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LETTER TO THE EDITOR
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Pheochromocytoma unmasked by stress cardiomyopathy

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Stress-induced cardiomyopathy was first described in Japan in 1990 and current medical knowledge is limited. Literature review revealed different underline causes of this cardiomyopathy.[1] Takotsubo syndrome is often triggered by a surge of stress hormones like cortisol, adrenaline and noradrenalin which put heart on sudden stress, causing temporary damages.[2] This syndrome can be defined as rapidly reversible heart failure (HF) that usually mimics the acute myocardial infarction (AMI) symptoms associated with characteristic regional wall motion abnormality without involvement of specific coronary artery territories.[3] Takotsubo syndrome can be classified in four types of apical type with apical akinesia and basal hypercontractility. Reverse type: basal akinesia and apical hypercontractility; midventricular type: midventricular ballooning and basal/apical hypercontraction and localized type.[4] Takotsubo syndrome is more common in postmenopausal woman (96%) while occurrence in younger group is relatively rare.[5] Also in the last decades, the frequency of the Takotsubo syndrome diagnosis is increasing but initial diagnosis remain challenging due to common similarities between Takotsubo syndrome and ST elevation myocardial infarction (STEMI).[6] Takotsubo syndrome probably accounts for 1%-2% of all the patients with suspected to AMI.[7] Although there is typically rapid and full spontaneous recovery of left ventricular function, long term follow up of these patients are not determined with large case control studies.[8] Intense, emotional, psychological and physical stresses such as grief, fear or sadness may also play a trigger role for Takotsubo syndrome.[9] Chronic anxiety disorders have been associated with Takotsubo syndrome.[10, 11] Hyperactivity of sympathetic nervous system is purposed to have main role in Takotsubo syndrome. Genetic predisposition, imbalance localization of β1, β2 adrenoreceptors between base and apical part of left ventricle also play important roles.[12] Transient epicardial coronary artery spasm, occlusion and reperfusion, micro vascular dysfunction, myocardial stunning, oxidative response to catecholamine's all are suspected mechanisms of Takotsubo syndrome.[13] Pheochromocytoma is a rare cathecholamin–secreting tumor with variable presentation.[14] In this letter, we present a case of reversed Takotsubo syndrome with underling cause of pheochromocytoma.

A 41-years old man presented to emergency department of Shahid Madani heart center, Tabriz, Iran with acute chest pain. He had a history of hypertension for which he wasn't getting any medications. He also had severe dyspnea, severe fatigue, nausea and vomiting which started after heavy lifting. His chest pain wasn't severe. However, the patient called the emergency due to his severe fatigue and dyspnea and was brought to the hospital by the emergency services. His initial vital signs a blood pressure of 90/40 mmHg, peripheral rate of 83 beats/min, respiratory rate of 17 and oxygen saturation of 96%. Electrocardiogram (ECG) revealed ST depression in precordial leads from V2 up to V6 (Figure 1) and increased troponin levels was also shown in his laboratory tests. Coronary angiography was immediately performed with a diagnosis of posterior myocardial infarction in which normal coronary arteries was shown with no stenosis. He was then hospitalized in coronary care

unit for further evaluations. First day post admission, he developed respiratory distress with an oxygen saturation of 73% which leaded him to undergo mechanical ventilation. Also, Bed side Transthoracic echocardiography (TTE) was performed on him and the results showed akinesia in the base of LV, hypokinesia in mid LV and hyperkinesia of apical segments (Video 1-3, Figure 2) with an ejection fraction (EF) of 35% compatible with reversed Takotsubo syndrome. Due to the patient's oxygen desaturation and the presence of bilateral rales, treatment for pulmonary edema was initiated. The regimen included 60 mg intravenous furosemide on the first day, 40 mg intravenous furosemide on the second day, 40 mg intravenous furosemide every 8 h on the third day, and 40 mg intravenous furosemide every 12 h as well as 40 mg oral captopril every 8 h from the third to the eighth day of hospitalization. The patient also received supplemental oxygen via nasal cannula. Following improvement in oxygen saturation and resolution of pulmonary crackles, the pulmonary edema treatment was discontinued. However, he had large blood pressure variation from 100/70 up to 200/120 mmHg. Later abdominal sonography was performed showing a mass in the liver along with another iso-echo 44 mm mass in right kidney. Further evaluation by abdominal computed tomography demonstrated a right adrenal mass in size of 48 mm. Urine biochemical analysis was also performed on him. The results showed high vanillylmandelic acid levels, normetanephrine = 1000 and metanephrin values = 1000 mg. Adequate alpha-adrenergic blockade was ensured and finally patient underwent laparoscopic adrenalectomy 28 days after his first admission. Pathology tissue diagnosis was positive for chromogranin A, confirming the diagnosis of pheochromocytoma. A rapid cardiac recovery was observed post tumor removal with complete recovery of ventricular wall motion and function with an EF of 54% (Video 4-6, Figure 3). One year post intervention his blood pressure was normal with no medication and left ventricular function improved up to 55.

