ORIGINAL PAPER

# Clinical, histological and immunohistochemical characteristics in patients with tumors of urinary bladder and renal failure

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**Abstract**

Chronic renal failure in patients with tumors of urinary bladder appears because of either familial tubulo-interstitial pielonephritis evolution (Balkan Endemic Nephropathy) or invasion and obstructive uropathy. A group of 27 clinical cases with tumors of urinary bladder and renal failure was available for our study between the years 2004–2005. Simultaneity of the two serious diseases, neoplasia and terminal renal failure made the prognostic more difficult and determined some other complications to appear. Identification of some clinical and histopathological features in due time led to a therapeutic algorithm favorable to a prolonged survival.

***Keywords*:** urinary bladder tumors, renal failure, Balkan Endemic Nephropathy.

## Background

Renal failure in patients with tumors of urinary bladder appears either because of the familial tubulo-interstitial pielonephritis evolution (Balkan Endemic Nephropathy – BEN) or because of altering the renal parenchyma by aggressive, recurrent and obstructive evolution of the urinary bladder tumors.

Increased incidence of urinary tract tumors in the areas of BEN is well-known [1].

BEN is a chronic familial tubulo-interstitial disease with an insidious debut and a slow evolution to terminal renal failure [2].

One of the most important BEN features is its association to the malign tumors of the urinary tract and the multicentricity of these urothelial tumors in 30% cases from BEN area [1].

Our study performed between the years 2004–2005 revealed a frequency of 69.77% of urinary bladder tumors from BEN area in Mehedinti County, Romania. A number of 27 cases were identified with urinary bladder tumors and renal failure.

## Material and methods

Our study was performed on a group of 27 patients diagnosed with urinary bladder tumors and renal failure, all of them hospitalized in the Department of Urology and watched by the Department of Nephrology and Hemodialysis, between the years 2004–2005.

Clinical and histological features have been studied and then immunohistochemical determinations have been made.

Those 27 patients were divided in two groups (A and B), taking into account the following criteria:

a. clinical aspect of the urinary bladder tumors (infiltrative or superficial);

b. the presence of the renal failure as a consequence of the tubulo-interstitial pielonephritis (decreased volume of the kidneys) or the tumoral evolution aggressivity by obstructive uropathy;

c. simultaneous or successive presence of the urothelial, uretheral, pielocalycial tumors and urinary bladder tumors.

Group A represented by 12 patients with an initial debut as chronic renal failure by tubulo-interstitial pielonephritis, with small kidney, presented hematuresis subsequently. They were diagnosed by echography, tomography, cystoscopy as having urothelial, pielocalyceal tumors or urinary bladder tumors. Histopathological analysis revealed superficial urothelial tumors in most of the cases.

Group B represented by 15 patients showed an initial debut as high urothelial tumors simultaneously to urinary bladder tumors or as primary bladder tumors. Renal failure sometimes present since the tumoral debut, developed subsequently by obstructive tumoral aggressivity as acute or chronic renal failure in terminal stage.

Histopathological analysis of the cases selected during that stage was made by using wax sections from the material of surgical pieces; then they were fixed in formaldehyde 10% and wax embedded. We also used Hematoxylin–Eosin staining.

In all the cases, we performed immunohistochemical

determinations by oncogene protein expressions (C-erb B2), oncosupressor p53 genes and proliferation factor Ki67.

Determinations for PTEN, MRP, and MDM2 were performed.

## Results

The 27 patients diagnosed with bladder tumors and chronic renal failure (CRF) was firstly examined by renobladder echography and latter on by cytoscopic investigation. All the cases cytoscopically confirmed with bladder tumors, of any type, underwent endoscopic resection (TUR–TV).

Diagnosis algorithm was completed by computer tomography (CT) in 12 cases (44.44%).

We also performed histological analysis and identified 10 cases (37.05%) of invasive urothelial carcinomas, two cases (7.40%) of carcinomas with clear cells with bladder starting point (Figures 1 and 2), and 15 cases (55.55%) with superficial transitional carcinomas.

