CASE REPORT

UDC: 616.15-006:616.61-006
DOI: 10.2298/VSP140323054C

# Lymphoproliferative neoplasms and renal cell carcinoma of clear cell type – Where is the link?

## Limfoproliferativne neoplazme i adenokarcinom bubrega – Da li postoji povezanost?

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**Abstract**

**Introduction.** The etiology of higher than expected occurrence of lymphoproliferative neoplasms (LPN) and renal cell carcinoma (RCC) in the same patient has not yet been clarified. Several explanations for this co-occurrence have been postulated: prior cytotoxic treatment, viral infections, immunomodulatory effects of tumor itself and shared genetic and/or environmental factors. **Case report.** Medical records of 680 consecutive patients with LPN and 570 consecutive patients with RCC diagnosed between January 1997 and December 2011 in two centers were retrospectively analyzed. Co-occurrence of both diseases was registered in five of the patients (3 males, 2 females) and their demographic, clinical and pathological characteristics were presented. **Conclusion.** Synchronous occurrence of LPN neoplasms and RCC or a short latent period between the diagnoses of these two malignancies in the same patient, as well as the lack of cytotoxic treatment for firstly occurring neoplasm implies a possible common pathobiology of both diseases.

**Key words:**
**lymphoproliferative disorders; neoplasms; kidney noplasms; comorbidity; risk factors; prognosis.**

**Apstrakt**

**Uvod.** Epidemiološkim studijama utvrđena je značajna povezanost limfoproliferativnih neoplazmi (LPN) i adenokarcinoma bubrega (*renal cell carcinoma* – CRC), ali uzrok ove povezanosti nije utvrđen. Kao mogući etiološki faktori navode se: efekat primenjene citotoksične terapije, infekcije virusima, imunomodulatorni efekat tumora, genetska predispozicija i uticaj faktora spoljašnje sredine. **Prikazi bolesnika.** Retrospektivnom studijom obuhvaćeno je 680 bolesnika sa LPN i 570 bolesnika sa adenokarcinomom bubrega dijagnostikovanih u dve ustanove u peridu januar 1997 – decembar 2011. godine. Udruženost oboljenja utvrđena je kod pet bolesnika (3 muškarca, 2 žene) čije su demografske i kliničkopatološke karakteristike prikazane. **Zaključak.** Istovremeno postavljanje dijagnoze ili suviše kratak latentni period između postavljanja dijagnoze LPN i adenokarcinoma bubrega kao i odsustvo primarne citotoksične terapije govore u prilog zajedničkoj patobiologiji ovih maligniteta.

**Ključne reči:**
**limfoproliferativni poremećaji; neoplazme; bubreg, neoplazme; komorbiditet; faktori rizika; prognoza.**

### Introduction

Lymphoproliferative neoplasms (LPN) and renal cell carcinoma (RCC) account for about 4% [1] and 3% [2] of all adult malignancies, respectively. In addition to the trend of steady increase in the incidence of both type of malignancies [1, 3], several population-based epidemiological studies have also confirmed previously reported clinical observations of higher than expected co-occurrence of both type of malignancies in the same patient. Thus, patients with RCC have 1.51 [4] and 1.86 [5] higher overall relative risk respectively of multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) than general population. On the other hand, the relative risk for developing RCC in patients with MM and NHL is 1.89 [4] and 2.67 [5], respectively. Several explanations for this co-occurrence have been postulated: prior cytotoxic treatment, viral infections, immunomodulatory effects of tumor itself and shared genetic and/or environmental factors [2, 6–11], yet the etiology of this association has not been clarified.

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**Case report**

Medical records of 680 consecutive patients with LPN and 570 consecutive patients with RCC (82% with clear cell histological type) diagnosed between January 1997 and December 2011 in the Clical Hospital Center Zemun and the Clinic for Hematology, Clinical Center Serbia were retrospectivelly analyzed. Co-occurence of both diseases was registered in five of the patients (2.5%, 3 males and 2 females). Their median age at the LPN diagnosis was 58 years (range 44–70) and median age at the RCC diagnosis was 57.8 years (range 44–69 years) as shown on Table 1.

