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Cushing's syndrome developing myasthenia gravis with takotsubo cardiomyopathy after adrenalectomy: a case report

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Abstract

Background Several cases of autoimmune disease onset after treatment for Cushing's syndrome have been reported.

Case presentation Herein, we report a case of myasthenia gravis crisis in a 51-year-old woman 2 months after adrenalectomy for adrenal Cushing's syndrome accompanied by takotsubo cardiomyopathy. The resolution of excessive endogenous cortisol after adrenalectomy may have triggered the onset of previously latent myasthenia gravis.

Conclusions Observing the similarities in symptoms between myasthenia gravis and adrenal crisis, which can sometimes be challenging to differentiate, is essential. Moreover, the presence of takotsubo cardiomyopathy as a non-motor manifestation of myasthenic crisis must be noted.

Keywords Cushing's syndrome, Myasthenia gravis, Autoimmune disease, Takotsubo cardiomyopathy, Cortisol

Background

Cushing's syndrome (CS) results from chronic exposure to excessive glucocorticoids, which can arise from either exogenous (i.e., pharmacological doses of corticosteroids) or endogenous cortisol sources [1]. Endogenous hypercortisolism may be adrenocorticotropic hormone (ACTH)-dependent or -independent. While pituitary adenomas are common in ACTH-dependent forms of CS, ACTH-independent CS occurs exclusively because of adrenal tumors such as adenomas and carcinomas [2]. Adrenalectomy is an effective therapeutic modality for adrenal tumor-associated ACTH-independent CS [3]. However, some autoimmune diseases (ADs) have been reported to occur after adrenalectomy, including myasthenia gravis (MG) [4, 5]. MG is a neurological AD primarily characterized by skeletal muscle weakness due to the disruption of neuromuscular junction transmission by antibodies targeting acetylcholine receptors (AChR), muscle-specific kinase, and lipoprotein receptor-related protein 4 [6]. Weakness may be generalized or localized and often involves the eye muscles with diplopia and ptosis. Weakness typically increases with exercise and repetitive muscle use and varies throughout the day and from day to day. Treatment of MG in the acute phase requires early fast-acting therapies, such as high-dose intravenous steroids, intravenous immunoglobulin therapy, and plasmapheresis, whereas oral prednisolone (PSL), immunosuppressants, and certain biological drugs are important

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to prevent relapse. In the chronic stage, acetylcholinesterase inhibitors may be used symptomatically. These agents inhibit the breakdown of acetylcholine, leading to increased concentrations of acetylcholine at the neuromuscular junction and thereby enhancing neurotransmission [6]. A myasthenic crisis is a life-threatening event in MG associated with respiratory failure and a high mortality rate; such is often triggered by stressors such as infection, surgery, childbirth, and medications [7]. However, myasthenic crises are rarely the initial presentation of MG. MG is a multisystem disorder sometimes associated with cardiac involvement, such as arrhythmias, pericarditis, and myocarditis. Takotsubo cardiomyopathy (TTC) is an important complication of myasthenic crisis [8]. TTC is a condition in which an echocardiogram or left ventriculogram shows a heart shape similar to that of a Japanese octopus fishing pot (i.e., takotsubo) and is characterized by transient systolic dysfunction of the apical and/or mid-segments of the left ventricle, mimicking acute myocardial infarction without obstructive coronary artery disease [9]. A myasthenic crisis can subsequently trigger TTC. Herein, we report a case of new-onset MG that developed myasthenic crisis in the subacute phase, accompanied by TTC, after adrenalectomy for the treatment of adrenal adenoma.

