Clinical case report based study

Reversible myocardial dysfunction following intraocular bevacizumab administration

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ABSTRACT

Heart failure has been reported as a rare side effect of bevacizumab, a chemotherapeutic agent, used in the treatment of breast cancer. However, reversible left ventricular systolic dysfunction with a pattern similar to stress-induced cardiomyopathy has not been reported. The etiopathogenesis of stress-induced cardiomyopathy is poorly understood. Given this uncertainty, we should always look out for other potential offenders causing similar presentation, rather than label all of them as “stress-induced”.

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1. Introduction

Stress-induced cardiomyopathy is a relatively new disease entity, with increasing incidence. Since its classic description as “apical ballooning” in the early 1990s, a few variations in the appearance have also been linked to the same disease process. Despite numerous case reports and series reported in the literature, the precise etiology and pathophysiology of this disease are still poorly understood. We present an atypical case of “stress-induced cardiomyopathy” following intraocular administration of bevacizumab (Avastin), a humanized monoclonal antibody against vascular endothelial growth factor A.

2. Case report

A 64-year-old white woman was being treated for macular degeneration with intraocular injections of bevacizumab (Avastin). On the day prior to admission, she received an intraocular injection and later developed chest pain. The chest pain waxed and waned and was associated with nausea and vomiting. She denied shortness of breath or diaphoresis. She presented to an outside emergency room for evaluation and was found on electrocardiogram (ECG) to have subtle ST-segment elevation in leads V2 and V3 with associated biphasic T-waves [Fig. 1]. She was initially treated with 324 mg of aspirin, metoprolol and IV morphine with resolution of her pain. Initial laboratory work showed a normal basic metabolic panel, but an elevated troponin I of 1.08 ng/ml. A diagnosis of acute

coronary syndrome was made and she was started on anti-coagulation with intravenous heparin. She was subsequently transferred to our facility for further management.

She had a past medical history of senile macular degeneration leading to posterior vitreous hemorrhage and a remote history of Lyme disease. She denied any history of diabetes or vascular disease. She is an ex-smoker, who quit smoking about 35 years ago, drinks alcohol in moderation and did not have a significant family history of premature coronary artery disease. She denied any acute psychosocial stressors.

On admission to our hospital she was chest pain free. She was afebrile, blood pressure was 128/78 mm Hg, pulse rate 70 bpm, respiratory rate 18/min and O₂ saturations were 96% on room air. On examination, she was comfortable at rest without respiratory distress. There was no jugular venous distension. Lungs were clear to auscultation. Cardiovascular examination revealed a normal first and second heart sound without any significant third or fourth sounds. There were no significant murmurs noted. Abdominal examination did not reveal organomegaly. She had no peripheral edema and her pedal pulses were palpable.

Her laboratory data was as follows: Hb% 13.6, WBC 5.3, platelet count 163, Na⁺ 138, K⁺ 4.7, BUN and creatinine 13 and 0.7, respectively, total cholesterol 173, HDL 63, LDL 85, total CK 162, with an MB fraction of 13.2 and a troponin T of 0.24 ng/ml. An admission ECG showed normal sinus rhythm with biphasic T-waves anteriorly and T-wave inversions in the lateral leads [Fig. 1].

Given the chest pain, positive biomarkers, and ECG changes, a cardiac catheterization was performed. Coronary angiography demonstrated a right dominant system with angiographically normal appearing epicardial coronary arteries. Left

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Fig. 1. ECG at presentation.

ventriculography demonstrated mildly depressed left ventricular systolic function and overall ejection fraction of 40%. There was akinesis of the mid-anterior and mid-inferior walls with sparing of the basal and apical segments [Figs. 2 and 3]. These regional wall motion abnormalities could not be explained by ischemia or infarction in any particular anatomical arterial distribution.

She was admitted to the telemetry floor for observation and remained stable without further chest pain or shortness of breath. Overnight telemetry monitoring did not reveal any evidence of significant arrhythmias. Guideline-based therapy for nonischemic cardiomyopathy was initiated and included metoprolol, lisinopril and low-dose aspirin. She was subsequently discharged home on hospital day 3 in a stable condition. A follow-up echocardiogram performed 2 months later demonstrated normalization of her left ventricular systolic function and wall motion [Fig. 4].

3. Discussion

Stress-induced cardiomyopathy (Takotsubo's cardiomyopathy or apical ballooning syndrome) is a growing problem. Since its first

description in Japan in 1991, the incidence has increased significantly. The hallmark of this disorder is left ventricular dysfunction including akinesis of the mid to distal anterior and inferior walls as well as the apex of the left ventricle but basilar sparing. However, the pathophysiology and the precipitating factors are still poorly understood. The most commonly accepted mechanism is catecholamine excess due to a variety of conditions including medical, psychological and social stressors.¹ Studies on canine hearts and human models of heart failure induced by catecholamine infusions have suggested an excess distribution of beta-adrenergic receptors in the apical regions of the left ventricle. This probably explains the vulnerability of these regions to catecholamine toxicity.² Although this sounds like a plausible explanation for the "typical" pattern of LV regional wall motion abnormality noted in most of these patients, this does not explain the "atypical", mid-cavity variant of this condition which spares both the apex and the base of the left ventricle.

There have been reports of patients who present with this condition, without a history of stress prior to presentation,

Fig. 2. Endsystolic frame of left ventriculogram.

Fig. 3. Enddiastolic frame of left ventriculogram.

Fig. 4. Repeat echocardiogram showing normal LV systolic function.

questioning the well-accepted theory of stress-induced catecholamine excess and resultant toxicity. There have also been studies that failed to demonstrate high serum levels of catecholamines in patients presenting with this disorder.³ Stress due to physical or mental illness is hard to quantify, making it almost impossible to draw an association between the “degree of stress” and this complication. Likewise, attributing all these cases purely to stress is also probably a premature conclusion and further potential offenders should be sought.

Heart failure is a well-known adverse effect of bevacizumab therapy, with a reported 5-fold increase in risk compared to placebo.⁴ Typically this complication has been observed in patients treated with intravenous bevacizumab for breast cancer. The complication of heart failure does not appear to be dose-dependent.⁴ On the other hand, intraocular injection of low-dose bevacizumab is considered as a safe and effective treatment for neovascular age-related macular degeneration.^{5,6} Observational studies have reported no significant short-term side effects and few

long-term cardiovascular side effects.^{6–8} To our knowledge, there have been no reports of acute cardiac complications with bevacizumab treatment. Our patient was under stress for many days due to her visual impairment, but there was no history of an acute stressor event that typically precedes the presentation of Takotsubo’s cardiomyopathy. It is unlikely that her presentation was due to coronary spasm or clot, as the wall motion abnormality was not confined to a particular arterial distribution. Although no causal relationship can be proved, this is the first report of an association between intraocular Avastin administration and “stress-induced cardiomyopathy”.

Conflicts of interest

All authors have none to declare.

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