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Recurrence of non-cardiogenic pulmonary edema and sustained hypotension shock in cystic pheochromocytoma*#

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Pheochromocytoma is a rare neuroendocrine tumor which derives from chromaffin cells of the adrenal gland or relevant to sympathetic nerves and ganglia. The clinical features of pheochromocytoma are various. Paroxysmal episodes of serious hypertension, headache, palpitation, and diaphoresis are the typical manifestations (Bravo, 2004). Hypotension shock, pulmonary edema, and acute coronary syndrome induced by pheochromocytoma are uncommon (Malindretos *et al.*, 2008; Batisse-Lignier *et al.*, 2015). In this study, we present a rare case of cystic pheochromocytoma causing recurrent hypotension shock, non-cardiogenic pulmonary edema, and acute coronary syndrome, and the possible mechanisms are discussed.

A 54-year-old woman presented to the emergency department with recurrent chest pain and dyspnea for 2 years, which have been aggravated for 4 h. She had no complaints of headache, cough, or palpitation. She had a history of pollen allergy but no other disease. On physical examination, the patient was afebrile. Her heart rate was 95 beats/min, blood pressure was 105/78 mmHg, respiratory rate was 21 breaths per minute, and oxygen saturation was 93% in ambient air. Much moist rale was audible, and examination of heart and abdomen had no abnormal findings. Emergency troponin I increased (2.34 μg/L; normal range 0–0.04 μg/L). An initial electrocardiogram (ECG) showed V4–V6 ST depression. Coronary angiography and computed tomography (CT) pulmonary angiogram were normal. Contrast-enhanced CT of the chest showed diffuse lesions in the lungs, large numbers of alveoli with inflammatory exudation (Fig. S1). IgE was positive, and influenza A and B virus antigens were negative. Brain natriuretic peptide was normal (62.7 pg/ml; normal range 0–100 pg/ml). The transthoracic echocardiogram was normal and left ventricular ejection fraction was 71.7%. She developed shock with hypotension (68/34 mmHg), and was stabilized with dopamine and norepinephrine for about 30 h. The initial diagnosis was hypersensitivity pneumonitis. After treatment with methylprednisolone and antibiotics, the patient got well and was discharged. One week later, serious chest pain and dyspnea attacked again, and abdomen B ultrasound showed weak echo mass (about 4 cm×3.5 cm×3.5 cm) in the retroperitoneum. Contrast-enhanced magnetic resonance imaging showed a cystic lesion of the left adrenal gland, which was considered as pheochromocytoma (Fig. 1). The patient recovered after surgery, and histological analysis (Fig. 2) confirmed the diagnosis of pheochromocytoma. At 1 year of follow-up, there was no recurrence of chest pain.

Pheochromocytoma has an estimated incidence of 0.005%–0.100% in the worldwide population and 0.1%–0.6% in the hypertension population (Omura *et al.*,

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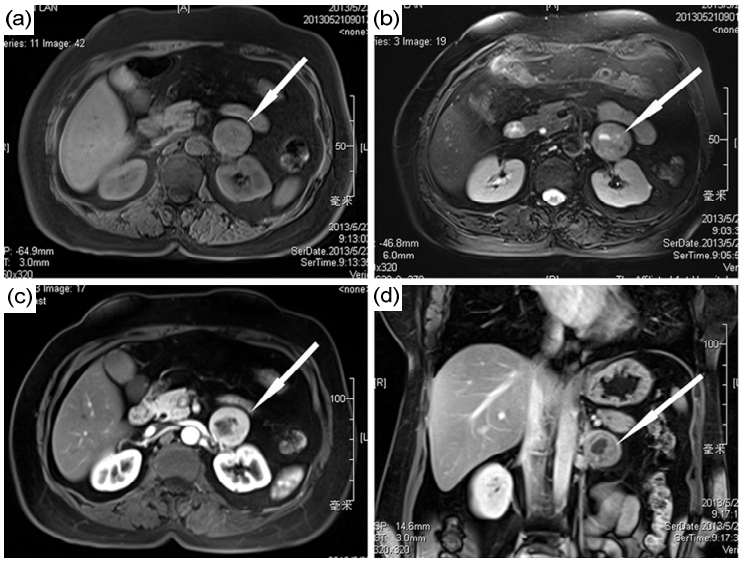

