



Acquired cystic disease and renal cell carcinoma in hemodialysis patients – A case report on three patients

Stečena cistična bolest i karcinom bubrega kod bolesnika na hemodijalizi

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Abstract

Introduction. Renal cell carcinoma (RCC) is derived from renal tubular epithelial cells and represents approximately 3.8% of all malignancies in adults. The incidence of renal cell carcinoma has been growing steadily and ranging from 0.6 to 14.7 for every 100,000 inhabitants. Patients with end-stage renal disease and acquired cystic kidney disease are at increased risk of developing RCC while undergoing dialysis treatment or after renal transplantation. **Case report.** We presented 3 patients undergoing hemodialysis, with acquired cystic kidney disease accompanied by the development of RCC. In all the patients tumor was asymptomatic and discovered through ultrasound screening in 2 patients and in 1 of the patients by post-surgery pathohistological analysis of the tissue of the kidney excised using nephrectomy. All the three patients had organ-limited disease at the time of the diagnosis and they did not require additional therapy after surgical treatment. During the follow-up after nephrectomy from 6 months to 7 years, local recurrence or metastasis of RCC were not diagnosed. **Conclusion.** Acquired cystic kidney disease represents a predisposing factor for the development of renal cell carcinoma in dialysis patients and requires regular ultrasound examinations of the abdomen aimed at early diagnosis of malignancies. Prognosis for patients with end-stage renal disease and RCC is mostly good because these tumors are usually of indolent course.

Key words:

renal dialysis; kidney diseases, cystic; hemodialysis; nephrectomy; treatment outcome.

Apstrakt

Uvod. Karcinom bubrega (*renal cell carcinoma* – RCC) nastaje iz renalnih epitelnih ćelija tubula i čini oko 3,8% svih maligniteta kod odraslih. Incidencija RCC je u stalnom porastu i iznosi 0,6 do 14,7 na 100 000 stanovnika. Bolesnici sa terminalnom bubrežnom insuficijencijom i stečenom cističnom bolešću bubrega su u povećanom riziku od razvoja RCC tokom lečenja dijalizom ili nakon transplantacije bubrega. **Prikaz bolesnika.** U radu su prikazana 3 bolesnika lečena hemodijalizom sa stečenom cističnom bolešću bubrega koja je bila udružena sa razvojem RCC. Kod svih bolesnika tumor je bio asimptomatski i otkriven je ultrazvučnim pregledom kod dva bolesnika, a kod jednog patohistološkom analizom tkiva bubrega odstranjenog nefrektomijom. Kod sva tri bolesnika bolest je bila organ-ograničena u vreme postavljanja dijagnoze i nije zahtevala primenu dodatne terapije nakon hirurškog lečenja. Tokom perioda praćenja od 6 meseci do 7 godina nakon nefrektomije, nije dijagnostikovano postojanje lokalne rekurencije ili metastaza RCC. **Zaključak.** Stečena cistična bolest bubrega predstavlja predisponirajući faktor razvoja RCC kod bolesnika na dijalizi i zahteva redovne ultrazvučne kontrole abdomena u cilju postavljanja rane dijagnoze maligniteta. Prognoza kod bolesnika sa terminalnom bubrežnom insuficijencijom i RCC u najvećoj meri je dobra jer su karcinomi bubrega kod ovih bolesnika, uglavnom, indolentnog toka.

Ključne reči:

bubreg, neoplazme; bubreg, cistični; hemodijaliza; nefrektomija; lečenje, ishod.

Introduction

Renal cell carcinoma (RCC) is derived from renal tubular epithelial cells. This type of cancer represents approximately 3.8%

of all malignancies in adults of the general population. The incidence of RCC has been growing steadily for the last 30 years, ranging from 0.6 to 14.7 for every 100,000 inhabitants¹⁻³. Treatment of RCC is the current oncologic problem, because, in spite

of modern diagnostic methods and surgical treatment a patient survival with RCC has not significantly improved in the last 15 years. At the time of diagnosis, 30% to 40% of patients either clearly show metastatic disease or it is clinically unrecognizable depending on the stage of the disease. Optimal treatment of kidney cancer is surgery, applying radical or partial nephrectomy for small tumors in order to maintain a functioning renal tissue^{3,4}.