Urothelial origin and the limit between the different histopathological degrees were more difficult for those tumors without papillary structure formations. Usually, infiltrative tumors are grouped as well, moderate or poor differentiated. There are no precise morphologic criteria for those differentiations. The cell morphologic character but not the architectural one as in the superficial papillary tumors was followed [3, 4].

In the cases of poor differentiated or non-differentiated tumors, a set of antibody can be used [2, 3] to identify the more frequent keratins in urothelium (CK7 and CK20). Those cytokeratines are cytoplasmatic or membranary positive, diffuse or zonal within the urothelial origin tumors. From the 12 cases with invasive bladder tumors, the invasion was expanded in five cases (41.66%), infiltrative in six cases (50.2%), and mixed in just one case (8.33%).

As concerning the histological degree, the tumors were G2 (Figure 3) and G3 in some cases with G1. In the tumors with external muscle invasion or in prevesical tissue, a number of eight cases (60.6%) had predominantly mixed and non-differentiated carcinomas.

Clinical staging correlation to the histopathological one showed a relative good concordance but it did not allow a precise prognostic. It was observed, both in the clinically analyzed and histopathological groups, that patients surviving could not be correlated to either TNM nor pTNM, and G-types as in the cases of the superficial papillary tumors [5, 6].

Immunohistochemically, we performed staining for monoclonal antibody: C-erb B2, Rbp, p53, Ki-67, pTEN, MRP3, and MOM2, taking into account the aggressivity, proliferation and prognostic index [7].

## Discussions

The diagnosis of the bladder tumors was made based on some clinical-imagistic parameters and based on the pTNM classifications histopathological parameters.

To an oncological following of the patients with achieved an oncologic paper containing the clinical-imagistic data, laboratory analysis prognostics factors and types of adjuvant treatment.

Clinico-imagistic methods used by us were ecographies, cytoscopies, surgical tumoral resections, clinical studies, CT and radiological investigations.

Echography as a non-invasive method offered data upon the echographic aspects of the kidneys (small kidneys, Figure 4) of the pielocalyceal tumors or the urinary bladder.

Computer tomography allowed us to explore and diagnose the pielocalyceal tumors in the uremic patients (Figure 5) confirmed by the surgical intervention (Figure 6).

Patients of the A group, which presented high urothelial tumors and terminal renal failure, they have been echographically and cystoscopically monitorized. Urinary bladder tumors appeared lately, between 12–24 months since the high urothelial tumors diagnosis were revealed in eight cases (29.62%). In the other four cases (14.81%) urinary bladder tumors initially started (three clinical cases) or they had a debut simultaneously to the urothelial tumors (one case).

We performed tumoral resection within endoscopic examination in all the cases and preliminary histopathological examination [4, 8] used pTNM classification (Figure 7).

Clinical staging used TNM 2000 classification [9] and the parameters followed by us were such as primary tumor (T) and tumoral tissue, TUR, which must contain muscle.

Because of those studies, we can state:

- Tx – primary tumor cannot be evaluated;
- Ta – non-invasive papillary carcinoma;
- Tis – carcinoma *in situ*;
- T1 – tumor invades the subepithelial connective tissue;
- T2 – tumor invades muscles;
- T2a – tumor invades the superficial muscles (external half);
- T2b – tumor invades the deep muscles (external half);
- T3 – tumor invades perivesical tissue (3a – microscopic, 3b – macroscopic);
- T4 – tumor invades the surrounding organs, prostate, uterus, vaginal wall, abdominal wall;
- T4a – tumor invades the prostate, uterus or vaginal wall;
- T4b – tumor invades the pelvic or abdominal wall (m is added to T to show multiple lesions).

Histopathological analysis of the selected cases followed all the results to pTNM classifying [10].

