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Takotsubo Syndrome Associated with Benzodiazepine Withdrawal: A Case Report

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Abstract Since the 1960s, benzodiazepines have been a clinical mainstay, utilized for sedation, anxiety, and withdrawal states. Between 1996 and 2013 alone, benzodiazepine prescriptions increased annually by 2.5%. Rather than risk symptoms of withdrawal such as muscle pain and severe cardiomyopathy, patients must be properly informed about how to taper their medications. A 75-year-old female with a history of anxiety, hypertension, lupus, and degenerative disc disease presented with palpitations, mid-sternal chest pain, diaphoresis, and progressive shortness of breath. The patient was found to have elevated troponins (peak troponin of 1.45) and EKG showed sinus rhythm and ST segment abnormalities. The patient stated that her chest pain started 24 hours ago, 48 hours after she had stopped taking lorazepam which she had been taking for the past 50 years for anxiety. Her PCP gave her a plan to taper down the dose of lorazepam safely, but the patient opted to stop "cold turkey." Due to the patient's typical chest pain and elevating troponin level, ACS protocol was initiated. Initial echocardiogram showed an ejection fraction of 35-40% with hypokinesis of the anterioseptal wall with impaired left ventricular diastolic filling. The cardiology team performed a catheterization which showed minimal coronary artery disease and no significant stenosis in the left anterior descending artery. Within the next few days, the patient's chest pain resolved and her troponins were negative. The medical team concluded that the physical stress from withdrawing from benzodiazepine caused the patient to go into Takotsubo Cardiomyopathy. This case illustrates the risks involved with benzodiazepine in an era of polypharmacy. More importantly, this case illustrates the strong need to taper benzodiazepines properly. Because this patient had taken a benzodiazepine for 50 years, the tapering should have been as slow as possible. The result was Takotsubo cardiomyopathy.

Keywords: *cardiomyopathy, takotusubo, benzodiazepine withdrawal, polypharmacy abuse*

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1. Introduction

As first described in Japan in 1990, Takotsubo syndrome (TTS) is a transient systolic dysfunction with a peculiar wall motion abnormality of the left ventricle without any evidence of obstructive coronary artery disease or plaque rupture, usually brought about by an intense physical or emotional event. [1] The condition is more prominent in post-menopausal women with a pre-existing neurological or psychiatric disorder. [2] While several physical and emotional stressors have been associated with TTS, [1] there has only been rare reports of TTS associated with medication withdrawal. [3,4] We present a rare case of TTS associated with benzodiazepine withdrawal in an elderly woman.

2. Clinical Presentation

We present a 75-year-old female with a history of anxiety, hypertension, systemic lupus erythematosus, degenerative disc disease, and chronic kidney disease stage 2 who came to the emergency department complaining of palpitations, tremor, chest pain, and severe anxiety. According to the patient, she had been taking Lorazepam 0.5mg thrice daily for the past 50 years and had stopped taking lorazepam three days prior, in order to start hydrocodone for chronic knee pain. Her primary care physician (PCP) informed her he would not simultaneously prescribe both an opiate and benzodiazepine. Rather than tapering her dosage as advised by her PCP, the patient stopped it abruptly. Apart from her elevated blood pressure of 163/79, other vital signs and physical

examination were unremarkable Upon admission, the patient was found to have elevated troponins (highest level 1.45), and electrocardiogram (EKG) showed sinus rhythm with left axis deviation. Her initial echocardiogram revealed an ejection fraction of 35% to 40% with severe hypokinetic mid and distal anterior, anteroseptal and anterolateral walls. There was also moderate to severe apical wall hypokinesis. Per acute coronary syndrome (ACS) protocol, aspirin, beta blocker, statin, enoxaparin, and clopidogrel were started. Patient's chest pain and palpitations resolved. Cardiac catheterization the following day showed minimal coronary artery disease (CAD) (Figure 1) and apical hypokinesis on left ventriculography. Based on patient's significant troponin elevation, no significant stenosis on angiogram, and regional wall motion abnormality on left ventriculography we made a diagnosis of TTS. In the absence of any other trigger for her TTS, we concluded that it was precipitated by her benzodiazepine withdrawal. Patient was discharged on beta-blocker and angiotensin converting enzyme inhibitor (ACEi) for her TTS and aspirin and statin for her mild CAD. Three months later a repeat echocardiogram showed a normal ejection fraction with no wall motion abnormalities.

