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Fixing the "Broken Heart": Pharmacologic Implications

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Broken-heart syndrome also known as Left ventricular apical ballooning syndrome or Stress-induced cardiomyopathy or Takotsubo cardiomyopathy is an important clinical entity, which presents clinically, similar to acute coronary syndrome with an acute onset of chest pain, ST-T changes in electrocardiogram, and moderate cardiac enzyme elevation. Recent studies have shown that it accounts for 1%–2% of cases of ST-elevation infarction. An episode of intense emotional or physiologic stress has been reported before its presentation and is presumed to be the triggering factor in the pathogenesis. The pathophysiology of this syndrome still remains unclear, and management is mostly empiric and supportive. In this review, we have discussed various pathophysiologic mechanisms underlying this cardiomyopathy and their pharmacological implications and role of medications such as aspirin, beta blockers, angiotensin-converting enzyme inhibitors, and statins for patients presenting with this syndrome in treatment and prevention.

Keywords: broken-heart syndrome, left ventricular apical ballooning syndrome, acute coronary syndrome, beta blockers, ACE inhibitors, aspirin, Takotsubo cardiomyopathy, catecholamines

INTRODUCTION

Broken-heart syndrome also known as Left ventricular apical ballooning syndrome, Stress-induced cardiomyopathy, Ampulla cardiomyopathy, and Takotsubo cardiomyopathy (TC) is a clinical entity first described in 1991 in Japan by Sato and coworkers[1] Since then, many case series have been reported from Japan.[2–10] It has since received increasing attention worldwide with many cases being reported the from United States[11–13] and from Europe.[14,15]

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It has been called Takotsubo cardiomyopathy because of *its classical appearance on echocardiogram* that is characterized by an akinetic left ventricular apex with hyperkinesis of the basal walls producing an elliptical shape, which resembles a Japanese fishing pot used to trap octopus (a Tako-tsubo).[1]

An episode of intense emotional or physiologic stress has been reported before presentation and is presumed to be the triggering factor in the pathogenesis. For this reason, the condition is known as "Broken-Heart syndrome" or "Stress-Induced Cardiomyopathy."[12] In 2006, the syndrome was reclassified within the subgroup of primary acquired cardiomyopathies. [16]

The clinical presentation is similar to that of myocardial infarction (MI) with an acute onset of chest pain, ST elevation in electrocardiogram (ECG), and moderate cardiac enzyme elevation. Despite its presentation as an acute coronary syndrome (ACS), it has normal coronary arteries on cardiac catheterization, and as long as the patient receives appropriate hemodynamic support, it typically undergoes spontaneous reversal.[17] Although >300 publications have

been written, pathophysiology of this syndrome still remains unclear. Many case series have reported high circulating levels of catecholamines in patients with this cardiomyopathy, which are thought to play an important role in the pathophysiology of this syndrome.[11]

REVIEW CRITERIA

A comprehensive search of the MEDLINE database from 1965 to March 1, 2010, was performed. Search terms included ''Tako-tsubo,'' ''ampulla-shaped cardiomyopathy,'' ''stress cardiomyopathy,'' ''Takotsubo,'' and ''apical ballooning.'' Additionally, the citation sections of retrieved articles were reviewed to identify additional relevant articles.

PREVALENCE

The true prevalence of apical ballooning syndrome still remains unclear. The national heart, lung, and blood institute estimated that in 2007, in the United States, about 1.2 million people would have an MI, and according to recent studies, apical ballooning syndrome accounts for 1%–2% of cases of ST-elevation infarction[18] suggesting that 12,000–24,000 Americans might have had this syndrome in 2007.

Most patients with TC are postmenopausal women. Furthermore, it has been estimated that among women presenting with ACS, as many as 6% may actually have TC.[19] Wittstein et al[11] reported that among patients with this syndrome, 86% were female with mean age of 67 years (95% CI 61–73 years) although cases of TC have been reported in individuals aged 10–91 years.

PATHOPHYSIOLOGY

The precise pathophysiology of TC is unknown. A number of features of TC, including its strong association with emotional or physical stress, suggest that catecholamines play an important role in the pathogenesis. Various mechanisms have been proposed, which include epicardial coronary artery spasm, coronary microvascular abnormality; catecholamines mediated direct myocardial damage and neurogenic myocardial stunning.