Case presentation

In August 2022, a 51-year-old woman was examined at our Endocrinology Department for an incidentally discovered 28-mm right adrenal tumor. The diagnosis of adrenal CS was established based on physical findings, including central obesity, moon facies, and subcutaneous hemorrhages, along with hormonal test results. Baseline blood tests revealed a suppressed ACTH level of 2.2 pg/mL and an elevated cortisol level of 20.2 μg/dL, raising suspicion of CS. A subsequent 1-mg dexamethasone suppression test demonstrated insufficient cortisol suppression, with a post-test level of 20.3 μg/dL. ^{131}I-adosterol scintigraphy showed increased uptake in the right adrenal gland and decreased uptake in the left. Additionally, elevated midnight cortisol levels and the absence of normal diurnal variation confirmed the diagnosis of adrenal CS. In November 2022, the patient underwent laparoscopic right adrenalectomy in the Department of Urology. The pathological diagnosis was benign adrenal cortical adenoma. Postoperatively, the patient received standard steroid therapy (intravenous hydrocortisone immediately after surgery followed by oral hydrocortisone [20 mg/day]). Shortly after surgery, the patient began feeling fatigued. In January 2023, the patient had difficulty speaking and swallowing, neck instability, unsteady gait, and double vision. The patient then developed difficulty breathing, which led to a visit to the Emergency Department of our hospital in March 2023. Chest radiography and computed tomography revealed no evidence of pulmonary disease. Creatine kinase was not elevated. However, there was a mild increase in troponin I levels. An electrocardiogram showed negative T waves in leads II, III, aVF, and V4–V6. Echocardiography revealed signs of basal cardiac hypercontraction and apical akinesis, while coronary angiography showed no stenosis or occlusion of the coronary arteries. Based on the results of the medical examination, TTC was suspected to be the cause of dyspnea, and the patient was admitted to the Cardiology Department.

On the third day of hospitalization, the patient developed sudden cardiopulmonary arrest. Although she was successfully resuscitated with prompt intervention, type 2 respiratory failure persisted, requiring continuous non-invasive positive pressure ventilation after invasive positive pressure ventilation. Although the plasma cortisol level in blood samples taken at rest in the early morning of that day was 560.07 nmol/L, considering the possibility of adrenal insufficiency, an intravenous infusion of hydrocortisone at a dose of 200 mg/day was initiated. Although this eventually improved her respiratory condition, respiratory difficulty worsened with steroid tapering. While attempting to identify differential diagnoses for the cause of type 2 respiratory failure, serum tests revealed positivity for anti-acetylcholine receptor antibodies. On day 43 of hospitalization, the patient was transferred to the Neurology Department with suspected myasthenic crisis as the cause of respiratory failure and TTC.

At first contact, she had no fever, but her blood pressure was elevated, and she presented with sinus tachycardia. Transcutaneous oxygen saturation was maintained at 99% with non-invasive positive pressure ventilation, and arterial blood gas analysis revealed marked respiratory acidosis. The patient had bilateral ptosis and dysphagia, as well as weakness in the upper limbs with a right-dominant preference. Manual muscle testing revealed muscle weakness in the neck and bilateral proximal upper extremities. The patient was easily fatigued, with worsening ptosis in the afternoon and an inability to lift her smartphone for prolonged periods. No sensory, coordination, or reflex abnormalities were observed. Repetitive nerve stimulation testing at a frequency of 3 Hz performed on the left accessory nerve showed a maximum decrease in amplitude of 31.8%, indicating waning (Fig. 1). No abnormal findings were observed on brain or cervical magnetic resonance imaging. Contrast-enhanced chest magnetic resonance imaging revealed a thymoma (Fig. 2). Serum anti-muscle-specific kinase and anti-striation antibodies (antibodies against titin and Kv1.4) were negative (Table 1). No other findings suggested complications from another AD.

Based on the symptoms and examination results, we diagnosed the patient with generalized

