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From atropine eye drops to takotsubo syndrome in an 89-year-old lady

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Abstract

A few hours after receiving atropine drops for an eye examination, an 89-year-old lady complained of compressive chest pain that was associated with an ST-segment elevation in the anterolateral and inferior leads. Emergency coronary angiography showed normal coronary arteries; however, contrast ventriculography showed an "apical ballooning" pattern (octopus trap) in end systole that is typical of takotsubo syndrome. The left ventricular function, monitored by a 2D echocardiogram, fully recovered at follow-up. Atropine eye drops can have systemic effects, especially in the elderly, inducing, through a sympathetic imbalance, an acute coronary microvascular dysfunction that may trigger takotsubo syndrome in the absence of classic emotional stress. This case report provides support for the hypothesis that takotsubo syndrome is a manifestation of acute microvascular dysfunction. ■ *Heart Metab*. 2018;75:29-32

Keywords: acute microvascular dysfunction; atropine; takotsubo syndrome

Introduction

Takotsubo syndrome was initially recognized in Japan[1] and later in the US, where the first report dates back to 1998. It is a condition where the signs and symptoms of acute myocardial ischemia occur in patients with no evidence of obstructive coronary atherosclerosis at angiography.[2] Given the established assumption that acute myocardial infarction is consistently associated with coronary atherothrombosis, the real nature of this syndrome has been strongly debated, with most cardiologists denying its ischemic nature and preferring to call it stress cardiomyopathy.[3] This case report of a female patient who was recently admitted to our coronary care unit offers the opportunity to review our understanding of this syndrome.

Clinical presentation

AT is a charming 89-year-old lady who has been followed in our outpatient clinic due to her history of hypertension, hypercholesterolemia, and chronic kidney disease. At the last echocardiographic examination, her left ventricular function was normal (ejection fraction, 62%), with normal chamber dimensions and wall thickness. On June 20th at 9 AM, she started complaining about chest pain shortly after receiving atropine drops for an eye examination. She presented to the emergency department at 10 AM. The physical ex-

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amination was unremarkable, the blood tests showed elevated high-sensitivity troponin T at 169 ng/L (normal value <14). The electrocardiogram showed a marked ST-segment elevation in the anterolateral and inferior leads *(Figure 1)*. Based on these data,

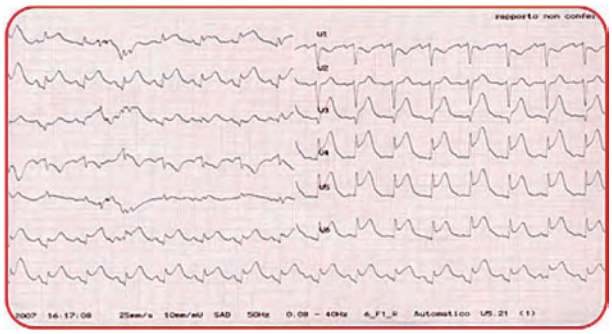

Fig. 1 *Electrocardiogram showing a marked ST-segment elevation in the anterolateral and inferior leads.*

the patient was given antithrombotic agents (aspirin + clopidogrel) at the recommended doses and referred to the catheterization lab for a primary percutaneous coronary intervention.

When the patient reached the catheterization table at 10:30 AM, she was still symptomatic and the ST segment was still elevated. Coronary angiography showed a normal left and right coronary artery *(Figures 2 and 3)*. Left ventricular angiography in the right anterior oblique view showed a normal diastolic profile of the ventricular cavity *(Figure 4)* that assumed the "apical ballooning" pattern (octopus trap) in end systole *(Figure 5)* that is typical of takotsubo syndrome.