Phaeochromocytomas are presented with variable signs and symptoms. Paroxysmal hypertension, sweating, palpitations and headache are the most common.[15] However, Pheochromocytoma induced Takotsubo syndrome is quite rare. There are a few recent reports of Takotsubo syndrome development due to pheochromocytoma.[16-18] Chest pain, tachycardia, hypertension, ST segment changes in ECG and left ventricular leading to

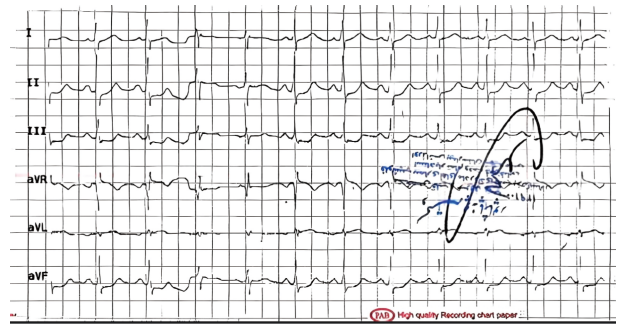

Figure 1 ECG of patients when he first visited the emergency department.

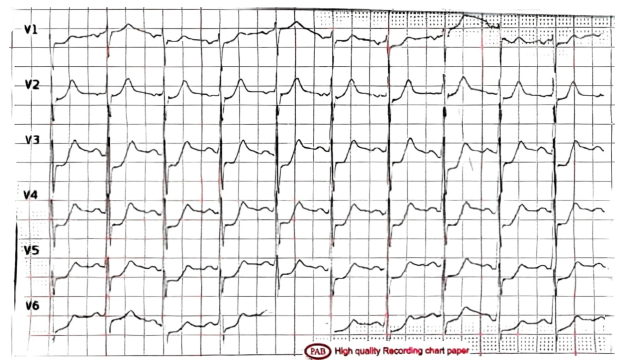

Figure 2 Global longitudinal strain (GLS). Reverse Takotsubo syndrome: severe hypokinesia of basal and mid segments and hyper contractile apical segments, EF= 37%.

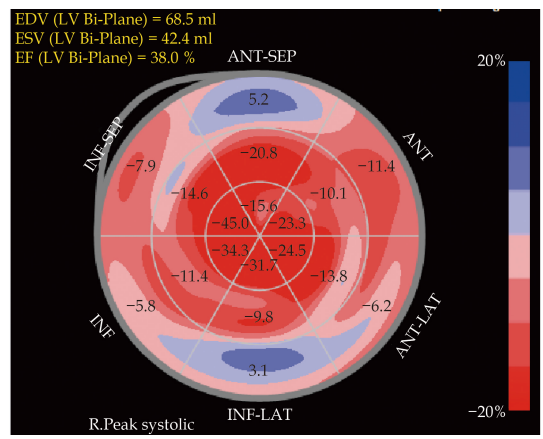

Figure 3 GLS improvement. EF= 54%.