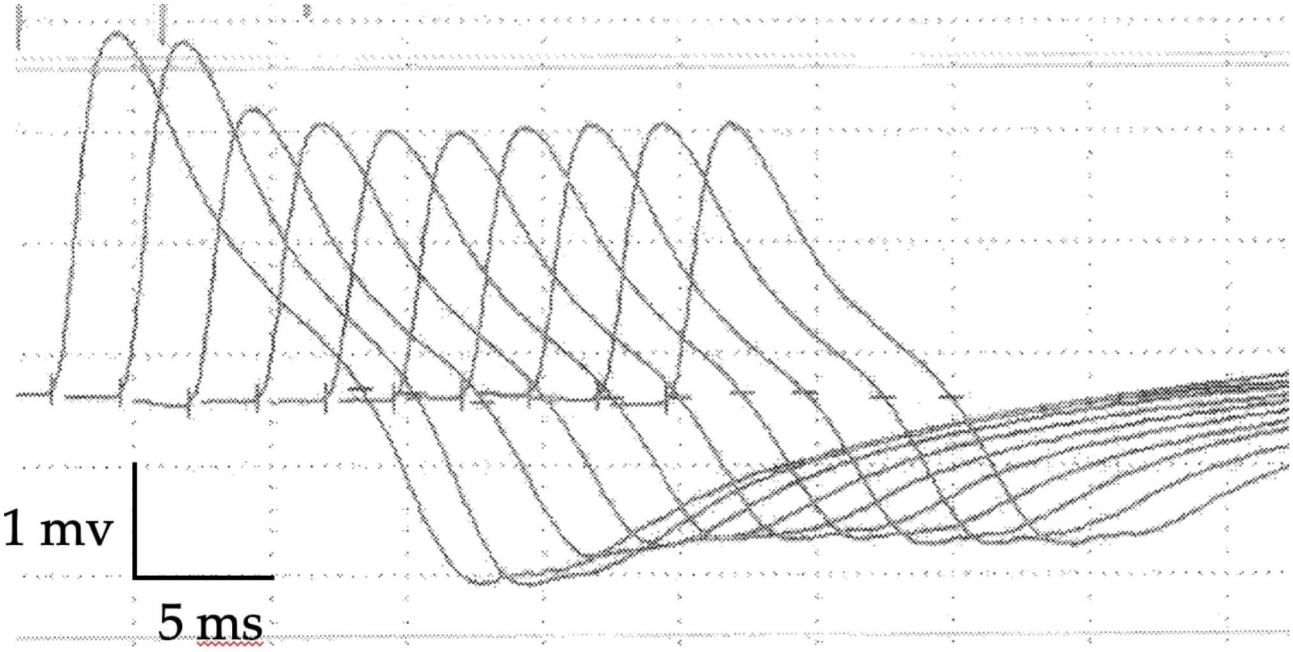

Fig. 1 Repetitive nerve stimulation tests (3 Hz) on the left accessory nerve, showing a waning phenomenon

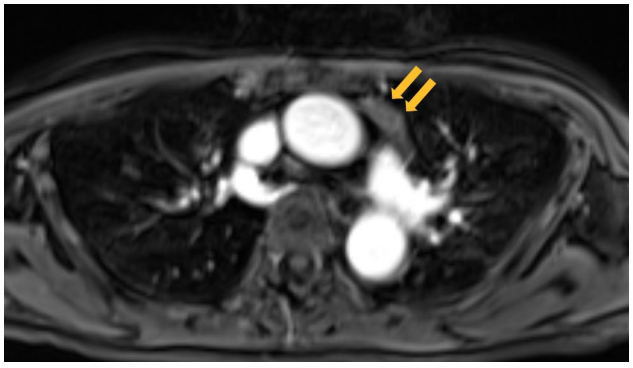

Fig. 2 Chest contrast-enhanced MRI revealing a 17-mm tumor in the anterior mediastinum without fatty components (arrow). MRI, magnetic resonance imaging

thymoma-associated MG in a myasthenic crisis state, corresponding to a Myasthenia Gravis Foundation of America Class V. Generalized thymoma-associated MG is characterized by AChR antibody positivity, symptoms that are not limited to the ocular muscles but affect the whole body, and the presence of a thymoma [10]. Early fast-acting therapies were initiated, including plasmapheresis, high-dose steroids, and intravenous immunoglobulin therapy (Fig. 3). Oral PSL (20 mg/day) and cyclosporine (150 mg/day) were administered. Her respiratory status gradually improved, and she was successfully weaned off the ventilator on day 67. Concomitantly, her ptosis and muscle strength improved in parallel with a decrease in AChR antibody titers. An extended thymectomy was performed on day 85, with a pathological diagnosis of a World Health Organization type B2 thymoma. The patient adhered to the recommended rehabilitation, and the PSL dose was gradually tapered; by the time of discharge on day 137, the PSL dose had been tapered to 10 mg/day. Symptoms indicative of neuromuscular transmission disruption were absent. Her echocardiographic findings on day 72 showed improvement, with normal wall motion observed.

