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CASE REPORT

A case of non-Hodgkin's lymphoma primary arising in both adrenal glands associated with adrenal failure

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Abstract It is known that adrenal insufficiency is one of the complications in primary adrenal lymphoma, especially those with bilateral adrenal involvement. A 73-year-old man was referred for general fatigue and high fever to the nearest hospital. The patient was transferred to our hospital for evaluation of bilateral adrenal tumors and hyponatremia. He was diagnosed as having non-Hodgkin's lymphoma (NHL) with primaries arising in both adrenal glands. Primary adrenal lymphoma (PAL) is a rare extranodal NHL. Although an appropriate treatment of this disease has not been established, our case has demonstrated that the combination of rituximab and THP-COP chemotherapy could be administered, and that it improved clinical manifestations. This case raises the suggestion that malignant lymphoma should be suspected in patients with bilateral adrenal tumors that present with progressive adrenal insufficiency.

Keywords Non-Hodgkin's lymphoma · Primary adrenal lymphoma · Adrenal failure · Bilateral adrenal tumors

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Introduction

Most cases of adrenal insufficiency caused by malignant neoplasms are due to metastases from lung, breast, or stomach tumors, or malignant lymphoma [1]. Although malignant lymphoma could occur in any organ, non-Hodgkin's lymphoma (NHL) arising in the endocrine system represents only 3% of extra-nodal malignant lymphomas, and is usually confined to the thyroid gland [2]. Primary adrenal lymphoma (PAL) is rare and difficult to quantify. The majority of the patients are elderly men with bilateral adrenal involvement, and the most common histology of PAL is the diffuse large B-cell type [3, 4]. Most cases of PAL are aggressive tumors, and the prognosis is usually poor with only one-third of patients achieving a complete or partial remission after treatment [3]. An appropriate treatment of PAL has not been well established. Here we report on a patient with primary bilateral adrenal non-Hodgkin's lymphoma associated with adrenal failure.

Case report

A 73-year-old man was brought to the hospital because of general fatigue and high-fever. He was diagnosed 7 years earlier with left hemiplegia due to cerebral infarction. Physical examination revealed a body temperature of 37.0°C, blood pressure of 112/56 mmHg, heart rate of 98/min, body weight of 60 kg. He was conscious and alert and mild pale conjunctiva was found. Skin pigmentation was observed, but there was no lymphadenopathy. Laboratory examination revealed a hemoglobin of 7.4 g/dl (13.5–16.5), an increased white blood cell count of 7,820/μl (4500–8500) (nue. 53.4%, lym. 35.3%), a c-reactive

peptide (CRP) concentration of 8.79 mg/dl (0–0.4), albumin concentration of 2.5 g/dl (4.0–5.5), sodium concentration of 129 mEq/l (134–143), glucose of 105 mg/dl (75–110). Endocrinological examination showed an elevated value of serum ACTH of 437 pg/ml (10–100). An adrenocorticotrophic hormone (ACTH) stimulation test revealed a baseline cortisol concentration of 5.4 μg/dl (5–15) with no rise of cortisol concentration at 30 and 60 min, demonstrating that he had adrenal insufficiency. Chest CT detected a consolidation, and an air-bronchogram of the bilateral posterior lung field diagnosed a bilateral aspiration pneumonia. Abdominal CT disclosed large bilateral adrenal masses. The right adrenal gland measured 4×4 cm^2, and the left adrenal gland measured 8×8 cm^2 at its greatest dimensions (Fig. 1). In addition to that finding, there was a thickness of the intestinal wall. No celiac lymph node enlargement was found. Positron emission tomography with 18F-fluorodexoxyglucose (FDG-PET) showed significant radiotracer uptake in the bilateral adrenal masses and intestinal wall (Fig. 2). Superior gastroenterological endoscopic examination disclosed a swelled and hemorrhagic mucosa of the duodenum

