# Plasmacytoid Bladder Cancer: Variant Histology With Aggressive Behavior and a New Mode of Invasion Along Fascial Planes

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**OBJECTIVE** To examine differences in disease progression and nature of tumor invasion that may lead to more accurate expectations of tumor behavior and improved management options for plasmacytoid variant (PCV) histology urothelial bladder cancer patients.

**METHODS** Using the Indiana University Bladder Cancer Database, we conducted a retrospective analysis of patients undergoing radical cystectomy from 2008 to June 2013 to identify patients with PCV, micropapillary variant (MPV), or nonvariant (NV) histology and either positive ureteral margins (+UM), paravesical surgical margins (+PSM), or lymph node (+LN) involvement. Pearson's chi-squared test and analysis of variance were used for descriptive analysis.

**RESULTS** Of 510 patients who met inclusion criteria, 30 had +UM on final pathology. The incidence of +UM in NV patients was 17 of 457 (3.7%), in MPV 5 of 28 (17.9%), and in PCV 8 of 25 (32.0%) ($P < .001$). *Carcinoma in situ* on the luminal margin was noted for all cases, except in 5 of the 8 PCV patients with +UM, in whom retrograde longitudinal invasion along the subserosal and adventitia was noted. +PSM and +LN were significantly higher for both PCV (28.0%, 72.0%) and MPV (10.7%, 64.3%) than NV (2.6%, 18.6%, $P < .001$, each).

**CONCLUSION** PCV exhibits a unique pattern of spread along the ureter. This proposes a new mode of invasion along the fascial sheath. The incidence of +PSM and +LN liken PCV to the known aggressive MPV, and in conjunction with the increased incidence of +UM, may lead to a paradigm shift, with surgeons and pathologists being more vigilant with surgical margins. UROLOGY 83: 1112–1116, 2014. © 2014 Elsevier Inc.

Variant histology in urothelial bladder cancer (UC) is poorly defined, with sparse literature describing individual variants and their prognostic implications. Plasmacytoid variant (PCV) is a rare variant that has only recently been published in larger series. The largest series comprised 31 and 32 patients and include patients with both metastatic and potentially curable disease.[1,2] As a large volume tertiary referral center for bladder cancer, we have experienced an increase in the number of patients who are identified with variant histology on transurethral resection or final pathology at cystectomy. It is unclear if this increase of variant histology is driven by causative factors or by improved awareness and recognition on pathologic review. As such, larger cohorts of these variants are beginning to be described in the literature, with new information emerging regarding their distinctive clinicopathologic characteristics and outcomes. PCV is one such UC variant seen with increasing frequency at our institution.

On histology, PCV tumor cells have an eccentrically placed nucleus and abundant eosinophilic cytoplasm reminiscent of plasma cells.[3] Most neoplastic cells have nuclei of low to intermediate nuclear grade, with occasional nuclear pleomorphism. PCV tumor cells have been described as discohesive cells, which may account for their aggressive nature. Such cells have also been noted to invade in single cell formation, known as "Indian file," with malignant cells manifesting distant from gross macroscopic disease.

Within our experience, an unexpected and ominous finding that has emerged during cystectomy for patients

*H.Z.K. was responsible for concept and design, data acquisition, data analysis and interpretation, and drafting of the manuscript. M.F.M. was responsible for data acquisition, data analysis and interpretation, drafting the manuscript, and statistical analysis. L.C. was responsible for data acquisition, analysis and interpretation, and critical revision of the manuscript. T.A.M. was responsible for concept and design and critical revision of the manuscript. K.C.C. was responsible for critical revision of the manuscript. J.A.P. was responsible for data acquisition, analysis, and interpretation, and critical revision of the manuscript. R.S.F. was responsible for critical revision of the manuscript. M.O.K was responsible for concept and design, critical revision of the manuscript, and supervision. R.B. was responsible for concept and design, critical revision of the manuscript, and supervision.*

**Financial Disclosure:** *The authors declare that they have no relevant financial interests.*

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*Submitted: November 27, 2013, accepted (with revisions): December 25, 2013*



0090-4295/14/$36.00
http://dx.doi.org/10.1016/j.urology.2013.12.035

**Table 1.** Patient characteristics, surgical pathology, and lymph node involvement of 510 patients undergoing radical cystectomy, 2008-2013

