A Case of Glucocorticoid Hypersensitivity Syndrome Associated With Underlying Rubella Virus Infection

Zhen Zhang, MS, Ying Feng, PhD, Yang Cao, PhD, Yan Chen, MS, Fangping Li, PhD *

Department of Endocrinology, The Seventh Affiliated Hospital, Sun Yat-sen University, China

ABSTRACT

Objective: The objective of this article is to report a rare case of glucocorticoid hypersensitivity syndrome, which may be associated with an underlying rubella virus infection.

Case Report: A 29-year-old man showed progressive weight gain for 16 months accompanied by a moon face, enlarged dorsocervical fat pad, central obesity, and purple striae. His cortisol circadian rhythm was normal, and plasma cortisol levels at 8:00 AM fluctuated between 3.2 and 9.54 μg/dL (reference range, 4.3-22.4 μg/dL). A dexamethasone suppression test with a very low dose (0.25 mg) of dexamethasone showed a marked decrease in plasma cortisol level to 0 μg/dL. Adrenal computed tomography and pituitary magnetic resonance imaging findings were normal. The Z-score of the bone density in the lumbar spine was −4.2. The IgM antibody for the rubella virus was positive. His erythrocyte sedimentation rate was 24 mm/hour (reference range, <15 mm/hour), and the C-reactive protein level was 9.22 mg/L (reference range, <5 mg/L). After 3 months, his symptoms resolved spontaneously. The erythrocyte sedimentation rate and C-reactive protein level returned to normal. The IgM antibody for the rubella virus turned negative, whereas the IgG antibody for the rubella virus was positive.

Discussion: According to the paradox between clinical manifestations and laboratory tests exogenous glucocorticoid hypersensitivity syndrome, cyclic Cushing syndrome, and glucocorticoid hypersensitivity syndrome all should be considered in the diagnosis. Detailed medical history inquiry, complete endocrine hormone testing, and continuous follow-up are all critical for diagnosis.

Conclusion: Consequently, the patient was diagnosed with glucocorticoid hypersensitivity syndrome. This case illustrates the need to consider the possibility of glucocorticoid hypersensitivity syndrome in a patient who has the manifestations of Cushing syndrome but paradoxical hypocortisolemia, especially after rubella virus infection.

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Introduction

Glucocorticoid hypersensitivity syndrome is a rare endocrinologic condition caused by cell hypersensitivity to glucocorticoids. Iida et al1 first described this disease in 1990. To date, only a few cases of glucocorticoid hypersensitivity syndrome have been reported in the literature. Patients diagnosed with this disease have typical clinical manifestations of Cushing syndrome, but the level of endogenous glucocorticoids is normal or even decreased.

A clear diagnostic criterion for glucocorticoid hypersensitivity syndrome has not yet been established. Before the diagnosis of glucocorticoid hypersensitivity syndrome, iatrogenic Cushing syndrome and surreptitious self-medication must be ruled out, which can lead to Cushing syndrome and paradoxical hypocortisolemia. Therefore, repeated and detailed medication history inquiry is very important, including asking whether the patient has taken traditional Chinese medicines and health care products and whether relatives and friends have autoimmune disorders. Cyclical Cushing syndrome also needs to be ruled out. Therefore, cortisol levels should be measured multiple times at different times. In addition, it is required to exclude the presence of clinical conditions associated with a decrease in corticosteroid-binding globulin level, in which despite low total cortisol levels, the level of its free fraction remains within the normal limit.2 Apart from typical cushingoid symptoms in the presence of low or normal serum cortisol level, a
dexamethasone suppression test with a very low dose (0.25 mg) of dexamethasone can lead to a marked decrease in plasma cortisol level,
and the corticotropin-releasing hormone and Synacthen stimulation tests show a poor response of adrenocorticotropic hormone (ACTH) and cortisol in a patient with glucocorticoid hypersensitivity syndrome. Moreover, some in vitro experiments have been performed to diagnose this disease. For example, it can be diagnosed by measuring the sensitivity of cultured skin fibroblasts to dexamethasone in vitro. Thymidine incorporation and dexamethasone-binding assays on peripheral blood mononuclear cells in association with the sequencing of the human glucocorticoid receptor (hGR) gene are also important methods to confirm the diagnosis.

