Author’s response to reviews

Title: Takotsubo cardiomyopathy after an Upper and Lower Endoscopy: A Case Report and Review of Literature

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Please see responses below. For the comments that did not require any responses (i.e. if the reviewers did not suggest any changes, we did not include below).

4. Does the article report the following information? Where information is missing, please specify

- Medical, family and psychosocial history:

Medications given during her hospitalization included: 10 mg oxybutynin extended-release oral tablet once a day for urinary symptoms; 40 mg omeprazole oral tablet once a day for GERD; 10 mg amlodipine oral tablet once a day for HTN; 300 mg bupropion extended-release oral tablet once a day for depression; 20 mg escitalopram oral tablet once a day for depression; 100 mg topiramate oral tablet once a day for neuropathy; 50 mg tramadol oral tablet as needed every four hours for pain; and 135 mg fenofibric acid delayed-release oral tablet once a day for HLD. She did not have any known allergies. Family history was significant for myocardial infarction in her father and cerebrovascular accident in her mother. She was married with two children, retired, previously worked for an advertising agency, and resided in Manhattan. She smoked one pack of cigarettes per day for 30 years and quit in 2001. She drank two alcoholic drinks per night.
b. The relevant physical examination findings.

Vitals at the time were: afebrile (36.8°C); heart rate of 101, blood pressure of 116/59, respiratory rate of 16, and oxygen saturation of 93% on room air. Our patient was a well appearing female, alert and in no acute distress. She was well-hydrated and well nourished. Skin color, texture, and turgor were all normal without any suspicious rashes or lesions. Head was normocephalic and atraumatic without any masses, lesions, or tenderness. Eye exam included anicteric sclera, with pupils that were equally round and reactive to light, with intact extraocular movements. Ears, nose, and throat exam were all normal. Neck was supple without any adenopathy. Thyroid was normal size, symmetric without any bruits. Lungs were clear to auscultation without any wheezing, rhonchi, or rales. Heart sounds included a regular rhythm and rate without murmurs, rubs or gales. Abdominal exam was normal, with a soft, non-tender abdomen, normoactive bowel sounds and was non-significant for masses or organomegaly. Extremities did not show any deformities, edema, skin discoloration, clubbing, or cyanosis, and had good capillary fill. There was no joint swelling, deformity, or tenderness. Peripheral pulses were normal. The patient was alert and oriented x 3. Speech was fluent with appropriate repetition and comprehension. Cranial nerves II-XII were intact without any deficits. Gait was normal and steady. Sensation (light touch, pinprick, position sense, and vibration sense) was grossly intact. Reflexes were 2+ and symmetric at the biceps, triceps, knees, and ankles. There was no pronator drift of out-stretched arms, muscle bulk and tone were normal, with full strength bilaterally.

c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month. Not-applicable

d. Diagnostic assessments, including:

- Diagnostic methods – Prior to presentation, the patient had three endoscopies, where her post-procedure course was uncomplicated. Upper and/or lower endoscopies took place on 03/11/2013, 05/29/2014, and 12/03/2015 for epigastric abdominal pain, periumbilical abdominal pain, and chronic diarrhea, respectively.
- Challenges (e.g., financial, language/cultural) – not applicable, patient social history is reported

- Reasoning and prognostic characteristics (e.g., staging), where applicable – not applicable

e. Types and mechanism of intervention: not applicable

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments: Yes-Needs to improve.

Takotsubo cardiomyopathy is a reversible cardiomyopathy that typically occurs in older women over the age of 50 and can mimic an acute coronary syndrome.1,2 It can be diagnosed in several ways, including one or more of these criteria: “transient left ventricular dysfunction presenting as apical ballooning or with focal wall motion abnormalities; an emotional, physical, or combined trigger; triggers of neurologic disorders; new ECG abnormalities; elevated cardiac biomarker (troponin and creatine kinase) levels; no evidence of infectious myocarditis; and/or postmenopausal women.”3

9. Additional comments for the author(s)?

Following are my comments and suggestions to the authors
1. Background:

Authors wrote 'While widely considered safe, adverse cardiovascular events can occur in high-risk patients undergoing endoscopy'. This statement needs some evidence and citations. Advice to elaborate on the topic for the reader to understand the potential cardiovascular events and it is important to diagnose the Takotsubo cardiomyopathy.