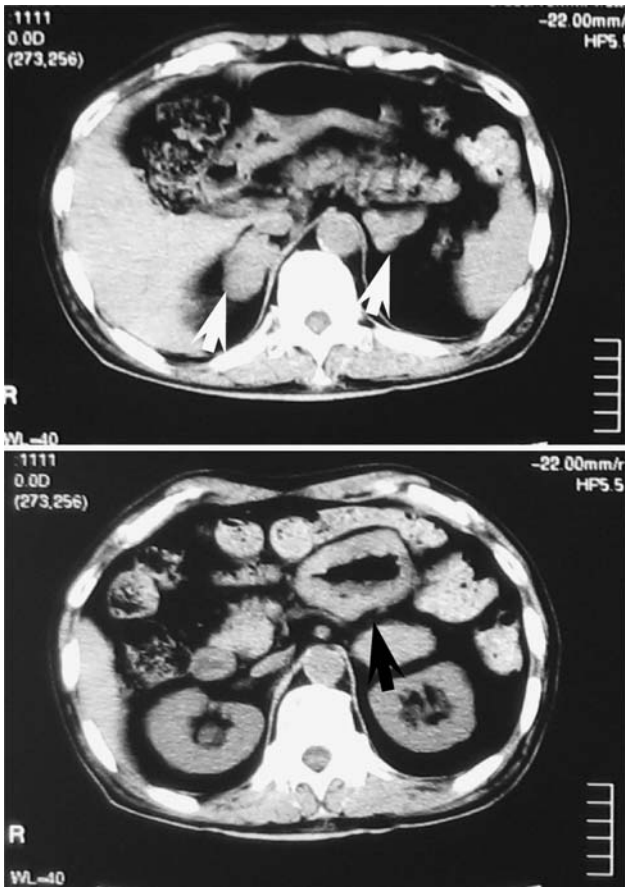

Fig. 1 Abdominal computed tomography disclosed large bilateral adrenal masses (⇒), and there was a thickness of the intestinal wall (➡)

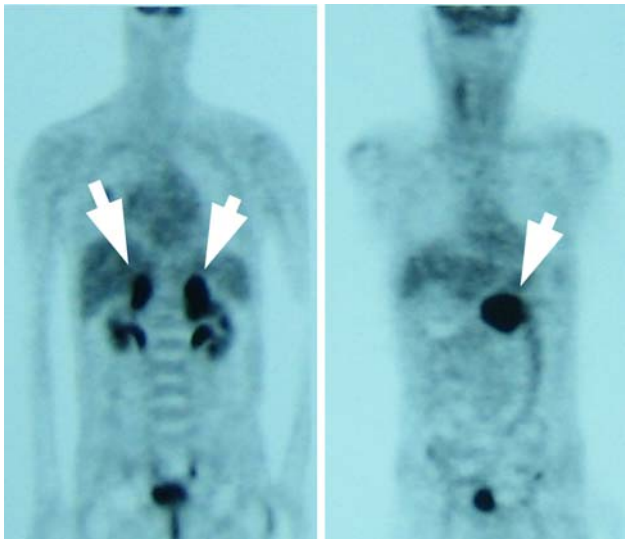

Fig. 2 FDG-PET disclosed abnormal uptakes in bilateral adrenal masses and intestinal wall

(Fig. 3). Histological examination of the biopsy specimen from the duodenal abnormal mucosa revealed complete and diffuse infiltration by large sized tumor cells with hypochromatic nuclei, prominent nucleoli at the periphery of the nuclear envelope, and a slightly eosinophilic cytoplasm (Fig. 4a). Immunohistochemical staining demonstrated that most tumor cells were positive for CD20/CD79α (B-cell markers) (Fig. 4b, c), some of them with large nucleoli and in mitosis, and negative for CD3/CD5/CD30CD45RO (T-cell markers) (Fig. 4d, e). The serum interleukin-2 receptor level was 1,376 U/ml (190–650).

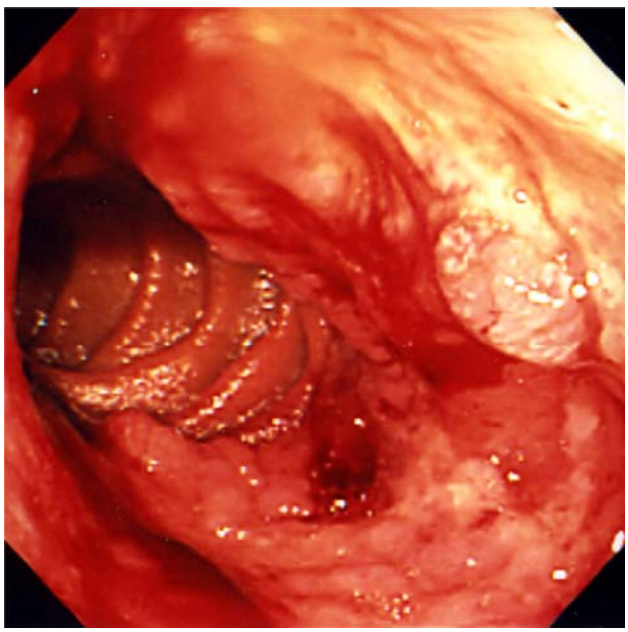

Fig. 3 Superior gastroenterological endoscopic examination disclosed a swelling and hemorrhagic mucosa of the duodenum