decrease in EF were the main clinical presentations of the patients reported. In this report it was the same and the same signs and symptoms were observed. Reverse Takotsubo syndrome is reported to be the most common atypical Takotsubo syndrome which is likely to result from regional variations regarding adrenergic sensitivity.[19] Development of reverse Takotsubo syndrome has been found to be more dependent on adrenergic re-

ceptors stimulation and secretion of catecholamines, rather than on emotional stress crisis.[20,21] Studies also report that norepinephrine can lay toxic effects on the myocardium. Also, it can decrease myocyte viability through cAMP-mediated calcium overload, resulting in contraction band necrosis, a pathological hallmark of Takotsubo syndrome.[22] Moreover, the conductive system of the heart is shown to be highly affected by the ratio of epinephrine to norepinephrine levels and its variation has been proved to have a distortion of hearts conductive system which can cause several ECG changes, such as deep symmetric T-wave inversion, prolongation of QT interval and ST-T segment abnormalities.[22,23] Previous reports also show a complete remission in both ECG changes as well as left ventricular akinesia after the removal of Pheochromocytoma which was also seen in our patient. Therefore, we recommend screening for underlying Pheochromocytoma especially in young patients and male gender when other suggestive symptoms of Pheochromocytoma are present. Table 1 demonstrates the results of previous studies reporting similar cases of Takotsubo syndrome unmasking pheochromocytoma. It is observed that chest pain along with dyspnea and nausea and vomiting, can be considered as the most common clinical presentations of this phenomenon. Also, almost all of these cases had similar echography findings which included apical hyperkinesia and basal hypokinesia of the left atrium. Also they had almost similar laboratory findings like elevated serum troponin as well as elevated serum and urine metanephrine and normetanephrine. Finally, ECG findings of these patients were more diverse and included types with ischemic changes to normal ECG. In this case it was no different as we observed the same clinical presentations in our patients. Consequently, given the nature of these two diseases and their unique manifestations, we suggest that clinicians consider pheochromocytoma as a possible reason for atypical types of Takotsubo syndrome.

Table 1 Summary of previous studies.

Study	Male/ Female	Age	Signs and symptoms	Reported complications	ECG findings	Echography findings	Laboratory findings	Management
Gervais, *et al.* in 2015[24]	-	36-55	High BP in 4 patients/ low BP in 1 patient/ tachycardia in 6 patients/ headache in 4 patients/ Diaphoresis in 1 patient/ palpitation in 1 patient/ acute chest pain in 5 patients/ dyspnea in 8 patients/ nausea and vomiting in 1 patient.	Cardiogenic shock in 2 patients/ acute respiratory distress in 3 patients/ metabolic acidosis and renal failure in 2 patients/ dysrhythmias in 3 patients/ heart failure in 4 patients	ST depression in the inferior leads in 6 patients/ ST depression in the precordial leads in 7 patients	Decreased EF from 18% to 40% in all 10 patients.	-	Treatment with β-adrenergic blockers in 4 patients/ Treatment with α-adrenergic blockers in 5 patients/ adrenalectomy in 7 patients
Tagawa, *et al.* in 2015[25]	Female	33	Headache, palpitations, chest pain, general Fatigue and dyspnea.	Near-syncope experience due to ventricular rhythm	inverted T wave in the V2-V6 leads	Severe diffuse hypokinesis except for in the apex and basal wall and an EF of 22%	Elevated leukocytes, CK, CK-MB and positive cardiac troponin, elevated serum and urine levels of adrenaline, noradrenaline, metanephrine, and elevated serum levels of dopamine	Treatment with milrinone and then surgical tumor resection.
Tafreshi, *et al.* in 2017[26]	female	26	Nausea, vomiting, headache and hypertension and sub sternal severe chest pain	Respiratory failure leading to mechanical ventilation	2 mm ST depressions in V3–V6	Regional LV systolic dysfunction with mild to moderately reduced EF at 38%. All basal and mid LV segments appeared severely hypo kinetic with preservation of the apical segments.	Elevated serum troponin, Cr, metanephrine and normetanephrine.	Treatment started on a slow titration of phenoxybenzamine 10 days prior to surgery followed by metoprolol tartrate. She then underwent an open adrenalectomy.