Multivessel epicardial coronary spasm

Dote et al[1] suggested that transient multivessel epicardial coronary spasm may be responsible for wall motion abnormality seen in patients with this syndrome. Increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease.[21] However, only the minority of studies have reported spontaneous or provocable epicardial coronary spasm during angiographic studies.[5,10,22] Moreover, multivessel spasm and ischemically stunned myocardium would cause a marked increase in cardiac enzymes and well-defined ECG changes, which is uncommon in patients with TC.

The duration of TC is usually longer than that observed in patients with coronary spasm. Moreover, many studies failed to show coronary vasospasm provoked by intracoronary acetylcholine in patients with this syndrome.[23]

On endomyocardial biopsy, the majority of patients with TC show mononuclear infiltrates and contraction bands without any evidence of necrosis, which is quite different from changes of coagulation necrosis seen in ischemic myocardium.[5,9,10,15]

Ibanez et al reported the presence of plaque rupture in patients with TC via intravascular ultrasound. However, the area of abnormal left ventricular wall motion would not be expected to extend beyond the territory normally supplied by the artery.[15]

Coronary microvascular dysfunction (ischemically stunned myocardium)

Reversible coronary microvascular dysfunction can play an important pathogenic role in patients with left ventricular apical ballooning syndrome. Left ventricle (LV) wall motion abnormalities occur in a relatively large area of apical myocardium, and abnormalities are dynamic rather than fixed.[24]

Abe et al[9] evaluated coronary microcirculation using the Doppler Guide wire and suggested that there was no significant microcirculatory abnormality in patients with this cardiomyopathy. In contrast, Kume et al[25] demonstrated that patients with TC have significant microcirculatory dysfunction in the acute phase. In another case series, it was found that the thrombolysis in myocardial infarction frame count, a validated index of coronary blood flow,[26] was significantly higher in patients with stress cardiomyopathy when compared with controls during both the acute phase and follow-up, suggesting coronary microvascular impairment.[27] Nuclear imaging studies that assessed myocardial perfusion using single photon emission computed tomography imaging have shown decreased perfusion in the absence of obstructive coronary lesions suggesting the presence of coronary microcirculation abnormalities in patients with TC.[5,7,11,17]

A recent study measured coronary flow reserve in patients with this syndrome in the acute stage and compared that with the coronary flow reserve after recovery phase. This showed that there was a significant improvement in the recovery phase in the same

patients correlating well with improvement in left ventricular function. This supports the hypothesis of microcirculatory postischemic stunning as a probable concurring phenomenon.[28]

However, It is still unclear that microcirculatory impairment is the primary cause of this cardiomyopathy or it is a consequence of increased mechanical wall stress resulting from apical ballooning.

Catecholamine-mediated myocyte toxicity (neurogenic myocardial stunning)

Elevated levels of catecholamines are thought to play a pivotal role in the pathogenesis of this cardiomyopathy.[11,29] Catecholamine surge is thought to occur secondary to acute emotional or physiological stress after activation of the adrenomedullary and sympathoneural systems.

High plasma catecholamine levels in patients with pheochromocytoma[30] and intracranial pathology such as subarachnoid hemorrhage[31] are well known to induce a similar type of clinical picture along with histopathological findings. Endomyocardial biopsy results in patients with TC show striking resemblance to catecholamine-induced cardiomyopathy in both animals[32] and humans.[33]

Elevated catecholamines directly decrease the viability of myocytes through cyclic adenosine monophosphate–mediated calcium overload[34] and oxygen dependent free-radical generation, which can be attenuated by using antioxidants in animal model.[35,36] A rat model of TC has been reported in which physical immobilization produces similar cardiomyopathy that is prevented by pretreatment with an alfa and beta adrenergic antagonist.[37]

This catecholamine-mediated 'metabolic myocardial stunning' is further supported by nuclear-imaging studies using metabolic tracers such as I-123 beta-methyliodophenylpentadecanoic acid and 18 fluorodeoxyglucose, which have shown marked reduction in regional free fatty acid metabolism and extracellular glucose transport in the segments with wall motion abnormalities in patients with this cardiomyopathy[5,7,38]

