Case Report

Myocardial Stunning Following Combined Modality Combretastatin-Based Chemotherapy: Two Case Reports and Review of the Literature

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ABSTRACT

Myocardial stunning, known as stress cardiomyopathy, broken-heart syndrome, transient left ventricular apical ballooning, and Takotsubo cardiomyopathy, has been reported after many extracardiac stressors, but not following chemotherapy. We report 2 cases with characteristic electrocardiographic and echocardiographic features following combined modality therapy with combretastatin, a vascular-disrupting agent being studied for treatment of anaplastic thyroid cancer. In 1 patient, an ECG performed per protocol 18 hours after drug initiation showed deep, symmetric T-wave inversions in limb leads I and aVL and precordial leads V_2 through V_6. Echocardiography showed mildly reduced overall left ventricular systolic function with akinesis of the entire apex. The patient had mild elevations of troponin I. Coronary angiography revealed no epicardial coronary artery disease. The electrocardiographic and echocardiographic abnormalities resolved after several weeks. The patient remains stable from a cardiovascular standpoint and has not had a recurrence during follow-up. An electrocardiogram performed per protocol in a second patient showed deep, symmetric T-wave inversions throughout the precordial leads and a prolonged QT interval. Echocardiography showed mildly reduced left ventricular function with hypokinesis of the apical-septal wall. Acute coronary syndrome was ruled out, and both the electrocardiographic and echocardiographic changes resolved at follow-up. Although the patient remained pain-free without recurrence of anginal symptoms during long-term follow-up, the patient developed progressive malignancy and died.

Introduction

Myocardial stunning, known as stress cardiomyopathy, broken heart syndrome, left ventricular apical ballooning, and Takotsubo cardiomyopathy is defined as: left ventricular apical ballooning on echocardiography or ventriculography; no angiographic stenoses > 50%; and no history of known cardiomyopathy. While the patient in the first of our 2 case reports fulfills these criteria, the second patient had a positive stress test following the incident but did not undergo coronary angiography, so ischemic heart disease was not excluded.

Combretastatin may precipitate acute coronary syndrome.[1] A 57-year-old male with pancreatic cancer developed chest pain 80 minutes after combretastatin, and ECG showed acute myocardial infarction. Coronary angiography demonstrated an occluded distal left anterior descending artery. A 77-year-old male developed ECG changes and elevated troponin I following combretastatin. Coronary angiography revealed 2-vessel coronary artery disease.

Although cardiovascular toxicities following combretastatin are known, the findings of regional wall-motion abnormalities, cardiac biomarker elevations, and angiographically-normal coronaries in 2 of our patients suggests a new toxicity for combretastatin.

Case Reports

Patient 1

A 71-year-old postmenopausal female with hypertension and anaplastic thyroid carcinoma was referred for combretastatin therapy. Baseline ECG showed normal sinus rhythm (NSR) and inferior Q-waves. Gated blood pool (MUGA) scan showed an ejection fraction (EF) of 74%. A pharmacologic nuclear stress test showed an EF > 65% without scar or ischemia. She received doxorubicin and cisplatin followed by external-beam radiation therapy for 5 days.

The patient received combretastatin (45 mg/m^2) on the sixth day, after which she had nausea and emesis. Routine ECG (Figure 1) performed per protocol 18 hours later

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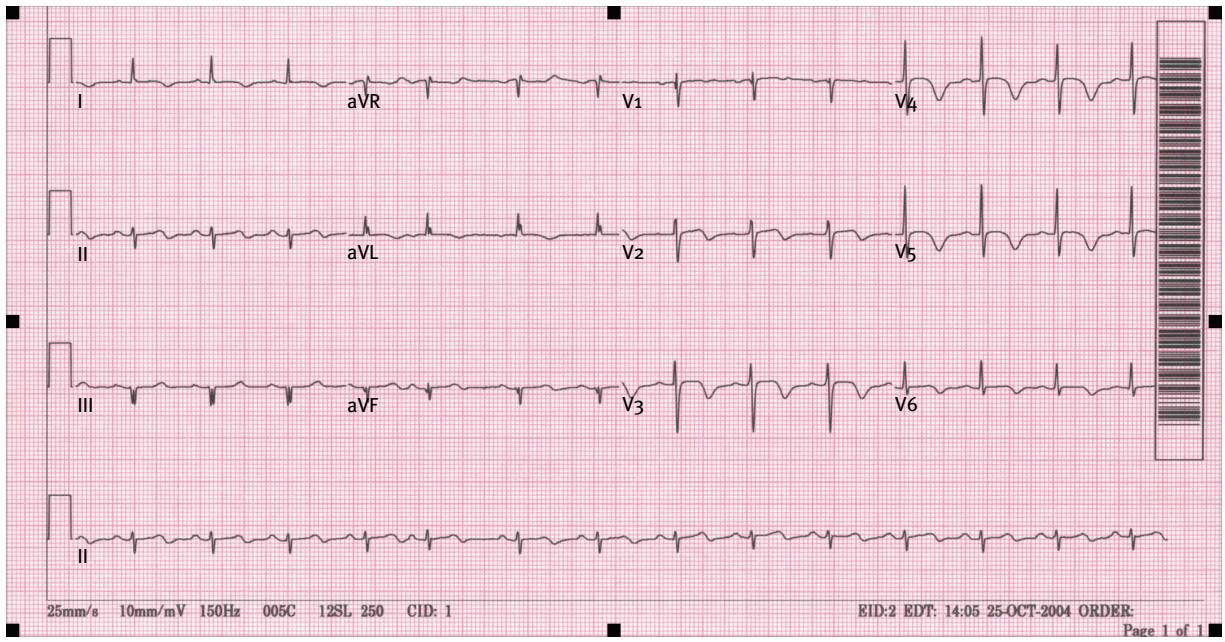