As concerning the clinical characteristics of the representative group, we found the following:

- The intermittent, insidious presence of hematuria in patients, with a clinical characteristic aspect made up of paletegments and yellowish color.
- Alteration of the protein metabolism with increased values of urea, creatinine and uric acid.
- Decreased volume of kidneys with hyperecogen parenchyma or other pathological of renal echostructure changes.

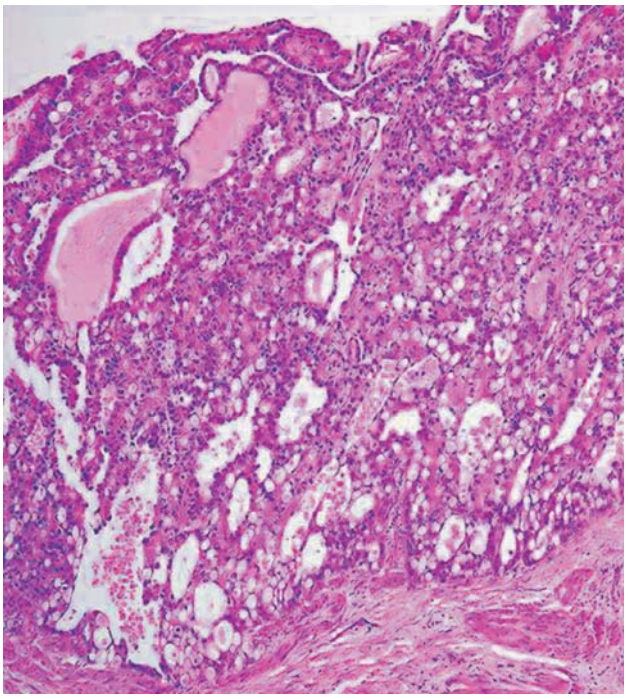


**Figure 1** – ***Clear cell carcinoma. Urinary bladder (HE staining, ×10)***

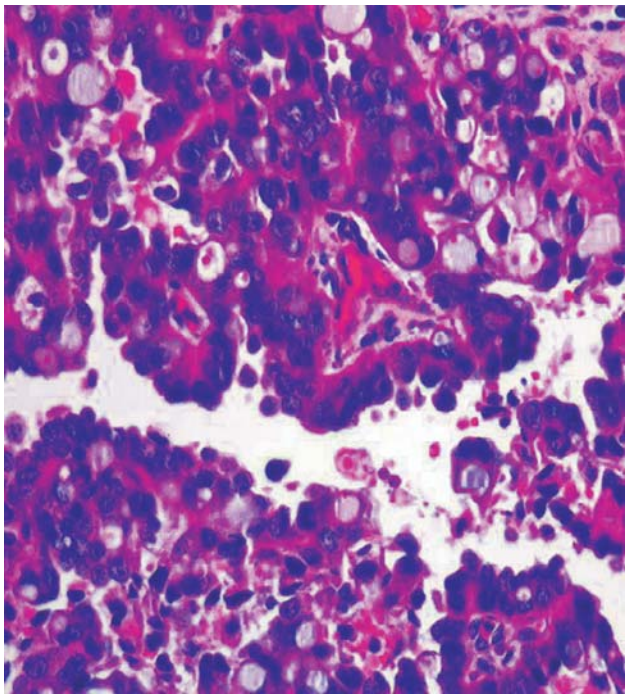
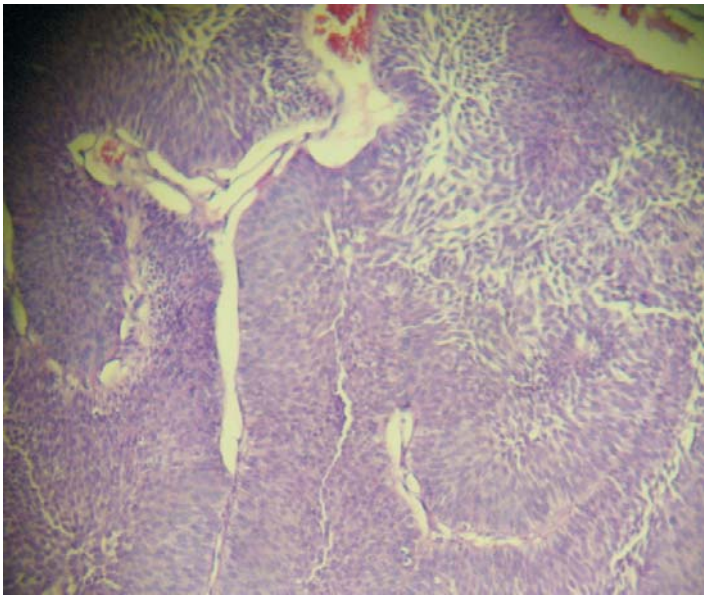