Case 1

A 69-year-old male underwent right nephrectomy due to 6.5 cm renal mass in January 2007. A pathological finding revealed early-stage RCC of clear cell type. Five months later he fell by accident and gained fractures of his right humerus and right shoulder blade. Since fractures had not been healed for the next three months, a bone biopsy was performed, which demonstrated plasmocytoma. He was referred to a hematologist who staged him as III B IgA kappa MM. At that time, he had multiple lytic bone lesions, renal failure (creatinine 912 μmol/L), monoclonal spike of 52.8 g/L IgA kappa and highly elevated beta-2 microglobulin (26.4 mg/L). The patient was initially treated with dexamethasone, hemodialysis and palliative radiation therapy. After normalization of renal function he received 6 cycles of vincristine-adriamycin-dexamethason (VAD) chemotherapy. As his MM progressed melphalan-prednisone-thalidomide (MPT) was introduced. He died 17 months after the MM diagnosis without clinical signs of RCC recurrence.

Case 2

A 44-year-old male presented in October 2004 with a large soft palate and tongue mass. Biopsy of the soft palate revealed diffuse large B-cell non-Hodgkin lymphoma (NHL) (DLBCL) and immunophenotyping showed the cells to be positive for CD19, CD20, CD79a, bcl-6 and negative for CD10, CD23. While staging, abdominal computed thomography (CT) scan revealed a large 7 × 5 cm right renal mass, with no hepatosplenomegaly and lymphadenopathy. Further evaluation by magnetic resonance imaging (MRI) excluded central nervous system or thoracic involvement. He had no peripheral lymphadenopathy, his hemogram and biochemistry were within normal ranges, his cerebrospinal fluid was acellular and bone marrow biopsy was unremarkable. It was decided to start with anti-lymphoma treatment. After 6 cycles of CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) regimen the lesion in the oral cavity completely resolved. However, abdominal CT scan showed further enlargement of the right kidney tumor mass. He underwent right nephrectomy, revealing early-stage clear cell RCC. At the tone of this report, the patient was still disease free from NHL and RCC.

Case 3

A 68-year-old female patient presented in November 1996 with abdominal pain. As her complete blood count (CBC) revealed mild lymphocytosis ($11 \times 10^9$/L) and abdominal CT scan showed a 50 × 62 × 62 mm lobulated mass with well-defined margins at the lower pole of the left kidney she was referred to the hematologist and urologist. Hematological evaluation revealed chronic lymphocytic leukemia (CLL) clinical stage (CS) 0. Then the patient underwent left radical nephrectomy and splenectomy, which showed renal cell carcinoma RCC with no lymph node involvement. Splenectomy was performed due to iatrogenic injury. At the patient CLL remained stable without treatment, and there was no signs of RCC recurrence.

Case 4

A 48-year-old female patient was diagnosed with early stage RCC of clear cell type after right nephrectomy in June 2000. Eighteen months later she presented with back pain

**Table 1**

**Summary of the patients' demographic, clinical and pathological characteristics**

| Patient | Gender | Age at RCC | RCC type/TNM stage | RCC treatment | LP | Age at LPN | LPN Type/ clinical stage | LPN treatment | Outcome & survival |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 69 | Clear cell type pT1N0M0 | right N | 8 | 70 | MM IgA kappa IIIB | VAD (VI cy) MPT (VI cy) | 17 months |
| 2 | Male | 44 | Clear cell type pT2N0M0 | right N | 0 | 44 | NHL DBCL IE (oral cavity) | CHOP (VI cy) | CR ≥ 9* years |
| 3 | Female | 68 | Clear cell type pT2N0M0 | left N | 0 | 68 | CLL A | ∅ | ≥ 17* years |
| 4 | Female | 48 | Clear cell type pT2N0M0 | right N | 18 | 50 | MM IgG kappa IIIB | VAD (VI cy) MP (X cy) | 25 months |
| 5 | Male | 60 | Clear cell type pT1N0M0 | right N | -28 | 58 | CLL A | ∅ | ≥ 7* years |

