Primary renal lymphoma: A case report and literature review

XIAODONG CHEN[1*], DANFEI HU[2*], LAIFU FANG[3], YICHEN CHEN[4], XIAOHANG CHE[4], JIN TAO[4], GUOBIN WENG[1] and XIAOLEI YE[4]

[1]Department of Urology, Ningbo Urology and Nephrology Hospital, Ningbo University, Ningbo, Zhejiang 315100; [2]Department of Radiation Therapy, Ningbo Medical Treatment Center Lihuili Hospital; [3]Department of Pathology, Ningbo Yin Zhou Hospital; [4]Division of Drugs and Pharmacology, Ningbo Institute of Medical Sciences, Ningbo, Zhejiang 315020, P.R. China

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Abstract. Primary renal lymphoma (PRL) is a rare disease, with no more than 70 cases reported in the literature. The present study reports the case of a 70-year-old woman with PRL. The patient was asymptomatic, however, a mass on the right kidney was identified incidentally during routine physical examination. Computed tomography revealed a mass in the right kidney that was 3.6 cm in diameter. Subsequently, right nephrectomy was performed. The histological evaluation of the nephrectomy specimen showed diffuse large B-cell non-Hodgkin's lymphoma. The patient was treated with 6-8 cycles of a cyclophosphamide, epirubicin, vindesine and dexamethasone regimen. Follow-up examination performed after 2 months of treatment revealed no evidence of local recurrence. The present study also reviewed 49 cases of PRL that have been reported since 1989. It was found that a shorter survival time was experienced by patients with bilateral PRL (mean, 21 months) compared with unilateral PRL (mean, 68 months). A shorter survival time was also experienced by patients who were treated with chemotherapy only (mean, 15.8 months) compared with those who were treated with combination chemotherapy and surgery (mean, 49.4 months).

Introduction

Primary renal lymphoma (PRL) is defined as a non-Hodgkin's lymphoma (NHL) involving the kidney in the absence of primarily extrarenal lymphatic disease. PRL is rare, as the kidney is an extranodal organ and does not contain lymphatic tissue (1). Therefore, the existence of a PRL has been continuously debated. In recent years, reports of PRL cases have confirmed the presence of the disease. PRL has been shown to account for 0.7% of all extranodal lymphomas in North America and 0.1% of all malignant lymphomas in Japan (2,3). No more than 70 cases of PRL have been reported in the literature and the majority are of NHL large B-cell type (4). The precise cause of PRL remains unknown. It has been suggested that PRL originates from the renal capsule and infiltrates the renal parenchyma. Another explanation is that chronic inflammatory conditions of the kidney attract the infiltration of lymphoid cells and eventually evolve into lymphoma (5).

PRL is often present on only one side of the kidney in adult patients, whereas it can be bilateral in pediatric patients (6,7). PRL lacks clear clinical manifestations and appears to be similar to renal cell carcinoma (RCC), renal abscess and other kidney tumor metastases. Patients with PRL may present with gross hematuria, acute/chronic kidney failure, and flank pain or weight loss. It has been suggested that flank pain is one of the most common symptoms of PRL (8).

The diagnosis of PRL includes: i) The presence of a renal mass; ii) no evidence of extrarenal lymphomatous involvement in the visceral organs or lymph nodes at first admission; and iii) the absence of a leukemic blood picture together with no evidence of myelosuppression (9). However, a kidney biopsy remains the gold standard for the diagnosis of primary renal lymphoma (10).

