

## Bilateral Adrenal Primary Diffuse Large B-Cell Lymphoma not Accompanied by Adrenal Insufficiency: A Report of Two Cases

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### Abstract:

Primary adrenal lymphoma (PAL) is uncommon in clinical settings, which is considered a rare high grade malignant lymphoma with a poor prognosis, patients with bilateral mass are rarer, and patients with normal adrenal function are extremely rare. We present 2 cases of patients with bilateral adrenal primary diffuse large B-cell lymphoma (PA-DLBCL) whose adrenal functions were normal. 2 patients were treated with unilateral adrenalectomy and a combination of chemotherapy. We summarized cases, reviewed the literature and discussed important issues with regard to the pathology change, diagnosis, treatment and prognosis.

**Keywords:** Bilateral primary adrenal lymphoma; Diffuse large B-cell lymphoma

### Case Report 1

A 64-year-old man was admitted into hospital because of bilateral adrenal mass were found during a body check-up. There are not special history of present illness and previous medical history in this patient, such as hypertension, diabetes, and other tumors, and there are not similar relevant diseases in his families. On examination: blood pressure 166/88 mmHg, heart rate 88/min, respiration rate 21/min, superficial lymph nodes swelling (-), heart, lungs, abdominal pathological sign (-). Lab findings: routine blood and urine check were normal; liver and kidney function and electrolytes level were normal; the blood glucose was 6.4 mmol/L (normal: 3.9-6.1mmol/L);

Aldosterone 74.02 pg/ml (normal: 73-239 pg/ml); Cortisol 330.34 nmol/L; ACTH 80.38 pg/ml; urine VMA divided into three times as 5.13, 6.41, 3.20 mg/24h. CXR: no abnormalities. Abdominal ultrasound: hypoechoic solid mass revealed on bilateral adrenal gland, right side 13 cm × 10 cm × 5 cm, left side 8.5 cm × 6 cm × 6.5 cm. CT scanhomogenous soft tissue mass on both adrenal area and entirely replacing adrenal gland, CT scan done with contrast enhancements was not obvious changes, right side 13 cm × 10 cm × 5 cm, left side 8.5 cm × 6 cm × 6.5 cm (Figures 1A-1C).

Pathology examination (right side): Gross photograph: a homogenous solid mass measured 13 cm × 10 cm × 5 cm, demonstrated a fish flesh-like cut surface, between gray-red and gray-white color, medium texture, ill-defined lobulation, with little hemorrhage and necrosis (Figure 2).

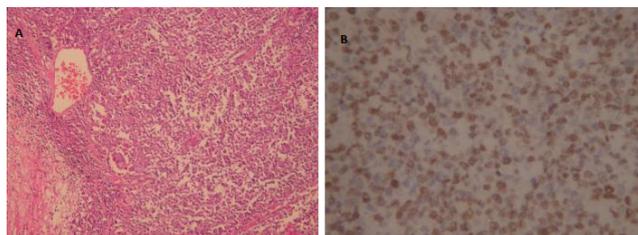


**Figure 1 (A-C):** CT scan about PAL of bilateral adrenal mass and kidney (transverse section); CT scan about PAL of bilateral adrenal mass (coronal section); CT scan about PAL of bilateral adrenal mass (transverse section).



**Figure 2:** Gross photograph of right adrenal, entirely replaced by a homogenous mass, with a fish flesh-like cut surface and ill-defined lobulation.

Microscope examination: diffuse distribution of tumor, similar rounded size, small amount of nuclear shaped cytoplasm could be observed scattered around the tumor cells. IHC: Bcl1-2 (+), Bcl-6 (weak+), CD20 (+), MUM-1 (+), CD3 (reactive T+), CD43 (partly+), CD138 (-), Kappa (-), Ki-67 (+70%), Lambda (+), CydinD1 (-), Mpo (-) (Figures 3A and 3B).



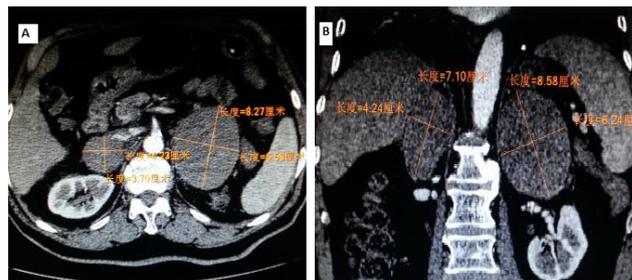
**Figure 3(A-B):** Cell block of aspirated material from right adrenal (H&E x200); Ki-67.

