able to achieve remission after the first round. The baseline cardiac function testing including echocardiography prior to starting chemotherapy was normal. Over the next six years he relapsed four times requiring multiple rounds of hyper-CVAD. During his last round of chemotherapy five months antemortem, he developed severe symptomatic congestive heart failure. The echocardiography showed an ejection fraction of 25%. He was started on carvedilol and enalapril which resulted in no significant clinical improvement. The chemotherapy was discontinued and the patient decided to transition to hospice care where he was managed symptomatically. While in hospice, he developed multiple chronic decubitus ulcers causing repeated episodes of sepsis. He died of respiratory failure due to pneumonia four months after discontinuing the chemotherapy.

On autopsy examination the heart showed hypertrophy (weight: 490 grams). There was marked biventricular dilation with a mitral valve circumference of 12.5 cm. (normal limit: 9–10 cm.) and tricuspid valve circumference of 13.8 cm. (normal limit: 11–12 cm.). The coronary arteries were normally distributed, with a right-dominant pattern, and showed no atherosclerosis. The myocardial tissue did not show any grossly identifiable evidence of acute or chronic ischemic damage. Microscopically, there was extensive multifocal patchy interstitial fibrosis. The fibrosis was mostly subepicardial and intramyocardial in distribution. (Figure 1). The subendocardial tissue appeared healthy and was entirely spared of these toxic changes (Figure 2). There were frequent large ballooned/vacuolated myocytes (Adria cells) adjacent to the areas of fibrosis (Figure 3). Frequent foci of fibroblast proliferation and histiocytic infiltration were also seen. The epicardial fat showed prominent leukemic infiltrates. In the absence of other significant cardiovascular risk factors, including hypertension, and given the history of multiple rounds of hyper-CVAD, these gross and microscopic findings in the heart were diagnostic of doxorubicin (Adriamycin)-related dilated cardiomyopathy.

Discussion

The estimated incidence of chronic doxorubicin cardiotoxicity is low (approximately 1.7%), but once congestive heart failure develops, the one year mortality rate is over 50%. The toxicity is usually evident within 30 days of administration of the last dose, but it may occur even after 6–10 years after administration. The incidence of doxorubicin cardiomyopathy is primarily related to its total cumulative dose. The incidence is about 4% when the dose of doxorubicin is 500–550 mg/m^2, 18% when the dose is 551–600 mg/m^2 and 36% when the dose exceeds 600 mg/m^2 [4,5]. Per clinical record, the total cumulative dose of doxorubicin given to this patient was between 530 – 560 mg/m^2.

Several other risk factors are also known to contribute to the development of doxorubicin induced cardiomyopathy and these include high peak serum levels of the drug, combination therapy with other cardiotoxic antitumor drugs (cyclophosphamide, taxanes, trastuzumab, and cyclooxygenase-2 inhibitor), concomitant mediastinal radiation therapy, age at the time of exposure (very young and very old are most susceptible), history of preexisting cardiac diseases, hypertension, and liver disease [1].

The proposed mechanisms of the anti-malignancy effects of doxorubicin include intercalation into DNA leading to inhibition of synthesis of macromolecules, generation of reactive oxygen species, DNA binding and DNA cross-linking; DNA damage by inhibition

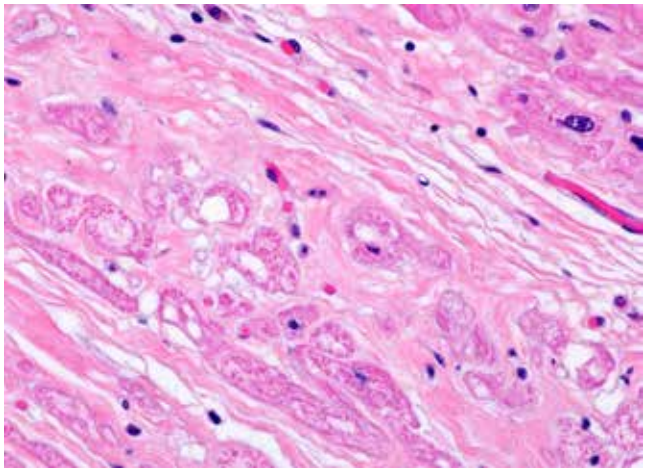

Figure 3. Ballooned/vacuolated myocytes (Adria cells) adjacent to an area of fibrosis