**Figure 2** – ***Clear cell carcinoma. Urinary bladder (HE staining, ×40)***

**Figure 3** – ***Urothelial G2 carcinoma. Urinary bladder***



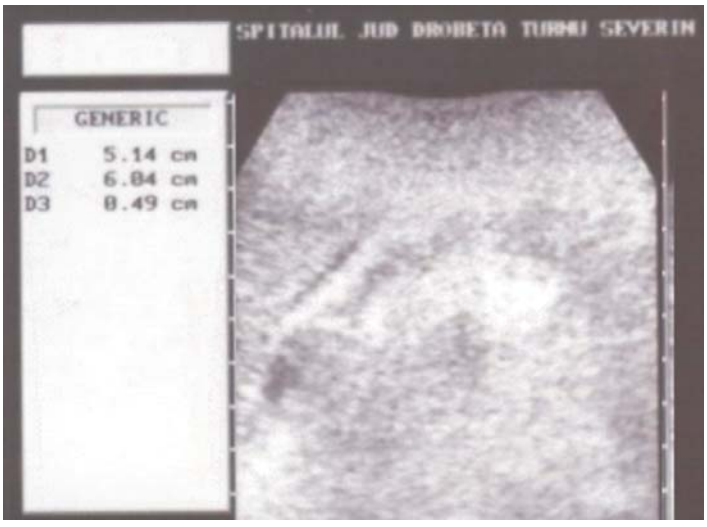



**Figure 4** – ***Echography: pielonephritic small kidney***

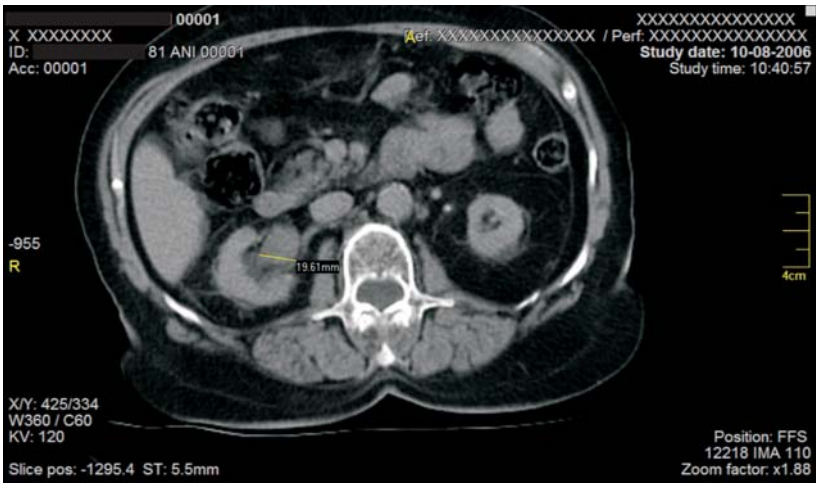



**Figure 5 –** ***Pielocalyceal tumor of a female patient with chronic renal failure***

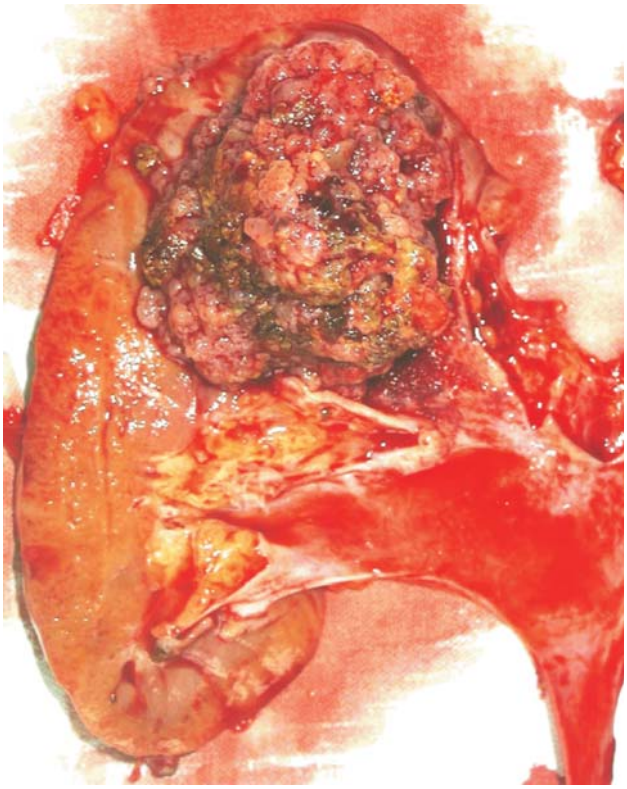


**Figure 6 –** ***Operatory specimen***

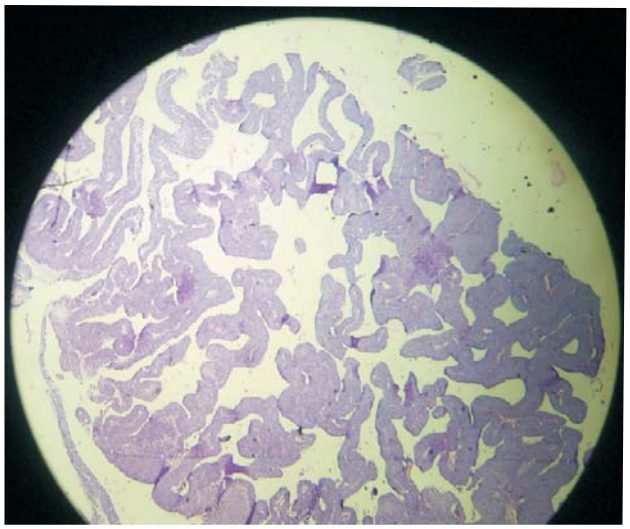


**Figure 7 –** ***Pielocalyceal urothelial G2 carcinoma***

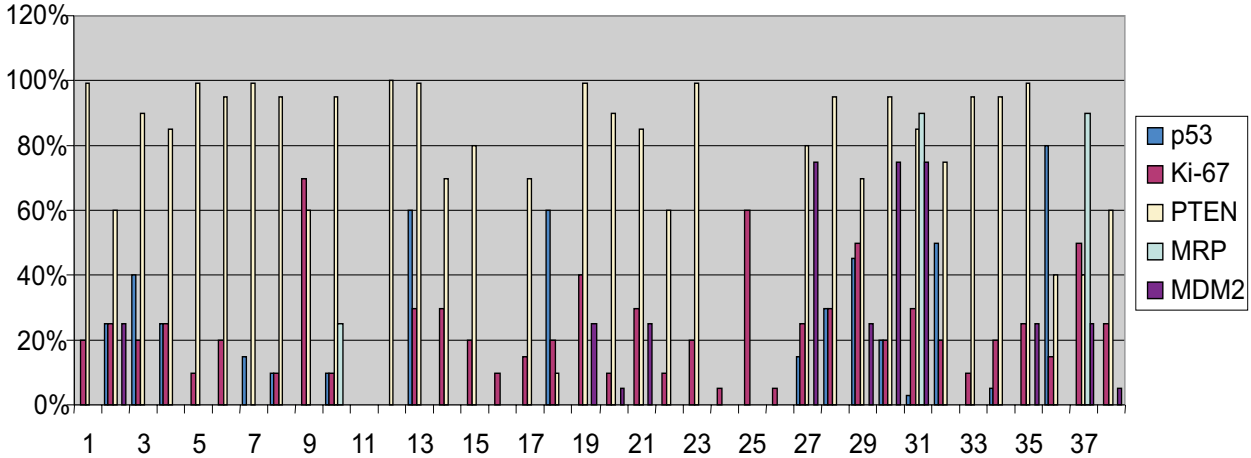



**Figure 8 –** ***Expression intensity between different factors of proliferation and prognostic***

▪ Patients born or resident in BEN area coming from BEN families.

Histological characteristics in the superficial bladder tumors have been represented by the tumoral degree, the number and dimensions of the tumors, recurrence, type Tis changes in the surrounding mucosa and the localization in the urinary bladder.

In the invasive tumors, it was assessed the level of the parietal, perineural invasion and those in the haematolymphatic vascular system [11, 12].

Obstructive uropathy was noted in seven clinical cases as well as antecedents of the high or superficial urothelial tumors.

