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ENDEMIC NEPHROPATHY AND UPPER UROTHELIAL CARCINOMA – NEW INSIGHTS IN MOLECULAR BIOLOGY

Ljubinka Jankovic Velickovic[1], Zana Dolicanin[2], Vladisav Stefanovic[3]

[1] Institute of Pathology, Faculty of Medicine, University of Nis, Nis, Serbia
[2] State University of Novi Pazar, Novi Pazar, Serbia
[3] Department of Clinical Research, Faculty of Medicine, University of Nis, Nis, Serbia

Corresponding Author: Professor Vladisav Stefanovic, Faculty of Medicine, Bul. Zorana Djindjica 81, 18000 Nis, Serbia; Tel. +381 18 45 70 029, Fax: +381 18 42 38 770, E-mail: stefan@ni.ac.rs; dravel@open.telekom.rs

Abstract

Upper Tract Urothelial Carcinoma (UTUC) is an uncommon disease which occurs more frequently in some regions of Balkan countries than in other areas in the world. Investigation of UTUC in the South Morava River basin and its tributaries where BEN is endemic revealed increased frequency not only of tumour of the renal pelvis and ureter but also of urinary bladder tumours. A comparative morphological and immunohistochemical study of UTUC in the BEN region and control rural and city populations free of BEN, identify growth pattern as the best morphological characteristic which differentiated BEN and control tumours, i.e. solid growth for BEN tumours and papillary for control tumours. Overexpression of tumour suppressor p53 as well as decreased expression of E-CD was detected in BEN tumours. Other cells cycle related molecular markers – Cyclin D1, p16, and HER-2 showed no difference in expression between groups, as well as the proliferative marker Ki-67. Investigation of apoptosis-related markers identifies Bax as a specific marker of BEN-associated UTUC. Decrease of the pro-apoptotic protein Bax together with alteration of Survivin may be indicative of specific disturbances of an intrinsic apoptotic pathway in UTUC arising in endemic areas.

Key words: Balkan Endemic Nephropathy, Upper tract urothelial carcinoma, E-cadherin, Cells cycle related markers, Apoptosis.

Introduction

Upper Tract Urothelial Carcinoma **(**UTUC) is an uncommon disease, presenting only 5 to 6% of all epithelial tumours of the urinary tract [1, 2]. In some regions of the world and in patients with certain tubulointerstitial nephritis, the incidence of urothelial neoplasms of the renal pelvis and ureter is quite high [3, 4]. These tumours were 57 and 61.8 times more frequent in endemic settlements than in control rural and city populations free of Balkan endemic nephropathy (BEN) [5]. Investigation of UTUC in the South Morava River basin and its tributaries where BEN is endemic revealed increased frequency not only of tumours of the renal pelvis and ureter but also of urinary bladder tumours. One of the major characteristics of the UTUC from BEN regions and in analgesic abusers is a slow growth of tumour mass [6, 7]. Factors such as age, tumour stage, grade, tumour location, lymph node involvement, lymphovascular invasion (LVI), and necrosis have been reported in the literature to be associated with prognosis of patients with UTUC [1, 2, 8, 9].

Today, after a broad micromorphological and immunohistochemical study of cells cycle related molecular markers, apoptosis and cell adhesion molecule in BEN-associated UTUC and control UTUC – free of BEN, we are in a

much better position to understand the molecular biology of this enigmatic disease.

Balkan Endemic Nephropathy

Balkan endemic nephropathy (BEN) is an interesting renal disease, because of its unique clinical, epidemiological and morphological characteristics [10–12]. BEN is a bilateral chronic slow progressive tubulointerstitial disease with a long evolution to terminal renal failure. In the fifties it was described as a disease of the population in the alluvial plains of South East Europe, BEN encountered in a high rate among the population of settlements along the tributaries of the River Danube in Serbia, Bosnia, Croatia, Bulgaria and Romania [10, 11].

The aetiology of the disease is still unknown. Although the importance of inheritance was suggested, the effect of environmental factors and the presence of disorders of the immune system are strongly supported. Environmental factors, which included toxicants, such as herbs containing aristolochic acid (AA), mycotoxins and organic compounds leached from coal deposits, have an influence in the pathogenesis of BEN [10, 13–17]. Also, epidemiological and pedigree analysis showed that genetic factors are important in BEN, but genetic factors interplay with the environmental factors [10].

