Normalization of Bilateral Adrenal Gland Enlargement after Treatment for Cryptococcosis

Yuka Muraoka,1 Shintaro Iwama,1,2 and Hiroshi Arima1

1Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
2Research Center of Health, Physical Fitness and Sports, Nagoya University, Nagoya 464-8601, Japan

Correspondence should be addressed to Shintaro Iwama; siwama@med.nagoya-u.ac.jp

Received 15 January 2017; Revised 10 March 2017; Accepted 14 March 2017; Published 26 March 2017

Case Report

1. Introduction

Cryptococcosis is a fatal fungal disease caused by infections with Cryptococcus species. Immunocompromised patients, such as those treated with immunosuppressants (including glucocorticoids), often develop cryptococcosis [1]. Although the lungs are commonly involved in cryptococcal infections, disseminated cryptococcosis can also affect the adrenal glands. Adrenal infections with Cryptococcus can cause bilateral enlargement of the glands [2] but the morphologic changes after treatment have not been described in detail. Herein we report a case involving an immunocompromised patient with cryptococcal meningitis, including the morphologic findings of the adrenal glands before and after antifungal treatment.

2. Case Presentation

A 24-year-old man with a protein-losing gastroenteropathy due to an intestinal lymphangiectasia was treated with glucocorticoids (prednisolone, 7.5 mg/day) and developed low-grade fevers 7 months before admission. He did not have any remarkable life histories. Five months before admission, the man complained of headaches, fatigue, and a hearing abnormality. Then, he experienced nausea, diarrhea, and drowsiness for 6 days and subsequently sought evaluation at our hospital. The physical examination at the time of admission revealed that he was slow to respond (Japan Coma Scale 1-1). The following measurements were obtained: height, 161.2 cm; weight, 51.0 kg; BMI, 19.6 kg/m²; blood pressure, 119/78 mmHg; heart rate, 62 bpm; and body temperature, 37.4°C. The remainder of the examination findings were normal, without any signs of meningitis.

The initial laboratory data showed a white blood cell count of 11700/μL, with 87.0% neutrophils (86% segmented and 1% band neutrophils), 2.0% lymphocytes, 10% monocytes, 0% eosinophils, 1% metamyelocytes, hemoglobin = 15.7 g/dL, and a platelet count of 157,000/μL. The serum C-reactive protein level was slightly elevated (0.80 mg/dL). Although the serum sodium level was slightly decreased (130 mEq/L), the potassium (4.6 mEq/L), chloride (97 mEq/L), creatinine (0.59 mg/dL), fasting glucose (85 mEq/L), and HbA1c (5.1%) concentrations were normal.

An abdominal computed tomography (CT) showed bilateral adrenal enlargement (right, 10.0 × 20.0 mm; left, 29.0 × 29.0 mm). A retrospective analysis of the CT images revealed...
that the enlargement in the left adrenal gland developed 5 months before admission (Figure 1(A)), which coincided with the onset of fevers and headaches. Subsequently, the bilateral adrenal enlargement progressed (Figure 1(B)). The differential diagnosis of adrenal enlargement includes metastatic carcinoma, bilateral adrenal hyperplasia, tuberculosis, and fungal infections. A whole-body examination failed to find a primary malignant lesion. The QuantiFERON-TB test and HIV antibody titer were negative. Although there were no signs of meningeal irritation, a diagnostic lumbar puncture was performed. The cerebrospinal fluid revealed an increased white blood cell count (240/μL), a normal protein level, a decreased glucose level (0.10 g/l), and a positive cryptococcal antigen titer. The pathologic specimen showed the presence of yeast-like organisms, such as Cryptococcus spp. on Alcian blue staining, which was subsequently determined to be Cryptococcus neoformans.

Although the level of serum adrenocorticotropic hormone (ACTH) was elevated (131.3 pg/mL; normal range, 7.2–63.3 pg/mL) at the time of the diagnosis of cryptococcosis (Table 1), cortisol release in response to ACTH (Cortrosyn), which was evaluated 1 day after prednisolone cessation, was increased (Table 2). Oral prednisolone (7.5 mg/day) was then resumed as treatment for the protein-losing gastroenteropathy. The other endocrinological data of adrenal gland ruled out the possibility of pheochromocytoma and aldosterone-secreting tumors in this patient (Table 2).

Amphotericin B (250 mg/day) was initiated, followed by the addition of fluconazole (400 mg/day). The symptoms improved gradually after beginning antifungal treatment. Fluconazole alone was continued after discharge. After the initiation of antifungal treatment, the elevated ACTH levels were decreased and varied during the treatment (Table 1), suggesting a stressed condition with infection at the diagnosis and unstable absorption of prednisolone due to the protein-losing gastroenteropathy. Mild hyponatremia probably due to relative adrenal insufficiency was improved to the normal range (138 mEq/L) one month after the initiation of the antifungal treatment.

