# **OncoReview**

# Mitral regurgitation after anthracycline exposure: a case report



Gregory R. Hartlage, MD, Palmer H. Cole, Aarti A. Patel, MD, C. Alberto Morales, MD, Eric E. Harrison, MD

> Division of Cardiology, Department of Medicine, University of South Florida/Memorial Hospital of Tampa Morsani School of Medicine, Tampa, Florida

### ABSTRACT

We report the case of a 66-year-old African American female with a history of breast cancer previously treated with anthracycline based chemotherapy presenting with significant mitral regurgitation. She initially had preserved left ventricular systolic function with normal cardiac chamber dimensions, however, she developed progressive left ventricular chamber dilation and mild reduction in systolic function, which prompted surgical correction of her mitral regurgitation. After surgical mitral valve repair, she developed overt left ventricular failure with severe systolic dysfunction; however, she responded well to subsequent medical therapy.

KEY WORDS: anthracycline, cardiomyopathy, cardiotoxicity, mitral regurgitation, mitral valve repair

### INTRODUCTION

Together, cardiovascular (CV) disease and cancer are responsible for nearly 48% of all deaths [1]. As efforts to combat these diseases continue to evolve, the prognosis of patients with CV disease and cancer has improved. Unfortunately, many anticancer treatments, such as anthracycline based chemotherapy regimens, pose significant threat to the heart. Published data suggests that more than 20% of patients treated with anthracycline exhibit evidence of left ventricular (LV) dysfunction late after chemotherapy, with approximately 5% developing overt heart failure [2]. Isolated mitral regurgitation (MR) after anthracycline exposure is not well characterized, although it develops in 10-15% of children with normal LV systolic function after anthracycline exposure [3, 4]. Furthermore, echocardiographic findings of MR may be an early predictor of anthracycline-induced cardiomyopathy [3]. We present the first case of an adult patient who developed significant MR with initially preserved left ventricular ejection fraction (LVEF) and normal cardiac chamber dimensions 5 years post anthracycline exposure.

# CASE SUMMARY

A 66-year-old African American female was referred to our clinic for discomfort and fullness in her chest with arm tingling for 3 weeks duration with an abnormal electrocardiogram showing a non-specific T wave abnormality. She had been previously diagnosed with lymph node negative breast carcinoma in 6 years prior and received a left radical modified mastectomy addition to 6 cycles of 5-fluorouracil, cyclophosphamide, and doxorubicin; followed by adjuvant tamoxifen for 5 years. She had a history of gastroesophageal reflux disease, hyperlipidemia, and mild hypertension for 30 years prior, which was treated with atenolol. Subsequent transthoracic echocardiography (TTE) revealed normal LV wall thickness and chamber dimensions, LVEF of 57%, moderate MR, and normal right ventricular systolic pressure (RVSP, Table 1). Subsequent stress echocardiography was normal, showing no wall motion abnormalities. The patient was reassured given these benign findings.

A follow-up TTE 2 years later (7 years post-anthracycline) revealed normal LV chamber dimensions, LVEF of 50%, mild MR, and normal RVSP. A follow-up TTE 2 years later (9 years post--anthracycline) revealed moderate to severe MR, left atrial enlargement (LAE), and stable LV chamber size, systolic function, and RVSP (Table 1). During the following 6 months, the patient developed orthopnea, exertional shortness of breath, and loss of stamina consistent with New York Heart Association class III congestive heart failure. Repeat TTE after the onset of these symptoms revealed LV chamber dilation (Table 1), LVEF of 48%, progressive LAE, and elevated RVSP of 48 mmHg. A B-type natriuretic peptide (BNP) blood level was 234.7 pg/mL (upper limit of normal 100 pg/mL). The patient was started on 80 mg of valsartan once daily and placed on a sodium-restricted diet.

A transesophageal echocardiogram (TEE) was performed to further assess the mechanism of her MR. The TEE revealed moderate to severe MR with left upper pulmonary vein systolic flow reversal. There were no structural abnormalities of the mitral valve leaflets or chordal structures, however the anterior and posterior leaflets did not coapt. The left ventricular contractility appeared to be minimally reduced. Due to her symptoms and significant MR with progressive LV dilation and systolic dysfunction, she was evaluated for mitral valve repair. Pre-operative cardiac catheterization confirmed moderate to severe MR, no obstructive coronary artery disease, and mild pulmonary hypertension with pulmonary artery systolic pressure of 43 mmHg. The patient underwent minimally invasive robotic mitral valve repair with placement of a #29 ATS annuloplasty ring (LeviBioMedica, Rome, Italy). Her immediate postoperative recovery was uncomplicated and she was discharged on the 4<sup>th</sup> postoperative day. After the surgery a TTE showed stable LV systolic function with an LVEF of 49%. The patient started cardiac rehabilitation and progressed well.

