Takotsubo Syndrome and Colitis Due to *Clostridium difficile:* Is There a Relationship?

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Takotsubo syndrome (TTS) or Takotsubo cardiomyopathy (TCM) is a cardiomyopathy that develops rapidly and is usually caused by mental or physical stress. It is usually a transient cardiomyopathy. The presumed cause of the onset of the syndrome is the increase and extreme secretion of adrenaline and norepinephrine due to extreme stress. An infectious disease such as sepsis can also be the cause [1].

One of the most widespread diagnostic tools is the revised version of Mayo Clinic Diagnostic Criteria for TTS (2008) [2], which incorporates transient wall-motion abnormalities, absence of a potential coronary culprit, myocarditis, and pheochromocytoma. The prognosis for TTS is usually favorable and resolves with complete recovery in 4–8 weeks in more than 90% of patients.

TSS, also known as stress cardiomyopathy, is a type of non-ischemic cardiomyopathy in which there is a sudden temporary weakening of the muscular part of the heart. It usually appears after a significant physical or emotional stressor. When it is caused by an emotional stressor, the condition is sometimes called *broken heart syndrome.* Examples of physical stressors that can cause TTS are sepsis, shock, subarachnoid hemorrhage, and pheochromocytoma. TTS represents approximately 2% of all patients (5–6% of all female patients) who are initially diagnosed with acute coronary syndrome and [1], which represents 0.02% of all hospitalizations in the United States.

About 90% of TTS patients are women. The average age is 68 years, 80% of patients are older than 50 years. The recurrence rate of the disease is about 1.8% per year [1]. In 2020, Jabri et al. [3] performed a cohort study that showed a significant increase in the number of confirmed TTS associated with the coronavirus disease 2019 (COVID-19) pandemic.

In addition, based on a retrospective case series, complications and mortality rates in secondary TTS associated with COVID-19 were higher in patients over 70 years of age and in those with low blood pressure (< 110 mmHg), left ventricular ejection fraction (LVEF < 45%), right ventricular (RV) involvement, and mitral regurgitation [2].

The pathophysiology is not well understood, but a sudden huge increase in catecholamines such as adrenaline and norepinephrine due to extreme stress (mental or physical) or a tumor that secretes these chemicals are central to the onset of the disease. When catecholamines are released directly by nerves that shape the heart muscle cells, they have a toxic effect and may lead to a decrease in cardiac muscle function stunning. There are two steps in the catecholamine hypothesis. The first is characterized by a massive release of catecholamines in response to stress. The second phase reflects a cardiovascular response to a rapid increase in the level of catecholamines in the plasma. As a result, left ventricular apical dysfunction, myocardial shock, and paradoxical vasodilation develop, which results in a decrease in cardiac output and acute heart failure. The current Mayo Clinic criteria are the gold standard for the diagnosis of TTS [2]. The symptoms may include transient hypokinesia, akinesia, or dyskinesia in the middle segments of the left ventricle with/without apical involvement; abnormalities of regional wall motion that usually extend beyond the distribution of individual epicardial vessels; a stressor; absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; new echocardiogram abnormalities (ST-segment elevations or T wave inversion) or moderate increase in cardiac troponin; and absence of pheochromocytoma and myocarditis.

PATIENT DESCRIPTION

A 96-year-old female patient was

hospitalized due to a severe infection as a result of severe colitis caused by *Clostridium difficile*. The patient also presented with chest pain, and ST-elevations and changes in the echocardiogram that corresponded to TTS. The patient was confined to a wheelchair but was lucid and lived at home with a caregiver. Medical history included hypertension, hypothyroidism, and ischemic heart disease 2 years earlier. She underwent catheterization due to chest pains, which showed normal coronary arteries. An echocardiogram from the same hospitalization showed normal systolic function without evidence of contraction problems of the left ventricular walls. She was admitted for the first hospitalization due to abdominal pain, watery diarrhea, and high fever. Two weeks before this admission, she was treated in the community with antibiotics (Augmentin and Zenith) with a working diagnosis of urinary tract infection. Laboratory results included a significant increase in inflammation indexes (C-reactive protein [CRP] 220 mg/dl, leukocytosis 30 mm^3) and worsening of kidney functions with creatinine 2.3 (base 1.5–2). The polymerase chain reaction test for COVID-19 was positive. An abdominal X-ray showed no free air or intestinal obstruction. An ultrasound of the kidneys and urinary tract was normal. A diagnosis of *Clostridium difficile* infection was determined and antibiotic treatment with vancomycin and metronidazole was started, with a significant benefit manifested clinically in the absence of fever, diarrhea, and improvement in abdominal pain.