PRL is difficult to diagnose by imaging alone due to its non-specific manifestations and can be roughly divided into multiple renal masses, solitary masses, renal invasion from contiguous retroperitoneal disease, perirenal disease and diffuse renal infiltration (11,12). PRL is shown as a low echo mass on ultrasound, and the use of enhanced computed tomography (CT) and magnetic resonance imaging (MRI) can improve the specificity of lymphoma. On CT scans, PRL generally presents as an isointense or low-density mass. On contrast-enhanced CT scans, PRL appears to be less dense than the adjacent renal parenchyma. On MRI, PRL exhibits a hypointense signal on T1-weighted images and an isointense to hypointense signal on T2-weighted images. PRL may also demonstrate restricted diffusion on diffusion-weighted

Correspondence to: Professor Guobin Weng, Department of Urology, Ningbo Urology and Nephrology Hospital, Ningbo University, 1 Qianhe Road, Ningbo, Zhejiang 315100, P.R. China
E-mail: ddwgb@aliyun.com

Dr Xiaolei Ye, Division of Drugs and Pharmacology, Ningbo Institute of Medical Sciences, 247 Renming Road, Ningbo, Zhejiang 315020, P.R. China
E-mail: yiexiaolei@163.com

*Contributed equally

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imaging (13). The mean apparent diffusion coefficient value has been reported as 2.18-2.30x10^{-3} mm^2/sec for the normal renal parenchyma, 0.88-0.90x10^{-3} mm^2/sec for papillary RCC, 1.23-1.70x10^{-3} mm^2/sec for clear cell RCC, 1.14-1.41x10^{-3} mm^2/sec for chromophobe RCC (14,15) and 0.64-0.76x10^{-3} mm^2/sec for lymphoma (16,17). It has also been shown that PRL exhibits an area of intense fluorodeoxyglucose (^{18}F-FDG) uptake on ^{18}F-FDG positron emission tomography/CT (PET/CT) images. The standardized uptake value (SUV) of PRL (SUV_{mean}, 6.37±2.28) is significantly higher than renal clear cell carcinoma (SUV_{mean}, 2.58±0.62), however, it is similar to that of RCC and renal collecting duct carcinoma (SUV_{mean}, 6.27±1.15) (18). The use of combined ^{18}F-FDG PET/CT greatly contributes to the accurate diagnosis and timely treatment of PRL, even prior to the biopsy results being obtained. This can also be used for the evaluation of the chemotherapy effect and the follow-up for PRL (19).

Chemotherapy is the most common treatment for PRL. This treatment generally includes 6-8 cycles of a cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP) regimen, or on the basis of this aforementioned plan, is combined with rituxan for cluster of differentiation (CD)20-positive NHL, in order to improve the patient's survival time to 5 years. However, the prognosis of PRL remains largely unknown. The 1-year mortality rates of PRL can be as high as 75% (20), the median survival time is only 8 months to 3 years, and the 5-year survival rate is only 40-50% (21).

The present study reports the case of a 70-year-old woman with PRL and provides a literature review of 49 cases of PRL that have been reported since 1989. Written informed consent was obtained from the patient.

Case report

In July 2014, a 70-year-old woman, with a medical history of type 2 diabetes mellitus for 7 years and arterial hypertension for 10 years, presented to Ningbo Yin Zhou Hospital (Ningbo, China) due to the sonographic detection of a mass in the right kidney. The patient did not report any night sweats, fever or weight loss. The physical examination was unremarkable and there was no sign of either lymphadenopathy or hepatosplenomegaly. The laboratory results were as follows: White blood cells (WBC), 7.9x10^9/l (normal range, 3.5-9.5x10^9/l); hemoglobin, 124 g/l (normal range, 115-150 g/l); platelets, 209x10^9/l (normal range, 125-350x10^9/l); blood urea nitrogen, 4.94 mmol/l (normal range, 2.9-8.2 mmol/l); and creatinine, 40 μmol/l (normal range, 45-84 μmol/l). Urine routine tests were negative for proteins, red blood cells (RBC) 1 particle/μl (normal range, 0-5 particle/μl), WBC 7 particle/μl (normal range, 0-9 particle/μl) and bacteria 164 particle/μl (normal range, 0-75 particle/μl). CT (Fig. 1A) revealed a 3.6-cm mass of right kidney without associated hydronephrosis or ureteral obstruction. The patient then underwent contrast-enhanced CT of the abdomen (Fig. 1B). The results showed that the mass of the right kidney exhibited continuous progressive enhancement, with a value of 100 HU in the corticomedullary phase. The mass was initially suspected to be a malignancy of the right kidney and subsequently, a right nephrectomy was performed. Tissue specimens were fixed with 10% formalin, embedded in paraffin and stained with hematoxylin and eosin. The histological evaluation of the nephrectomy specimen (Fig. 1C) revealed diffuse proliferation of large