At 10 months post-mitral valve repair (10 years post-anthracycline), the patient was admitted to the hospital with exertional shortness of breath and TTE revealed an ejection fraction of 26% with global left ventricular dysfunction, a well-repaired mitral valve with trace MR, and an RVSP of 45 mmHg (Table 1). The patient was instructed to continue valsartan and change atenolol to carvedilol. Follow-up TTE 4 months later revealed persistent LV systolic dysfunction with an LVEF of 20% (Table 1), and spironolactone was added to her medical regimen.

Within the following year, she reported improvement in her shortness of breath and fatigue. A repeat BNP level was 38 pg/ mL. By 2 years post-mitral valve repair (12 years post-anthracycline) her LVEF improved to 45% on medical therapy (Table 1). At 3 years post-mitral valve repair (13 years post-anthracycline), her LV systolic function had normalized with an LVEF of 60% (Table 1).

#### DISCUSSION

We reported the case of an adult patient presenting with significant MR and initially preserved LVEF with normal cardiac chamber dimensions after anthracycline exposure. She developed progressive LV chamber dilation and mild reduction in systolic function, which prompted surgical correction of her MR. After surgical mitral valve repair, she developed overt LV TABLE 1.

Overview of changes to anthracycline exposure, MV repair, relevant echocardiography findings, medications, and changes to medications from June 2002 through April 2010.

	6.14.2002	6.22.2004	12.14.2006	3.22.2007	7.2.2007	4.7.2008	8.25.2008	6.1.2009	4.13.2010
Time since AC Exposure (months)	67	92	121	125	128	137	142	151	161
Time since MV repair (days)	_	_	_	_	11	291	431	711	1027
MR grade*	2+	1+	3+	3-4+	0	0-1+	2+	1+	0
LVEF	57%	50%	48%	48%	49%	26%	20%	45%	60%
LVEDD (mm)	50	52	60	52	48	53	52	42	38
LVESD (mm)	36	37	45	40	36	47	47	30	26
RVSP (mmHg)	37	37	32	43	-	45	_	42	30
Medications	atenolol 50 mg	atenolol 50 mg	atenolol 50 mg	atenolol 50 mg, valsartan 80 mg	atenolol 50 mg, valsartan 80 mg	atenolol 50 mg, valsartan 80 mg	carvedilol 25 mg BID, valsartan 80 mg	carvedilol 25 mg BlD, valsartan 80 mg spironolactone 25 mg	carvedilol 25 mg BID, valsartan 80 mg spironolactone 25 mg
Medication changes	5		added valsartan 80 mg			changed atenolol to carvedilol 25 mg BID	Added spironolactone 25 mg		

AC – anthracycline, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, LVESD – left ventricular end-systolic diameter, MR - mitral regurgitation, MV - mitral valve, RVSP - right ventricular systolic pressure.

\* MR grading: 0 - none, 1+ - mild, 2+ - moderate, 3+ - moderate to severe, 4+ - severe.

failure with severe systolic dysfunction, however, she responded well to subsequent medical therapy.

Subclinical anthracycline induced regional myocardial dysfunction may be demonstrated as abnormalities in regional myocardial contractile function (identified by LV strain imaging), often most pronounced in inferior myocardial segments, despite normal LVEF [5]. Regional subpapillary myocardial dysfunction may impair lateral shortening between the papillary muscles, which tethers the leaflet edges and impairs systolic leaflet closure, resulting in functional MR, even in the absence of LV and mitral annular dilation [6]. Therefore, functional MR may be a sign of subclinical anthracycline induced left ventricular dysfunction (i.e. abnormal myocardial contraction demonstrated by reduced LV strain despite normal LVEF). Indeed, MR occurs more often in children after anthracycline exposure compared to normal controls, and may herald the later development of overt anthracycline cardiomyopathy [3].

Anthracycline induced cardiac toxicity also increases the sensitivity of the LV to loading conditions. In particular, increased afterload may precipitate LV systolic dysfunction after anthracycline exposure [7, 8]. In turn, patients with anthracycline exposure history often have abnormal myocardial contractile reserve in response to stress, which may identify higher risk for subsequent overt LV systolic dysfunction [9]. Significant MR causes a low resistance pathway for LV systolic ejection due to the relatively lower pressure in the left atrium compared to the aorta, which reduces overall LV afterload. Due to the removal of the low resistance regurgitant lesion with surgical correction, LV afterload can increase significantly after mitral valve repair or replacement [10]. This increase in LV afterload may precipitate cardiomyopathy with reduced LVEF [11, 12], particularly in patients with poor contractile reserve such as those with anthracycline exposure history [13].