of topoisomerase II, and induction of apoptosis by inhibition of topoisomerase II [6]. The mechanism behind doxorubicin cardiotoxicity is unclear but several theories have been proposed which include increased oxidative stress [7], decreased levels of antioxidants and sulfhydryl groups [8], inhibition of nucleic acid and protein synthesis [9], release of vasoaactive amines, altered adrenergic function and decreased expression of cardiac-specific genes [1].

Although invasive, endomyocardial biopsy has the greatest specificity and sensitivity in diagnosing doxorubicin-induced cardiomyopathy. Characteristic light microscopic findings include areas of widespread patchy myocardial interstitial fibrosis. Adjacent to these areas of fibrosis are large, vacuolated cardiomyocytes referred to as the 'Adria cells'. The areas of fibrosis are usually widespread, while areas of acute myocyte damage are infrequent. In our case the fibrosis was mostly centered in the subepicardial tissue with sparing of the subendocardium. This feature differentiates it from ischemic fibrosis which almost always involves the subendocardial tissue [10].

Electron microscopic features include loss of myofibrils, distention of sarcoplasmic reticulum, and vacuolization of the cytoplasm. A grading scale is used to grade injury on a scale of 1 to 3. Biopsy samples in which fewer than 5% of cells show changes typical of doxorubicin injury are given a grade of 1; those with changes in 5% to 15%, 16% to 25%, 26% to 35%, and greater than 35% of cells are graded 1.5, 2, 2.5, and 3, respectively. This grading is helpful for clinical determination of whether additional use of doxorubicin is appropriate. If a biopsy shows grade 1 changes, more doxorubicin can be given. On the other hand, no further doxorubicin should be given when a biopsy shows grade 3 changes, regardless of whether hemodynamic parameters are normal. Patients with biopsy grades 1.5 or 2 can receive more doxorubicin, whereas a grade 2.5 biopsy would indicate only one additional dose of doxorubicin may be given without further evaluation [11]. Early studies and reviews suggested, that routine monitoring with EMB in patients treated with anthracycline chemotherapeutic agents was appropriate. However, recent guidelines conclude, that EMB is best suited for situations in which the cause of cardiomyopathy is unclear, or for determining whether higher doses of an anthracycline can be given [12].

Adequate measures for prevention must be considered for patients who are candidates for cumulative anthracycline doses. For instance, replacing bolus administration with slow infusions over 24–96 hours reduces the peak plasma anthracycline levels and decreases the penetration of the drug into cardiac tissue. Significant reduction in cardiotoxicity can also be achieved by replacing conventional anthracyclines with liposome-encapsulated ones. Liposomal formulations do not cross the gap junctions of endothelial linings in the heart. Replacing doxorubicin with a less cardiotoxic anthracycline agents like 4'-epi-doxorubicin and amrubicin should also be considered in selective cases. Concomitant administration of dexrazoxane with anthracyclines has shown marked reduction in rates of anthracycline-related cardiotoxicity in many clinical studies of both childhood and adult cancer patients [13].

Primary prevention of anthracycline cardiotoxicity should also involve common sense procedures, that apply to any patient at risk for cardiac events. Preexisting comorbidities (hypertension, systolic dysfunction or metabolic disorders) or unfavorable lifestyle choices (smoking, overweight or reduced physical activity) should be rigorously corrected as they have long been known to increase the risk of cardiotoxicity in patients exposed to anthracyclines [14]. Significant cardiac protection was seen in studies of carvedilol (α_1 and $\beta_{1\text{-}2}$ adrenoceptor blocker), nebivolol (β_1 blocker) or carvedilol in combination with the angiotensin-converting enzyme inhibitor, enalapril. A reduced degree of protection was documented with metoprolol (β_1 blocker) or enalapril alone. In a recent study, the angiotensin II receptor blocker, candesartan, prevented the decline of systolic dysfunction in breast cancer patients receiving adjuvant anthracycline with or without subsequent trastuzumab [13].