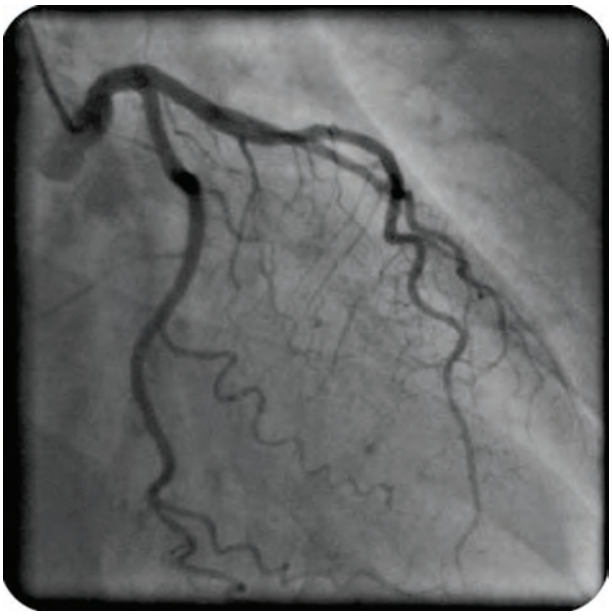

Fig. 2 *Coronary angiography showing a normal left coronary artery.*

A diagnosis of takotsubo syndrome was confirmed and the patient was transferred to the coronary care unit. At arrival, she was still complaining of chest pain; the physical examination showed bilateral rales with fine crackles on the entire lungs, a further increase in cardiac biomarkers (high-sensitivity troponin, 754 ng/L; creatine kinase–myocardial isoenzyme [CK-MB], 23.75 ng/mL [normal value <6.3]), elevated white blood cell count, and elevated blood glucose levels. Chest x-rays confirmed augmented extravascular lung water and a dilated heart. The echocardiogram showed akinesis of the apex, mid, and api-

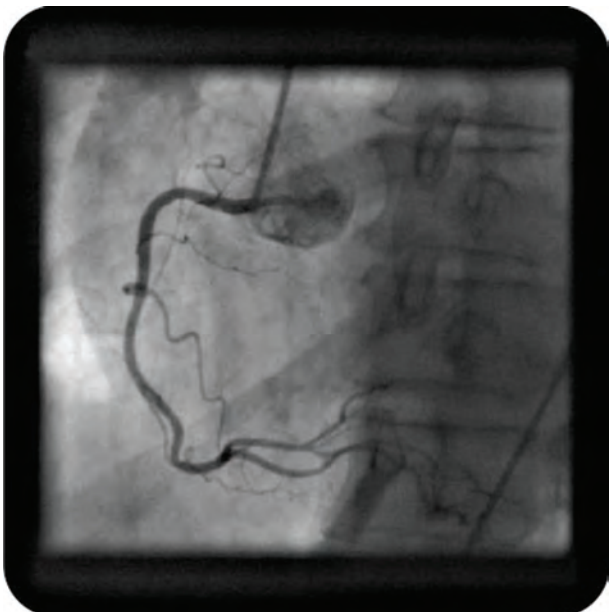

Fig. 3 *Coronary angiography showing a normal right coronary artery.*

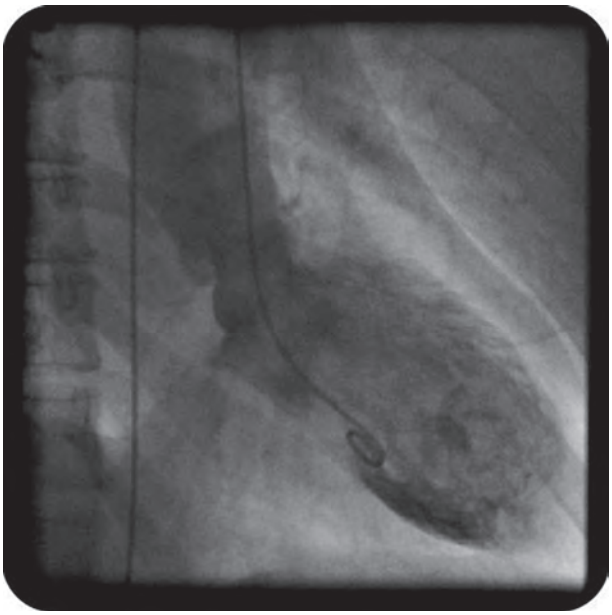

Fig. 4 *Left ventricular angiography in the right anterior oblique view showing a normal diastolic profile of the ventricular cavity.*

cal segments in all left ventricular segments, severe systolic dysfunction with an ejection fraction of 15%, mild mitral regurgitation, and pulmonary hypertension (pulmonary artery pressure, 65 mm Hg).

The patient was treated with IV diuretics and morphine. The next day, June 21st, the patient had tachycardia, chest pain, dyspnea, and a further increase in cardiac markers. Ivabradine and ramipril were added to the treatment regimen. The patient's symptoms, physical examination, and CK-MB normalized on June 25th. Atrial fibrillation appeared on the echocardiography monitor, but it spontaneously reverted to sinus rhythm on June 27th. The echocardiogram showed hypoakinesis of the apex and mid-distal segments in all ventricular walls, with hyperkinesis of the proximal segments, severe global systolic dysfunction with an ejection fraction of 25%, and pulmonary hypertension (pulmonary artery pressure, 46 mm Hg). The patient was discharged on June 28th. She was prescribed ramipril, aspirin, dabigatran, and trimetazidine.