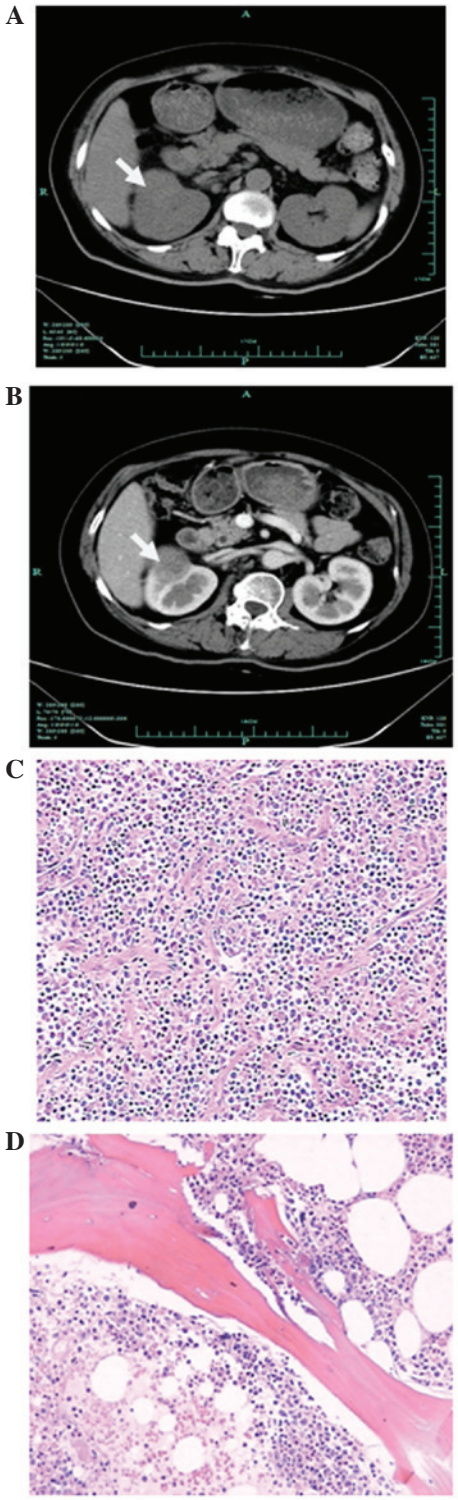

Figure 1. (A) Computed tomography (CT) revealing a 3.6-cm mass at the right kidney without associated hydronephrosis or ureteral obstruction. (B) Contrast-enhanced CT showing that the mass of the right kidney exhibited continuous progressive enhancement, with a value of 100 HU in the corticomedullary phase. (C) Histological evaluation of the nephrectomy specimen showing a diffuse large B-cell non-Hodgkin's lymphoma. (D) Bone marrow biopsy showing no morphological involvement of lymphoma.

Table I. Literature review of the 49 cases of primary renal lymphoma reported in the literature since 1989.