TC is characterized by akinesis or hypokinesis at apical and midventricular regions of LV along with basal hyperkinesis. The reason for this distinctive pattern is less well understood. Local release of catecholamines from cardiac sympathetic efferent neurons is an unlikely explanation, given the higher norepinephrine content[39] and greater density of sympathetic nerves at the base of the heart[40] than in the apex. However, the LV apex contains a higher concentration of adrenoceptors, making it more vulnerable to sudden surges in circulating catecholamine levels.[41] Lyon et al[42] have hypothesized that high circulating epinephrine levels might trigger a switch from Gs to Gi intracellular protein signaling in beta-2 adrenoceptors leading to negative inotropy. As beta-2 receptor concentration as higher at apex rather than at base, apical wall motion abnormality is commonly seen in patients with this cardiomyopathy.

Majority of patients affected by this cardiomyopathy are female. The basis of this biological predisposition is unknown. Sex hormones exert an important influence on coronary vasoreactivity[43] as they have on the sympathetic neurohormonal axis.[44] Men have higher levels of basal sympathetic activity than do women, produce higher levels of plasma catecholamines in response to emotional stress,[45] and are more sensitive to catecholamine-mediated vasoconstriction.[46] However, women seem to be more vulnerable to sympathetically mediated myocardial stunning. Postmenopausal decline in estrogen levels along with reduction in its cardioprotective effects might predispose women to this syndrome.

In summary, the available pathophysiological information indicates that high local concentration of catecholamine-induced metabolic myocardial stunning associated with or without coronary microvascular dysfunction is the main pathogenic mechanism producing TC.

CLINICAL PRESENTATION

The clinical presentation of TC is usually similar to ACS. The patients with this syndrome usually present with chest pain, dyspnea, ST-segment elevation, and moderately elevated cardiac biomarkers similar to those of MI. As a result, all the guidelines have acknowledged TC as an important differential diagnosis of ACS.[47]

The onset of symptoms is usually sudden and occurs after an emotional or physiological stressor.[2–15] Ito et al showed the presence of a preceding emotional stressor in 30% of patients, whereas a preceding physiological stressor was present in 40% of the patients with this syndrome (Table 1).[7]

Symptoms

The common reported symptoms include chest pain, dyspnea, syncope, nausea, fatigue, and back pain. According to a systemic review, chest pain was reported to be the cardinal presenting symptom in 67.8% of patients with dyspnea being the other common presentation in 17.8% of the cases.[48] Other less common presenting symptoms are Hypotension, Syncope, Back pain, Fatigue, and Nausea.

The degree of symptom severity varies widely. Sometimes, patients may present with acute pulmonary edema or significant left-sided heart failure.

Table 1. Emotional stressors associated with a ''Broken Heart''.[11,48–57]

Car accident
Fear of procedure
Armed robbery
Domestic abuse
Devastating business
Fear of choking
Surprise party
Unexpected death of relative or friend
Gambling losses
Public performance
Confrontational argument
Surprise reunion
Natural disasters like earthquakes
Catastrophic medical diagnosis

Presentation might get complicated sometimes by the presence of arrhythmias such as ventricular tachycardia and fibrillation (1.5%) or cardiogenic shock (4.2%).[48]

Electrocardiography

Abnormalities on ECG are common at the time of presentation. The most common finding is convex ST-segment elevation seen more frequently in anterior precordial leads. Most series have reported ST elevation in >80% of the patients with stress cardiomyopathy at the time of presentation. Deep symmetric T wave inversion is another common finding present in up to 60% of cases. It is usually seen within 24–48 hours after presentation accompanied by QT interval prolongation. Pathological Q waves are also seen in up to one-third of the patients. However, Q waves typically get resolved before hospital discharge with restoration of normal R wave progression.[11]

No ECG criteria have been identified that can reliably discriminate between stress-induced cardiomyopathy and MI.[58]

Cardiac Enzymes

Small but brisk elevation in cardiac enzymes, troponin I, and creatine kinase-MB (CK-MB) is common in the patients with apical ballooning syndrome. Most case series have shown that 85% patients have elevated troponin I, whereas 70% patients have elevated CK-MB, although this increase is significantly less in comparison to patients with acute MI. According to a study, >95% patients with acute MI show more than 3- to 11-fold increase in Troponin I and 2-fold increase in CK-MB.[59]

