Cardiac myxoma as a potential trigger of takotsubo cardiomyopathy: A brief review on mechanistic and clinical perspectives

Kenan Yalta[1], Ugur Ozkan[1], Tulin Yalta[2], Ertan Yetkin[3]

[1]Cardiology Department, Trakya University, Edirne; [2]Pathology Department, Trakya University, Edirne; [3]Cardiology Department, Derindere Hospital, Istanbul, Turkey

Abstract

In clinical practice, cardiac myxomas constitute the majority of benign cardiac neoplasms, and might potentially present with a variety of embolic, obstructive as well as constitutional symptoms. On the other hand, these neoplasms might be potentially associated with the evolution of takotsubo cardiomyopathy (TTC) that is universally considered as a transient form of acute myocardial dysfunction. Accordingly, the present paper primarily aims to focus on potential mechanisms and associated clinical implications of TTC evolution in the setting of cardiac myxomas.

Introduction

Takotsubo cardiomyopathy (TTC) is a reversible form of cardiomyopathy, and appears to be triggered by various physical and emotional stressors associated with significant adrenergic discharge mostly in post-menopausal females [1,2]). It usually arises in the absence of culprit coronary stenosis, and presents with characteristic left ventricular (LV) wall motion abnormalities (mostly apical ballooning) accompanied by cardiovascular symptoms (including chest pain and dyspnea), certain electrocardiographic (ECG) changes (including precordial ST segment elevation and T wave inversion) as well as moderate elevation of myocardial enzymes (including troponins) [2]. Therefore, TTC strongly mimics acute myocardial infarction (AMI) in clinical practice [2]. Even though the pathogenesis of this phenomenon is potentially multifactorial, myocardial stunning in response to sudden adrenergic discharge seems to be the most likely mechanism accounting for characteristic wall motion abnormalities [2]. In the acute setting, TTC might be complicated by heart failure (HF), thromboembolic events and various cardiac arrhythmias potentially aggravating its short-term prognosis [2]. Importantly, assessment of certain parameters including ventricular ejection fraction, type of the stressor (physical versus emotional) and age might be of significant value in the risk-stratification of patients with TTC [2].

On the other hand, cardiac myxomas constitute the major portion of benign cardiac neoplasms, and mostly originates from the left atrium potentially presenting with embolic, obstructive (including dyspnea) as well as constitutional (including fatigue, anorexia, myalgia and skin rash associated with augmented systemic inflammation) symptoms and signs mostly in females (30 to 60 years of age) [3,4]. Interestingly, cardiac myxomas were previously suggested to serve as potential triggers of TTC in the clinical setting [1,3]. Importantly, eventual abnormalities in brain-heart interaction (largely due to neurological complications) might significantly contribute to TTC evolution in patients with cardiac myxoma. Accordingly, the present paper aims to highlight potential potential mechanisms and clinical implications of TTC evolution in the setting of cardiac myxomas.

Correspondence: Kenan Yalta, Cardiology Department, Trakya University, Edirne, Turkey.
Tel. 00905056579856.
E-mail: kyalta@gmail.com, akenanyalta@trakya.edu.tr

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Acute cerebrovascular embolism in the setting of cardiac myxomas: A potential trigger of TTC evolution

TTC evolution in the setting of cardiac myxomas might be attributable to systemic embolism in a portion of cases [1,3]. Embolic events generally emerge in 30%-40% of cardiac myxomas (mostly in the form of acute cerebrovascular events) [3]. Accordingly, a recently published article [1] has reported an interesting case of TTC (presenting with acute HF) triggered by an ischemic stroke attributable to a left atrial myxoma. The severe stress induced by the neurological event seems to be the primary trigger of TTC evolution in this report [1]. Similarly, a case of

TTC was previously reported in the setting of acute limb ischemia associated with an embolus originating from a left atrial myxoma [3]. The authors suggested TTC evolution as a consequence of severe physical and emotional stress (due to pain, motor weakness associated with limb ischemia, *etc*.) in their patient [3].

