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【 CASE REPORT 】

Coronary Spastic Angina Induced by Adrenal Insufficiency

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Abstract:
Adrenal insufficiency patients are treated with glucocorticoid replacement therapy. However, mimicking the *in vivo* circadian rhythm of cortisol levels is challenging, and suboptimal replacement increases the risk of mortality from cardiovascular disease. We herein report a case of coronary spastic angina (CSA) with simultaneous low early-morning serum cortisol levels in a patient undergoing corticosteroid replacement therapy for primary adrenal insufficiency. Steroid therapy is reportedly effective for refractory angina, but underlying adrenal deficiency has never been revealed. Our case intimates the probable risk of CSA as a complication of relative adrenal insufficiency and highlights the effectiveness of dexamethasone in these patients.

Key words: adrenal insufficiency, coronary vasospasm, steroid replacement

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Introduction

Adrenal insufficiency is a condition in which the adrenal glands fail to produce sufficient amounts of steroid hormones, particularly glucocorticoids. Primary adrenal insufficiency is principally causedby autoimmune disorders and other conditions, such as adrenal infection, metastasis, and adrenalectomy (1). Patients with adrenal insufficiency generally receive glucocorticoid replacement therapy. However, mimicking the circadian rhythm of glucocorticoid levels is challenging, and temporary relative adrenal insufficiency sometimes occurs (2). Although adrenal insufficiency is known to be a risk factor for cardiovascular disease (CVD) (3, 4), there are no reports of coronary spastic angina (CSA) associated with adrenal insufficiency.

We herein report a case of CSA caused by relative adrenal insufficiency and highlight the importance of glucocorticoid replacement therapy.

Case Report

A 60-year-old Japanese man with a history of bilateral adrenalectomy and pituitary irradiation for Cushing's disease who had received hydrocortisone replacement (hydrocortisone 20 mg/day; 15 mg after breakfast and 5 mg in the afternoon) for 50 years visited our emergency department with epigastric pain and palpitations. The symptoms manifested without any obvious cause when the patient was at rest and lasted for approximately 1 minute. The pain radiated to the left shoulder, accompanied by severe fatigue. The patient was an ex-smoker (he had quit smoking almost 30 years ago) and did not drink alcohol. He had a history of bronchial asthma, but this was well controlled without the need for medication. He had been aware of palpitations since he was in his 30s, when he had been diagnosed with ventricular extrasystole. He did not have hypertension or diabetes mellitus.

A physical examination revealed no abnormalities, and an electrocardiogram (ECG) did not show any abnormalities such as ST changes or extrasystoles (Fig. 1). Additional laboratory tests revealed no elevated serum cardiac enzyme levels that might have signified myocardial infarction or damage (Table 1). Eosinophil levels were within normal limits. Since lethal diseases manifesting as chest pain were unlikely, the patient was discharged from the hospital. However, his transient palpitations and severe fatigue continued, and he re-visited the outpatient clinic the following day; he was subsequently admitted to our department. On admission, his blood pressure was 150/71 mmHg, and his pulse rate was 59 beats/min and regular. He was alert and conscious and exhibited no abnormal physical signs. Transthoracic

