Takotsubo Cardiomyopathy: Pathologic Insights from a Fatal Case
R Hudacko, B Fyfe, A Mehra, A Moreyra

Citation

Abstract
Takotsubo cardiomyopathy is a rare disease that mimics the presentation of acute coronary syndrome. A fatal case with unique findings of global subendocardial ischemia as well as histologic evidence of microvascular and intramyocardial C4d deposition on endomyocardial biopsy and at autopsy is herein presented.

INTRODUCTION
Takotsubo cardiomyopathy (TCM), transient left ventricular apical ballooning syndrome, broken heart syndrome, and stress cardiomyopathy are synonyms for the same clinical syndrome - a cardiomyopathy with the characteristic finding of transient left ventricular wall motion abnormalities involving the apex and mid-wall with basal sparing in the absence of critical coronary artery stenosis. The classical clinical presentation mimics acute coronary syndrome and usually follows a physically/emotionally stressful situation which is believed to lead to inappropriate catecholamine surge. Left ventricular function usually improves in days to weeks from the time of presentation. The reported incidence is 0.7-2.5% of patients presenting as acute coronary syndrome. It is most frequently seen in women (90%) with a range of 62-76 years of age. The most common symptoms are chest pain and dyspnea. The electrocardiogram (EKG) shows ST-segment elevation and T-wave inversion, mostly in the precordial leads. The prognosis is usually excellent, recurrence rate is less than 10%, and the treatment is supportive care.

Prior pathologic studies have reported non-specific findings (interstitial fibrosis and inflammation) in 21 endomyocardial biopsies. Only one case report described myocyte necrosis with contraction bands. We report a fatal case with pre- and post-mortem features consistent with catecholamine-induced myocyte injury and suggest that immunohistochemical staining for C4d may be an important investigational tool in this situation.

CASE REPORT
A 30 year-old-woman with bipolar disorder treated with quetiapine and lamotrigine and mild intermittent asthma, called emergency medical services for dyspnea and was found unresponsive in ventricular fibrillation. She was defibrillated to normal sinus rhythm and intubated. Her anoxic time was estimated at 25 minutes. After initial defibrillation, EKG showed a junctional rhythm with prolonged QT interval (495 ms) (Figure 1).

Figure 1
Figure 1. Electrocardiogram at presentation (post-defibrillation) showing an accelerated junctional rhythm, a prolonged corrected QT interval of 495 ms, and nonspecific ST/T changes.

Subsequent EKG showed normal sinus rhythm with no evidence of ischemia. A CT scan of the head was normal. An initial echocardiogram showed normal left ventricular function. She was transferred to the critical care unit for further management.

One day after admission she became hemodynamically...
unstable and was started on pressors. A repeat EKG showed diffuse ST segment elevations (Figure 2).

**Figure 2**
Figure 2: Electrocardiogram showing sinus tachycardia with diffuse ST changes.

Cardiac enzymes peaked at creatine kinase (CK) of 16,991 U/L (25-210), CK-MB fraction of 134.4 ng/mL (0-6.3), and troponin-I of 10.92 ng/mL (0-0.5). The initial spill of cardiac enzymes was thought to be secondary to cardiopulmonary resuscitation. A repeat echocardiogram showed reduced left ventricular function with severe anterior wall hypokinesis.

The patient was taken emergently to the cardiac catheterization laboratory for coronary angiography and possible intervention. She had normal coronary arteries with no presence of obstructive disease. The left ventriculogram revealed an akinetic anterior wall, apex, and distal inferior wall with a normally contracting basal region. The calculated ejection fraction was 21%, and the patient was rendered a diagnosis of TCM.

On hospital day 3, cardiac magnetic resonance imaging was performed which showed no evidence of myocardial infarction or myocarditis. An endomyocardial biopsy showed non-specific changes including myocyte necrosis with contraction bands, perivascular edema, and microvascular endothelial swelling with no evidence of myocarditis. Immunohistochemical staining for C4d was strongly positive along the microvasculature and in rare individual myocytes with contraction band injury (Figure 3).

**Figure 3**
Figure 3: 20X. Positive C4d staining (brown) in microvasculature (top) and in rare necrotic myocytes

On hospital day 4, the patient showed significant improvement in hemodynamics and was taken off all pressors. Another echocardiogram was performed which showed marked improvement in left ventricular function with an estimated ejection fraction of 45-50%. Although the patient’s cardiac function seemed to revert back to normal, her overall recovery was poor. Her neurologic function never improved due to the anoxic insult, and she died on day 13 of hospitalization.

**PATHOLOGICAL FINDINGS**
A full autopsy was performed. The heart weighed 390 grams (normal female 200-280), and the circumference of the valves and width of the ventricular walls were within normal limits. The foramen ovale was patent, and there was bulging of the intra-atrial septum into the left atrium. The right ventricular wall was thin. The cut surfaces of the papillary muscles were mottled. The coronary arteries were patent and without atherosclerotic changes. The left anterior descending and right coronary arteries demonstrated short and shallow myocardial bridging in the proximal portion of the vessels. Viral cultures of myocardial tissue were negative. Two cross-sections of mid-ventricular myocardium were incubated in triphenyl tetrazolium chloride (TTC), and there was a global lack of staining in the subendocardial region (Figure 4).
On histologic examination, global subendocardial coagulative myocyte necrosis was present, corresponding to the areas that failed to stain with TTC (Figure 5).