Surgical findings: Tumor found above kidney, right kidney obviously displaced downwards by compression, renal pedicle vessel are displaced by tumor, proximal to the vena cava, medium in texture, poor blood supply, no obvious adhesion with surrounding tissues, size 13 cm × 10 cm × 5 cm, no swollen lymph nodes were observed around tumor, Complete tumor resection. Left side did not undergo surgery. Post operation therapy: chemotherapy with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone). Follow up in 9 months.

## Case Report 2

A 77-year-old man was admitted to our hospital with a 3-month history of abdominal pain. There are not similar relevant diseases in his patients' families. Previous medical history was unremarkable other than slight hypertension and there are not special history of present illness. On examination: His blood pressure was 170/100 mmHg, heart rate 81/min, respiration rate 19/min, superficial lymph nodes swelling (-), heart, lungs, abdominal pathological sign (-). Lab findings: Routine blood and urine check normal; liver and kidney function and electrolytes level normal; blood glucose 9.8 mmol/L

(normal: 3.9-6.1 mmol/L); The serum epinephrine concentration was 28.4 pg/ml (normal 0-20 pg/ml) and the norepinephrine(NE) concentration was 865.3 pg/ml (normal 1-100 pg/mL). Aldosterone 104.62 pg/ml (normal: 73-239 pg/ml); Cortisol 420.34 nmol/L; ACTH 94.25 pg/ml; urine VMA divided into three times as 8.83, 6.09, 5.77mg/24 h. CT scan showed bilateral adrenal glands solid masses. Uniformed density, CT scan with contrast enhancements was not obvious changes, right side 3.7 cm × 4.2 cm × 7.1 cm, left side 11.6 cm × 8.2 cm × 6.5 cm (Figures 4A and 4B).



**Figure 4 (A-B):** CT scan about PAL of bilateral adrenal mass (transverse section); CT scan about PAL of bilateral adrenal mass (coronal section).

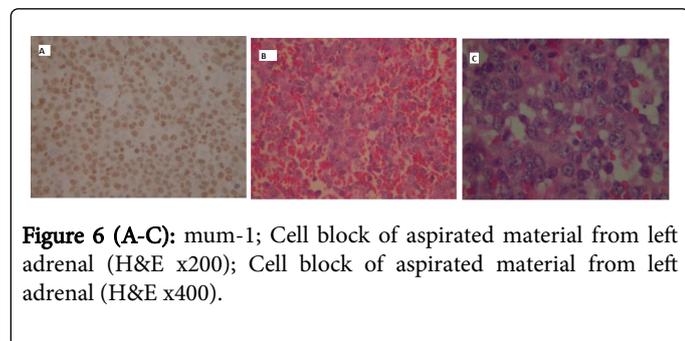
Surgical findings: The patient underwent left adrenalectomy, tumor found above kidney, left kidney displaced downwards by compression, resection for left adrenal tumor that entirely replaced adrenal gland and a little adhesion with surrounding tissues; no swollen lymph nodes were observed around tumor. Medium in texture, rich blood supply, size 11.6 cm × 8.2 cm × 6.5 cm. Complete tumor resection, cut surface of tumor demonstrated a gray-red and gray-yellow color, right side did not undergo surgery. He received 2 cycles of chemotherapy with CHOP after operation; however, he died of abdominal metastases 3 months postoperatively. pathology examination (left side): Gross photograph: size 11.6 cm × 8.2 cm × 6.5 cm, cut surface between gray-red and gray-yellow color, medium texture, with a little hemorrhage and necrosis (Figure 5).



**Figure 5:** Gross photograph of left adrenal, entirely replaced by a homogenous mass.

Microscope examination: showed a relative diffuse population of medium to large lymphoid cells. IHC: Bcl-2 (+), Bcl-6 (+), CD10 (-),

CD20 (+), CD3 (-), CD5 (-), CD21 (-), Ki-67 (+80%), MUM-1 (+) (Figures 6A-6C).