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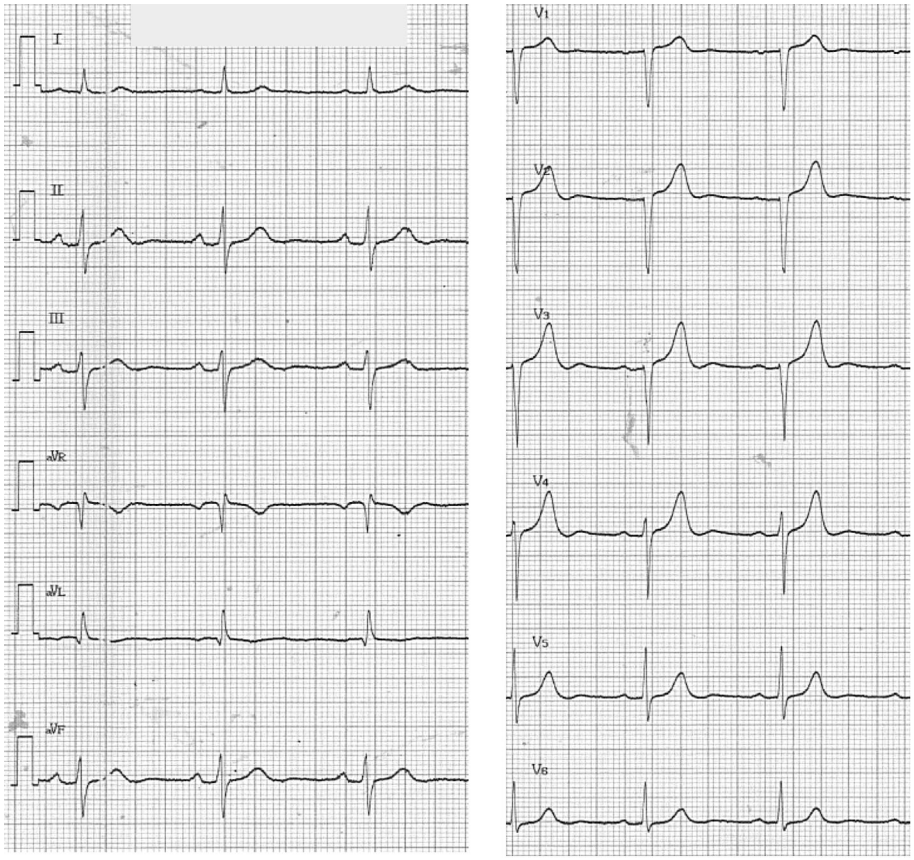

Figure 1. **An electrocardiogram (ECG) on admission. The ECG did not reveal any abnormalities, such as ST elevations or extrasystoles.**

Table 1. **Patient's Laboratory Data on Admission.**

WBC (/μL)	5,700	TP (g/dL)	7.8	LDL-C (mg/dL)	153
Lym (%)	29.6	Alb (g/dL)	4.6	CK (U/L)	56
Neu (%)	64.6	AST (U/L)	17	Na (mmol/L)	136
Mon (%)	2.3	ALT (U/L)	13	K (mmol/L)	4.5
Eos (%)	3.0	ALP (U/L)	232	Cl (mmol/L)	102
Bas (%)	0.5	LD (U/L)	139	Glc (mg/dL)	90
RBC (10^6/μL)	5.61	G-GT (U/L)	34	CRP (mg/dL)	0.16
Hb (g/dL)	16.7	T.Bil (mg/dL)	1.39	CK-MB (U/L)	<4
MCV (fL)	83.8	UN (mg/dL)	14.8	Tn-T (ng/mL)	0.008
MCHC (g/dL)	35.5	Cr (mg/dL)	0.84		
Plt (10^4/μL)	27.1	UA (mg/dL)	8.0		

All the data, including the levels of those cardiac enzymes that might have signified myocardial infarction or damage, were in the normal range.

WBC: White Blood Cell, Lym: Lymphocyte, Neu: Neutrophil, Mon: Monocyte, Eos: Eosinophil, Bas: Basophil, RBC: Red Blood Cell, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, MCHC: Mean Corpuscular Hemoglobin Concentration, Plt: Platelet, TP: Total protein, Alb: Albumin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, LD: Lactate Dehydrogenase, G-GT: Gamma-Glutamyl Transpeptidase, T.Bil: Total Bilirubin, UN: Urea Nitrogen, Cr: Creatinine, UA: Uric acid, LDL-C: Low Density Lipoprotein Cholesterol, CK: Creatine Kinase, Na: Sodium, K: Potassium, Cl: Chloride, Glc: Glucose, CRP: C-Reactive Protein, CK-MB: Creatine Kinase MB, Tn-T: Troponin T

echocardiography revealed no significant findings, such as asynergy or valvular disease.

