Microcystic transitional cell carcinoma: a rare tumor of the urinary bladder

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Summary
Microcystic urothelial carcinoma is a rare variant of invasive transitional cell carcinoma recognized by the WHO classification. It is characterized by its deceptively benign appearance. The clinical course of this uncommon variety of carcinoma is not well known and their histological and immunohistological features are not well defined. We report a case of a 37-year-old man with a microcystic transitional cell carcinoma of the urinary bladder. He was diagnosed 4 years ago with cystitis glandularis lesions and nephrogenic adenoma. Through this observation we will try to define the clinical and pathological features of this uncommon tumor which must be differentiated from a number of proliferative lesions of the urothelium. The poor prognosis and aggressiveness of this tumor seems to be related to a higher stage and grade at diagnosis.

Introduction
Invasive transitional cell carcinoma is usually composed of nests, and cords of large atypical cells. However the current WHO classification recognizes several new variants. Some of them have a deceptively benign appearance such as the nested urothelial carcinoma and the microcystic urothelial carcinoma. These variants may cause difficulties in the differential diagnosis. The microcystic variant is rare. Since the first description by Youn and Zukerberg in 1991, few cases have been reported mainly as single case reports. More recently Antonio Lopez Beltran et al. reported 20 cases of bladder carcinoma with microcystic features. To our knowledge, it was the largest series that analyzed this uncommon variant of urothelial carcinoma.

We report a rare and new case of microcystic urothelial carcinoma of the urinary bladder developed on cystitis glandularis lesions associated with nephrogenic adenoma. We will present the histological features of this tumor and compare our findings with the literature data.

Case presentation
A 33-year-old man presented to an outside institution with a suspicion of bladder cancer. He underwent transurethral resection (TUR), twice in the same year, with the diagnosis of nephrogenic adenoma developed on cystitis glandularis lesions. Four years later, he was admitted in our hospital, complaining of dysuria. Abdominal and pelvic ultrasound showed a homogenous urinary bladder with a thickened wall and two large diverticula located on both left and right side walls and measuring respectively 9 and 8 cm. It also showed a bulging lesion over the bladder-base next to the neck, measuring 4.5 cm. Uro-scan revealed an important dilation of the pyelocaliceal cavities, a hypertonic bladder with a thickened wall, two diverticula and a bulging lesion infiltrating the bladder neck (Fig. 1). Biopsy concluded to cystitis glandularis with no signs of histological malignancy. Partial cystectomy with bladder enlargement and sampling of the bulging lesion were performed. Histological examination showed a low grade tumor invad-
ing the lamina propria and the muscularis mucosae (pT1) measuring 1.5 x 1 cm. The smooth detrusor muscle was not sampled. The tumor was composed of small nests and microcysts lined by a single layer of atypical flattened cells. No macrocysts were observed. Lumens were empty. Neoplastic cells had a round to oval hyperchromatic nuclei without nucleoli (Fig. 2). There was no conventional urothelial component or urothelial carcinoma in situ. This tumor was developed on the bulging lesion in association with usual and intestinal type cystitis glandularis (Fig. 3). Immunohistochemical study demonstrated strong immunoreactivity with cytokeratin 7 and cytokeratin AE1/AE3 (Fig. 4). Regarding all these findings, the diagnosis of microcystic urothelial carcinoma was established. The patient had a second cystoscopy with bladder and urethral biopsies. At microscopic examination, specimens were free of residual tumor but they showed cystitis glandularis lesions associated with a nephrogenic adenoma. The patient did not receive any adjuvant treatment. He was doing well with no symptoms of recurrence 1 year later.

Discussion

More than 90% of bladder carcinomas are of urothelial type. Unusual variants of urothelial carcinoma can occasionally be encountered, representing approximately 15% of cases. These variants are significant from diagnostic, prognostic and/or therapeutic perspectives. These uncommon entities are distinct enough to be recognized separately in the current WHO classification system.

The microcystic variant of invasive urothelial carcinoma is one of the rarest variants of urothelial carcinoma (1.2% according to Paz et al.) and is characterized by the formation of microcysts, macrocysts, or tubular structures. Lopez Beltran et al. reported, in their case series, that the mean age of patients was 63 years (range: 45-75 years) and the haematuria was the most presenting symptom. No patient had a history of cystitis glandularis or nephrogenic metaplasia. However, in our case the patient was younger (37 years), his tumor was discovered when investigating dysuria and he has cystitis glandularis lesions.

