

## Original Article

# Primary renal non-Hodgkin's lymphoma: a clinicopathologic study of six cases and review of the literature

Hua Xiang, Weixiang Zhong, Qiqi Gao, Yanfeng Bai, Zhaoming Wang

Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

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**Abstract:** Primary renal lymphoma (PRL) is a rare disease and the information about pathogenesis, prognosis and treatment for PRL is extremely limited. We describe six patients primary appearing with symptoms or signs related to lymphoma predominantly or exclusively involving one kidney. The patients including two males and four females, aged at 55-73 years (median, 64 years). Two of them had other malignant lesion previously or simultaneously. Abdominal and/or flank pain were the most common symptoms. Five cases were initially considered to be primary carcinomas of the kidney on clinical evaluation, and the other one was diagnosed as hydronephrosis. The lymphomas were subclassified as diffuse large B-cell lymphoma (DLBCL, five cases) and small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL, one case). Extrarenal lesions were excluded by bone marrow aspiration or biopsy, thoracoabdominal computed tomography (CT) and positron-emission tomographic CT. According to the Ann Arbor system, four patients were diagnosed as stage IE non-Hodgkin's lymphoma (NHL); the other two were diagnosed as stage IIE. Radical nephrectomy was performed in four patients, and two of them subsequently received combination chemotherapy. The other two received chemotherapy immediately after kidney biopsy showing DLBCL. After a median follow-up time of 15.5 months (6 to 73 months), two patients were alive, and the other patients died from progressive disease 6 to 73 months after diagnosis. PRL is a rare disease with undefined etiology and pathogenesis, and there is no standardized treatment for it till now. According to our experience and other recently published studies, we hypothesize that early diagnosis combined with CHOP + rituximab could improve the prognosis of the patients.

**Keywords:** Renal neoplasms, non-Hodgkin's lymphoma, prognosis

## Introduction

Primary renal lymphoma (PRL) is a controversial and very rare disease, accounting for less than 1 percent of primary extranodal lymphomas. It is defined as an NHL arising in the renal parenchyma, not resulting from invasion of an adjacent lymphomatous mass and without evidence of systemic involvement [1, 2]. In 1980, Coggins reported the first patient diagnosed with a PRL [3]. Since then, many cases have been reported in the medical literatures, but clear diagnostic criteria have not yet been established. Subsequent paper has demonstrated that most of the reported cases are questionable because of incomplete staging or the presence of extrarenal disease [4]. As the

absence of clinical trials due to a shortage of cases, there is no standardized treatment for PRL. The earlier limited literature reviews reported a poor prognosis of patients with PRL, with a median survival less than one year after diagnosis [5, 6]. However, the majority of recent case reports have suggested a survival more than one year [7-10]. Herein, we report six cases of PRL, emphasizing on their clinicopathologic features and clinical outcomes.

## Materials and methods

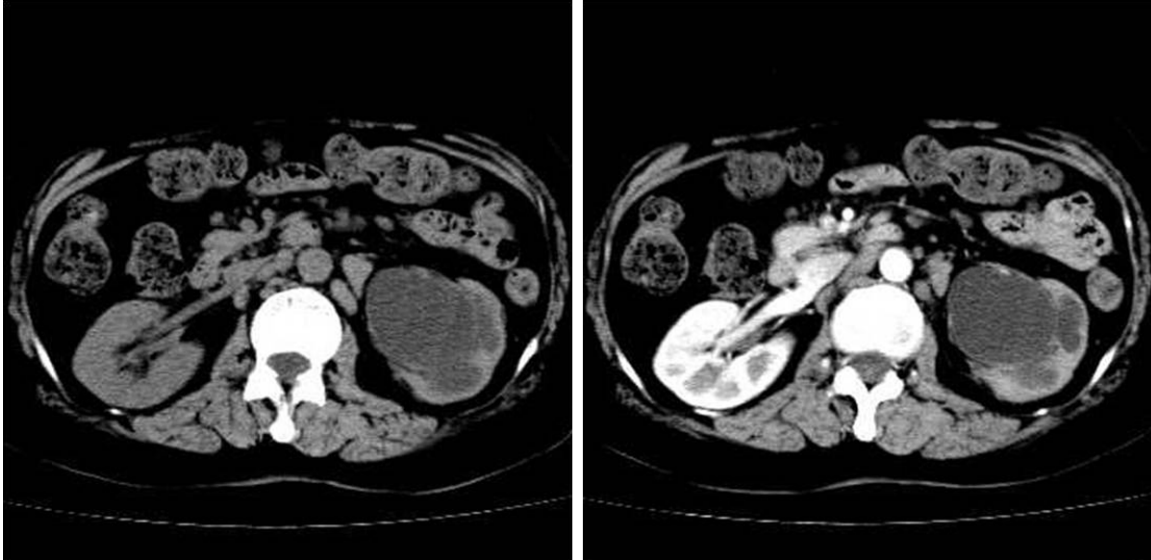
Six cases of PRL were identified in a search of the archive files of the author's institutions from 2005 to 2015 years. Available clinical information was recorded, including patient's age, gen-