Systemic embolism due to cardiac myxomas, though mostly presents with cerebrovascular events, might occasionally involve coronary and renal arteries, and more rarely, also emerges in a multiregional pattern [3]. Of note, augmented systemic inflammation generally denotes tumoral fragility, and has the potential to facilitate systemic embolism in the setting of cardiac myxomas [4,5]. On the other hand, systemic embolism in cardiac myxomas is not only associated with tumoral fragments, but also with fibrin clots originating from the tumoral tissue [3] (with or without pre-existing thrombus formation on the tumoral surface). Therefore, it seems plausible to initiate antiplatelet or anticoagulant therapy as a preventive strategy in the presence of high-risk myxoma features for systemic embolism (irregular surface, previous cerebral embolism) mostly as a bridging-therapy until surgical excision, or occasionally as an alternative approach to surgery in surgically-high risk patients (very elderly patients with serious co-morbidities, etc.) [6,7]. Management of established systemic embolism is generally organ specific, and includes anticoagulant therapy, surgical embolectomy as well as thrombolytic therapy in select cases [3,6].

Taken together, previous publications have suggested systemic embolism (with overt clinical findings) as a potential trigger of TTC evolution in patients with cardiac myxoma [1,3]. Physical and/or emotional stressors associated with the acute embolic event seem to be the fundamental trigger of TTC evolution in these reports. However, TTC evolution in this setting seems to have an organic basis particularly associated with impairment of certain parts of central nervous system (CNS) (insular cortex, specific subcortical forebrain parts including amygdala) due to the embolic event [8]. Consistent with this, middle cerebral artery occlusion, when associated with insular infarcts, was experimentally demonstrated to trigger adrenergic discharge leading to QT interval prolongation and myocytolysis [8]. In other terms, structural cerebral alterations following ischemic cerebrovascular events (as in the setting of cardiac myxomas) might lead to significant autonomic dysfunction both in the short and long term [9] potentially leading to extreme adrenergic discharge with consequent TTC evolution [8]. However, a TTC episode might be overlooked in the presence of systemic embolism which might conceal cardiovascular symptoms and signs in patients with cardiac myxoma. Of note, cardiac myxomas might occasionally present with AMI due to coronary embolism [10]. Therefore, TTC in the setting of cardiac myxomas should also be differentiated from possible coronary embolic events that might manifest in a similar fashion in terms of symptoms and signs (chest pain, dyspnea, ECG changes).

Interestingly, acute cerebrovascular embolism in patients with cardiac myxoma (complicated by a TTC episode) might just arise as a consequence, and not a trigger of TTC. In other terms, a variety of non-embolic stressors (myxoma- related factors (as described later) and/or other concomitant triggers) might lead to a TTS episode which, in turn, directly accounts for the subsequent cerebrovascular embolism. Mechanistically, TTC is well known to predispose to systemic embolism through a variety of factors including wall motion abnormalities, systemic inflammation and activation of coagulation cascade [11,12]. However, a pooled analysis of observational studies (comprising 29.410 patients with TTC) demonstrated a cerebrovascular event (and LV thrombus) rate of only 2% among patients with TTC [11]. This number appears to be significantly lower as compared with that of other cardiovascular conditions including AMI [11]. Therefore, it seems likely that cerebrovascular embolism more likely emerges as a trigger rather than a consequence of TTC.

Importantly, temporal characteristics of clinical findings might be of crucial importance to comprehend the cause-consequence relationship between acute cerebrovascular embolism and TTC in patients with cardiac myxoma. In these patients, emergence of cardiovascular manifestations (including dyspnea, angina) generally precede neurological findings in the setting of TTC complicated by subsequent cerebrovascular embolism. Conversely, cerebrovascular embolism, as the primary pathology, mostly accounts for TTC evolution in patients with preceding neurological manifestations or in those with an undetermined temporal relation between neurological and cardiovascular symptoms. However, it should be borne in mind that only a minority of patients with cardiac myxoma (with or without acute cerebrovascular embolism) suffer a co-existing TTC episode in clinical practice.

