Addison’s Disease Induced by Miliary Tuberculosis and the Administration of Rifampicin

Toshinobu Yokoyama, Reiko Toda, Yoshizo Kimura, Makiko Mikagi and Hisamichi Aizawa

Abstract

We herein report a rare occurrence of Addison’s disease caused by acute adrenal gland tuberculosis occurring in association with miliary tuberculosis and the administration of rifampicin. An 82-year-old woman with miliary tuberculosis was treated with antituberculous chemotherapeutic agents including rifampicin (RFP), but she still demonstrated general malaise in addition to hyponatremia. Abdominal CT showed an enlargement of the right adrenal gland. However, after discontinuing RFP, the patient’s symptoms improved. We carefully reinitiated the administration of RFP. The patient’s condition thereafter did not worsen, and the treatment could thus be maintained. It is extremely important to immediately recognize adrenal crisis precipitated by the administration of RFP.

Key words: Addison’s disease, adrenal crisis, adrenal gland tuberculosis, miliary tuberculosis, rifampicin

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Introduction

Addison’s disease is an adrenal gland insufficiency which occurs due to various etiologies. In the past, tubercular Addison’s disease was more common than idiopathic Addison’s disease or other etiologies. However, this phenomenon reflects the decrease in the incidence of tuberculosis. As a result, tubercular Addison’s disease is rare today (1). However, there are no specific symptoms for Addison’s disease, and it is therefore possible for a patient to fall into an adrenal crisis when this disease is not identified in a timely manner. As a result, when treating tuberculosis it is important to keep in mind that rifampicin administration has the potential to sometimes induce adrenal crisis. We herein describe the clinical course and adrenal gland image findings and discuss the occurrence of rifampicin-induced adrenal crisis in a patient demonstrating Addison’s disease with miliary tuberculosis.

Case Report

An 82-year-old woman with symptoms of fever, fatigue, and appetite loss who developed a miliary shadow according to chest radiographs was transferred to our hospital. The illness began in December 2001. Chest radiograph and computed tomography findings of the chest showed a miliary shadow in both lung fields (Fig. 1). She was admitted our hospital in January 2002. Her vital signs upon admission were an alert state of consciousness, blood pressure 126/70 mmHg and body temperature 38.4°C. The physical findings on admission were height, 133 cm; and body weight, 45.3 kg. Whole body pigmentation was observed. No rales were evident on auscultation of both lungs. Her abdomen was soft and flat. Laboratory findings included a red blood cell count of 527×10⁴/μL; hemoglobin (Hb), 15.2 g/dL; hematocrit, 44.3%; white blood cell count (WBC), 5,200/μL; (neutrophils, 76.9%; lymphocytes, 14.1%; monocytes, 8.0%; eosinophils, 0.2%; basophils, 0.8%); platelet count, 31.2×10⁴/μL; aspartate aminotransferase, 73 IU/L; alanine aminotransferase, 36 IU/L; lactate dehydrogenase, 309 IU/L; ALP 548 U/L, glucose, 123 mg/dL; c-reactive protein (CRP), 4.36 mg/dL and an erythrocyte sedimentation rate (ESR) of 23 mm/1 hr. The serum sodium, potassium and chloride levels were normal. A chest radiograph on admission revealed diffuse miliary nodules in both lungs and this was confirmed by computed tomography (CT) of the chest (Fig. 1). Tuberculin skin tests were negative (anergy). Myco-
**Figure 1.** Chest computed tomography on admission showing a diffuse micronodular shadow in both lung fields.

*bacterium tuberculosis* was not detected by a smear, but it was detected by PCR and culture in the sputum. No resistance to any antitubercular agents was revealed. A bone marrow biopsy specimen showed epithelioid cell proliferation. The patient was therefore diagnosed to have miliary tuberculosis.

