

Takotsubo syndrome and pheochromocytoma: an insidious combination

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Abstract

Pheochromocytoma is a rare adrenal tumor characterized by the secretion of catecholamines and vasoactive peptides. It can cause a catecholaminergic storm and lead to acute coronary syndromes. We present the case of a 53-year-old man, without any medical history, who arrived at the hospital following a spinal trauma due a fall. He presented with retrosternal and back pain, a clinical status of acute pulmonary edema, sinus tachycardia with left bundle branch block, left ventricular apical ballooning and depressed systolic function. Blood tests showed a very marked increase in troponin and transaminases. Contrast CT of the chest-abdomen revealed a solid right adrenal mass with a diameter of 78 mm, partial capsular laceration, and compression of the inferior vena cava and hepatic parenchyma. The patient's clinical condition rapidly worsened from a respiratory and hemodynamic point of view, with the onset of cardiogenic shock, anuria and sepsis; these were refractory to all medical treatments, and the patient died. Autopsy confirmed that the abdominal mass was a pheochromocytoma, which was ruptured during the man's fall. The resulting catecholaminergic storm caused myocardial ischemia, Takotsubo syndrome and cardiogenic shock. This unfortunate case

confirms that pheochromocytoma is a major risk factor for the onset of Takotsubo syndrome, and illustrates how dramatic and severe a catecholaminergic storm can be.

Learning objective

Rupture of a pheochromocytoma is rare. It is very dangerous, as it can cause Takotsubo syndrome and multisystem crisis. Pheochromocytoma must be immediately recognized and promptly treated, and should always be suspected in the presence of a Takotsubo syndrome.

Introduction

Takotsubo syndrome (TTS) is an increasingly recognized acute and reversible cardiomyopathy; it usually follows intense physical or emotional stress and is associated with an elevated catecholamine level, transient left ventricular dysfunction and wall-motion abnormalities [1]. In some cases, TTS may be induced by a catecholamine surge due to a pheochromocytoma (PH). Although reports of PH causing TTS are not uncommon, TTS due to the rupture of a PH is extremely rare [2].

Here, we report an unfortunate case of a patient who developed TTS and multiorgan failure following the rupture of an adrenal PH.

Case Report

We present the case of a 53-year-old man, without significant medical history, who arrived at the emergency room following a spinal trauma due to a fall from a "donut water tube" towed by a motorboat. On arrival, the patient presented back pain and retrosternal pain, dyspnea and tachypnea, elevated blood pressure (220/120 mmHg) and clinical features of acute pulmonary edema and respiratory distress. The electrocardiogram showed sinus tachycardia (145 bpm) and complete left bundle branch block.

The echocardiogram revealed diffuse left ventricular hypokinesia, with apical ballooning, sparing of contraction of the left ventricular basal segments, ejection fraction 20%, and mild mitral regurgitation (Figure 1).

Blood tests showed a very marked increase in myocardial-specific enzymes (ultra-sensitive Troponin T: 596 ng/L on first determination, >10,000 ng/L three h after arrival; myoglobin >30,000 ng/ml; CPK 8476 U/l); D-Dimer: 41,997 ng/ml; increased

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transaminases (AST >7000 U/l, ALT >7000 U/l); creatinine: 6.14 mg/dl; and WBC 35,000/mm³. Hemogasanalysis showed pH 7.05, pO₂ 53 mmHg, pCO₂ 63 mmHg, and HCO₃ 17 mmol/L. Lactates progressively increased from 9.3 mmol/l to 15 mmol/l.

A contrast CT scan of the chest-abdomen documented a solid encapsulated right adrenal mass, with a maximum diameter of 78 mm and partial capsular laceration, compressing the inferior vena cava and the hepatic parenchyma. CT also revealed multiple hepatic contusions without glissonian capsule injury (Figure 2).

The patient's clinical condition rapidly worsened, with the appearance of respiratory acidosis, the need for oro-tracheal intubation and mechanical ventilation support, a drop in blood pressure, and anuria, indicating a status of cardiogenic shock and multiorgan failure, which was refractory to all medical treatments administered (inotropic support with amines, plasma expander, diuretics, antibiotics). This clinical instability and rapid worsening led to cardiac arrest; the patient died before abdominal surgery could be performed to remove the adrenal mass and treat the liver lesions.