An abdominal CT, which was routinely obtained during follow-up, showed that the size of the adrenal glands decreased following antifungal therapy and became normal without any abnormal findings, including calcifications, 6 months after starting treatment (Figure 1(C)).
Glands were infected with antifungal therapy. The data herein suggest that the adrenal gradually increased before treatment but decreased after treatment with amphotericin B; however, the report which shows a decrease in adrenal gland enlargement after antifungal treatment has not been precisely described. There is only one report which shows a decrease in adrenal gland enlargement after treatment with amphotericin B; however, the images obtained after treatment clearly showed adrenal gland enlargement. This is the first report of a dynamic change in the size of adrenal glands infected with Cryptococcus from the exacerbation to recovery phase. Although it is well known that adrenal tuberculosis often causes calcifications of the adrenal glands [2], the morphology of the adrenal glands in patients with tuberculosis [17, 18] or overproduction of vitamin D from inflammatory cells [19, 20]. Given the normal serum calcium levels (4.6 mEq/L) and the improvement of the enlarged adrenal glands without calcification, it is possible that there is a different process between tuberculosis and cryptococcosis in calcification.

Despite the long-term use of prednisolone (7.5 mg/day), the basal ACTH level was elevated and cortisol release was increased in response to ACTH injection in our patient. These data suggest that (1) prednisolone administered orally was not absorbed enough to suppress the ACTH release due to the protein-losing gastroenteropathy, (2) the patient was in a stressed condition with the disease, and/or (3) he had partial adrenal insufficiency. There are several case reports which have shown the development of adrenal insufficiency in patients with adrenal cryptococcosis, especially when accompanied by meningoencephalitis [5, 6, 11, 13, 21]. It is thus important to follow adrenal function serially in our patient, although he must continue prednisolone therapy for the underlying disease. The finding that the morphology of the adrenal glands infected with Cryptococcus improved completely after treatment in our patient, together with the possibility that cryptococcosis can cause adrenal insufficiency, suggests that we should consider previous adrenal cryptococcosis as a possible cause of adrenal insufficiency, even if the adrenal glands are morphologically normal. In addition, since the enlargement showed slow progression, adrenal cryptococcosis may be considered as a differential diagnosis when the bilateral enlargement is present especially in immunocompromised patients. In conclusion, adrenal enlargement by Cryptococcus is completely reversible without any abnormality after antifungal treatment, which may be a unique characteristic from other diseases, including tuberculosis.

| Time after initiation of antifungal treatments | Time of the diagnosis | 2 months | 4 months | 6 months |
|-----------------------------------------------|-----------------------|----------|----------|----------|
| ACTH (pg/mL)                                  | 131.3                 | 4.6      | 28.1     | 1.9      |
| Cortisol (µg/dl)                              | 38.4                  | 16.9     | 14.1     | 6.7      |
| Dehydroepiandrosterone-sulfate (DHEA-s) (µg/dL) | 482                   |          |          |          |
| Epinephrine (ng/ml)                           | 0.332                 | 0.015    |          |          |
| Norepinephrine (ng/ml)                        | 0.487                 | 0.089    |          |          |
| Dopamine (ng/ml)                              | 0.027                 | 0.012    |          |          |
| Urine metanephrine (ng/mg Cr)                 | 328                   | 119      |          |          |
| Urine normetanephrine (ng/mg Cr)              | 63                    | 176      |          |          |
| Plasma renin activity (ng/mL/hr)              | 3.2                   |          |          |          |
| Aldosterone (pg/mL)                           | 202.0                 |          |          |          |

Table 2: Rapid ACTH test.

| Time   | 0 min | 30 min | 60 min |
|--------|-------|--------|--------|
| Cortisol (µg/dl) | 23.5  | 32.0   | 36.6   |
Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
All authors were concerned with the treatment, drafted the manuscript, and read and approved the final manuscript.