Plasma catecholamines and brain natriuretic peptide

Patients with this syndrome show increased levels of catecholamines and brain natriuretic peptide (BNP) in comparison with normal subjects and patients with MI. On hospital day 1 or 2, the plasma levels of catecholamines and BNP among patients with TC were 2–3 times higher than among the patients with Killip class 3 MI and 7–34 times higher than among normal subjects. By hospital day 7, 8, or 9, the plasma levels of most catecholamines were one-third to half their peak values but remained substantially higher than those in patients with MI. The plasma BNP levels, however, declined rapidly with improving left ventricular function and by day 7, 8, or 9 were lower than those in patients with MI.[11]

Cardiac catheterization and echocardiography

Despite the clinical presentation, patients with TC typically do not have angiographically identifiable obstructive epicardial coronary artery disease that could account for observed wall motion abnormality.[2,15] Spontaneous or provocable multivessel epicardial spasm has been reported only in the minority of the patients.[5,10]

The left ventriculogram typically shows apical and midventricular akinesis or hypokinesis along with basal hyperkinesis (Tako-tsubo appearance). Atypical cases of isolated basal left ventricular dysfunction (known as inverted Takotsubo pattern) or global left ventricular hypokinesis have also been reported.[60–63]

Figure 1 shows the end-diastolic (left) and end-systolic (right) frames from the Left ventriculogram of a patient with ''Broken-Heart syndrome'' showing apical ballooning during systole.

A systemic case series demonstrated that EF in patients with this syndrome is typically reduced ranging between 20% and 49% at the initial presentation. However, over a period of days to weeks, all patients showed improvement in EF with a value between 58% and 75%.[15]

DIAGNOSIS

TC is often considered a diagnosis of exclusion, which is usually identified after a coronary angiography reveals the absence of obstructive CAD with a history of intense emotional or physical stress and an echocardiogram that shows a characteristic balloon-like appearance of the LV.

Proposed Mayo criteria for the diagnosis are as follows:

(1) transient hypokinesis, akinesis, or dyskinesis of the LV apical and/or midsegments extending beyond a single epicardial coronary artery distribution;
(2) absence of obstructive epicardial CAD or angiographic evidence of acute plaque rupture that could be responsible for the observed wall motion abnormality;

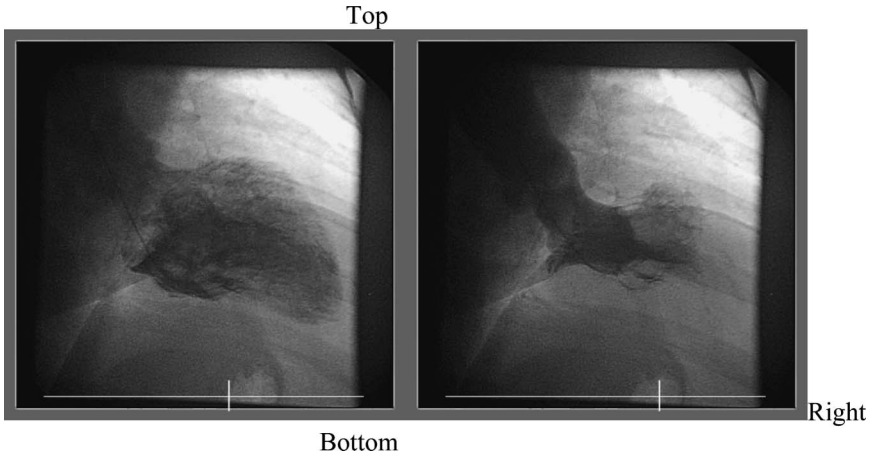

FIGURE 1. End-diastolic (left) and end-systolic (right) frames from the left ventriculogram of a patient with ''Broken-Heart syndrome'' showing apical ballooning during systole (right).

(3) new ECG abnormalities (ST elevation and/or T wave inversion) or elevated cardiac Troponin I;
(4) absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive epicardial coronary artery disease, myocarditis, and hypertrophic cardiomyopathy.[20]

All the 4 criteria need to be met for a diagnosis to be made. These criteria have been modified recently[64] and accepted by the American College of Cardiology/American Heart Association for diagnosis of this cardiomyopathy.