Case no.	Gender	Age, years	Site	Renal impairment	Presenting symptoms	Treatment	Chemotherapeutic agents	Histology	Follow-up post-treatment	(Ref.)
1	Female	53	Bilateral	Yes	Poor appetite, meat repulsion and progressive weight loss	Chemotherapy	CHOP	Non-Hodgkin's lymphoma	Died at 3 days	(1)
2	Female	58	Bilateral	Yes	Anorexia, weight loss, night sweats, malaise	Chemotherapy	CHOP	B-cell non-Hodgkin's lymphoma	Unknown	(22)
3	Female	49	Bilateral	Yes	Renal impairment with diuresis, fever, weight loss, lower back pain	Chemotherapy	CHOP	Centroblastic lymphoma	Died at 10 weeks	(23)
4	Female	5	Bilateral	No	Fever, weight loss, sweats	Chemotherapy	M-BACOD	Lymphoblastic B-cell lymphoma	Died at 20 months	
5	Male	4	Bilateral	No	Fever, nausea, vomiting	Chemotherapy	LSA2-L2	Unknown	Died at 16 months	
6	Male	62	Bilateral	Yes	Macroscopic hematuria, acute urinary retention, and bilateral hydronephrosis	Chemotherapy	CHOP	B-cell lymphoma of the follicular type	Died at 2 months	(5)
7	Male	45	Right	Yes	Unknown	Surgery + chemotherapy	B-ALL	B-cell lymphoma of the Burkitt-like type	Alive at 47 months	
8	Male	14	Bilateral	Yes	Intermittent headache, flank pain, emetic weight loss and hypertension	Chemotherapy	CCG-5942	Diffuse large B-cell lymphoma	Alive at 2 weeks	(24)
9	Male	79	Left	Yes	Generalized body aches, weakness and decreased urine output	Surgery	None	Marginal-zone B-cell lymphoma	Alive at 2 months	(25)
10	Male	43	Right	Unknown	Left flank pain	Surgery	None	B-cell lymphoma of MALT	Alive at 28 months	(26)
11	Male	46	Bilateral	Yes	Unknown	Surgery + chemotherapy	Pro-MECE-Cyta BOM + Flu-Ctx-Idec	Diffuse large B-cell lymphoma	Alive at 67 months	(27)
12	Female	70	Right	No	Anorexia, malaise, and daily low-grade fever	Surgery + chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 8 months	(28)
13	Female	65	Left	Unknown	Unknown	Surgery + chemotherapy + radiation	R-CHOP	Diffuse large B-cell lymphoma	Alive at 18 months	(6)
14	Female	68	Bilateral	Yes	Bilaterally severe flank pain and dysuria	Unknown	Unknown	Large B-cell lymphoma	Died at 10 days	(29)
15	Male	2	Bilateral	Yes	Progressive abdominal distention, decreased urine output	Chemotherapy	cpa + L-asp + Vcr + Prednisolone	T-cell lymphoma	Unknown	(30)

Table I. Continued.

Case no.	Gender	Age, years	Site	Renal impairment	Presenting symptoms	Treatment	Chemotherapeutic agents	Histology	Follow-up post-treatment	(Ref.)
16	Female	71	Left	No	Weight loss and fever	Surgery + chemotherapy	CHOP	B-cell lymphoma	Died at 4 months	(31)
17	Male	50	Right	No	Abdominal pain	Surgery + chemotherapy	CHOP	Diffuse large B-cell lymphoma	Alive at 1 month	(32)
18	Male	62	Left	No	Gross hematuria	Surgery + chemotherapy + interferon	R-CHOP	Diffuse B-cell lymphoma	Alive at 5 years	
19	Male	84	Left	Yes	Unknown	Surgery + chemotherapy + interferon	COP	B-cell lymphoma	Alive at 5 years	
20	Male	58	Right	Unknown	Headache and short-term memory loss	Surgery + chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Unknown	(33)
21	Female	21	Bilateral	Yes	Fever, weight loss, abdominal pain and abdominal masses	Chemotherapy	VACOP-B	Diffuse large B-cell lymphoma	Unknown	(34)
22	Male	5	Bilateral	Yes	Hypertension	Chemotherapy	CCG-1961	T-cell lymphoblastic lymphoma	Died at 2 months	(35)
23	Male	57	Bilateral	Yes	Dyspnea, renal failure and anemia	Chemotherapy + autologous stem cell transplantation	R-CHOP	Unknown	Unknown	(36)
24	Male	62	Right	Unknown	Low-grade fever and dull, non-radiating right flank pain	Surgery + chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 1 year	(21)
25	Female	77	Left	Yes	Anorexia, astenia and malaise	Surgery + chemotherapy	CVP	Diffuse large B-cell lymphoma	Alive at 15 months	(37)
26	Male	46	Right	Unknown	Weight loss, evening fever and upper abdominal pain	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 7 months	
27	Male	47	Renal graft	Unknown	Chronic graft dysfunction	Surgery	None	B-cell lymphoma	Alive at 6.5 years	
28	Male	74	Left	Unknown	Unknown	Surgery + chemotherapy	Unknown	Diffuse small B-cell lymphoma	Died after chemotherapy course 2	(38)
29	Male	71	Right	Unknown	Unknown	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 2 years	
30	Female	75	Left	Unknown	Unknown	Surgery + chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 1 year	
31	Male	81	Right	Unknown	Macroscopic hematuria	Surgery + chemotherapy	Unknown	Small B-cell lymphoma	Unknown	

