Sarcoidosis Presenting Addison’s Disease

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Abstract

We herein describe a second Japanese case of sarcoidosis presenting Addison’s disease. A 52-year-old man was diagnosed with sarcoidosis based on clinical and laboratory findings, including bilateral hilar lymphadenopathy and elevated levels of serum angiotensin-converting enzyme and lysozyme, as well as the presence of noncaseating epithelioid granulomas. The patient also exhibited general fatigue, pigmentation, weight loss, hypotension and hyponatremia, suggestive of chronic adrenocortical insufficiency. An endocrine examination confirmed primary adrenocortical insufficiency. This case suggests the direct involvement of sarcoid granuloma in the adrenal glands.

Key words: sarcoidosis, Addison’s disease, adrenal insufficiency, steroid psychosis, positron emission tomography

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Introduction

Sarcoidosis is a systemic disease characterized by the presence of epithelioid granulomas without caseation necrosis in affected organs (1). There are accumulated data suggesting that the immune response to Propionibacteria acnes or Mycobacterium tuberculosis may contribute to the onset of the disease (2, 3) and that an enhanced Th1/Th17 immune response is involved in the pathogenesis of sarcoidosis (4, 5). Sarcoidosis involves multi-organ systems, mainly the lungs and lymph nodes, in addition to affecting the eyes, skin and heart. Sarcoidosis less frequently involves the kidney, liver, nerves, salivary glands, joints and muscles and uncommonly involves endocrine organs, including the thyroid gland, hypothalamus and pituitary gland (6-8). However, there have been only a few case reports of adrenocortical insufficiency associated with sarcoidosis involving the adrenal glands (6, 9).

Addison’s disease is defined as primary adrenocortical insufficiency resulting from the destruction of over 90% of the bilateral adrenal glands according to a variety of etiologies (10). Seventy percent of cases of Addison’s disease are caused by autoimmune adrenalitis induced by anti-adrenocortical antibodies (11, 12). Other causes include infectious diseases, such as tuberculosis, adrenal tumors and others (12). In contrast, sarcoidosis has rarely been reported as a cause of Addison’s disease (6, 9).

We herein describe a second Japanese case of sarcoidosis presenting Addison’s disease.

Case Report

A 52-year-old man visited our hospital because of a four-month history of muscle pain of the limbs, coughing, general fatigue and loss of appetite that had developed gradually during this period. He also noticed a brown-colored change in the skin lasting for two to three months. On a physical examination, he was found to be sick and hardly able to walk. His vital signs were as follows: height 161 cm, weight 51 kg (eight-kilogram weight loss over this period), body temperature 37.2°C, blood pressure 84/50 mmHg and pulse rate 72 bpm. The neck, chest, abdomen and extremities were normal, except for findings showing that the skin was brown-colored with pigmentation. Neurological and musculoskeletal examinations were also normal. Laboratory data showed an elevated white blood cell count (11,400/µL with 5.6% eosinophils), slightly high level of C-
reactive protein (0.28 mg/dL), renal impairment (urea nitrogen 31 mg/dL, creatinine 1.37 mg/dL), hyponatremia (126 mEq/L) and hypercalcemia (10.2 mg/dL, corrected value: 10.7 mg/dL). The creatine kinase level was normal (50 U/L), whereas the serum angiotensin-converting enzyme (ACE) and lysozyme levels were increased at 33.5 U/L and 33.3 μg/mL (normal range: 8.3-21.4 and 5-10.2), respectively. Moreover, the soluble IL-2 receptor level was slightly elevated (1,120 U/mL), although a urine analysis and immunological data were normal. Chest X-ray showed left hilar lymph node enlargement with reticulolinear shadows in the lung fields, while focal ground-grass opacity was visible with peribronchovascular thickening on high-resolution computed tomography (CT) of the lungs (Fig. 1a). Although the findings of an electrocardiography (ECG) and ultrasonic cardiogram were normal, contrast-enhanced CT showed systemic lymphadenopathy of the bilateral hilar, mediastinal, portal and para-aortic lymph nodes. A tuberculin test and as-
say for interferon γ production to Mycobacterium tuberculosis (T-SPOT®.TB) were negative, as was an HIV test, and the βD-glucan level was normal. Therefore, he was admitted to our hospital under suspicion of sarcoidosis for a further evaluation of the abnormal findings.

