

A Case of Primary Bilateral Adrenal Lymphoma (PAL) with Central Nervous System (CNS) Involvement

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Primary adrenal lymphoma (PAL) is a very rare disease and usually does not have disease elsewhere, and if present, it is frequently extranodal. Several cases of PALs, with central nervous system (CNS) involvement, gastrointestinal tract or other endocrine organs involvement, have been reported in Western literature. We experienced a case of PAL with CNS involvement, which was previously unreported in Korea. The patient, a 61 year-old male, was admitted with left abdominal pain. After imaging study and needle aspiration biopsy (NAB), a bilateral primary adrenal lymphoma (large B-cell type), with bilateral hemorrhage, was confirmed. Combination chemotherapy, with CEOP regimen, was used. A follow-up abdominopelvic CT scan, after the second CEOP chemotherapy, showed the previous adrenal masses had nearly disappeared. However, about 2 months after diagnosis (day 52), he showed recent memory loss, obtundation, disorientation and drowsy mental status. The brain MRI revealed multifocal scattered lesions with increased signal intensity. The result of a brain biopsy was diffuse large B-cell lymphoma. After 5½ cycles of chemotherapy, with CEOP regimen, and whole brain radiotherapy, he is still surviving 6 months later, and has become alert with nearly normalized cognitive function.

Key Words: Primary adrenal lymphoma, CNS involvement

INTRODUCTION

Primary adrenal lymphoma (PAL) is extremely rare, although secondary involvement of the adrenal gland is relatively frequent, in association with the advanced disease. Several autopsy series have shown that 20-25% of patients with non-

Hodgkin's lymphoma (NHL) have adrenal gland involvement at some time during the course of their disease.^{1,2} Patients with primary adrenal lymphoma, however, usually do not have disease elsewhere, and if present it is frequently extranodal. Several cases of central nervous system, gastrointestinal tract and other endocrine organs involvements of PALs have been reported abroad.³⁻⁵ In Korea, there have been some case reports of PALs with, or without, adrenal insufficiencies, but PAL with CNS involvement has not yet been reported.⁶⁻⁹

Systemic central nervous system lymphoma (SCNSL) is defined as non-Hodgkin's lymphoma involvement both within and outside the central nervous system (CNS). CNS involvement of NHL has been reported to occur in 10-20% of patients with systemic lymphoma and is associated with very poor prognosis.^{10,11}

We report here a very rare case of primary bilateral adrenal lymphoma with central nervous system involvement. To the best of our knowledge, this is the first case of PAL with CNS involvement in Korea.

CASE REPORT

A 61 year-old male was admitted to our hospital complaining of pain in the left abdomen for one week. His past medical and family history were not contributory. There was no history of weight loss, fever or night sweat.

Physical examination on admission revealed the following: blood pressure 140/90 mmHg; pulse rate 80/min; respiration rate 17/min; and body temperature 36.0°C; there was direct tenderness on

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the left side of the abdomen without rebound tenderness. Hepatomegaly of two finger breaths was noted along the right costal margin. However, there was no palpable lymph node or splenomegaly.

Laboratory tests revealed the following: hemoglobin, 10.8g/dl; hematocrit, 32.8%; white cell count (WBC), 3,530/ul with 62.7% polymorphonuclear cell; platelet count, 152,000/ul; sodium, 138 mEq/L; potassium, 4.0mEq/L; chloride, 103mEq/L; bicarbonate, 25 mEq/L, calcium, 9.7 mg/dl; phosphate, 4.7 mg/dl; blood urea nitrogen, 7.7 mg/dl; creatinine, 0.9 mg/dl; total protein, 6.2g/dl; albumin, 3.7g/dl; globulin, 2.5g/dl; total bilirubin, 0.5 mg/dl; alkaline phosphatase, 87IU/L; AST, 22 IU/L; ALT, 16 IU/L; the r-GT, 45 IU/L; uric acid, 5.9mg/dl; lactate dehydrogenase (LDH), 845 IU/L with normal proportions of LDH isoenzymes; erythrocyte sedimentation rate (ESR), 45 mm/hr (< 15); β_2 -microglobulin, 2.96 mg/L (0.8 - 2.0); EBV Ab EA IgM, negative; cortisol (8AM), 144.090 ng/ml (70 - 250); cortisol (4PM), 69.59 ng/ml (20 - 90); adrenocorticotropic hormone (ACTH) (8AM), 31.020 pg/ml (4.7-41); renin (supine), 1.54 (0.68 - 1.36); renin (upright), 5.12 (0.24 - 4.7); aldosterone (supine), 54.8 (10 - 160); aldosterone (upright), 145.9 (40 - 310); A corticotropin stimulation test was done, but no definite adrenal insufficiency was confirmed.