Fig. 1 Contrast-enhanced magnetic resonance imaging of upper abdomen
Pheochromocytoma mass (arrows) in left gland: heterogeneous signal on T1 and T2 weighted images (a, b); hyperintense signal in solid area and non-enhancing cystic lesion in center on enhancement scan (c, d)

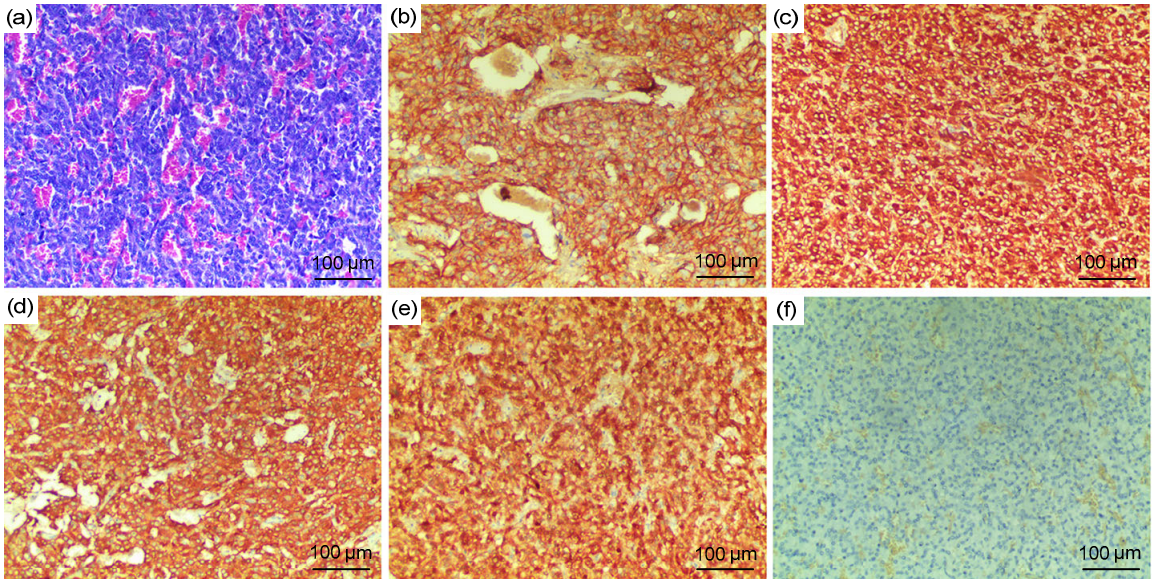

Fig. 2 Histopathology analysis of left adrenal gland
(a) H & E staining (10×): nested arrangement of cells with granular basophilic cytoplasm and prominent nucleolus. (b–f) Immunohistochemical staining (10×): (b) CD56 (+); (c) CgA (+); (d) Syn (+); (e) S-100 (+); (f) Ki-67 (−), confirming the diagnosis of pheochromocytoma. H & E: hematoxylin and eosin; CgA: chromogranin A; Syn: synaptophysin

2004; Dahia, 2006; Malindretos *et al.*, 2008). The symptoms of pheochromocytoma are due to catecholamine release and up to 30% of the tumors are asymptomatic (Kopetschke *et al.*, 2009). Only a few cases of cystic pheochromocytoma have presented according to the literature. That is because cystic pheochromocytoma is often asymptomatic; most catecholamine is metabolized in the tumor (Sarveswaran *et al.*, 2015). Our patient of cystic pheochromocytoma with several severe features including sustained hypotension shock, non-cardiogenic pulmonary edema, and acute coronary syndrome was rarely reported.

