

## A Case of Primary Adrenal Diffuse Large B-cell Lymphoma Achieving Complete Remission with Rituximab-CHOP Chemotherapy

Primary adrenal lymphoma is a very rare extranodal lymphoma; its clinical features consist of a high incidence of bilateral adrenal involvement and diffuse large B-cell lymphoma. We report a patient with primary bilateral adrenal diffuse large B-cell lymphoma who achieved complete remission with R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. A 52-yr-old man presented with fever and progressive fatigue for 3 months. Computed tomography (CT) scans of the abdomen and pelvis demonstrated large bilateral adrenal masses, and a needle biopsy of the left adrenal mass revealed diffuse large B-cell lymphoma. After 6 cycles of R-CHOP chemotherapy, CT scans showed no residual disease. To our knowledge, this is the second report to date of a patient with primary bilateral adrenal diffuse large B-cell lymphoma who achieved complete remission using R-CHOP chemotherapy.

**Key Words :** Primary Adrenal Lymphoma; Lymphoma, Large B-Cell, Diffuse; R-CHOP; Complete Remission

Kyung Min Kim<sup>1</sup>, Dok Hyun Yoon<sup>1</sup>,  
Seung Geun Lee<sup>1</sup>, Sung Nam Lim<sup>1</sup>,  
Lyu Jin Sug<sup>2</sup>, Jooryung Huh<sup>2</sup>,  
and Cheolwon Suh<sup>1</sup>

Departments of Internal Medicine<sup>1</sup>, Nuclear Medicine<sup>2</sup>,  
and Pathology<sup>3</sup>, Asan Medical Center, University of  
Ulsan College of Medicine, Seoul, Korea

Received : 30 June 2007

Accepted : 27 February 2008

### Address for correspondence

Cheolwon Suh, M.D.

Department of Internal Medicine, Asan Medical Center,  
388-1 Pungnap 2-dong, Songpa-gu, Seoul 138-736,  
Korea

Tel : +82.2-3010-3209, Fax : +82.2-3010-6961

E-mail : csuh@amc.seoul.kr

### INTRODUCTION

Although secondary involvement of the adrenal gland has been reported to occur in up to 25% of patients with non-Hodgkin's lymphoma (NHL) (1), primary adrenal lymphoma (PAL) is very rare, with only about 80 cases reported in the English language literature (2). Treatment of PAL is similar to that of other types of lymphoma, but prognosis is poor. Therapeutic modalities include surgery, combination chemotherapy, and/or radiotherapy. Among the chemotherapy regimens utilized are CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), and MACOP-B (adding methotrexate and bleomycin) (2). Here, we describe a patient with primary bilateral adrenal diffuse large B-cell lymphoma who achieved complete remission after treatment with rituximab plus CHOP (R-CHOP).

### CASE REPORT

A 52-yr-old man with no prior medical history was admitted for a 3-month history of fever and progressive fatigue. He appeared chronically ill, but alert. Blood pressure was 100/70 mmHg, pulse rate was 102 bpm, respiratory rate was 22 bpm, and body temperature was 38.5°C. Examination of head and neck was unremarkable; no abnormality was found in chest; no hepatosplenomegaly or mass was detected in the abdomen;

and there was no evidence of lymphadenopathy or abnormal skin lesions.

