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# Nephrology Dialysis Transplantation

## Case Report

### Bilateral primary renal lymphoma treated by surgery and chemotherapy

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We report a case of bilateral PRL successfully treated by surgical resection leading to a three-quarters ablation of native renal mass followed by combination chemotherapy.

#### Introduction

Secondary renal involvement in advanced non-Hodgkin's lymphomas is quite common, but primary renal lymphoma (PRL) is a rare disease. It accounts for 0.7% of all extra-nodal lymphomas in North America and 0.1% in Japan, and 65 cases have been reported in the worldwide literature. PRL is also a debated disease because kidneys do not contain lymphatic tissue [1,2]. General agreement exists about the criteria needed to define the diagnosis of PRL: (i) renal failure as the first presentation in the absence of other causes of renal impairment; (ii) rapid improvement of renal function following therapy; (iii) increase of the kidneys' size without any urinary tract obstruction; (iv) absence of other nodal or extra-nodal involvement; and (v) definite diagnosis made by histological examination.

The median age at PRL diagnosis is 64 years, and the disease is more frequent in males than in females. Acute renal failure, flank pain and detection of a renal mass are the most frequent manifestations [3]. Renal failure may result from a large variety of causes, such as lymphomatous infiltration of renal tissue or hypercalcaemia [4]. Histological examination is mandatory, as clinical and radiological findings often evoke renal carcinoma [5].

The prognosis is poor, but long-term survivors have been reported occasionally after surgical resection and combination chemotherapy, in unilateral renal lymphoma [2]. Bilateral renal involvement has a prevalence of 43% [6]: in this case, the prognosis is very severe and chemotherapy is the usual proposed treatment because surgery has never been described (Table 1).

#### Case

A 46-year-old male with a history of chronic renal failure (creatinine 230 µmol/l; creatinine clearance 45 ml/min) from chronic pyelonephritis was admitted in October 1997 due to rapid worsening of renal failure and hypercalcaemia. Ten months earlier, following sonographic detection of a mass in the right kidney, the patient had been studied in another hospital where the histological diagnosis of inflammatory pseudotumour of the right kidney was made by computed tomography (CT)-guided renal biopsy. Cortical scarring and caliceal deformity of the left kidney was also described and diagnosed as chronic pyelonephritis. At admission, physical examination was unremarkable; no oedema, dyspnoea, fever, pruritus or body weight loss were present. Arterial blood pressure was 140–80 mmHg, body weight 97 kg, body mass index 30.2 kg/m<sup>2</sup>. Biochemistry showed serum creatinine 521 µmol/l, creatinine clearance 15 ml/min, serum calcium 3.45 mmol/l, intact parathyroid hormone 6 pg/ml, 25-hydroxy vitamin D 44 pg/ml, 1,25 dihydroxy vitamin D 96 pg/ml, lactate dehydrogenase 620 U/l. The white blood cell count was  $8.7 \times 10^9/l$  (N 56, L 30, M 10, B 0.5, E 1.6%). The red blood cell count was  $5.1 \times 10^{12}/l$ , haemoglobin 2.17 mmol/l and haematocrit 0.44. Urine analysis showed microhaematuria (40–50 red cells) and mild proteinuria (50 mg/dl).

Values found to be in the normal range were those for serum uric acid, phosphorus, sodium, potassium, glucose, cholesterol, triglycerides, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum and urine protein electrophoresis, hepatitis C virus and hepatitis B virus.

The patient's chest X-rays were normal. Abdominal sonography showed an enlarged right kidney diameter

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**Table 1.** List of the bilateral PMLs described in the literature, their treatment and outcome

