Clinicopathological Features of Plasmacytoid Urothelial Carcinoma of the Bladder: Case Report and Review of the Literature

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Abstract

Plasmacytoid Urothelial Carcinoma (PUC) is a rare histological variant of bladder cancer accounting for 1% to 3% of all urothelial bladder cancer worldwide. This aggressive tumor is associated with poor prognosis and is often metastatic at diagnosis. These characteristics lead to the need of a differential diagnosis where histopathological examination, together with the use of immunohistochemistry are crucial. In this case report we report a 62-year-old female patient affected by urothelial carcinoma with plasmacytoid differentiation.

Keywords: Histology; Pathology; Plasmacytoid; Urothelial Carcinoma; Urinary Bladder Cancer

Introduction

Bladder cancer ranks as 7th among most common cancers and is 3-4 times more frequent in male than in female population [1]. Urothelial Carcinoma (UC) accounts for 90% of whole bladder cancers in industrialized countries and for 80% in the rest of the world, affirming itself as the most widespread type of bladder cancers [2]. Plasmacytoid Urothelial Carcinoma (PUC) is a rare histological variant of urothelial neoplasms, which accounts for 1% to 3% of invasive UC of the bladder [3,4]. Differently from conventional UC, PUC exhibits unique clinical and histopathological features. Since its first description in 1991, PUC has been characterized by a highly aggressive clinical behavior and poor prognosis [5]. Indeed, it often presents with advanced stage at diagnosis (e.g., muscle-invasive disease and/or occurrence of metastases at presentation) and a rapid metastatic spread [6]. Moreover, although hematuria is the typical presenting symptom of conventional UC, in the PUC variant specific clinical characteristics are usually missing, making its diagnosis more challenging [7]. Due to the late presentation and the propensity of invasion (both local and systemic), a deeper knowledge of this rare entity is of clinical importance for an early proper diagnosis and for an optimal management strategy [8].

Case Report

We report the case of a 62-year-old Caucasian woman referred to the urology outpatient department after an abdominal and pelvic Magnetic Resonance Imaging (MRI) performed for a nearly 9-months history of left lumbar pain revealed multiple bone metastases (i.e., vertebral column and ribs) and left hydronephrosis. At urological consultation, she also complained recent development of pollakiuria associated with urge urinary incontinence; she denied any history of gross hematuria. Her past medical history included tobacco smoking (10 cigarettes per day) and gastroesophageal reflux disease; she also underwent open partial colon resection for bowel obstruction 20 years ago and appendectomy. Physical examination did not reveal any particular findings. Urinary cytology was negative. Contrast-enhanced whole-body Computed Tomography (CT) scan was indicated, revealing a marked and diffuse wall thickening on the left lateral, anterior and posterior bladder wall (depth 11 mm) and left obstructive uropathy with hydronephrosis. Distant metastases in multiple bone sites (i.e., D11 vertebral body, right temporal and occipital bones, sternum, ribs) as well as lymph nodes (i.e., para-aortic caval) were documented. The patient was indicated for cystoscopy under general anesthesia, which revealed a white solid area (30x40 mm) on the left lateral wall of the bladder, involving the left ureteric orifice (no sessile or papillary masses were detected). Transurethral Resection Of The Bladder Tumor (TURBt) was performed. The patient was discharged after catheter removal on the third post-operative day, without any complications. Specimens were sent for histopathological assessment. The pathological examination revealed a High-Grade (G3) Muscle-Invasive (pT2) UC with plasmacytoid features (Figure 1).

Figure 1: A: Plasmacytoid urothelial carcinoma showing expression of GATA3. B: Plasmacytoid urothelial carcinoma showing expression of Uroplachin II. C: Plasmacytoid urothelial carcinoma showing expression of CD138. D: Plasmacytoid urothelial carcinoma showing aberrant expression of GCDFP-15.
Histopathological Examination