Gross autopsy examination of BEN patients deceased due to end-stage renal failure has revealed shrunken smooth-surface kidneys. The kidneys are bilaterally and symmetrically involved with severe superficial cortex atrophy and sclerosis. They are usually very small and weigh between 20 and 60 gr. Light microscopic findings in those kidneys show enormous interstitial fibrosis predominantly localized in the cortex and associated with huge tubular atrophy. Absence of interstitial inflammation is a characteristic morphologic feature of BEN. Glomerular sclerosis and hyalinization may be found in subcapsular areas, where the morphological changes are the most severe [10–12].

Renal biopsy examination in the early stage of the disease has predominantly shown changes to proximal tubules. Focal tubular atrophy has been accompanied by interstitial edema and fibrosis. In cases with less intensive involvement, scattered areas of interstitial fibrosis are usually observed in the superficial cortex [10]. Vascular changes in the kidney, in the early stages of BEN, included high expression of laminin in the interstitial capillaries. In advanced stages kidneys showed severe arteriolar hyalinosis, intimal and medial fibrous hyperplasia of inter-lobular arteries and thickened peritubular capillary basement membranes [7, 10]. However, classical morphological pictures of ischaemic lesions due to vascular changes are different and at the final stage there is fine granular nephrosclerosis in contrast to smooth shrunken kidneys in the case of BEN [12].

Renal interstitial fibrosis is the main morphological feature of BEN and at the same time the major cause of chronic renal failure in those patients. Renal interstitial fibrosis is an abnormal process associated with the deposition of huge amounts of the extracellular matrix, which has a complex structure composed of different connective tissue elements such as collagen types I to VII, laminin, fibronectin, tenascein, elastin, proteoglycans, etc. The architectural structure of the tubulointerstitium in healthy and nonfibrotic kidneys is based on the balance between different parts of the renal components: interstitial cells, the extracellular matrix, tubular and endothelial cells. Whenever any of these components are altered, the others are also involved in the disease process. Renal interstitial fibrosis will develop only when an imbalance between these components appears, and it seems that each of them could actively participate in triggering and developing fibrosis. In addition to fibroblast, myofibroblast could also be involved in developing renal interstitial fibrosis. It seems that these cells are more fibrogenic than fibroblasts. Renal interstitial myofibroblasts derive from the differentiation of fibroblasts or migration from perivascular smooth muscle cells. Also, tubular epithelial cells are able to transdifferentiate into myofibroblasts and therefore could be responsible for inducing interstitial fibrosis [12].

Lipkovski et al. have evaluated the incidence of BEN from the morphological point of view for the last decade. Therefore they analyzed material obtained from autopsies, kidney biopsies and nephrectomy due to UTUC from the patients, who were divided into two groups: those with permanent residence in BEN areas and those from nonendemic areas. The inci-

dence of UTUC over the last five years in BEN regions has significantly decreased, whereas at the same time in non-BEN regions it has remained on the same level. There was no morphological difference of the renal tissue adjacent to tumours between patients from BEN and non-BEN regions [18].

The Histology of Upper Tract Urothelial Carcinoma (UTUC)

Upper Tract Urothelial Carcinoma **(**UTUC) is an uncommon disease, presenting only 5 to 6% of all epithelial tumours of the urinary tract [1, 2, 19]. Conventional urothelial carcinoma accounts for most carcinomas of the urinary tract lining. More than 95% of urothelial carcinomas are derived from the urothelium and correspond to UTUCs or bladder tumours. Other histological subtypes include squamous cell carcinomas of the upper urinary tract (< 10%) and adenocarcinomas (< 1%) [20, 21]. Neoplastic urothelium has the capacity to demonstrate enormous plasticity. In addition, urothelial carcinoma has a propensity to demonstrate divergent differentiation with glandular, squamous, small cell neuroendocrine, lymphoepithelioma-like, sarcomatoid or other elements [22].

The classification and morphology of UTUCs are similar to those of bladder carcinomas. All variants of urothelial tumours described in the bladder can also be observed in the upper urinary tract. Thus the 2004 WHO classification now takes histological data into account to distinguish among three groups of non-invasive tumours: papillary urothelial neoplasia of low malignant potential; low-grade carcinomas; and high-grade carcinomas (Figs. 1 and 2). There are almost no tumours of low malignant potential in the upper urinary tract [21].

Also, some high-grade and high stage UTUC may additionally show aberrant differentiation, such as squamous or glandular differentiation, which is a result of metaplastic change (Fig. 3) [20, 23, 24].

Many factors, clinical and morphological, have been reported in the literature to be associated with prognosis of patients with UTUC [1, 8, 19, 25–28]. UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 (Fig. 3) [21].

