Plasmocytoid urothelial carcinoma - clinical, histological, immunohistochemical and molecular aspects

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Abstract

Plasmacytoid (PUC) variant is a rare and aggressive form of urothelial cancer representing 1 to 3% of the bladder cancer. The main differential diagnosis is the bladder involvement by lymphoma-plasmocytoma or metastasis from lobular breast cancer or diffuse gastric cancer. Immunexpression of cytokeratin 7 and GATA3 is the rule, but CD138 may be positive in high percentage of cases. CDH1 somatic mutation or, more rarely, methylation of the gene promoter is the main genetic characteristic of PUC, but germinative mutation is always negative. The recognition of this special histology is very important for the correct management of the patients because of the high rate of positive surgical margins and atypical disease progression. PUC is responsive to cisplatin-based chemotherapy but recurrence is the rule. Peritoneal dissemination is frequent and cancer specific mortality is as high as 56% in a range of 19 to 23 months.

Keywords: Urinary bladder, Plasmacytoid, Urothelial carcinoma, Bladder, Variant, Immunohistochemistry, E-cadherin, Chemotherapy

Introduction

Bladder cancer is the 10th most common form of cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths in 2018 (Bray et al. 2018).

The WHO publication of 2016 recognizes 10 variants of urothelial carcinoma (UC), significant from the diagnostic, prognostic, and/or therapeutic perspective (Table 1).

In 1991 Sahin et al. (Sahin et al. 1991) and Zukerberg et al. (Zukerberg et al. 1991) described almost simultaneously a new variant of bladder cancer simulating lymphoma, that was later recognized by the World Health Organization (WHO) classification system in 2004. This rare and very aggressive form is called plasmacytoid urothelial carcinoma (PUC), also known as poorly cohesive or diffuse carcinoma.

This review will describe the clinical, histological, immunohistochemical and molecular aspects of the PUC, whose identification is essential for the correct management of patients.

Epidemiology and clinical features

PUC is a rare variant of bladder cancer, representing 1–3% of urothelial cancer. Eighty to 90% of patients are male and the age of diagnosis ranges from 45 to 89 years old. The main symptoms are gross hematuria, dysuria, nocturia and urinary frequency (Mai et al. 2006; Fritsche et al. 2008; Baldwin et al. 2005; Lopez-Beltran et al. 2009; Fox et al. 2017), although abdominal pain and ascites has been described as a consequence of peritoneal dissemination (Shao et al. 2017; Jibril and Stevens 2018). Unusual presentation as scrotal (Wang et al. 2016) or penile invasion (Messina et al. 2016) and urinary and intestinal obstruction have been reported.

Pathologic findings

There are no details about the gross examination in the literature, but sessile and protruding isolated or multiple tumor masses, as well as diffuse infiltration of the bladder has been described.

The definition of PUC is variable in the literature, being called plasmacytoid when represents at least 50 to 90% of the tumor, but others consider any percentage...
suitable for this classification (Li et al. 2019). PUC are by definition a high-grade urothelial cancer. Tumor cells are small to medium size, discohesive with eccentrically placed oval to round, and hyperchromatic nuclei. The cytoplasm is moderate to abundant and eosinophilic, resembling plasma cells. Binucleation is rare and mitotic figures are frequently seen. The nucleoli can be identified but is not prominent in the majority of cases. Plasmacytoid morphology represents between 5 and 100% of the tumor sample (Fig. 1). Around half of them are pure, but conventional UC, sarcomatoid, micropapillary, nested and small cell carcinoma can also be identified. The cells are arranged in cords, single files, small nests, solid sheetlike and occasionally assume a deceptive benign appearance, mimicking an inflammatory process (Fig. 2). The stroma may present a myxoid appearance, and cytoplasm vacuoles can be seen, but true signet cells are not identified (Fig. 3). In 30–43% of the cases vascular invasion is present (Fig. 4). Tumor stage is pT3 or higher in 56–100% and lymph node metastasis is present in 20–73% of the reported cases. Diffuse infiltration pattern, local spread and extension along pelvic fascial planes, involving perivesical, perirectal, and periureteric soft tissues are very common (Fig. 5) (Kaimakliotis et al. 2014a), and the peritoneal spread, occurs in 33–68% of patients (Sato et al. 2009; Ricardo-Gonzalez et al. 2012). Because of these characteristics, it is critical for pathologists to recognize PUC preoperatively, for prognostic and therapeutic purposes, including orientation regarding surgical margins. The rate of positive radical surgical margin ranges from 11 to 60%, and ureteral margin can be positive in up to one third of the cases, which is much more then <4% of conventional UC (Kaimakliotis et al. 2014a; Cockerill et al. 2017).

