Case Letter

Acute cardiovascular manifestations of hypocortisolism

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Cardiovascular (CV) manifestations of adrenal insufficiency have been previously documented through several case reports, with heart failure (HF) and dilated cardiomyopathy as the most frequently reported presentations. Accelerated coronary artery disease (CAD) has been associated with adrenal insufficiency, typically with abrupt discontinuation of exogenous glucocorticoid. This poses a challenge in distinguishing whether the accelerated CAD results from corticosteroid usage or the resultant insufficiency. We present a rare case in which multiple CV manifestations prompted the diagnosis of hypocortisolism in a patient with no prior glucocorticoid use, with complete resolution after appropriate adrenal insufficiency therapy.

A 37-year-old male, without known CV risk factors, presented to the emergency department (ED) with left constricting chest pain. He had been experiencing exertional dyspnea, fatigue, and unexplained weight loss (20 kg) over a 5-month period. At the ED, blood pressure was 92/49 mmHg (1 mmHg=0.133 kPa) and a twelve-lead electrocardiogram (ECG) showed sinus tachycardia (104 beats/min) with a biphasic T wave in V3 and T wave inversion from V4-V6 (Supplementary Figure 1). An urgent transthoracic echocardiogram (TTE) revealed left ventricular ejection fraction (LVEF) of 43% without regional wall motion abnormalities (RWMA) (Supplementary Video 1). During the TTE, the patient experienced a recurrence of chest pain, recorded live with a simultaneous *de novo* apical hypokinesia (Supplementary Video 2). He underwent emergent coronary angiography that revealed a mild (<30%) stenosis in the left anterior descending artery and a 70% lesion in the proximal left circumflex artery, the latter treated with a drug eluting stent. The patient was admitted to the coronary care unit (CCU) after the procedure and was started on aspirin 100 mg/d, ticagrelor 90 mg twice daily, and transdermal nitroglycerin (5 mg/d). As the coronary anatomy failed to explain the RWMA on TTE or the anterior T-wave inversions, vasospastic angina (VA) was strongly suspected as the main cause of symptoms.

Blood work-up on admission is shown in Table 1. Maximum high-sensitivity T troponin was 62 pg/mL. Six days after admission, he experienced another episode of severe chest pain. ECG revealed ST-segment elevation in the precordial leads and recurrence of apical hypokinesia. Symptoms, ECG, and echocardiographic abnormalities completely subsided 15 min after sublingual nitroglycerin, and repeat coronary angiography was not performed.

One day after the second vasospastic episode, while remaining asymptomatic, follow-up transthoracic echocardiography demonstrated an LVEF of 44% with no residual regional wall motion abnormalities. He presented with constitutional symptoms, including asthenia and low fasting glucose levels. Even though the LVEF was only moderately reduced, the patient remained hypotensive, albeit euvolemic and with a normal lactate level (0.9 mg/dL). Further blood work-up revealed a persistent euvolemic hypo-osmolar hyponatremia (131 mEq/L) with normal to elevated serum potassium (K^+ 5.4 mEq/L). This prompted further evaluation of the hyponatremia that revealed very low serum cortisol levels (0.36 μg/dL; normal range 4.82–19.5 μg/dL) and inappropriately low serum adrenocorticotrophic hormone (ACTH) levels (4.56 pg/mL; normal range 4.70–48.80 pg/mL), consistent with secondary adrenal insufficiency. The patient denied any

use of corticosteroids. Brain magnetic resonance imaging (MRI) was normal, including a normal Sella turcica. Anti-hypophyseal antibodies were negative, suggesting isolated corticotropin deficiency. He was started on hydrocortisone 20 mg/d and a decision was made not to start guideline recommended medical therapy for HF. He was discharged five days after initiation of therapy without recurrence of chest pain and a normalization of blood pressure.

Two months after discharge he showed complete resolution of constitutional symptoms and did not experience any episodes of chest pain while on hydrocortisone and nitrate. The latter was stopped at the 2-month follow-up appointment and TTE showed recovery of LVEF to 54%. Three years after the acute episode, the patient remains asymptomatic, with a LVEF 56% and global longitudinal strain (GLS) -21%. A complete timeline of events is depicted in Figure 1.

Adrenal insufficiency is an endocrine disorder characterized by adrenal hypofunction, with inadequate production of glucocorticoids.[1] Isolated corticotropin deficiency is a form of secondary adrenal insufficiency with low or absent cortisol production and normal secretion of hypophyseal hormones other than ACTH, in the absence of structural hypophyseal defects.[2] We present a case of isolated corticotropin deficiency in a young man with left ventricular dysfunction, VA, and atherosclerotic CAD. Causality was considered based on the patient's age, few risk factors, and full recovery after hypocortisolism treatment. Supplementary Figure 2 shows the pathophysiology between cortisol deficiency and CV manifestations.

HF has been reported in primary, secondary, and tertiary adrenal insufficiency in different age groups,[3,4] with the potential to reverse the condition using corticosteroid replacement therapy. Oakley and Cidlowski[5] used mouse models with inactivation of the glucocorticoid receptors and reported diminished expression of genes responsible for cardiac contractility, increased myocardial hypertrophy and fibrosis. Furthermore, inflammatory mediators, such as interleukins-1 (IL-1) and IL-6 are reported to correlate with cortisol level.[6] In our case, glucocorticoid deficiency likely led to decreased myocardial contractility as well as activation of proinflammatory genes, leading to systolic HF.