Here, we report a case of glucocorticoid hypersensitivity syndrome, present the clinical manifestations and endocrinologic evaluation, and discuss its etiology.

**Case Report**

A 29-year-old man presented with a history of progressive weight gain, accompanied by the development of acne on the face and violaceous striae on the armpits and thighs since December 2018. Over the last 16 months, his body weight increased by 5 kg. In July 2019, he had weakness in both lower limbs, and his blood potassium level was 3.0 mmol/L. After potassium supplementation, his muscle strength recovered, and the blood potassium level returned to 3.8 mmol/L. Without obvious causes, he had back pain and suffered compression fractures of the thoracic and lumbar vertebrae in January and March 2020, respectively. He was in good health before and had no history of smoking or drinking. His father died of esophageal cancer 1 year ago, and his mother and two brothers are in good health. He is mentally healthy and cooperative during hospitalization. After repeated inquiries and checking his medical records, we learned that he did not take any medicines and health care products before the onset of illness.

On admission, his blood pressure was 151/100 mm Hg, his height was 166 cm, his weight was 68.5 kg, and his body mass index was 24.9 kg/m². Physical examination revealed a moon face with acne, enlarged dorsocervical fat pad, central obesity, and thin skin with wide purple striae on both sides of the armpits and inner thighs (Fig. 1).

![Fig. 1. Moon face and purple striae.](image1)

Table 1: Cortisol and ACTH Tests of the Patient in Different Days and Times

| Date   | Time | Cortisol (µg/dL) | ACTH (pmol/L) |
|--------|------|-----------------|---------------|
| 15 Apr | 8 AM | 8.07            | 6.17          |
|        | 4 PM | 6.92            | 5.91          |
|        | 0 AM | 2.08            | 3.08          |
| 21 Apr | 8 AM | 9.54            | 9.56          |
|        | 4 PM | 2.98            | 2.64          |
|        | 0 AM | 0.56            | 1.76          |
| 18 Jun | 8 AM | 3.2 ‡           | 5.6           |
| 03 Jul | 8 AM | 4.1 ‡           | -             |
|        | 4 PM | 2.9             | -             |
|        | 0 AM | <0.8            | -             |
| 14 Jul | 8 AM | 5.3             | -             |
|        | 4 PM | 5.0             | -             |
|        | 0 AM | <0.8            | -             |
| 05 Aug | 8 AM | 6.3             | -             |
|        | 4 PM | 4.1             | -             |
|        | 8 AM | 7.1             | -             |
| 16 Sept| 8 AM | 7.1             | -             |
|        | 4 PM | 5.7             | -             |
|        | 0 AM | <0.8            | -             |
| 13 Dec | 8 AM | 4.01 ‡          | 4.55          |

Abbreviation: ACTH = adrenocorticotropic hormone.
Reference values of cortisol (8:00 AM): 4.3-22.4 µg/dL.
Reference values of ACTH (8:00 AM): 1.6-13.9 pmol/L.
Reference values of UFC: 3.5-45 μg/24 hours.
Reference values of 17-OHCS: 6-25 mg/24 hours.
Reference values of 17-KS: 2-8 mg/24 hours.

### Table 2

| Date     | UFC (μg/24 hours) | 17-OHCS (mg/24 hours) | 17-KS (mg/24 hours) | Urine volume (L) |
|----------|-------------------|------------------------|---------------------|------------------|
| 15 Apr   | <1.11 μg/24 hours | 2.9 μg/24 hours        | 1.3 μg/24 hours     | 1.2 L            |
| 18 Jun   | 13.8 μg/24 hours  | 6.0 μg/24 hours        | 1.8 μg/24 hours     | 1.5 L            |

Abbreviations: UFC = urinary free cortisol; 17-OHCS = 17-hydroxycorticosteroid; 17-KS = 17-ketosteroid.

### Table 3

| Parameters  | Value | Reference range |
|-------------|-------|-----------------|
| TSH (uIU/mL) | 0.91 | 0.35-4.94 |
| FT3 (pg/mL)  | 3.03 | 1.71-3.71 |
| FT4 (ng/dL)  | 1.13 | 0.70-1.48 |

Abbreviations: FT3 = free triiodothyronine; FT4 = free throxine; TSH = thyroid-stimulating hormone.

