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【 CASE REPORT 】

Panhypopituitarism Mimicking Acute Coronary Syndrome

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Abstract:

A 59-year-old man suspected of having myocardial infarction with sinus bradycardia, a decreased blood pressure, and ST-change on an electrocardiogram was referred to our hospital's emergency department. Emergent coronary angiography revealed no significant findings. However, the patient experienced shock and required intensive care. Curiosity rose when his urination volume was not disturbed; we suspected hormonal abnormalities. A hormonal examination and imaging analysis revealed panhypopituitarism caused by a Rathke's cyst. Appropriate hormonal replacement therapy improved his symptoms and led to normalization of his electrocardiogram findings. Acute coronary syndrome (ACS) is a fatal disease; however, clinicians must not discount panhypopituitarism, as it may mimic ACS symptoms.

Key words: panhypopituitarism, acute coronary syndrome, Rathke's cyst

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Introduction

Chest or epigastric pain can be a symptom of many serious life-threatening diseases, such as acute coronary syndrome (ACS), pulmonary embolism, and aortic dissection to name a few. When cases are accompanied by abnormal vital signs, a prompt and correct diagnosis is required to save lives (1, 2).

Chest or epigastric pain, sometimes called chest pain syndrome, can be caused by non-thoracic organ abnormalities (3). Hormonal abnormality, especially adrenal insufficiency, occasionally causes abdominal or joint pain, myalgia (4), or hypotension (5). However, reports of panhypopituitarism as a cause of chest pain are rare.

We herein report a case of panhypopituitarism owing to a Rathke's cyst in a patient whose clinical manifestation included epigastric pain, hypotension, bradycardia, and electrocardiogram (ECG) abnormalities mimicking ACS.

Case Report

A 59-year-old man was referred to our hospital from his family clinic with epigastric pain and loss of appetite lasting a week. He had a history of skin disease, for which he used a steroid-containing ointment once a week. He had no history of diabetes, hypertension, or hyperlipidemia. No familial history of heart disease was observed. He had a smoking history of 25 pack-years and reported a low alcohol intake. He reported feeling stressed with his job recently.

A physical examination performed at arrival showed that he was afebrile and alert, with a blood pressure level of 80/ mmHg, pulse rate of 40 bpm, and SpO_2 of 97% (ambient air). The patient had no visual field defects and reported progressive epigastric pain. Chest X-ray showed no remarkable cardiac silhouette enlargement nor pulmonary congestion. Electrocardiography indicated ST-segment elevation in leads II, III, and aVF and flattened T-wave in all leads along with sinus bradycardia at a rate of 44/min. Reciprocal changes were not evident. Low voltage in limb leads was seen. Neither a typical shortened RR interval nor a widened P wave in lead II, findings often seen in hyponatremia, were observed (Fig. 1). Although no abnormalities in myocardial-derived enzymes were observed, laboratory tests showed decreased serum sodium levels (Table 1). Based on these findings, we suspected cardiogenic shock due to acute coronary syndrome. Unfortunately, due to the emergent situation, findings by cardiac ultrasound were not recorded.

During transport to the cardiac catheterization interventional suite for emergent coronary angiography, his systolic

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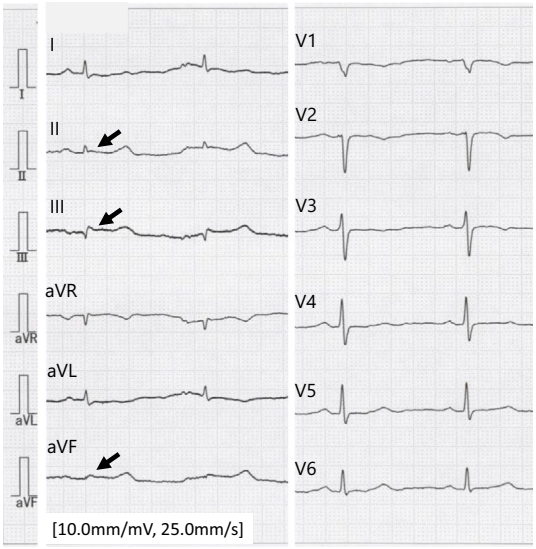

Figure 1. The electrocardiogram at arrival. ST-segment elevation in leads II, III, and aVF (black arrow) and flattened T-wave in all leads with sinus bradycardia at a rate of 44/min are shown. Reciprocal changes were not evident. Low voltage in limb leads was seen.

blood pressure level dropped to 50 mmHg, and noradrenaline was initiated intravenously to maintain his hemodynamics. Coronary angiography did not reveal any significant stenosis or coronary spasm (Fig. 2). However, after entering the intensive-care unit, his systolic blood pressure level did not stabilize and suddenly dropped to 50/- mmHg despite intravenous administration of noradrenalin.