COMPLICATIONS

Table 2 gives the complications associated with Stress Cardiomyopathy.[20,48,65,66]

MANAGEMENT

As TC is a novel syndrome, there are yet no randomized double blind studies for management guidelines. As such patients with TC are initially managed on the lines of acute ST elevation MI or ACS although there are certain important differences in treatment strategies in comparison to ACS. Patients are initially managed with aspirin, nitrates, and beta blockers. Many patients even undergo coronary angiography and are found to have normal or nonobstructive coronary arteries.

In 1 multicentric study, 36 patients affected by TC were analyzed retrospectively for the benefits of a treatment with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, aspirin, and calcium channels blockers started in the early phases of the disease and continued for 30 days. The results obtained from the study failed to show any statistically significant difference in the percentages of improvement in the LV ejection fraction evaluated at the admission to the hospital, before the discharge, and after 30 days of treatment between each treated group and the control group of nontreated patients. Also, there was no statistically significant difference in hospitalization times between treated patients and controls, and this analysis also suggested that chronic treatment with beta blockers, ACE inhibitors, calcium channels blockers, and aspirin does not provide any additional benefit in patients with TC.[67] Thus, it seems important to obtain an early correct differential diagnosis to avoid any chronic treatment in these patients.

In another retrospective analysis of 45 patients affected by TC, the use of a drug therapy with inotropics, ACE-inhibitors, or beta blockers did not give any advantage in the improvement of cardiac performance. Instead, a worse outcome was reported in patients treated with a low dose of dobutamine and diuretics groups.[68] Nitrates are often used to relieve chest pain in patients with ACS or stable angina. But their role in management of TC is not well established. In 1 case series, patients despite being on nitrates, developed TC.[57]

Table 2. Complications associated with stress cardiomyopathy.[20,48,65,66]

Ventricular arrhythmias
Left ventricular mural thrombus formation
Cardiogenic shock
Transient complete atrio ventricular block
Left ventricular failure with or without edema
Left ventricular outflow obstruction
Left ventricular free wall rupture
Mitral regurgitation from systolic anterior motion of mitral valve leaflet

Patients with TC often present to the emergency room with an acute ST-elevation myocardial infarction. Some of these patients present with a clinical picture of cardiogenic shock. The management of hemodynamic instability in these patients is different from patients with ST-elevation myocardial infarction. Although hemodynamic instability in the setting of ST-elevation MI is usually treated with vasopressors and intraaortic balloon counterpulsation, these therapies can increase left ventricular outflow tract (LVOT) pressure gradients in patients with this syndrome and lead to a worsening of shock.[69] Thus, an accurate diagnosis and correct management are essential to prevent mortality in these patients, who will usually go on to have good long-term outcomes. Patients with apical ballooning syndrome who present with hypotension should be evaluated for a dynamic intraventricular pressure gradient in the LV cavity and LVOT by either echocardiography or left heart catheterization. Hemodynamic instability in patients with dynamic intraventricular obstruction is managed by the administration of beta blockers to increase diastolic ventricular filling time and end-diastolic volume and administration of fluid resuscitation if pulmonary congestion is not present.[70,71] Phenylephrine, an alfa agonist, can also be added to increase the afterload.[72]

If LVOT obstruction is absent, vasopressors or intra-aortic balloon pump can be used for resuscitation. However, catecholamines-induced myocardial stunning is generally accepted as the basis for this syndrome, and controversy exists over the use of vasopressors for hypotension. As there have been case reports of development of LVOT obstruction during dobutamine infusions, the use of catecholamine-based vasopressors during is still controversial.[73] A newer medication known as Levosimendan, a calcium-sensitizing agent, has shown good results in patients with cardiogenic shock. It improves ventricular relaxation during diastole and demonstrates antistunning and vasodilator effects by opening the ATP-sensitive K^+-channel. Padayachee et al[74] and De Santis et al[75] have proposed that Levosimendan is the inotrope of choice in TC with cardiogenic shock.

