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CASE REPORT

Cardioembolic Stroke Secondary to Massive Stress-Induced Apical Thrombosis: A Clinical Conundrum Relating to Anticoagulation Initiation

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Abstract

Takotsubo cardiomyopathy or stress cardiomyopathy is a condition characterized by acute and transient left ventricular systolic dysfunction in the absence of coronary heart disease, occurring after an acute emotional or physical stressful event. Cardiac dysfunction in these patients is suspected to be secondary to catecholamine induced cardiac myocyte injury via cyclic AMP-mediated calcium overload or due to endothelial dysfunction. Even though left ventricular dysfunction in takotsubo cardiomyopathy is transient, it can lead to acute complications. Left ventricular thrombus formation is a widely reported complication and has an incidence of around 5−14% in Takotsubo cardiomyopathy patients and can lead to thromboembolic events like stroke. We report a case of takotsubo cardiomyopathy with an apical LV thrombus, complicated by a large cardioembolic stroke. This case constitutes a clinical conundrum, as LV thrombus would warrant prompt initiation of anticoagulation, while the severe ischemic stroke would be a contraindication for immediate anticoagulation.

Keywords: Stress cardiomyopathy, Takotsubo cardiomyopathy, Cardioembolic stroke, Left ventricle thrombus, Anticoagulation

1. Introduction

Takotsubo cardiomyopathy or stress cardiomyopathy is a condition characterized by acute and transient left ventricular systolic dysfunction in the absence of coronary heart disease, occurring after an acute emotional or physical stressful event.[1,2] It was first reported in 1990 in Japan.[3] Its prevalence is estimated to be around 1−2% of patients who present with acute coronary syndrome symptoms.[4,5]

Cardiac dysfunction in these patients is suspected to be secondary to catecholamine induced cardiac myocyte injury via cyclic AMP-mediated calcium overload or due to endothelial dysfunction.[6,7] It has been shown that plasma catecholamine levels are critically elevated in these patients.[8]

Even though left ventricular dysfunction in takotsubo cardiomyopathy is transient,[1] it can lead to acute complications. Left ventricular thrombus formation is a widely reported complication and has an incidence of around 5−14% in Takotsubo cardiomyopathy patients and can lead to thromboembolic events like stroke.[9−11] While Heart failure was the most commonly reported major complication, thromboembolism was found to be the second most common complication in takotsubo patients.[10] Multiple recent large studies have reported that the

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rates of cardiovascular shock and death in takotsubo patients were similar to patients who present with acute coronary syndrome.[12–14]

We report a case of takotsubo cardiomyopathy with an apical LV thrombus, complicated by a large cardioembolic stroke. This case constitutes a clinical conundrum, as LV thrombus would warrant prompt initiation of anticoagulation, while the severe ischemic stroke would be a contraindication for immediate anticoagulation.

2. Case presentation

A previously healthy 77-year-old male with no significant past medical history was brought to the ER for evaluation of altered mental status of 3 days duration. Vitals revealed a blood pressure of 110/70 mmHg, heart rate of 98/min, respiratory rate of 18/min, and patient was afebrile. Physical examination was significant for aphasia, right sided nasolabial fold flattening, and right-sided hemiplegia. Labs were noted to be unremarkable. Per family member, the patient went through a very stressful event of losing his son about a month ago. There was no family history of cardiovascular disease or malignancy. Social history was non-significant for alcohol/tobacco/illicit drug use, and there was no record of patient taking any home medications. EKG showed nonspecific T wave abnormalities. CT head w/o contrast (Fig. 1) showed a 4 × 2 cm hypodensity extending from the left periventricular area to the basal ganglia and thalamic area. He underwent an MRI of the brain and CT angiogram of the neck per non-TPA stroke protocol, that showed 100% occlusion of the left common carotid artery, internal carotid artery, and external carotid artery and no occlusion in the right carotid artery by NASCET criteria. Transthoracic echocardiogram (Fig. 2) showed global hypokinesis of the left ventricle with massive large apical thrombus and a 40–45% ejection fraction. Given the patient's massive ischemic stroke, neurology recommended delaying anticoagulation for 4–14 days to limit the combined risk of hemorrhagic conversion and recurrent cerebral infarcts. However, vascular surgery recommended starting IV heparin drip to alleviate the large burden of left ventricle thrombi and reduce the risk of further embolization. After weighing the risk-benefit ratio, the patient was started on full-dose anticoagulation. Cardiac catheterization was not performed on account of the acute cerebrovascular accident. On the third day of hospitalization, despite the above interventions, the patient developed changes in mental status that led to a code stroke. The NIH stroke scale score was 26. CT head showed an evolving infarct. Patient's family wished to transition him to comfort care.

