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CASE REPORT

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Adrenal insufficiency caused by primary aggressive non-Hodgkin's lymphoma of bilateral adrenal glands: report of a case and literature review

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Abstract A 64-year-old woman was hospitalized because of poor general condition, gastrointestinal upset, unexplained fever, electrolyte imbalances, and an incidental finding of bilateral huge adrenal masses on computerized tomography (CT) of the abdomen. Non-Hodgkin's lymphoma (NHL) of B-cell origin was proven by ultrasound-guided aspiration biopsy of the left adrenal gland. Meanwhile, primary adrenal insufficiency was confirmed by her low serum cortisol level, high ACTH level, and inadequate adrenal response to the rapid ACTH stimulation test. The diagnosis of primary adrenal NHL was supported by detailed physical examinations, bone marrow examination, and such imaging studies as CT scan and sonography. She received three courses of chemotherapy with cyclophosphamide, vincristine, and prednisolone and there was an initial transient response, but she died of sepsis and progression of NHL three and a half months later.

Key words Adrenal gland · Aggressive non-Hodgkin's lynphoma · Primary adrenal insufficiency

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Introduction

The most common disorders which may cause primary adrenal insufficiency (PAI) include autoimmune diseases, chronic infectious diseases, and cancers [1–2]. Of the cancerous diseases, metastatic carcinoma of the lung, breast, and gastrointestinal tract are most frequently encountered [3–6]. The association between PAI and non-Hodgkin's lymphoma (NHL) is, however, very rare [7–27]. We report herein a unique case of primary bilateral adrenal NHL in a patient who initially presented with PAI.

Case report

A 64-year-old woman was transferred to our hospital because of nausea, vomiting, diarrhea, low-grade fever, and general weakness that had lasted for 2 weeks. Bilateral huge adrenal glands had been found incidentally on an abdominal computed tomography (CT) scan at other hospital. She had a 10-year history of non-insulin-dependent diabetes mellitus and was a carrier of chronic hepatitis B. On admission, her vital signs were all within normal limits. Her Karnofsky performance status was 20%. Pertinent physical findings revealed pallor and some hyperpigmentation spots over her lower lip. A complete blood count showed a hemoglobin of 8.0 g/dl, a white blood cell count of 3200/μl with 52% segmented neutrophils, 20% lymphocytes, and 24% monocytes, and a platelet count of 115,000/μl. Serum sodium was 117 mEq/l, potassium 5.10 mEq/l, glucose 165 mg/dl, C-reactive protein 4.5 mg/dl, anti-nuclear antibody 1:160, ferritin 867 ng/ml (normal, 7–37), and iron 11 μg/dl (normal, 49–181). Arterial blood gas measurement on an oxygen cannula at 2–3 l/min revealed pH 7.46, $PaCO_2$ of 25.9 mmHg, HCO_3^- of 18.6 mmol/l, and PO_2 of 101 mmHg. Other laboratory examinations including thyroid function test, tuberculin skin test, diagnostic mammography, bone marrow examination, chest roentgenogram, and a CT scan of her chest were unremarkable. Clinical suspicion of adrenal insufficiency was confirmed by the finding of a low serum cortisol level of 70.20 ng/ml at 06:30 a.m.(normal, 173–218 ng/ml), a high ACTH level of 433.8 pg/ml (normal 9–52 pg/ml), and a low cortisol level of 68.97 ng/dl 1 h after the cosyntropin stimulation test (250 μg intramuscular injection). Throughout the rest of her hospital stay, she received maintenance therapy with intravenous hydrocortisone 100 mg every 8 h daily while her diagnostic workup proceeded. Bilateral adrenal enlargement, with the right gland