**Figure 6 (A-C):** mum-1; Cell block of aspirated material from left adrenal (H&E x200); Cell block of aspirated material from left adrenal (H&E x400).

## Discussion

### Background and pathogenesis

PAL is uncommon in clinical setting, and it is often related to adrenal insufficiency, However, PAL not accompanied by decrease in adrenal function is extremely rare. Primary adrenal diffuse large B-cell

lymphoma (PA-DLBCL) generally originated from lymphatic tissue hyperplasia and led to malignancy. it is a type of extra nodal lymphoma, with a poor prognosis, frequently observed in the older, male than female, presented as fever, limb pain, weight loss, fatigue, decrease in adrenal function. The disease is rare, there are more cases of secondary type than primary types. Most of PA-DLBCL do not have any endocrine functions, they would not produce any signs of hypertension or any commonly seen signs of adrenal diseases, symptoms only appear when the tumor grow large enough to compress against neighbouring organs [1]. The adrenal gland lack any lymph tissue, current research points out that malignant adrenal tumors are caused by undifferentiated mesenchymal cells. Bilateral PA-DLBCL causes a decrease in adrenal function when the tumor ruptures, patients with normal adrenal function are extremely rare, these 2 cases of study discusses about the rarity of normal adrenal function. PA-DLBCL is higher in the older according to documented cases (Table 1). Most of PA-DLBCL is accompanied by decrease in adrenal function, and most literature about PAL is only one case report, Bin Gu et al. reported a patient with bilateral PA-DLBCL who has normal adrenal function [2], but there two cases of PA-DLBCL in this paper and both of patients are not accompanied by decrease in adrenal function.

Num	Year	Age/sex	Reference	Size of tumor (L/R) cm	Initial symptoms	Treatment	Outcome
1	2009	52/M	Kyung Min Kim [13]	4 × 2/6 × 3	Fatigue, Fever	CHOP	CR
2	2012	60/F	Jakob Holm [17]	4 × 7/6 × 3	Nausea, Vomit, Fatigue, Fever, Wt loss	Surgery	Died 3 mo later
3	2009	77/F	Luisa Barzon [3]	7 × 7/5 × 5	Wt loss	No treatment	Died 5 mo later
4	2013	63/M	Yasuhiro [16]	3 × 3/1 × 1	Fever	CHOP	Died 8 mo later
5	2010	58/M	Kazuhiko [11]	10 × 10/10 × 10	Anemia, Liver dysfunction, Back pain	CHOP; Radiation	Brain Me 5 mo later, Died 9 mo later
6	2003	66/F	Ayurni [6]	3 × 3/5 × 5	Fatigue, Nausea, Vomit, Diarrhea, Wt loss	CHOP	Brain Me and died 11 mo later
7	2012	54/F	Quan Wang [7]	20 × 15/3 × 3	Abdominal pain, Hypertension	Bilateral adrenalectomy; CHOP	Died 8 mo later
8	2009	63/M	Bin Gu [2]	13 × 7/8 × 5	Abnormal abdominal Ultrasound findings	Bilateral adrenalectomy; CHOP	Un
9	2009	50/M	Vineet Narang [10]	4 × 3/6 × 4	Fatigue, Body ache, Wt loss	R:Adrenalectomy, L: biopsy	Un

**Table 1:** List of documented cases of primary bilateral adrenal diffuse large B-cell lymphoma in literature of this article; CR: Complete Remission; L: Left; R: Right; mo: Month; NM: Not Mentioned; Wt: Weight; Un: Uneventful Recovery; Me: Metastasis.

This disease is idiopathic, Luisa Barzon reported that this disease might be related to EVB and JCV infections [3]. There are journals which reported a rare condition of multicentric Castleman's disease (MCD) accompanied by cervical diffuse large B-cell non-Hodgkin's lymphoma [4], MCD is a kind of disseminating lymphatic disease, and death is always caused by infection or malignant tumors such as lymphoma or Kaposi's sarcoma [5]. PA-DLBCL clinical presentation is

complex; most common are back pain, upper abdominal pain, weight loss, fever and decrease in adrenal function [6]. It is easily misdiagnosed as other diseases of the retroperitoneal space, as it is hard to differentiate with adrenal tumors, especially when the same kidney is affected, such as adrenal cortical carcinoma, pheochromocytoma, neuroendocrine carcinoma, melanoma, secondary lymphoma. Bilateral PA-DLBCL usually presented as rapid

decrease in adrenal function, caused by high levels of serum soluble interleukin receptors and LDH [7].

