



COLLECTING DUCT CARCINOMA AND ENDEMIC NEPHROPATHY – CASE REPORTS AND LITERATURE REVIEW

Matej Knežević¹, Karla Tomić², Damir Dittrich³, Ivana Vuković Lela^{4,5},
Boris Ružić^{1,4}, Borislav Spajić^{1,4}, Krešimir Karlović³ and Goran Štimac¹

¹Department of Urology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia;

²Department of Pathology, Dr Josip Benčević General Hospital, Slavonski Brod, Croatia;

³Department of Urology, Dr Josip Benčević General Hospital, Slavonski Brod, Croatia;

⁴School of Medicine, University of Zagreb, Zagreb, Croatia;

⁵Department of Nephrology, Arterial Hypertension and Dialysis, Zagreb University Hospital Centre, Zagreb, Croatia

SUMMARY – Although collecting duct carcinoma is a subtype of renal cell carcinoma, several studies implicate association with urothelial carcinoma. The coexistence of collecting duct carcinoma and another renal neoplasm is rare. Endemic nephropathy is a renal disease causing chronic renal failure. It is highly associated with urothelial neoplasm and occurs in endemic villages in Bosnia, Croatia, Bulgaria, Romania and Serbia. Recent studies have confirmed the important role of exposure to aristolochic acid as an etiologic factor. We present three cases of collecting duct carcinoma with literature overview. In one case, we describe collecting duct carcinoma with metachronous urothelial carcinoma of the pyelon and urinary bladder in an endemic nephropathy patient. To our knowledge, this is the first case report describing this coexistence. Certain similarities between collecting duct carcinoma and urothelial carcinoma were found, e.g., higher incidence in female compared to male, higher mean age, and multifocal and multicentric occurrence of the tumor. Our observations support the hypothesis that collecting duct carcinoma and urothelial carcinoma could be connected.

Key words: *Collecting duct carcinoma; Bellini duct carcinoma; Endemic nephropathy; Kidney neoplasm; Renal failure; Urothelial carcinoma*

Introduction

Collecting duct carcinoma (CDC) or Bellini duct carcinoma is a rare epithelial neoplasm of the kidney that accounts for 0.4% to 2.6% of all renal neoplasms¹. These tumors behave in an aggressive manner with metastatic spread in one-third of patients at the time of diagnosis^{2,3}. It predominantly occurs in younger male patients (mean age at diagnosis 43 years, male to female ratio (M/F) 2:1)⁴. Endemic nephropathy (EN) is a renal disease affecting inhabitants of rural areas in

Bosnia, Croatia, Bulgaria, Romania and Serbia. It causes chronic renal failure and has strong association with the high incidence of urothelial carcinoma of the upper urinary system (UC)⁵. Recent studies confirmed the important role of exposure to aristolochic acid as the etiologic factor⁶.

Case Reports

Case 1

A 69-year-old woman from an endemic village presented with right renal colic and massive hematuria. Medical history revealed previous nephroureterectomy of the left kidney due to invasive UC of the renal pelvis (pT3, G2), consistent with EN. On ultrasound

Correspondence to: *Matej Knežević, MD*, Department of Urology, Sestre milosrdnice University Hospital Centre, Vinogradska c. 29, HR-10000, Zagreb, Croatia

E-mail: matejknezevic1@gmail.com

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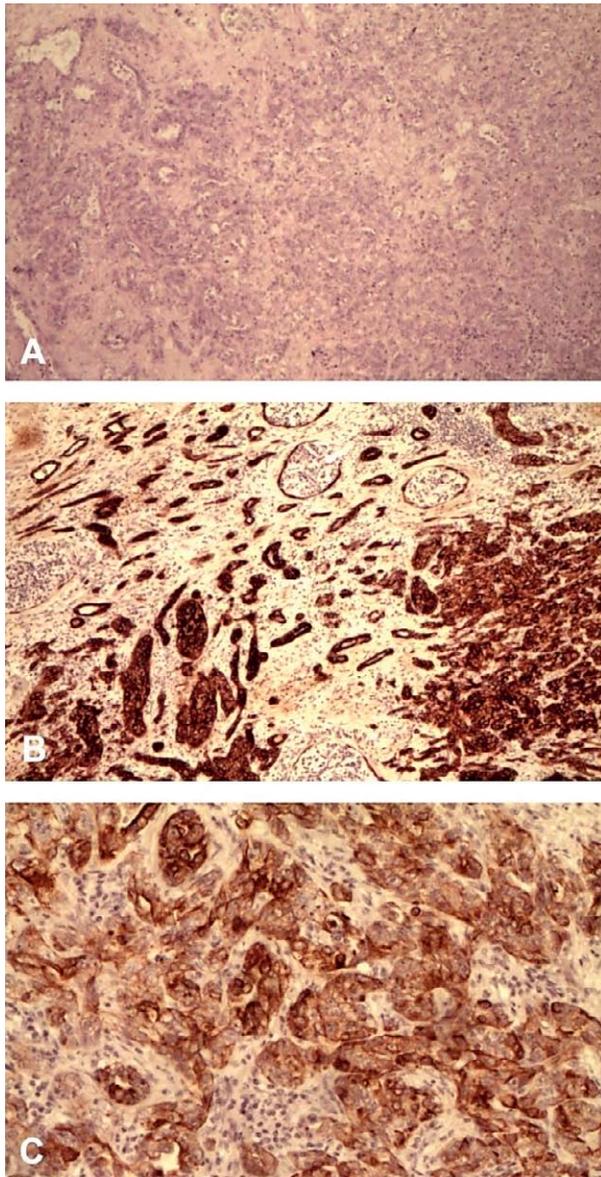