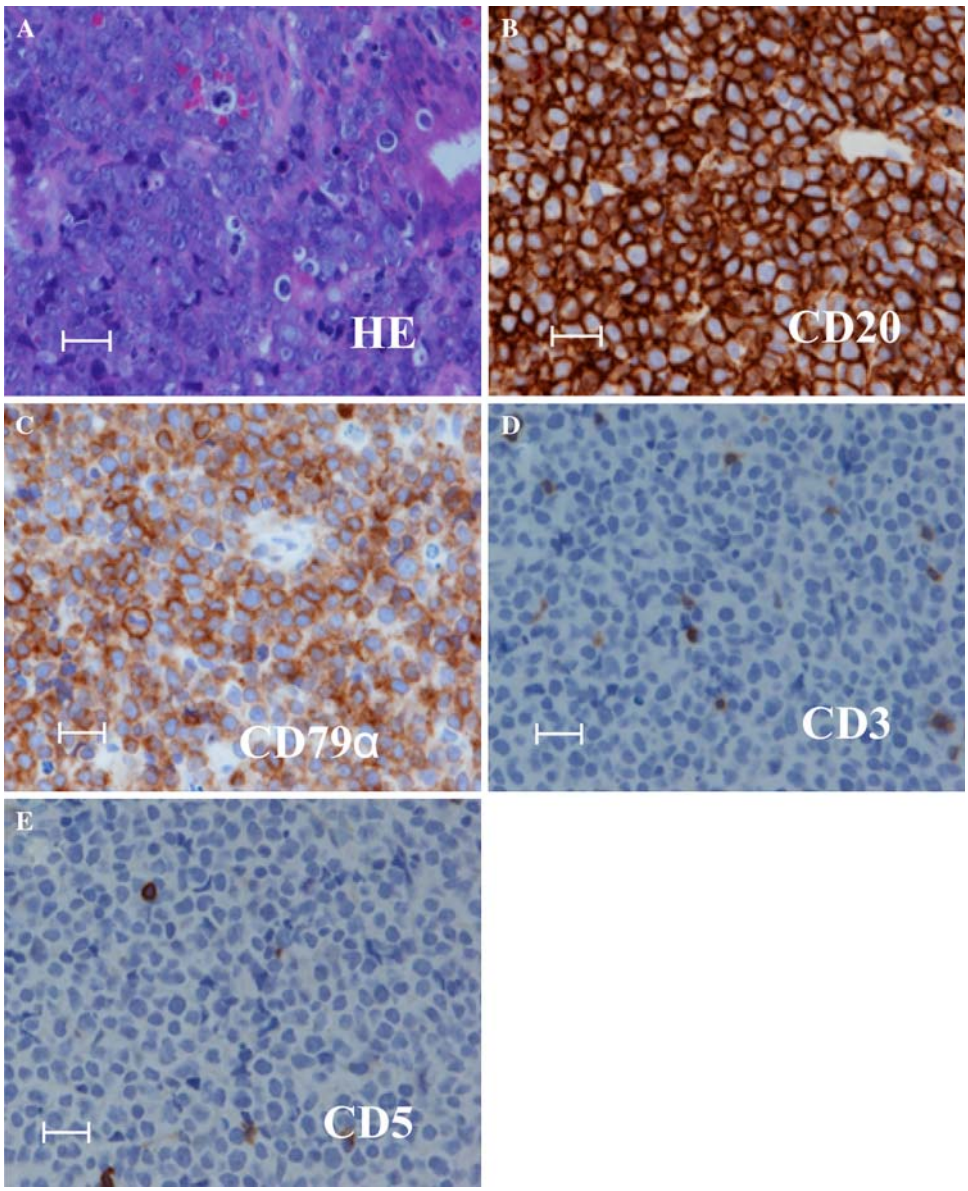

Fig. 4 DLBCL: malignant lymphoid cells, tissue section. **a** Hematoxylin-eosin stain; HE ×200. **b** CD20 immunostain ×200. **c** CD79α immunostain ×200. **d** CD3 immunostain ×200. **e** CD5 immunostain ×200

Based on those assessments, we finally diagnosed that the patient had an advanced primary bilateral adrenal lymphoma of the diffuse large B-cell NHL (DLBCL) type. The disease was staged as IVb according to the Ann Arbor system, and it was high grade according to the international prognostic index.

The patient was administered hydrocortisone replacement therapy, resulting in immediate improvement of symptoms. He also received antibiotics for treatment of the aspiration pneumonia. For the treatment of PAL, rituximab (375 mg/m^2) in combination with THP-COP (cyclophosphamide 750 mg/m^2, pirarubicin 40 mg/m^2, vincristine 1.4 mg/m^2, and prednisolone 100 mg/body) was administrated in one cycle during 1 week, resulting in partial remission (Fig. 5). No significant adverse events were noted after this treatment cycle. The patient recovered gradually and was discharged from our hospital.