**Clinical Course of The Patient**

She was treated with antituberculous chemotherapy including rifampicin (RFP) (450 mg/day), isoniazid (INH) (300 mg/day) and ethambutol (EB) (750 mg/day). However, few days after the administration of these agents, the overall condition of the patient dramatically deteriorated with a worsening of her general malaise. She demonstrated appetite loss and vomiting. Nine days after the administration of RFP, her body weight decreased to 42.4 kg (-2.9 kg). Her serum electrolyte concentration at pre-treatment was Na 136 mEq/L, K 4.0 mEq/L and Cl 97 mEq/L. Seven days after the administration of RFP, hyponatremia (89 mEq/L) and hyperkalemia (5.6 mEq/L) was revealed. The laboratory data for the adrenal gland revealed a normal-level for cortisol (8.3 μg/dL), a low-level for 24-h urinary 17-ketosteroid (17-KS) concentration (2.4 mg/day), a normal-level for 24-h urinary 17-hydroxycorticoids (17-OHCS) concentration (3.4 mg/day), a high-level for renin activity (6.2 ng/mL/h), and a high-level for ACTH (440 pg/mL) in the plasma. Nine days after treatment, the fever subsided. However, the administration of rifampicin was thus discontinued. The patient continued to be treated by other antituberculous agents (streptomycin instead of RFP) and was given saline to correct hyponatremia. Due to an improvement in the symptoms of hyponatremia with these treatments, her general malaise thereafter greatly improved. Computed tomography of the abdomen detected a swelling of right adrenal gland. Because of these laboratory data and the clinical symptoms, especially pigmentation, the patient was diagnosed to have tubercular Addison’s disease and the adrenal crisis induced by the administration of rifampicin. The administration of rifampicin was thus discontinued, and the patient was thereafter treated by a combination of INH, EB and streptomycin. Gradually, her condition and adrenal gland insufficiency improved. Enhanced computed tomography of the right adrenal gland revealed a low attenuation area widely inside the organ, thus suggesting the presence of necrosis inside the right adrenal gland (Fig. 2). Hyponatremia improved to a normal level without correction, and an upregulation of the cortisol level was also recognized by the rapid ACTH test.

The rapid ACTH challenge test showed the serum concentration of cortisol to be below the pre-challenge level, namely 5.5 μg/dL; at 30 minute after challenge, the level was 8.6 μg/dL; while at 60 minute after the challenge, it was 10.6 μg/dL. As a result, rifampicin was then carefully re-administered (450 mg/day). Thereafter, no symptoms of adrenal crisis were again observed, and therefore the treatment regimen with RFP+INH+EB could thus be continued. After the re-administration of RFP, the laboratory data for the adrenal gland revealed a normal level for cortisol (5.5 μg/dL), 24-h urinary 17-KS concentration was low (1.5 mg/day), 24-h urinary 17-OHCS concentration was 2.9 mg/day, a high-level for ACTH (193 pg/mL) in the plasma and serum electrolyte concentration; Na 131 mEq/L, K 5.8 mEq/L, Cl 97 mEq/L. Therefore, the adrenal function was still insufficient, however, the patient was symptom free. She was discharged 4 months after admission, and thereafter her treatment was administered on an outpatient basis. Initially, the swollen size of the right adrenal gland (55×25 mm) decreased slightly on the CT findings. However, it was still swollen (44×24 mm) after chemotherapy at 1 year and 4 months after the initial presentation. In addition, the presence of calcification inside the right adrenal gland was a distinct characteristic in the course of the disease (Fig. 2). Concerning the adrenal function, the plasma cortisol, serum sodium, potassium and chloride levels were all normal. However, the plasma ACTH level still remained elevated even after the administration of antituberculous chemotherapy. However, no clinical symptoms were observed. As a result, she was observed without medication for both Addison’s disease and tuberculosis.

**Discussion**

Addison’s disease is divided into two types based on its clinical features. One type presents with acute adrenocortical crisis or insufficiency, while the other type demonstrates subclinical adrenocortical insufficiency which can later develop into acute adrenal crisis with infection, surgery, trauma and other stress. The present case was diagnosed to have Addison’s disease which was considered to have been caused by adrenal tuberculosis complicated with miliary tuberculosis based on her clinical symptoms, whole body pigmentation, adrenal function data, hyponatremia, hyperkalemia and images of a swollen adrenal gland with calcification. In this case, the serum cortisol level responded to the rapid ACTH challenge test, but it was not a strong response.

Figure 2. Abdominal computed tomography (A-upper; plain, A-lower; enhanced) showing swelling of the right adrenal gland (arrowhead) (March), a slight decrease in size later (B-upper; plain, B-lower; enhanced) (June), and also calcification (C-upper; plain, C-lower; enhanced) (B; June, C; October.).