Patients with end-stage renal disease (ESRD) and acquired multiple renal cysts are at increased risk of developing RCC during dialysis or after renal transplantation. The prevalence of RCC in this group of patients is 3% to 5%, which corresponds to the rate 100 times higher than sporadic RCC type in the general population^{2,3}. Acquired cystic kidney disease (ACKD) is an independent risk factor for the development of RCC in these patients. ACKD is defined by the presence of multiple renal cysts (three or more per kidney), filled with serous fluid, in a patient with ESRD. Patients with ACKD have 50 times higher risk of developing RCC compared to the general population^{4,5}. To date, the pathogenesis of ACKD and RCC associated with it remain undetermined⁵⁻⁷. Several factors are considered to contribute to development of ACKD and RCC in ESRD patients: ischemia, uremic toxins like p-cresol, increased secretion of parathyroid hormone and growth factors, depressed immunity, viral infections, obstruction of renal tubules due to fibrosis and oxalate deposits, and other factors⁴⁻⁷. The prevalence of ACKD in dialysis patients is from 30% to 90% and increases with the duration of dialysis. ACKD was reported to be observed in 20% of patients with ESRD in the period before dialysis, rising to 60–80% in patients more than 4 years on dialysis and approximately in 90% of those on dialysis more than 8 years⁸.

The association of RCC and ESRD is manifested in specific clinical and pathological characteristics in relation to RCC in the general population. Common clinical symptoms typical for the most forms of sporadic renal cancer, such as hematuria, lumbar pain, infection and elevated temperature, are generally absent in patients with ESRD and RCC. This group of patients are diagnosed with papillary renal cell carcinoma in more than 40% of cases, in contrast to clear cell renal cell carcinoma diagnosed in approximately 70% of the sporadic forms of the tumor⁴. In comparison with the sporadic RCC, these tumors are more frequent in pT1 stage (smaller than 70 mm), low-grade malignancy and rarely with the appearance of distant and regional lymph nodes metastases⁹. The prognosis for patients with ESRD and RCC is mostly good because these tumors are usually of indolent course¹⁰.

The aim of this article was to show clinical and histopathological characteristics in 3 surgically treated patients with ESRD and ACKD associated with RCC. In all the patients malignant disease was asymptomatic. There were no complications related to the surgery, general anesthesia and the cardiovascular system during or immediately after nephrectomy.

The presented patients were still treated according to the protocol of ESRD and controlled in accordance with the recommendations of the European Association of Urology Guidelines on Renal Cell Carcinoma¹¹. During the clinical follow-up after nephrectomy from 6 months to 7 years, local recurrence or metastatic RCC was not diagnosed.

Case 1

A 35-year-old patient was admitted for a pretransplantation proceeding for potential living related renal transplantation. The main disease which caused end-stage renal disease was systemic lupus erythematosus and lupus nephritis. The patient was treated with hemodialysis for 4 years. We performed regular ultrasound examination of the abdomen and diagnosed the presence of circular, hyperechogenic formation in interpolar part of the right kidney, whose diameter was 23 mm. Both kidneys were reduced in size, the longitudinal diameter of each was about 9 cm, reduced parenchyma, with multiple cysts. The largest diameter of individual cyst was 1.5 cm. Based on ultrasound examination, the patient was suspected to having tumor of the right kidney. Multislice computed tomography (MSCT) of the abdomen was performed and diagnosed the existence of a tumor, 22 × 25 × 30 mm in diameter, with no signs of breaking kidney capsula. The patient underwent a radical right nephrectomy. Histopathological examination showed the existence of tumor whose largest diameter was 20 mm, mostly with hemorrhagic necrosis. Malignancy was diagnosed as: Renal cell carcinoma cysticum et necroticum, Fuhrman grade 2, stage T1Nx (Figure 1). There were a number of renal cysts lined with flattened epithelium, without atypia. Pathology assessment of the non-tumor specimen revealed chronic diffuse and global glomerular and interstitial lesions within the class IV lupus nephritis. The tumor was organ-confined and application of additional therapy was not indicated. Seven years after the operation there was no occurrence of RCC progression.

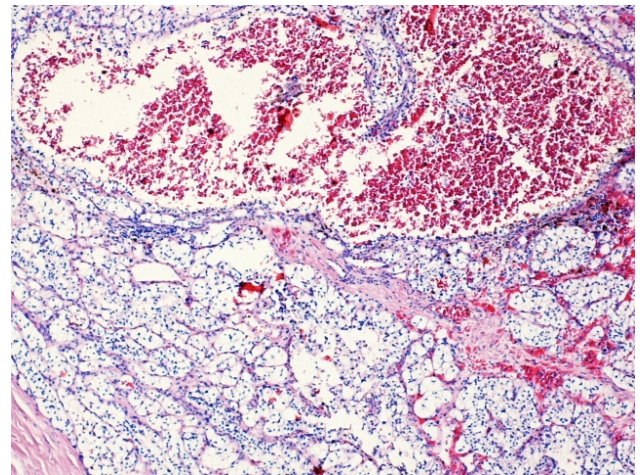


Fig. 1 – Large field of cystic degeneration and hemorrhagic necrosis in clear renal cell carcinoma, Fuhrman grade 2 (Hematoxylin-eosin, ×75).

