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CASE REPORT

New-Onset Sarcoidosis After Remission of Cushing's Syndrome

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Abstract

Exposure to high levels of endogenous or exogenous glucocorticoids suppresses the inflammatory response genes. Excessive endogenous hypercortisolism may mask the active inflammatory diseases. Rebound immune modulation may occur after Cushing's syndrome (CS) remission, leading to the new onset of autoimmune diseases. Here, we report a 27-year-old female patient who was recently diagnosed with sarcoidosis after remission of CS. Normal thorax imaging showed that the patient was free of disease during the course of CS and without any symptoms of sarcoidosis. After complete remission of CS, she was diagnosed with sarcoidosis based on clinical and radiological evidence. Excessive hypercortisolism may suppress the active inflammatory stage of sarcoidosis. However, the disease became apparent after the reduction of cortisol levels following the treatment of CS.

KEY WORDS: Sarcoidosis, Cushing's syndrome, hypercortisolism

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INTRODUCTION

Cushing's syndrome (CS) comprises a large group of signs and symptoms that reflect prolonged and inappropriately high exposure of tissue to glucocorticoids [1]. Endogenous or exogenous glucocorticoids suppress the inflammatory response; therefore, they are the most preferred treatment options in inflammatory diseases. Persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy [2]. Excessive endogenous hypercortisolism may mask the active inflammatory disease. Rebound immune modulation may occur after CS remission, thus leading to the new onset of autoimmune diseases that focus mainly on thyroid autoimmune diseases [2].

Sarcoidosis is a systemic inflammatory disease characterized by the presence of granulomatous inflammation in affected tissues. The peripheral lymph nodes, lungs, eyes, and skin are the most involved organs [3]. The etiology of the disease remains unknown. However, the prevailing hypothesis is that various unidentified, poorly degradable antigens of either infectious or environmental origin could trigger an exaggerated immune reaction in genetically susceptible hosts [4].

New-onset sarcoidosis after remission of CS is reported in few cases in the literature. Here, we report a case with new-onset sarcoidosis after complete remission of CS due to adrenal adenoma.

CASE PRESENTATION

A 27-year-old female was admitted to our hospital with a right adrenal adenoma that was discovered during examination for right flank pain. She had a history of hypertension for 3 years and complained of a 23-kg weight gain in 2 years. The patient was normotensive. She was treated with valsartan/hydrochlorothiazide (160 mg and 12.5 mg, respectively) once daily. She had no history of hypertensive spells and other past medical records. On physical examination, she had moon face with facial plethora, buffalo hump, acne, abdominal obesity with body mass index (BMI) 32 kg/m^2, purple abdominal stria, and easy bruising.

Laboratory evaluation revealed normal glucose levels, complete blood count, and liver and renal functions. Functional screening of the adrenal adenoma was performed to eliminate Conn's syndrome, Cushing's sydrome, and pheochromocytoma. Twenty-four hour urinary free metanephrine and normetanephrine levels were within normal limits. Plasma aldosterone/plasma rennin activity ratio was < 20 with normal serum potassium levels. She had high midnight serum cortisol levels (14 ug/dL), and the cortisol levels were not suppressed with two day 2 mg dexamethasone suppression test. Twenty-four hour free cortisol levels showed a 4-fold increase (1292 mg/dL), and Cushing's sydrome (CS) was diagnosed. Basal ACTH levels

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were < 5 pg/mL in three occasions, thus reflecting an adrenal-dependent cause.

Plain chest X-ray and computed tomography (CT) of the patient were normal (Figure 1a, 2a). Adrenal CT demonstrated right adrenal mass, which was 50 mm in diameter (Figure 3). It had clear margins in addition to its low density on CT, which were indicative of an adenoma. The patient underwent right adrenalectomy with corticosteroid coverage. The post-operative period was uneventful, and she was discharged with corticosteroid replacement. The pathology of the adrenal mass was a benign cortical adenoma.