Fig. 1. Histologically, the tumor was composed of small tubules with highly atypical cells and marked desmoplastic stroma (hemalaun/eosin $\times 100$) (A); immunohistochemically positive CK7 $\times 100$ (B); and CK34&E12 $\times 200$ (C).

(US) and computer tomography (CT) scan, a tumor mass measuring 85x65x55 mm was found in the superior part of the contralateral right kidney. The patient underwent radical nephroureterectomy. Histologically, the tumor was composed of small tubules with highly atypical cells and marked desmoplastic stroma. Immunohistochemical analysis with CK7, CK34&E12, CD10 and vimentin confirmed the diagnosis of CDC

(pT3, G2) (Fig. 1 A, B, C). Postoperatively, the patient was referred to hemodialysis and discharged home in good condition. After eight months, she was readmitted to the hospital due to severe hematuria. Cystoscopy revealed a tumor of the urinary bladder. Salvage cystectomy was performed. Histopathologic analysis showed UC (pT1, G2, high grade according to the World Health Organization (WHO) classification from 2004). The patient died 11 months after the initial diagnosis due to malignant disease.

Case 2

A 66-year-old male was admitted to the hospital due to lower urinary tract symptoms. Routine US described suspicious hypoechogenic zones in the right kidney, and CT confirmed a tumor mass measuring 44x43 mm. Radical nephrectomy was performed. Histopathologic examination with immunohistochemistry diagnosed CDC (pT3a, G4). After 10 days, the patient was discharged in a satisfactory condition. Due to poor general state, chemotherapy and radiotherapy were not indicated. Eight months after the initial diagnosis, the patient's condition deteriorated (with malaise and loss of weight) and the patient died.

Case 3

A female patient aged 61 suffering from hematuria and right lumbar pain was admitted. US showed a right kidney tumor. CT detected a soft tumorous mass measuring 40x35x30 mm in the lower and middle group of calices. Radical nephrectomy of the right kidney was performed. Immunohistologically, the tumor was diagnosed as Bellini duct carcinoma with positive regional lymph nodes (pT3N1, G3). Six days after surgery, the patient was discharged in good condition. Chemotherapy was administered (M-VAC protocol and sorafenib). The patient developed lung metastases after 10 months. Liver and bone metastases were found in additional 6 months. The patient died 18 months after the initial diagnosis due to primary disease.

All procedures performed in the studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An informed consent was obtained from all patients included in the study.

Discussion

Collecting duct carcinoma is a rare neoplasm with 1% incidence of all renal tumors⁷. The coexistence with another renal neoplasm has been rarely described, usually with other subtypes of renal cell carcinoma (RCC) and UC⁸. According to the WHO, CDC is a subtype of RCC, although some authors implicate association and similarities with UC⁹. The possible association of CDC and UC may reflect their common embryologic origin in Wolf's duct¹⁰. Our observations suggest some similarities between CDC and UC.

We analyzed all nephrectomy cases treated for renal and ureteral tumor at the Department of Urology in the endemic nephropathy region during the 2008-2010 period. During the study period, 84 cases were diagnosed as renal or ureteral tumor (M/F=1:1.27, mean age 68.2). RCC was diagnosed in 29 cases (M/F=1.63:1, mean age 63.9), UC in 52 cases (M/F=1:1.88, mean age 74.3), and CDC in 3 cases (M/F=1:2, mean age 66.6). The incidence of CDC in our Department was 3.57% of all renal tumors including upper urinary tract (pyelon, ureter), which was higher than expected concerning literature data¹⁰.