A complete blood count showed hemoglobin 10.4 g/dL, hematocrit 30.0%, white blood cell count 5,000/ $\mu$ L, and platelet count 104,000/ $\mu$ L. Sodium level was 126 mM/L (normal range, 133-150 mM/L), but potassium and calcium levels were normal. Serum  $\beta_2$ -microglobulin concentration was 4.7  $\mu$ g/mL (normal range, 1-2.4  $\mu$ g/mL), serum lactate dehydrogenase (LDH) level was 476 IU/L (normal range, 120-250 IU/L), serum cortisol concentration at 8 AM was 2.9  $\mu$ g/dL (normal range, 7-25  $\mu$ g/dL), plasma ACTH level at 8 AM was 210 pg/mL (normal range, 9-52 pg/mL), and serum aldosterone concentration was 56.2 pg/mL (normal range, 20-160 pg/mL). Urinalysis showed that 24 hr excretion of vanillylmandelic acid was 5.9 mg/day (normal range, 0-8 mg/day), of epinephrine was 21.5  $\mu$ g/day (normal range, 0-20  $\mu$ g/day), of norepinephrine was 202.1  $\mu$ g/day (normal range, 1-130  $\mu$ g/day), and of total metanephrine was 0.6 mg/day (normal range 0-1.3 mg/day). Rapid cosyntropin (analog of ACTH) stimulation test, using 250  $\mu$ g of intravenous cosyntropin, demonstrated plasma cortisol concentrations at 0, 30 and 60 min of 9.5, 10.0 and 10.5  $\mu$ g/dL, respectively (reference range, at least 7  $\mu$ g/dL at 0 min, 16  $\mu$ g/dL at 30 min, and 18  $\mu$ g/dL at 60 min), strongly suggesting adrenal insufficiency.

Chest radiography was normal without evidence of hilar lymphadenopathy. Computed tomography (CT) scans of abdomen and pelvis demonstrated large bilateral adrenal masses. The right adrenal gland measured 5.8  $\times$  2.7 cm, and the left



Fig. 1. Abdominal pelvic CT scan showing bilateral adrenal masses.

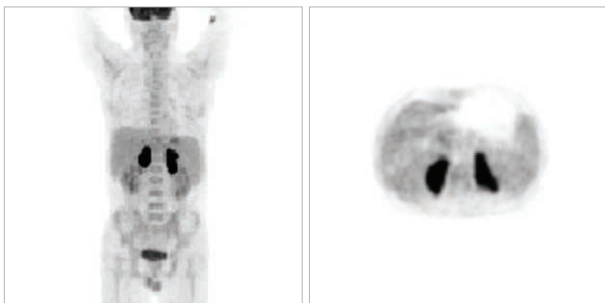


Fig. 3. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showing intense FDG accumulation in both adrenal glands. There was no abnormal FDG uptake in the rest of the body.

adrenal gland measured  $3.7 \times 2.0$  cm in its greatest dimension (Fig. 1).

A CT-guided core needle biopsy of the left adrenal mass was performed. The tumor was comprised of large cells, which were immunohistochemically positive for CD20, but negative for CD3 and CD30. The Ki-67 labeling index was about 90%. The tumor was diagnosed as a diffuse large B-cell lymphoma (Fig. 2).

Bone marrow biopsy was negative for lymphomatous involvement. An F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed intense FDG accumulation in both adrenal glands. There was no abnormal FDG uptake in the rest of the body (Fig. 3).

The patient was administered adrenal hormone replacement therapy with 20 mg hydrocortisone at 8 AM and 10 mg at 4 PM. He was also administered R-CHOP chemotherapy, consisting of rituximab ( $375 \text{ mg/m}^2$  i.v.), cyclophosphamide ( $750 \text{ mg/m}^2$  i.v.), doxorubicin ( $50 \text{ mg/m}^2$  i.v.), and vincristine ( $1.4 \text{ mg/m}^2$  i.v.), on day 1, and prednisolone (100 mg p.o.) on days 1-5, every 3 weeks. After completing 6 cycles of R-CHOP chemotherapy, there was no evidence of tumor on follow-up CT and FDG-PET scans (Fig. 4). To date, this patient has been followed regularly at our outpatient clinic for the