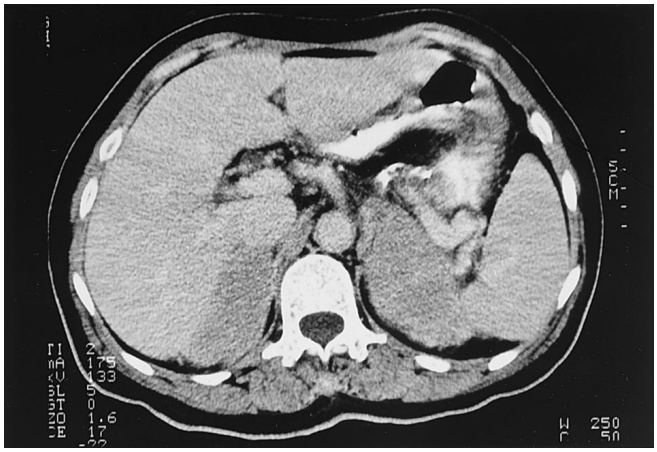

Fig. 1. Bilateral adrenal enlargement on initial abdominal CT scan

measuring about 10×7×4 cm and the left 10×8×7 cm, was demonstrated by CT scan (Fig. 1). An ultrasound-guided needle biopsy of the left adrenal gland showed malignant diffuse large cell lymphoma of B-cell origin (Fig. 2). She received chemotherapy with cyclophosphamide, vincristine, and oral prednisolone on a monthly basis for only three courses and obtained a transient partial response to chemotherapy.Two weeks after the third course of chemotherapy, she suffered from chemotherapy-induced neutropenia, pneumonia, and septic shock. Meanwhile, she experienced recurrent symptoms and signs of PAI with anorexia, weakness, hyponatremia of 125 mEq/l, hyperkalemia of 6.59 mEq/l, and low serum cortisol of 44.15 ng/ml. Repeated CT scan of the abdomen showed heterogeneous mass lesions with central necrosis involving bilateral suprarenal regions with spread to the retroperitoneum involving the right kidney and encasement of the retroperitoneal great vessels with massive ascites. She unfortunately died of progression of NHL and sepsis about three and a half months after the incidental finding of adrenal masses had been made. No autopsy was performed.

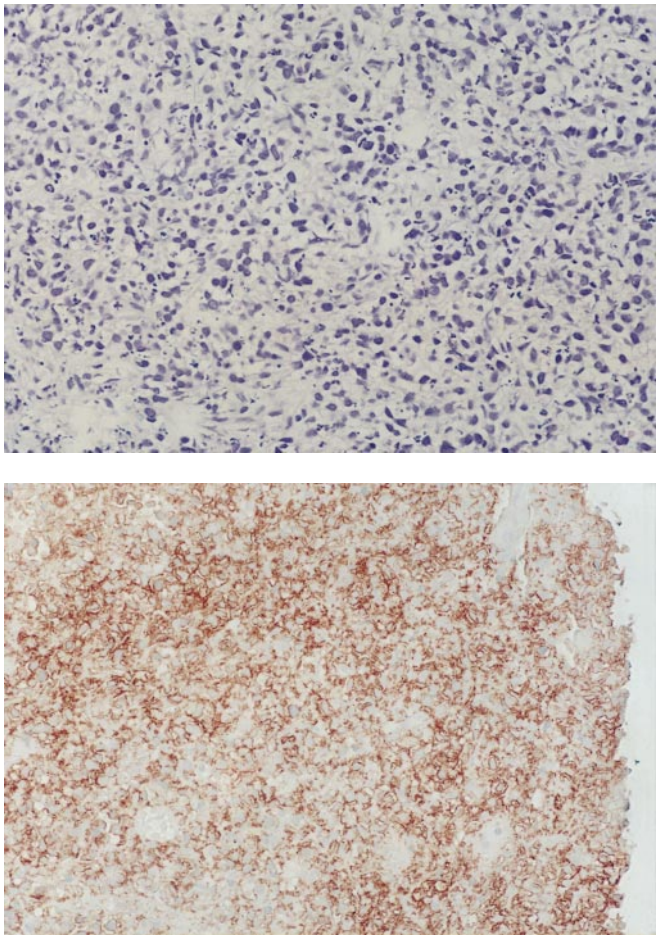

Fig. 2a,b. Homogeneous lymphoma cell infiltration in the biopsied specimen obtained from left adrenal mass. (**a**) Histological section, (H&E, ×200). (**b**) Immunohistochemical study showing tumor cells positively stained for L-26, a B-lymphocyte marker (×400)

Discussion

Adrenal involvement by NHL is not uncommon. In a post-mortem study, the incidence of such an association was as high as 25% [6]. NHL patients with adrenal involvement usually have widespread disease, and the adrenal gland is usually unilaterally involved [6]. Primary adrenal lymphoma initially manifesting as bilateral adrenal masses and PAI is rare. Two thirds of the patients with bilateral adrenal NHL show adrenal insufficiency, which is not commonly seen in unilateral adrenal NHL [28, 29].

The typical clinical symptoms of PAI include skin pigmentation, hyponatremia, hyperkalemia, inappropriately low spot plasma cortisol, and the absence of a plasma cortisol response to tetracosactrin. Because more than 90% of the adrenal glands are destroyed before clinical or biochemical evidence of PAI develops [3, 4], PAI rarely appears in the early stage of bilateral adrenal NHL. However, NHL should be listed in the differential diagnosis of bilateral adrenal masses with PAI.

In addition to the present patient, only 28 cases of adrenal NHL with PAI had been reported in the English literature (Table 1). Among these, men were more frequently affected than women, with a ratio of 3:1. Their age ranged from 42 to 89 years, with a median of 67. There were 13 cases reported of primary bilateral adrenal NHL with PAI (cases 3, 4, 8–10, 17–23, 27). Only three of the 29 patients achieved a good response, with either complete remission (case 16) or recovery of adrenal function and regression of the tumor (cases 4, 19) after treatment. In case 16, the patient was successfully treated with bilateral adrenalectomy and subsequent chemotherapy as well as hormone support [26]. All of the others died within 9 months because of rapid disease progression and infection.