After being fixed, processed, embedded in paraffin and stained with hematoxylin and eosin, the TURBt chips were analyzed under the microscope. The sections showed fragments of the bladder mucosa partially covered by urothelium without significant atypia and a proliferation of atypical cells, often with a surrounding desmoplastic stromal response, present in the lamina propria and infiltrating the underlying detrusor muscle in small loose clusters or discohesive single cells, simulating indian-file pattern as in lobular breast carcinoma. At high magnification, these cells exhibited a disco-sticky pattern and were mostly characterized by a large eosinophilic cytoplasm, eccentrically arranged nucleus without prominent pleomorphism, inconsistent nucleolar prominence that may also contain occasional vacuoles or form signet ring cells with focal intra-cytoplasm mucin resembling plasma cells (Figure 2). Immunohistochemical analysis demonstrated positivity staining for CKAE1/AE3, CK7, GATA3, CK8/18, CD138, pCEA, GCDFAP15, Uroplakin and negativity immunostains for CK20, CDX2, CD45, CD68, E-cadherin, Heppar1, p63, MUM1, CD38, β-catenin and ER; no HER2 expression was observed; PDL-1 expression was less than 1% on neoplastic cells (Figures 1,3). After the diagnosis of invasive PUC of the bladder was established, the condition of the patient was consulted with the Oncology Department, and systemic chemotherapy was planned. The patient was given 3 cycles of a combined regimen with cisplatin and gemcitabine, starting 1 month after surgery. Contrast-enhanced whole-body CT scan performed at 3 months of follow-up, showed partial regression of the lymph node lesions, as well as of the bladder wall thickening. In the light of the partial radiographic response, radical cystectomy plus bilateral lymphadenectomy was indicated, yet surgery was refused by the patient. The patient was followed-up and no recurrence 15 months after TURB was detected.

Figure 2: A: Transurethral bladder tumor resection; tumour cells at low magnification (HE, × 2,5) can be overlooked as inflammatory cells. B: Plasmacytoid urothelial carcinoma; singly scattered neoplastic cells in the lamina propria forming loose aggregates and cords. C: Plasmacytoid urothelial carcinoma; discohesive single cells with eccentrically placed nuclei and abundant eosinophilic cytoplasm. Note the prominent desmoplastic response of the surrounding stroma. D: Plasmacytoid urothelial carcinoma involving the muscularis propria. Note the discohesive and infiltrating nature of the neoplastic cells with both signet ring cell and classic plasmacytoid morphology.
PUC is a rare variant of UC enclosed in the 2004 World Health Organization (WHO) classification of urothelial neoplasms and refined in the updated version in 2016 [3,9]. It was first described by Sahin et al in 1991, who reported a case of PUC in a 63-year-old man presenting with bone metastatic lesions (i.e., ribs and skull), who was misdiagnosed as multiple myeloma [5]. After III decades from its initial description, primarily due to the rarity of this entity, a limited number of PUC cases has been reported in the literature, mostly from case reports and small case series [10]. One of the main concerning aspects regarding PUC is the challenging clinical diagnosis. Indeed, although hematuria is the typical presentation of conventional UC, this symptom is usually missing in the plasmacytoid variant, leading to a late diagnosis [11,12]. Often patients present with no specific genitourinary complaints, yet with aspecific clinical symptoms or signs due to metastatic spread of the disease. Of note, in our case report the patient denied any history of gross hematuria yet complained left lumbar pain (left hydroureteronephrosis was then documented on imaging) together with a recent development of irritative urinary symptoms (i.e., frequency associated with urge urinary incontinence). Moreover, the lack of an identifiable tumor in the urinary bladder that has been associated with PUC - more than conventional UC - is a characteristic that could further delay the diagnosis. On cystoscopy examination, even in cases with advanced disease, PUC could exhibit a macroscopic aspect that might not always be easily to detect (e.g., as a plaque-like lesion, as a mucosal induration or as an aspecific irregularity of the mucosa), rather than a sessile or papillary mass [11,13,10]. In our case, appearance on cystoscopy was that of a white solid area on the left lateral bladder wall (consistent with the exuberant stromal reaction of desmoplastic subtype of PUC [14]), yet not a lesion with a clear malignant macroscopic aspect (diffuse wall thickening on CT scans further supported the treatment decision process, i.e., TURBT).

In cases with clinical suspicion of UC, yet without the detection of clear lesions on cystoscopy, multiple biopsies are taken; especially in these cases with smaller biopsies, PUC could represent a diagnostic dilemma for pathologists. Histopathologically, PUC is characterized by plasmacytoid tumor cells arranged in cords and single-file pattern, small nests, solid sheet-like growth or diffuse discohesive architecture, with eccentrically placed nuclei, and abundant amphophilic cytoplasm with eosinophilic paranuclear hoof reminiscent of plasma cells. PUC represents a challenge also for pathologists since its architecture resembles that of other benign and malignant lesions (e.g., cystitis with plasma cell infiltration, plasma cell-derived neoplasms, lymphomas, lymphoepitheliomas and metastatic breast or gastric carcinomas) that could represent cause of misdiagnosis [15]. Thus, properly recognizing its morphological distinction from other entity with plasmacytoid phenotype is crucial for a correct diagnosis and subsequent clinical management. In this regard, immunohistochemistry plays an essential role. Initially, it can lead to mistaken for a plasma cell neoplasm because of their morphology and metastatic sites like bone. These cells express CD138, like plasma cells but also express epithelial marker like CKAEl/AE3, CK7 and are negative for other plasma cell markers as MUM1 and CD38 [16]. To the best of our knowledge, a study performed on 49 cases showed the positivity for cytokeratin, CD138, GATA3 and uroplakin II and negativity for e-cadherin. Loss of cell adhesion due to lack of E-cadherin is reported in many studies [17,18].