A complete autopsy was performed. Thorough examination of the coronary arteries revealed the absence of atheroma or acute thrombus, an absence which is typical of TTS. Histological examination revealed disseminated damage to cardiac myocytes, particularly with evidence of areas of "contraction band necrosis" resulting from the collapse of the myofibrillar apparatus, and areas with marked interstitial polymorphonuclear leukocyte infiltrates, typical of a recent acute myocardial infarction (Figure 3 a,b).

The autopsy confirmed the presence of the abdominal mass, the capsule rupture and the intralesional hemorrhage, these latter probably resulting from the trauma suffered.

Histological examination revealed a proliferation of mildly atypical monomorphic cells with abundant granular cytoplasm organized in nests and trabeculae, separated by areas of hemorrhage. The morphological features and an intense immunoreactivity for Chromogranin A prompted a diagnosis of PH with capsule rupture (Figure 3 c-e).

The resulting catecholaminergic storm caused myocardial ischemia and TTS; together with respiratory failure, these caused cardiogenic shock, multiorgan failure and death.

Discussion

PH is a rare adrenal tumor arising from chromaffin cells in the adrenal medulla, and is characterized by the secretion of catecholamines and vasoactive peptides. Its classic symptoms include episodic headache, palpitations and profuse sweating, accompanied by paroxysmal or sustained hypertension. PH usually results in a paroxysmal increase in catecholamine levels (sometimes massively elevated), which may trigger serious cardio-cerebrovascular complications, such as TTS, heart failure, cerebral hemorrhage and sudden death [3]. The spontaneous or traumatic rupture of PH is even rarer [2], but the prevalence of TTS in patients with PH may be as high as 3%; for this reason, PH has recently been included as a risk criterion for TTS [4].

Our clinical case highlights how insidious and dangerous a PH rupture can be and how complicated the management of the resulting emergency is. Given the critical clinical condition and multiorgan failure of our patient, coronary angiography was not performed, as it was not considered as priority. However, the echocardiographic picture, with apical ballooning, was quite suspicious for TTS, and indeed autopsy examination confirmed the absence of coronary stenosis.

TTS usually has a good prognosis, with recovery of myocardial function. In our patient, the prognosis was poor, essentially for two reasons: the severe multiorgan failure caused by the catecholaminergic storm, and the impossibility to perform abdominal surgery to remove the ruptured adrenal mass. Although surgery would probably have limited the release of catecholamines, it was precluded by the patient's rapidly worsening clinical condition.

The pathophysiological mechanism of TTS resulting from PH is not well understood. PH with extremely elevated catecholamine levels may be a strong physical trigger of TTS induction, most probably through hyperactivation of the sympathetic nervous system, including cardiac sympathetic nerve terminal disruption with norepinephrine see the and spillover [5].

Catecholamines play a vital role in triggering TTS, and their blood concentrations are extremely high, usually remaining elevated for 7-9 days [6]. Wittstein *et al.* compared the blood concentrations of catecholamines in 13 patients with TTS and 7 subjects hospitalized for acute myocardial infarction in Killip III class on admission to hospital. They found that catecholamine levels were higher in patients with TTS, suggesting that this may be the etiological factor underlying ventricular dysfunction [6].

The histological changes described in TTS are very similar to those found in animals and humans with catecholaminergic cardiotoxicity: contraction band necrosis, mild neutrophilic infiltrate, and fibrosis. These findings are associated to persistent activation of calcium channels, which is typical of catecholaminergic hypersecretion [7].

Acute hemorrhagic rupture as the initial manifestation of a PH is extremely rare. Surgical treatment is considered even if the ruptured adrenal mass is shrunken and absorbed into the retroperitoneal hematoma. Surgery for a ruptured PH may be either emergency or elective. Emergency surgery is associated with a high mortality rate, whereas no mortality has been reported in patients

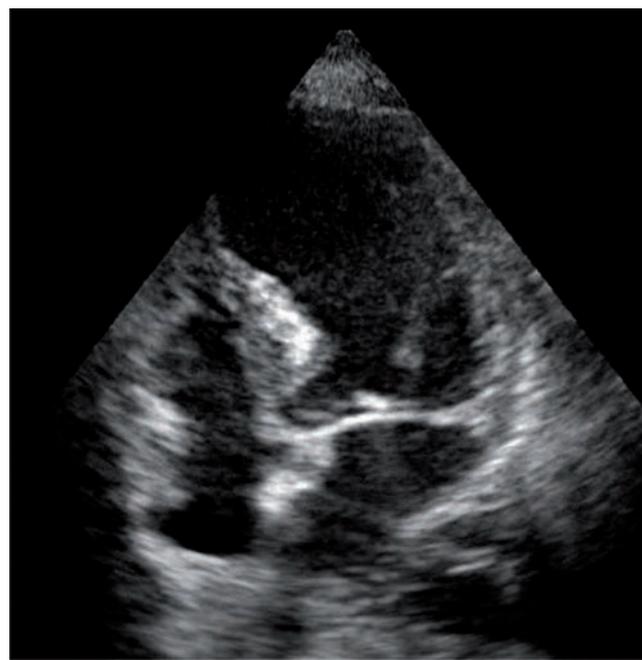


Figure 1. Four-chamber echocardiographic apical view with evidence of left ventricular apical ballooning.

