

The Histological Variants of Urothelial Carcinoma of the Bladder: It Is Affecting the Prognosis?

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Abstract

Urothelial carcinomas (UC) are likely to have particular morphological features that distinguish them from the typical form. These original aspects are called “histological variants of urothelial carcinoma”. They can constitute all or part of the tumor and concern mainly muscle invasive UC and high grade. Their frequency varies according to the type, but the knowledge of these variants is essential because of the diagnostic difficulties, and the implication of their presence on the prognosis.

Keywords

Urothelial Carcinoma, Variants, Prognosis

1. Introduction

Urothelial carcinomas (UC) are likely to have particular morphological features that distinguish them from the typical form. These original aspects are called “histological variants of urothelial carcinoma”. They can constitute all or part of the tumor and concern mainly the muscle-invasive and high grade UC [1]. Their frequency is variable depending on the type (some variants are very exceptional). Knowing these variants is important because of the diagnostic difficulties, and the implication of their presence on prognosis [2]. Through this literature review, we present the different epidemiological, clinical, histological, prognostic and therapeutic aspects of each histological variant of urothelial carcinoma.

2. Histological Variants

2.1. The Differentiations

Urothelium has a strong metaplastic power, which is expressed during chronic inflammatory processes as well as in tumor proliferations. Urothelial carcinoma with a differentiation occurs when the metaplastic component represents less than 95% of the tumoral mass examined [1].

1) The squamous differentiation

The replacement of urothelium by stratified squamous cells can be observed in 10% to 20% of CU's of the bladder [2] [3]. Chronic aggression, particularly with tobacco and bilharziasis, seems to favor its appearance. No specific clinical symptoms have been described. Microscopically, nests of polygonal cells can be observed that can show dyskeratoses, keratinization foci or intercellular bridges associated with carcinoma in situ or invasive [4] (**Figure 1**). For immunohistochemical (IHC) study, L1 antigen and cytokeratin (CK) 14 are positive in areas of squamous differentiation [4]. Areas of abundant squamous differentiation under the microscope are associated with a poor prognosis [5]. Radical cystectomy is the gold standard treatment, but chemotherapy and radiotherapy appear to be ineffective according to some studies [2] [6].

2) Glandular differentiation

Described the first time in the literature in 1968 by GRACE and WINTER [7], glandular differentiation is observed in 6% of the CU of the bladder [3] [4]. Symptomatology is aspecific. Microscopically, the presence of true glandular spaces within the urothelial component of the tumor is characteristic (**Figure 2**). It can also take the form of tubular or enteric glands, aligned on a single layer of prismatic epithelium often associated with mucosecreting cells [8] [9]. IHC is characterized by Apomucin MUC5AC and CK7 positive labeling and CDX2, CK20 and villin negative. The prognosis is worse when foci of glandular differentiation are numerous [5]. Radical cystectomy is the treatment of choice and resistancy to radio-chemotherapy is possible [5].

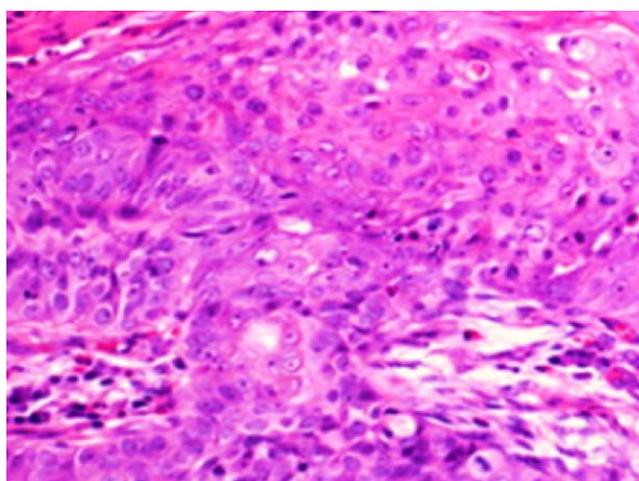


Figure 1. Microscopic appearance of urothelial carcinoma with squamous differentiation.