Case 2

A 76-year-old patient was on chronic hemodialysis for 2 years. The main disease which caused end-stage renal disease was ischaemic nephropathy. Laboratory blood tests were within the range typical for patients undergoing hemodialysis. We performed regular ultrasound examination of the abdomen and incidentally diagnosed the presence of circular formation

in the lower half of the left kidney, dimensions 30 × 35 mm, which was suspected to the presence of tumor. Both kidneys were reduced in size, the right kidney was 8 cm and the left one 9 cm, thinned, echogenic parenchyma, with multiple cysts in both kidneys. The largest diameter of individual cyst was 1 cm. MSCT of the thorax and abdomen was performed showing well-vascularized tumor in the lower pole of the left kidney, measuring 33 × 33 mm, with no signs of local and distant metastases. Radical left nephrectomy along with adrenalectomy and regional lymphadenectomy was performed. Pathology assessment of the nephrectomy specimen revealed Fuhrman grade 2, clear cell renal carcinoma, staged as T1N0, with involvement of tumors vascular space. Due to the localized disease further application of treatment was not indicated.

Case 3

A 58-year-old patient was admitted for nephrectomy of the right dysfunctional kidney. The disease which caused end-stage renal disease was reflux nephropathy. The patient had been on home hemodialysis for 21 years and had recurrent urinary tract infections that required frequent use of antibiotics. That was the reason why the patient had radical left nephrectomy a month before. MSCT of abdomen was performed preoperatively and showed the existence of reduced kidneys size, the right kidney was 9.5 cm and the left one 7.5 cm, markedly thinned parenchyma, with the present small cystic changes. Histopathological examination showed the existence of the atrophic left kidney with cortical cysts. Then, the patient underwent a radical right nephrectomy and the lesion histologically proved to be the subtype of RCC, labeled as acquired cystic disease-associated renal cell carcinoma of nuclear grade Fuhrman 1, stage T1N0 (Figures 2 and 3). Since the disease was organ-confined, urological-oncology data indicated regular controls, with repeated ultrasound and CT examinations, as recommended for the treatment of RCC.

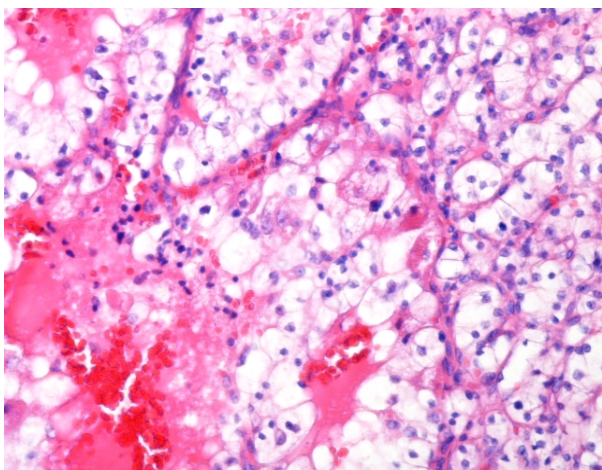


Fig. 2 – Small papillary structures composed of the light of neoplastic cells within the acquired cystic disease-associated renal cell carcinoma, Fuhrman grade 1 (Hematoxylin-eosin, ×75).

Discussion

Patients with ESRD have an increased risk of developing RCC in their native kidneys and ACKD represents the predisposing factor for its onset⁵. Continuous research on the correlation between RCC and ACKD has been on-going for more than half a century. The first results of this correlation were autopsy findings. A group of authors from Oxford, Dunnill et al.¹², published the autopsy results of 30 patients with ESRD in 1977. Cystic kidney disease, now ACKD, was present in 14 of the patients, of which 6 also had RCC. One autopsy report also showed dissemination of RCC. Thanks to the results of this analysis, ACKD initially obtained a complex definition as macroscopically visible cystic structures which covered at least 25% of the renal parenchyma or more than 3 cysts in the kidney in patients with kidney insufficiency, with negative family medical history regarding cystic kidney disease.