## Diagnosis

We mentioned nine cases of PA-DLBCL in literature of this article (Table1), all of cases are bilateral adrenal lymphoma, and the symptoms, treatment, outcome are representative. When PA-DLBCL is suspected, an ultrasound, CT scan or MRI can be done to confirm diagnosis, if any symptoms appear and a mass could be observed from the CT scan, the possibility of PA-DLBCL should be considered.

Also, a CT guided biopsy has a higher value of diagnosis [8], CT characteristics of PA-DLBCL are a larger soft tissue mass, homogenous density, CT scan done with contrast enhancements was not obvious changes, and laparoscopy could be a diagnostic or therapeutic tool. Under microscopy, the tumor mainly grows diffusely, poorly differentiated cells show obvious atypia and different levels of differentiation, and usually large area of necrosis could be observed. IHC techniques could be used for diagnosis differentiation purposes. It is similar to intra nodular lymphomas, but combining both morphology and the phenotype of the disease, it could be differentiated clearly, and complete history taking, cell count phenotype can be used to confirm diagnosis [9].

## Treatment

PA-DLBCL is an invasive and highly malignant lymphoma, it has a poor prognosis. Surgery treatment could decrease the tumor's burden on the patient, but it is difficult to completely resect the tumor or to completely treat the disease, therefore, an extra step has to be taken after surgery. As soon as PA-DLBCL is diagnosed, the first choice of treatment should be CHOP combined with either chemotherapy or radiotherapy [10]. Early diagnosis and early combined therapy are heavily related to the patient's prognosis, 35%-40% of patients could be cured in accordance with above-mentioned. But long term survival rates do not exceed 40%, most patients are not sensitive to therapy, unable to reach CR, the subsequent treatment is difficult, most patients died caused by tumor relapse or metastasis.

The age factor is related to the prognosis, the higher the age, the worst the prognosis [11]. According to reports, the average survival time is 15 months, lower than DLBCL on other organs, the reasons could be the larger size of the tumor, the rearranging of the BCL-6 gene, the rich supply of sinusoids and the complex endocrine function might be related [12]. This study summarized reports of bilateral PA-DLBCL, most patients died 3-9 months after treatment due to metastasis, relapse. In this paper, the patient in case 2 died because of abdominal metastases 3 months postoperatively, which accorded with the feature of PA-DLBCL that has a poor prognosis. And the patient in case 1 had not evaluated because of short follow-up time. Kyung Min Kim et al. reported a series of PA-DLBCL cured through Rituximab-CHOP (R-CHOP) chemotherapy, these cases were confirmed of diagnosis through CT guided needle biopsy, and did not undergo surgery treatment [13]. Ana Mozos et al. summarized 10 cases of PA-DLBCL patients, which 5 are affected bilaterally, during 4.5 months of random visitations, 7 cases died of lymphoma, 1 died of unrelated disease, 1 survived with the disease, 1 cured and survived [14]. Satoshi Ichikawa et al. analyzed 7 cases of PA-DLBCL patients, 5 affected bilaterally, underwent R-CHOP chemotherapy, 2 year survival rate was 57% [15]. Yu Ri Kim et al. analyzed 31 cases of PA-DLBCL, considered R-CHOP is an effective first line treatment, and they thought age, size

of tumor, damage of adrenal gland function are relates to prognosis [16]. Yasuhiro Nakashima et al. reported a case of PA-DLBCL, used self-produced hematopoietic stem cells implants before R-CHOP and a large dose of methotrexate as treatment, results were obvious, adrenal function returned to normal after treatment [17]. Jacob Holm reported that adrenal lymphoma is mostly diffused B-cell lymphoma. PA-DLBCL usually occur as bilateral adrenal glands up to 70%, it has a poor prognosis, old age, tumor size, LDH levels, adrenal gland function are evidence of a poor prognosis [18].

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