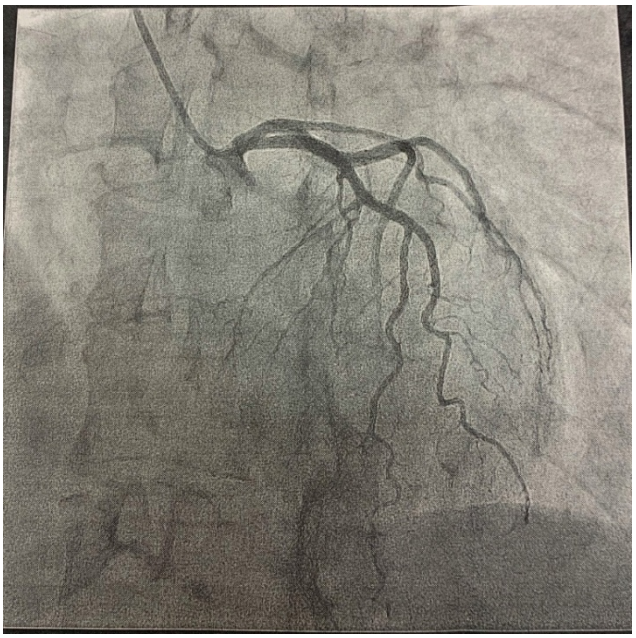

Figure 1. Angiogram showing minimal coronary artery disease

3. Discussion

TTS is a temporary left ventricular wall motion abnormality with clinical presentation that is often indistinguishable from ACS. Patient typically present with acute chest pain and/or dyspnea, as well as elevated cardiac biomarkers and EKG changes suggestive of ACS. However, in contrast to ACS, patients with TTS typically present with normal or non-obstructive coronary arteries at angiography and wall motion abnormality on echocardiogram or left ventriculography as was seen in our patient. [5] Coronary angiography with left ventriculography remains the gold standard diagnostic tool to confirm TTS, [1] and four variants of TTS have been recognized base on regional wall motion abnormalities. [6] While most TTS show apical ballooning (typical TTS form), other atypical TTS wall motion abnormalities including (1) midventricular, (2) basal, and (3) focal, wall motion abnormalities have been recognized. [6]

Although the precise pathophysiology of TTS is incompletely understood, considerable evidence from clinical studies supports the hypothesis that sympathetic stimulation with excess catecholamine concentration is central to the pathogenesis of TTS. [1,7] For our patient, we propose that an increase in catecholamines during her benzodiazepine withdrawal was the trigger for her TTS, although we did not measure circulating catecholamine level during her TTS.

3.1. Epidemiology

TTS has been increasingly diagnosed in almost all countries of the world. [1] Approximately, one to two percent of all patients presenting to hospitals with suspected acute coronary syndrome have been found to have TTS. [8,9] If considering only female patients, up to 10% of female patients presenting to hospitals with suspected acute coronary syndrome have TTS. [10] TTS predominantly affects post-menopausal women, although it affects men and have also been reported in children. [11,12] Women older than 55 years old have five times higher odds for developing TTS when compared with women younger than 55 years old and ten times higher odds than men. [10] TTS has been reported in different races but appears to be uncommon in African Americans and Hispanics. [1]

3.2. Triggers

The distinctive feature of TTS is its association with a preceding stressful physical or emotional event, although about one third of patients present without evidence of an identifiable preceding stressful event. [2] Initially, most reported triggers were emotional stressors such as grief, fear, anxiety, etc. but physical stressors such as stroke, pregnancy, etc. are now commonly reported. [2] While most emotional stressors preceding TTS were negative stressors such as grief which made TTS to be nickname "broken heart syndrome", positive emotional events that evoke joy and excitement have also been reported to provoke TTS and this entity have been described as "happy heart syndrome". [13] Interestingly, emotional stressors are more commonly reported in females, and physical stressors are more commonly reported in males. [2] TTS have also been reported with cocaine and alcohol use. [1]

3.3. Prognosis and Treatment

TTS was initially regarded as a benign disease, but recent studies have shown that TTS may be associated with severe clinical complications including death that are comparable to ACS patients. [2,14] Though TTS is a reversible condition, serious adverse in-hospital events occur in about one-fifth of TTS patients which necessitates close monitoring and early intervention in TTS patients. [2,14] There are no TTS treatment

guidelines based on prospective randomized clinical trials and therefore current treatment strategies are based on clinical experience and expert consensus. [14] The use of ACEi or angiotensin receptor blockers (ARBs) have been associated with lower incidence of TTS recurrence and improved survival at one year follow-up. Conversely, beta blockers have not shown any survival benefit in TTS patients and one third of patients who experienced TTS recurrence were on beta-blockers. [2,14] However, use of beta-blockers may be justifiable in the presence of elevated catecholamine levels in TTS, but its benefit is not yet supported by clinical trials. [14] The use of aspirin and statin is appropriate in the presence of concomitant coronary atherosclerosis, [14] as was the case with our patient.

In summary, we present a rare case of TTS in the setting of benzodiazepine withdrawal who presented with symptoms of ACS and TTS was diagnosed with coronary angiography with left ventriculography. Patient was discharged home on ACEi and beta-blocker.

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