Plasmacytoid Carcinoma of the Bladder: A Urothelial Carcinoma Variant With a Predilection for Intraperitoneal Spread

Roberto Rafael Ricardo-Gonzalez, Michael Nguyen, Neriman Gokden, Ankur R. Sangoi, Joseph C. Presti, Jr.* and Jesse K. McKenney†

From the Departments of Pathology (RRRG, MN, ARS, JKM) and Urology (JCP, JKM), Stanford University Medical Center, Stanford and Department of Pathology, El Camino Hospital (ARS), Mountain View, California, and Department of Pathology, University of Arkansas for Medical Sciences (NG), Little Rock, Arkansas

Submitted for publication July 7, 2011.

Study received institutional review board approval.

* Financial interest and/or other relationship with Progros DX and Myriad.

† Correspondence: Department of Pathology, Stanford University Medical Center, 300 Pasteur Dr., Room L235, Stanford, California 94305 (e-mail: jmck@stanford.edu).

For another article on a related topic see page 1071.

Purpose: Bladder plasmacytoid carcinoma is an invasive urothelial carcinoma subtype that is emphasized for its morphological overlap with plasma cells and metastatic carcinoma. Our experience suggests frequent intraperitoneal spread that is not typical of conventional urothelial carcinoma.

Materials and Methods: We identified cases of plasmacytoid urothelial carcinoma diagnosed on radical cystectomy. Patient age, gender, American Joint Committee on Cancer (7th edition) stage, metastatic spread/recurrence sites and clinical disease status at last followup were recorded.

Results: A total of 10 male and 5 female patients 42 to 81 years old were identified. One tumor was pT2, 11 pT3 and 3 pT4. Six of 15 patients (40%) presented with lymph node metastasis and 5 (33%) had intraperitoneal metastasis at cystectomy. These initial sites of metastatic spread included the prerectal space, ovary and vagina, ovary and fallopian tube, bowel serosa, and omentum and bowel serosa in 1 case each. Three patients had subsequent metastasis involving the prerectal space, pleural fluid and small bowel serosa, and bowel serosa in 1 each. Eight patients had followup information available, including 3 who died of disease, 3 with disease and 2 with no evidence of disease.

Conclusions: Of the patients 33% with the plasmacytoid variant of urothelial carcinoma presented with intraperitoneal disease spread and 20% had subsequent metastasis involving serosal surfaces. The possibility of noncontiguous intraperitoneal spread involving serosal surfaces should be recognized to ensure proper intraoperative staging and clinical followup for patients with plasmacytoid carcinoma.

Key Words: urinary bladder, urothelium, carcinoma, neoplasm invasiveness, peritoneum

VARIOUS histological variants/subtypes of urothelial carcinoma have been described in the diagnostic pathology literature and are accepted by the WHO classification for urothelial neoplasia.[1] Some subtypes, such as small cell and micropapillary carcinoma, have significant prognostic, therapeutic and diagnostic implications.[2] Plasmacytoid carcinoma of the bladder is a well recognized subtype that was originally described due to its histological mimicry of reactive or neoplastic plasma cells. In addition to the diagnostic importance of recognizing this histologically subtle carcinoma, published series of plasmacytoid carcinoma have confirmed frequent presentation with high stage disease, often with lymph node metastasis.[3–7]

It is our experience that intraperitoneal disease spread, which is not

0022-5347/12/1873-0852/0
THE JOURNAL OF UROLOGY®

Vol. 187, 852-855, March 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.10.145

typical of urothelial carcinoma, is a relatively common finding in patients with plasmacytoid carcinoma that has not been previously emphasized. We present a clinicopathological series of 15 patients who underwent cystectomy for invasive plasmacytoid urothelial carcinoma of the bladder. We highlight the patterns of metastatic spread and recurrence to emphasize possible intraoperative staging and clinical followup implications.

MATERIALS AND METHODS

Under an approved institutional review board protocol we retrospectively identified radical cystectomy specimens from the surgical pathology archives at 3 hospitals where the surgery was done between January 1998 and July 2011. All cases were diagnosed as invasive urothelial carcinoma with plasmacytoid histological features. All hematoxylin and eosin stained glass slides were retrieved and reviewed to confirm the diagnosis using the WHO definition of "lymphoma-like and plasmacytoid variants."[1]

Patient age, gender, American Joint Committee on Cancer (7th edition) tumor stage, nodal metastasis, metastatic disease sites at presentation or subsequent followup and last known clinical disease status were recorded. Any subsequent disease recurrence and/or metastasis was identified by chart review. Additional archived pathological specimens documenting any subsequent disease were also retrieved and re-reviewed.