The chest X-ray was normal without evidence of hilar lymphadenopathy. The neck computerized tomographic (CT) scan showed no visible mass. The chest CT scan showed small amount of left pleural effusion. The abdomino-pelvic CT scan, and magnetic resonance imaging (MRI), showed bilateral adrenal gland masses with left adrenal pseudocyst formation. Both masses were 5.8 × 3.0 cm in size, and the left adrenal pseudocyst was about 6.3cm × 6.8cm in size, and thought to be due to hemorrhage of the left adrenal mass. The hemorrhage extended to the perinephric area, anterior pararenal space and left paraaortic gutter (Fig. 1). A whole body bone scan (WBBS) showed degenerative changes of the lower lumbar spine, thoracic and upper cervical spine, and the bilateral knee joint without metastasis. Positron emission tomography (PET) showed a bilateral adrenal mass with hemorrhage and marginal viable tumors, and posterosuperior extension of

the right adrenal tumor to the liver (Fig. 2).

Needle aspiration biopsy was carried out at the left adrenal mass, and showed individually scattered, large pleomorphic, cells expressing LCA and CD22, without immunoreactivity for Cytokeratin and CD3, consistent with large B-cell lymphoma (Fig. 3). Bone marrow study showed no lymphomatous involvement.

On day 15, following hospitalization, he sud-



Fig. 1. The initial abdomino-pelvic computerized tomography (CT) showing bilateral adrenal gland masses, with left adrenal pseudocyst formation due to hemorrhage, of the left adrenal mass. The hemorrhage extended to the perinephric area, anterior pararenal space and left paraaortic gutter.



Fig. 2. The Positron emission tomography (PET) showing bilateral adrenal mass with hemorrhage and marginal viable tumors, and posterosuperior extension, of the right adrenal tumor to the liver.

denly developed right upper quadrant pain, and laboratory test showed a decreased hemoglobin level. An immediate ultrasonography was performed, and showed an intratumoral hemorrhage of the right adrenal mass. Fortunately, the hemorrhage was controlled without further extension, probably due to fatty capsule and renal fascia surrounding the adrenal gland.

Systemic chemotherapy was started with CEOP (Cytosan, Epirubicin, Vincristine, Prednisolone) regimen. After the second CEOP chemotherapy, a follow-up abdomino-pelvic CT scan showed, residual hematomas in the resolving process, and the previous adrenal masses had nearly disappeared. However, on day 52 following hospitalization, he developed recent memory loss, obtundation, disorientation and a drowsy mental status. A brain MRI was carried out, which revealed multifocal scattered lesions, of increased signal intensity, in the right superior and middle frontal gyrus and the adjacent subcortex, the left superior frontal gyrus and subcortex, the bilateral basal ganglia's, cerebral peduncles of the mid

brain and the right middle cerebellar peduncle (Fig. 4). Brain biopsy, of the frontal lobe, showed scattered infiltration of atypical lymphocytes, expressing LCA, CD 79a and L26, but without immunoreactivity for CD 3, consistent with malignant lymphoma B-cell type (Fig. 5). The spinal