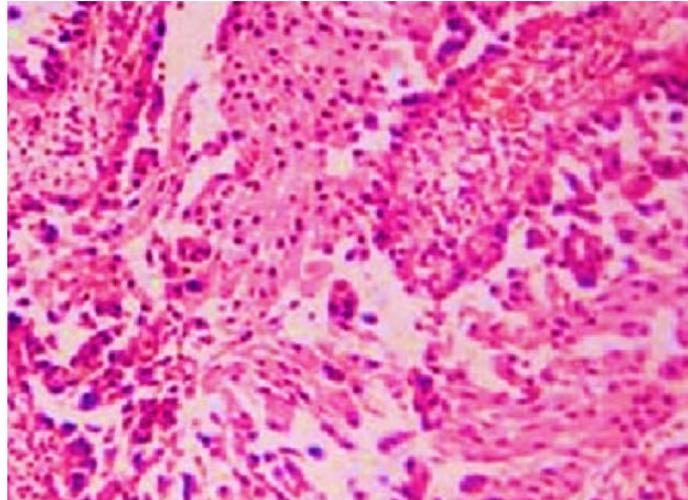


Figure 2. Microscopic appearance of urothelial carcinoma with glandular differentiation.

3) The trophoblastic differentiation

The trophoblastic differentiation has been described for the first time by DJEWITZKI *et al.* in 1904 [10]. Since then, only about forty cases have been described in the literature [11] [12]. Men are more affected with a sex ratio of 2.4:1 with an average age of 63.9 [13]. In male cases, gynecomastia is frequently observed. The HCG rate is high in almost all cases. Histologically, they are characterized by the presence of cytotrophoblastic-type mononuclear cells or the intermediate trophoblast and multinucleated large cells with abundant eosinophilic cytoplasm of syncytiotrophoblastic appearance. Rarely, this contingent is associated with areas of micropapillary or sarcomatoid differentiation [14] [15] [16]. At IHC, the tumor cells express beta-HCG, human placental lactogen (HPL) and GATA3, but do not show labeling with CK7 and P63, which distinguishes them from cells of the classical urothelial challenge [17]. The prognosis seems to be bad: at the time of diagnosis, about 47% of cases present metastases [13] [15]. The treatment of these cancers is not well standardized and remains mainly surgical. In addition, it has been reported that HCG secretion is associated with radio-resistance, which may explain the low efficiency of radiotherapy on this type of tumor [18].

2.2. Sarcomatoid Carcinoma (Fusiform Cells)

Sarcomatoid carcinoma with fusiform cells is a variant that is probably less exceptional than the figures in the literature (0.6% - 1%) describe [19] [20]. It mainly affects men (1.7 to 4 men for 1 woman), with an average age of 66.4 years (21 - 91 years) [21] [22]. Some cases have been described at a pT1 stage. Spindle cell carcinoma may be only a partial differentiation of urothelial carcinoma, but in general it constitutes the entire tumor mass [5]. The clinical presentation is aspecific, dominated by hematuria, dysuria, nocturia and acute retention of urine [14] [23]. Macroscopically, these tumors form large polyploid buds protruding into the bladder lumen [5]. Histologically, the fusiform contingent is va-

riable in appearance, abundance, uniform, epithelioid or heterologous differentiation of chondrosarcoma or osteosarcoma [5] (Figure 3). It merges with the urothelial contingent. Immunolabeling with Cytokeratin and EMA to confirm the epithelial nature is sometimes essential [5] [16]. Markers P63, CK5/6 and HMWCK are positive in 10% to 40% of cases. It is a very aggressive variant, generally diagnosed at an advanced stage, and its evolution is unfavorable, with rapid onset of pulmonary or hepatic metastases and a 5-year survival of about 20 to 50% [21] [24], despite a treatment combining cystectomy and complementary radiotherapy [5]. Most published cases have been treated with radical cystectomy, sometimes associated with postoperative radiotherapy. It would seem that this type of tumor is radiosensitive [21].

2.3. The Nest Variant

In 1979, STERN described a variant of urothelial carcinoma with nests contiguous to each other [25]. In 1989, TALBERT and YOUNG describe this entity and give it the name of “nested carcinoma” [26] [27]. This very rare variant (0.3%) must be known because it can be difficult to identify by a superficial biopsy [1]. Less than one hundred cases have been described in the literature. The age of onset of this tumor does not differ from that of classical urothelial carcinoma [5] [14] [28] [29], with predominance for males. Symptoms are dominated by hematuria, urgency and signs of ureteral obstruction [30]. On resection specimens, cell proliferation leaves a non-atypical flat epithelium on the surface and infiltrates the chorion as small cell nests resembling Von Brunn islands. These cellular nests are rounded, ovoid, or in the shape of a “heart” surrounded by a basement membrane. The cells are relatively regular, not atypical, which is very misleading. Only at the periphery of certain nests and in the deepest nests are atypical cells identified with a large hyperchromatic nucleus [5]. According to the WHO, this variant is considered low grade however, several authors propose