C-erb B2 was positive in 43.2% and negative in 56% cases in the patients group with infiltrative bladder tumors. Somewhat increased positivity that in literature was significantly appreciated by marking +, ++, +++. Positivity +++ was appreciated by a positive reaction of intense and continuous membrane with minimum cytoplasmatic staining witch can be found all over the section [12, 13].

We did not establish any correlation between C-erb B2 positivity and the tumoral grading or other immunohistochemical markers in the patients with infiltrative bladder tumors. Such a clinical case presented C-erb B2 +++ and G2 and, in other cases, with G3 C-erb B2 was negative. This is in concordance to the most of the reports in literature [14] though there are authors holding the contrary.

Rbp gene protein tested for the groups of patients with infiltrative bladder tumors was zonal cytoplasmatic positive in 80% analyzed cases and nuclear in only 11% of cases.

As for the groups of patients with superficial bladder tumors it appeared positive in 65% cases, 8% if which nuclear. Practically it may be considered positive only the nuclear localization of the reaction. While the plasmatic positivity was intense relatively both in the infiltrative bladder tumors and in the superficial ones, nuclear positivity was just in isolated cells.

Immunohistochemical reaction for PTEN was well expressed both in the infiltrative and in the superficial bladder tumors.

Reaction at the nuclear level was intense and extended in the invasive tumors but the same staining pattern appeared in the most of the superficial tumors of well-differentiated urothelial carcinoma type [15].

MRP3 protein showed negative values in the most of the cases both in the infiltrative and in superficial bladder tumors. Rare nuclei have been noted in non-differentiated carcinomas thus suggesting that the mechanisms of chemoresistance installing are dealt to other factors [14, 16].

Immunohistochemical reaction for p53 in the patients with infiltrative bladder tumors was positive in 72% cases, there fore indicating a biologic aggressivity of the tumor. We found that both p53 and especially Ki67 could be correlated to the type of infiltrative or superficial tumors and the surviving when the patients did not present terminal renal failure. It could be noted that the Ki67 proliferation nuclear factor is the most constant of all the immunohistochemical markers, with diagnosis and prognosis values. The greatest number of cases appeared in the histological G2–G3 types [15].

Expressions of proliferation and prognostic factors are presented in the Figure 8.

## Conclusions

Bladder tumors, besides their infiltrative or superficial clinical forms, associated to renal failure presented a reduced period of surviving. Obstructive, infections and cardiac complications appeared relatively early (6–8 months) since the clinical debut. Infiltrative bladder tumors in patients with terminal renal failure besides the surgical intervention and renal substitution presented surviving cases for 24–36 months.

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