The patient came back for a programmed follow-up visit on July 18th. She was asymptomatic, the lungs were clear, the electrocardiogram had reverted to normal, and the left ventricular function had markedly improved with an ejection fraction of 50%).

Discussion

In spite of extensive research in recent years, takotsubo syndrome remains a challenging entity with elusive and heterogeneous epidemiological, pathophysiological, and clinical features. Initially described in Japan, it is now increasingly recognized in the Western world, including Italy and the US, and accounts for 5% of all admissions with acute coronary syndromes. Described as a benign and self-limiting disease, it is now associated with a 5% intrahospital mortality and an approximate 10% chance of recurrences in the mid- to long-term follow-up. Even more surprising, it was initially described as a stress cardiomyopathy, and therefore, a primary disease of the muscle, but it is now considered a transient, severe abnormality of the coronary microcirculation, which mirrors in an atypical distribution of the wall motion abnormalities, shifting the focus from the myocardium as the culprit to the myocardium as a victim of the abnormal microcirculation.[4] This change in thinking has important potential therapeutic implications, since we have several drugs that target the coronary microcirculation, which could potentially be useful in patients with takotsubo syndrome.

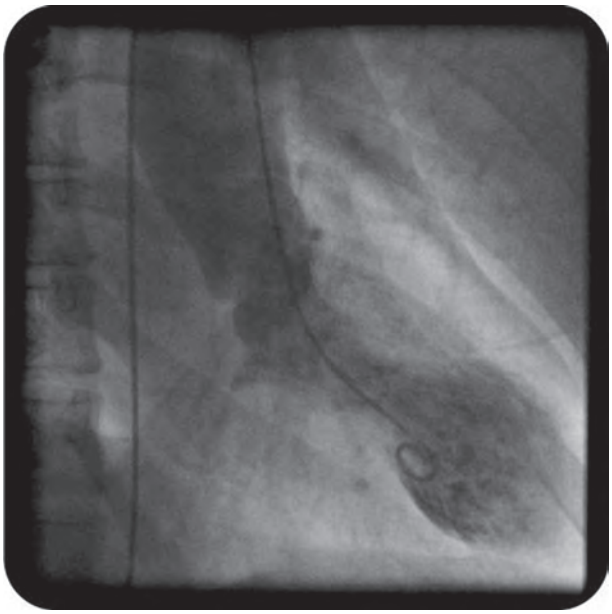

Fig. 5 *Apical ballooning pattern (octopus trap) in end systole that is typical of takotsubo syndrome.*

In the new pathophysiological perspective, takotsubo syndrome is just another point in the spectrum of coronary microvascular disease,[5] with a trigger that is linked to a neurohormonal storm, particularly to an excess of circulating catecholamines, produced by structures mediating the stress response in both the central and autonomic nervous system.[6] The same storm (and the same effect on myocardial wall motion) can be iatrogenically induced during exogenous catecholamine infusion, during dobutamine stress, or in patients with brain hemorrhages who suffer from a catecholamine surge that provokes takotsubo syndrome–like abnormalities (also called takotsubo syndrome phenocopy). The trigger event is usually an emotional or psychological stress, which is missing in the described case. In this perspective, it is interesting that the triggering event in our 89-year-old patient was the administration of the parasympatholytic agent atropine. Eye drops can have systemic effects, and systemic adverse events have been described after commonly used ophthalmic preparations, especially in the elderly who are more likely to have elevated systemic drug concentrations due to impaired drug metabolism and renal excretion. In particular, mydriatic agents, such as atropine, can cause hypertension and tachycardia due to a sympathetic imbalance, which is especially likely in the presence of renal insufficiency, as with our patient.[7]

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The responsibility of the microcirculation in takotsubo syndrome has also been witnessed in clinical studies showing a transient, profound, reversible impairment in coronary flow velocity reserve that slowly and spontaneously improves over days or weeks, paralleling the recovery in left ventricular function.[8] Coronary microvascular dysfunction may be effectively targeted by cardiometabolic agents. Ivabradine has been shown to increase the coronary flow reserve in angina patients, with and without diabetes, in the poststenotic territory as well as areas remote from the epicardial coronary stenosis.[9,10] It remains to be clarified with prospective randomized studies whether an improvement, anecdotally described in this case and possibly achieved with drugs, such as ivabradine (and/or trimetazidine, which is also effective with a different cardiometabolic effect in patients who are still symptomatic on standard therapy), modifies the long-term prognosis of patients with takotsubo syndrome. In particular, the role of trimetazidine has a strong pathophysiological rationale, since takotsubo syndrome also affects the microcirculation, which cannot be treated with revascularization, and is the preferential target of trimetazidine treatment.[11] ■

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