Subsequent laboratory results showed a significant decrease in blood inflammation indexes and improvement in kidney function. After a negative urine culture, the patient was released to a home setting in stable general condition with continued antibiotic treatment with vancomycin.

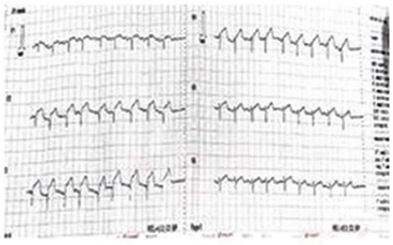
The next day the patient returned to the emergency department due to a decline in her general condition, complaints of generalized abdominal pain, multiple watery diarrheas, chest pain and shortness of breath. On admission, she was 99% sedated in room air, respiratory rate 20, temperature 37.8°C, blood pressure 152/80 mmHg. On physical examination, the patient was fully conscious, uncooperative, and pale with no signs of jaundice. She had regular heart sounds, systolic murmur 3/6 aural point, third sound heard well at the apex. Electrocardiogram ST-segment elevations in leads V2 V3 V4 and ST-depressions in II III aVF were found [Figure 1A]. Laboratory results included leukocytosis 61 mm^3 with deviation to the left without anemia and platelets 500, CRP 340 mg/dl, creatinine 2.9 (latest 1.4), and normal electrolytes. Liver function test results included alkaline phosphatase 130, gamma-glutamyltransferase 52, l-lactate dehydrogenase 290, normal aspartate transaminase / alanine transaminase, and coagulation international normalized ratio 1 prothrombin time 13 partial thromboplastin time 25. Troponin on admission was 300 with a repeat test 8000. In a urine test, leukocytes were moderate, nitrites were negative.

Head computed tomography (CT) showed no acute intracranial hemorrhage or other acute finding and isolated lacunar infarcts in basal ganglia on both sides. A CT scan of the chest, abdomen, and pelvis was performed and a large amount of pleural effusion on the left and a moderate amount on the right was found [Figure 1B].

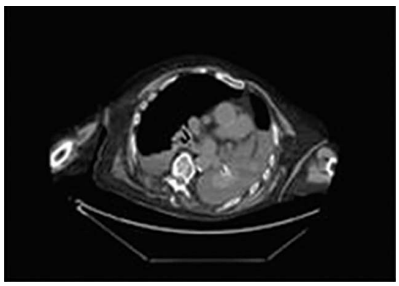
Figure 1. Electrocardiogram and computed tomography results

CT = computed tomography, EKG = electrocardiogram, ECHO = echocardiogram

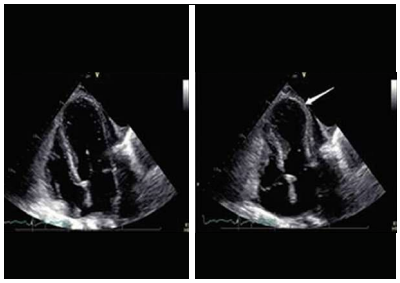
[A] ST-segment elevations in check junctions (EKG)



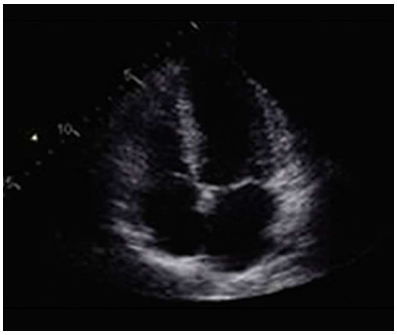
[B] Large amounts of pleural effusions on the left and a moderate amount on the right (CT)



[C] 4-chamber view shows two atriums and two ventricles, left chamber showing signs of akinesis of the anterior wall and apex, apical ballooning (ECHO)



[D] 4-chamber view shows normal sized chambers (ECHO)



There was no evidence of free fluid in the abdominal cavity or of free air. Elongated thickening of the wall of the large intestine was more pronounced than recto-sigma with the differential diagnosis of colitis.