After hospital admission, from midnight to early morning, the patient complained of similar repeated episodes of chest pain that radiated to his left shoulder, and ventricular tachycardia and ST elevation were recorded on an electrocardiogram (ECG) monitor when symptoms occurred (Fig. 2A). A Holter ECG showed ST elevation, while the patient experi-

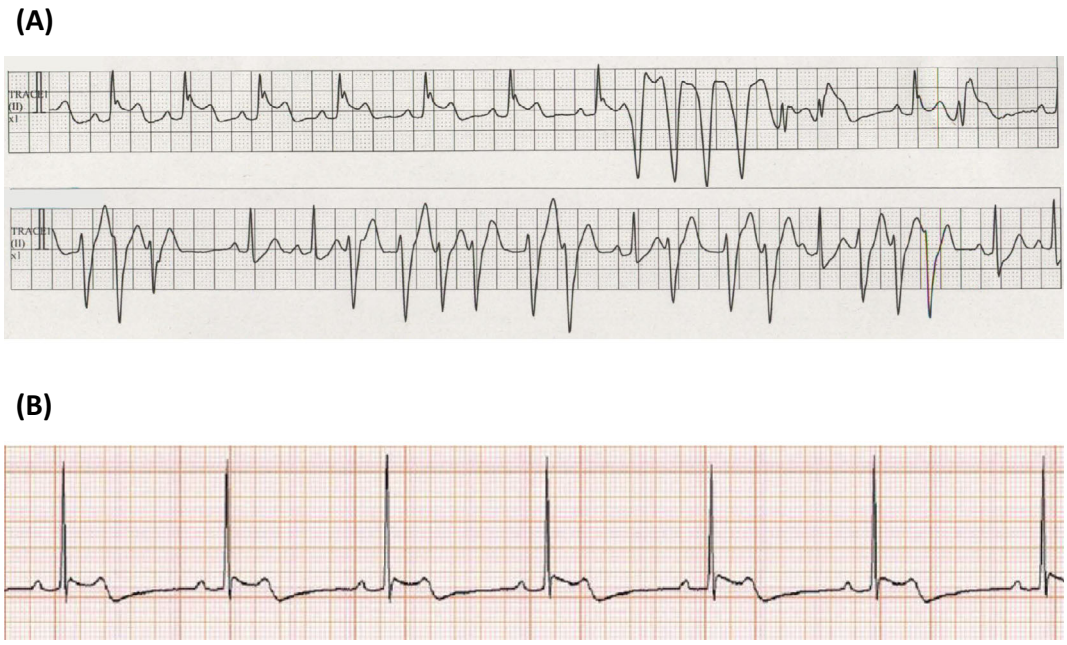

Figure 2. **(A) Electrocardiogram (ECG) monitoring of the timing of the patient's early-morning palpitations and chest pain. Ventricular tachycardia and ST elevation were recorded by ECG monitoring (B) A Holter ECG. Abrupt ST elevation was also observed in the early morning.**