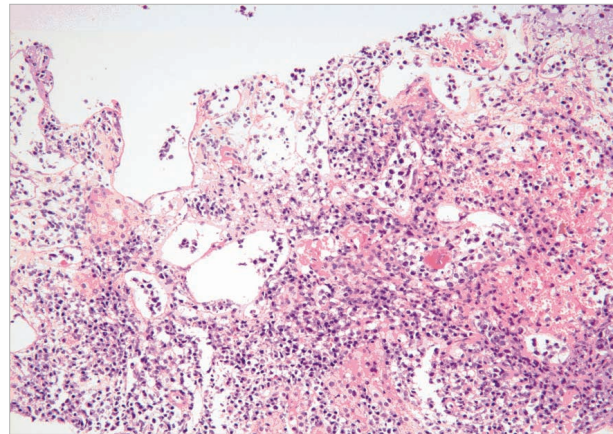


Fig. 2. CT-guided core needle biopsy of the left adrenal mass showing a tumor comprised of large cells, immunohistochemically positive for CD20 but negative for CD3 and CD30. The Ki-67 labeling index was about 90%. The tumor was diagnosed as a diffuse large B-cell lymphoma.

past 12 months, with no evidence of tumor recurrence.

## DISCUSSION

PAL is a very rare lymphoma, with only about 80 cases reported in the English language literature (2, 3). Histologically, the most common type is diffuse large B-cell lymphoma, with most originating in both adrenal glands (Table 1). PAL is most common in elderly men; the mean age at diagnosis is 68 yr and the male-to-female ratio is 2.2:1. Clinical symptoms of PAL include fever, weight loss, local pain, and symptoms of adrenal insufficiency (8). Immune dysfunction may be a predisposing factor in some patients (3). A review of 55 PAL patients showed that 8 (15%) had a concurrent or past history of carcinoma, 2 (4%) had human immunodeficiency virus (HIV) infection, and 7 (13%) had concomitant autoimmune disease (8).

On CT and magnetic resonance imaging (MRI), PALs tend to appear as complex masses of variable density and often have areas of necrosis and/or hemorrhage, with most tumors being bilateral (8). Because most PAL patients have adrenal involvement only, without any nodal involvement, whole body FDG-PET, which measures increased glucose metabolism and has been used in tumor diagnosis and staging, in monitoring response to treatment, and detecting recurrence, has shown intense FDG uptake only in the adrenal glands (2). In our patient, whole-body FDG-PET demonstrated FDG uptake in the adrenal masses, with no evidence of abnormal uptake in extraadrenal regions.

Tissue samples can be obtained by CT- or ultrasound-guided biopsy or by surgical excisional biopsy (3, 8, 11). Histologically, the most common type of PAL is diffuse large B-cell lymphoma (2, 3, 8). These neoplastic cells express antigens specific to B lymphocytes, such as CD20, CD74, CDw75,

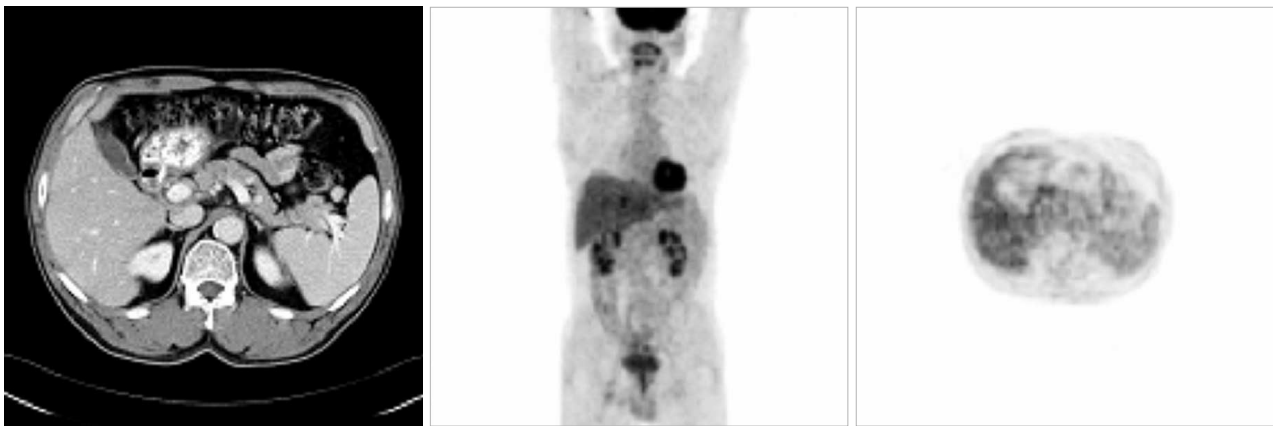


Fig. 4. Follow-up CT and FDG-PET scans after 6 cycles of R-CHOP chemotherapy showing no evidence of tumor.