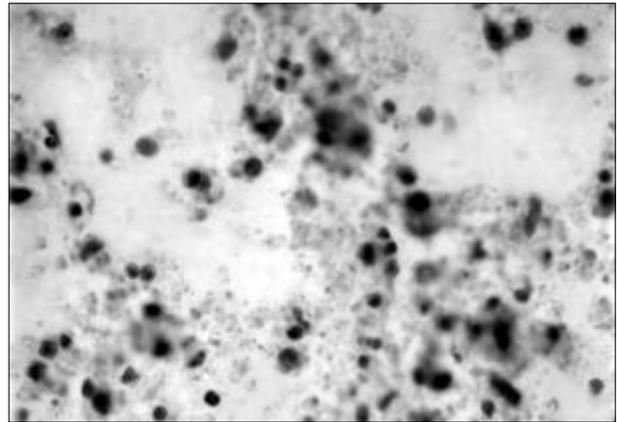


Fig. 3. The microscopic findings of aspirate in the left adrenal gland shows individually scattered large pleomorphic cells consistent with large B-cell lymphoma (H&E \times 400).

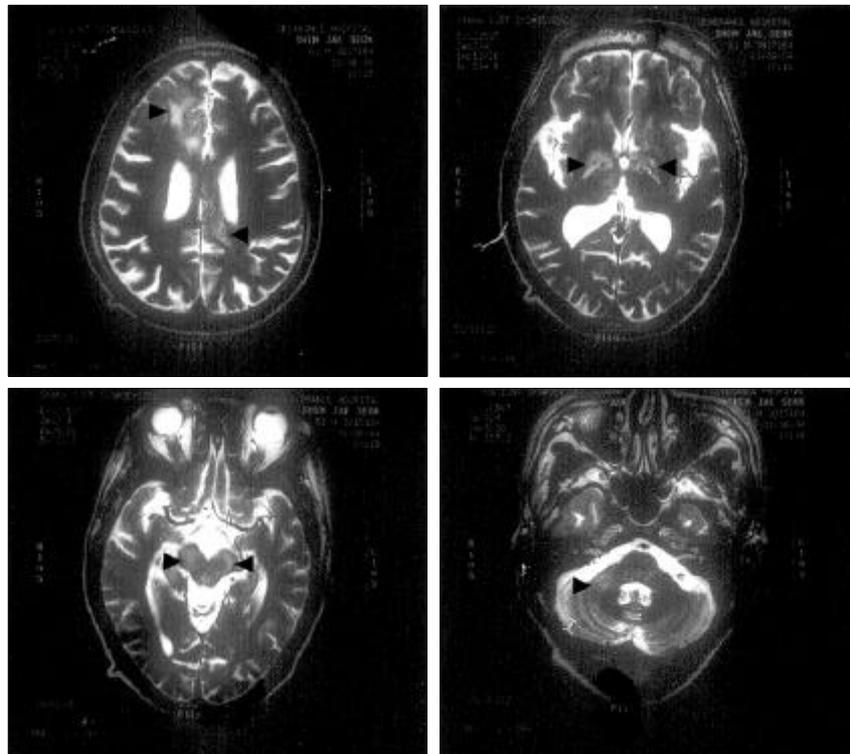


Fig. 4. The brain MRI shows multifocal scattered lesions of increased signal intensity in the right superior and middle frontal gyrus and the adjacent subcortex, the left superior frontal gyrus and subcortex, the bilateral basal ganglia, and cerebral peduncle of the mid brain and the right middle cerebellar peduncle.

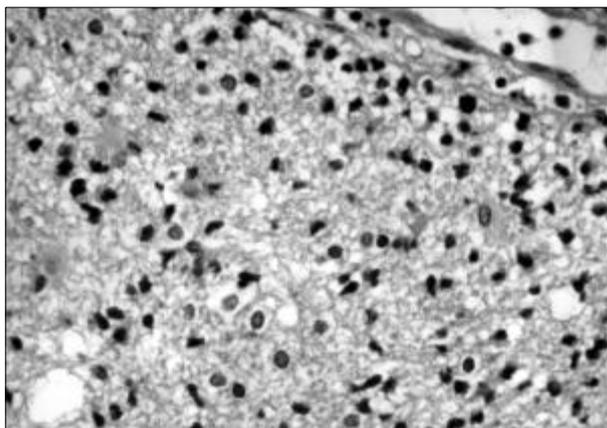


Fig. 5. The microscopic findings in the frontal lobe of the brain shows scattered infiltration of atypical lymphocytes consistent with malignant lymphoma B-cell type (H&E × 400).

fluid revealed no abnormal malignant cells. He underwent whole brain radiotherapy, with a total irradiation of 4,500cGy, and was given 5½ cycles of CEOP chemotherapy, after which the restaging, including abdomino-pelvic CT, revealed complete remission. His mental status has markedly improved, and he has become alert with nearly normalized cognitive function.