The therapeutic implications of significant MR with normal LV systolic function and dimensions after anthracycline are not clear. Given that MR may reflect subclinical myocardial dysfunction, initiation of aggressive medical therapy with selective beta--blockers and angiotensin converting enzyme inhibitors may be

© Medical Education. For private and non-commmercial use only. Downloaded from https://www.journalsmededu.pl/index.php/OncoReview/index: 19.05.2024; 00:15,05

reasonable [14]. Due to the risk of overt cardiomyopathy with reduced LVEF after surgical MR correction, optimization of medical therapy prior to intervention is likely prudent. Whether or not medical therapy can secondarily affect the course and severity of MR is unknown. Our case does, however, reinforce the value of aggressive goal directed medical therapy for heart failure, including aldosterone antagonists, in patients with anthracycline-induced cardiomyopathy.

# CONCLUSION

Significant MR may develop despite normal LV size and systolic function after anthracycline exposure in adults as well as in children as presented in this case report. This finding may be associated with subclinical anthracycline cardiotoxicity, heralding the future development of overt anthracycline cardiomyopathy. Cardiac hemodynamics associated with mitral valve repair may put these patients at higher risk for the development of postoperative LV systolic dysfunction; however, aggressive medical heart failure therapy demonstrated utility in for clinical and echocardiographic improvement in our patient.

#### Abbreviations

B-type natriuretic peptide (BNP) Cardiovascular (CV) Left atrial enlargement (LAE) Left ventricle (LV) Left ventricular end diastolic diameter (LVEDD) Left ventricular ejection fraction (LVEF) Left ventricular end systolic diameter (LVESD) Mitral regurgitation (MR) Right ventricular systolic pressure (RVSP) Transesophageal echocardiogram (TEE) Transthoracic echocardiogram (TTE).

#### References

- 1. Hoyert DL, Xu J. Deaths: preliminary data for 2011. Natl Vital Stat Rep 2012. 61(6): 1-51.
- 2. Steinherz LJ, Steinherz PG, Tan CT et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991; 266(12): 1672-7.
- 3. Allen J, Thomson JD, Lewis IJ, Gibbs II. Mitral regurgitation after anthracycline treatment for childhood malignancy. Heart 2001; 85(4): 430-2.
- 4. Friedberg MK, Solt I, Weyl-Ben-Arush M et al. Cardiac function in long-term survivors of childhood lymphoma. Cardiol Res Pract 2011; 2011: 316927.
- Toro-Salazar OH, Gillan E, O'Loughlin MT et al. Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. Circ Cardiovasc Imaging 2013; 6(6): 873-80.
- Kalra K, Wang Q, McIver BV et al. Temporal changes in interpapillary muscle dynamics as an active indicator of mitral valve and left ventricular interaction in ischemic mitral regurgitation. J Am Coll Cardiol 2014; 64(18): 1867-79.
- 7. Göldel N, Autenrieth G, Werdan K et al. [Echocardiography with angiotensin administration in the diagnosis of adriamycin-induced cardiomyopathy]. Z Kardiol 1989; 78(5): 320-7.
- 8. Silber JH. Role of afterload reduction in the prevention of late anthracycline cardiomyopathy. Pediatr Blood Cancer 2005; 44(7): 607-13.
- 9. Guimaraes-Filho F, Tan D, Braga J et al. Ventricular systolic reserve in asymptomatic children previously treated with low doses of anthracyclines. Am J Cardiol 2007; 100(8): 1303-6.
- 10. Murakami T, Nakazawa M, Nakanishi T, Momma K. End-systolic wall stress is a major determinant of postoperative left ventricular dysfunction in patients with congenital mitral regurgitation. Cardiol Young 2002; 12(3): 236-9.
- 11. Enriquez-Sarano M, Schaff HV, Orszulak TA et al. Congestive heart failure after surgical correction of mitral regurgitation. A long-term study. Circulation 1995; 92(9): 2496-503.
- 12. Enriquez-Sarano M, Tajik AJ, Schaff HV et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol 1994; 24(6): 1536-43.
- Leung DY, Griffin BP, Stewart WJ et al. Left ventricular function after valve repair for chronic mitral regurgitation: predictive value of preoperative assessment of contractile reserve by exercise echocardiography. J Am Coll Cardiol 1996; 28(5): 1198-205.
- 14. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer, 2013; 49(13): 2900-9.

**Correspondence:** 

Gregory R. Hartlage, MD 602 S Audubon, Suite B Tampa, Florida 33609 tel.: (+678) 953-0178 fax: (+813) 875-4149 e-mail: ghartlagemd@gmail.com