Table I. Continued.

Case no.	Gender	Age, years	Site	Renal impairment	Presenting symptoms	Treatment	Chemotherapeutic agents	Histology	Follow-up post-treatment	(Ref.)
32	Female	52	Bilateral	Yes	Back pain, headache, dysuria pollakisuria, hematuria, nonoliguric acute renal failure, hypertension	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 2 years	(39)
33	Male	3	Bilateral	No	Abdominal distension, abdominal pain and fever	Chemotherapy	BFM-90	B-cell lymphoma	Died after chemotherapy course 5	(40)
34	Male	60	Right	No	Dyspnea, intermittent claudication and fatigue	Surgery + chemotherapy	CHOP	Follicular non-Hodgkin's lymphoma	Unknown	(12)
35	Male	70	Right	Unknown	Macroscopic hematuria	Surgery	None	Diffuse large B-cell lymphoma	Unknown	(41)
36	Male	32	Left	No	Heaviness in epigastric region, dull ache in left flank and loss of appetite and weight	Surgery + chemotherapy	CHOP	B-cell lymphoma	Died at 2 months	(42)
37	Male	72	Left	Yes	Left flank pain, weakness and weight loss	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 15 months	(4)
38	Female	7	Bilateral	No	Intermittent fever, joint pain, severe anemia and distended abdomen	Chemotherapy	CHOP	Unknown	Unknown	(43)
39	Female	67	Bilateral	Yes	Epigastric pain, radiating to the back and associated with vomiting and nausea	Chemotherapy	R-CHOP	Large B-cell lymphoma	Alive at 4 weeks	(10)
40	Female	77	Left	Yes	Anorexia, weakness, malaise	Surgery + chemotherapy	CVP + R	Diffuse large B-cell lymphoma	Alive at 5.5 years	(44)
41	Male	46	Left	Yes	Weight loss and left flank pain	Surgery + chemotherapy + radiation therapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 5 years	
42	Male	73	Right	Yes	Unknown	Surgery	No	Large B-cell lymphoma	Unknown	(45)
43	Female	82	Right	Yes	Dizziness, palpitations or loss of consciousness	Chemotherapy	R-CHOP	B-cell lymphoma	Unknown	(46)
44	Female	27	Bilateral	Yes	Nausea, vomiting and fever	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Unknown	(47)
45	Male	77	Left	No	Gross hematuria	Radiation therapy	No	Marginal zone B-cell lymphoma	Alive at 3 years	(48)

Table I. Continued.