Year	Author	Age/sex	Treatment	Follow-up (months)	Outcome
1946	Ferifeld	17/M	Rx-therapy	<12	Death
1950	Allen	41/M	Rx-therapy	<12	Death
1951	Davis	67/M	–	<12	Death
1976	Klener	20/M	Rx-chemotherapy	<12	Death
1980	Coggins	30/M	Rx-therapy	6	Remission
1983	Laxer	14/M	Rx-therapy	1	Remission
1983	Gilboa	5/M	Chemotherapy	15	Death
1986	Camitta	3/F	Rx-chemotherapy	36	Remission
1987	Truong	59/M	Rx-chemotherapy	13	Death
1987	Truong	26/M	Chemotherapy	5	Death
1987	Koolen	61/M	Chemotherapy	1.5	Death
1988	Berard	60/M	Chemotherapy	2	Remission
1988	Leoncini	50/F	Chemotherapy	6	Remission
1989	Kutluk	4/M	Chemotherapy	>14	Remission
1989	Paganelli	53/F	Chemotherapy	1	Death
1990	Mijake	47/M	Chemotherapy	17	Remission
1991	Dobkin	10/M	Chemotherapy	29	Remission
1991	Jeandel	70/F	Chemotherapy	1	Death
1991	Sheil	29/F	Chemotherapy	3	Death
1992	Van Gelder	58/F	Chemotherapy	10	Death
1992	Carrasco	64/M	Rx-chemotherapy	24	Remission
1992	Mills	77/F	Chemotherapy	2	Death
1993	Kindle	49/M	Chemotherapy	?	Unknown
1993	Vandermolen	58/F	Chemotherapy	14	Remission
1994	Malbrain	45/M	Chemotherapy	31	Remission
1994	Brouland	57/F	Rx-chemotherapy	5	Death
1994	Arraz Arijia	49/F	Chemotherapy	3	Death
1994	Arraz Arijia	5/F	Chemotherapy	24	Death
1994	Arraz Arijia	4/M	Chemotherapy	14	Death
1995	Okuno	63/F	Chemotherapy	12	Death
1996	Baldus	72/F	Chemotherapy	7	Death
2000	Stallone	22/M	Chemotherapy	12	Death
2001	O'Riordan	52/M	Chemotherapy	13	Death
2002	Gellrich	62/M	Chemotherapy	2	Death

with irregular borders, mesorenal scarring and hypertrophic areas; the left kidney measured 9 cm in diameter with irregular borders. No signs of stones or urinary tract obstruction were detected. No enlarged lymph node was detected by sonography of the neck, inguinal and axillary regions.

Hypercalcaemia was treated by saline and furose-mide, leading to normalization of serum calcium to 2.5–2.7 mmol/l and progressive reduction of serum creatinine to 309  $\mu$ mol/l.

Abdominal magnetic resonance confirmed a right kidney of increased size, with multiple nodules and complete subverting of the normal structure. The larger nodule measuring 8 cm diameter was located in the upper posterior region of the right kidney; a nodule involving the upper pole of the left kidney was also detected, whereas the remaining kidney tissue appeared preserved (Figure 1). No abnormalities were described as far as lymph nodes, liver or spleen were concerned.

Fine-needle percutaneous renal biopsy was performed using a free-hand ultrasound-guided procedure on the lower pole of the right kidney where nodular hypertrophic areas were detected. Microscopy showed the presence of some atypical lymphocytes.