In Case 1, EN presenting with UC of the renal pelvis and urinary bladder occurred metachronously with CDC. To our knowledge, this is the first case report of this rare coexistence in the English literature. Nowadays, EN and UC are considered to be different clinical presentations of one disease that is influenced by exposure to aristolochic acid⁶. Following metabolic activation, aristolochic acid reacts with genomic DNA to form aristolactam-DNA adducts that generate a unique A:T to T:A transversions in the nontranscribed TP53 mutational spectrum. Therefore, these, otherwise rare mutations are a biomarker of exposure to aristolochic acid¹¹. Upper UC is present in 50% of EN cases, while they account for only 5% of all urinary tract cancers worldwide⁵. Specific UC mortality in the EN region compared to Croatia is 55 times higher (with female predominance)¹². Patients from endemic region with UC tend to have impaired kidney function. According to the modified WHO criteria, EN is defined by living in endemic region for more than 15 years, impaired kidney and anemia with exclusion of other causes of chronic kidney disease. Typical renal histopathology in early stages of EN shows extensive cortical tubular atrophy and dense interstitial fibrosis with gradient and little inflammation, but due to secondary changes, it is frequently insufficient for making

the diagnosis of EN in older population. Our first case of a patient from a Bosnian endemic village met the EN criteria; according to the epidemiologic survey, the patient had been exposed to aristolochic acid, and apart from Bellini duct carcinoma, had UC of the pyelon and a severely reduced kidney function (eGFR 17 mL/min). Histopathologic examination also revealed chronic pyelonephritis with already advanced interstitial fibrosis. Tumor TP53 mutational spectrum, using p53 AmpliChip Technology, demonstrated specific A:T to T:A transversions, which are the biomarker of exposure to aristolochic acid, and consequently EN marker. Therefore, this is a unique case of two different rare conditions and urothelial tract tumors in the same patient.

Our analysis confirmed that in the EN region, UC occurs more frequently than RCC, with a female predominance and higher mean age at onset. It is also observed that UC in EN regions is more frequently bilateral, multifocal and multicentric¹³. CDC from our endemic region shared some similarities with UC, e.g., higher incidence in female than male, higher mean age, and metachronous urothelial carcinoma of the pyelon and urinary bladder in one patient. CDC might be distinct from conventional RCC but shares biologic features with UC, with consequent implications for its management⁹. Because of the close relationship between CDC and UC (a common embryologic origin that arises from the mesonephrons), CDC could also have similarities with UC from endemic region in risk factors and showing a higher incidence in endemic region.

The understanding of the CDC is still insufficient. It is a disease with poor prognosis, survival and response to target therapies^{3,14}. The cases reported in this paper could contribute to deeper understanding of the rare CDC entity. Regarding this, our study supports the hypothesis that CDC and UC could be connected. Further larger studies on the possible connection to EN are needed.

Conclusion

The coexistence of CDC with other renal neoplasms is rare. We report the first case of CDC coexisting with UC of the pyelon and urinary bladder in an EN patient. Recently, aristolochic acid was confirmed as an etiologic factor for EN. On the other hand, the

understanding of CDC is still insufficient. This report presents an intriguing connection between CDC and UC of the upper urinary tract. The cases reported in this paper could contribute to better understanding of the rare CDC entity.

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Sažetak

KARCINOM SABIRNIH KANALIĆA I ENDEMSKA NEFROPATIJA – PRIKAZI SLUČAJA I PREGLED LITERATURE

M. Knežević, K. Tomić, D. Dittrich, I. Vuković Lela, B. Ružić, B. Spajić, K. Karlović i G. Štimac

Iako je karcinom sabirnih kanalića podvrsta karcinoma bubrežnih stanica, određena istraživanja ukazuju na povezanost ovog entiteta s karcinomom prijelaznog epitela. Istodobna pojava karcinoma sabirnih kanalića i drugih bubrežnih neoplazma je rijetka. Endemska nefropatija je bubrežna bolest koja dovodi do kroničnog bubrežnog zatajenja. Vrlo je povezana s urotelnim tumorima i javlja se u endemskim selima u Bosni, Hrvatskoj, Bugarskoj, Rumunjskoj i Srbiji. Nedavna istraživanja potvrdila su značajnu ulogu izloženosti aristolohičnoj kiselini kao etiološkom čimbeniku. Predstavljamo tri slučaja karcinoma sabirnih kanalića s pregledom literature. U jednom slučaju opisujemo karcinom sabirnih kanalića s metakronom pojavom urotelnog karcinoma pijelona te mokraćnog mjehura u bolesnika s potvrđenom endemskom nefropatijom. Prema našim saznanjima ovo je prvi slučaj koji opisuje ovakvu koegzistenciju. Pronađene su određene sličnosti između karcinoma sabirnih kanalića i karcinoma prijelaznog epitela, a to su veća učestalost u ženskoj populaciji, viša prosječna dob, multifokalna i multicentrična pojava tumora. Naša zapažanja podupiru hipotezu o mogućoj povezanosti karcinoma sabirnih kanalića i karcinoma prijelaznog epitela.

Ključne riječi: *Karcinom sabirnih kanalića; Karcinom Bellinijeva kanalića; Endemska nefropatija; Bubrežna novotvorina; Bubrežno zatajenje; Karcinom urotela*