DISCUSSION

The characteristics of primary adrenal lymphoma have not been defined completely, but they usually appear with bilateral, large masses sometimes accompanied by adrenal insufficiency or hypercalcemia, with older men being most frequently affected.^{2,12,13} Wang et al. have reviewed 55 cases of PALs. According to their report, 73% of primary adrenal lymphomas were bilateral, with sizes ranging from 3 to 17 cm in diameter. Male to female ratio was 2.2 to 1, with a median age for PAL patients of 68 years, ranging from 39 to 89.¹²

Clinical symptoms of PAL include fever, weight loss, abdominal pain, and the symptoms associated with adrenal insufficiency such as weakness, skin pigmentation, hyponatremia, and hyperkalemia.^{12,14} Adrenal insufficiency can result from infiltration of the adrenal glands by malignant cells, requiring almost total replacement of the adrenal tissue before insufficiency becomes

apparent.^{2,15,16} Because destruction of approximately 90% of the adrenal cortex is necessary before adrenal insufficiency becomes apparent, not all cases of adrenal glands, involved with neoplasms, result in adrenal insufficiency.^{17,18} About 19% of patients with metastatic cancer, and enlarged adrenal glands, on imaging studies demonstrate symptomatic adrenal insufficiency.² With bilateral PAL, however, about two thirds of the patients show adrenal insufficiency.¹⁹ According to Wang et al., even small PAL can be present as Addison's crisis, suggesting that there may be no correlation between the size of tumor and adrenal insufficiency.¹² In our case, initially there was no demonstration of definite adrenal insufficiency in the adrenal function test, but over the course of therapy he developed marked general weakness, even lethargy, and laboratory study showed hyponatremia (to 127 mEq/L) and hyperkalemia (to 6.04 mEq/L). These manifestations were considered, possibly, to be attributed to adrenal insufficiency, and was rapidly corrected with corticosteroid. Thereafter, small doses of prednisolone were given continuously. Since Addisonian crisis may lead to the catastrophic consequences, immediate replacement therapy must be considered if adrenal insufficiency is suspected.²⁰

The diagnosis of PAL has been made intraoperatively, by ultrasound, at autopsy and by CT guided biopsy. Ultrasound, CT and MRI are useful tools for detection of adrenal masses. PAL appears to have a predilection for necrosis and hemorrhage, which may cause a cystic appearance on CT, and calcification has been represented as a unique feature of PAL.²¹ However, the confirmatory diagnosis is based on pathologic examination. With our case, needle aspiration biopsy (NAB) showed a large B cell lymphoma, which is the most common cell type with adrenal lymphomas.¹²

The therapeutic modalities for PAL include: surgery, combination chemotherapy, surgery followed by chemotherapy and/or radiation therapy, in addition to corticosteroid. Radiation therapy appears to be ineffective.^{12,22} There is inconclusive evidence that a combination of surgery and chemotherapy offers the best chance for long term survival.¹³ The regimens that have been used include: CHOP (cyclophosphamide, doxorubicin,

vincristine and prednisone), CHO (cyclophosphamide, doxorubicin, vincristine), prednisolone, CVP (cyclophosphamide, vincristine and prednisone) and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) with varying success.² However, prognosis of PAL has been very poor, and most patients die within 1 year.⁶ Ayako Kuyama et al. reported a case of a 69 year-old woman with PAL, who had continued in complete remission for 50 months with the CHOP regimen.²⁰