RESULTS

We identified 15 patients with plasmacytoid urothelial carcinoma at radical cystectomy (see table). In all cases the plasmacytoid component was the predominant pattern, comprising greater than 90% of the tumor. Four cases had focal, typical invasive urothelial carcinoma and 3 had another carcinoma variant pattern present focally, including 1 with a nested pattern and 2 with squamous differentiation. Patient age was 42 to 81 years (mean 66.7, median 69). Ten patients were male and 5 were female. One tumor was pT2, 11 pT3 and 3 pT4. Six of 15 patients (40%) presented with lymph node metastasis.

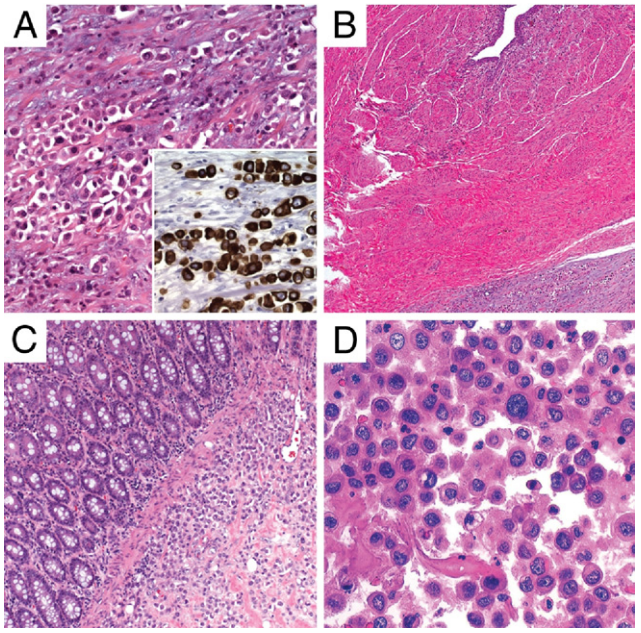
Two to 22 lymph nodes (mean 9, median 7) were sampled and 1 to 5 were involved nodes. Five of 15 patients (33%) had intraperitoneal metastasis at cystectomy and staging. These initial sites of metastatic spread included the prerectal space, the ovary and vagina, the ovary and fallopian tube, bowel serosa, and omentum and bowel serosa in 1 case each. Three patients had subsequent metastasis involving the prerectal space, pleural fluid and small bowel serosa, and bowel serosa in 1 each (see figure). Eight patients had followup information available and 6 were lost to followup. Three patients died of disease at 4, 17 and 20 months, 3 survived with disease at last followup at 24, 12 and 2 months, and 2 had no evidence of disease at last evaluation at 41 and 11 months, respectively. One patient who was recently diagnosed had been followed less than 1 month.

DISCUSSION

Invasive urothelial carcinoma of the bladder is a histologically diverse disease.[1,8,9] Although some variants are relatively common, such as urothelial carcinoma with squamous differentiation, many less common subtype/variant forms of urothelial carcinoma are also described in the diagnostic pathology literature. Several subtypes are now recognized as having prognostic and in some cases therapeutic

Clinicopathological features

Pt No.—Age—Gender	pT Stage	Lymph Nodes	Extravesical Disease Sites	Clinical Followup (mos)
1—69—M	pT4	+	Periureteral soft tissue + seminal vesicle at primary surgery	Dead of disease (20)
2—77—M	pT3a	–	None	Lost to followup
3—55—M	pT3a	+	None	Dead of disease (17)
4—61—F	pT3a	Not evaluated	Omentum, small bowel + colon serosa at primary surgery	Dead of disease (4)
5—79—M	pT3b	+	Prerectal space at primary surgery	No disease evidence (11)
6—70—M	pT3a	–	None	Lost to followup
7—71—F	pT3a	–	None	No disease evidence (41)
8—81—M	pT3a	Not evaluated	None	Lost to followup
9—72—M	pT4	+	Periureteral soft tissue + seminal vesicle at primary surgery	Lost to followup
10—66—M	pT2	Not evaluated	None	Lost to followup
11—58—M	pT3b	Not evaluated	Bowel serosa at primary surgery, small bowel serosa at 2 mos	Disease (2)
12—63—F	pT4	+	Ovary + vagina at primary surgery, bowel wall at 12 mos, pleural fluid at 24 mos	Disease (24)
13—42—M	pT3b	–	None	Lost to followup
14—70—F	pT3b	–	Perirectal at 12 mos	Disease (12)
15—66—F	pT3b	Not evaluated	Fallopian tube + ovary at primary surgery	New diagnosis