However, a large amount of urine was observed with a volume of 100-250 mL/h despite his affected hemodynamics and circulation. Therefore, 6-8 h after his arrival, a urinalysis was performed (Table 2). The presence of a large amount of urine with normal sodium excretion despite evidence of shock aroused questions. Based on these findings, endocrine disorders were considered as possible diagnoses.

We assessed the thyroid and adrenal function. The results showed low levels of thyroid-stimulating hormone (TSH), free T4 (FT4), adrenocorticotropic hormone (ACTH), and cortisol (Table 3). Therefore, the patient was diagnosed with central hypothyroidism and secondary adrenal insufficiency.

The basal levels of other anterior pituitary hormones, such as prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH),

Table 1. Laboratory Data on Arrival.

Hematology			**Biochemistry**		
WBC	6,400	/μL	TP	6.0	g/dL
Neutro	49.3	%	Alb	3.4	g/dL
Eosino	34.5	%	AST	41	U/I
Baso	10.4	%	ALT	33	U/I
Mono	5.5	%	γ-GTP	47	U/I
Lymph	0.3	%	ALP	190	U/I
RBC	440	×10⁴/μL	LDH	141	U/I
Hb	12.8	g/μL	CK	142	U/I
Ht	35.3	%	CK-MB	5	ng/mL
MCV	80.2	fL	Troponin T	0.01	ng/mL
MCH	29.1	pg	T-Bil	1.4	mg/dL
MCHC	36.3	g/dL	D-Bil	0.4	mg/dL
Plt	26	×10⁴/μL	BUN	15.8	mg/dL
			Cre	0.83	mg/dL
Blood coagulation			eGFR	73.8	mL/min/1.73 m²
APTT	52.5	s	Na	121	mmol/L
PT-INR	0.99		K	3.8	mmol/L
Fib	279	μg/mL	Cl	92	mmol/L
FDP	5.9	μg/mL	Glu	139	mg/dL
D-dimer	<1.00	μg/mL	CRP	0.13	mg/dL

WBC: white blood cell, Neutro: neutrophil, Eosino: eosinophil, Baso: basophil, Mono: monocyte, Lymph: lymphocyte, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Plt: platelet, APTT: activated partial thromboplastin time, PT-INR: prothrombin time-international normalized ratio, Fib: fibrinogen, FDP: fibrin degradation product, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine transaminase, γ-GTP: γ-glutamyl transferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CK: creatine kinase, CK-MB: creatine kinase MB, T-Bil: total bilirubin, D-Bil: direct bilirubin, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, Cl: chloride, Glu: glucose, CRP: C-peptide immunoreactivity