Echocardiogram showed the left ventricle was normal in size, the septum was slightly wide, and its function was poor. Apical and immediately anteroseptal akinesia was demonstrated, with an image of apical ballooning. The right ventricle was normal in size and function. Mild to moderate tricuspid leak and moderately increased pulmonary pressure was noted [Figure 1C]. In an interdepartmental discussion after evaluation of the echocardiogram, no coronary catheterization was performed because the patient was not interested in surgical/invasive intervention.

During her stay in the ward, the patient was under antibiotic treatment for *Clostridium difficile* infection. As part of treatment, the patient received treatment with diuretics, angiotensin-converting enzyme -I and beta-blockers treatment. In a repeat echocardiogram 2 weeks later, preserved systolic function of the left ventricle was demonstrated around 55%, diastolic disturbance grade II, without evidence of disturbance in the contraction of the walls of the left ventricle, and no apical ballooning was observed [Figure 1D].

COMMENT

Infectious diseases and sepsis can disrupt the heart's ventricular function, systolic blood pressure, ventricular dilatation, circulatory volume, and vascular tone by intracellular and extracellular mechanisms; therefore, they are considered important etiological factors for TCM. Case reports are available in the medical literature indicating the development of TCP as a result of Staphylococcus methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumonia*, methicillin-resistant *Staphylococcus saprophyticus*, *Streptococcus pneumonia*, *Klebsiella oxytoca*, *Escherichia coli*, Streptococcus Group B, *Aeromonas hydrophila*, *Clostridium tetani*, *Staphylococcus gallinarum*, and *Staphylococcus aureus* [4]. Furthermore, TCM cases due to viral diseases such as cytomegalovirus and herpesvirus 6 and 12 have been diagnosed. There are also various reports on the relationship between sepsis and TCM. The most widely accepted hypotheses for the pathogenesis of TCM are catecholamine toxicity and microvascular dysfunction. *C. difficile* as a classic anaerobic bacterium is associated with the sympathetic drive. Virulent strains of *C. difficile* release two large molecular weight protein exotoxins identified as toxins A and B. Xia et al. [5] demonstrated that *C. difficile* toxin A causes the prevention of sympathetic inactivation of the intestinal microcircuits that create intestinal motor activity and other intestinal behaviors during *C. difficile* enteritis. Patients predisposed to TCM have elevated endogenous levels of catecholamines and a differential distribution of adrenergic receptors across the myocardium. This situation is further strengthened by highlighting the role of other sympathetic hyperdrive conditions such as acute pancreatitis, pheochromocytoma, stroke, and subarachnoid hemorrhage caused by TCM. In addition, the shock that develops with *C. difficile* infection may cause transient myocardial dysfunction and microvascular hypoperfusion. The pathophysiological mechanism of the development of TCM in our patient may have been caused by an increase in catecholamine due to *C. difficile* and hypovolemia. However, the exact pathogenesis of the induced TCM remains to be determined and needs further investigation. In our patient, who was hospitalized with severe colitis and changes in electrocardiogram and echocardiography that passed a week later without coronary intervention and without anti-ischemic treatment, it is more likely that the cardiac picture in the patient is TTS.

CONCLUSIONS

The present case is a rare report of TCM associated with *C. difficile* infection. Although rare, additional clinical studies are needed to expand the scope of our knowledge about this relationship and formulate guidelines for standardizing the treatment of these patients. Physicians involved in the treatment of patients with *C. difficile* infection must be aware of this complication and should consider TCM in those who develop chest pain accompanied by echocardiogram and echocardiogram changes.

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