undergoing elective surgery if by means of alpha-adrenergic blocker and fluid infusion therapy [8].

Our patient had an unusual presentation of PH; before his accident, he had never had any symptoms, hypertension, tachycardia or headache. The tumor mass probably did not secrete catecholamines, and only its rupture suddenly released catecholamines into the circulation.

In our patient, the hypothesis of an association between PH rupture and TTS appears to be highly plausible. However, we cannot rule out the possibility that TTS was triggered by the spinal trauma, given that the catecholaminergic storm was not documented. Nevertheless, we believe that the clinical presentation, hyper-

tensive crisis and multiorgan failure, together with the pathological finding of the ruptured PH, indicate catecholaminergic shock as the cause of the severe clinical status.

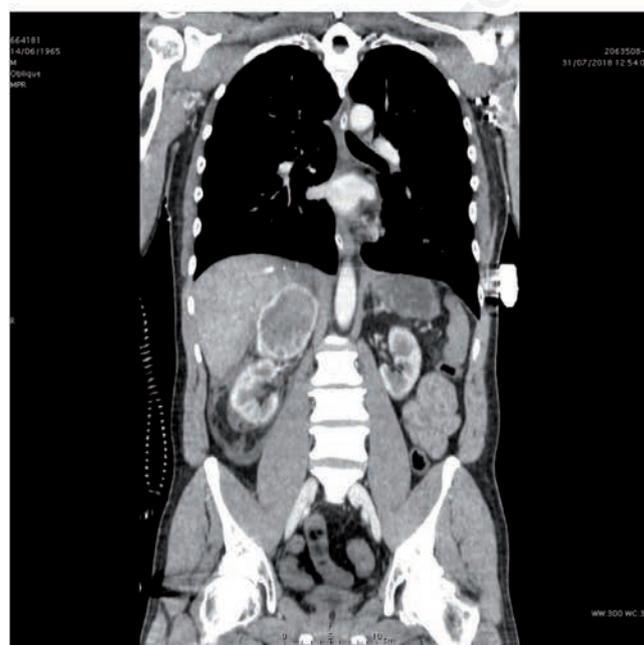
The treatment of PH-induced TTS mainly consists of supportive therapy, preoperative medical management, and tumor resection. Recently, a retrospective study of case-reports revealed that complications (such as cardiogenic shock and heart failure) were more frequent in patients with PH-induced TTS than in those with primary TTS [9]. In the preoperative management of patients with PH-induced TTS, alpha-adrenergic receptor blockers are the first choice, in order to prevent perioperative cardio-cerebrovascular complications. It should be noted that most patients with primary



a



b



c

Figure 2. Chest-abdomen computed tomography with axial (a), coronal (b) and sagittal (c) views. The figures show a solid encapsulated right adrenal mass, with a maximum diameter of 78 mm, and partial capsular laceration; this mass compresses the inferior vena cava and the hepatic parenchyma.