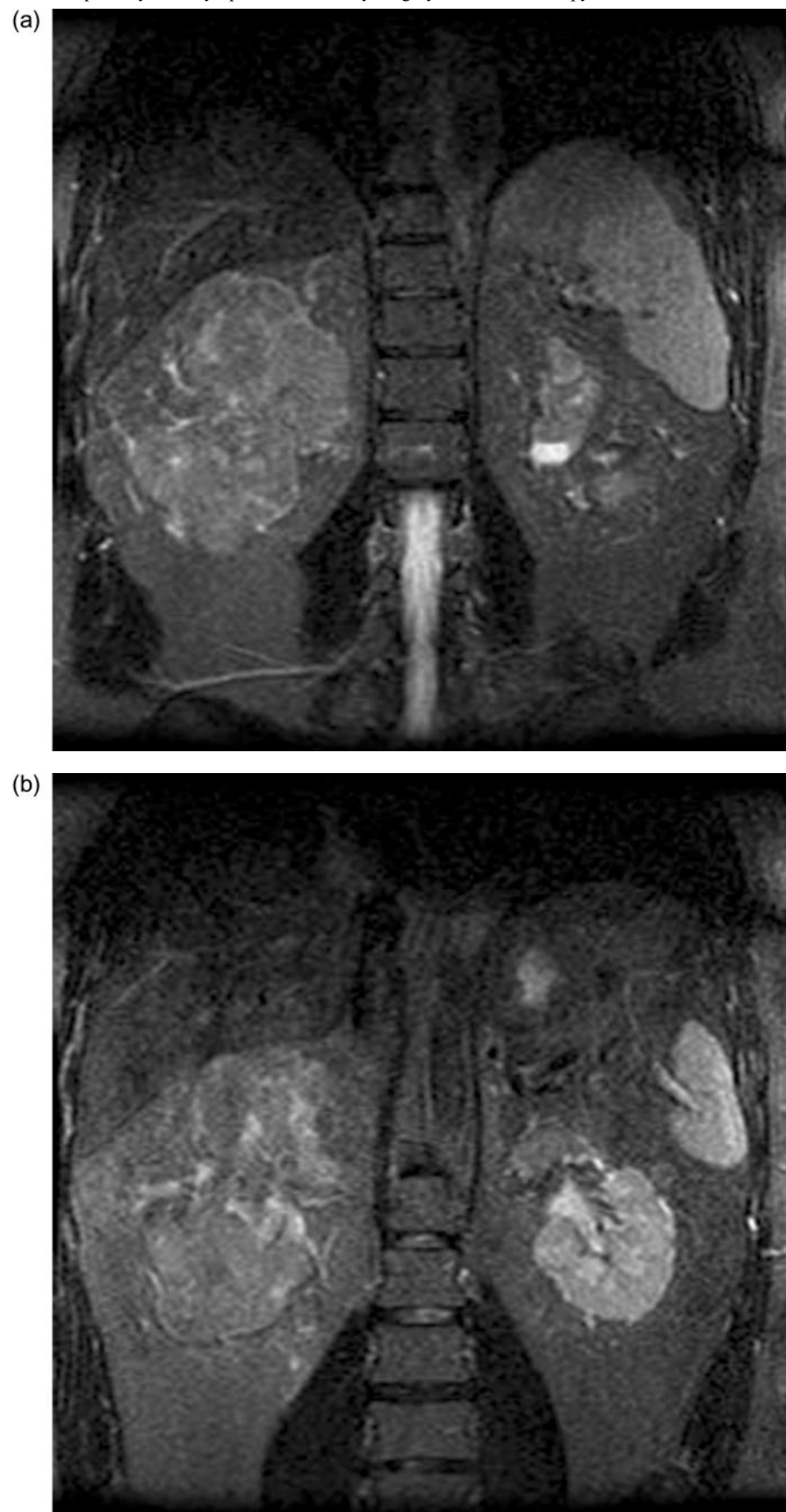
Suspicion of a cancer or of a lymphoproliferative disease with bilateral renal involvement arose. Therefore, the patient underwent xiphopubic laparotomy.

The right kidney appeared completely subverted by proliferative tissue, while exploration of the left kidney confirmed a proliferative lesion apparently limited to its upper region.

Consequently, right radical nephrectomy and upper pole resection of the left kidney were performed, preserving approximately half of the left kidney. Seven inter-aortic lymph nodes were sampled. The abdominal exploration was unremarkable. The right kidney measured 15  $\times$  8  $\times$  8 cm and the removed portion of the left kidney measured 6  $\times$  3  $\times$  3 cm.

Histological examination showed a diffuse, large B-cell lymphoma (REAL classification), centroblastic variant, which diffusely infiltrated interstitium and glomeruli. This variant was composed of medium to large sized lymphoid cells with oval to round, vesicular nuclei with fine chromatin and 2–3 membrane-bound nucleoli. This case was characterized by many multi-lobated cells. The immuno-phenotype was CD20<sup>+</sup>, CD79a<sup>+</sup> and Bcl-2<sup>+/+</sup>. These findings were observed both in the right and in the left kidney tissue. However, adrenal glands, peri-renal fat or inter-aortic lymph nodes were not involved.

During the days following nephrectomy, serum creatinine improved to 247  $\mu$ mol/l together with reduction of serum calcium (2.3 mmol/l) and calcitriol (6.0 pg/ml) serum levels.