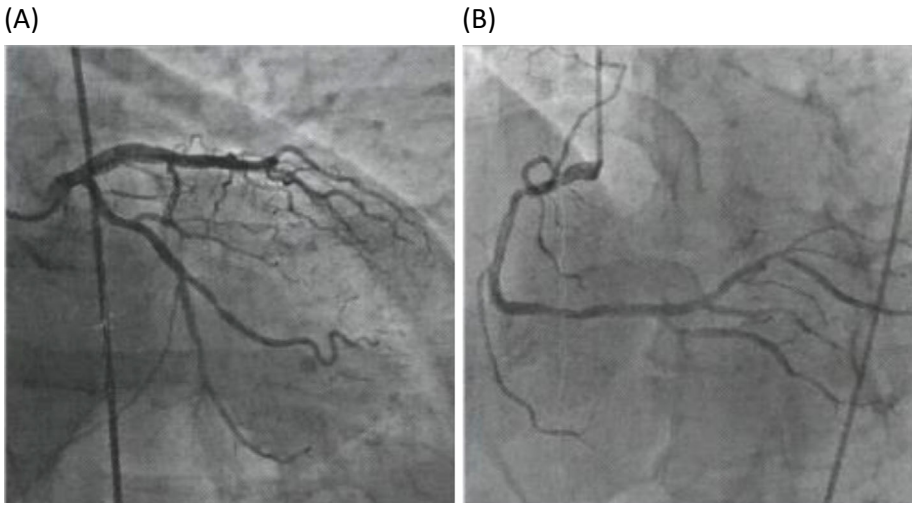

Figure 2. **Emergent coronary angiography. (A) Left coronary artery. (B) Right coronary artery. In both arteries, no significant stenosis or vasospasm was seen.**

Table 2. **Urinalysis.**

Urinalysis	
Protein	(-)
Glucose	(-)
Na	216 mmol/L
Cl	130 mmol/L
K	36.5 mmol/L
Osmolality	744 mOsm/kg

Table 3. **Endocrine Associated Examination.**

Endocrine		Normal range
TSH	0.53 μIU/mL	0.610-4.230
FT4	0.098 ng/mL	0.90-1.70
PRL	1.08 ng/mL	1.5-10.0 (adult, men)
ACTH	3.0 pg/mL	7.2-63.3
Cortisol	2.3 μg/mL	2.7-15.5
LH	0.35 mIU/mL	1.6-9.5 (adult, men)
FSH	1.41 mIU/mL	1.2-15.0 (adult, men)
GH	0.18 ng/mL	<3.0
IGF-1	55 ng/mL	median 142 ±2SD: 80-233 (Japanese, 59yr, men)
Serum osmolality	276 mOsm/kg	275-290
Urine osmolality	591 mOsm/kg	50-1,300
ADH	0.8 pg/mL	

TSH: thyroid stimulating hormone, FT4: free thyroxine, PRL: prolactin, ACTH: adrenocorticotropic hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, GH: growth hormone, IGF-1: insulin-like growth factor 1, ADH: anti-diuretic hormone

were also low. Regarding antidiuretic hormone (ADH), the presence of diabetes insipidus was deemed unlikely because the ability to concentrate urine was conserved (Table 3). In addition, he tested negative for anti-thyroglobulin antibody and anti-thyroid peroxidase antibody. We then performed an insulin (regular insulin 0.067 U/kg)-thyrotropin-releasing hormone (TRH) (0.1 mg)-luteinizing hormone-releasing hormone (LHRH) (0.5 mg) loading test with the patient's informed consent on the 6th hospital day when the likelihood of ischemic heart disease had decreased. Effective hypoglycemic stimulation was obtained because the plasma glucose level decreased to 43 mg/dL at 45 min after administration. The TSH levels did not respond to TRH stimulation, but the plasma PRL levels slightly responded (Fig. 3A). Plasma LH and FSH did not respond to LHRH stimulation (Fig. 3B). While plasma ACTH levels did respond to insulin-induced hypoglycemia, cortisol levels (Fig. 3C) and GH did not (Fig. 3D).

Brain computed tomography (CT) without contrast displayed cystic lesions in the pituitary gland. Brain magnetic resonance imaging (MRI) showed a low-signal-intensity cystic mass on T1-weighted imaging (Fig. 4A, B) and a high-intensity mass on T2-weighted imaging (Fig. 4C). The normal T1 posterior pituitary bright spot had disappeared. Contrast-enhanced T1-weighted imaging indicated no enhancement of the cyst, although a thin, enhancing rim surrounding compressed pituitary tissue was seen (Fig. 4D, E). Thus, the patient was diagnosed with panhypopituitarism due to Rathke's cyst.

Hydrocortisone at a daily dose of 200 mg was initiated as hormone replacement therapy. On the 6th day after starting treatment, levothyroxine sodium hydrate was initiated at a daily dose of 25 μg. He was discharged after three weeks of hospitalization. The patient's hormonal replacement therapy was adjusted at our outpatient center. The adjustment prescribed was as follows: hydrocortisone 10 mg in the morning and 5 mg in the afternoon for adrenocortical dysfunction, levothyroxine sodium hydrate 62.5 μg per day for hypothyroidism, and somatropin 0.2 mg per day for adult growth hormone deficiency, as the patient met the severe type criteria. We decided against administering sexual hormones for hypogonadism, since the patient's daily life activities were unaffected.