Case no.	Gender	Age, years	Site	Renal impairment	Presenting symptoms	Treatment	Chemotherapeutic agents	Histology	Follow-up post-treatment	(Ref.)
46	Female	12	Right	No	Gross hematuria	Surgery + chemotherapy	vcr+dex+cpa+mtx +ara-c+other drugs	Diffuse large B-cell lymphoma	Alive at 3 years and 2 months	(49)
47	N/A	8	Bilateral	Yes	Intermittent fever, joint pain, severeanemia, and distended abdomen	Chemotherapy	R-CHOP	B-cell lymphoma	Alive at 1 year	(19)
48	Male	49	Right	Unknown	Pain and mass per abdomen	Surgery	No	B-cell lymphoma	Alive at 1 year	(50)
49	Male	42	Left	Yes	Abdominal pain and a mass in the abdomen	Chemotherapy	R-CHOP	Diffuse large B-cell lymphoma	Alive at 28 months	(51)

MALT, mucosa-associated lymphoid tissue. Chemotherapeutic agents: C/ctx/cpa, cyclophosphamide; H, hydroxydaunorubicin; O, oncovin; vincristine; P, prednisone; R, rituximab; M, methotrexate; B, bleomycin; D, dex/dexamethasone; Flu, fludarabine; L-asp, L-asparaginase; mtx, methotrexate; ara-c, cytarabine. CHOP, R-CHOP, B-ALL, LSA2-L2, CCG5942, Pro-MECE-CytaBOM, Flu-Ctx-Idec, VACOP-B, CCG-1961, CVP and BFM-90 are combinations of chemotherapeutic agents used to treat lymphoma.

lymphoid cells, which indicated diffuse large B-cell NHL. Immunohistochemical analysis revealed that the tumor cells were positive for CD5 (monoclonal rabbit anti-human antibody; 1:100; #ZA-0510; Zhongshan Jinqiao Biological Technology Co., Ltd., Beijing, China), CD3 (monoclonal rabbit anti-human antibody; 1:200; #Kit-0003; Fuzhou Maixin Biotech Co., Ltd., Fuzhou, China), CD79α (monoclonal rabbit anti-human antibody; 1:200; #ZM-0293; Zhongshan Jinqiao Biological Technology Co., Ltd.), CD20 (monoclonal mouse anti-human antibody; 1:100; #MAB-0669; Fuzhou Maixin Biotech Co., Ltd.), CD43 (monoclonal mouse anti-human antibody; 1:200; #ZM-0048; Zhongshan Jinqiao Biological Technology Co., Ltd.), CD10 (monoclonal mouse anti-human antibody; 1:200; #M7308; Dako, Glostrup, Denmark), Ki-67 (monoclonal mouse anti-human antibody; 1:400; #Kit-0005; Fuzhou Maixin Biotech Co., Ltd.) (85%) and mutated melanoma-associated antigen 1 (monoclonal rabbit anti-human antibody; 1:200; #ZA-0583; Zhongshan Jinqiao Biological Technology Co., Ltd.), and negative for B-cell lymphoma (Bcl)-2 (monoclonal mouse anti-human antibody; 1:200; #ZM-0010; Zhongshan Jinqiao Biological Technology Co., Ltd.), CD23 (monoclonal rabbit anti-human antibody; 1:100; #ZA-0516; Zhongshan Jinqiao Biological Technology Co., Ltd.), CD21 (monoclonal rabbit anti-human antibody; 1:100; #ZA-0525; Zhongshan Jinqiao Biological Technology Co., Ltd.), cyclin D1 (monoclonal rabbit anti-human antibody; 1:100; #M3642; Dako), p53 (monoclonal mouse anti-human; 1:800; #ZM-0408; Zhongshan Jinqiao Biological Technology Co., Ltd.) and Bcl-6 (monoclonal mouse anti-human antibody; 1:200; #ZM-0011; Zhongshan Jinqiao Biological Technology Co., Ltd.). Next, a bone marrow biopsy was performed, which showed no morphological involvement of lymphoma (Fig. 1D). The NHL was finally considered to be PRL, as the imaging and biopsy results confirmed that there was no sign of peripheral lymphadenopathy or hepatosplenomegaly. The patient was treated with 6-8 cycles of a CHOP regimen (a combination of 1 g cyclophosphamide on day 1, 80 mg epirubicin on day 1, 3 mg vindesine on day 1, and 10 mg dexamethasone on days 1-5) (1 cycle, 28 days) and has completed three courses of treatment to date. On a CT scan following the third course of treatment, the patient showed a complete response to the treatment and no major discomfort was reported. Follow-up examination performed after 2 months of treatment revealed no local recurrence of the lymphoma. Follow-up every 3 months is planned for the first 2 years after treatment, and every 6 months in subsequent years.