Continued

Study	Male/ Female	Age	Signs and symptoms	Reported complications	ECG findings	Echography findings	Laboratory findings	Management
Leitch, *et al.* in 2020[27]	Female	24	Progressive retrosternal tightness and shortness of breath, tachypnea andbilateral basal crackles	This patient was 35 weeks pregnant. She was first presented with abdominal pain and absence of fetus movement which lead to urgent surgical delivery of the baby.	-	Globally dilated LV with severe systolic dysfunction and basal and mid-segment hypokinesis/akinesis and apical segment hyperkinesis, severe mitral regurgitation, and mild-to-moderate tricuspid regurgitation		Patient underwent laparoscopic right adrenalectomy after 1 year
Sakul, *et al.* in 2020[28]	Female	23	Nausea, vomiting for 1 day, and chest pain	Pulmonary embolism due to ruptured pheochromocytoma	Sinus tachycardia with a right bundle branch block	Akinesia of one-half to two-thirds of proximal LV, with a hyperdynamic functioning distal one-third LV and an estimated EF of 31%	Elevated serum troponin and an elevated D-dimer, elevated, plasma metanephrines and normetanephrines	-
Itagane, *et al.* in 2021[29]	Female	34	Dyspnea, nausea, vomiting and diaphoresis on micturition	Signs and symptoms developed 2 hours after uneventful vaginal delivery of a full-term infant	Sinus tachycardia with diffuse ST elevation on precordial leads	Diffuse hypokinesis with apical ballooning. There was no right heart dysfunction, valvular disease or pericardial effusion	Elevated serum CK and troponin levels	Treatment with doxazosin was started and a surgical left adrenalectomy was performed.
Trongtorsak, *et al.* in 2021[30]	Male	50	Dull chest pain associated with severe dyspnea, nausea, and vomiting	Cardiogenic Shock	ST elevation at V2-4 and inverted T wave at V1	Poor EF with basal hypokinesia and preserved apical wall motion	Elevated serum troponin	Patient underwent right adrenalectomy
Ahmad, *et al.* in 2023[31]	-	59	Worsening chronic headaches and new-onset difficulty breathing, tachycardia, tachypnea and elevated BP	Respiratory failure leading to intubation	Sinus tachycardia with probable left atrial enlargement and borderline right axis deviation with no ST segment changes	Mildly to moderately reduced EF, increased contractility at the apex, and decreased contractility at the base of the heart	Elevated WBC, Cr, LFT and rapidly rising troponin	Patient underwent right adrenalectomy
Go, *et al.* In 2024[32]	Male	40	Acute respiratory distress, tachycardia, bilateral lung crepitations and cold peripheries.	-	Sinus tachycardia with no ischaemic changes	Severely impaired systolic function, EF of 25%, and regional wall motion abnormality	Elevated troponin, NT-proBNP, CRP and LFT along with raised plasma-free metanephrine, normetanephrine 24-h urine epinephrine and norepinephrine	Treatment started with intravenous phentolamine and esmolol, as well as a high sodium diet along with oral phenoxybenzamine followed by elective laparoscopic left adrenalectomy
This study	Male	41	Acute chest pain	Respiratory failure leading to intubation	ST depression in precordial leads from V2 up to V6	Akinesia in the base of LV, hypokinesia in mid LV and hyperkinesia of apical segments with an EF of 35%	Elevated serum troponin and high urine vanillylmandelic acid, normetanephrin and metanephrin values	Treatment started with alpha-adrenergic blockade and patient underwent laparoscopic adrenalectomy

BP: blood pressure; CK: creatinine kinase; Cr: creatinine; EF: ejection fraction; LV: left ventricle; LFT: liver function test; NT pro BNP: N-terminal prohormone of brain natriuretic peptide; CRP: C-reactive protein

Left ventricular hypokinesia accompanied by hypertension or fluctuating blood pressure may indicate the presence of a pheochromocytoma alongside Takotsubo syndrome. Therefore, awareness of this rare condition and it is important to consider this condition in the differential diagnosis.

Declarations

Ethics approval and consent to participate

The ethics committee of the Tabriz University of Medical Science reviewed and approved the study protocol

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Author contribution statement

E.B: conceptualization, investigation and writing-original draft; A.N: methodology, investigation; S.H: writing-original draft, methodology; S.G: data gathering, writing original draft and revising the manuscript; A.H: methodology; R.S: writing-original draft; A.S: conceptualization, supervision; P.P: conceptualization, supervision; E.J: writing-review and editing, supervision, conceptualization and investigation; E.F: writing-original draft, methodology, investigation. All authors approved the final version for submission.

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