Discussion and conclusions

We encountered a case of MG complicated by TTC that developed subacutely after adrenalectomy for adrenal adenoma. Although several ADs have been reported to develop after adrenalectomy, this is the first report of a newly developed MG detected during myasthenic crisis, with presenting symptoms that were difficult to differentiate from adrenal insufficiency.

Petramala et al. [5] previously reported the case of a 62-year-old woman with thymoma-associated MG who developed bilateral ptosis, diplopia, and proximal muscle weakness 5 months after adrenalectomy for adrenal adenoma. The authors additionally investigated the incidence of ADs in patients after CS treatment, including the aforementioned case [4]. The study included 147 patients with CS, 109 of whom underwent surgery. Patients were evaluated up to 24 months after clinical and biochemical remission, with nine (8.3%) patients developing a novel AD: four, autoimmune thyroiditis (Basedow-Graves' disease or Hashimoto's thyroiditis); one, systemic lupus erythematosus; one, rheumatoid arthritis; one, psoriasis; one, giant cell arteritis; and one, MG. The mean age of the nine patients complicated by AD (CS with AD group)

Table 1 Laboratory findings at the time of transfer

Hematological analyses			**Blood chemistry**			**Immunoserological tests**		
WBC	7300	/μL	TP	6.9	g/dL	ANA	< 40×	
RBC	532	$\times 10^3$/μL	Alb	4.0	g/dL	anti-SS-A ab	< 0.4	U/mL
Hb	16.6	g/dL	T-Bil	0.8	mg/dL	anti-dsDNA ab	< 0.6	U/mL
Ht	49.1	%	BUN	5.8	mg/dL	anti-ARS ab	(–)	
PLT	26.9	$\times 10^4$/μL	Cre	0.3	mg/dL	anti-Titin ab	0.42	A.U. (< 1.0)
			AST	20	U/L	anti-Kv1.4 ab	0.71	A.U. (< 1.0)
			ALT	16	U/L	anti-AChR ab	19.8	nmol/L
			LDH	305	U/L			
Blood gas analyses (FiO_2 0.4)			CK	61	U/L			
pH	7.093		CRP	0.2	mg/dL			
pCO_2	109.8	mmHg	Na	142.1	mEq/L	**Coagulation tests**		
pO_2	206.8	mmHg	K	3.5	mEq/L	PT	≥ 100	%
HCO_3^-	32.8	mmol/L	Cl	103.4	mEq/L	PT-INR	0.93	
B.E.	-1.4	mmol/L	BNP	34.4	pg/mL	APTT	32.2	s
Lactate	2.04	mmol/L	Glu	98	mg/dL	D-dimer	1.24	μg/mL

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; PLT, platelet; PT, prothrombin time; INR, international normalized ratio; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CRP, C-reactive protein; BNP, brain natriuretic peptide; Glu, glucose; ANA, antinuclear antibody; SS-A, Sjögren syndrome-related antigen-A; dsDNA, double-stranded DNA; ARS, aminoacyl-tRNA synthetase; AChR, acetylcholine receptor