This sentence has been removed, as there is very limited literature out there on high risk patients undergoing endoscopy and cardiovascular events in the setting of cardiomyopathy. We describe the cases in the report, but there are not much data out there besides what we reported.

Authors wrote 'To date, there have only been six reported cases of stress cardiomyopathy in patients post-endoscopy. We present the second reported case of Takotsubo cardiomyopathy following an upper and lower endoscopy'. They say 6 reported cases and then mention their case is the second reported case. Confusing and needs clarification.

To date, there have only been six reported cases of stress cardiomyopathy in patients post-endoscopy. We present the second case of takotsubo cardiomyopathy following both an upper and lower endoscopy.
2. Case presentation:

- Please mention patients’ current medications, allergy, social and brief family history.

Medications given during her hospitalization included: 10 mg oxybutynin extended-release oral tablet once a day for urinary symptoms; 40 mg omeprazole oral tablet once a day for GERD; 10 mg amlodipine oral tablet once a day for HTN; 300 mg bupropion extended-release oral tablet once a day for depression; 20 mg escitalopram oral tablet once a day for depression; 100 mg topiramate oral tablet once a day for neuropathy; 50 mg tramadol oral tablet as needed every four hours for pain; and 135 mg fenofibric acid delayed-release oral tablet once a day for HLD. She did not have any known allergies. Family history was significant for myocardial infarction in her father and cerebrovascular accident in her mother. She was married with two children, retired, previously worked for an advertising agency, and resided in Manhattan. She smoked one pack of cigarettes per day for 30 years and quit in 2001. She drank two alcoholic drinks per night.

- Patient has a diagnosis of Lymphocytic colitis. Has she had any prior endoscopies? If she did then how was she during those procedures?

- Why did she have the procedures scheduled?

- What anesthetic agents and pre-procedural medications were used? Eg: There are reports on meperidine (used for pre-colonoscopy sedation) causing the takotsubo syndrome (1) – please note, meperidine was not used for our patient

Prior to presentation, the patient had three endoscopies, where her post-procedure course was uncomplicated. Upper and/or lower endoscopies took place on 03/11/2013, 05/29/2014, and 12/03/2015 for epigastric abdominal pain, periumbilical abdominal pain, and chronic diarrhea, respectively.
Pre-procedural medications for her lower endoscopy included the Prepopik prescription medicine, which is a combination of sodium picosulfate (a stimulant laxative) and magnesium citrate (an osmotic laxative), used to prepare for a colonoscopy. The anesthetic agents she received during the procedure included: 50 mcg of fentanyl; 1 mg of midazolam; and 280 mg of propofol. Biopsies were taken throughout the esophagus, stomach, duodenum, jejunum, ileum, and colon. The upper endoscopy and lower endoscopy took 5 and 25 minutes to complete, respectively.

-Please provide reference ranges for all the laboratory parameters.

All normal ranges have been added throughout the report.

-Provide images of the 2D ECHO.

This has been added as figure 2.

3.Discussion and Conclusions:

- Table 1. Needs to provide references.

References are listed as subheadings and also within the column of the table.

-Please discuss any available literature on how to evaluate and prevent the Takotsubo before the endoscopies. Any evidence on post-procedure care or monitoring in patients.
There is very limited literature on preventing takotsubo in patients before an endoscopy due to the rarity of the two presenting together.

-If possible, please provide the diagnostic criteria for the takotsubo syndrome:

Takotsubo cardiomyopathy is a reversible cardiomyopathy that typically occurs in older women over the age of 50 and can mimic an acute coronary syndrome.1,2 It can be diagnosed in several ways, including one or more of these criteria: “transient left ventricular dysfunction presenting as apical ballooning or with focal wall motion abnormalities; an emotional, physical, or combined trigger; triggers of neurologic disorders; new ECG abnormalities; elevated cardiac biomarker (troponin and creatine kinase) levels; no evidence of infectious myocarditis; and/or postmenopausal women.”3

- Authors wrote' Myocardial infarction has a similar clinical presentation to that of Takotsubo cardiomyopathy; however, they have significant differences in treatment, prognosis, and complications'. Needs a reference.

References have been added

Myocardial infarction has a similar clinical presentation to that of takotsubo cardiomyopathy; however, there are significant differences in treatment, prognosis, and complications.1,2

The case report should include social, environmental, family and employment history.

Did the patient smoke, and/or consume alcohol?
Give detailed neurological examination on admission. What was the pulse, blood pressure and temperature, on admission?