Plasmacytoid carcinoma characteristics. *A,* discohesive epithelial cells with prominent eosinophilic cytoplasm and eccentric nuclei. Inset, cytoplasmic immunoreactivity with pan-cytokeratin. Reduced from ×600. *B* to *D,* unusual patterns of disease spread. *B,* periureteral soft tissue (purple area) with stromal desmoplasia. Reduced from ×60. *C,* bowel serosa with invasion of bowel wall in this photomicrograph. Reduced from ×300. *D,* cell block section from aspirate shows body cavity effusions. Reduced from ×900.

significance, which is particularly true for small cell, micropapillary and sarcomatoid differentiation.[2] As molecular comparative studies are done of the variant subtypes of urothelial carcinoma, increasing therapeutic relevance may be elucidated.

In 1991 the plasmacytoid variant of urothelial carcinoma was described by 2 groups.[10,11] This histological pattern was originally emphasized to highlight the close resemblance to plasma cells or other hematopoietic cells, leading to the possibility of pathological misdiagnosis. However, multiple case series have now confirmed that this represents an aggressive carcinoma subtype that typically presents as high stage disease.[3–7,12,13] Other urothelial carcinomas described in the literature as urothelial carcinomas simulating malignant lymphoma and (urothelial) carcinoma mimicking lobular carcinoma of the breast seem closely related and were combined with plasmacytoid carcinoma in the current WHO classification.[1,11,14]

Some studies suggest an underlying defect in E-cadherin expression in plasmacytoid carcinoma of the bladder, which may be the common factor in bladder carcinoma with a histologically discohesive pattern of growth and may help explain its aggressive behavior.[3,12,15] Notably lobular carcinoma of the breast and diffuse type gastric carcinoma, eg signet ring carcinoma, also share loss of E-cadherin expression, are histologically characterized by discohesive growth similar to that of plasmacytoid carcinoma of the bladder and often show discontinuous intraperitoneal spread.[16]

Currently recognizing bladder plasmacytoid carcinoma remains important to make a correct pathological diagnosis. If the original diagnostic biopsy was not done at the hospital where definitive surgery is performed and the previous pathology material is not re-reviewed as a matter of institutional policy, it is critical that the pathologist be alerted to any unusual morphological variants of urothelial carcinoma, particularly plasmacytoid histology. This is important for certain reasons.

1) In this series 2 patients had carcinoma extension along the periureteral soft tissue. Carcinoma grows as individual cells, which can easily be misinterpreted as inflammatory cells if one does not have a high index of suspicion at intraoperative frozen section evaluation of the ureters. The 2 cases that we describe with periureteral soft tissue extension were identified at frozen section analysis but each was known to have plasmacytoid morphology and this histological feature was carefully considered.

2) Any serosal or soft tissue surfaces in the radical cystectomy specimen must be sampled more liberally than for urothelial carcinoma of no special type, given the propensity for these carcinomas to show discontinuous intraperitoneal spread. Although it was not previously emphasized, other reports of plasmacytoid carcinoma include some cases with peritoneal carcinomatosis, further supporting our findings.[3,17,18] Several groups evaluated common sites of disease recurrence and metastasis in urothelial carcinoma cases, including bladder/pelvis, bone, lymph nodes, lung and liver but not intraperitoneal spread.[19,20]

Like other retrospective case series of bladder cancer variants, our study is limited by the retrospective nature of the study design. Also, case numbers were limited due to the rarity of this type of carcinoma. Many patients in this series presented to 1 of the 3 collaborating institutions for radical cystectomy but were subsequently treated and followed in their local community. This limited our available followup data and adjuvant treatment information.

These issues underscore the need to evaluate variant subtypes as a variable in prospective clinical trials of bladder carcinoma. Despite the limitations we are confident that the pattern of disease spread, ie peritoneal dissemination, is distinct from that of typical invasive urothelial carcinoma. This fact with clinical management implications is not generally

recognized and has not been previously emphasized in the literature.

Given the potential for this unique discontinuous intraperitoneal involvement and for carcinomatous effusions, we argue that known cases of plasmacytoid urothelial carcinoma should have a careful intra-abdominal staging evaluation of the peritoneal surface, bowel wall and omentum at initial staging surgery, similar to ovarian cancer staging. In regard to clinical followup care unusual sites of parenchymal involvement or body cavity effusions should be considered likely metastatic spread until proven otherwise.