was significantly younger than that of the CS without AD group (52.3 vs. 61.0 years, respectively). The CS with AD group showed significantly higher mean plasma cortisol levels before surgery for CS (818.1 vs. 459.5 nmol/L, respectively), and the difference in plasma cortisol levels before and after treatment in the CS with AD group was greater than that of the CS without AD group (444.6 vs. 41.5 nmol/L, respectively). They discussed the possibility that excessive endogenous cortisol in CS may suppress the onset of an underlying AD, which became evident after treatment, and speculated that an underlying AD may trigger higher endogenous cortisol production [4]. In our case, the patient was 51 years old, younger than the mean age of the CS with AD group. Moreover, although the plasma cortisol level immediately before adrenalectomy was 543.45 nmol/L, it decreased to 41.39 nmol/L after adrenalectomy, corresponding to a 502.06 nmol/L difference. Such difference was larger than the mean difference in plasma cortisol levels before and after treatment in the CS with AD group previously reported. The sudden decrease in plasma cortisol levels after adrenalectomy may have triggered the onset of MG, and the symptoms may have gradually worsened. Additionally, the onset of AD occurred despite the administration of standard steroid therapy with hydrocortisone after adrenalectomy. In general, physiological cortisol secretion in humans is equivalent to a hydrocortisone dose of 20 mg/day (equivalent to 5 mg/day PSL). Therefore, hydrocortisone supplementation at approximately 20 mg/day is common in patients with adrenal insufficiency [11]. In adrenal CS, if the hypothalamic–pituitary–adrenal axis is suppressed preoperatively, rapid postoperative adrenal insufficiency may occur, requiring glucocorticoid or mineralocorticoid administration. Cortisol production in the remaining contralateral, healthy adrenal gland usually takes approximately 6 months to begin. Thus, steroid supplementation is typically tapered over 6 months to 1 year [12, 13]. Although standard steroid therapy can prevent adrenal insufficiency, it may be insufficient to prevent the development of MG in some cases of postsurgical CS. Our patient had difficulty speaking and swallowing, neck instability, and unsteady gait 2 months after adrenalectomy; however, plasma cortisol levels were sufficient to suppress the onset of AD at that time. Although plasma cortisol levels were high when the patient first reported symptoms, minor symptoms, such as fatigue and mild muscle weakness, which were not recognized as abnormal, may have begun after adrenalectomy when plasma cortisol levels were very low. Considering the potential impact of the surgical burden of adrenalectomy on the onset of MG is necessary as well. Furthermore, the gradual decline in plasma cortisol levels observed between March and August 2023 was presumed to be attributable to PSL administration over an extended period.

In the present case, the patient developed TTC, which is a potential cause of cardiac arrest. TTC is a critical non-motor manifestation of myasthenic crisis [8]. Although the possibility of concomitant myocarditis was considered, it was rejected owing to the absence of characteristic anti-striated muscle antibodies (anti-Kv 1.4 and anti-titin antibodies) and the lack of remarkable creatine kinase elevation throughout the clinical course [14]. Patients with adrenal insufficiency may present with nonspecific symptoms, such as prolonged fatigue, and, at times, may also exhibit severe conditions [15]. Therefore, distinguishing adrenal insufficiency from MG symptoms