**N – nefrectomy; LPN – lymphoproliferative neoplasms; LP – latent period (in months); minus represents primary LPN occurence; TNM – tumor; nodes, metastasis; ∅ – "watch and wait"; * – alive; RCC – renal cell carcinoma; MM – multiple myeloma; NHLDBCL – non-Hodgkin lymphoma diffuse B-cell; CLL –chronic lymphocytic leukemia; VAD – vincristine, adriamycin dexamethasone; MP – melphalan, prednisone, thalidomide; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisone; Cy – cycles.**

with subsequent diagnosis of MM IgG kappa CS IIIB (monoclonal IgG kappa 72 g/L, hemoglobin 72 g/L, creatinine 139 mmol/L, multiple lytic bone lesions with compression fracture of the thoracic vertebra). The patient was given 6 cycles of VAD chemotherapy together with palliative spinal radiotherapy. As her MM progressed she received ten cycles of melphalan-prednisone regimen, and died 25 months after MM diagnosis without signs of RCC recurrence.

Case 5

A 60-year-old male patient was referred to the urologist in February 2006 because of hematuria and a 3 × 2.5 cm solid mass at lower pole of right kidney without lymph node enlargement seen on abdominal CT scans. The patient's past medical history revealed the diagnosis of CLL CS 0 established 28 months prior the RCC diagnosis. He underwent right nephrectomy which showed RCC, clear cell type. At present, 8 years from diagnosis of CLL and 6 years from the diagnosis of RCC he was without evidence of CLL progression or RCC recurrence.

**Discussion**

Based on data from the National Cancer Institute's Surveillance, Epidemiology and Results Program (SEER) database the median age at the diagnosis of cancer of the kidney and renal pelvis was 64 years while the age-adjusted incidence rate was 15.3 *per* 100,000 men and women per year with male preponderance (male:female ratio = 2 : 1). These rates are based on cases diagnosed in 2006–2010. Using statistical models for analysis, rates for new kidney and renal pelvis cancer cases have been rising on average 1.7% each year. In the same period the age-adjusted incidences of CLL, NHL and MM were 4.3, 19.7 and 5.9 *per* 100,000 people, respectively [12]. Rates for new leukemia, non-Hodgkin lymphoma and myeloma cases have been rising much slower (0.1%, 0.5% and 0.7%, respectively) [12]. A reciprocal increase in the risk of RCC and after LPN and *vice versa* have been implicated several decades ago by Travis et al. [13, 14]. Evaluating data from SEER database they reported that, comp ared with the general population, NHL patients were at significantly increased risk of developing RCC with the observed to expected ratio 1.47 in 10-year survivors, and 2.07 after 15 years [14]. Two large recently published population based studies – one based on data of the Swedish Family cancer Database [3] and another based on data of the Cancer Registry of Norway [15] confirmed a higher standardized incidence ratio (SIR) for NHL in RCC patients, i.e. 2.09 and 2.47, respectively. Higher SIR for concomitant occurrence of NHL and RCC in the same patient was also found in large hospital-based studies [2, 5]. Based on data registered in the SEER between 1973 and 2006 the risk of hematologic malignancies was highest in the first six months after the diagnosis of RCC, but declined thereafter [16]. Lossos et al. [17] reported the elevated risk of RCC after NHL persisting over 10 years after RCC diagnosis.

Concerning the association between MM and RCC, the largest so far reported population-based study revealed that the relative risk of MM occurrence was 51% higher among patients with RCC than in the general population and that the relative risk of RCC occurrence was 89% higher among MM patients than in the general population. The highest risk of second malignancy was within the first year after the diagnosis of first malignancy [4]. In reported case series based on single institution data, an increased association between MM and RCC was also observed [9, 10, 18].

Hitherto, only two reports with differing results had been published by Rabbani et al. [19, 20]. Notably, in both studies patients with RCC and antecedent or synchronous diagnosis of the second cancer were excluded from analysis of the observed and expected numbers of second cancers that may bias the data away from finding association.