At our institutions the information from this case series has underscored the need to re-review prior biopsy material before definitive surgery since the additional information on variant subtype may influence the pathologist interpretation of frozen section slides. It also allows urologists the opportunity to meticulously examine serosal surfaces for the possibility of subtle metastatic deposits.

CONCLUSIONS

The plasmacytoid variant of invasive urothelial carcinoma of the bladder is a rare subtype/variant of urothelial carcinoma that often presents at high stage. This carcinoma subtype may present or recur with discontinuous intraperitoneal disease spread, often involving serosal surfaces. This unusual pattern of disease spread has not been emphasized in the literature and should be considered by urologists at staging and on clinical followup imaging.

REFERENCES

1. Lopez-Beltran A, Sauter G, Gasser T et al: Infiltrating urothelial carcinoma. In: Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Edited by JN Eble, G Sauter, JI Epstein et al. Lyon: IARC Press 2004; pp 93–109.
2. Black PC, Brown GA and Dinney CP: The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 2009; **27:** 3.
3. Fritsche HM, Burger M, Denzinger S et al: Plasmacytoid urothelial carcinoma of the bladder: histological and clinical features of 5 cases. J Urol 2008; **180:** 1923.
4. Lopez-Beltran A, Requena MJ, Montironi R et al: Plasmacytoid urothelial carcinoma of the bladder. Hum Pathol 2009; **40:** 1023.
5. Mai KT, Park PC, Yazdi HM et al: Plasmacytoid urothelial carcinoma of the urinary bladder report of seven new cases. Eur Urol 2006; **50:** 1111.
6. Nigwekar P, Tamboli P, Amin MB et al: Plasmacytoid urothelial carcinoma: detailed analysis of morphology with clinicopathologic correlation in 17 cases. Am J Surg Pathol 2009; **33:** 417.
7. Ro JY, Shen SS, Lee HI et al: Plasmacytoid transitional cell carcinoma of urinary bladder: a clinicopathologic study of 9 cases. Am J Surg Pathol 2008; **32:** 752.
8. Amin MB: Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Mod Pathol, suppl., 2009; **22:** S96.
9. Young RH and Eble JN: Unusual forms of carcinoma of the urinary bladder. Hum Pathol 1991; **22:** 948.
10. Sahin AA, Myhre M, Ro JY et al: Plasmacytoid transitional cell carcinoma. Report of a case with initial presentation mimicking multiple myeloma. Acta Cytol 1991; **35:** 277.
11. Zukerberg LR, Harris NL and Young RH: Carcinomas of the urinary bladder simulating malignant lymphoma. A report of five cases. Am J Surg Pathol 1991; **15:** 569.
12. Keck B, Stoehr R, Wach S et al: The plasmacytoid carcinoma of the bladder—rare variant of aggressive urothelial carcinoma. Int J Cancer 2011; **129:** 346.
13. Raspollini MR, Sardi I, Giunti L et al: Plasmacytoid urothelial carcinoma of the urinary bladder: clinicopathologic, immunohistochemical, ultrastructural, and molecular analysis of a case series. Hum Pathol 2011; **42:** 1149.
14. Baldwin L, Lee AH, Al-Talib RK et al: Transitional cell carcinoma of the bladder mimicking lobular carcinoma of the breast: a discohesive variant of urothelial carcinoma. Histopathology 2005; **46:** 50.
15. Lim MG, Adsay NV, Grignon DJ et al: E-cadherin expression in plasmacytoid, signet ring cell and micropapillary variants of urothelial carcinoma: comparison with usual-type high-grade urothelial carcinoma. Mod Pathol **24:** 241.
16. Schrader KA, Masciari S, Boyd N et al: Hereditary diffuse gastric cancer: association with lobular breast cancer. Fam Cancer 2008; **7:** 73.
17. Aldousari S, Sircar K and Kassouf W: Plasmacytoid urothelial carcinoma of the bladder: a case report. Cases J 2009; **2:** 6647.
18. Sato K, Ueda Y, Kawamura K et al: Plasmacytoid urothelial carcinoma of the urinary bladder: a case report and immunohistochemical study. Pathol Res Pract 2009; **205:** 189.
19. Sengelov L, Kamby C and von der Maase H: Pattern of metastases in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma. J Urol 1996; **155:** 111.
20. Sternberg CN, Yagoda A, Scher HI et al: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 1989; **64:** 2448.