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**Table 1.** Clinicopathologic features of 6 patients with primary renal lymphoma

Case	Sex/Age	Size (cm)	Specimen obtained by	Pathological diagnosis	History of malignancy	Stage	Treatment	Chemotherapy Protocols (cycles)	Follow-up	
									Results	During of time (months)
1	F/55	3.2x2.5	FNAB	DLBCL (non-GCB type)	none	IE	chemotherapy	CHOP (6); MINE (6)	death	39
2	F/67	5x7	nephrectomy	DLBCL (non-GCB type), with extension into the left psoas muscle	none	IE	radical nephrectomy plus chemotherapy	CHOP (8); R-CHOP (6)	death	73
3	M/63	11x6	nephrectomy	DLBCL (non-GCB type), with one renal pedicle lymph node was early metastatic involvement	coexistence with IUCB (T <sub>3</sub> N <sub>0</sub> M <sub>0</sub> )	IIE	radical nephrectomy	DHAP (4); none	death	6
4	M/62	10x10	nephrectomy	DLBCL (non-GCB type), with extension into perinephric fat	none	IE	radical nephrectomy plus chemotherapy	CHOP (6)	death	13
5	F/73	5x5.5	FNAB	DLBCL (non-GCB type)	none	IIE	chemotherapy	R-CHOP (6); GDP (1)	survival	18
6	F/65	none	nephrectomy	SLL/CLL	radical cystectomy for IUCB 6 years ago (T <sub>2a</sub> N <sub>0</sub> M <sub>0</sub> )	IE	radical nephrectomy	none	survival	12

F, female; M, male; FNAB, fine needle aspiration biopsy; DLBCL, Diffuse large B-cell lymphoma; SLL/CLL, Small lymphocytic lymphoma/Chronic lymphocytic leukemia; IUCB, invasive urothelial carcinoma of the bladder.



**Figure 1.** Computed tomography scan revealed that the cortex became thin, the enhancement in renal parenchyma significantly decreased, and the collection system and ureter became dilated and hydronephrotic of the left kidney in case 6.

der, clinical presentation, history of malignancy, tumor size, clinical stages, treatment, and scheduled follow-up data. Macroscopic findings were obtained from surgical pathology reports. 4  $\mu$ m-thick, 4% buffered formalin-fixed, paraffin-embedded sections of all cases were stained with hematoxylin and eosin (H&E) for routine microscopic examination. Immunohistochemical analysis of all cases was performed using the avidin-biotin complex immunoperoxidase technique with a panel of commercially available primary antibodies to the following antigens: cytokeratins (AE1/AE3), CD3, CD20, CD79a, CD30 (Ki-1), CD5, CD10, Bcl-2, Bcl-6, ALK, EBV, MUM1, ki-67, PAX-5, CD21, CD23, Cyclin D1, Kappa ( $\kappa$ ), Lambda ( $\lambda$ ) and C-myc. Appropriate positive and negative controls were used in each case.