Figure 1. ECG performed 18 hours following administration of combretastatin. Note the deep, symmetric T-wave inversions in leads I, aVL, and V_2 through V_6, new compared to her baseline ECG, consistent with acute anterolateral ischemia. Also note the significantly prolonged QTc of 533 ms, which peaked at 571 ms approximately 6 hours later.

showed inverted T-waves in I, aVL, and V_2 through V_6 consistent with anterolateral ischemia. Cardiac biomarkers showed equivocal troponin I, peaking at 0.85 ng/mL (negative < 0.15, positive > 1.50) 32 hours after study drug was administered and 14 hours after initial ECG changes. Echocardiography showed an EF of 40% to 50% with apical akinesis (Figure 2A,B). Coronary angiography showed no flow-limiting stenoses. Follow-up echocardiography (Figure 2C,D) 1 month later showed an EF of 55% to 65% with improvement in the periapical akinesis. Cardiac magnetic resonance imaging showed normal left ventricular systolic function and normal gadolinium contrast uptake.

Patient 2

A 78-year-old postmenopausal female with hypertension, dyslipidemia, essential thrombocytosis, and anaplastic thyroid carcinoma was referred for therapy with combretastatin. Baseline ECG showed NSR. Gated blood pool scan revealed an EF of 63% without wall-motion abnormalities. She received doxorubicin and cisplatin and daily hyperfractionated external-beam radiation therapy followed by combretastatin. She complained of nausea and vomiting followed by left breast pressure. ECG showed NSR and deep, symmetric T-wave inversions in multiple precordial leads. Echocardiography revealed an EF of 50% to 55% with apical septal hypokinesis. She remained asymptomatic without evidence of infarction.

Repeat ECG, 4 weeks later, showed resolution of the T-wave changes. Echocardiography showed improvement in EF of 60% to 65% with resolution of wall-motion abnormalities. A pharmacologic nuclear stress test showed mild anterolateral and anteroseptal ischemia. She deferred coronary angiography and additional chemotherapy. She developed progressive malignancy and died.

Precipitating Factors and Clinical Features

One series reported acute emotional stress preceding all cases, with more than half following news of an unexpected death.[2] Myocardial stunning is reported following subarachnoid hemorrhage.[3] A total of 95% of cases in 1 series occurred in women.[2] Another series following subarachnoid hemorrhage found that all women were postmenopausal.[3] Patients present within 1 to 5 hours with chest pain or dyspnea.[2,4] Some develop pulmonary edema and cardiogenic shock.[2] A total of 9% were complicated by ventricular fibrillation.[5]

Laboratory Features

Electrocardiography shows ST-segment changes and inverted T-waves. QTc prolongation occurred in 26% of patients in 1 series, with a mean QTc of 542 ms.[2] A total of 11% had inverted anterior precordial T-waves.[2] ST-segment elevation with Q-waves occurred in 37% of cases.[2] ECG changes resolve slowly (average of 119 d, range, 43–400 d).[2] While resolution of Q-waves and QTc interval prolongation occurs