In the emergency room, the patient was noted to be afebrile, tachycardic to the low 100s, normotensive (116/59), and respiring at 93% on room air with a respiratory rate of 16. Vitals at the time were: afebrile (36.8°C); heart rate of 101, blood pressure of 116/59, respiratory rate of 16, and oxygen saturation of 93% on room air. Our patient was a well appearing female, alert and in no acute distress. She was well-hydrated and well nourished. Skin color, texture, and turgor were all normal without any suspicious rashes or lesions. Head was normocephalic and atraumatic without any masses, lesions, or tenderness. Eye exam included anicteric sclera, with pupils that were equally round and reactive to light, with intact extraocular movements. Ears, nose, and throat exam were all normal. Neck was supple without any adenopathy. Thyroid was normal size, symmetric without any bruits. Lungs were clear to auscultation without any wheezing, rhonchi, or rales. Heart sounds included a regular rhythm and rate without murmurs, rubs or gallops. Abdominal exam was normal, with a soft, non-tender abdomen, normoactive bowel sounds and was non-significant for masses or organomegaly. Extremities did not show any deformities, edema, skin discoloration, clubbing, or cyanosis, and had good capillary fill. There was no joint swelling, deformity, or tenderness. Peripheral pulses were normal. The patient was alert and oriented x 3. Speech was fluent with appropriate repetition and comprehension. Cranial nerves II-XII were intact without any deficits. Gait was normal and steady. Sensation (light touch, pinprick, position sense, and vibration sense) was grossly intact. Reflexes were 2+ and symmetric at the biceps, triceps, knees, and ankles. There was no pronator drift of out-stretched arms, muscle bulk and tone were normal, with full strength bilaterally.

Give the doses of all medications that were given:
Medications given during her hospitalization included: 10 mg oxybutynin extended-release oral tablet once a day for urinary symptoms; 40 mg omeprazole oral tablet once a day for GERD; 10 mg amlodipine oral tablet once a day for HTN; 300 mg bupropion extended-release oral tablet once a day for depression; 20 mg escitalopram oral tablet once a day for depression; 100 mg topiramate oral tablet once a day for neuropathy; 50 mg tramadol oral tablet as needed every four hours for pain; and 135 mg fenofibric acid delayed-release oral tablet once a day for HLD.

Give all results of laboratory findings (i.e. electrolytes, calcium, mag, CBC, liver and renal functions), urinalysis, serology etc).

Initial laboratory studies revealed a hemoglobin of 11.5 g/dL (normal range for females: 12.0 to 15.0 g/dL), which was the patient’s baseline hemoglobin, a troponin I (normal range: 0 to 0.4 ng/mL) of 8 ng/mL, and a B-type natriuretic peptide of 2900 pg/mL (normal range: up to 100 mg/L). Other laboratory findings, including electrolytes, liver function tests, renal function tests, complete blood counts, serology and urinalysis were all within normal limits.

Give information about follow-up for at least 6 months.

Nine months post-discharge, she was admitted for worsening lower extremity edema. A transthoracic echocardiogram (TTE) at the time was significant for a high left ventricular outflow tract (LVOT) gradient (peak LVOT gradient of 42 mmHg at rest and 122 mm Hg with Valsalva maneuver). Ejection fraction (EF) (normal range: 55-70%) at the time was 81% and pertinent results from TTE included: fibrocalcific changes of the aortic valve with mildly reduced opening; moderate mitral annular calcification; systolic anterior motion of the anterior mitral valve leaflet; and normal functioning left atrium, right ventricle, tricuspid valve, and pulmonic valve. She was discharged with instructions on avoiding diuresis and beginning initiation of metoprolol (6.25 mg every 6 hours) for negative inotropy and to decrease systolic anterior motion.

Expand the paragraph at the end of the Introduction and explains why this case report is presented (what is unique and adds to the medical knowledge)
This case is published to help other health professionals understand what medical management was used when treating at-risk patients who underwent endoscopies and experienced symptoms of stress cardiomyopathy, as this presentation is generally uncommon.

Medications given on admission should be presented when you describe the admission events.

Please note, the patient was on the same list of medications prior to admission, during her hospitalization, and after she was discharged. In addition, the medications list has been moved lower down in the background section.