A recent study by Cardinale et al. involving 2625 patients (mean follow-up 5.2 years), showed a 9% overall incidence of cardiotoxicity after anthracycline treatment and 98% of cases occurred within the first year and were asymptomatic [15]. This indicates that anthracycline-induced cardiotoxicity is most likely a phenomenon characterized by continuous progressive decline in left ventricle ejection fraction. Many affected patients may initially be asymptomatic with clinical manifestations appearing years later. In light of these findings, the European Society of Cardiology (ESC) recommends baseline cardiac function assessment for all patients receiving anthracyclines. If systolic dysfunction is found, the patient should be discussed with the oncology team and options for non-anthracycline-containing chemotherapy and/or cardioprotection should be considered. If used, a second assessment of cardiac function should be performed at the end of the treatment, particularly when the patient has an increased risk for cardiotoxicity or consecutive treatment with potentially cardiotoxic targeted therapies will follow. Non-invasive tests for monitoring of cardiac function suggested by the ESC include echocardiography, nuclear cardiac imaging, cardiac magnetic resonance, and serum levels of troponin I, high sensitivity troponin I, and brain natriuretic peptide [16].

Once congestive heart failure is established, there is no specific treatment for doxorubicin induced cardiomyopathy. Beta adrenergic blocking agents, diuretics and angiotensin-converting enzyme inhibitors are used, similarly to other forms of systolic heart failure. However, none of the treatments employed for ischemic or idio-

pathic dilated cardiomyopathy have been demonstrated to improve the prognosis of patients with doxorubicin cardiomyopathy. Cardiac transplantation has been the only treatment reported to improve long-term prognosis of the patients, in whom the primary malignancy is cured following chemotherapy [17].

References

1. Takemura G and Fujiwara H. Doxorubicin-Induced Cardiomyopathy. From the Cardiotoxic Mechanisms to Management. Progress in Cardiovascular Diseases 2007; 49: 330–352.
2. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. A retrospective analysis of three trials. Cancer 2003; 97: 2869–2879.
3. Chatterjee K, Zhang J, Honbo N, Karliner J. Doxorubicin Cardiomyopathy. Cardiology 2010;115:155–162
4. Lefrak EA, Pitha J, Rosenheim S, et al. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973; 32: 302–314.
5. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91: 710–717.
6. Gewirtz DA. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics Adriamycin and daunorubicin. Biochem Pharmacol 1999; 57: 727–741.
7. Singal PK, Deally CM, Weinberg LE. Subcellular effects of Adriamycin in the heart: a concise review. J Mol Cell Cardiol 1987; 19: 817–828.
8. Singal PK, Segstro RJ, Singh RP, Kutryk MJ. Changes in lysosomal morphology and enzyme activities during the development of Adriamycin-induced cardiomyopathy. Can J Cardiol 1985; 1: 139–147.
9. Monti E, Prosperi E, Supino R, Bottiroli G. Free radical-dependent DNA lesions are involved in the delayed cardiotoxicity induced by Adriamycin in the rat. Anticancer Res 1995; 15: 193–197.
10. Billingham ME, Mason JW, Bristow MR, et al. Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 1978; 62: 865–872.
11. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987; 82: 1109–1118.
12. From AM, Maleszewski JJ, Rihal CS. Current Status of Endomyocardial Biopsy. Mayo Clinic Proceedings. 2011;86(11):1095–1102. doi:10.4065/mcp.2011.0296.
13. Menna P, Salvatorelli E. Primary Prevention Strategies for Anthracycline Cardiotoxicity: A Brief Overview. Chemotherapy 2017; 62:159–168.
14. Minotti G, Menna P, Salvatorelli E, et al. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004; 56:185–229.
15. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015; 131:1981–1988.
16. Zamorano J, Aboyans V, Achenbach S, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. European Heart Journal 2016; 37:2768–2801
17. Arico M, Pedroni E, Nespoli L, Vigano M, Porta F, Burgio GR. Long-term survival after heart transplantation for doxorubicin-induced cardiomyopathy. Arch Dis Child 1991; 66:985–986.