VA indicates a form of angina caused by coronary artery spasm. Few cases in literature have reported VA associated with adrenal insufficiency.[6] The following mechanisms may explain the pathophysiology of hypocortisolism leading to VA: (i) a proinflammatory state - infiltration of inflammatory cells in coronary arteries has been found in patients with CAS;[7] (ii) hemoconcentration leading to impaired coronary microcirculatory flow;[5] and (iii) VA may be induced by vascular smooth muscle cell hyperactivity or allergic angiitis, with the release of histamine and cytokines inducing the vasospasm.[8] The latter could occur because adrenal insufficiency often leads to eosinophilia, as the lack of cortisol removes its suppressive effect on white blood cells.[9] This immunosuppressive property is one of the reasons cortisol is considered a potent anti-inflammatory.[10] Interestingly, cortisol has been used in refractory VA in patients with allergic angiitis and hypereosinophilia, with complete symptom resolution.[11] In our case, the patient exhibited typical angina with transient ST-segment elevation and a non-culprit coronary lesion. A presumptive diagnosis of VA was made (albeit the absence of an intracoronary provocation test).[12] After the diagnosis of hypocortisolism, glucocorticoid therapy was initiated and despite no

Table 1. Laboratory values on hospital admission

Indicators	Value (Normal range)
Hemoglobin, g/L	12.6 (13–17)
Leucocytes, $\times10^9$/L	7.8 (4.0–10.0)
Lymphocytes, $\times10^9$/L	2.5 (1.0–3.0)
Neutrophiles, $\times10^9$/L	4.0 (2.0–7.0)
Eosinophiles, $\times10^9$/L	0.2 (0.0–0.5)
Creatinine, mg/dL	0.62 (0.70–1.20)
Blood urea, mg/dL	31 (<50)
Hs-TnT, ng/L	25 (<14)
Total CK, U/L	115.40
NT-proBNP, pg/mL	1,358 (<135)
Total cholesterol, mg/dL	122
LDL cholesterol, mg/dL	79
HDL cholesterol, mg/dL	24
Triglycerides, mg/dL	95
HbA1c, %	5.3 (3.8–5.8)
Sedimentation rate, mm	50 (<13)
Ferritin, ng/mL	733 (30–40)
Iron, μg/dL	64 (33–193)
Transferrin saturation, %	33

CK: creatinine kinase; Hs-TnT: high sensitivity T troponin; NT-proBNP: N-terminal pro-brain natriuretic peptides; LDL: low density lipoprotein; HDL: high density lipoprotein; HbA1c: glycated hemoglobin A1c.

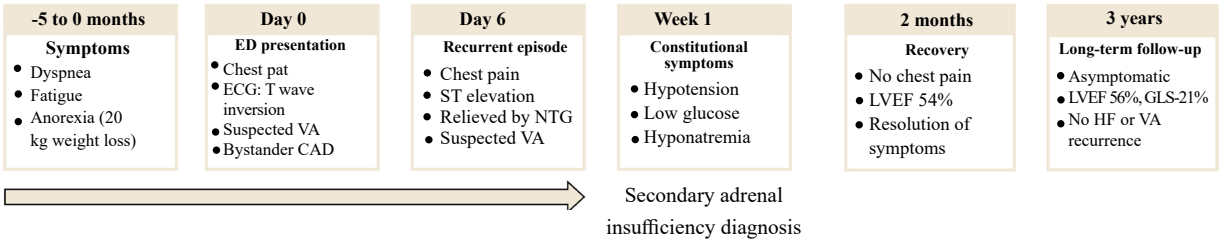

Figure 1. The timeline of events of this patient. ECG: electrocardiogram; VA: vasospastic angina; CAD: coronary artery disease; NTG: nitroglycerin; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; HF: heart failure.

peripheral eosinophilia or allergic background, the patient did not experience any vasospastic symptoms on follow-up.

Our case is also unique in that accelerated CAD was noted. Zhao et al[13] summarized 11 cases in literature of Addison disease associated with heart disease. The emergence of early-onset CAD can be linked to the hypocortisol state, which triggers inflammation, hemoconcentration and disturbances in glucose and lipid metabolism.[14] Even though cortisol deficiency can explain a proinflammatory state, most case reports focus on primary adrenal insufficiency (with high ACTH), while cases on secondary adrenal insufficiency (low to normal ACTH) are scarce.[13,15] In a 2021 cohort study with 6,821 patients with adrenal insufficiency, Ngaosuwan et al[15] reported an increased CV mortality risk - specifically ischemic heart disease - in both primary and secondary adrenal insufficiency, with a higher burden of events in primary adrenal insufficiency. Glucocorticoid usage could explain part of the increased CV risk, but the difference between primary and secondary adrenal insufficiency suggests that factors beyond glucocorticoid replacement contribute to the excess of CV disease.[16] It remains possible that our patient's CAD is due to unmeasured risk factors and represents a bystander (i.e., increased homocysteine). In fact, the patient's symptoms were attributed to coronary vasospasm rather than an acute coronary syndrome, and therefore stent implantation would have not been indicated.[17]

In our patient, treatment with hydrocortisone led to recovery of LVEF and GLS, with no new episodes of chest pain. Recovering without the need for guideline-recommended medical therapy for HF further supports the reversibility of the disease and obviates the need for life-long medication. In retrospect, percutaneous coronary intervention (PCI) may have been avoidable with aggressive CV risk-factor control being a preferable strategy. Our case highlights the importance of searching for reversible causes of HF while integrating the full picture of events. Nevertheless, it is important to note that chronic treatment of adrenal insufficiency is also associated with HF and accelerated atherosclerotic disease.[10] Achieving a balance of adrenal hormones is essential, as they exert both positive and negative effects on the myocardium.

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All the supplementary files in this paper are available at http://wjem.com.cn.

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