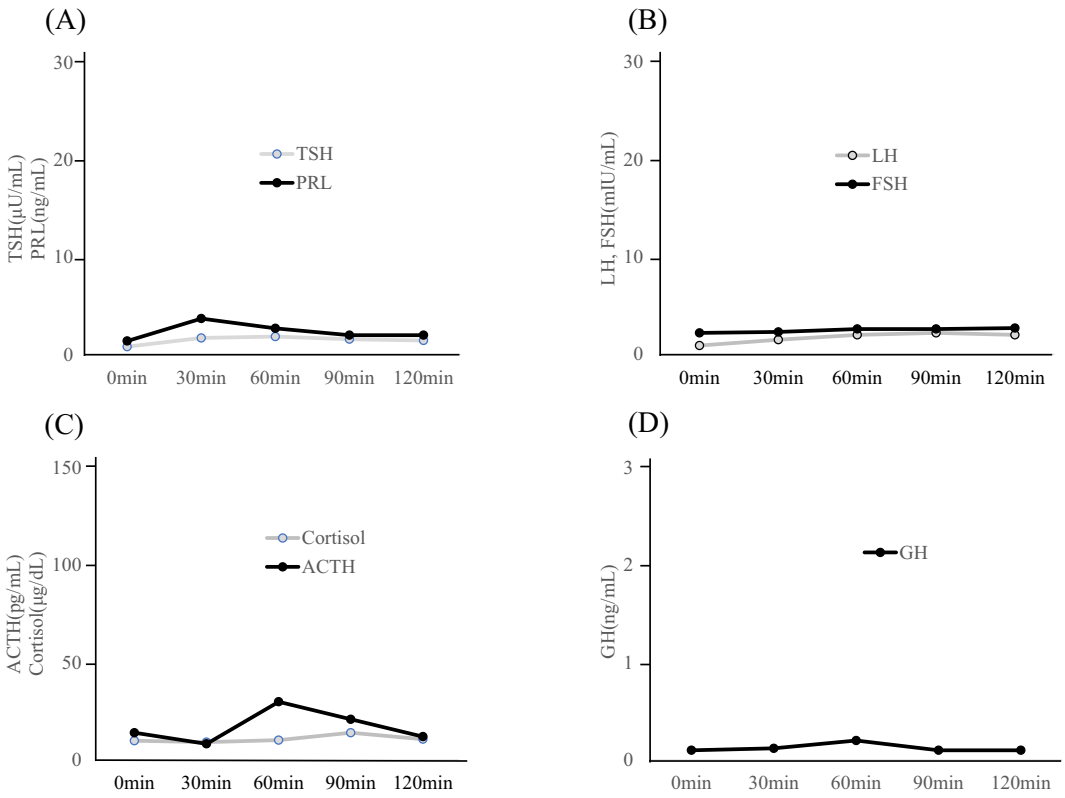

Figure 3. **Insulin-TRH-LHRH test. (A) TSH did not respond to TRH stimulation, but PRL slightly respond. (B) Plasma LH and FSH did not respond to LHRH stimulation. (C) Cortisol did not respond to insulin-induced hypoglycemic stimulation while ACTH did respond. (D) GH did not respond to insulin-induced hypoglycemic stimulation.**

Three months after starting the treatment, the therapeutic effect was judged using the Adult Hypopituitarism Questionnaire score (AHQ) (6). The psychosocial score improved from a pre-treatment level of 44.1 to a post-treatment level of 53.4. The physical score improved from a pre-treatment level of 42.9 to a post-treatment level of 51.7. After hormone replacement, ECG changes were normalized (Fig. 5).