The usual radiologic examinations is useful to estimate the depth of tumor invasion and extension, they are usually inadequate to differentiate the nature of the tumor. In the series of Lopez Beltran et al, muscle invasion was present in 65% of cases. In our case, radiological examination did not reveal any muscle invasion.

Microscopic features of microcystic urothelial carcinoma listed by Venyo et al. include: intracellular or intercellular prominent lumina/microcysts surrounded by neoplastic urothelial or squamous cells. The lumina tend to be empty, but may contain granular eosinophilic debris, necrotic cells, or mucin. The cysts may be oval or round, variable in size (they may be up to 2 mm); and
they are lined by urothelium. The cells are flattened cells or low columnar cells; however, they are not colonic epithelium or goblet cells. The cysts tend to be infiltrative and they may invade the muscularis propria. The very unusual morphologic appearance could misdiagnose this tumor with benign lesions, such as cystitis glandularis, cystitis cystica, or nephrogenic metaplasia, especially in limited biopsy samples. The main criteria for the differential diagnosis between cystitis cystic / cystitis glandularis and microcystic urothelial carcinoma are the variation of shape and size of the cysts, the deep location, the irregular arrangement, and the invasion of the muscle. The cytological criteria are less helpful because the atypia are often minimal with no significant mitotic activity. Nephrogenic adenoma/metaplasia are small hollow tubules, similar to mesonephric tubules, lined by a single layer of bland cuboidal or hobnail cells, surrounding eosinophilic or basophilic secretions, which are typically not cystic; they have minimal atypia and few mitotic figures. There is no true invasion. In our case, the tumor was associated with cystitis glandularis (intestinal and usual type) and nephrogenic adenoma. This association may be explained by the degeneration of the intestinal type cystitis glandularis which is considered to be a precancerous lesion. To our knowledge, this combination has never been reported in the literature. Microcystic urothelial carcinoma can also be misdiagnosed with other neoplastic conditions like urothelial carcinoma with glandular differentiation, adenocarcinoma and nested urothelial carcinoma. This latter variant is also rare and can show tubular differentiation. In our case, the association of both microcysts and small nests highlight the fact that these two variants can frequently overlap. However, some authors propose that these two entities should be separated.

Immunohistochemical characteristics of microcystic transitional cell carcinoma include positive staining with cytokeratin HMW, p63, cytokeratin 7, uroplakin, and thrombomodulin and negative staining with -methyl-coenzyme A racemase. Over expression of Ki-67 and p53 is noted in high-grade cancers. Lopez Beltran et al. suggested that lower expression of MUC1, low Ki67 labeling index, low to negative p53 nuclear accumulation and up-regulation of p27 Kip1 ob-

Fig. 2. (a) Biopsy of the budding lesion showing an infiltrative carcinoma with an ulcerated urothelium at the surface (hematoxyline eosine x 100). (b) Note the extent through the muscularis mucosae (HE x 400). (c) The tumor is composed of microcysts with empty lumina and small nests (hematoxyline eosine x 400). (d) Microcysts are lined by flattened cells with minimal cytological atypia (hematoxyline eosine x400).
served in cystitis glandularis, could be used to separate microcystic carcinoma from cystitis glandularis. Misinterpretation as benign changes has to be avoided and may be supported by using basal cell markers CK5 and CD44.

The number of cases of microcystic urothelial carcinoma documented is not sufficient to draw conclusions regarding its optimal treatment. Some reported cases indicate that aggressive therapy is associated with good control of the disease.

Microcystic urothelial carcinomas are typically diagnosed at an advanced stage and a high grade. Metastases to lungs, liver, and penis have been reported. Evolution is characterized by early death. Lopez Beltran et al. claimed that, despite therapy, 70% of patients had poor outcome. Some reported cases with a
favorable prognosis seem to be related to a low pT category (pTa/pT1) and pseudo glandular changes. The tumor in our case was diagnosed at low grade and stage (pT1). This fact explains the relatively good prognosis in our patient.

Conclusions

Microcystic variant of urothelial carcinoma is a rare tumor and to our knowledge we report the first case associated to cystitis glandularis and nephrogenic adenoma. Attention to histological and immunohistochemical features, together with clinical history helps to distinguish microcystic urothelial carcinoma from benign proliferative lesions. Correct and early diagnosis of this tumor is essential to avoid diagnosis at an advanced stage. New cases of the tumor should be reported in order to document its biological behavior.

References