Medications taken prior to admission, during hospitalization, and after discharge included: 10 mg oxybutynin extended-release oral tablet once a day for urinary symptoms; 40 mg omeprazole oral tablet once a day for GERD; 10 mg amlodipine oral tablet once a day for HTN; 300 mg bupropion extended-release oral tablet once a day for depression; 20 mg escitalopram oral tablet once a day for depression; 100 mg topiramate oral tablet once a day for neuropathy; 50 mg tramadol oral tablet as needed every four hours for pain; and 135 mg fenofibric acid delayed-release oral tablet once a day for HLD.

No need to give the medications given during the endoscopies.

These medications have been removed.

Pre-procedural medications for her lower endoscopy included the Prepopik prescription medicine, which is a combination of sodium picosulfate (a stimulant laxative) and magnesium citrate (an osmotic laxative), used to prepare for a colonoscopy. The anesthetic agents she received during the procedure included: 50 mcg of fentanyl; 1 mg of midazolam; and 280 mg of propofol.
This sentence that does not make sense and need to be rewritten and divided to several ones:

"A 73-year-old female with esophageal dysmotility, gastroesophageal reflux disease (GERD), lymphocytic colitis, chronic obstructive pulmonary disease, essential hypertension (HTN), hyperlipidemia (HLD), neuropathy, and depression presented with substernal pleuritic chest pain and lightheadedness that began two hours after an uncomplicated outpatient upper and lower endoscopy performed two days prior to admission."

A 73-year-old female with a past medical history of esophageal dysmotility, gastroesophageal reflux disease (GERD), lymphocytic colitis, chronic obstructive pulmonary disease, essential hypertension (HTN), hyperlipidemia (HLD), neuropathy, and depression presented with substernal pleuritic chest pain and lightheadedness that began two hours after an uncomplicated outpatient upper and lower endoscopy performed two days prior to admission.

What medications was the patient receiving prior to diagnosis? This should be added in the initial history section.

Please see above.

What medications was the patient receive after discharge.

Please see above.

Give information about follow-up for at least 6 months after the last admission.
The patient did well after discharge. Nine months post-discharge, she was admitted for worsening lower extremity edema. A transthoracic echocardiogram (TTE) at the time was significant for a high left ventricular outflow tract (LVOT) gradient (peak LVOT gradient of 42 mmHg at rest and 122 mm Hg with Valsalva maneuver). Ejection fraction (EF) (normal range: 55-70%) at the time was 81% and pertinent results from TTE included: fibrocalcific changes of the aortic valve with mildly reduced opening; moderate mitral annular calcification; systolic anterior motion of the anterior mitral valve leaflet; and normal functioning left atrium, right ventricle, tricuspid valve, and pulmonic valve. She was discharged with instructions on avoiding diuresis and beginning initiation of metoprolol (6.25 mg every 6 hours) for negative inotropy and to decrease systolic anterior motion.

(Was an autopsy performed, and what were the findings?) – the patient is still alive.

Discussion – add a paragraph at the beginning of the Discussion that summarizes the case and describes what is unique in this case compared to what is available in the literature.

This case reports the clinical course for a rare presentation of stress cardiomyopathy after an upper and lower endoscopy. We do a literature review of all reported cases of takotsubo cardiomyopathy cases after endoscopy, and what the clinical presentation was along with medical management of each.

Also explain how the patient was treated during her admission and discharge. Was her emotional status taken into account in the treatment and follow-up?

The patient did not require any further intervention or medical management. Please note her emotional status was not taken into account and therefore is not reported.

The Discussion is too short and superficial. Please briefly review the literature discussing diagnosis and treatment.
Myocardial infarction (MI) has a similar clinical presentation to that of takotsubo cardiomyopathy without coronary artery obstruction; however, there are significant differences in treatment, prognosis, and complications, possibly due to underlying emotional and physical stress, triggering catecholamine excess and sympathetic nervous system hyperactivity.6,7,10,14–17 Examples of stressors include: surgery; medical conditions (trauma, sepsis, stroke, malignancy, acute respiratory failure), outpatient procedures (chemotherapy, endoscopy, biopsy, stress testing), and exacerbation of COPD.16 It is crucial to distinguish ACS from takotsubo cardiomyopathy. We report a rare case of stress cardiomyopathy post-upper and post-lower endoscopy in a patient with no known history of cardiopulmonary disease. Though the mechanism in our case is unclear, it is thought that perhaps the insertion of the scope triggered an overdrive of the sympathetic nervous system resulting in tachycardia-induced cardiomyopathy.7,9 It is important for health professionals to be aware of potential post-endoscopic cardiac complications those who may be susceptible to stress cardiomyopathy per diagnostic criteria.8

