Primary Bilateral Adrenal Intravascular Large B-cell Lymphoma Associated with Adrenal Failure

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Abstract

We report a rare case of bilateral primary adrenal non-Hodgkin’s lymphoma with adrenal failure. A 66-year-old woman developed symptoms of adrenal failure. The cause of adrenal failure was suspected to be malignant lymphoma based on the high levels of serum soluble interleukin-2 receptor and LDH. Bilateral adrenalectomy was performed and pathological examination showed intravascular large B-cell lymphoma (IVL). Although complete remission was achieved, recurrence occurred three months later with brain metastases. IVL should be suspected in patients with bilateral adrenal tumors who present with rapidly progressive adrenal failure. (Internal Medicine 42: 609-614, 2003)

Key words: soluble IL-2 receptor, rapid progressive type, bilateral adrenal tumors, intravascular lymphoma, adrenal failure

Introduction

Malignant lymphoma could occur in any body organ. However, non-Hodgkin lymphoma (NHL) arising in the endocrine system represents only 3% of extranodal malignant lymphomas, and is usually confined to the thyroid gland (1). Moreover primary adrenal lymphoma is extremely rare. Since the adrenal gland has a sufficient reserve, development of adrenal insufficiency requires destruction of more than 90% of the adrenal gland tissue (2).

We report a female patient who was diagnosed as adrenal failure caused by primary bilateral adrenal lymphoma. Primary lymphoma in both adrenal glands is typically considered to be of the diffuse large B cell NHL type. The final diagnosis was intravascular large B-cell lymphoma (IVL) based on histopathological examination.

Case Report

A 66-year-old woman was diagnosed previously with diabetes mellitus and subsequently treated with voglibose (0.9 mg) and glimepiride (6 mg) by her general practitioner. She complained of general fatigue, nausea, vomiting, diarrhea, weight loss of 15 kg in early April 2001, and then developed progressive generalized pigmentation in early June of the same year. The clinic endocrinological findings showed plasma ACTH 620 pg/ml, plasma cortisol 8.9 µg/dl, and abdominal computed tomography (CT) revealed bilateral adrenal tumors in July. In August 2001, she was admitted to our hospital to determine the relationship between adrenal failure and bilateral adrenal tumors.

Physical examination on admission showed body height of 138.6 cm and weight 46.4 kg, blood pressure 120/68 mmHg, pulse rate of 84 beats/minute and body temperature of 36.6°C. There was no anemia, icterus, or palpable superficial lymph node. Systemic pigmentation was evident on the trunk, limbs, and lips, together with defluxion of hircus and pubes. Physical examination of the abdomen and extremities was unremarkable and neurological examination was negative.

Laboratory tests (Table 1) showed normal complete blood count and no abnormal findings on urinalysis. Biochemical analysis revealed a high LDH level (397 IU/l). Serum electrolyte examination showed no hyponatremia but elevated levels of serum potassium, leading to suspicion of adrenal failure. Elevated levels of serum CRP (1.6 mg/dl), ESR (49 mm/h) and soluble interleukin-2 (IL-2) receptor (1,830.4 U/ml) were also noted.

Table 2 lists the basal hormonal levels. Plasma ACTH level was markedly elevated and plasma cortisol level was low. Furthermore, urinary 17-KS, urinary 17-OHCS, urinary cortisol, serum DHEA-S, serum estradiol, and plasma
The results of rapid and continuous ACTH tests are shown in Table 3. Plasma cortisol levels remained low and showed no response in both of the rapid and continuous ACTH tests, revealing primary adrenal failure.

Abdominal enhanced CT detected two masses measuring 5.0 cm and 3.0 cm in the right and left adrenal gland, respectively, with comparable and homogeneous density (Fig. 1A). No celiac lymph node enlargement was detected on abdominal CT. Magnetic resonance images (MRI) of the left adrenal tumor revealed comparatively normal form on T2-weighted, but the right adrenal tumor was slightly heterogeneous with irregular surface on T2-weighted MRI (Fig. 1B). Therefore, we suspected metastatic adrenal tumors and examined the entire body for the primary lesion. However, we could not detect any primary carcinoma. 67Ga scintigram did not reveal abnormal uptake in the adrenal glands and other organs.

Repeated serum electrolyte examinations revealed no exacerbation after admission. Since hypoglycemia was frequently detected while the patient was still on voglibose (0.9 mg/day) and glimepiride (6 mg/day), both medications were withheld. Replacement therapy for primary adrenal failure commenced on August 30, 2001 with 30 mg/day hydrocortisone, which resulted in immediate improvement of nausea, vomiting, and general fatigue, and disappearance of hypoglycemia. However, blood sugar levels gradually increased, ne-
Adrenal Intravascular Lymphoma

Figure 1. (A) Abdominal enhanced computed tomography showed bilateral tumors arrows in adrenal glands. (B) T2-weighted abdominal magnetic resonance images showed slightly heterogeneous tumors arrows in both adrenal glands.