Hypertension is the most common manifestation of pheochromocytoma. However, there are about 5% patients with pheochromocytoma who present normal blood pressure and hypotension, especially in patients with familial tumors and tumors secreting large quantities of vasodilating substances (Park *et al.*, 2009).

Sustained hypotension shock was rarely reported and most severe hypotension induced by pheochromocytoma was associated with operation and anesthesia (Prejbisz *et al.*, 2011). The mechanism of hypotension in pheochromocytoma is still unclear. The tumors stop releasing catecholamine suddenly and down-regulation of adrenergic receptors with long-term catecholamine may be the main reasons to induce hypotension, but tumor hemorrhagic necrosis, cardiac output decrease, and hypovolemia should also be considered (Schifferdecker *et al.*, 2005; Grasselli *et al.*, 2008; Prejbisz *et al.*, 2011). In our case, the patient did not have hypertension or low cardiac output, and was without hemorrhagic necrosis according to pathology. The possible mechanism may be due to the abrupt cessation of catecholamine secretion.

Pulmonary edema is a rare clinical manifestation of pheochromocytoma, especially in patients with normal blood pressure or hypotension (Eschen *et al.*, 2007; Giavarini *et al.*, 2013). In most pheochromocytoma cases, pulmonary edema is cardiogenic and is caused by myocardial infarction, cardiomyopathy, and severe arrhythmias. Non-cardiogenic pulmonary edema, such as this case, is very rare, which maybe results from a transient increase in pulmonary capillary pressure induced by catecholamine and the promotion of pulmonary neutrophil accumulation caused by catecholamine excess (Prejbisz *et al.*, 2011).

Acute coronary syndrome caused by pheochromocytoma has been recorded for many years, but only a few cases had significant coronary artery stenosis. The mechanism of pheochromocytoma-induced myocardial injury is catecholamine excess, including catecholamine-related hemodynamic instability and catecholamine-mediated cardiomyocyte toxic effect (Prejbisz *et al.*, 2011; Li *et al.*, 2016). From this case, we know that chest pain, sweating, and dysphoria may be the only syndromes of pheochromocytoma crisis, so pheochromocytoma should be considered when the diagnosis is difficult.

In conclusion, the patient had an atypical presentation of cystic pheochromocytoma with recurrent non-cardiogenic pulmonary edema, sustained hypotension shock, and acute coronary syndrome. Pheochromocytoma can have a lot of cardiovascular manifestations, even circulatory failure. Early and timely diagnosis of pheochromocytoma is very important and can alleviate suffering and improve prognosis, because some symptoms and signs are extremely dangerous and deadly. Pheochromocytoma should be considered when diagnosis is still indefinite with such severe clinical features as described here.

Compliance with ethics guidelines

Jin DAI, Shen-jie CHEN, Bing-sheng YANG, Shu-min LÜ, Min ZHU, Yi-fei XU, Jie CHEN, Hong-wen CAI, and Wei MAO declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from the patient for being included in the study.

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List of electronic supplementary materials

Fig. S1 Contrast-enhanced computed tomography scan of chest

中文概要

题　目：囊性嗜铬细胞瘤复发非心源性肺水肿和持续性低血压休克

概　要：本文介绍一例以胸痛、呼吸困难为主要表现，反复发生非心源性肺水肿、持续性低血压和急性冠脉综合征的囊性嗜铬细胞瘤患者。囊性嗜铬细胞瘤合并多种严重并发症临床上少有报道，容易误诊和漏诊。对于出现肺水肿、持续性低血压和急性冠脉综合征等严重体征，临床诊断又不明确的患者，需要考虑嗜铬细胞瘤的可能。

关键词：囊性嗜铬细胞瘤；非心源性肺水肿；持续性低血压；急性冠脉综合征