There was also patchy contraction band injury with interstitial hemorrhage along the periphery of the area of myocyte necrosis. The areas surrounding the ischemic changes were infiltrated by macrophages, and there were scattered foci of mild interstitial fibrosis. The conduction system and the coronary arteries were unremarkable. C4d staining showed strong positivity in the areas of necrotic myocytes and in individually necrotic myocytes away from large areas of necrosis (Figure 6).

There were scattered foci of strong capillary staining and moderate intimal positivity in larger vessels. Other significant autopsy findings included acute tubular necrosis, hepatosplenomegaly with congestion, patchy organizing pneumonia, and diffuse mild to moderate hypoxic changes in the cerebrum, cerebellum, and brainstem.

**DISCUSSION**

Although the clinical features of TCM have been extensively documented in multiple studies, the pathological correlates have not been identified because endomyocardial biopsy is not required to render the diagnosis, and the majority of patients recover completely. In a study by Akashi, et al that identified 7 patients with TCM of which 5 had undergone biopsies, the pathological findings included myocardium with fatty infiltration in 1 patient, mild interstitial fibrosis in 1 patient, and small numbers of mononuclear cells in the interstitium suggestive of chronic myocarditis in 2 patients. The last patient’s biopsy showed only adipose tissue. Another study, which obtained biopsies in 6 patients, reported that 100% of the biopsies showed interstitial fibrosis, 50% showed myocyte hypertrophy, and 50% contained small amounts of cell infiltration without significant inflammatory infiltrate or necrosis. The third clinical study only reported negative biopsy results.

A recent case report discusses the pathological findings in a patient diagnosed with inverted TCM, a stress-related syndrome with inverted echocardiographic findings, i.e. left ventricular akinesis except at the apex. Histologic
examination showed foci of myocyte necrosis with contraction bands without evidence of fibrosis or inflammation, which is the characteristic histologic feature of catecholamine-induced cardiovascular injury as described in an experimental rat model for TCM.9

Theories of the etiology of TCM include myocarditis, coronary vasospasm, microvascular injury, direct myocyte injury by catecholamines, and excessive activation of cardiac catecholamine receptors. The results from all 3 clinical studies4,5,6 indicate that the most likely pathogenesis of this entity is high plasma catecholamine concentration and/or hyperactive cardiac catecholamine receptors.

The deposition of C4d, an inactive split product of C3 convertase in the complement cascade, indicates recent complement activation through the classical pathway. Immunohistochemical staining for C4d is used as one of the criteria for antibody-mediated cardiac transplant rejection and was found to correlate well with anti-donor serum alloantibodies.10 C4d deposition was also reported in some cases to occur by complement fixation through the innate immune system.11 Complement is known to be involved in exacerbation of myocarditis, as a mediator of ischemic injury in myocardial infarction and in reperfusion injury,12 and as a possible contributor to the progression of dilated cardiomyopathy.13 C4d has also been shown to stain necrotic myocytes after myocardial infarction.14,15

Interestingly, in our case, there was very strong C4d staining along the microvasculature and in the rare myocytes with contraction band injury in the original endomyocardial biopsy. The presence of C4d within the vessels suggests that there was recent activation of the complement cascade which is likely secondary to subendocardial ischemia due to catecholamine surge. At autopsy, strong C4d staining was still present in scattered foci within the microvasculature. In addition, the large areas of necrotic myocardium and individually necrotic myocytes with contraction band injury also exhibited strong positivity. The pathological findings in this case support microvascular injury and most likely catecholamine-induced injury as factors in the pathogenesis of TCM as demonstrated by the results of the C4d staining.

To further support our evidence of C4d positivity in cases of microvascular injury, we examined C4d staining in an autopsy case with definite catecholamine-induced injury caused by excessive pressor use in a patient with hypotensive shock. The sections of myocardium showed global subendocardial ischemia with diffuse C4d positivity along the microvasculature and in necrotic myocytes (Figure 7).

Figure 7
Figure 7: 4X. C4d positivity (brown) along microvasculature and in necrotic myocytes from a case with definite catecholamine-induced myocardial injury.

Not only is C4d a marker for antibody-mediated transplant rejection, our findings implicate C4d as a robust marker for myocardial necrosis as well. Additionally, our findings indicate that global subendocardial ischemia may follow severe cases of TCM, and C4d staining of a right ventricular endomyocardial biopsy may be used as a diagnostic tool to better predict the presence of injury elsewhere.

References
Author Information

Rachel M Hudacko, MD
Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School

Billie S Fyfe, MD
Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School

Aditya Mehra, MD
Department of Medicine, Division of Cardiovascular Diseases and Hypertension, Robert Wood Johnson Medical School

Abel E Moreyra, MD
Department of Medicine, Division of Cardiovascular Diseases and Hypertension, Robert Wood Johnson Medical School