### Table 4

| Parameters               | Value | Reference range |
|--------------------------|-------|-----------------|
| Testosterone (nmol/L)    | 26.94 | 4.94-32.01 |
| LH (mIU/mL)              | 3.18  | 0.57-12.07 |
| FSH (mIU/mL)             | 4.53  | 0.95-11.95 |
| Prolactin (ng/mL)        | 21.04 | 3.46-19.4 |

Abbreviations: LH = luteinizing hormone; FSH = follicle-stimulating hormone.

### Table 5

| Time (h) | Glucose (mmol/L) | Insulin (μU/mL) |
|----------|------------------|-----------------|
| Disease active phase | 0  | 4.61 | 2.1 |
|             | 2  | 10.54 | 83.46 |
| Disease resolution phase | 0  | 4.0 | 7.93 |
|             | 2  | 6.2 | 28.02 |

The blood glucose level in 2 hours of the oral glucose tolerance test in the disease active phase is higher than 7.8 mmol/L, indicating impaired glucose tolerance.

### Table 6

| Parameters             | Value | Reference range |
|------------------------|-------|-----------------|
| Calcitonin (pg/mL)    | 3.86  | <6.4 |
| 25-Hydroxyvitamin D (ng/mL) | 16.26 | >30 |
| Parathyroid hormone (pg/mL) | 29.9 | 15.0-68.3 |
| Bone alkaline phosphatase (μg/mL) | 56.11 | 17.9-31.9 |

Fig. 2. Adrenal computed tomography image.

The aldosterone level was 125.12 pg/mL (reference range, 10-160 pg/mL), and simultaneous potassium level was 3.86 mmol/L (reference range, 3.5-5.5 mmol/L). His thyroid function is shown in Table 3. His testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin levels are shown in Table 4. His growth hormone level was 1.58 ng/mL (reference range, 0.03-2.47 ng/mL). The oral glucose tolerance test suggested impaired glucose tolerance (Table 5). Bone metabolism markers are shown in Table 6. Adrenal computed tomography and pituitary magnetic resonance imaging did not reveal any abnormalities (Fig. 2 and 3). The bone density of the lumbar spine evaluated by a dual-energy X-ray densitometer showed the presence of severe osteoporosis (Z-score, −4.2). X-rays of the spine showed compression fractures of the 7th to 11th thoracic vertebrae and the 1st and 2nd lumbar vertebrae. The IgM antibody for the rubella virus was positive, whereas the IgG antibody for the rubella virus was negative.

### Discussion

In this case, we describe a patient who presented with typical clinical manifestations of Cushing syndrome including moon face, buffalo hump, central obesity, skin purple striae, hypertension, impaired glucose tolerance, hypokalemia, and pathologic fracture, but his plasma cortisol and ACTH levels were normal or decreased paradoxically. How can we explain this paradox?

Detailed inquiry and medical records revealed no history of exogenous glucocorticoid administration. Therefore, the possibility of exogenous Cushing syndrome was ruled out. At first, the diagnosis of cyclical Cushing syndrome was assumed. Cyclical Cushing syndrome is a pattern of hypercortisolism in which the biochemical activity of cortisol production fluctuates rhythmically. Cortisol cycling has been defined as the presence of at least three peaks and two troughs of cortisol production. However, after 7 months of follow-up, no cortisol peak was found in this patient. The patient's plasma cortisol was sustained at a low level. A poor response of cortisol to Synacthen stimulation indicated that the hypothalamic-pituitary-adrenal (HPA) axis in the patient was suppressed. Moreover, a marked decrease in plasma cortisol level caused by a dexamethasone suppression test with a very low dose of dexamethasone indicated that the sensitivity of the glucocorticoid receptor to glucocorticoid in this patient increased.

Although we did not perform any in vitro experiment, both the clinical picture and
results of the endocrinologic evaluation were sufficient to establish the diagnosis of glucocorticoid hypersensitivity syndrome.