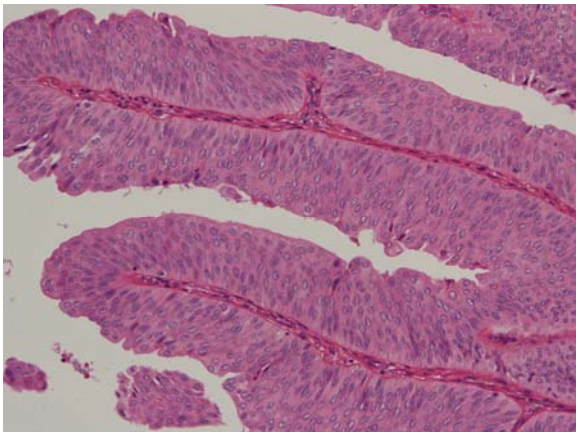

Figure 1 – Papillary low-grade upper tract urothelial carcinoma

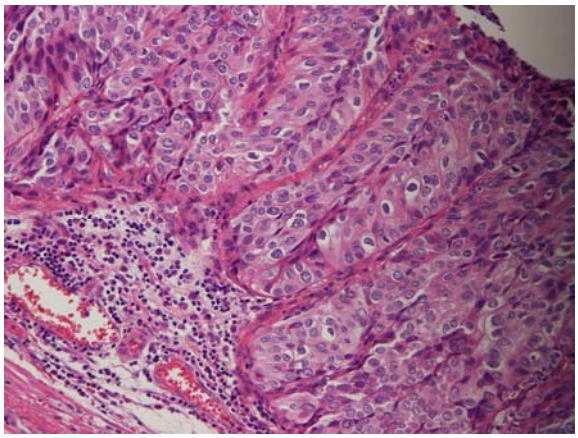

Figure 2 – Solid high-grade upper tract urothelial carcinoma

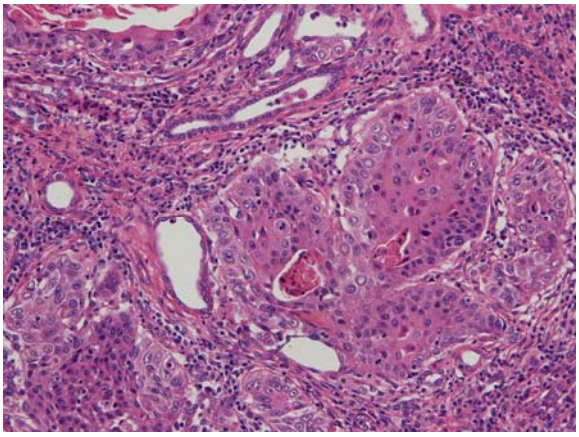

Figure 3 – Squamous divergent diferentiation in high-grade and high-stage upper tract urothelial carcinoma

According to the most recent classifications, the primary recognized prognostic factors are tumour stage and grade. Extranodal extension appears to be a powerful predictor of

clinical outcomes in patients with UTUCs and positive lymph node metastases. According to the most recent findings, the initial location of the tumour within the upper urinary tract (e.g. ureter vs. renal pelvis) is a prognostic factor. There is a prognostic impact of tumour location when adjusted for tumour stage: ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours. Lymphovascular invasion is present in approximately 20% of UTUCs and is an independent predictor of survival. Lymphovascular invasion status should be systematically included and specifically reported in the pathological report of all specimens. Extensive tumour necrosis is an independent predictor of clinical outcomes and it can be defined as > 10% of the tumour area (Fig. 4). The tumour architecture (e.g., papillary vs. sessile) of UTUCs appears to be associated with the prognosis. A sessile growth pattern is associated with the worst outcomes [21, 25, 28].

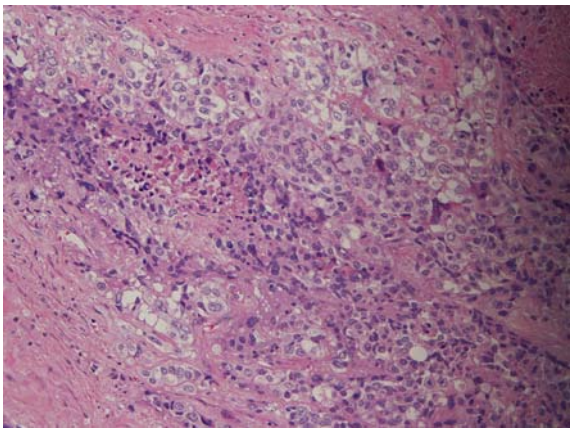

Figure 4 – Microscopic necrosis in high-grade upper tract urothelial carcinoma

BEN-associated Upper Tract Urothelial Carcinoma (UTUC)