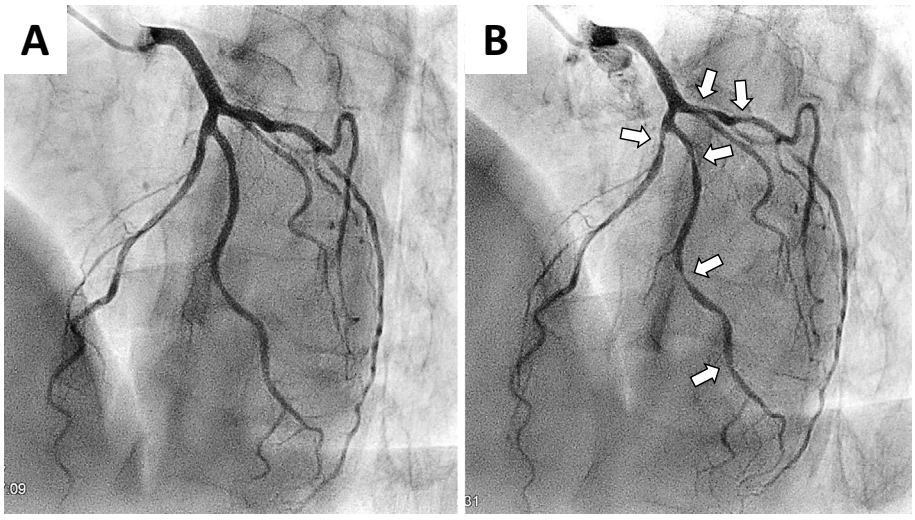

Figure 3. **Coronary angiograms before and after the administration of ergometrine (A and B). Diffuse spasm of the coronary artery accompanied by ST elevation on electrocardiogram and chest pain were provoked by the administration of ergometrine.**

Table 2. **Patient's Early-morning Basal Pituitary Hormone Levels.**

Adrenocorticotropic hormone (pg/mL)	143
Cortisol (μg/dL)	<0.1
Thyrotropin (μU/mL)	6.94
Free thyroxine (ng/dL)	1.19
Follicle-stimulating hormone (mIU/mL)	10.8
Luteinizing hormone (mIU/mL)	4.4
Prolactin (ng/mL)	15.2
Growth hormone (ng/mL)	0.11
Insulin-like growth factor-I (ng/mL)	116

enced chest pain in the early morning (Fig. 2B). As CSA was suspected, coronary angiography was performed. Although there was no significant visible stenosis, diffuse spasm of the left anterior descending artery, ST elevations on ECG, and chest pain were provoked after ergometrine administration (Fig. 3).

CSA was diagnosed, and nifedipine and nicorandil were administered, but chest pain and fatigue persisted. The urinary free cortisol (UFC) level was sufficient (70 μg/day); however, additional endocrinological tests revealed that the early-morning cortisol level was below the detection sensitivity, although adrenocorticotropic hormone (ACTH) secre-

tion appeared to be increased (Table 2 and Fig. 4). As temporal adrenal insufficiency was suspected, dexamethasone 0.25 mg/day was administered at bedtime, whereupon the early-morning chest pain and palpitations totally resolved.

Discussion

Adrenal insufficiency is a condition in which the adrenal glands fail to produce sufficient amounts of steroid hormones, particularly glucocorticoids. Bilateral adrenalectomy is the third-most common cause of primary adrenal insufficiency (1). In patients with adrenal insufficiency, glucocorticoid replacement therapy is mainly administered with hydrocortisone (5). However, it is very difficult to completely mimic the *in vivo* circadian rhythm of glucocorticoid levels (2), and it is challenging to prevent temporary overtreatment or undertreatment (6). Suboptimal glucocorticoid replacement therapy in adrenal insufficiency patients has been reported to increase the risk of mortality from CVD (3, 4).

It is interesting that not only overtreatment but also temporary adrenal insufficiency increases the risk of CVD (7). Inflammatory mediators, such as interleukin 1, interleukin 6, and tumor necrosis factor, are reported to correlate with the cortisol level (8-12), and elevated levels of these mediators may be associated with an increased risk of cardiovascular events (7). In addition, glucocorticoid deficiency is reported to be associated with a low expression of K^+ channels in the heart ventricles (13) and Ca^{2+} transporter dysfunction in the heart membrane (14), thus reducing the cardioprotective effect (15). Furthermore, glucocorticoid deficiency has been reported to cause hyperthyroidism, owing to the inappropriate secretion of thyroid-stimulating hormone (16), which is known to be associated with cardiovascular complications (17). Some as-yet-unidentified mechanisms may underlie the relationship between adrenal insufficiency and increased cardiovascular risk.