Although the patient’s cortisol was suppressed, ACTH was still at a normal level. Plasma ACTH levels may be normal or low in primary generalized glucocorticoid hypersensitivity. The reason why there is a lack of complete suppression of the HPA axis in glucocorticoid hypersensitivity remains unknown. Perhaps, it is because the patient’s peripheral tissues are hypersensitive to cortisol; however, the sensitivity of glucocorticoids in the brain and pituitary is normal. Hypertension and hypokalemia are key features in this case. A case report also described a patient with cortisol hypersensitivity syndrome whose blood pressure was high. The glucocorticoid receptor is widely expressed in a number of organ systems relevant to blood pressure regulation, including the kidney, brain, and vasculature. In the kidney, glucocorticoids can act on glucocorticoid receptors to promote renal sodium reabsorption. In vascular smooth muscle, studies have observed an upregulation in angiotensin II type I receptors induced by glucocorticoids, which are hypothesized to result in alterations in blood pressure. In the vascular endothelium, studies have suggested that glucocorticoids regulate vascular reactivity via suppression of the production of vasodilators, such as prostacyclin and nitric oxide, leading to hypertension. Therefore, it is reasonable that cortisol hypersensitivity can cause high blood pressure. The cause of hypokalemia in this patient is still unknown. Glucocorticoids may also upregulate angiotensin II type I receptors in the kidney and cause hypokalemia.

The precise etiology of glucocorticoid hypersensitivity syndrome remains unknown. At the cellular level, the actions of glucocorticoids are mediated by the hGR, which is a member of the steroid hormone receptor family of the nuclear receptor superfamily of transcription factors. The mutations or polymorphisms in the hGR gene have been attributed to the molecular mechanism of glucocorticoid hypersensitivity syndrome, which increases the transcriptional activity of glucocorticoid-responsive genes. However, to date, only one patient has been reported with manifestations of glucocorticoid hypersensitivity syndrome caused by a novel hGR gene mutation, which resulted in an aspartic acid (D) to histidine (H) substitution at amino acid position 401 in the amino-terminal domain of hGRz. In addition to activating hGR gene mutations, N363S and BclI polymorphisms are associated with increased glucocorticoid sensitivity. Studies have found that the polymorphisms of N363S and BclI are associated with higher sensitivity to glucocorticoids in vivo, hypertension, visceral adiposity, elevated cholesterol and triglyceride levels, lower bone mineral density, and higher incidence of coronary artery disease. Besides hGR gene mutations or polymorphisms, there have been a few cases with glucocorticoid hypersensitivity syndrome of no defect in the hGR gene.

Whole-exome sequencing tests were performed and found no mutations or polymorphisms of the hGR gene in our case, including alpha or beta isoform. What is the mechanism leading to glucocorticoid hypersensitivity in our case? Nicolaides et al reported a case of glucocorticoid hypersensitivity syndrome; a 9-year-old girl presented with an 8-month history of clinical manifestations suggestive of Cushing syndrome and paradoxically hypocortisolemia, whose symptoms resolved spontaneously over the ensuing 3 months. Moreover, RNA-sequencing analysis in peripheral blood mononuclear cells revealed that compared with the resolution phase, 106 genes were upregulated in the disease active phase. Most of those differentially expressed genes were related to immune and inflammatory responses, especially NF-κB and its subunits, suggesting that a virus- or bacterium-encoded molecule activates the NF-κB signaling pathway, enhances glucocorticoid signal transduction, and leads to glucocorticoid hypersensitivity syndrome. Although we did not perform transcriptomic analysis of the peripheral blood mononuclear cells in our case, the increases in the ESR and C-reactive protein level in the disease active phase indicate the presence of inflammation. A positive rubella virus IgM antibody prompts that the patient had active rubella during the disease active phase. A positive rubella virus IgG antibody is evidence for a past history of rubella. The etiology of glucocorticoid hypersensitivity syndrome in our case may be associated with the rubella virus infection.

**Conclusion**

In conclusion, we present a patient with glucocorticoid hypersensitivity syndrome who gradually recovered spontaneously. It is likely that rubella virus infection may be associated with a transient postreceptor defect and enhanced glucocorticoid signal transduction, thereby leading to the corresponding clinical manifestations and compensatory hypoactivation of the HPA axis. To our
knowledge, this is the first report about glucocorticoid hypersensitivity syndrome associated with an underlying rubella virus infection.

Disclosure

The authors have no multiplicity of interest to disclose.

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