Discussion

We herein report a patient who, upon admission to our hospital, presented with symptoms of ACS but was instead diagnosed with panhypopituitarism caused by Rathke's cyst. A Rathke's cyst is a non-neoplastic cystic lesion that arises from the remnant tissue of an embryonic origin, Rathke's pouch. Rathke's cysts require treatment, as they may cause various symptoms due to compression of the surrounding tissues. Panhypopituitarism, a manifestation of a large Rathke's cyst, refers to a condition in which the secretion of multiple pituitary hormones is impaired. Several histological types of hypophysitis have been reported to co-exist with Rathke's cyst (7-9). Although typical lymphocytic hypophysitis shows a thick enhanced area surrounding cystic lesion on contrast-enhanced MRI (10, 11), an accurate diagnosis can be made pathologically with a biopsy sample. However, in the present case, the patient refused to consent to a biopsy.

Loss of posterior pituitary bright spot (PPBS) has been reported in central diabetes insipidus (CDI). However, in this case, CDI was deemed unlikely because the ability to concentrate urine was conserved. Instead, hormonally, a syndrome of inappropriate ADH secretion-like condition, which is often seen in adrenal insufficiency, was present. Loss of PPBS is also seen physiologically (12). In the absence of CDI, the high-volume urination observed on admission seemed to be due to the administration of a high dose of saline (over 3,000 mL) for resuscitation and osmotic diuresis due to increased Na excretion caused by impaired ACTH secretion.

There have been several cases of panhypopituitarism with cardiac manifestations. Placido et al. reported an association between takotsubo cardiomyopathy (TTC), which mimics acute coronary syndrome, and adult-onset panhypopituitarism (13). Panhypopituitarism itself is a stressful condition; it raises sympathetic tone to confront daily physical and emotional stress, leading to TTC. Kang et al. reported a case of panhypopituitarism, QT prolongation, and torsades de pointes (TdT) (14). Supplementation with thyroid and adrenal hormones improved QT prolongation and tent-like T-waves on the ECG, and TdT did not recur. Albakri et al. reported a case of cardiogenic shock due to self-interruption of hormone replacement after pituitary adenoma removal (15). They described the role of the pituitary gland in maintaining proper cardiovascular status.