Augmented systemic inflammation due to cardiac myxomas: Implications in TTC evolution and prognosis

Pathogenetically, systemic inflammation associated with cardiac myxomas might contribute to TTC evolution in certain settings. A significant portion of cardiac myxomas present with constitutional symptoms largely attributable to augmented systemic inflammation as determined with increased levels of cytokines such as interleukin-6 (IL-6), anemia, leukocytosis, *etc*., in the absence of infections [3,4]. Interestingly, cardiac myxomas might also be infected by certain microorganisms originating from distant sources particularly in the setting of certain risk factors including invasive procedures and immunocompromised status potentially leading to further systemic inflammatory response [4,5]. However, bacterial seeding associated with severe systemic inflammation has been a rare phenomenon in the setting of cardiac myxomas, and is generally considered as a form of infective endocarditis that requires urgent antibiotic therapy and, where necessary, surgical excision [5].

In the clinical setting, systemic inflammation, on top of adrenergic discharge, was previously suggested to be associated with the evolution of TTC (and with its relatively unfavorable prognosis) [13]. Mechanistically, systemic inflammation (if severe) might directly trigger TTC, or more likely, might lower the threshold for TTC evolution in response to other triggers largely through induction of myocardial adrenergic hypersensitivity and impaired myocardial contractility [14,15]. Furthermore, augmented systemic inflammation harbors the potential to stimulate adrenergic discharge [16] that is usually labeled as a '*sine qua non*' in the genesis of TTC [2]. Therefore, inflammation-induced TTC evolution might also apply to the setting of cardiac myxomas presenting with augmented systemic inflammation. However, systemic inflammation, rather than serving as a direct trigger, seems to facilitate the impact of neurological stressors on TTC evolution in patients with cardiac myxoma (owing to the modest nature of systemic inflammation in most myxoma patients). Importantly, systemic inflammation in the setting of cardiac myxomas might also be associated with a variety of adverse outcomes including acute HF [1], malignant arrhythmias as well as coronary micovascular dysfunction (as demonstrated with coronary slow flow (CSF) during the course of the associated TTC episode [13]. This may also suggest anti-

inflammatory strategies in an effort to improve the short-term prognosis of the associated TTC episode [17,18].

Involvement of central autonomic pathways due to distant tumoral seeding: A subtle trigger of TTC evolution in patients with cardiac myxoma

TTC evolution due to cardiac myxomas might be due to cerebral parenchymal or vascular involvement through distant tumoral seeding in certain settings. Mechanistically, TTC evolution in certain neurological diseases were previously ascribed to the direct involvement of the cardiovascular centre in the brain stem (rostral ventrolateral medulla (RVLM) located in medulla oblongata [8]) with consequent adrenergic discharge [17,18]. Involvement of the cardiovascular centre was also suggested to be associated with more severe and prolonged adrenergic discharge in patients with TTC potentially associated with adverse events including malignant arrhythmogenesis and coronary ischemic complications (due to coronary microvascular dysfunction as confirmed with a pattern of CSF [19,20]) that might be evaluated with TIMI frame counts on coronary imaging) in the acute setting [17,18]. In the long-term, TTC associated with neurological diseases also has a higher risk for future recurrences [17-20] possibly due to the relapsing nature of the primary neurological pathology. Interestingly, atypical takotsubo variants (including reverse and midventricular variants) are more likely to be associated with severe neurological diseases including subarachnoid hemorrhage and multiple sclerosis (MS) characterized by relatively high levels of adrenergic discharge [21-23]. Therefore, it might also be suggested that neurological diseases, as compared with other TTC stressors, might trigger atypical TTC episodes in a more frequent manner.