Table 1. List of documented cases of primary bilateral adrenal diffuse large B-cell lymphoma in the English language literature

Age/sex	Reference	Year	Initial symptoms	Treatment	Outcome
72/F	Utsunomiyal et al. (4)	1992	Fatigue, fever	Surgery, CHP	Died 1yr later
69/M	Kato et al. (5)	1996	Abdominal pain, Wt. loss	NS	NS
61/F	Al-Fiar et al. (6)	1997	Wt. loss, nausea	CHOP	Died 11 mo later
55/M	Nasu et al. (7)	1998	Fever, Wt. loss, hyperpigmentation	BACOD-Et + CHOP	Died 8 mo later
64/F	Hsu et al. (9)	1999	FUO, nausea, vomiting	COP	Died 15 day later
27/M	Salvatore, Ross (10)	1999	Nausea, vomiting, fever	CHOP	NS
63/M	Yamamoto et al. (12)	1999	Idiopathic thrombocytopenic purpura	ACOEP	CR 6 yr
69/F	Kuyama et al. (13)	2000	Fatigue, Wt. loss	CHOP	CR 50 mo
62/M	Clemens, Pins (14)	2000	Fever, fatigue, Wt. loss	CHOP + IT MTX	NS
73/F	Suga et al. (15)	2000	NM	Chemotherapy	No response
62/F	Yamashita et al. (16)	2000	NM	Chemotherapy	Response on CT
56/F	Viswanathan, Middleton (17)	2001	FUO	NM	NM
71/M	Schocket et al. (18)	2002	Decreased visual acuity	CHOP	CR 7 yr
61/M	Hahn et al. (19)	2002	Abdominal pain	CEOP, radiation	improved
80/M	Lu et al. (20)	2002	Nausea, Wt. loss, hyperpigmentation	COP	Died after 4 mo
NM	Xu et al. (21)	2003	Wt. loss, fever	Surgery	Died in 3 mo
NM	Xu et al. (21)	2003	Wt. loss, fever	CHOP	Died after 2 cycles
59/F	Wang et al. (22)	2003	NM	CHOP	Died after 6 mo
86/M	Gillett, Haak (23)	2003	Lethargy, sweats, Wt. loss	CEOP	CR 10 mo
55/M	Grigg, Connors (3)	2003	Hypoadrenalism	Chemotherapy	Died
70/M	Zar et al. (24)	2004	Wt. loss, abdominal pain	CHOP	Died after 1 cycle
60/F	Singh et al. (25)	2004	Headache	CHOP, radiation	Died after 9 mo
27/M	Singh et al. (25)	2004	Right leg swelling	CHOP, radiation	CR 8 mo
55/F	Singh et al. (25)	2004	Abdominal discomfort	CHOP	Died after 7 mo
67/M	Kumar et al. (2)	2005	Fatigue, Wt. loss, fever	Chemotherapy	CR
54/F	Airaghi et al. (27)	2006	Paresthesia in left cheek	Chemotherapy	CR

A, adriamycin; B, bleomycin; B/L, bilateral; C, cyclophosphamide; CR, complete remission; D, dexamethasone; E, epirubicin; Et, etoposide; FUO, fever of unknown origin; H, doxorubicin; IT, intrathecal; L, left; M, mitozantrone; Met, metastasis; MTX, methotrexate; mo, month; NM, not mentioned; NS, not specified; O, vincristine; P, prednisolone; R, right; Wt, weight.

and CD79a, while not expressing antigens specific to T lymphocytes, such as CD3, CD5, CD43, and CD45RO (26).