## Results

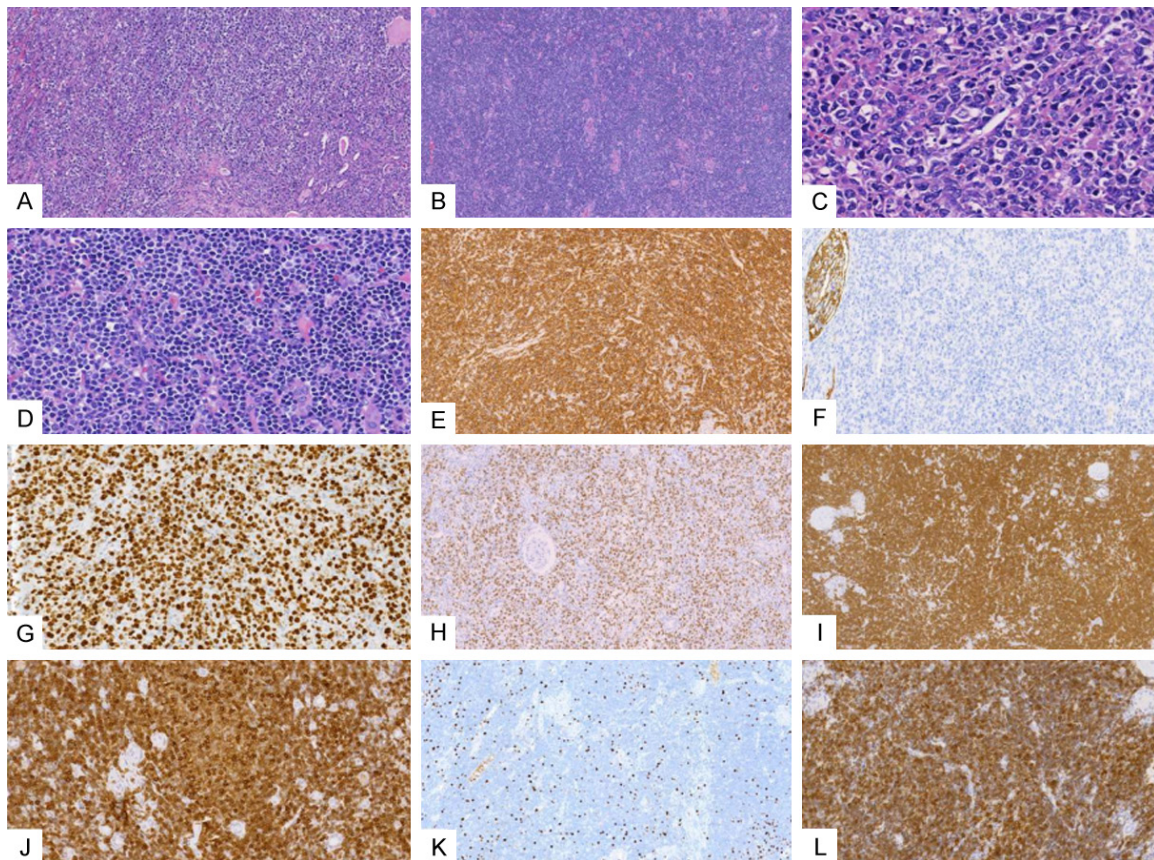
### Clinical features

The clinical and pathologic findings of the six cases of PRL are summarized in **Table 1**. There were two males and four females with age at admission ranging 55 to 73 years (median, 64 years). The main clinical manifestations were flank and/or abdominal pain (five patients), and fever (one patient). All tumors located in the left kidney. Five cases were initially considered on

clinical evaluation to be primary carcinomas of the kidney, and the last one was taken as hydronephrosis. Radical nephrectomy was performed on four patients, two of them subsequently received combination chemotherapy. Case 3 was a 63-year-old man, who simultaneously had invasive urothelial carcinoma of the bladder (IUCB, T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>), couldn't tolerate the side effects of chemotherapy, and only received surgery. In case 6, the patient had been performed radical cystectomy because of IUCB (T<sub>2a</sub>N<sub>0</sub>M<sub>0</sub>) 6 years ago, 3 years ago she had been found hydronephrosis of left kidney and nephrostomy had been performed 9 months ago. She had the symptoms of left flank swelling pain and fever for 10 days. Contrast material-enhanced CT scan and glomerular filtration rate (GFR) measurement revealed hydronephrectasia and renal failure of left kidney (**Figure 1**), so she received left nephrectomy. Considering of the patient's age, the adverse events of chemotherapy and good prognosis of this type of lymphoma, she received closely monitoring of her condition without additional treatment after radical nephrectomy. Case 1 was a 55-year-old woman, who had the symptoms of fever and abdominal pain since past two weeks. A contrast-enhanced CT scan showed an infiltrative mass, measuring about 3.2×2.5 cm in size, arising from the lower pole of left kidney without any nodal involvement.



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**Figure 2.** Histologic and immunohistochemical findings. Low-power magnification demonstrates tumor composed of atypical lymphoid cells diffusely infiltrating the renal parenchyma (A and B). Higher-power magnification demonstrates a widespread proliferation of large atypical lymphoid cells with increased nuclear-cytoplasmic ratio, prominent nucleoli, and mitotic figures in five cases (C). Tumor was composed of small uniform lymphoid cells in case 6 (D). The Lymphoma cells were positive for CD20 (E), MUM-1 (H), and negative for CD10 (F), with high proliferation index (G) in five cases. The Lymphoma cells were positive for CD20 (I), CD5 (J) and CD23 (L), with low proliferation index (K) in case 6. (A, B, E, H, I and K: x 100; C and D: x 400; F, G, J and L: x 200).