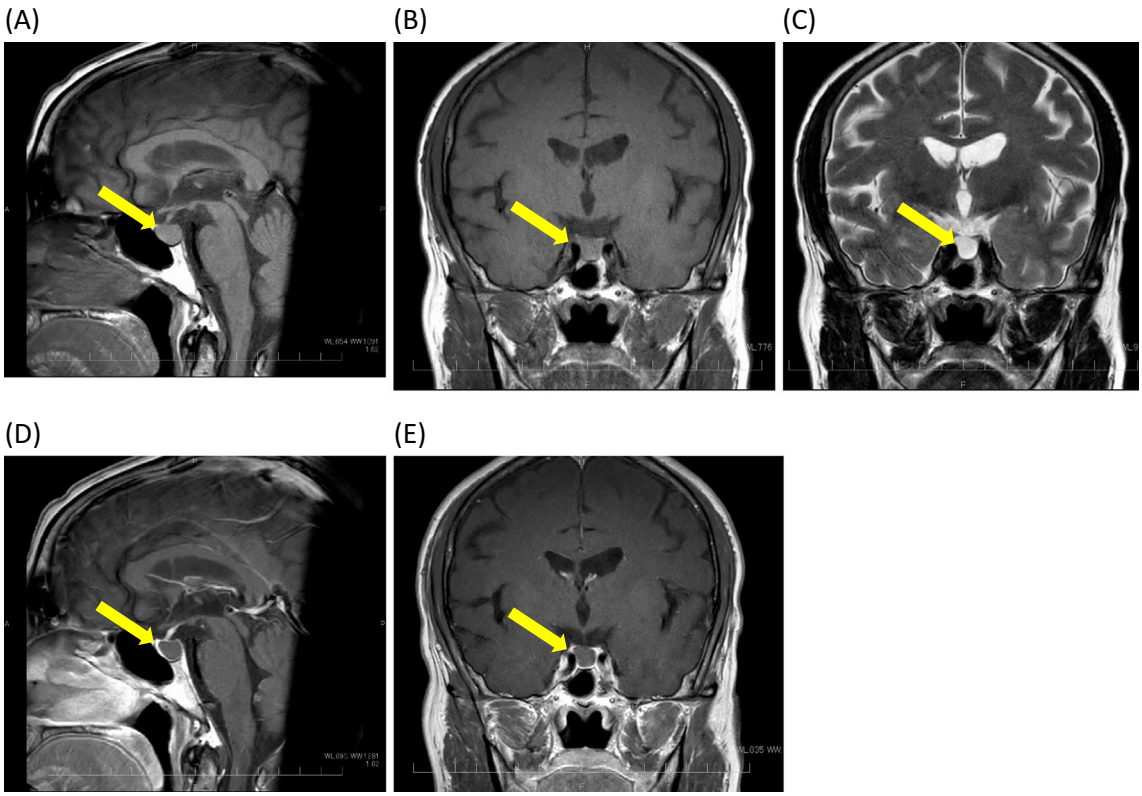

Figure 4. **Brain MRI scan image. (A) T1-weighted sagittal image, (B) T1-weighted coronal image, (C) T2-weighted coronal image, (D) T1-weighted post-gadolinium sagittal image, (E) T1-weighted post-gadolinium coronal image. The T1-weighted image indicated slight hyperintensity, and the T2-weighted image showed a remarkably hyperintense cystic lesion in the seller region (yellow arrow). No contrast enhancement of the cyst was seen; however, a thin, enhancing rim of surrounding compressed pituitary tissue was apparent (yellow arrow). The normal T1 posterior pituitary bright spot had disappeared; however, this did not indicate the presence of central diabetes insipidus (see the text).**

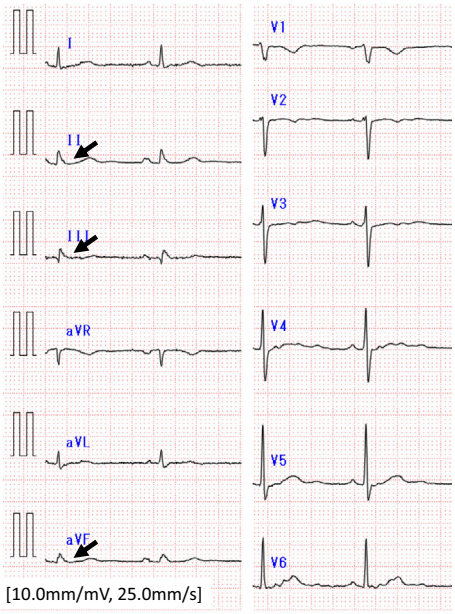

Figure 5. **Electrocardiogram findings at three months after hormone replacement therapy initiated. Elevated ST-segment in leads II, III, aVF became normalized (black arrow).**

In the present case, no remarkable arrythmia or TTC, such as cardiac dyskinesis, was observed. However, chest pain and shock were observed. Furthermore, ST-segment elevation on ECG manifested in leads II, III, and aVF with sinus bradycardia. This prompted us to suspect inferior myocardial infarction. Hypothyroidism is known to cause bradycardia, ST-T change, QT elongation, and impaired cardiac contractility (16, 17). An abnormal ST-T segment in hypothyroidism can indicate either depression, inversion, or elevation (18). Hypothyroidism is known to be a possible cause of symptoms in cases of suspected coronary heart disease with normal angiogram findings (19). Although the precise mechanism underlying the ST-T elevation in this case was unclear, hypothyroid is known to cause coronary endothelial dysfunction directly via an effect on the coronary vascular bed (20) or indirectly via low-grade inflammation (21) or by weakening the effect of the beta adrenergic hormone (22). GH deficiency is also known to reduce cardiac contractility (16, 17). Both thyroid and growth hormones were reduced in this case. Although the mechanism underlying the musculoskeletal pain caused by adrenal insufficiency was unclear (4), the reason for the chest pain might have been due to adrenal insufficiency. Furthermore, considering the

anti-inflammatory effect of cortisol, a decreased cortisol level might have led to a reduction in the anti-inflammatory effect in the coronary arteries to coronary spasm (17). The presence of catecholamine-unresponsive shock and diuresis with sodium loss led us to conclude that hormone deficiency was the root cause.

To our knowledge, this is the first report of panhypopituitarism mimicking ACS. ACS is a major medical emergency. Likewise, panhypopituitarism is also a fatal disease if left untreated. With this in mind, clinicians must not discount the possibility of panhypopituitarism mimicking ACS symptoms and should thus differentiate the two.

Written informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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