Because of the rarity of PAL, therapeutic regimens have not been defined in detail (2), with most patients treated with regimens similar to those used to treat other types of lymphoma. Therapeutic modalities include surgery, combination chemotherapy, and radiation (8). Most patients with PAL have been treated with CHOP and the remainder with CVP

or MACOP-B (2). The roles of radiation therapy and surgical excision of the adrenal glands in the context of bilateral involvement are not known (3). The prognosis of patients with PAL is very poor, with uncertain duration of survival (3, 8, 22). Poor prognosis is thought to be due to advanced age at diagnosis, large tumor size, increased LDH level, bilateral adrenal involvement (regarded as stage IV disease), and adrenal insufficiency at the time of presentation, indicating extensive adre-

nal destruction (3).

The most common regimen of PAL is CHOP, with a 71-yr-old man with primary bilateral adrenal diffuse large B-cell lymphoma reported to have continued in complete remission for 7 yr after treatment with the CHOP regimen (18). Recent evidence suggests that the outcome of elderly patients with diffuse large B-cell lymphoma is improved by the addition of rituximab to CHOP (28). Our patient, who was administered 6 cycles of R-CHOP every 3 weeks, showed complete remission on follow-up CT and FDG-PET. Although a 62-yr-old man with primary bilateral diffuse large B-cell lymphoma who was treated with a left adrenalectomy, R-CHOP, radiotherapy, and high-dose chemotherapy with autologous peripheral blood stem cell transplantation, has been disease-free for 2 yr, this report was in Japanese (29). Moreover, in contrast to this patient, our patient received only R-CHOP chemotherapy, without surgery, radiation or high-dose therapy.

In conclusion, this may be the second report of a patient with primary bilateral adrenal diffuse large B-cell lymphoma who achieved complete remission using R-CHOP chemotherapy.