In some regions of the world, and in patients with certain tubulointerstitial nephritis, the incidence of urothelial neoplasms of the renal pelvis and ureter is quite high [10]. These tumours were 57 and 61.8 times more frequent in endemic settlements than in control rural and city populations free of BEN [6]. Investigation of UTUC in the South Morava River basin and its tributaries where BEN is endemic, revealed increased frequency not only of tumours of the renal pelvis and ureter but also of urinary bladder tumours [6, 10]. Carcinomas may occur alone or in combination with BEN. Some authors suggest that the same factor has some influence in the development of the tubulointerstitial disease and UTUC [17, 29].

One of the major characteristics of the UTUC from BEN regions and in analgesic abusers is a slow growth of tumour mass, i.e. UTUC from BEN regions were found less malignant than those outside these regions in former Yugoslavia, comparing tumour grade and stage [29].

The comparative morphological study of UTUC between patients from endemic and non-endemic areas showed that UTUC in the BEN region present as tumours with high histological grade (62.5%), a trabecular and infiltrative pattern of invasion (59.4%) and a high stage (57.5%). These characteristics are indicative of the agressiveness of BEN tumours. Control tumours were of predominantly low grade (60.4%), nodular pattern of invasion (71.1%), and low stage (58.3%). However, this study did not find any significant difference in the pathological stage of BEN and control tumours. Discriminant analysis of BEN and control tumours indicated that among many morphological characteristics, the most important variable which discriminates them is growth pattern. Solid growth is characteristic of BEN tumours, while papillary growth is the best characteristic of control tumours [30].

A fifty-year retrospective study of 477 cases with pathologically confirmed UTUC in the region of the South Morava River in Serbia, in two periods (first 1969 to 1988, second 1989–1998), showed that in the first period UTUC had a 57.1-fold increased incidence in endemic over nonendemic areas, but in the second period there was only a 11.2-fold increase. UTUC from endemic settlements was of a lower grade in the period from1957 to 1986, but in the period from1987 to 2006 they were predominantly high grade. Low tumour stage (pTa-pT1) predominated in transitional cell carcinoma from the endemic and adjacent but not the control settlements in the period from 1957 to 1986. However, in the last 20 years, UTUC stage increased, the highest in the period from 1997 to 2006 in all settlements studied. The authors concluded that an increased number of UTUC in endemic settlements was

observed, markedly decreasing in the last decade [31].

Molecular Markers in Upper Tract Urothelial Carcinoma

Several research groups are working on UTUC characteristics and carcinogenesis pathways. Several studies have investigated the prognostic impact of various tissue-based markers that are related to cellular processes such as cell adhesion (E-cadherin), angiogenesis (hypoxia-inducible factor-1α and metalloproteinases), cell proliferation (Ki67), apoptosis (Bcl-2 and survivin) and other molecular markers. However, because of the rarity of the disease, the main limitations shared by these studies are their retrospective nature and their small sample size [21, 32].

E-cadherin (E-CD) is one of the most frequently examined molecules, which has a cardinal role in cell adhesion. The integrity of the cell adhesion mechanism is crucial for tissue architecture maintenance. Loss of E-CD expression leads to a dissociation of cells from cohesive tissues and correlates with dedifferentiation and invasiveness in a variety of solid tumours. Many studies have verified the association between the loss of E-CD expression and the ability of many tumours, urothelial carcinoma included, to be metastatic or invasive [32–34].

Our comparative study of E-CD expression in 85 patients with UTUC from BEN and control regions (rural and city populations free of BEN) more often showed decreased E-CD expression in BEN tumours than in control tumours (Fig. 5). BEN low grade and low stage tumors have a more important reduction of E-CD expression than control tumours. Advanced tumours showed abnormal E-CD immunoreactivity in 53%, while no difference was found between high grade and high stage tumours in both groups. Decreased expression of E-CD in BEN tumours was linked with the growth of the tumour, while expression of E-CD in control tumours is associated with the tumour grade [35].

Most urothelial cells are not dividing under physiological conditions. Many proteins act during the process of the DNA replication, but also in cell grown regulation. Defects in the regulation of the DNA replication can lead to cancer. Activated cell proliferation may produce the loss of cell cycle arrest due to encoding of cellular regulatory genes or deactivation of tumour-suppressor genes [36–38].