Distant tumoral seeding of benign neoplasms has always been regarded as an interesting phenomenon that strongly mimics the concept of 'metastasis' encountered in advanced malignancies. In this context, cardiac myxomas were previously suggested to implant and grow at distant sites with eventual organ damage [3,24]. Of note, cerebrovascular involvement in the setting of cardiac myxomas might not always emerge as rampant acute ischemic strokes (due to fully occclusive embolic fragments), yet; might occasionally present with slowly progressive cranial aneurysms (due to destruction of vessel wall) and/or multiple parenchymal solid brain lesions (due to transmigration of myxoma cells through vascular endothelium) accompanied by variable degrees of intracerebral haemorrhage on imaging modalities including magnetic resonance imaging (MRI) and digital substraction angiography (DSA) [4,24,25]. In certain patient series with myxoma-associated neurological symptoms, CNS paranchymal solid brain lesions and cranial aneurysms were encountered in 50% and 67% of cases [24]. However, these ratios were found to be much lower in other case series [26]. Cerebrovascular involvement might also manifest as chronic infarcts due to slowly progressive obliterative vascular lesions in certain patients with cardiac myxoma [24]. Histopathological and immunohistochemical features of these secondary myxomas at distant cerebrovascular sites were found to be identical to those of their primary cardiac source (presence of mucoid matrix with benign spindle cells, expression of calretinin, and high levels of IL-6 and matrix metalloproteinase-2 (MMP-2) potentially associated with their distant seeding) [25]. Mechanistically, IL-6 was previously suggested to have a central role in the invasion of vascular wall by the myxoma cells largely through augmentation of intercellular adhesion molecule-1 (ICAM-1) [4,25,27]. Based on these notions, it seems highly likely that systemic inflammation associated with cardiac myxomas generally facilitates distant tumoral seeding [4], and possibly correlates with the the extent of distant tumoral invasion. Parenchymal lesions and intracranial aneurysms (usually multiple) in the setting of myxoma-associated CNS disease most likely involve anterior supratentorial structures, and distal parts of middle and posterior cerebral arteries, respectively [24]. However, they possibly have the potential to involve any CNS site.

Clinically, CNS lesions associated with cardiac myxomas are generally associated with neurological symptoms including dizziness, seizures, headache, etc. [24]. In particular, TTC might also arise as a potential cardiac manifestation of these CNS lesions. In other terms, it seems reasonable that cardiac myxomas might also have the potential to involve the brain stem (where primary cardiovascular centre is located) and other associated CNS sites governing autonomic regulation (insula, amygdala, anterior deep supratentorial structures, etc.) through distant tumoral seeding ultimately leading to a particular TTC episode that is more likely to have a worse prognosis, atypical pattern along with a higher recurrence risk. Interestingly, clinical manifestations of these distant CNS myxomas (neurological findings and associated TTC) might emerge even long after the resection of primary cardiac myxoma suggesting their insidious and slowly progressive nature [4,24,25].

Management strategies should be primarily based on the extent and location of the parenchymal and vascular CNS lesions associated with myxomas along with patient characteristics. Early excision of the cardiac myxoma (even in the absence of symptoms) seems mandatory for the prevention of possible systemic embolism and CNS seeding [24,28]. In the first years following surgical excision, patients should be serially examined for potential recurrence of cardiac myxoma and new-onset neurological signs through various imaging modalities including echocardiogram, MRI and digital substraction angiography (DSA) [24]. In cases with established parenchymal or vascular CNS lesion(s) (arising before or after excision of cardiac myxoma), surgical clip or catheter embolization (for vascular aneurysms), surgical excision (if possible), chemotherapy (ifosfomide, doxorubicin, etoposid, etc.) and radiotherapy have been used with variable success rates [4,24,28-30]. Chemo and/or radiotherapy seem as a reasonable option particularly in the setting of extensive CNS involvement or in surgically ineligible patients [30].

In particular, since neurological lesions associated with TTC evolution generally involve critical CNS areas including brainstem, deep supratentorial structures, etc., management of these lesions may be quite challenging. Therefore, besides surgical modalities including satellite ganglione blockade [18], chemotherapy might be regarded as the primary option in these precarious patients in an effort to prevent future TTC recurrences along with other surgical modalities including satellite ganglione blockade. In this context, certain antiinflammatory agents might posssibly have adjunctive therapeutic benefit owing to the pathogenetic implications of systemic inflammation in the setting of TTS [31]. However, therapeutic implications of antiinflammatory agents in TTS still remains to be established [31]. More specifically, paradoxical elevation of orexin (a unique neuropeptide associated with the state of wakefulness) was suggested to have a potential association with TTC evolution in the setting of CNS diseases [18]. Accordingly, drugs targeting modulation of pathways asssociated with orexin and certain agents with favorable effects on CNS functions (including sulfanylureas, vinpocetine, trimetazidine) [32-34] might be of significant benefit in the mitigation and