This is related with a higher disease grade and stage and can be explained by a loss of cadherin-1 (CDH1) mutation or hypermetilation of the promoter region [18,16]. Al-Ahmadie et al showed frequent somatic CDH1 loss-of-function mutations in invasive plasmacytoid bladder cancer [19]. This mutation might lead to characteristic single-cell growth pattern and is known to be present in lobular breast cancer or diffuse type of gastric cancer which have morphologic resemblance to PUC [20]. These last two are the carcinomas that enter first in the differential diagnosis with PUC [21]. In our case CDX2 was negative and p-CEA positive but they have limited specificity in differentiating plasmacytoid UC from signet ring gastric origin because a subset of PUC may express CDX2. GATA3 and Uroplakin however are not expressed by gastric carcinomas and β-catenin staining was negative, confirming

**Figure 3:** Plasmacytoid urothelial carcinoma showing expression of pancytokeratin.
PUC’s diagnosis [21]. GCPDFP-15 and GATA3 are positive in lobular carcinoma, compounding the problems in distinguishing PUCs from this neoplasm. Plasmacytoid UC however is always negative for breast marker ER and lobular carcinoma is negative for Uroplakin and thus inclusion of immunostains in a panel may facilitate the diagnosis [22]. The available data suggests that PUC is associated with an advanced disease (i.e., advanced stage at surgery and high rate of metastases) and poor prognosis [23]. However desmoplastic PUC subvariant appear to have slightly worse overall survival compared with classic and pleomorphic subvariants [14]. In the study from Kaimakliotis et al [24] 80% of patients with cT1 disease were up-staged to pT3 at radical cystectomy. In the series of Dayyani et al [6], among 31 patients diagnosed with PUC, 48% initially presented with metastatic or locally unresectable disease. Furthermore, also after adjusting for tumor stage and lymph node status, PUC has been associated with poor oncological outcomes [4,20]. Of note, in our case, the presence of diffuse metastases was documented at the time of initial work-up (both in bones and lymph nodes), further supporting the evidence of an aggressive clinical behavior of this variant type. A recent meta-analysis evaluating 8 studies on the plasmacytoid variant of UC demonstrated that PUC was strongly associated with adverse clinico-pathological features, yet its effects on overall survival outcome failed to reach statistical significance after adjusting for other clinico-pathological features (i.e., age, gender, performance status, tumor grade and stage, margin status and systemic chemotherapy) [19]; authors concluded that the small number of cases reported in the literature could have affected the statistical power of this result. Thus, further evidence is still needed to ensure a proper knowledge of this rare entity, specifically in terms of prognostic value. The main clinical interest on PUC is its significance from a therapeutic and prognostic perspective. To date, a tailored therapeutic strategy for the PUC variant has not been yet established [1,25]. The available evidence, mostly based on case reports, series and few retrospective case-control studies, has limited the possibility to assess guidelines for the proper management. A multimodal approach has been most frequently reported (surgery, both conservative and radical, with or without Chemotherapy (CHT), as neoadjuvant or adjuvant approach).

To date, radical cystectomy has been considered as the best surgical approach to treat PUC variant. However, successful conservative treatment with TURBt has been described [11]. In our case report, following TURBt, and on the basis of the histological examination and response to CHT, radical surgery was indicated. After 15 months of follow-up from initial diagnosis, no evidence of recurrence was detected, suggesting potential satisfactory survival outcomes also with a conservative approach. On the contrary, some authors reported poorer oncological outcomes [23], highlighting that conservative management could be associated with the risk of under-treatment.

Also, the role of CHT is still not fully understood. Whether a neoadjuvant or adjuvant CHT should be administered is still a matter of debate [19]. In our case, after a multidisciplinary consultation, CHT (with a combination of cisplatin and gemcitabine) was planned, starting 1 month after the bladder resection. The patient was given 3 cycles of CHT, and CT scan at 3 months of follow-up showed partial regression of the lesions. According to the radiographic response, further radical surgery was indicated, yet not performed based on patient’s decision. In the light of the role of multimodal treatment in this aggressive variant type, systemic CHT should be further investigated, in order to establish a proper timing of administration and regimen for the management of PUC.

Conclusion

PUC is a rare variant of UC with particularly aggressive behavior that may initially be confused with other types of neoplasms. An adequate understanding of this uncommon variant is of clinical importance, in order to distinguish this entity, thus avoiding a potential misdiagnosis, and to properly guide treatment-decision making.

References