## REFERENCES

- Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF. *Lymphosarcoma: a review of 1269 cases. Medicine (Baltimore) 1961; 40: 31-84.*
- Kumar R, Xiu Y, Mavi A, El-Haddad G, Zhuang H, Alavi A. *FDG-PET imaging in primary bilateral adrenal lymphoma: a case report and review of the literature. Clin Nucl Med 2005; 30: 222-30.*
- Grigg AP, Connors JM. *Primary adrenal lymphoma. Clin Lymphoma 2003; 4: 154-60.*
- Utsunomiya M, Takatera H, Itoh H, Tsujimura T, Itatani H. *Bilateral primary non-Hodgkin's lymphoma of the adrenal glands with adrenal insufficiency: a case report. Hinyokika Kyo 1992; 38: 311-4.*
- Kato H, Itami J, Shiina T, Uno T, Arimizu N, Fujimoto H, Mikata A, Tamaru J, Araki A. *MR imaging of primary adrenal lymphoma. Clin Imaging 1996; 20: 126-8.*
- Al-Fiar FZ, Pantalony D, Shepherd F. *Primary bilateral adrenal lymphoma. Leuk Lymphoma 1997; 27: 543-9.*
- Nasu M, Aruga M, Itami J, Fujimoto M, Matsubara O. *Non-Hodgkin's lymphoma presenting with adrenal insufficiency and hypothyroidism: an autopsy case report. Pathol Int 1998; 48: 138-43.*
- Wang J, Sun NC, Renslo R, Chuang CC, Tabbarah HJ, Barajas L, French SW. *Clinically silent primary adrenal lymphoma: a case report and review of the literature. Am J Hematol 1998; 58: 130-6.*
- Hsu CW, Ho CL, Sheu WH, Harn HJ, Chao TY. *Adrenal insufficiency caused by primary aggressive non-Hodgkin's lymphoma of bilateral adrenal glands: report of a case and literature review. Ann Hematol 1999; 78: 151-4.*
- Salvatore JR, Ross RS. *Primary bilateral adrenal lymphoma. Leuk Lymphoma 1999; 34: 111-7.*
- Fearon P, Rahilly M. *Primary adrenal B cell lymphoma. Hosp Med 1999; 60: 759-60.*
- Yamamoto E, Ozaki N, Nakagawa M, Kimoto M. *Primary bilateral adrenal lymphoma associated with idiopathic thrombocytopenic purpura. Leuk Lymphoma 1999; 35: 403-8.*
- Kuyama A, Takeuchi M, Munemasa M, Tsutsui K, Aga N, Goda Y, Kanetada K. *Successful treatment of primary adrenal non-Hodgkin's lymphoma associated with adrenal insufficiency. Leuk Lymphoma 2000; 38: 203-5.*
- Clemens JQ, Pins MR. *NonHodgkin's lymphoma presenting as bilateral testicular and adrenal masses. J Urol 2000; 163: 241-2.*
- Suga K, Ishikawa Y, Matsunaga N, Motoyama K, Hara A. *Ga-67 and I-131 adosterol scintigraphic findings of bilateral primary adrenal lymphoma. Clin Nucl Med 2000; 25: 718-20.*
- Yamashita E, Kobayashi T, Suzuki Y. *Primary bilateral adrenal involvement of non-Hodgkin's lymphoma shown on a Ga-67 citrate scan. Clin Nucl Med 2000; 25: 721-2.*
- Viswanathan V, Middleton ML. *Primary adrenal lymphoma: a case report. Clin Nucl Med 2001; 26: 787-8.*
- Schocket LS, Syed NA, Fine SL. *Primary adrenal lymphoma with choroidal metastases. Am J Ophthalmol 2002; 134: 775-6.*
- Hahn JS, Choi HS, Suh CO, Lee WJ. *A case of primary bilateral adrenal lymphoma (PAL) with central nervous system (CNS) involvement. Yonsei Med J 2002; 43: 385-90.*
- Lu JY, Chang CC, Chang YL. *Adrenal lymphoma and Addison's disease: report of a case. J Formos Med Assoc 2002; 101: 854-8.*
- Xu A, Xiao X, Ye L, Hong B, Wang X. *Primary adrenal lymphoma. Leuk Lymphoma 2003; 44: 739-40.*
- Wang FF, Su CC, Chang YH, Pan CC, Tang KT, Jap TS, Lin HD, Won JG. *Primary adrenal lymphoma manifesting as adrenal incidentaloma. J Chin Med Assoc 2003; 66: 67-71.*
- Gillett M, Haak S. *Not just another fall in the elderly. Bilateral adrenal lymphoma presenting with adrenal insufficiency causing weakness. Aust Fam Physician 2003; 32: 248-50.*
- Zar T, Khan F, Petit W Jr, Bernene JR. *Primary adrenal lymphoma presenting as adrenal insufficiency. A case report and review of literature. Conn Med 2004; 68: 7-10.*
- Singh D, Kumar L, Sharma A, Vijayaraghavan M, Thulkar S, Tandon N. *Adrenal involvement in non-Hodgkin's lymphoma: four cases and review of literature. Leuk Lymphoma 2004; 45: 789-94.*
- Libe R, Giavoli C, Barbeta L, Dall'Asta C, Passini E, Buffa R, Beck-Peccoz P, Ambrosi B. *A primary adrenal non-Hodgkin's lymphoma presenting as an incidental adrenal mass. Exp Clin Endocrinol Diabetes 2006; 114: 140-4.*
- Airaghi L, Greco I, Carrabba M, Barcella M, Baldini IM, Bonara P, Goldaniga M, Baldini L. *Unusual presentation of large B cell lymphoma: a case report and review of literature. Clin Lab Haematol 2006; 28: 338-42.*
- Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. *CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235-42.*
- Shirao S, Kuroda H, Kida M, Watanabe H, Matsunaga T, Niitsu Y, Konuma Y, Hirayama Y, Kohda K. *Effective combined modality therapy for a patient with primary adrenal lymphoma. Rinsho Ketsueki 2006; 47: 204-9.*