Generally, in normal subjects, the serum concentration of cortisol shows a level of over 18-20 μg/dL at 30-60 minute after performing the rapid ACTH test. In this case, the serum concentration of cortisol showed a response to the test, but it was a weak response (below of 18-20 μg/dL). In this case, only the right adrenal gland had tuberculosis while the left adrenal gland was unaffected. As a result, adrenal insufficiency occurred. There is a study describing a patient in which the adrenal function remained normal after only the unilateral adrenal gland was newly infected with tuberculosis (2). The serum cortisol concentration in this case was in the normal range, but it was relatively low. In addition, even at serum cortisol levels of less than 10 μg/dL, adrenal insufficiency can still sometimes occur. An adrenal crisis can be induced by the administration of RFP (3-6). The mechanism of induction of adrenal crisis caused by administration of RFP is due to the fact that RFP induces 6β-hydroxylase. Thereafter, the hepatic enzymes play a role in increasing the metabolism of corticosteroid. Liver biopsy studies have demonstrated that patients receiving RFP have an increased cytochrome P450 activity and an intense proliferation of the smooth endoplasmic reticulum (7, 8). The pharmacological half-life of cortisol decreased when RFP was administered, but it returned to normal when RFP was stopped (3). This situation resulted in the occurrence of corticosteroid deficiency. Some cases with tubercular Addison’s disease demonstrated adrenal crisis induced by the administration of RFP or similar cases have been reported (9, 10). This case should be distinguished from drug allergy of RFP or initial aggravation induced by the administration of RFP. A drug allergy to RFP is distinguishable from Addison’s disease based on the lack of drug eruptions, no eosinophilia and a decrease in the patient’s temperature when continuing to administer RFP. The initial aggravation induced by the administration of RFP is also debatable because no such aggravation was observed in the chest X-ray findings and no adrenal function disorder was seen. In the diagnosis of Addison’s disease, CT is able to accurately identify adrenal gland enlargement (11). In particular, in cases with tubercular Addison’s disease, CT clearly depicts both adrenal enlargement and calcification. Nomura et al described that in patients with tuberculous Addison’s disease, the period from the preceding nonadrenal tuberculosis to the onset of Addison’s ranged from 0 to 50 years, with a mean of 31.9±14.9 (SE) years, therefore, tubercular Addison’s disease is considered to have a relatively late onset (1). However, Sanford and Favour reported that many patients may have active tuberculosis in the presence of an established and diagnosed adrenal insufficiency (active tuberculosis plus Addison’s) or post-Addison’s disease (12). The present case was suggested to have latent tuberculosis which later progressed to miliary tuberculosis due to either the aging process or for some other unidentified reason. Even though this case was a rare case, it was nevertheless an intriguing case because Addison’s disease occurred as a complication of active extra-adrenal gland tuberculosis simultaneously, and furthermore the administration of RFP induced adrenal crisis in the clinical course. When rifampicin was re-administrated, no symptoms of adrenal crisis were thereafter again observed. The reason why no recurrence of adrenal crisis occurred when she was
re-administered RFP is speculated to be due to the fact that there was no stress of high-fever caused by miliary tuberculosis, and therefore the administration of RFP alone as a trigger was not sufficient to induce adrenal crisis. Whole body pigmentation in this case means that the serum ACTH level of the patient had been chronically elevated. Another possibility is that the patient may have had a latent impairment of the adrenal gland before the present episode, which was not related to miliary tuberculosis. Not only the stress of the onset of miliary tuberculosis, but also the administration of RFP may therefore sometimes trigger adrenal insufficiency. Generally, the replacement therapy with corticosteroids for the adrenal insufficiency observed in Addison’s disease is essential. We therefore should have administered corticosteroids as a replacement therapy, however, we did not do so. Some cases with tuberculosis have been known to show a worsening of their disease symptoms after the administration of glucocorticoids. The present patient demonstrated miliary tuberculosis which is considered to be the most severe state of tuberculosis. Furthermore, no repeated adrenal crisis was observed after the careful re-administration of RFP. The clinical course of the patient was good. At present, she has no fever, and her general fatigue has also improved dramatically. The plasma ACTH level still remains elevated, and this suggests that some latent adrenal insufficiency may thus still exist. The reason why no adrenal crisis was further induced by the administration of RFP without glucocorticoid replacement is unclear. The present case provides important information regarding the necessity to re-administer RFP or replacement therapy with glucocorticoids in patients with tubercular Addison’s disease. This case may therefore be instructive regarding both the use of replacement therapy with corticosteroids and the re-administration of RFP.

References