Systemic central nervous system lymphoma (SCNSL) is defined as NHL involvement, both within and outside the central nervous system (CNS).¹¹ CNS metastasis has been reported to occur in 10-20% of patient with systemic lymphoma, but incidences of CNS lymphoma have been increasing, partly due to immunodeficiency following chemotherapy with multi-agent regimen.¹⁰ With regard to SCNSL, a very rare case for PAL, also involves the CNS. CNS involvement in malignant lymphoma is a complication with high morbidity and mortality, and does not respond to standard therapy.¹⁰ According to Hollender et al., who reported 140 cases of SCNSL, the patients with CNS involvement at diagnosis, either relapse, or their progression during treatment for NHL had a median survival of 5.4, 3.8 and 1.8 months, respectively.¹¹

The most common site of CNS involvement was the leptomeninges, followed by the cerebrum and multiple metastases. The neurological symptoms, at the time of presentation, are personality change, obtundation, headache, vomiting and hemiparesis.¹⁰

The confirmatory diagnosis can be made by cerebrospinal fluid cytology or by brain imaging, followed by a biopsy of the cerebral lesion. With our case, stereotactic brain biopsy played a very important role in the diagnosis of SCNSL, because the brain MRI, which showed multifocal scattered lesions of increased signal intensity in many parts of brain, strongly suggested opportunistic infection or progressive multifocal leukoencephalopathy (PML). Without a brain biopsy, it might be very difficult to make the decision for whole brain radiotherapy, and catastrophic result could occur.

Treatment of SCNSL can be composed of systemic chemotherapy, radiotherapy and intrathecal

chemotherapy. However, a treatment modality, has not yet been clearly established. Some questions that need answering including: optimum duration of intrathecal therapy and dosage of radiotherapy. Also, neurotoxicity of these CNS-active treatments must be considered for establishing the treatment modality. Leukoencephalopathy is a well known late neurotoxicity. With primary central nervous system lymphoma (PCNSL), a combination of radiotherapy and chemotherapy, based on high-dose methotrexate (HD-MTX), seems to be the most efficient in terms of survival rates.²³ However, the neurotoxicity of this combination therapy is substantial, especially with patient over 60. The neurotoxicity is believed, in part, to be due to the breakdown of the blood-brain barrier, initiated by the cranial irradiation, allowing neurotoxic agents greater penetration into normal brain structures, so administration of drugs prior to cranial irradiation is thought to be less neurotoxic than when the drug follows cranial irradiation, or are given concurrently. However, it was reported that even though methotrexate was administered before whole brain radiotherapy, patients 60 years of age or older at diagnosis had a 100% incidence of late neurotoxicity 24 months after diagnosis, whereas those under 60 years of age had a maximal risk of 30% at 96 months.²⁴⁻²⁶ Therefore, recently some investigators are trying chemotherapy alone for PCNSL. Standard lymphoma regimens, like CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOD (cyclophosphamide, doxorubicin, vincristine and dexamethasone), failed to produce sustained remissions in PCNSL. These failures must be partly attributed to the inability of these drugs to penetrate a relatively intact blood-brain barrier. Drugs that penetrate the blood-brain barrier are essential. Freilich et al. used high-doses of methotrexate, with vincristine and procarbazine, or thiotepa, for PCNSL, and observed a response of 92% of patients, with a median survival of 30 months without neurotoxicity.^{26,27}

As with PCNSL, neurotoxicity as a side effect of CNS-active therapies can also complicate the treatment of SCNSL, therefore treatment modalities that minimize this complication, as well as controlling the disease, are required for the treatment

of SCNSL. It is also of concern that CNS involvement was not the primary cause of death in the majority of patients with SCNSL. The mean survival of patients with CNS involvement seemed to depend more on the control of the systemic disease, not the control of CNS involvement.¹⁰

Following 5½ cycles of CEOP chemotherapy, and whole brain radiotherapy of total 4,500cGy, our patient has survived 6 months, and has become alert with nearly normalized cognitive function. We have experienced a very rare case of PAL with CNS involvement, and there are many aspects to be uncovered about treatments of PAL and SCNSL.

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