The corticosteroid treatment reduced gradually and lasted till the end of the 18 month. During the last dose decrement, she started to complain of cough without sputum or fever. Physical examination of the respiratory system was normal. Chest X-ray revealed bilateral hilar and right paratracheal enlargement (Figure 1b). Bilateral hilar and mediastinal lymphadenopaties were present in the in thorax CT (Figure 2b). The biggest lymphadenopathy was nearly 3.5 cm in size at the subcarinal region. The serum calcium level was within normal limits. The tuberculin skin test result was 0 mm in the scar positive BCG vaccinated patient. The level of serum angiotensin converting enzyme was increased (178 U/L; normal range: 0-52 U/L). Carbone monoxide diffusion capacity (DLCO) was decreased (71%), while the pulmonary function test was normal. Fiberoptic bronchoscopy showed that main and right secondary carinas were edematous and the entry of the left upper lobe was narrowed by mucosal edema. Bronchoalveolar lavage (BAL) and fine needle aspiration were taken. Flow cytometric evaluation of the bronchoalveolar fluid showed lymphocytic alveolitis (17.1%). CD4/CD8 ratio was 6.71. The histopathological evaluation of the fine needle aspiration showed that there were noncaseous granulomas. The patient was diagnosed with sarcoidosis after the clinical, radiological, and histopathological evaluations. She will be followed up 3 months later with thorax CT for restaging. Corticosteroid treatment will be initiated if there is additional parenchymal involvement.

DISCUSSION

Endogenous CS is caused either by excess adrenocorticotropic hormone (ACTH) secretion or by autonomous cortisol release from the adrenal cortex. Glucocorticoids are the main endogenous mechanism to suppress the inflammatory response genes [2]. Exposure to persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy, thereby resulting in immunosuppression [5]. On the other hand, in post-stressful situations, transient rebound thymic hyperplasia may be observed in children and adolescents [5]. Similar situations may be observed after remission of CS of all types, which

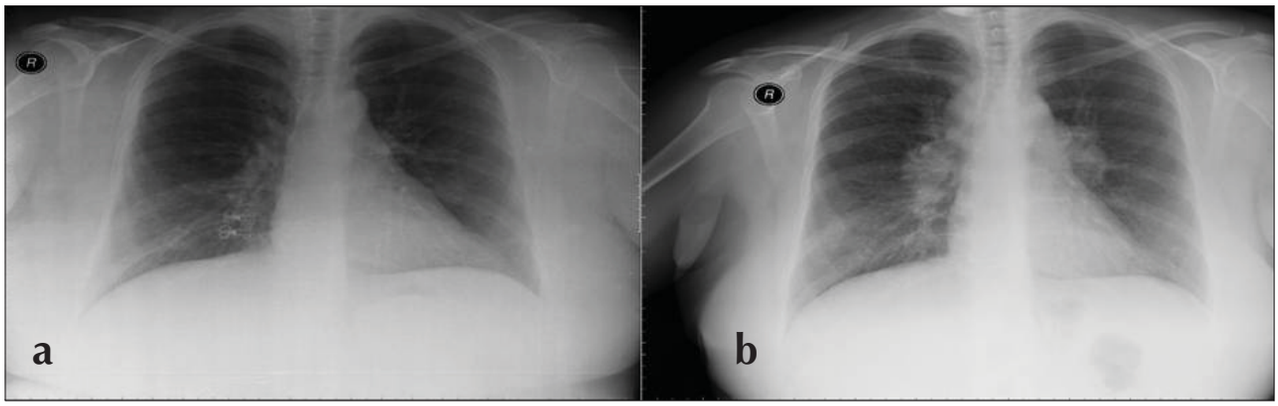

Figure 1. a, b. Plain chest X-ray of the patient: (a) before treatment of CS and (b) after treatment of CS.
CS: Cushing syndrome.