In the US, stress cardiomyopathy is more common in post-menopausal women and in those who have cardiovascular risk factors.18 Studies have shown takotsubo cardiomyopathy associated with increased brain natriuretic peptide levels when compared to ST-elevation myocardial infarction (STEMI).19 The product of peak troponin I levels and left ventricular ejection fraction (LVEF) have been studied and can help distinguish between takotsubo syndrome and STEMI.20 Troponin-LVEF product was lower in takotsubo syndrome versus higher in STEMI with a p<0.001.20

There are not any reliable ECG findings in the acute phase (i.e. within 12 hours of trigger or symptoms onset) that can differentiate stress cardiomyopathy from ACS.15,16 Changes during the acute phase include ST-segment elevation, new left bundle branch block, or ST-segment depression. ECG changes that develop 24-48 hours after symptoms or trigger may include Q waves with deep and widespread T-wave inversion with QT prolongation.15 Takotsubo cardiomyopathy can be differentiated from acute MI by observing T waves: negative T waves in lead aVR and no negative T wave in lead V1.21 In addition, patients with stress cardiomyopathy and ST-segment elevation greater than or equal to 5.5 mm are linked with increased risk of complications.25
Management is supportive, however risk stratification can be used when determining treatment. Those with LVEF > 45% and no complications are low-risk. High-risk patients can be monitored closely in a unit, telemetry, and resuscitation equipment. Sympathomimetic medications and ionotropic agents are contraindicated, however beta blockers can be considered in those who are high-risk with reduced LVEF, levosimendan can be considered in those with severe cardiogenic shock and end-organ failure when mechanical support is unavailable. Examples of mechanical support include: intra-aortic balloon counterpulsation, extracorporeal membrane oxygenation (ECMO), or temporary left ventricular assist devices (LVAD). It is recommended that patients be followed for 3-6 months post-discharge. Several medications can be considered for management of patients with stress cardiomyopathy. Patients with low complication risks can be considered for early discharge (i.e. if LVEF >45%) or starting heart failure medications (if LVEF 35%-45%). Angiotensin-converting enzyme (ACE) inhibitors should be avoided in patients with a normal cardiac output as there is potential for changes in peripheral sympathetic nerve activity with low peripheral vascular resistance. Those who are at high-risk for complications should consider stopping sympathomimetic agents. Inotropes are generally contraindicated. High-risk patients can be started on beta blockers when hemodynamically stable, with atrial or ventricular tachyarrhythmias, and in those with hemodynamically significant left ventricular outflow tract obstruction (LVOT obstruction > 40 mm Hg and systolic blood pressure < 110 mm Hg). Selective alpha-1-agonists are another option in those with LVOT obstruction. For anti-coagulation therapy, oral anticoagulation with dual antiplatelet therapy or unfractionated/low-molecular-weight heparin can be started upon initial evaluation as clinicians may suspect MI, and once excluded, anticoagulation can be stopped. In those who have intraventricular thrombus and without high risk of bleeding, anticoagulation is recommended until LV function is recovered and thrombus is resolved. Of note, beta blockers, ACE/angiotensin receptor blockers (ARB), and aspirin may not reduce recurrence and may not have any preventative benefits of takotsubo syndrome in patients. Beta blocker use before development of takotsubo syndrome may not be able to reduce severity of the condition.
A little over half of patients experience a complication from takotsubo syndrome: acute heart failure (most common), involvement of right ventricle, LVOT obstruction, mitral regurgitation, cardiogenic shock, arrhythmias, left ventricle thrombus formation, pericardial tamponade, and ventricular wall rupture.15,16 In-hospital mortality (1% - 5% of patients) is usually due to refractory cardiogenic shock or ventricular fibrillation.26 Increased levels of brain natriuretic peptide and higher levels of white blood cell counts upon admission has been associated with higher risk of in-hospital cardiac complications.24 Cardiac abnormalities arising from stress cardiomyopathy are generally associated with favorable prognosis as these changes are reversible.15,16 Left ventricular contraction returns to normal over a couple of weeks.

Therefore, clinicians should be aware of rare stress cardiomyopathy complications that can result after upper and lower endoscopies and utilize current literature to determine the optimal options for management.