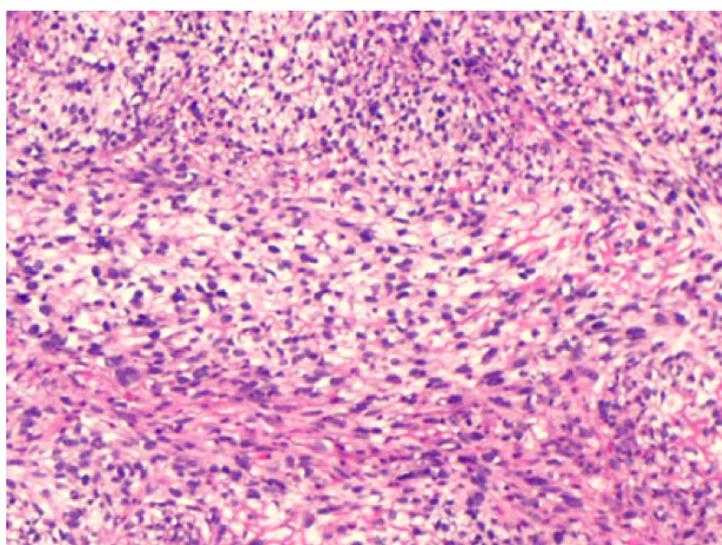


Figure 3. Microscopic appearance of sarcomatoid urothelial carcinoma.

to reclassify it as high grade [31] [32] [33]. Regarding IHC, overexpression of P53 and MIB-1 has been described [31]. Despite treatment, the evolution is unfavorable with survival between 4 and 40 months after diagnosis [34]. Neoadjuvant chemotherapy appears to increase survival in some patients. Radical cystectomy is the treatment of choice [5] [35] [36].

2.4. Plasmocytoid Carcinoma

First described by SAHIN and COLL in 1991 [37] and since then only about 100 cases have been reported in the literature [38]. The diagnosis is most often made at an advanced stage of the disease [38]. According to several authors, the average age at diagnosis is 65 years with a clear male predominance [38] [39]. The plasmocytoid variant of the bladder is rare, its incidence varies between 0.5% and 2.7% of urothelial carcinomas [40] [41]. According to WASCO *et al.*, the symptomatology is not specific [35]. Microscopically, it is a poorly differentiated or even undifferentiated carcinoma, and is often associated with a conventional high-grade UC or sarcomatoid carcinoma. The tumor cells are diffuse non-cohesive, oval or round with a loose, myxoid stroma, contained in abundant eosinophilic cytoplasm and eccentric nuclei (Figure 4). The plasmocytoid component can represent between 30% to 100% of the tumor [5]. This variant is characterized by cell labeling with anti-CK7, CK20, AE1/AE3, EMA and CD138, associated with a negativity of the labeling for LCA, S100, HMB45 and CD79- α [40] [41]. The prognosis in advanced forms is poor [42] [43]. Cystectomy is the treatment of choice associated with adjuvant chemotherapy [42] [44]. Dayyani reports a median overall survival of 45.8 months [42].

2.5. The Micropapillary Variant (VMCP)

First described in 1994 by AMIN *et al.* in a series of patients [45]. Micropapillary carcinoma is a rare variant (0.6% to 2%) of urothelial carcinoma. The age of onset

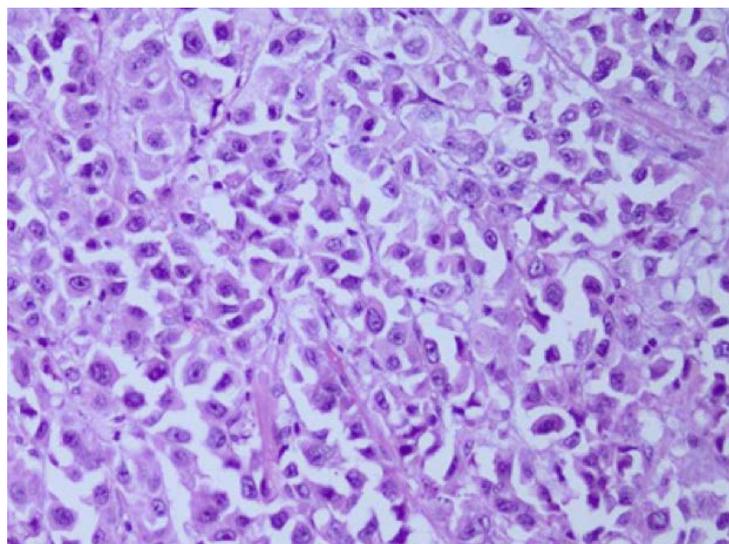


Figure 4. Microscopic appearance of plasmocytoid urothelial carcinoma.