**Fig. 1.** Nuclear magnetic resonance before surgery. Two coronal sections showing (a) enlargement and complete structural subverting of the right kidney; and (b) a mass involving the upper pole of the left kidney, with the remaining kidney tissue apparently preserved.

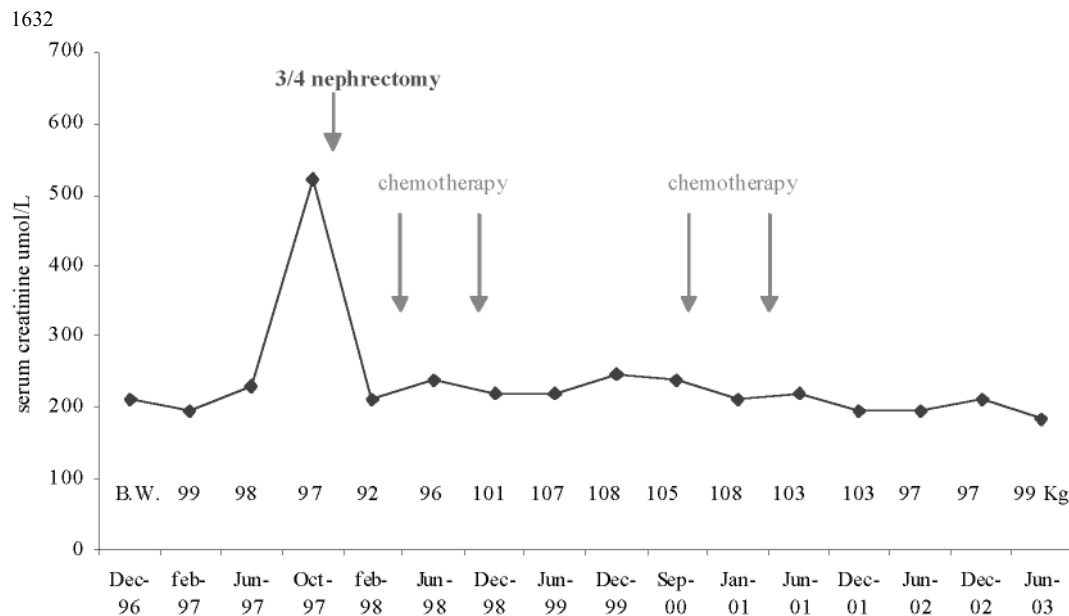


Fig. 2. Behaviour of serum creatinine with time, from December 1996 to June 2003. Body weight is also reported.

Additional post-operative staging, including whole body CT and bone marrow biopsy, did not show any abnormality or lymphomatous localization.

Six months after surgery, re-staging of the disease was carried out, leading to detection of a bone marrow infiltration. Translocation of the Bcl2 gene was detected using polymerase chain reaction (PCR) for clonal immunoglobulin heavy chain (IgH) gene rearrangement [7]. Thus the patient underwent chemotherapy according to the Pro-MECE-CytaBOM schedule and, after four cycles, residual infiltration of the bone marrow was detected by PCR analysis for IgH rearrangement. Therefore, a second line chemotherapy was performed according to the Flu-Ctx-Idex protocol (four cycles) [8]. Successive examination did not show any relapse and renal function remained stable with time; serum creatinine ranged between 186 and 210  $\mu\text{mol/l}$ . Follow-up consisted of regular physical examination and biochemistry. Bone marrow biopsy, chest X-ray and sonography were performed every 6 months for 3 years, and then once a year. Abdomen CT scans were performed every year for the first 3 years and then every 2 years. At this time, 67 months after surgery and 36 months after the end of the chemotherapy, no sign of disease relapse has been detected. Serum creatinine remains stable at  $\sim 186 \mu\text{mol/l}$  (Figure 2).

## Discussion

Although a number of reported PRL cases are in fact questionable due to incomplete staging or the presence of extra-renal involvement at the time of diagnosis, revision of the available literature suggests that PRL does exist [2]. Our case fulfilled the diagnostic criteria for identification of a PRL: acute renal failure

at presentation, enlargement of the kidney, rapid improvement of renal function after treatment, diagnosis made by histology of the renal mass, and absence of other organ or nodal involvement.