The authors Matson and Cohen¹³ drew attention to the significance of the duration of dialysis for the onset of ACKD and its correlation to RCC in 1990. The correlation of RCC and ACKD ranged from 0.3% to 14%, depending on the number of patients involved in studies, but most often they ranged from 3 to 5%^{3,4,13,14-16}. Some epidemiological studies show significant differences compared to the presence of RCC in patients on dialysis. The number of patients on dialysis and with newly onset RCC increased by 15 times in Japan in the last three decades, but the correlation of ACKD and RCC is still lower than 6%¹⁴. Compared to the same group of patients in Europe and North America, this number is 4 to 5 times lower⁴.

The results of a great number of studies especially draw attention to the correlation between the duration of dialysis and the onset of RCC¹³⁻¹⁶. In the study of Kojima et al.¹⁴ on 2,624 patients with ESRD, RCC was also diagnosed after 11.2 years of dialysis therapy on the average in 44 (1.68%) of the patients of which ACKD was already present in 36

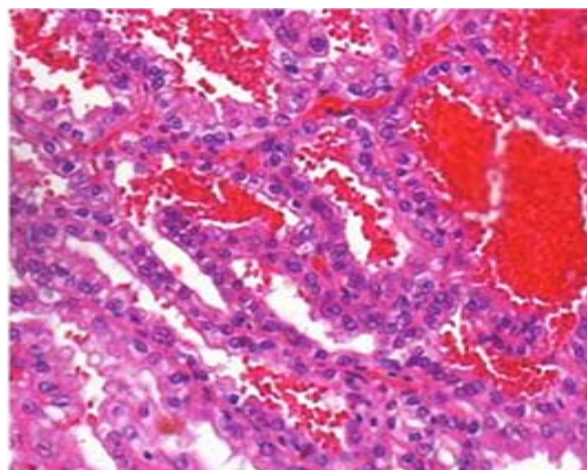


Fig. 3 – Tubular structures within the acquired cystic disease-associated renal cell carcinoma, coated with cubic neoplastic cells and surrounded by hemorrhagic necrosis (Hematoxylin-eosin, ×100).

(81.8%) of them. The results of one of the latest and largest studies which monitored more than 7,000 dialysis patients show that in 22 (0.3%) of them RCC was diagnosed and surgically treated, while at the same time in 18 (82%) patients the acquired cystic kidney disease was already present alongside cancer¹⁵. Only one of our 3 patients was on a long-term dialysis therapy (21 years), while the other two patients spent significantly less time on hemodialysis (4 and 2 years). All patients were treated with hemodialysis and they had manifested ACKD.

There were no surgery or post-surgery complications in the patients on dialysis with ACKD and RCC in our analysis. Patients on dialysis with RCC are a high-risk group for surgical procedures, especially due to the worsening of cardiologic and respiratory complications which are already present within the basic chronic kidney disease¹⁷.

In dialysis patients, most kidney cancers are detected during ultrasound screening because of ACKD, due to the fact that they are most often asymptomatic⁴. The widespread and modern application of radiologic diagnostic procedures for the detection of presymptomatic tumors in patients with ESRD can be linked to the significant increase of RCC incidence¹⁴⁻¹⁸. The asymptomatic landscape in relation to RCC was also present in the patients from our study. Kidney tumors were diagnosed in 2 of the patients during routine ultrasound screenings, while in the third patient it was undetected within the kidney cysts. In 2 of the 3 patients, the suspected presence of kidney tumor with ACKD was confirmed by both ultrasound and MSCT examination. On the basis of the conducted radiological examinations, tumorous changes in the right kidney were not suspected in the third patient. Small tumor with cystic degeneration was masked by multiple cysts within ACKD, so the diagnosis of the entity "acquired cystic disease-associated renal cell carcinoma" (ACDAC) was established by the post-surgery pathohistological analysis of the tissue of the removed kidney.

ACDAC represents a more recent pathohistological entity which is often diagnosed in patients with terminal renal insufficiency and with acquired multiple cysts of the kidney. Compared to sporadic RCC, ACDAC has better prognosis due to the fact that it gets detected in its early stages and rarely metastasises^{19,20}. The pathohistological diagnosis of ACDAC is established in 46% of patients with ESRD. The macroscopic appearance of the cystic structure is its most common presentation and it occurs in around 67% of patients⁹.