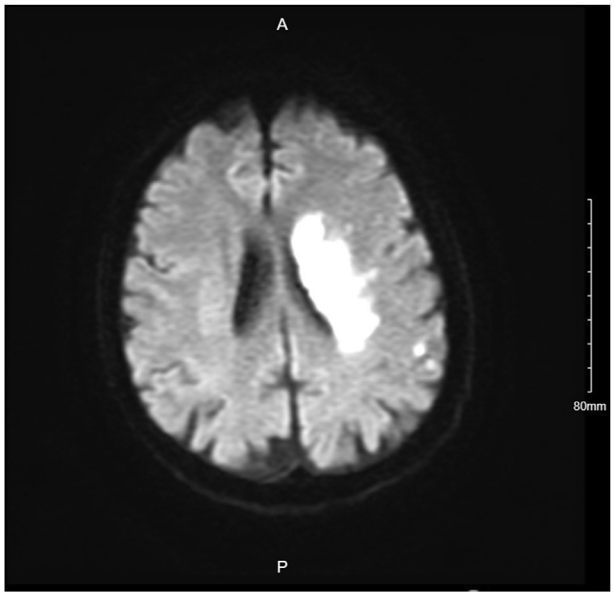

Fig. 1. CT head w/o contrast.

3. Discussion

Left ventricle (LV) thrombosis in Takotsubo syndrome (TTS) or stress cardiomyopathy is a resultant of stasis caused by LV regional wall akinesis/hypokinesis and ballooning of LV.[14] A massive LV apical thrombus formation is uncommon and has an increased risk of emboli complications, causing stroke, and resulting in high mortality like in our patient.

LV thrombi have been documented in 1%–8% of patients with TTS. 2%–14% of people with TTS have

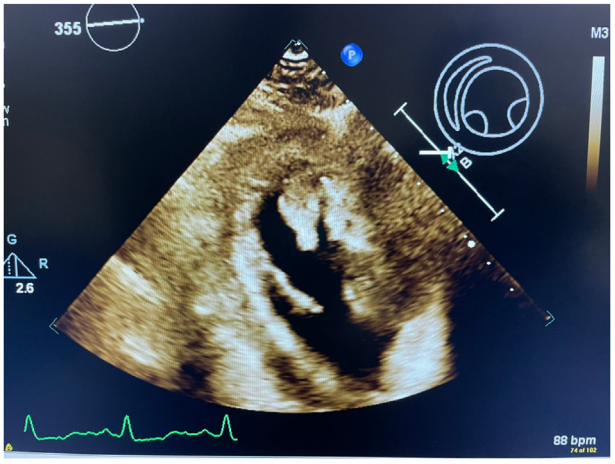

Fig. 2. Transthoracic echocardiogram: Massive apical thrombus in the left ventricle.

been documented to have thromboembolism in general. In those with LV thrombi in TTS, cardiovascular events have happened in 17%−33% of cases. Cerebral, renal, and peripheral limb arteries are the most often reported sites of cardio-embolic problems.[10,11,15−18]

Early initiation of anticoagulation in patients with a very severe stroke remains a clinical dilemma and should be up to the physician's discretion. It is to be noted that, as per the guidelines from American Heart Association/American Stroke Association (AHA/ASA), anticoagulation can be delayed up to 4−14 days due to increased risk of hemorrhagic transformation in patients with cardioembolic stroke.[19] The European Society of Cardiology/European Heart Rhythm Association (ESC/EHRA) recommends delaying anticoagulation for up to 12−14 days in patients with severe stroke.[20,21]

A brief review of thromboembolism, LV thrombosis, and cardioembolic events in TTS patients is shown in Table 1. The authors did not examine all TTS patients, but only those whose TTS was complicated by thromboembolism.

Haghi et al. conducted a retrospective study on 52 TTS patients. Echocardiography revealed LV thrombi in four patients (8%). Serum C-reactive protein(CRP) levels were elevated in all four patients. Thrombocytosis was also present in two patients. In all cases, treatment with low molecular weight heparin resulted in thrombus resolution.[22] Thus CRP elevations and thrombocytosis may indicate an increased risk of thrombus formation.

According to a systematic review done by Gregorio et al., 33% of TTS patients with LV thrombus had a cardioembolic phenomenon, and patients started on anticoagulation had thrombus resolution within 9−90 days.[9] This highlights the significance of initiating anticoagulation in these patients as soon as possible. Although the exact mechanism of thrombus formation is unknown, catecholamine-induced platelet activation and low blood flow due to wall motion abnormalities are thought to contribute to its formation.[23,24]

Mitsuma et al. studied 21 patients with TTS. Three patients (14%) were found to have thromboembolism, making it the second most common cardiovascular complication after heart failure. One of the three patients had a LV thrombus, and the other two had cardioembolic stroke. According to this study, thromboembolism is a common complication in the acute phase of Takotsubo cardiomyopathy, and anticoagulation therapy should be administered to all patients until wall motion abnormalities improve.[10]

Sharkey et al. conducted an imaging study on 136 patients with TTS. Cardiovascular magnetic resonance (CMR) imaging revealed three distinct ventricular contraction patterns, usually with a rapid return to normal systolic function, although with a delay of more than 2 months in 5%. RV and/or LV thrombi were found in five patients (mostly via CMR imaging), two of whom had embolic events. 25 patients (18%) were taking beta-blockers at the time of TTS events. 3 patients (2%) died in the hospital, and 116 (85%) survived, with 5% having nonfatal recurrent TTS events. This study found that beta-blocking drugs were not completely protective, and that TTS was a predictor of increased non-cardiac mortality. These findings support expanded management and surveillance strategies, such as CMR imaging and anticoagulation consideration.[17]