Upper endoscopy and colonoscopy were performed to exclude malignancy and demonstrated normal findings. Positron emission tomography (PET) with 18fluorodeoxyglucose (18FDG)/CT was also performed, showing accumulation in the right lung, with systemic lymphadenopathy of the bilateral hilar, mediastinal, portal, mesenteric and para-aortic lymph nodes, pancreas, shoulder and knee joints as well as subcutaneous and muscular tissues of the extremities (Fig. 1b, c). A biopsy of the left gastrocnemius muscle showing the accumulation of 18FDG revealed an epithelioid granuloma without caseation necrosis (Fig. 2a, b). Similarly, a lip biopsy showed noncaseating granulomatous sialadenitis (Fig. 2c, d). Therefore, the patient met the criteria for a diagnosis of sarcoidosis: a clinical and radiological presentation with evidence of noncaseating granulomas and no evidence of alternative diseases (13).

Because chronic adrenocortical insufficiency was suspected based on the presence of general fatigue, pigmentation, weight loss, hypotension and hyponatremia, we performed endocrinological examinations to measure the serum or plasma hormone values. The adrenocorticotropic hormone (ACTH) level was elevated, whereas the cortisol level was undetectable in both the serum and urine throughout the day, even under stimulation with Cortrosyn® (Table 1, 2), and the serum aldosterone level was also very low (Table 1). Meanwhile, the secretion of pituitary hormones was sustained on a pituitary hormone-releasing hormone challenge test (Table 3), and anti-adrenocortical antibodies against the steroidogenic enzyme, 21-hydroxylase (14) were not detected. These findings established a definitive diagnosis of primary adrenocortical insufficiency, Addison’s disease. Hence, the patient was diagnosed with Addison’s disease associated with sarcoidosis, although an adrenal biopsy was not performed due to invasiveness.

Oral prednisolone (PSL) at 40 mg/day was started for the treatment of sarcoidosis, and the patient’s symptoms, including general fatigue and loss of appetite, improved signifi-
Sarcoidosis is a systemic noncaseating granulomatous disease of unknown etiology (1). Sarcoidosis involves the lungs, lymph nodes, eyes, skin and heart. Sarcoidosis uncommonly involves endocrine organs, including the thyroid gland, hypothalamus and pituitary gland, but rarely the adrenal glands. We then initiated glucocorticoid and mineralocorticoid replacement therapy.

**Discussion**

Sarcoidosis is a systemic noncaseating granulomatous disease of unknown etiology (1). Sarcoidosis involves the lungs, lymph nodes, eyes, skin and heart. Sarcoidosis commonly involves endocrine organs, including the thyroid gland, hypothalamus and pituitary gland, but rarely the adrenal glands (6-9). In this case report, we showed that adrenocortical insufficiency was caused by sarcoidosis involving the adrenal glands, as possible causes of Addison’s disease other than sarcoidosis (11, 12, 14-16) were excluded; that is, autoimmune adrenalitis, infections with tuberculosis, fungi or HIV and metastasis of carcinoma were ruled out based on the clinical findings and laboratory data. It has been shown that the onset of adrenocortical insufficiency in patients with sarcoidosis is most likely due to an autoimmune