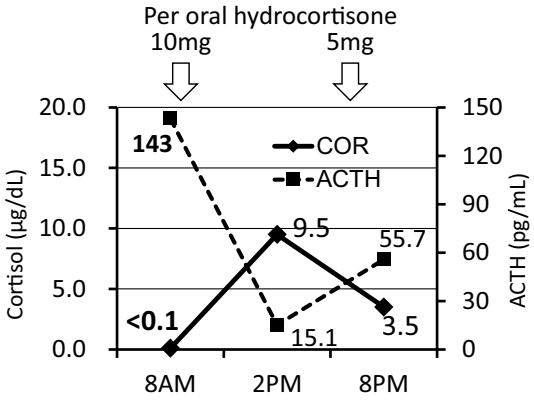

Figure 4. Diurnal rhythm of the cortisol level. Early-morning cortisol levels were below the detection sensitivity, although the adrenocorticotropic hormone (ACTH) secretion appeared to be increased.

CSA is transient myocardial ischemia attributable to coronary artery vasospasm (18). Our patient demonstrated typical symptoms of CSA, with attacks prevalent in the early morning while at rest and continuing for no more than 10 min (18, 19). CSA and its attacks are usually well-treated and controlled with drugs such as nitrates, calcium channel blockers, or nicorandil; however, 14% of CSA cases are refractory, as observed in our patient (18).

For such refractory CSA cases, steroids are an available treatment option. Previous reports have shown that the symptoms exhibited by six patients with CSA were relieved after corticosteroid administration (Table 3) (20-22). All of the patients had some allergic comorbidities, and five of them had a history of asthma. Two of them had worsening symptoms of asthma, and another two demonstrated eosinophilia and elevated immunoglobulin E (IgE) levels concurrent with their CSA symptoms. These reports suggest that the CSA spasm may be induced by arterial hyperactivity or allergic angiitis caused by local inflammation, and corticosteroids can suppress the spasm by alleviating inflammation in the vessel wall (20, 21). In the cases detailed in Table 3, five out of six patients were treated with prednisolone, although in our patient's case, a small dose of dexamethasone was administered at bedtime in addition to regular hydrocortisone replacement. Prednisolone and dexamethasone are potent long-acting corticosteroids that exert 4 and 25 times the potency of glucocorticoid action, respectively, compared to hydrocortisone (23), suggesting that they may have been effective in suppressing the spastic attacks resulting from CSA in our patient.

The present patient exhibited refractory CSA simultaneously with low early-morning serum cortisol levels. The relative adrenal insufficiency in the early morning may have increased inflammatory mediators and induced local inflam-

Table 3. Reported Coronary Spastic Angina Patients with Refractory Spasms Relieved by Corticosteroid Treatment.

Case No.	Age, Sex	Comorbidities	Characteristic of time course	Steroid treatment
1 (20)	39, Female	Chronic thyroiditis, MI	(-)	Prednisolone 40 mg/day
2 (20)	43, Female	Asthma	Asthma worsening	Hydrocortisone 600 mg/day
3 (20)	55, Male	Asthma, HT, HL	Asthma worsening	Prednisolone 30 mg/day
4 (20)	43, Female	Asthma, HT	(-)	Prednisolone 30 mg/day
5 (21)	48, Male	Asthma, Chronic eosinophilia	Eosinophilia and IgE elevation	Prednisolone 20 mg/day
6 (22)	43, Male	Asthma, Allergic rhinitis, MI	Eosinophilia and IgE elevation	Prednisolone 30 mg/day

HL: hyperlipidemia, HT: hypertension, IgE: immunoglobulin E, MI: myocardial infarction

mation, leading to the development of coronary spasm. Although the eosinophil and IgE levels were within normal limits, the patient's history of asthma may have affected his risk of developing spasms. Five cases (except for Case No. 4) in Table 3 may have been associated with long-term corticosteroid use; this may explain the iatrogenic adrenal insufficiency-induced CSA.