Kurisu et al. studied 95 patients with TTS and found LV apical thrombi in 5 (5.3%) of them. After anticoagulant therapy, LV apical thrombus disappeared in four patients. One patient experienced a stroke. LV dysfunction was resolved in all patients during follow-up.[16]

LV thrombi can develop early in the course of TTS, even before admission, and in some cases, it can lead to cardioembolic complications such as stroke. LV thrombus was present at the time of diagnosis in three of the four patients reported by Haghi et al. The thrombus was initially absent in one patient and developed later.[22] Nerella et al. reported an apical TTS case with no detectable LV thrombus on the first day. On day five, repeat echocardiography revealed LV thrombus.[25] Otani et al.[26] presented a case of a cerebral embolus as a TTS complication and reviewed 19 other cases that were similar. They discovered no evidence of LV thrombus in ten (50%) of the twenty patients. Thus, cardioembolic events can occur in both TTS with obvious LV thrombus and TTS without obvious LV thrombus.

Thus in order to avoid serious thromboembolic complications in TTS, LV thrombi should be looked for and detected as soon as possible, and appropriately treated with anticoagulation. Cardiac imaging should be performed as soon as possible during the admission days and should be repeated. The most accessible and feasible image modality for this task is echocardiography. It can be done at the patient's bedside and repeated without risk to the patient. However, echocardiography may be limited in its ability to clearly visualize the left ventricular apex, where LV thrombosis typically occurs. CMR imaging or contrast computed tomography may be required in such cases to reveal LV thrombi.

Table 1. A brief review of thromboembolism, LV thrombosis, and cardioembolic events in TTS patients.

Authors	No of patients with TTS	No of patients with thrombo-embolism (both LVT and cardioembolism) (%)	No of patients with LVT (%)	No of patients with cardioembolism	Localization of the cardiac embolus	Others
Haghi et al.	52	4 (8%)	4 (8%)	0 (0%)	–	One patient had thrombosis of the abdominal aorta, renal infarction, and iliac artery occlusion before the onset of TTS
Mitsuma et al.	21	3 (14%)	1 (4.8%)	2 (9.5%)	Stroke in 2 patients	–
Sharkey et al.	136	5 (3.7%)	5 (3.7%)	2 (1.5%)	Cerebral in 1 patient, and both cerebral and pulmonary in 1 patient	LVT in 4 patients and both LVT and RV thrombus in 1 patient.
Kurisu et al.	95	5 (5.3%)	5 (5.3%)	1 (1.1%)	Cerebral infarction in 1 patient	Mural thrombus and immobile in 2 patients, and protruding and mobile in 3 patients
De Gregorio et al.; review of single cases	Review of 14 studies (13 single case studies and 2 cases), total 15 patients with TTS and thrombo-embolism	15	14	5	Stroke i 3 patients, renal infarction in 1, and popliteal artery in 1	All patients with LVT and apical or mid-apical pattern of TTS
Haghi et al.; review of single cases	Review of 14 literature cases with TTS and LVT	14	14	3	Stroke in 1, TIA in 1 and renal infarction in 1	–

Abbreviations: LVT, left ventricular thrombus; No, number; RV, right ventricle; TIA, transient ischemic attack; TTS, takotsubo syndrome.

As a result, LV thrombi and cardioembolic complications should be treated as soon as possible with anticoagulation. Even cases with extensive mid apical ballooning, where the risk of thromboembolism is high, should be treated as a precaution. Increased troponin levels (troponin I level >10 ng/mL) and apical ballooning were strongly associated with the occurrence of LV thrombi in a recent study by Santoro et al.,[18] and anticoagulation should be considered as a prophylactic treatment in such cases.

Warfarin is the anticoagulant of choice, with an INR goal of 2–3, however, direct oral anticoagulants (DOACs) are recommended when the patient is unable to tolerate warfarin use.[27] Anticoagulation should be continued for at least 2–3 months, or until the left ventricle wall-motion-abnormality (LVWMA) and LV thrombi have resolved. When the LVWMA improves or resolves, the LV thrombi usually resolves.

Take away points:

- Ventricular thrombus is the 2nd most common complication of takotsubo cardiomyopathy.
- Thromboembolism is more common in apical and mid-apical patterns of takotsubo cardiomyopathy.
- Echocardiography can be a very useful and most readily available tool to detect ventricular thrombus.
- All patients with takotsubo cardiomyopathy and presence of ventricular thrombus should be promptly treated with anticoagulants. Warfarin is the anticoagulant of choice, with an INR goal of 2–3, however, direct oral anticoagulants (DOACs) are recommended when the patient is unable to tolerate warfarin use. The anticoagulation should be continued for 2–3 months or at least until the left ventricle wall-motion-abnormality and LV thrombus have resolved.
- High risk patients as mentioned above (apical and mid-apical patterns, high troponin levels) can be considered for prophylactic anticoagulation.

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Conflict of interest

The authors deny any conflicts of interest associated with the study.

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