In our series five patients with concomitant LPN and RCC were identified. Concerning RCC, the most common histological subtype is clear cell RCC representing 75–80% of RCC [21]. Our experience is similar – 82% of 570 evaluated consecutive patients with RCC had clear cell hystological subtype. Ohsawa et al. [6] reported that the distribution of histological subtypes of RCC in 42 patients with associated lymphoma is almost similar to that in sporadic RCC. Notably, clear cell RCC was the exclusive RCC histological subtype in our series and all the patients in our series had early-stage RCC requiring only nephrectomy.

Concerning the LPN type, two patients in our series had advanced stage multiple myeloma, two early stage CLL requiring no treatment, while the only patient with NHL and RCC had extranodal DLBCL. In a report of Kunthur et al. [7] four of six patients with NHL and RCC had extranodal lymphoma. In a case series reported by Serefhanoglu et al. [11] the only patient with NHL and RCC also had extranodal lymphoma presented as paravertebral mass. There are also several interesting case reports of concurrent extranodal NHL and RCC [22–24]. Ohsawa et al. [6] commented that the frequency of extranodal lymphoma was higher that would be expected. Reasons for eventual higher extranodal lymphoma occurrence in RCC patients are not yet clarified.

Of interest is that two patients in our series had synchronous occurrence of RCC and LPN (patients 2 and 3). One patient immediately underwent left nephrectomy (patient 3), but in another patient right kidney tumor mass was initially misdiagnosed as another extranodal localization of NHL (patient 2). Not until the cytotoxic treatment for NHL had been completed the patient underwent nephrectomy, and fortunately his RCC didn't spread for that period.

Such disease timing and lack of prior cytotoxic treatment suggests common etiologic factors as an explanation for common relationship between LPD and RCC. The increased incidence of dual malignancy may be explained by common genetic mutations [25, 26]. Structural abnormalities of chromosomes 17 and 8 involving the p53 and c-myc genes are present in MM patients and carry a poor prognosis [25], and an over-expression of c-myc located in 8q24 has been observed in up to 20% of clear cell RCC resulting in cell cycle promotion and renal oncogenesis [26]. Documented alterations of immune system in LPN and RCC may be caused by first malignancy or predispose to both malignanci-

es [27–29]. Interleukin-6 (IL-6) is known for its ability to support cell growth and prevent apoptosis of multiple myeloma, lymphoma and leukemia cells [27], Vascular endothelial growth factor (VEGF) is one of the important endogenous factors that promote angiogenesis in hematological malignancies [28, 29]. An increase in IL-6 and VEGF was also observed in the serum of patients with RCC [30]. So far, several anti-IL-6/IL-6 receptor monoclonal antibodies and five drugs targeting VEGF or its receptors (bevacizumab, sunitinib, sorafenib, pazopanib and axitinib) have been developed for targeted therapy in cancer patients, including LPN i RCC and have demonstrated promising results in both preclinical studies and clinical trials [31–33]. Obesity and smoking are the most consistently established epidemiological predisposing factor for RCC and LPD [34, 35], but none of our patients was obese, and only two (patients 1 and 5) were smokers.

**Conclusion**

Even though the number of patients in our series is small, our results suggest that association of lymphoproliferative neoplasms and renal cell carcinoma cannot be explained by chance alone. Synchronous appearance and lack of chemo-, imuno- or radiation therapy for first malignancy in our series favors the common biology of these malignancies. From the clinical perspective, this emphasizes the need for more careful follow-up of patients with localized renal cell carcinoma within the first years following nephrectomy. On the other hand, for the patients with non-Hodgkin lymphoma the histological confirmation of solid tumor masses must be provided to distinguish the spread of initial neoplasm from the occurrence of another cancer. This may enhance the chances for accurate diagnosis, better treatment timing and favorable prognosis.

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Received on March 23, 2014.
Accepted on June 26, 2014.
Online First July, 2015.