Discussion

PRL is extremely rare and a thorough review of PRL cases has been largely lacking in the literature. The present study reviewed all 49 cases of PRL reported in the literature since 1989 (Table I). A finding of diffuse large B-cell lymphoma is the most common pathological sign. Of all 49 cases, 30 were male, 18 were female and 1 had an unrecorded gender. There were more male patients than female patients, and the ratio was ~1.6:1. In addition, the site of PRL can be age-related. The literature review found that PRL generally appears to be bilateral in patients who are younger than 18 years old and

unilateral in adult patients. Fever is one of the most common symptoms in younger patients (56%), while abdominal and flank pain are common (62%) in patients aged from 18-50 years. Weight loss and gross hematuresis are the most common symptoms (37%) for patients who are older than 50 years. The patients aging from 18-50 years have the highest survival rate (mean, 62.8 months) compared with patients aged from 0-18 years old (mean, 17.6 months) and >50 years (mean, 48.2 months). In addition, 19 cases of bilateral PRL experienced a mean survival time of 21 months, and 30 cases of unilateral kidney experienced a mean survival time of 68 months. It appears that younger patients and bilateral PRL results in a shorter survival time and more rapid progression of the disease. Therefore, special procedure should be considered for those patients, including the combination of surgery, chemotherapy or radiotherapy.

To date, chemotherapy remains the main treatment for PRL. Among all 49 cases, chemotherapy treatment alone was implemented in only 21 patients, and the mean survival time was only 15.8 months. The mean survival time for the 15 patients treated with the combination of chemotherapy and surgery was 49.4 months. However, the different survival times were not significantly different (P=0.255) as determined by Kaplan-Meier analysis using SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA) whereby P<0.05 was considered to indicate a statistical significant difference. Despite the lack of statistical significance, the combination of chemotherapy and surgery produced longer survival times than single chemotherapy treatment, and the combined treatments may greatly slow disease progression. However, early detection and effective treatment is required to improve the prognosis.

Our review of 49 reported cases of PRL revealed that a combination of chemotherapy and surgery resulted in longer survival times than chemotherapy treatment alone. Therefore, the present patient was treated with 6-8 cycles of CHOP following nephrectomy. However, the literature review had several limitations. Firstly, all follow up data was obtained from different cases and thus, follow-up durations differ. Secondly, the follow-up durations were reported using different units of time, therefore, the mean survival time was calculated in months. Thirdly, a number of studies did not report the patients last follow-up date. Thus, further studies are required regarding the prognosis of the disease. The early diagnosis of PRL requires identification of the high-risk population, vulnerable organs, symptoms and image results. Pathological diagnosis is important for an early diagnosis. Chemotherapy is the preferred treatment, but its combination with radiotherapy, surgery and other means should be considered for patients with younger ages or bilateral PRL.

In conclusion, the patient in the present study was diagnosed incidentally with a mass in the right kidney during a routine physical examination and exhibited no clinical symptoms. The mass was initially suspected as renal cell cancer and, subsequently right nephrectomy was performed. However, histological evaluation of the nephrectomy specimen indicated diffuse large B-cell NHL. The patient was treated with 6-8 cycles of the CHOP regimen. Follow-up examination performed after 2 months of treatment revealed no local recurrence of the lymphoma.

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