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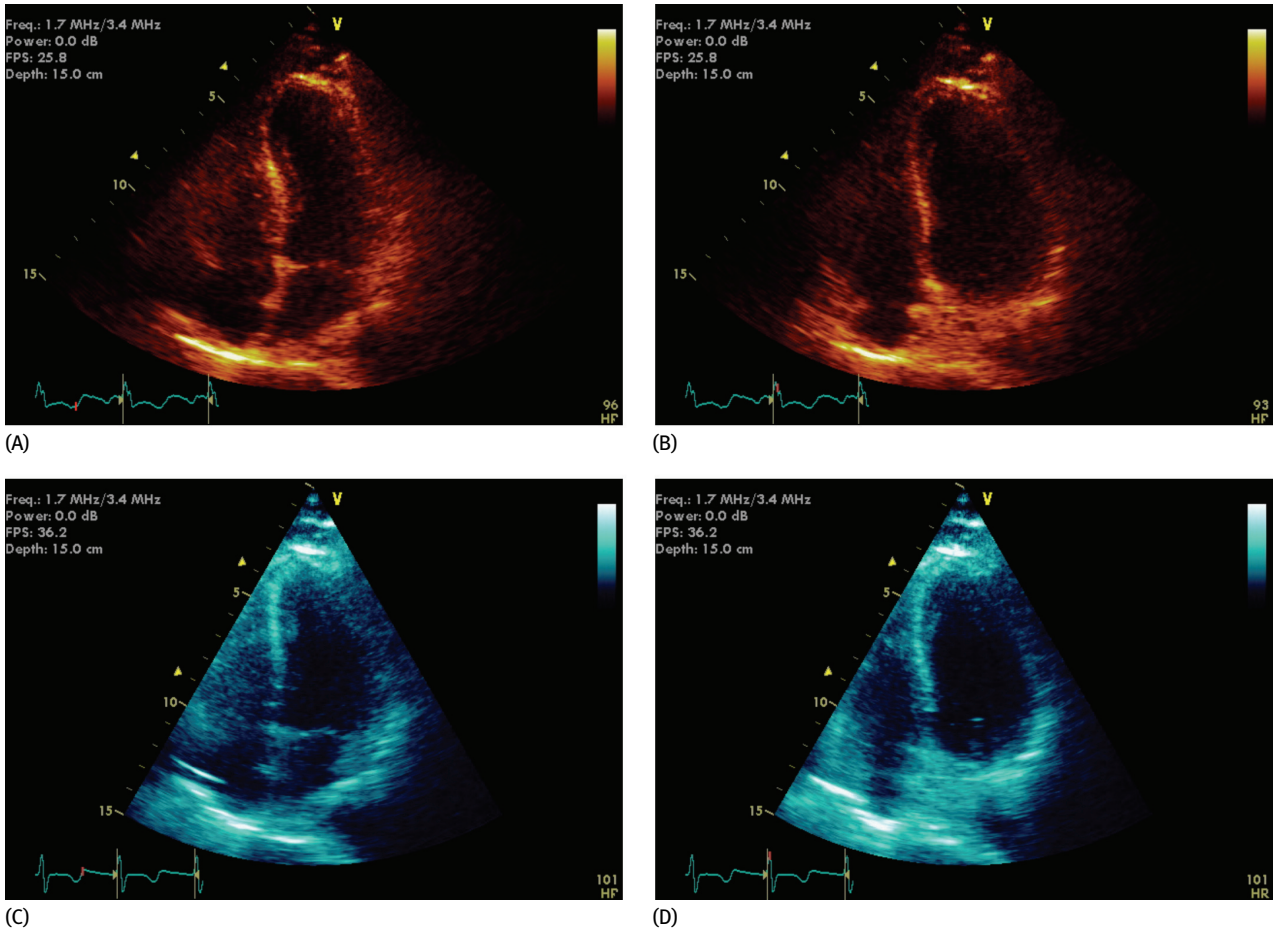

Figure 2. Echocardiography at end-systole (A) and end-diastole (B) 1 day following combretastatin administration. Note the periapical thinning suggestive of aneurysm formation. Follow-up echocardiography at end-systole (C) and end-diastole (D) performed 3 weeks following initial echocardiogram was remarkable for significantly improved LVEF and periapical wall-motion abnormality seen earlier.

within days, T-wave changes resolve slowly and sometimes, only partially.[2]

Cardiac biomarkers show mild troponin I elevations (mean of 0.18 ng/mL, normal < 0.06 ng/mL).[2] Wittstein et al found elevated serum catecholamines during the acute episode. Brain natriuretic peptide levels in myocardial stunning patients decreased significantly by days 7 to 9. Elevated neuropeptide Y, stored with catecholamines in postganglionic sympathetic nerves, has been reported.[2]