Case 5 was a 73-year-old female, who had the symptoms of abdominal pain, in local hospital, the abdominal CT showed a homogeneously enhancing mass lesion about 5×5.5 cm in size, which occupied upper and mid pole of the left kidney. Two enlarged lymph nodes appeared 1 to 2 cm in size in the renal hilar. Chemotherapy was administrated immediately after imaging-guided fine needle aspiration biopsy (FNAB) of kidney in cases 1 and 5.

Further staging by bone marrow aspiration or biopsy and imaging study, such as thoracoabdominal CT or positron-emission tomographic CT (PET/CT), excluded extrarenal disease in all cases. According to the Ann Arbor system, four patients were diagnosed with stage IE non-Hodgkin's lymphoma (NHL), B-cell type, and the

others were diagnosed with stage IIE NHL, B-cell type. After a median follow-up time of 15.5 months (6 to 73 months), two patients were alive, and the other patients died of progressive disease 6 to 73 months after diagnosis.

### *Pathologic findings*

Gross examination of nephrectomy specimens in case 2, 3 and 4 revealed fleshy or firm, yellowish-white tumors, from 7 to 11 cm in greatest dimensions with varying degrees of hemorrhage and necrosis, occupied the renal parenchyma that occasionally invaded perinephric fat and adjacent structures. In case 6, the left kidney was enlarged diffusely, accompanied with hydronephrosis. Low-magnification micro-

scopic examination showed that renal parenchyma and adjoining neoplasm were composed of diffuse sheets of a monotonous population of atypical lymphoid cells, tending to spare normal structures, and even cases with grossly circumscribed nodules demonstrate this pattern of growth histologically (**Figure 2A, 2B**). Areas of necrosis and hemorrhage were found interspersing within the tumor cells. Under high-power microscope, H&E sections of five lesions revealed a widespread proliferation of large, atypical neoplastic lymphoid cells with increased nuclear-cytoplasmic ratio, prominent nucleoli, and mitotic figures (**Figure 2C**). In case 6, the tumor was composed of small uniform lymphoid cells diffusely infiltrating the renal parenchyma (**Figure 2D**).

In immunohistochemical studies of case 1 to 5, the neoplastic lymphoid cells were positive for CD20, PAX-5, CD79a, Bcl-6 and MUM-1, but negative for CD10, CD21, CD23, CD30, CD3, CD5, EBV, ALK, Cyclin D1 and C-myc (**Figure 2E-H**). In addition, approximately 70% to 90% of nuclei were positive for ki-67. The histological analysis led to the diagnosis of diffuse large B-cell lymphoma (DLBCL), non-GCB type. In case 6, the tumor cells were positive for CD20, CD79a, CD5, Bcl-2, CD23 and negative for CD3, Bcl-6, CD10, Cyclin D1. The proliferation index as detected by ki-67 was 10% (**Figure 2I-L**). These findings were consistent with a diagnosis of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL).

### Discussion

It has been a controversial issue whether PRL is a primary disease or the first manifestation of a rapidly progressive systemic disease. Because renal parenchyma lacks lymphatic tissue, some investigators doubted the presence of PRL [6]. Nevertheless, several subsequent reports with adequate roentgenographic information supported the presence of primary lymphoma of the kidney [11, 12]. The following diagnostic criteria must be satisfied for a diagnosis of PRL: (1) physical examination should exclude any extrarenal primary site, (2) CT of abdomen and thorax must rule out extrarenal disease, (3) a tissue diagnosis is necessary, (4) a peripheral blood smear must demonstrate a normal pattern, (5) a bone marrow trephine and an aspirate must show normal patterns [5, 13-16]. As described above, all of the present

cases fulfilled the criteria for the diagnosis of PRL.

PRL is a rare disease, therefore, large-scale study on PRL has rarely been done, and information regarding PRL remains extremely limited. Because renal tissue usually contains no lymphoid tissues, it has been suggested that a primary renal lymphoma may originate in the lymph nodes of the renal sinus or in the lymphatic network of the renal capsule and that it forms cords of cells that subsequently penetrate the renal parenchyma [17, 18]. In other extranodal organs, lymphoid tissues formed by chronic inflammation are regarded as the sources for development of malignant lymphoma [13]. With the exception for case 6, however, we could not confirm the presence of lymphoid tissue. Review of the medical histories in most of the present cases did not reveal any particular past history, including chronic inflammatory diseases or autoimmune disease.