References
[1] M. Chayakulkeeree and J. R. Perfect, “Cryptococcosis,” Infectious Disease Clinics of North America, vol. 20, no. 3, pp. 507–544, 2006.
[2] W. F. Paolo Jr. and J. D. Nosanchuk, “Adrenal infections,” International Journal of Infectious Diseases, vol. 10, no. 5, pp. 343–353, 2006.
[3] H. E. Bowman and J. O. Ritchey, “Cryptococcosis (torulosis) involving the brain, adrenal and prostate,” The Journal of Urology, vol. 71, no. 3, pp. 373–378, 1954.
[4] A. J. Rawson, L. H. Collins Jr., and J. L. Grant, “Histoplasmosis and torulosis as causes of adrenal insufficiency,” The American Journal of the Medical Sciences, vol. 215, no. 4, pp. 363–371, 1948.
[5] B. F. Walker, C. J. Gunthel, J. A. Bryan, N. B. Watts, and R. V. Clark, “Disseminated cryptococcosis in an apparently normal host presenting as primary adrenal insufficiency: diagnosis by fine needle aspiration,” The American Journal of Medicine, vol. 86, pp. 715–717, 1989.
[6] B. Shah, H. C. Taylor, I. Pillay, M. Chung-Park, and R. Dobrinich, “Adrenal insufficiency due to cryptococcosis,” The Journal of the American Medical Association, vol. 256, no. 23, pp. 3247–3249, 1986.
[7] Y.-C. Liu, D.-L. Cheng, C.-Y. Liu, M.-Y. Yen, and R.-S. Wang, “Isolated cryptococcosis of the adrenal gland,” Journal of Internal Medicine, vol. 230, no. 3, pp. 285–287, 1991.
[8] C. N. Powers, G. M. Rupp, S. J. Maygarden, and W. J. Frable, “Fine-needle aspiration cytology of adrenal cryptococcosis: a case report,” Diagnostic Cytopathology, vol. 7, no. 1, pp. 88–91, 1991.
[9] R. Cocker, S. A. McNair, L. Kahn et al., “Isolated adrenal cryptococcosis, diagnosed by fine-needle aspiration biopsy: a case report,” Diagnostic Cytopathology, vol. 42, no. 10, pp. 899–901, 2014.
[10] Z.-S. Hung, Y.-H. Lai, Y.-H. Hsu, C.-H. Wang, T.-C. Fang, and B.-G. Hsu, “Disseminated cryptococcosis causes adrenal insufficiency in an immunocompetent individual,” Internal Medicine, vol. 49, no. 11, pp. 1023–1026, 2010.
[11] A. Takeshita, H. Nakazawa, H. Akiyama et al., “Disseminated cryptococcosis presenting with adrenal insufficiency and meningitis: resistant to prolonged antifungal therapy but responding to bilateral adrenalectomy,” Internal Medicine, vol. 31, no. 12, pp. 1401–1405, 1992.
[12] H.-M. Cheng, A. S.-B. Chou, K.-H. Chiang, H.-W. Huang, P.-Y. Chang, and P.-S. Yen, “Primary adrenal insufficiency in isolated cryptococcosis of the adrenal gland: CT and MR imaging appearances,” European Journal of Radiology Extra, vol. 75, no. 3, pp. e111–e113, 2010.
[13] M. Kawamura, S. Miyazaki, S. Mashiko et al., “Disseminated cryptococcosis associated with adrenal masses and insufficiency,” American Journal of the Medical Sciences, vol. 316, no. 1, pp. 60–64, 1998.
[14] Y. Matsuda, H. Kawate, Y. Okishige et al., “Successful management of cryptococcosis of the bilateral adrenal glands and liver by unilateral adrenalectomy with antifungal agents: a case report,” BMC Infectious Diseases, vol. 11, article 340, 2011.
[15] P. Ranjan, M. Jana, S. Krishnan, D. Nath, and R. Sood, “Disseminated cryptococcosis with adrenal and lung involvement in an immunocompetent patient,” Journal of Clinical and Diagnostic Research, vol. 9, no. 4, pp. OD04–OD05, 2015.
[16] P. Benešová, V. Buchta, J. Cerman, and P. Žá, “Cryptococcosis—a review of 13 autopsy cases from a 54-year period in a large hospital,” APMIS, vol. 115, no. 3, pp. 177–183, 2007.
[17] A. Roussos, I. Lagogianni, A. Gonis et al., “Hypercalcemia in Greek patients with tuberculosis before the initiation of anti-tuberculosis treatment,” Respiratory Medicine, vol. 95, no. 3, pp. 187–190, 2001.
[18] F. Shai, R. K. Baker, J. R. Addrizzo, and S. Wallach, “Hypercalcemia in mycobacterial infection,” Journal of Clinical Endocrinology and Metabolism, vol. 34, no. 2, pp. 251–256, 1972.
[19] J. Cadranel, A. J. Hance, B. Milleron, F. Paillard, G. M. Akoun, and M. Garabedian, “Vitamin D metabolism in tuberculosis. Production of 1,25(OH)2D3 by cells recovered by bronchoalveolar lavage and the role of this metabolite in calcium homeostasis,” American Review of Respiratory Disease, vol. 138, no. 4, pp. 984–989, 1988.
[20] J. Cadranel, M. Garabedian, B. Milleron, H. Guillolo, G. Akoun, and A. J. Hance, “1,25(OH)2D3 production by T lymphocytes and alveolar macrophages recovered by lavage from normocalcemic patients with tuberculosis,” Journal of Clinical Investigation, vol. 85, no. 5, pp. 1588–1593, 1990.
[21] W. R. Salyer, C. L. Moravec, D. C. Salyer, and P. F. Guerin, “Adrenal involvement in cryptococcosis,” American Journal of Clinical Pathology, vol. 60, no. 4, pp. 559–561, 1973.