Figure 2. Histopathological examination of the adrenal glands. (A, B) HE stain, (C) CD20 stain, magnification; (A) x10, (B) x20, (C) x10; Note the presence of large pleomorphic lymphoid cells with heteromorphic nuclei. These cells show extensive infiltration mainly into the sinusoids and venules within the tumor mass.
cessitating treatment with voglibose (0.9 mg/day) and nateglinide (270 mg/day).

Several imaging studies were subsequently conducted to detect the cause of adrenal tumors. The differential diagnosis at that stage included malignant lymphoma, metastatic adrenal tumors, and adrenal cortical carcinomas. Therefore, she was transferred to The Department of Urology for resection of both adrenal tumors, which was performed on September 25 using the celiotomy approach.

Gross examination showed both tumors were 5.0 cm in diameter, and the right tumor was adherent to the inferior vena cava and liver. However, no diagnosis could be made under the operation apart from carcinoma, and therefore bilateral adrenalectomy was performed. Histopathologically, both tumors contained large pleomorphic lymphoid cells with heteromorphous nuclei (Fig. 2A, B). These cells showed extensive infiltration mainly into the sinusoids and venules within the tumor mass. Immunohistochemical staining demonstrated that the most tumor cells were positive for B cell markers, CD20 and CD79a (Fig. 2C). Furthermore, although the tumor cells were stained for bcl-2, they did not stain for CD5 (data not shown).

Based on histopathological assessment, the final diagnosis was intravascular large B-cell lymphoma (IVL), a subtype of extranodal diffuse large B-cell lymphoma characterized by the presence of lymphoma cells in the lumina of small vessels. Following the resection of bilateral adrenal glands, serum electrolytes and blood glucose levels improved under the replacement therapy with hydrocortisone (30 mg/day). Moreover, the skin pigmentation improved gradually, and plasma ACTH decreased to 17.6 pg/ml. However, after the operation, persistence of symptoms of general fatigue, appetite loss, low-grade fever, steal sweat and elevation of CRP, LDH, soluble IL-2 receptor, was noted. The activity of NHL

![Figure 3. (A) Brain magnetic resonance imaging showed multiple heterogeneous intensity areas. (B) Bone magnetic resonance imaging showed slightly enhanced tumors with an irregular of surface within the upper and middle dura.](image-url)
remained high. On October 12, 2001, abdominal enhanced CT revealed multiple low intensity areas in the liver and celiac lymph node enlargement, which had not been detected until then. Therefore, the stage of the disease was determined as clinical stage IVB, according to the Ann Arbor System. Combination chemotherapy was started as follows from October 15, 2001: two cycles of biweekly CHOP (cyclophosphamide, doxorubicin, vincristine sulfate, and prednisolone), and one cycle of double CHOP (cyclophosphamide 650 mg, doxorubicin 40 mg, vincristin sulfate 1.3 mg, and prednisolone 40 mg). Chemotherapy resulted in improvement of LDH levels, a fall in soluble IL-2 receptor level, and improvement in lymph node enlargement with normalization of the CT, suggestive of complete remission. After two cycles of biweekly CHOP, four cycles of double CHOP, and one cycle of CHOP, the patient was discharged on February 24, 2002. However, she was admitted again on March 2, 2002 due to the reappearance of general fatigue and fever. Subsequently, the patient developed various neurological symptoms including motor ataxia, dysarthria, Gerstmann syndrome, and dysbasia. Brain MRI revealed multiple heterogeneous-intensity areas with internal hemorrhage and peripheral high-intensity areas due to hypervascularity (Fig. 3A), indicating brain metastases. Moreover, bone metastases were detected on bone MRI (Fig. 3B). Chemotherapy using EPOCH (etoposide 65 mg, vincristine sulfate 0.5 mg, doxorubicin 13 mg, and prednisolone 80 mg) combined with whole brain and myelic irradiation failed to induce any clinical improvement and the patient died due to high disease activity. Her family refused postmortem examination.

**Discussion**

We treated a 66-year-old woman who was diagnosed with bilateral primary adrenal malignant lymphoma. The most common manifestations of malignant lymphoma are the involvement of the amygdale, stomach and pharynx, in addition to the lymph nodes, although the involvement of various other organs has been described. Involvement of the adrenal gland in malignant lymphoma cases is reported to be 25% at autopsy (3), but malignant lymphoma arising in the endocrine glands represents only 3% of extranodal malignant lymphomas, and is usually confined to the thyroid gland. Therefore, primary adrenal malignant lymphoma is rare (1).