Several prognostic factors of primary adrenal NHL have been addressed. Old age, initial presentation with PAI, huge tumor size, elevated serum LDH level, and involvement of other organs generally carry a poor prognosis [18, 25, 27]. Patients with widespread disease

Table 1 The clinical characteristics of adrenal lymphoma with adrenal insufficiency in 29 patients

Case No	Authors	Sex/Age	Primary adrenal lymphoma	Associated lesion sites	Diagnostic procedure	Pathology	Cell type	Major treatment	Outcome
1	Osei	M/55	No	Pancreas, kidney	No	Diffuse large noncleaved plasmacytoid lymphoma	NS	Steroid replacement	Died
2	Shea	M/81	No	Retroperitoneum	Needle biopsy	Large cell	NS	Steroid replacement	Died
3	Schnitzer	M/74	Yes	No	Open biopsy	Diffuse large immunoblastic	T	Steroid replacement	Died
4	Carey	M/57	Yes	No	Needle biopsy	Diffuse large cell	NS	C/T	Regression of tumor and recovery of adrenal function
5	Chung	M/60	No	Kidney, liver	Needle biopsy	Diffuse histiocytic	B	C/T	Died
6	Huminer	F/73	No	Stomach, pancreas, spleen, kidney	Needle biopsy	Large cell	NS	No	Died
7	Pagliuca	M/59	No	Spleen, liver	Needle biopsy	Centroblastic high grade	B	C/T	Died
8	Khan	M/59	Yes	No	Needle biopsy	Centroblastic high grade	B	C/T	Died
9	Oppong	M/60	Yes	No	Needle biopsy	NS	T	C/T	Died
10	Prayson	F/69	Yes	No	Autopsy	Angiotropic large cell	B	No	Died
11	Gamelin	M/75	No	Liver, pancreas, R't kidney	Autopsy	Diffuse large cell	NS	No	Died
12	Gamelin	F/67	No	Kidney, bone marrow, paraaortic LNs	Needle biopsy	Immunoblastic	B	C/T	Died
13	Gamelin	M/75	No	Lt axillary LNs	Needle biopsy	Immunoblastic	B	C/T	Died
14	Gamelin	F/77	No	Stomach Lt axillary LNs	Needle biopsy	Diffuse large cell	NS	C/T	Died
15	Baskal	M/49	No	Thyroid glands	Needle biopsy	Immunoblastic type	NS	C/T	Died
16	Dobnig	M/59	No	Rt axillary LNs	Needle biopsy	Centroblastic high grade	B	Bil adrenectomy	Complete remission
17	Gunn	M/68	Yes	No	Needle biopsy	Centroblastic type	B	C/T&R/T	Died
18	Utsunomiya	F/72	Yes	No	Operation	Diffuse large cell	B	Lt adrenectomy C/T	Died
19	Serrano	M/71	Yes	No	Needle biopsy	Small cleaved	NS	C/T	Regression of tumor and recovery of adrenal function
20	Kato	M/69	Yes	No	Needle biopsy	Diffuse large cell type	B	NS	NS
21	Efrermidis	M/73	Yes	No	Operation	Centroblastic, high grade	NS	Lt adrenectomy & C/T	Died
22	Sone	M/60	Yes	No	Autopsy	Centroblastic high grade	B	No	Died
23	Pimentel	M/42	Yes	No	Needle biopsy	Large cleaved cells	T	C/T	Died
24	Levy	M/60	No	Kidneys	NS	Diffuse large cell type	B	C/T	Died
25	Levy	M/70	No	Gallbladder	NS	Cutaneous T cell	T	None	Died
26	Levy	M/77	No	Liver, spleen	NS	Diffuse large cell type	B	None	Died
27	Levy	F/89	No	Spleen, Kidneys, Liver	NS	Diffuse large cell type	B	None	Died
28	Levy	M/77	No	Lung, Kidneys	NS	Small noncleaved	B	C/T	Died
29	Present case	F/64	Yes	None	Needle biopsy	Large cell type	B	C/T	Died

NS = not stated; LNs = lymph nodes; C/T = chemotherapy; R/T = radiotherapy; L't = left; R't = right

and recurrent PAI who were refractory to chemotherapy rarely survived longer than 1 year after diagnosis. They frequently died of severe infection, pulmonary embolism, or NHL progression.

Concerning management, immediate replacement therapy to avoid the catastrophic consequence of addisonian crisis and then intensive chemotherapy play an important role in reducing the risk of mortality [8, 13,

14, 21, 25, 26]. Some investigators suggested that surgical debulking with subsequent chemotherapy for large masses could provide a better complete response rate [13]. Alternatively, radiotherapy could be given to a bulky mass lesion in order to prevent local recurrence [12, 21]. Our patient was treated with a less intensive chemotherapeutic regimen of cyclophosphamide, vincristine, and oral prednisolone because she had a very poor performance status. This regimen obviously was unable to effectively kill lymphoma cells and therefore should not be encouraged for patients with bilateral adrenal lymphoma and a good performance status in the future.

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