This subtype of kidney cancer manifests microscopic variations of the growth pattern from papillary and cystic to solid and acinar, in part with cribriform areas. Tumorous cells are abundant eosinophil or oncocytic cytoplasm, of prominent nucleoli, at times also with intratumoral deposits of calcium oxalate crystals^{9, 19, 20-22}. In the results of previous studies, this type of carcinoma was often diagnosed as clear cell carcinoma with cystic degeneration. According to the latest recommendations of the International Society of Urological Pathology (ISUP), ACDAC has been identified as separate entity²². Rare cases of transformation of ACDAC into RCC showing sarcomatoid or rhabdoid differentiation^{9, 20, 21} have also been described. The diagnostics of sarcomatoid RCC, as the RCC with the greatest malignant potential are often linked to the

duration of dialysis. The results of the study of Sassa et al.²⁰ in a group of 23 patients with a dialysis period of longer than 20 years show that the sarcomatoid type of RCC was diagnosed in 6 patients. This result shows that dialysis therapy lasting more than 10 years represents a significant risk-factor for the development of a more aggressive type of RCC. In this presentation of the patient 3, with dialysis therapy lasting more than 20 years, the tumor was diagnosed which had the histological features of ACDAC but which was of low malignancy, Fuhrman grade 1, pT1a, L0V0. This patient was subjected to bilateral nephrectomy. In fact, in patients with ACKD bilateral nephrectomy is rarely indicated. Indications for bilateral nephrectomy include ACKD patients with complications of ACKD such as intra- and pericystic bleeding, rupture with retroperitoneal hemorrhage and malignant transformation. Borràs et al.²³ presented the case of spontaneous bilateral cyst rupture with retroperitoneal hemorrhage and hemoperitoneum in the PD patient with ACKD which is an indication for bilateral nephrectomy. Ghasemian et al.²⁴ presented experience with bilateral laparoscopic radical nephrectomy performed in 10 patients with ACKD and renal lesions suspicious for carcinoma. Our patient had recurrent (an average of 6 episodes *per* year) urinary tract infections in the last 5 years of dialysis treatment, often followed by high temperature and fever. That was the reason for the repeated and prolonged antibiotic administration in this patient and therefore we indicated bilateral nephrectomy.

The duration of kidney disease, less often than the dialysis itself, can be a more significant determining factor in the development of ACKD and RCC¹⁶. This can explain the development of RCC in our female patient after only 4 years of dialysis therapy; bearing in mind the fact that the patient was treated for systemic erythematous lupus in the previous 21 years with various immunosuppressive drugs (cyclophosphamide, corticosteroids), as well as plasma exchanges. RCC diagnostics is extremely rare in patients with SLE. Hematological neoplasms are often observed in these patients; especially lymphomas and lung carcinoma, as well as hormone-dependant breast and uterus carcinomas²⁵. Patients with SLE also demonstrate multiple defects in both humoral and cellular immunity, so the onset of lymphoma can be indirectly linked to the onset of the pathological clone of B lymphocyte²⁶. According to the available literature, only two cases of RCC diagnostics in patients with systemic lupus have been published so far²⁷.

Moderately impaired kidney function may be an independent risk factor for cancer in older men with a graded increase in the risk as glomerular filtration rate (GFR) declines²⁸. This group of patients has the higher mortality of liver cancer, kidney cancer and urinary tract cancer²⁹. In our patient 2, RCC developed after only 2 years of dialysis therapy, which could be explained by the fact that the patient was 76 years old man at the time of the diagnosis.

The prognosis for dialysis patients with the diagnosed RCC is better than in nonuremic patients with RCC, due to the low incidence rate of metastatic abnormalities¹⁰. All the three of our patients had organ-limited disease at the time of the diagnosis without any signs of nodal or distant metastases, and they did not require additional therapy after surgical treat-

tment. The patients were regularly examined, and in the follow-up period, which was 6 months in the patient 3, and up to 7 years in the patient 1, no RCC recurrence or dissemination was diagnosed.

Conclusion

This report on the 3 patients on hemodialysis with acquired multiple renal cysts shows that hemodialysis duration of more than 10 years, older age, and duration of treatment of

kidney disease that led to end-stage renal disease may be predisposing factors for the development of renal cell carcinoma. The outcome of surgically treated patients on maintenance hemodialysis with the diagnoses of renal cell carcinoma is usually good because acquired cystic kidney disease-associated carcinomas are of low pathological stage.

Acquired cystic kidney disease represents a predisposing factor for the development of renal cell carcinoma in dialysis patients and requires regular ultrasound examinations of the abdomen aimed at the early diagnosis of malignancies.

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