Nicorandil is an antianginal drug, which acts by activating ATP-sensitive potassium channels ands acts as a nitrous oxide donor. It also protects cardiac mitochondria against permeability transition induced by ischemia reperfusion.[76] Ito et al showed that intracoronary nicorandil can acutely reduce the level of ST-segment elevation.[77] In 1 case series, nicorandil was used in 4 patients after the onset of TC, and none had the recurrence of tako-tsubo cardiomyopathy during the 3-year follow-up. However, larger studies are required to establish the role of nicorandil in TC.[67]

Patients presenting with heart failure are usually treated initially with diuretics, ACE I, and beta blockers as tolerated. Still long-term therapy with these agents after ventricular function has been normalized remains controversial.

Short-term anticoagulation should be considered in patients with significant left ventricular systolic dysfunction to prevent left ventricular mural thrombus formation. This therapy should be continued until left ventricular function has improved.[78]

In this syndrome, the patient's vulnerability to arrhythmic trigger is increased due to the high level of catecholamine as demonstrated by Wittstein et al.[20] Beta blockers could be of particular interest in such ventricular arrhythmias. However, in the clinical setting, treatment with antiarrhythmic medications does not significantly differ from standard guidelines of managing cardiac arrhythmia.

Another cornerstone in managing these patients, which is equally thought important nowadays is identifying the stressor and providing targeted emotional support in addition to the standard psychological counseling provided to all cardiac patients. There have been case reports suggesting that emotional support along with medications like sedatives have aborted chest pain and other symptoms with an equally good long-term outcome in comparison to other pharmacological therapies.[79] A multidisciplinary approach including social worker, pastoral care and mental health care providers has been found beneficial for patients suffering from this cardiomyopathy.

Regarding primary or secondary prophylaxis of this syndrome, randomized trials are required to evaluate efficacy of various medication such as aspirin, beta blockers, and statins, which are used as prophylactic therapy for patients with or at high risk for coronary artery disease. One retrospective analysis of 21 patients with this syndrome showed that stress-induced cardiomyopathy could occur despite pretreatment with calcium channel blockers, nitrates, beta blockers, statins, or aspirin, suggesting limitation of these medications to prevent tako-tsubo cardiomyopathy.[80]

Thus, management of this syndrome is largely supportive and empiric. Data are mostly retrospective with a small number of patients. The precise role of various medications is less well established. Larger randomized prospective studies are required to clearly define pathophysiology and study the role of various medications in treatment and in prophylaxis.

CLINICAL OUTCOME AND PROGNOSIS

The prognosis of patients with this cardiomyopathy is generally favorable. The reported in-hospital mortality

is low (1%–3%).[20,48,56] Mortality is usually due to complications associated with this syndrome. Heart failure with or without pulmonary edema is the most commonly reported complication.[48] Most patients recover left ventricular function within ensuing 1–3 months.

Data regarding the risk of recurrence are limited. However, most studies suggest that the recurrence rate in the first few years after presentation is likely to be in the range of 2.7%–15%.[10,12,14,20] Still long-term follow-up studies are required to estimate true recurrence.

CONCLUSIONS

Broken-heart syndrome is a common occurrence specifically among postmenopausal women after sudden emotional or physiological stress. Its clinical presentation is similar to ACS although there are certain important differences. The classical appearance of apical ballooning on echocardiogram, normal coronary arteries on angiogram, and return of the cardiac function within weeks of the initial event are the hallmark of this cardiomyopathy. Although the exact pathophysiological mechanism underlying this cardiomyopathy remains less well understood, catecholamine-induced myocardial stunning is one of the most favored theory explaining cardiac dysfunction in this syndrome. Patients with this syndrome are usually initially treated on the lines of management of ACS, but the effectiveness of this therapy still remains to be established in randomized control trials. This cardiomyopathy presents as a diagnostic and therapeutic dilemma; these patients who often present as having ACS are treated with medications such as Beta Blockers, ACE inhibitors, calcium channel blockers, statins, and aspirin, which do not provide any benefit in improving the ventricular function or hospitalization time. Due to differences in efficacy and role of pharmacotherapeutic agents in management of this syndrome, this cardiomyopathy needs to be differentiated from ACS. Larger prospective randomized trials are required to evaluate the role of pharmacotherapy in treatment and in prevention of Broken-Heart syndrome.

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