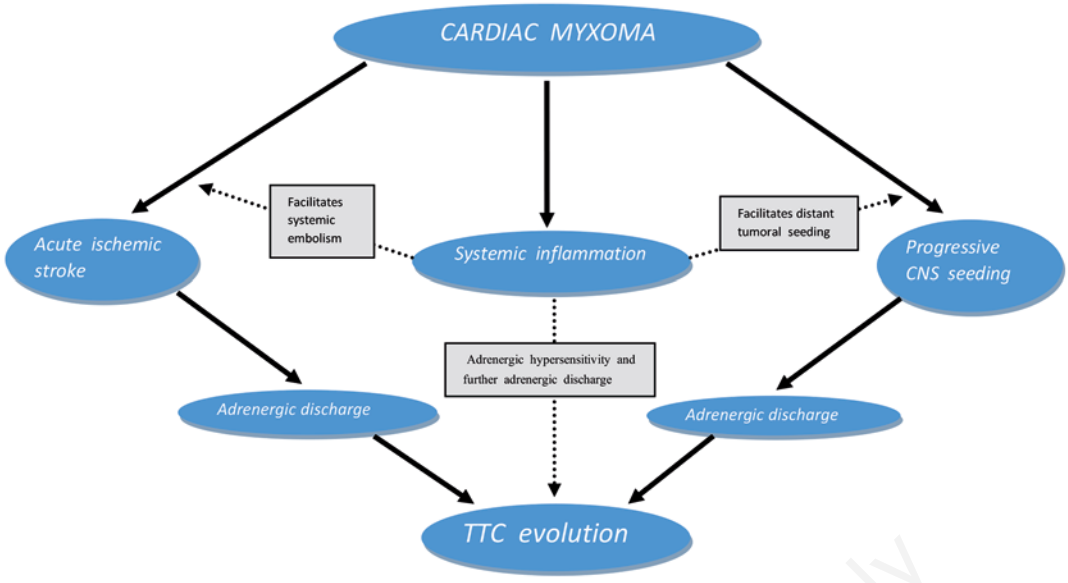

Figure 1. Potential mechanisms of TTC evolution in the setting of cardiac myxomas. CNS, central nervous system; TCC, takotsubo cardiomyopathy.

prevention of TTC episodes [18] due to myxomatous CNS lesions or infarcts. However, these notions currently remain speculative, and warrants clinical studies testing the efficacy of these agents in the setting of TTC episodes associated with cardiac myxomas.

Finally, co-existence of TTC and cardiac myxomas might occasionally arise as a coincidental phenomenon due to the similar age and gender predilection of these entities. Accordingly, a case of left atrial myxoma was previously reported to be diagnosed coincidentally on cardiac imaging during the evaluation of a TTC episode associated with an epileptic seizure [35].

Potential mechanisms of TTC evolution and general characteristics of TTC episodes in the setting of cardiac myxomas are summarized in Figure 1 and Table 1, respectively.

Conclusions

Cardiac myxomas might induce TTC evolution most likely through a variety of neurological mechanisms such as acute cerebrovascular embolism and progressive involvement of central autonomic pathways including primary cardiovascular centre (by cerebral parenchymal and vascular lesions) through distant tumoral seeding. Of note, augmented systemic inflammation in patients with cardiac myxoma might not only predispose to neurological complications, but also seems to lower the threshold for TTC evolution in response to neurological stressors. Importantly, TTC in association with cardiac myxomas might have a worse in-hospital prognosis due to adverse impact of associated factors including severe adrenergic discharge, systemic inflammation. On the other hand, TTC due to cardiac myxomasappears to be a potentially underdiagnosed phenomenon requiring a high index of suspicion for its detection.

Therefore, emerging HF manifestations (dyspnea, hypotension, etc.) and/or typical chest pain in patients with a confirmed diagnosis of cardiac myxoma (on imaging modalities) might not only suggest worsening obstructive symptoms or coronary embolism, but might also signify an existing new-onset TTC, and hence; warrant repeat imaging along with basic diagnostic tools (ECG, troponins, etc.) for further management strategies. However, further aspects of TTC evolution in the setting of cardiac myxomas still remain to be fully established.

Table 1. Potential characteristics of TTC episodes in the setting of cardiac myxomas.

Potential underdiagnosis
Higher incidence of atypical variants
Higher levels of adrenergic discharge and/or systemic inflammation
Relatively worse in-hospital outcomes
Higher risk of recurrence
Presence of co-existing neurological findings

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