| Characteristics | NV (%) | MPV (%) | PCV (%) | *P* Value |
|---|---|---|---|---|
| Number | 457 | 28 | 25 | |
| Age, mean (SD) | 66.6 (11.0) | 72.0 (9.1) | 66.2 (9.3) | .038 |
| Sex (female) | 97 (21.2) | 4 (14.3) | 5 (20.0) | .677 |
| Race (Caucasian) | 436 (95.4) | 28 (100) | 22 (88.0) | .113 |
| Neoadjuvant chemotherapy | 63 (14) | 5 (18) | 5 (20) | .592 |
| Stage | | | | |
| ≤pT1 | 220 (48) | 0 | 1 (4) | <.001 |
| pT2 | 105 (23) | 10 (36) | 4 (16) | |
| pT3 | 94 (21) | 11 (39) | 9 (36) | |
| pT4 | 38 (8) | 7 (25) | 11 (44) | |
| +Ureteral margin | 17 (3.7) | 5 (17.9) | 8 (32.0) | <.001 |
| Average ureteral FS specimens (SD) | 1.4 (1.0) | 2.4 (1.3) | 2.3 (1.4) | .017 |
| Tumor at ureteral margin | 16 *CIS* | 5 *CIS* | 3 *CIS*, 5 PCV cells at subserosa/adventitia | |
| Concurrent bladder *CIS* | 264 (57.8) | 18 (64.3) | 12 (44.0) | .301 |
| +Paravesical margin | 12 (2.6) | 3 (10.7) | 7 (28.0) | <.001 |
| +Lymph nodes | 85 (18.6) | 18 (64.3) | 18 (72.0) | <.001 |

*CIS*, *carcinoma in situ*; FS, frozen section; MPV, micropapillary variant; NV, nonvariant; PCV, plasmacytoid; SD, standard deviation.

with PCV is the extent of disease, both in terms of lymph node (+LN) involvement and spread along serosal surfaces and fascial planes. We report in this study on clinicopathologic findings noted at cystectomy in patients diagnosed with PCV compared with a less aggressive nonvariant (NV) population, but also compared with a known aggressive variant, micropapillary variant (MPV) histology.[4] We sought to examine differences in disease progression and nature of tumor invasion in an attempt to delineate more accurate expectations of tumor behavior and explore improved management options for patients with PCV.

## METHODS

The Indiana University Bladder Cancer Database was retrospectively analyzed after obtaining Institutional Review Board approval. We identified all patients who underwent radical cystectomy with primary UC from 2008 to June 2013. On the basis of histopathologic interpretation by dedicated genitourinary pathologists, we identified patients with variant histology present on cystectomy pathology. For the purpose of this study, we chose to focus primarily on patients with PCV and compare these patients with MPV, a known aggressive variant of UC, and with NV UC. As such, all patients with other urothelial variants identified at cystectomy during the same period were excluded from this cohort, as were primary squamous, small cell, rhabdomyosarcoma, and adenocarcinoma bladder cancer patients. We chose not to use a cutoff for component of variant histology, which means that some of our patients had focal variant histology, whereas others had 100%. In the event of mixed histology, primary variant was assigned to the variant with >50% of total variant histology. Patients undergoing radical cystectomy with known metastatic disease, lymphadenopathy >1.5 cm preoperatively, or radiation therapy preoperatively were also excluded. Our primary outcomes of interest were positive ureteral margins (+UM), positive paravesical soft tissue margins, and +LN involvement. Additional variables of interest that were extracted from the pathology report were the number of intraoperative ureteral frozen section margins and the tumor morphology identified at the ureteral margin.

To perform descriptive analysis comparing the variant cases with the NV, Pearson's chi-squared test was used for categorical variables and analysis of variance for continuous variables. Relative risk ratios were calculated using NV cases as the comparison group. All samples with +UM were re-evaluated by 1 pathologist (L.C.).

## RESULTS

A total of 624 patients were identified as having undergone radical cystectomy during the defined period. Of these, 510 had either PCV, MPV, or NV histology. Four hundred fifty-seven (89.6%) patients were identified with NV histology, 28 (5.5%) with MPV, and 25 (4.9%) with PCV. Thirty (5.9%) patients had +UM on final pathology. Each of these patients had either negative frozen intraoperative surgical margins or several attempts at a negative frozen section with the continued presence of *carcinoma in situ* (*CIS*). No patient left the operating room with known tumor at the ureteral margin unless multiple resections for *CIS* were approaching removal of kidney or need for complete ureteral interposition. Of the patients with +UM on final pathology, 5 were MPV, 8 PCV, and 17 NV (Table 1). The incidence of +UM in NV histology patients was 3.7%; however, among MPV patients it was 17.9%, and 32.0% in the PCV ($P$ <.001). This corresponds to PCV patients being at 8.6 times increased risk of developing +UM compared with the NV patients ($P$ <.001). Similarly, MPV patients had a 4.8 times increased risk of developing +UM ($P$ <.001).

Patients with PCV underwent an average of 2.3 intraoperative surgical frozen margin resections for each involved ureter, in an attempt to obtain negative margins, vs 2.4 for MPV and 1.4 for NV cases ($P$ = .017) (Table 1). *CIS* on the endoluminal ureteral margin was noted for all cases with +UM, except in 5 of the 8 PCV cases. These patients exhibited retrograde longitudinal invasion of PCV tumor cells along the subserosal and adventitial ureteral planes (Fig. 1). This was noted