The present patient showed typical symptoms and endocrinological findings of adrenal failure. Moreover, both rapid and continuous ACTH tests revealed no response, thus indicating primary adrenal failure. Primary adrenal malignant lymphoma was described in 24 patients of 67 reported cases complicated with adrenal failure including subclinical or partial adrenal failure (4, 5). In other words, 36% of cases with primary adrenal malignant lymphoma were complicated with adrenal insufficiency (Table 4). These reports showed certain characteristic features for primary adrenal malignant lymphoma, such as male predilection, involvement of both adrenal glands and being of the diffuse large B cell type.

Thus, malignant lymphoma was suspected in our case based on the high levels of LDH and soluble IL-2 receptor, bilateral adrenal tumors, rapidly progressive adrenal insufficiency. However, ⁶⁷Ga scintigram, did not demonstrate increased uptake in the adrenal glands, and T2-weighted MRI revealed heterogeneous tumors in our case. The heterogeneous tumors on imaging studies are usually tumors with bleeding and necrosis, making it very difficult to differentiate malignant lymphoma form adrenal metastatic tumors or adrenal cortical carcinomas (6, 7). Therefore, the complication of two or more diseases was considered in our case. Accordingly, surgery was performed to allow rapid histopathological examination under operation for the final diagnosis. However, no diagnosis could be made under the operation apart from carcinoma, and therefore bilateral adrenalectomy was performed.

The final diagnosis was IVL based on histopathological examination. IVL was classified as diffuse large B-cell lymphoma subtype, according to the new WHO classification (8). Several cases of IVL have been reported since the first patient was reported by Pfleger and Tappeiner (9). Generally, antemortem diagnosis of IVL is very difficult because of the exceedingly rapid clinical course and protean presentation of the disease. Additionally, the poor prognosis of IVL results partially from delays in diagnosis. IVL is characterized by massive proliferation of atypical mononuclear cells within arterioles, capillaries, and venules. This disease is therefore rarely diagnosed clinically but could present with various clinical features, such as fever, skin

| Table 4. Case Reports of Primary Adrenal Lymphoma in the Japanese Literature |
|----------------------------------|--------------|-------------|
| Number of reported cases | 67 | Present case |
| Site | Bilateral | 47 |
| | Unilateral | 10 |
| | unknown | 10 |
| Adrenal failure (+) | 24 (+) |
| Subclinical | 1 |
| Partial | 1 |
| Adrenal failure (−) | 10 |
| Pathology | Unknown | 33 |
| | Diffuse | 42 (IVL=5) |
| | Follicular | 0 |
| Size | Large | 30 |
| | Medium | 13 |
| | Small | 13 |
| Cell type | B cell | 36 |
| | T cell | 5 |
| Sex | Male | 39 |
| | Female | 26 |
| Age (year, n=48) (mean±SD) | 67.1±10.6 | 66 |
eruptions, neurological symptoms, and weight loss (10, 11). Moreover, the most common manifestations of IVL are infiltration of the skin and central nervous system, although infiltration of atypical cells has been described in various organs (12). Numao et al (13) indicated that primary and secondary adrenal gland infiltration of IVL was detected in 67% of patients diagnosed with IVL. The present case also showed infiltration of the central nervous system and liver and the clinical course progressed rapidly. Five cases of primary adrenal IVL had been reported until now in Japan, and two of these cases showed central nervous system infiltration, as described in our case (12–15). Therefore, central nervous system infiltration is described in 50% of Japanese patients with primary adrenal IVL including our case, and we consider central nervous system infiltration to be very important for the diagnosis of primary adrenal IVL. Furthermore, in cases with lymphoma cell infiltration detected in both glands and atypical imaging examination, and rapidly progressive adrenal insufficiency, the possibility that imaging examination is modified by bleeding caused by embolism of lymphoma cells in blood vessels, should be considered.

On the other hand, the sensitivity of IVL to systemic chemotherapy is very high and particularly when early diagnosis is made followed by treatment at an early stage. Therefore, early diagnosis and treatment of IVL is crucial for prognosis. Recent studies showed that de novo CD5+ diffuse large B-cell lymphoma (CD5+ DLBCL) is phenotypically and genotypically different from CD5- DLBCL (16). The survival of patients with CD5+ DLBCL is significantly worse than that of patients with CD5- DLBCL. Moreover, several patients with CD5+ IVL have been described (17, 18). However, in the present case the tumor cells did not stain for CD5.

In conclusion, we reported a rare and important case of bilateral primary adrenal non-Hodgkin lymphoma presenting as adrenal failure. Our patient was diagnosed as NHL with IVL. IVL is often very difficult to diagnose despite the multitude of laboratory tests and imaging studies. Thus, IVL should be suspected in patients with bilateral adrenal tumors who present with rapidly progressive adrenal failure.

References