PRL is usually seen in adults in their sixties, with a slightly male preponderant, although females were majority in our study as well as in the cases reported by Okuno et al [5]. Renal involvement is normally unilateral. The clinical presentation is similar to other renal malignancies. Flank pain is the most common presenting symptom [5, 11, 13, 19]. Other symptoms include abdominal mass, hematuria, and systemic symptoms such as fever, weight loss, and fatigue. Renal insufficiency developed during the course in case 6 with unilateral renal involvement in this study. In previous reports, renal insufficiency usually occurred in patients with parenchymal involvement of bilateral kidneys [20-24]. In addition, it has been reported in literatures that some PRL have a history of one or more other prior, concomitant or subsequent malignancy [25, 26]. Two patients in this study also have other type of malignant tumors simultaneously (case 6) or previously (case 3) on the diagnosis of PRL. The cause of these phenomena is still unclear.

Although the diagnosis of PRL can be challenging, an awareness of the spectrum of imaging findings can help to differentiate lymphoma from other renal malignancies such as renal cell carcinoma (RCC) and can lead to appropriate recommendations for biopsy. An accurate diagnosis is critical because renal lymphoma is treated by chemotherapy whereas RCC is typi-



cally managed by surgery or ablation [27]. On ultrasound, renal lymphoma is usually hypoechoic or anechoic. Diffuse nephromegaly may be also seen. However, sonographic appearances of renal lymphoma are usually nonspecific and lead to further investigation with CT or MRI. A PRL usually appears as a hypovascular mass with a minimal and a characteristic homogeneous contrast enhancement on CT scan [16, 27]. This feature can help to differentiate it from the more common hypervascular tumors such as RCC, oncocytoma, and angiomyolipoma. Although CT is the most common imaging modality used for the evaluation of renal lymphoma, MRI may be useful in patients with renal insufficiency or a history of contrast medium allergy or in those in whom there is a heightened concern for radiation exposure such as children and young adults. Like most malignant and inflammatory renal lesions, lymphoma exhibits hypointense signal on T1-weighted MR images and is slightly hypointense or isointense relative to normal renal cortex on T2-weighted images. In addition, MR imaging has proved superior to CT in depicting involvement of the bone marrow [15]. PET/CT may be useful in the diagnosis because renal lymphoma is intensely FDG-avid whereas RCC including the papillary and chromophobe subtypes may not show intense FDG uptake [27]. However, a percutaneous biopsy is always required to confirm the diagnosis. In addition, PET/CT is also useful in the staging of lymphomas and assessing response to therapy [15].

Etiology of PRL is still unknown and many classes of NHL have been described. Large cell lymphoma is more common than small cell lymphoma and Hodgkin's lymphoma [28]. Diffuse large B-cell lymphoma (DLBCL) is the most common histological type of PRL, and almost all subtypes have been described [19, 29, 30]. Systemic chemotherapy is currently the first treatment option for PRL. Although most authors believe that the CHOP protocol should be an elective option (as it is in non-Hodgkin's B-cell lymphoma), there is no agreement upon standard treatment regimen for PRL. The earlier reviews report a poor prognosis for patients with PRL, with a median survival of less than one year [5, 13], but the recent reports suggest a better survival probably due to the addition of rituximab to the combination chemotherapy [7, 9, 31]. Two cases (case 2 and 5) in our series received R-CHOP protocol. At the time of this

writing, case 5 remains disease free 18 months after initial diagnosis, and case 2 died from progressive disease 73 months after her diagnosis.

Besides DLBCL, the other relatively common type of primary renal non-Hodgkin's B-cell lymphoma is marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) [1, 32]. MALT-type lymphoma have a striking tendency to be confined at diagnosis and may be cured with local therapy, although the treatment of MALT lymphoma arising from the kidney has not been established, [33]. The 5-year overall survival and incidence reports of lymphoma-related death of patients with MALT lymphomas arising in the genitourinary tract were 75.6% and 12.4%, respectively [34]. Although the accurate prognosis of patients with MALT lymphoma arising from the kidney is unknown, they may be within the aforementioned ranges. Some cases of renal MALT lymphoma without any postoperative recurrence have been reported [1, 33, 35]. Except for DLBCL, case 6 had been diagnosed of SLL/CLL, who received close monitoring without additional treatment after radical nephrectomy, and had a disease-free survival about 12 months in the subsequent follow-up. To the best of our knowledge, this type of PRL has never been reported in literature.

In summary, PRL is a rare disease and there is currently no standard treatment. The treatment protocol and prognosis depend on histological subtype and clinical stages. Based on our experience and other recently published literatures, we hypothesize that early diagnosis combined with CHOP + rituximab could improve the prognosis of the patients.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Hua Xiang, Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, Zhejiang, China. Tel: +86-571-87236362; Fax: +86-571-87236364; E-mail: Xianghua820@hotmail.com

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