Echocardiography shows preserved basal left ventricular (LV) function with mid-LV dysfunction and apical akinesis and dyskinesis.[2] Whereas electrocardiographic changes resolve in weeks or months, echocardiographic changes resolve within 1 week.[4] Cardiac magnetic resonance imaging demonstrates no contrast hyper-enhancement and is consistent with viable myocardium in the affected areas.[2] Although coronary angiography is normal, LV end-diastolic pressure can be elevated.[2] A total of 18% of patients in 1 series had an intracavitary pressure gradient similar to that in LV outflow tract obstruction.[5]

Pathophysiology

Cultured cardiomyocytes exposed to norepinephrine show increased cyclic adenosine monophosphate (AMP)-mediated calcium overload via verapamil-sensitive calcium channels leading to creatine kinase release and decreased metabolism and viability.[6] Increased catecholamines causes contraction-band necrosis, characterized by monocyte infiltration,[2] which is seen also in other high catecholamine states such as pheochromocytoma and subarachnoid hemorrhage.[2] The cardiac apex is more responsive to catecholamines, which may explain the regional myocardial dysfunction. Compared to men, women with acute stress, subarachnoid hemorrhage, and neurologic injuries show

higher circulating catecholamines, explaining the female preponderance of myocardial stunning.

Microvascular spasm is likely.[5] Iodine-123 metaiodobenzylguanide scanning during myocardial stunning demonstrated decreased coronary flow reserve,[2] consistent with abnormal thrombolysis in myocardial infarction (TIMI) frame counts on coronary angiography[4] and decreased coronary flow reserve measured by intracoronary Doppler.[7] Catecholamine-induced diffuse coronary microvascular spasm remains an intriguing hypothesis.

Combretastatin induces cytoskeletal changes in endothelial cells, increases vascular permeability, and inhibits blood flow.[8] Some patients receiving combretastatin complain of chest pain within 6 hours, which resolves in 1 day.[9] Combretastatin causes endothelial cell apoptosis.[10] Positron emission tomography (PET) demonstrated decreased cardiac output, attributable to increased peripheral vascular resistance induced by combretastatin and not to myocardial toxicity.[11] Combretastatin induces apoptosis of human proliferating endothelial cells and umbilical vein endothelial cells[12] and disrupts endothelial networks formed in type I collagen.[13] Positron emission tomography demonstrated decreased blood flow to spleen and kidney.[14] Combretastatin enhances endothelial toxicity, which may be enhanced further by cisplatin, another known endothelial-damaging agent. Combretastatin may increase myocardial radiosensitivity.

Combretastatin and its effect on myocardial function differs from doxorubicin (adriamycin), which is related commonly to myocardial damage. Doxorubicin's effects on cardiomyocytes include: formation of reactive oxygen species, apoptosis, inhibition of gene expression necessary for cardiomyocyte survival, and changes in molecular signaling.[15] Doxorubicin cardiotoxicity is worse when given concomitantly with paclitaxel.[16] Studies on its exact cardiotoxicity mechanism suggest that calcium blockers and vitamins A and E may reduce and/or prevent doxorubicin toxicity.[17]

Treatment and Prognosis

For myocardial stunning, β-blockers and verapamil may be beneficial. The benefit of calcium-channel blockers is supported by the role of diffuse coronary microvascular spasm. The deleterious effects of elevated catecholamines suggest that vasopressors and inotropes may be harmful. Wittstein et al suggest a benefit of intra-aortic balloon counterpulsation in myocardial stunning complicated by cardiogenic shock, secondary most likely to decreasing afterload during intense vasoconstriction.[2] While half of cases were complicated by heart failure and/or cardiogenic shock, 1 case series identified only 1 recurrence at 8 months.[4] A 4-year follow-up in another series identified no recurrences or deaths.[2] In a larger series, 2 out of 44 patients had a recurrence at a mean follow-up of 13 months.[5]

Conclusion

Our patients are unique for several reasons. First, their syndromes were not preceded by the acute emotional stressors that usually precede myocardial stunning. Second, after developing ECG and echocardiographic abnormalities, both patients remained asymptomatic. Although their symptoms may represent atypical angina in elderly women—a group at risk of presenting with atypical symptoms during an acute coronary syndrome—it is unclear whether their symptoms were related to the cardiac syndrome. Third, despite decreased LV systolic function and significant wall-motion abnormalities, both patients remained stable and uncomplicated. Our report raises the possibility of another cause of myocardial stunning, a well-described and increasingly recognized syndrome. Combretastatin, as part of combined-modality adjuvant therapy, and the possibility of associated myocardial dysfunction should be explored further. All patients who develop cardiac events following combretastatin should be followed closely, as these patients frequently are elderly with multiple cardiovascular risk factors and are at risk for future cardiovascular events.

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