Discussion

The most common manifestations of malignant lymphoma are the involvement of the amygdala, stomach, and pharynx, in addition to the lymph nodes, although the involvement of various other organs has been described [5]. Involvement of the adrenal gland in malignant lymphoma is reported to be 25% at autopsy [6, 7], but malignant lymphoma arising in the endocrine glands represents only 3% of extra-nodal malignant lymphomas, and

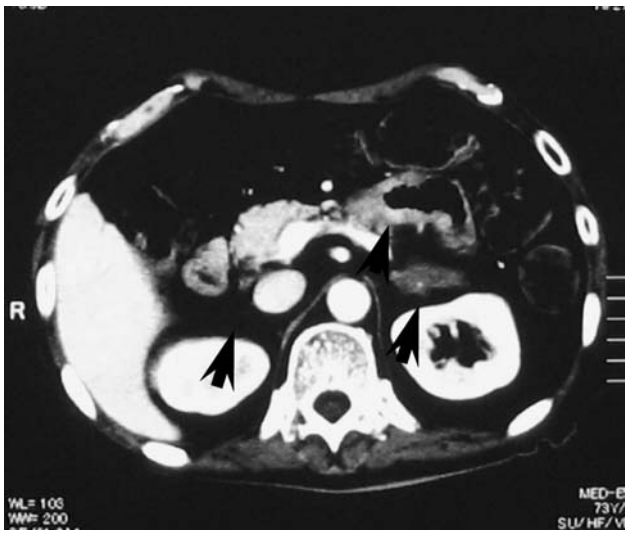

Fig. 5 Abdominal computed tomography revealed the reduction of bilateral adrenal tumors and intestinal wall thickness (➡) after one cycle of the R-THP-COP chemotherapy

is usually confined to the thyroid gland. Therefore, primary adrenal malignant lymphoma (PAL) is rare.

About 90% of PAL is of the diffuse B-cell type, about 70–80% has bilateral adrenal involvement, and adrenal insufficiency is one of the complications in PAL [4, 8]. On the other hand, bilateral adrenal tumors due to metastasis from lung or stomach tumors arise in about 50% of the cases and the complication of adrenal insufficiency occurs in about 1–2% of them [9]. The importance of early awareness of the possibility of PAL in patients with bilateral adrenal masses complicated with adrenal insufficiency should be emphasized, and early suspicions should lead to careful investigations.

Rituximab is a chimeric anti-CD20 monoclonal antibody [10]. Recently, the combination of rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy has shown improvement in clinical outcome, when compared to CHOP alone, in patients with diffuse large B-cell lymphomas [10, 11]. Therefore, initial treatment with R-CHOP is a reasonable treatment option in diffuse large B-cell lymphoma/PAL. In treating elderly non-Hodgkin's lymphoma (NHL) patients, it is particularly important to use drugs that have a low incidence of adverse events and high efficacy. Mori et al. [12] reported that THP (pirarubicin)-COP (cyclophosphamide, vincristine, and prednisolone) was compared to a two-thirds dosage of the full CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen with regard to both adverse events and efficacy. In a third group, etoposide (E) was added to the THP-COP regimen (THP-COPE) in order to achieve high dose intensity. The subjects in their study were 486 previously untreated patients, aged 65 years or older (range, 65–92 years; median, 74 years), with NHL. Subjects were randomly assigned to receive THP-COP, two-thirds CHOP, or THP-COPE. In aggressive lymphoma, there were no differences in complete response (CR) rates (45.3% in THP-COP, 44.9% in CHOP, 48.0% in THP-COPE), overall survival, and progression-free survival among these groups [12]. Because adverse cardiac events were reported only in CHOP, adverse cardiac events might be low in the THP group. Pirarubicin may be more useful for elderly non-Hodgkin's lymphoma (NHL) patients than doxorubicin. In this case, in which PAL was complicated with adrenal insufficiency that resulted in poor performance status and severe general conditions, the use of aggressive combination chemotherapy as initial treatment may not be advisable. When the patient had received efficient hydrocortisone replacement therapy, rituximab combined with chemotherapy could be administered without significant toxicities.

In conclusion, PAL should be suspected in patients with bilateral adrenal tumors that present with progressive adrenal failure. Rituximab combined with THP-COP chemotherapy in the treatment of PAL with adrenal insufficiency is safe after appropriate glucocorticoid replacement therapy and has potential clinical benefits. Moreover, this therapy is adaptable and useful especially to elderly patients like our case.

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