| Hormone         | Measurement | Normal value | Unit   |
|-----------------|-------------|--------------|--------|
| ACTH            | 1,240       | 7.2-63.3     | (pg/mL) |
| Cortisol        | <1.0        | 4.0-18.3     | (µg/dL) |
| DHEA-S          | 35          | 38-313       | (µg/dL) |
| PRA             | 11          | 0.3-2.9      | (ng/mL/h) |
| Aldosterone     | <10.0       | 29.9-159     | (µg/mL) |
| Androstenedione | 0.9         | 1.0-2.5      | (µg/mL) |
| GH              | 8.85        | ≤2.47        | (ng/mL) |
| LH              | 2.33        | 1.14-8.75    | (mIU/mL) |
| FSH             | 3.53        | 0.95-11.95   | (mIU/mL) |
| Prolactin       | 34.73       | 2.58-18.12   | (ng/mL) |
| TSH             | 1.58        | 0.35-4.94    | (mIU/L) |
| HVA             | 13.1        | 4.4-15.1     | (ng/mL) |
| VMA             | 17.3        | 3.3-8.6      | (ng/mL) |
| Adrenalin       | <5          | ≤100         | (µg/mL) |
| Noradrenalin    | 374         | 100-450      | (µg/mL) |
| Dopamine        | 20          | ≤20          | (µg/mL) |

| Hormone | Measurement | Normal value | Unit |
|---------|-------------|--------------|------|
| ACTH    | 1,020       | 1,130        | 1,000| 1,230| 1,120 (pg/mL) |
| Cortisol| <1.0        | <1.0         | <1.0 | <1.0 | <1.0 (µg/dL) |
| GH      | 2.25        | 25.5         | 44.4 | 34.4 | 22.9 | 13.8 (ng/mL) |
| LH      | 1.92        | 9.75         | 17.04| 17.70| 17.79| 15.84 (mIU/mL) |
| FSH     | 3.14        | 4.36         | 5.94 | 6.31 | 6.79 | 6.76 (mIU/mL) |
| Prolactin| 35.03       | 70.92        | 73.07| 65.21| 59.91| 54.12 (ng/mL) |
| TSH     | 2.06        | 12.47        | 19.02| 17.21| 16.25| 14.12 (mIU/L) |

Corticotropin-releasing hormone (CRH) 100 µg, growth hormone-releasing hormone (GH-RH) 100 µg, gonadotropin-releasing hormone (GnRH) 100 µg, and thyrotropin-releasing hormone (TRH) 500 µg were administered intravenously and the levels of pituitary hormones and cortisol were evaluated at 15 to 120 min.

**Table 3. Pituitary Hormone-Releasing Hormone Stimulation Test.**

| Hormone                        | Measurement | Normal value | Unit |
|--------------------------------|-------------|--------------|------|
| ACTH                           | 1,020       | 1,130        | 1,000| 1,230| 1,120 (pg/mL) |
| Cortisol                       | <1.0        | <1.0         | <1.0 | <1.0 | <1.0 (µg/dL) |
| GH                             | 2.25        | 25.5         | 44.4 | 34.4 | 22.9 | 13.8 (ng/mL) |
| LH                             | 1.92        | 9.75         | 17.04| 17.70| 17.79| 15.84 (mIU/mL) |
| FSH                            | 3.14        | 4.36         | 5.94 | 6.31 | 6.79 | 6.76 (mIU/mL) |
| Prolactin                      | 35.03       | 70.92        | 73.07| 65.21| 59.91| 54.12 (ng/mL) |
| TSH                            | 2.06        | 12.47        | 19.02| 17.21| 16.25| 14.12 (mIU/L) |

Synthetic adrenocorticotropic hormone (ACTH) (Cortrosyn<sup>®</sup>) 250 µg was administered intravenously and the levels of cortisol, renin and aldosterone were evaluated at 30 min and 60 min.