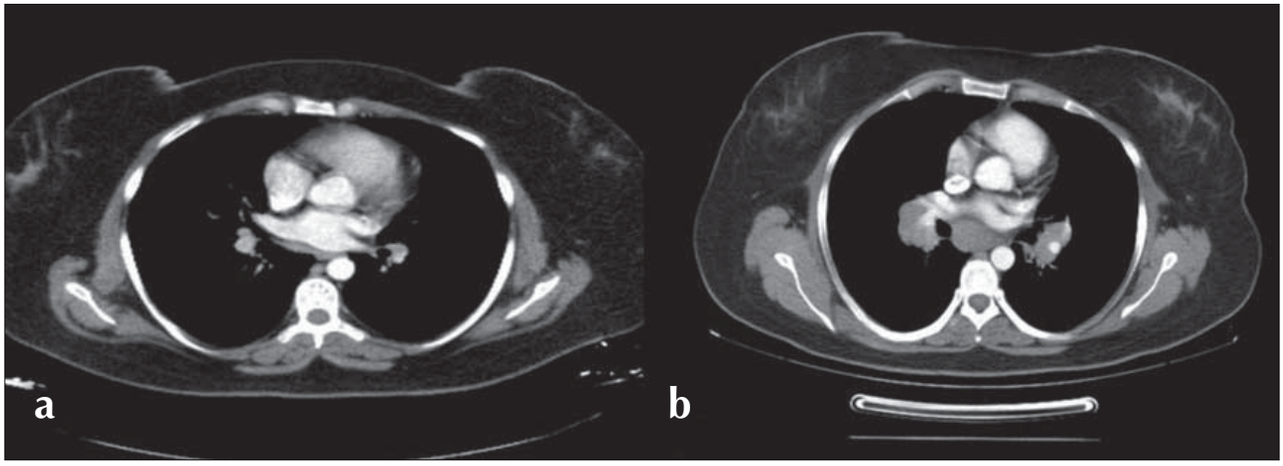

Figure 2. a, b. Axial view of thorax CT of the patient: (a) before treatment of CS and (b) after treatment of CS.
CS: Cushing syndrome.

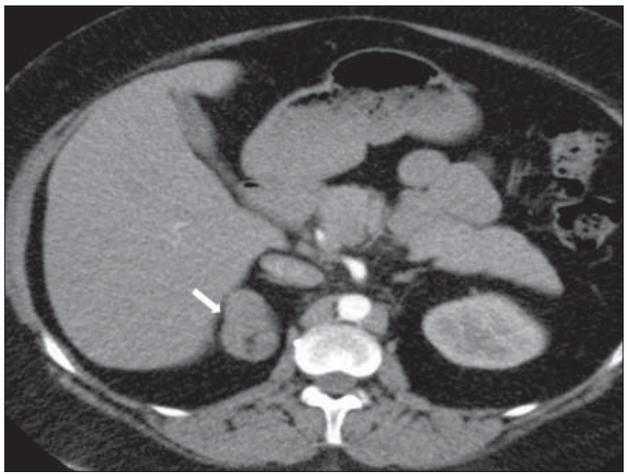

Figure 3. Axial view of adrenal CT of the patient. The arrow shows a 5 cm right adrenal mass.
CT: computed tomography.

reflects immune reactivation. We reported a case of sarcoidosis diagnosed after the remission of CS that may support this hypothesis.

The standard mortality ratio in patients with persistent moderate hypercortisolism due to untreated CS is increased 3.8-5.0-fold compared with that in the general population [6]. However, after successful normalization of cortisol levels, the mortality rate was similar to age matched population [6]. In a recent study, CS mortality was mainly attributed to cardiovascular causes and infection/sepsis in 50% and 21.4% of the cases, respectively [7]. The increased rate of infection mostly results from immunosuppression. The glucocorticoids affect lymphocyte proliferation through the inhibition of IL-1 and IL-2 production [8]. They also influence IL-10 secreting regulatory T cells [9]. Therefore, endogenous hypercortisolism contributes to immunosuppression in patients with CS.

Sarcoidosis is characterized by noncaseating granulomas and has been shown to be associated with other autoimmune disorders. The number of T cells in the granulomatous process are increased in this disease. Lungs are the most frequently involved organ in sarcoidosis. The identification of disease involvement can generally be determined by pulmonary function testing and chest imaging. Pulmonary function tests demonstrate decreased volumes and DLCO [4]. Bilateral hilar and symmetric and non-compressive lymphadenopathies are characteristic features and are often associated with right paratracheal and aortic-pulmonary window lymph node involvement in chest X-ray and thorax CT.

The patient was diagnosed with stage I sarcoidosis based on the presence of the noncaseous granulomas in the histopathologic evaluation of the fine needle aspiration and the supporting evidences such as radiologic findings, lymphocytic alveolitis, and increased serum ACE level and CD4/CD8 ratio.

After treatment of CS, rebound immunity occurs, particularly in patients with overt disease [2]. In rare cases, the treatment of CS may result in unmasking or aggravation of diseases responsive to glucocorticoid medication, such as thyroid, rheumatologic, and allergic diseases [2-10]. Sarcoidosis after remission of CS has been reported in few cases in the literature. Most of these patients were represented and diagnosed with cutaneus manifestations; however, our patient only had lung involvement [10]. The disease in our patient became symptomatic just after the corticosteroid replacement treatment decreased to lower levels. Therefore, high doses of glucocorticoids administered after remission of CS until restoration of pituitary adrenal axis may still be enough to suppress rebound immunity. This would be an explanation why the onset of symptoms was observed after a longer latency period in some cases.

In conclusion, excessive hypercortisolism may suppress the active inflammatory stage of sarcoidosis. However, the disease would become apparent after the reduction of cortisol levels following the treatment of CS.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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