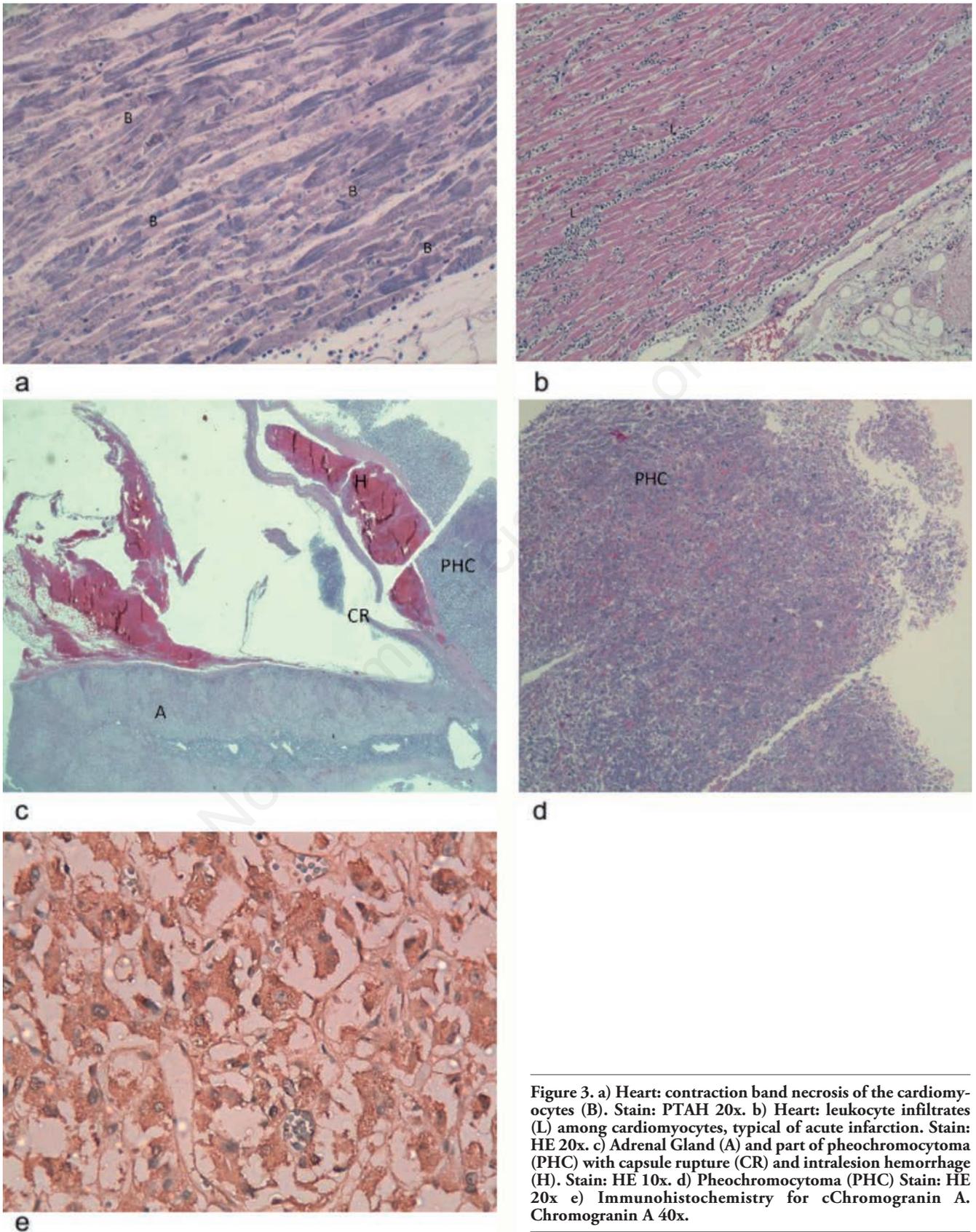


Figure 3. a) Heart: contraction band necrosis of the cardiomyocytes (B). Stain: PTAH 20x. b) Heart: leukocyte infiltrates (L) among cardiomyocytes, typical of acute infarction. Stain: HE 20x. c) Adrenal Gland (A) and part of pheochromocytoma (PHC) with capsule rupture (CR) and intralesion hemorrhage (H). Stain: HE 10x. d) Pheochromocytoma (PHC) Stain: HE 20x e) Immunohistochemistry for cChromogranin A. Chromogranin A 40x.

TTS are usually treated with beta-adrenergic receptor blockers; however, selective blockade of beta-adrenergic receptors may cause hyperactivation of alpha-adrenergic receptors in patients with PH, further aggravating the illness. Therefore, in patients with suspected PH-induced TTS, alpha- and beta-adrenergic receptor blockers should be administered simultaneously [10].

In our patient, no alpha- or beta-blockers were used: upon arrival of the patient in the emergency room, when a hypertensive crisis (220/120 mmHg) was ascertained, nitrate therapy was undertaken, as there was a clinical status of pulmonary edema and a PH was not yet suspected. The situation then rapidly evolved into one of cardiogenic shock and multiorgan failure, and support with additional amines (dopamine and noradrenaline) was also attempted, unfortunately without success.

Conclusions

We have presented this clinical case because the rupture of a PH is very rare. We want to emphasize the extreme severity of the cardiac and systemic damage caused by a catecholaminergic storm and once again stress the need to exclude the presence of a PH when we treat a patient with TTS.

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