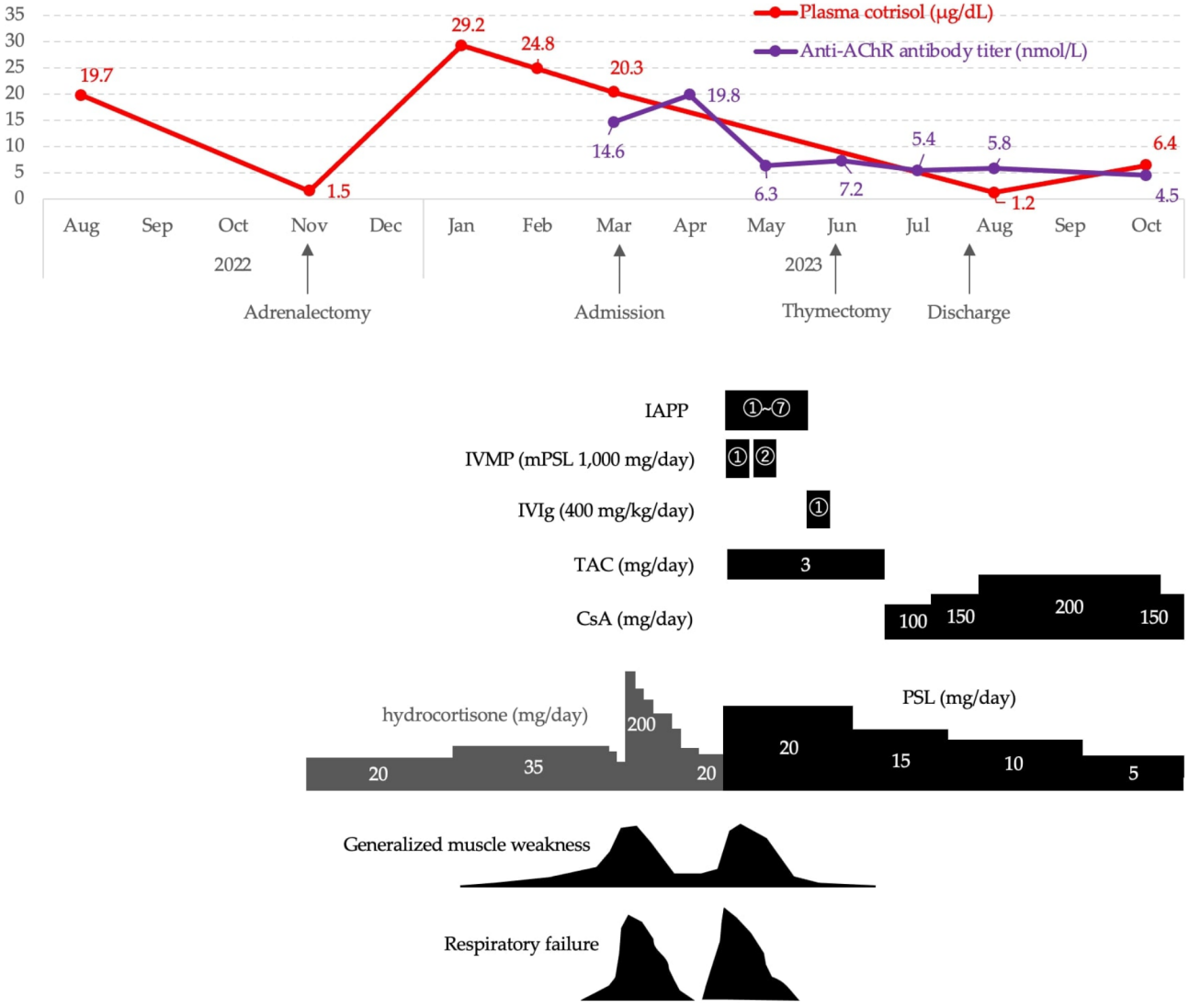

Fig. 3 Entire clinical course of the patient. IAPP, immunoabsorption plasmapheresis; IVMP, intravenous methylprednisolone; mPSL, methylprednisolone; IVIg, intravenous immunoglobulin; TAC, tacrolimus; CsA, cyclosporine A; PSL, prednisolone; IPPV, invasive positive pressure ventilation; AChR, acetylcholine receptor

may be challenging. In cases of cardiac arrest after adrenalectomy for adrenal adenoma that develops into MG, considering TTC as a differential diagnosis of adrenal insufficiency is necessary. The detection of thymoma and TTC provided an opportunity for earlier diagnosis and treatment initiation for MG; however, an earlier initiation of MG treatment might have prevented cardiac arrest.

In conclusion, patients with CS should be offered screening for potential coexisting ADs, which may be masked by excessive glucocorticoids, by obtaining full history, clinical examination, and relevant investigations prior to surgery. However, it is important to note that hypercortisolism may mask biomarkers of ADs. Patients may also require vigilant monitoring for the onset of AD after decreased plasma cortisol levels. When complicated by MG, recognizing that there may be an immediate risk of life-threatening conditions, such as TTC and myasthenic crisis, in some patients after adrenalectomy for ACTH-independent CS is essential. Finally, a comprehensive understanding of the complexity of neuroendocrine networks requires further investigation. This case, representing the second reported instance worldwide of MG triggered by adrenalectomy, highlights the uncertainties surrounding long-term prognosis. Further accumulation of similar cases is essential to enhance our knowledge in this area.

Abbreviations

AChR	Acetylcholine receptor
ACTH	Adrenocorticotropic hormone
AD	Autoimmune disease
CS	Cushing's syndrome
MG	Myasthenia gravis
PSL	Prednisolone

TTC Takotsubo cardiomyopathy

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Author contributions
KY: Visualization, Writing – original draft; TK: Writing – review & editing; SK: Writing – review & editing; KM: Writing – review & editing; YM: Writing – review & editing; AM: Writing – review & editing; HM: Supervision, Writing – review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the participant for the publication of any potentially identifiable images or data included in this article.

Consent for publication
Written informed consent was obtained from the patient for this publication of this report and any accompanying images.

Competing interests
The authors declare no competing interests.

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