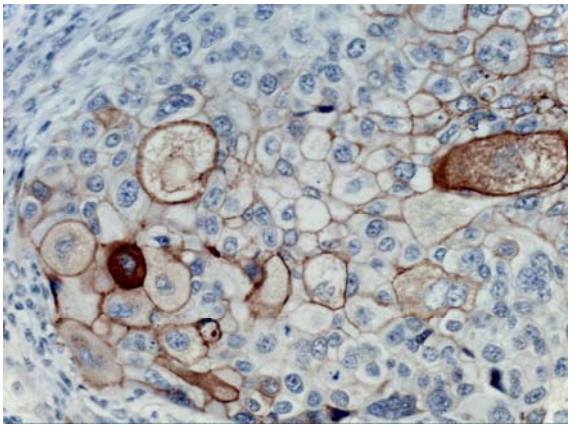

Figure 5 – Focal membranous and cytoplasm immunostaining of E-cadherin in BEN upper tract urothelial carcinoma

Deregulation of the normal cell cycle is common in UTUC. A comparative study of cell cycle related markers in BEN and control UTUC showed relationships between conventional pathological parameters and immunohistochemical staining of p53, p16, cyclin D1, HER-2 and Ki-67 in BEN and control UTUC. In regression analysis, between investigated cells related molecular markers, only tumour suppressor p53 was identified as a specific indicator of the UTUC arising in patients with BEN (Fig. 6). BEN UTUC has a significantly higher p53 labelling index and alteration of p53 (more than 10% of the tumour cell nuclei) than control tumours. On the other hand, proliferative marker Ki-67 correlated with the morphological characteristics of UTUC in the best way, but not with the group (Fig. 7) [39].

Some authors have suggested that accumulation of p53 protein in 10% or more of the tumour cell nuclei strongly correlates with mutations in the p53 gene [40]. Our investigation showed that 42% of BEN tumours and 20% of control tumours had an alteration of nuclear p53 immunoreactivity, with a statistically significant difference. Krasteva et al. [41] screened 90 Bulgarian BEN patients for p53 gene mutations and found that tumour-suppressor gene mutations were present in BEN patients.

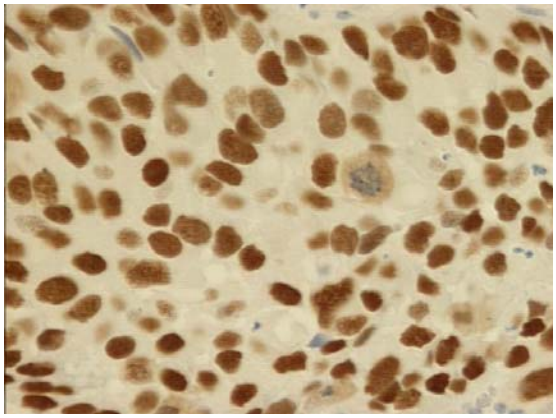

Figure 6 – Immunostaining of p53 in BEN-associated high grade urothelial carcinoma, with strong nuclear p53 activity

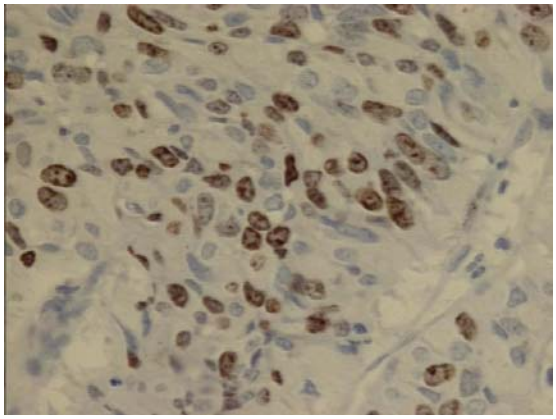

Figure 7 – Ki-67 nuclear reactivity in high grade upper tract urothelial carcinoma

The results obtained support their hypothesis that p53 gene alterations are possibly involved in BEN genetic pathways. Also, Grollman et al. [42] demonstrated AA adducts associated with p53 mutation in UTUC from a BEN region in Croatia. In AA nephropathy (AAN) there is an increased incidence of UTUC. Rodent models of AAN may be used to study biotransformation of AA and repair of AL-DNA adducts and, importantly, to validate the use of AL-DNA adducts as biomarkers of disease. The murine model will be particularly useful for determining genetic susceptibility to AAN and, by implication, to BEN [11].