Conclusions

We experienced a case of CSA associated with temporary steroid deficiency. The present findings suggest that temporal and relative adrenal insufficiency may contribute to the development of coronary vasospasm. Allergic mechanisms may play an important role in spasm development, for which the administration of long-acting steroids is an effective treatment option.

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

References

1. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab **101**: 364-389, 2016.
2. Choudhury S, Lightman S, Meeran K. Improving glucocorticoid replacement profiles in adrenal insufficiency. Clin Endocrinol (Oxf) **91**: 367-371, 2019.
3. Bensing S, Brandt L, Tabaroj F, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf) **69**: 697-704, 2008.
4. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab **91**: 4849-4853, 2006.
5. Amin A, Sam AH, Meeran K. Glucocorticoid replacement. BMJ **349**: g4843, 2014.
6. Oprea A, Bonnet NCG, Pollé O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther Adv Endocrinol Metab **10**: 2042018818821294, 2019.
7. Rahvar AH, Haas CS, Danneberg S, Harbeck B. Increased cardiovascular risk in patients with adrenal insufficiency: a short review. Biomed Res Int **2017**: 3691913, 2017.
8. Mastorakos G, Paltoglou G, Greene M, et al. Inappropriately normal plasma ACTH and cortisol concentrations in the face of increased circulating interleukin-6 concentration in exercise in patients with sarcoidosis. Stress **16**: 202-210, 2013.
9. Papanicolaou DA, Tsigos C, Oldfield EH, Chrousos GP. Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency? J Clin Endocrinol Metab **81**: 2303-2306, 1996.
10. Tsigos C, Kyrou I, Chrousos GP, Papanicolaou DA. Prolonged suppression of corticosteroid-binding globulin by recombinant human interleukin-6 in man. J Clin Endocrinol Metab **83**: 3379, 1998.
11. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. J Clin Endocrinol Metab **77**: 1690-1694, 1993.
12. Sarwar N, Butterworth AS, Freitag DF, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet **379**: 1205-1213, 2012.
13. Takimoto K, Levitan ES. Glucocorticoid induction of Kv1.5 K^+ channel gene expression in ventricle of rat heart. Circ Res **75**: 1006-1013, 1994.
14. Narayanan N. Effects of adrenalectomy and in vivo administration of dexamethasone on ATP-dependent calcium accumulation by sarcoplasmic reticulum from rat heart. J Mol Cell Cardiol **15**: 7-15, 1983.
15. Tokudome S, Sano M, Shinmura K, et al. Glucocorticoid protects rodent hearts from ischemia/reperfusion injury by activating lipocalin-type prostaglandin D synthase-derived PGD2 biosynthesis. J Clin Invest **119**: 1477-1488, 2009.
16. Tamada D, Onodera T, Kitamura T, et al. Hyperthyroidism due to thyroid-stimulating hormone secretion after surgery for Cushing's syndrome: a novel cause of the syndrome of inappropriate secretion of thyroid-stimulating hormone. J Clin Endocrinol Metab **98**: 2656-2662, 2013.
17. Klein I, Danzi S. Thyroid disease and the heart. Circulation **116**: 1725-1735, 2007.
18. Group JJW. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J **78**: 2779-2801, 2014.
19. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J **34**: 2949-3003, 2013.
20. Takagi S, Goto Y, Hirose E, et al. Successful treatment of refractory vasospastic angina with corticosteroids: coronary arterial hyperactivity caused by local inflammation? Circ J **68**: 17-22, 2004.
21. Nomura T, Keira N, Taminishi S, et al. Corticosteroid therapy was effective in controlling refractory coronary vasospasms complicated by hypereosinophilia. Intern Med **53**: 735-738, 2014.
22. Takano T, Ozaki K, Tanaka K, Yanagawa T, Ozawa T, Minamino T. Efficacy of corticosteroid treatment for refractory multivessel vasospastic coronary angina with hypereosinophilia. Intern Med **57**: 3111-3115, 2018.
23. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med **63**: 200-207, 1977.