The immunohistochemical profile (Fig. 6) shows strong and diffuse positivity to CK7 (89–100%) and CK20 (31–100%). CD138 is reported in 11–100%, but LCA is always negative. Considering the differential diagnosis between a primary bladder tumor or spread from the breast or gastrointestinal tract, a panel of 8 markers was proposed by Bohan et al. (Borhan et al. 2017). Gross cystic disease fluid protein 15 (GCDFP-15), progesterone receptors, CDX2, and polyclonal carcinoembryonic antigen (p-CEA) showed positive staining in 24.4, 13.3, 17.7, and 48.8% of the cases, respectively. GATA 3 and uroplakin II immunostaining was expressed in 82.2 and 33.3% cases, respectively. All of the cases of plasmacytoid variant of UC were negative for estrogen receptor (ER) and mammaglobin.

**Table 1** 2016 WHO Classification of tumor of the urothelial tract

| Urothelial tumors (infiltrating urothelial carcinoma) |
|-----------------------------------------------------|
| Nested, including large nested                      |
| Microcystic                                         |
| Micropapillary                                      |
| Lymphoepithelioma-like                              |
| Plasmacytoid / signet ring cell / diffuse           |
| Sarcomatoid                                         |
| Giant cell                                          |
| Poorly differentiated                               |
| Lipid-rich                                          |

**Fig. 1 a and b.** PUC characterized by isolated cells with eccentric nuclei with eosinophilic cytoplasm giving them a plasmacytoid appearance

**Fig. 2 (a)** Tumor cells arranged in blocks or in indian files and (b): Deceptive nuclear polymorphism mimicking an inflammatory process

**Fig. 3**
Molecular aspects
All variant bladder cancer histologies were excluded from The Cancer Genome Atlas (TCGA) and their molecular basis remains ill defined. E-Chaderin loss resulting from CDH1 Y68fs mutation is so far typical of PUC, although in rare cases methylation of the gene promoter region has been detected (Al-Ahmadie et al. 2016). E-cadherin encoded by CDH1 Gene is a transmembrane glycoprotein, member of the cadherin family of molecules, predominantly expressed at the basolateral membrane of epithelial cells, where it exerts cell-cell adhesion and invasion-suppression functions (Nagar et al. 1996). It participates in maintenance of polarization and epithelial differentiation during development (Wijnhoven et al. 2000). E-cadherin loss (Fig. 7), leads to the enhanced cellular migration and invasive properties characteristic of plasmacytoid-variant tumors. Study conducted by Al-Ahmadie shows that with the exception of CDH1 alterations the genomic profile of plasmacytoid-variant tumors was not substantially different from the NOS-UC. Frequent mutations in the tumor suppressors TP53 and RB1, in the chromatin remodeler ARID1A, in kinases ERBB2 and PIK3CA and in telomerase reverse transcriptase (TERT) have also be seen in PUC in the TCGA study and in the Memorial Sloan Kettering prospective cohorts (Al-Ahmadie et al. 2016; Palsgrove et al. 2018). Loss of E-cadherin expression by germline mutation seen in most diffuse gastric cancers and in lobular breast cancers (Hirosashi 2000), is not identified in PUC, despite the high morphological similarity with these carcinomas.

Treatment and outcome
Treatment includes surgery, radiotherapy and adjuvant or neoadjuvant chemotherapy, but the optimal treatment strategy has not yet been elucidated due to the small number of patients. Although chemosensitive, recurrence, mainly peritoneal carcinomatosis is common, and survival outcomes are inferior for PUC (Kaimakliotis et al. 2014b; Dayyani et al. 2013a). In the largest series reported, the cancer specific mortality is higher than 56% in a period variable from 19 to 23 months, being the adjusted risk to die from cancer 2.1 for PUC histology compared to NOS-UC (Fox et al. 2017; Dayyani et al. 2013b; Keck et al. 2013). The new gold standard for high grade UC is the neoadjuvant chemotherapy, but the response is variable for different histologies, and there are few reports regarding PUC. Gunaratne et al. (Gunaratne et al. 2016) treated a 58 years-old male with 4 cycles of neoadjuvant gemcitabine and cisplatin that have led to a complete histologic response (pT0). The patient remained free of disease at 14 months of follow-up. On the contrary Dayyani et al. (Dayyani et al. 2013b) treated 5 from 16 patients with localized PUC with neoadjuvant chemotherapy with...
cisplatin-based regimens (methotrexate/vinblastine/Adriamycin/cisplatin or gemcitabine/cisplatin). There were 4 pathologic downstaging, being 3 complete responses (ypT0N0). Despite the pathological downstaging there was no difference in survival and the peritoneal recurrence was common, even in patients who had pathological complete response. Peritoneal recurrence, infiltration of abdominal wall, scrotum and penis can occur and some response to chemotherapy has been reported (da Fonseca et al. 2014).

**Conclusion**

Pathologists have to be aware to distinguish and report PUC, an aggressive variant of UC characterized by CDH1 somatic mutation with poor prognosis, locally infiltrative pattern and high risk for relapse despite surgery and chemotherapy.

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**Fig. 6 (a)** Immunohistochemistry showing strong and diffuse positivity for cytokeratin 7 and (b) GATA3

**Fig. 7 a and b** Immunohistochemistry showing the loss of E-Chaderin expression in the plasmacytoid type of urothelial carcinoma.
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