Historically, the patient has been diagnosed with a chronic pyelonephritis and a pseudo-inflammatory tumour in the right kidney. It is known that this lesion can precede the onset of a lymphoproliferative disease. Moreover, as far as the involvement of other extra-nodal organs is concerned, the lymphoid tissue formed by chronic inflammatory disease is regarded as the source for the development of malignant lymphoma [9].

The rapid deterioration of the residual renal function was likely to have been related to parenchyma infiltration and to the hypercalcaemia, probably induced by vitamin D overproduction from the lymphoid cell mass. Accordingly, after restoration of normal calcium levels and subtotal ablation of the renal mass, renal function did ameliorate and returned to the patient's basal values (Figure 2).

Because of the low incidence of this disease, randomized studies aiming to compare different therapy approaches have not been reported. Systemic chemotherapy, with or without radiotherapy, is a widely used treatment for PRL [10], as well as the option of surgery in the case of PRL affecting one kidney.

The limited available literature reports that the prognosis of patients affected by PRL is poor, despite no disseminated disease. Chemotherapy usually improves or normalizes the renal function, but the few cases reported showed a high prevalence of deaths because of rapid relapse or infections incurred in the course of neutropenia. Long-term survivors occasionally have been reported after combined surgery-chemotherapy treatment where one kidney is involved [1]. The patients whose lymphomatous masses were removed completely by surgical resection, and who were treated by



combination chemotherapy, had longer disease-free and overall survival: this usually occurs in monolateral cases. Patients with bilateral involvement or with residual lymphoma mass after surgical resection show a very bad prognosis. Our patient showed bilateral renal involvement with no signs of other nodal or extra-nodal localization. Bone marrow involvement was found only several months following the surgical resection, and nodal involvement was never detected. This phenomenon is difficult to interpret, but certainly this is not in keeping with a lymphomatous infiltration of the kidney in disseminated lymphoma.

Bilateral renal lymphomas are usually treated by aggressive chemotherapy as front line therapy [1,5]: this approach could preserve the organ function, but generally the prognosis is poor. Alternatively, bilateral nephrectomy invariably leads to the need for dialysis treatment.

In our patient, the resection of the apparent tumour mass preserved approximately one-quarter residual renal mass which successfully allowed the patient to avoid dialysis. The choice of initial surgery depended on the need for a definite diagnosis, on the presence of an underlying chronic renal failure and on the importance of the tumour mass.

The present case report suggests that surgery can be beneficial in the treatment of renal lymphoma with bilateral involvement. This kind of treatment was possible because the left kidney had macroscopic involvement limited to the upper pole. Although microscopic involvement could also be present in the remaining renal tissue, a conservative surgical resection was possible in the left kidney, allowing for a residual renal function sufficient to make the patient free from the need for dialysis. The tumour mass was dramatically reduced, thus increasing the likelihood of success of the ensuing chemotherapy treatment. A 67 month period of survival in bilateral renal lymphoma has been never described in the literature: we believe that, as is typical with other types of cancers, reduction of tumour cell mass is a crucial point for successful treatment and response to chemotherapy.

Table 1 lists the cases of PRL with involvement of both kidneys which exist in the literature. The overall poor prognosis is evident, as only 11 cases of remission at 1–36 months are reported. Various combined chemotherapy regimens were the main therapeutic strategy adopted, but surgery was never described. Actually, the urological intervention represents the most original aspect of the present case and it is likely that this could have contributed to the favourable outcome of the disease by means of a critical reduction of neoplastic cell mass giving more chance of a better

response to chemotherapy. The surgical approach we used is the same as is usually performed in bilateral renal cancer, i.e. the removal of as much tumour mass as possible, provided there is preservation of enough (macroscopically) tumour-free kidney tissue.

In conclusion, this case report shows a case of bilateral PRL successfully treated by extensive surgical resection and combination chemotherapy. It is difficult to discuss the relative role of surgery and chemotherapy in the favourable outcome of this patient. Nevertheless, the unusual long-term remission, together with preservation of a residual renal function, shows that surgery, in association with a combined chemotherapy protocol, may be an option in selected cases of bilateral PRL.

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*Conflict of interest statement.* None declared.

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