is between 50 and 90 years with an average age of 66 years with marked predominance in men [4] [46]. Clinical manifestations are dominated by hematuria [30]. Histologically, the tumor infiltrates the wall in the form of masses of papillary masses underlined by retraction spaces. Tumor proliferation consists of abundant cytoplasmic eosinophilic cells with irregular nuclei and a high nucleocytoplasmic ratio. The micropapillary areas can represent 10% to 90% of the tumor. Lymphatic and vascular emboli are frequently associated with them. The immunohistochemical study is useful, with a panel of antibodies including: uroplakin, CK20, TTF-1 (to exclude thyroid origin), estrogen receptor, WT-1, or PAX8, and mammaglobin (to exclude an origin metastatic cancer of the ovary or breast cancer). In case of need, the best markers in favor of a urothelial origin are uroplakin, GATA3 and CK20 [47] [48]. The expression of MUC1 is limited to the basal pole of cells whereas it can be intracytoplasmic or intercellular in conventional UC [47]. It is always a very high grade, advanced (>pT2) tumor with a poor prognosis (5-year survival of less than 25%) [35]. Tumor stage and survival are correlated with the proportion of the micropapillary quota [47] [48] [49]. According to several teams, it is strongly recommended to perform a second resection before treatment, in search of a muscular invasion unnoticed although this is controversial [49]. Some teams propose a cystectomy from the outset to improve patient survival [48].

2.6. Lymphoepithelial Carcinoma

First described in 1991 by ZUKERBERG *et al.* [50], it is a rare variant (0.4 to 1.6%) of urothelial carcinoma [51]. It occurs mainly in the elderly with a marked predominance in men [4] [51]. According to ALLENDE *et al.*, the symptomatology is dominated by hematuria [52]. The microscopic study describes a high-grade minority urothelial contingent surrounded by an abundant inflammatory stroma, excessively rich in lymphocytes, plasma cells, histiocytes, and polymorphonuclear neutrophils. Epithelial cells express cytokeratin (AE1/AE3) as well as differentiation markers CK7 and CK8 but rarely CK20. The lymphoid stroma expresses CD45 with CD20+ and CD3 components. This rare variant is characterized by an unfavorable evolution, a discovery often at an advanced stage (>pT2) at the time of diagnosis and a survival rate at 5 years after cystectomy of 57% [5] [53]. Pure forms respond well to chemotherapy [51] [54].

2.7. Microcystic Carcinoma

Microcystic urothelial carcinoma resembles carcinoma “in nests” with images of cystic cavitation of “nests” [9] [55]. The difficulty is to distinguish with a benign lesion such as cystic and glandular cystitis and nephrogenic metaplasia [55]. The diagnosis of malignancy is based on the presence of cytonuclear atypia and/or the infiltrative nature of the lesion and/or the existence of a more typical urothelial carcinoma contingent. The aggressive reputation of microcystic carcinoma stems from the fact that it is difficult to recognize on shallow specimens and

is therefore diagnosed at a late stage. At the slightest doubt, one must know how to ask for a new resection [55].

2.8. Giant Cell Carcinoma

It is an exceptional variant, by definition always associated with conventional urothelial carcinoma [56]. It is composed of poorly differentiated, pleomorphic cells with abundant eosinophilic or amphophilic cytoplasm. Nuclear atypias are marked, with many nucleoli, like giant cells observed in pulmonary neoplasia [56] [57]. At IHC, epithelial markers are positive, including cytokeratin and EMA, sometimes for HCG [56] [57].

3. Conclusion

A good histological classification of invasive urothelial carcinoma is essential for a better knowledge of the prognosis as well as the possible therapeutic strategies. One of the major difficulties in understanding UC is its extremely heterogeneous genetic profile. It is already being seen that urothelial carcinoma will not be treated in the future solely by histological data alone, but that gene profiles start to play a major role, helping to select chemo-sensitive patients, but also to avoid overly heavy, ineffective treatments for chemo-resistant patients. Nevertheless, the histology will keep an important place to allow a quick diagnosis, and at a lower cost.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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