Investigation of apoptotic related markers (Survivin, Bcl-2, Bax, Fas and Caspase 3) in UTUC associated with BEN detected less frequent alteration of pro-apoptotic protein Bax in UTUC arising in endemic regions than in control tumours. However, the difference in cleaved Caspase 3 activity, effective apoptosis, between the investigated groups was not statistically significant. On the other hand, altered expression of Survivin was more often in BEN UTUC with high grade and solid growth than in control tumours (Fig. 8). Our findings suggest that decreased pro-apoptotic activity of Bax together with higher Survivin expression may indicate specific disturbances of the intrinsic apoptotic pathway in UTUC arising in endemic areas [43].

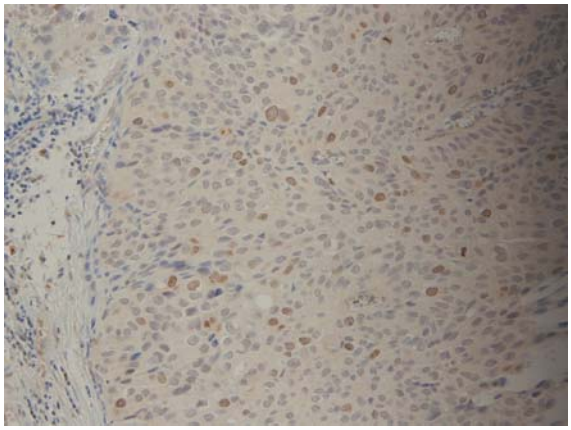

Figure 8 – Immunostaining of Survivin in BEN-associated upper tract urothelial carcinoma with solid growth

Conclusion

Investigation of UTUC in the South Morava River basin and its tributaries where BEN is endemic revealed growth pattern as the best morphological characteristic which differenttiated BEN and control tumours; over expression of tumour-suppressor p53 as well as decreased expression of E-CD in BEN tumour. Investigation of apoptosis-related markers identifies Bax as a specific marker of BEN-associated UTUC. Decrease of pro-apoptotic protein Bax together with alteration of Survivin may be indicative of specific disturbances of the intrinsic apoptotic pathway in UTUC arising in endemic areas.

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Резиме

ЕНДЕМСКАТА НЕФРОПАТИЈА И КАРЦИНОМ НА ГОРНИОТ УРОТЕЛИУМ – НОВИ СОЗНАНИЈА ОД МОЛЕКУЛАРНАТА БИОЛОГИЈА

Љубинка Јанковиќ Величковиќ[1], Зана Доличанин[2], Владисав Стефановиќ[3]

[1] Институт за патологија, Медицински факултет, Универзитет во Ниш, Ниш, Србија
[2] Државен универзитет во Нови Пазар, Нови Пазар, Србија
[3] Оддел за клинички истражувања, Медицински факултет, Универзитет во Ниш, Ниш, Србија

Карциномот на горниот уротелиум (UTUC) е невообичаена болест која се јавува почесто во некои региони на балканските земји отколку во други области во светот. Испитувањето на UTUC во сливот на реката Јужна Морава и нејзините притоки, каде што БЕН е ендемична со зголемена фреквенција не само на тумор на бубрежната карлица и уретерот, но, исто така, и на туморите на мочниот меур. Компаративна, морфолошка и имунохистохемиска студија на UTUC во регионот на БЕН и контрола на селското и на градското население што нема БЕН го идентификуваат моделот на раст како најдобра морфолошка карактеристика која ја диференцира БЕН и контролните тумори, односно солиден раст за туморите на БЕН и папиларен за контролните тумори. Преголемата експресија на тумор супресорот p53, како и намалената експресија на E-CD беа откриени кај туморите на БЕН. Други молекуларни маркери поврзани со циклусот на клетката – Циклин D1, p16, и HER-2 не покажаа никаква разлика во експресијата меѓу групите, како и пролиферативниот маркер Ki-67. Испитувањето на маркерите поврзани со апоптоза го идентификува Bax како специфичен маркер на UTUC поврзан со БЕН. Намалувањето на проапоптичниот протеин Bax заедно со алтерацијата на Survivin може да биде показател за специфични нарушувања на внатрешниот апоптотичен пат во UTUC што се јавува во ендемските области.

Клучни зборови: балканска ендемска нефропатија, карцином на горниот уротелијален тракт, E-cadherin, маркери поврзани со циклусот на клетката, апоптоза.