**Table 2. Rapid ACTH Stimulation Test.**

| Hormone | Measurement | Normal value | Unit |
|---------|-------------|--------------|------|
| Cortisol| <1.0        | <1.0         | <1.0 (µg/dL) |
| PRA     | 8.3         | 8.9          | 10 (ng/mL/h) |
| Aldosterone | 14.0 17.5 | (pg/mL) |
| DHEA-S  | 28          | 29           | 26 (µg/dL) |

PSL: plasma renin activity, DHEA-S: dehydroepiandrosterone sulfate

**Figure 3. Treatment and clinical course of our patient with sarcoidosis presenting with Addison’s disease.** The prednisolone (PSL) dose, symptoms and serum sodium, ACE and lysozyme levels are shown. PSL at 40 mg/day was initiated for the treatment of sarcoidosis; however, steroid psychosis developed on the fourth day of treatment. The dose of PSL was then decreased to 10 mg/day, and the steroid psychosis subsided within a week. PSL at 10 mg/day improved the patient’s general fatigue, loss of appetite and hyponatremia and decreased the ACE level to the normal range.

| Hormone | Measurement | Normal value | Unit |
|---------|-------------|--------------|------|
| ACTH    | 1,020       | 1,130        | 1,000| 1,230| 1,120 (pg/mL) |
| Cortisol| <1.0        | <1.0         | <1.0 | <1.0 | <1.0 (µg/dL) |
| GH      | 2.25        | 25.5         | 44.4 | 34.4 | 22.9 | 13.8 (ng/mL) |
| LH      | 1.92        | 9.75         | 17.04| 17.70| 17.79| 15.84 (mIU/mL) |
| FSH     | 3.14        | 4.36         | 5.94 | 6.31 | 6.79 | 6.76 (mIU/mL) |
| Prolactin| 35.03       | 70.92        | 73.07| 65.21| 59.91| 54.12 (ng/mL) |
| TSH     | 2.06        | 12.47        | 19.02| 17.21| 16.25| 14.12 (mIU/L) |

Corticotropin-releasing hormone (CRH) 100 µg, growth hormone-releasing hormone (GH-RH) 100 µg, gonadotropin-releasing hormone (GnRH) 100 µg, and thyrotropin-releasing hormone (TRH) 500 µg were administered intravenously and the levels of pituitary hormones and cortisol were evaluated at 15 to 120 min.

**ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, PRA: plasma renin activity, GH: growth hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, TSH: thyroid stimulating hormone, HVA: homovanillic acid, VMA: vanillylmandelic acid**
endocrine disease, autoimmune polyglandular syndrome type II (Schmidt syndrome) (17, 18). However, autoimmune polyglandular syndrome type II was ruled out in this case according to the absence of anti-adrenocortical antibodies and the normal thyroid function. In addition, the normal pituitary function excluded the possibility of secondary adrenocortical insufficiency caused by hypopituitarism due to sarcoidosis. Therefore, we suggest that the adrenocortical insufficiency in this case resulted from the direct involvement of sarcoid granuloma in the adrenal glands.

This case is the second case of diagnosed sarcoidosis presenting with Addison’s disease in Japan, as far as we were able to determine. Compared with the first reported case (9), both patients had bilateral hilar lymphadenopathy and lung parenchymal abnormalities without abnormalities of the eyes, skin, heart or pituitary gland. In addition, our case exhibited the involvement of skeletal muscles and salivary glands, whereas the first case did not. This difference in organ involvement is crucial because sarcoid myositis generally must be treated with high-dose corticosteroids. Furthermore, in the first case, a tuberculin test was positive and data for anti-adrenocortical antibodies were not available; therefore, it is difficult to establish the etiology of primary adrenocortical insufficiency (9).

A histological analysis is required to ensure the diagnosis of sarcoidosis. 18F-FDG-PET/CT has recently been recognized to be a useful tool for identifying extrathoracic lesions for the purpose of a diagnostic biopsy in cases of sarcoidosis (19). In the current case, 18F-FDG-PET/CT showed an unexpected and isolated patchy 18F-FDG uptake in the left lower leg without any symptoms. We safely performed a biopsy of the left gastrocnemius muscle and consequently obtained a leg without any symptoms. We safely performed a biopsy of the leg without any symptoms.

In conclusion, we herein described the second Japanese case of sarcoidosis presenting Addison’s disease. Furthermore, 18F-FDG-PET/CT is a useful tool for determining the safe and right biopsy site for obtaining a diagnosis of sarcoidosis.

The authors state that they have no Conflict of Interest (COI).

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