

Ductal Adenocarcinoma of the Prostate

Ronald L. Shazer, MD
Daniel Luthringer, MD
David B. Agus, MD
Mitchell E. Gross, MD, PhD

Louis Warschaw Prostate Cancer Center
Cedars-Sinai Medical Center

Case Report

An 81-year-old male presented in July 2002 with newly diagnosed prostate cancer. The patient's pertinent medical history dates back to 1997 when a mildly elevated prostate specific antigen (PSA) was noted. The patient began having symptoms of prostatism which eventually progressed to acute urinary obstruction in October 2000. The prostate was enlarged (>150 g, estimated by ultrasound). He was treated with a retropubic prostatectomy. One hundred grams of benign prostatic tissue was removed. No evidence of malignancy was found in the surgical specimen. Urinary symptoms improved and the PSA was measured at 5.2 ng/mL several months after surgery. The patient experienced an episode of gross hematuria 21 months after the surgery. The serum PSA was elevated at that time to 15.3 ng/mL. A cystoscopy was attempted, but was abandoned due to extrinsic compression. A transurethral resection of the prostate (TURP) was performed to relieve the urinary obstruction. Pathological review of the TURP specimen revealed extensive involvement with high-grade adenocarcinoma of prostate (approximately 70% of tissue) with ductal-type histology. Histologic features included malignant cells growing with villoglandular and cribriform architecture, along with foci of comedonecrosis. Cellular morphology demonstrated high-grade cytologic abnormalities including anisocytosis, anisonucleosis, elevated nuclear:cytoplasmic ratio and prominent, eosinophilic nucleoli. Mitotic activity with abnormal mitotic forms was present. Immunohistochemical stains were performed to confirm prostatic origin: cytokeratin-20 and 34βE12 cytokeratin were negative; cytokeratin-7, PSA, prostatic acid phosphatase (PAP), and androgen receptor (AR) were

Address correspondence to: Mitchell Gross, MD, Louis Warschaw Prostate Cancer Center, Cedars-Sinai Medical Center, 8631 W. Third Street, Suite 1001E, Los Angeles, CA 90048; e-mail: mitchell.gross@cshs.org.

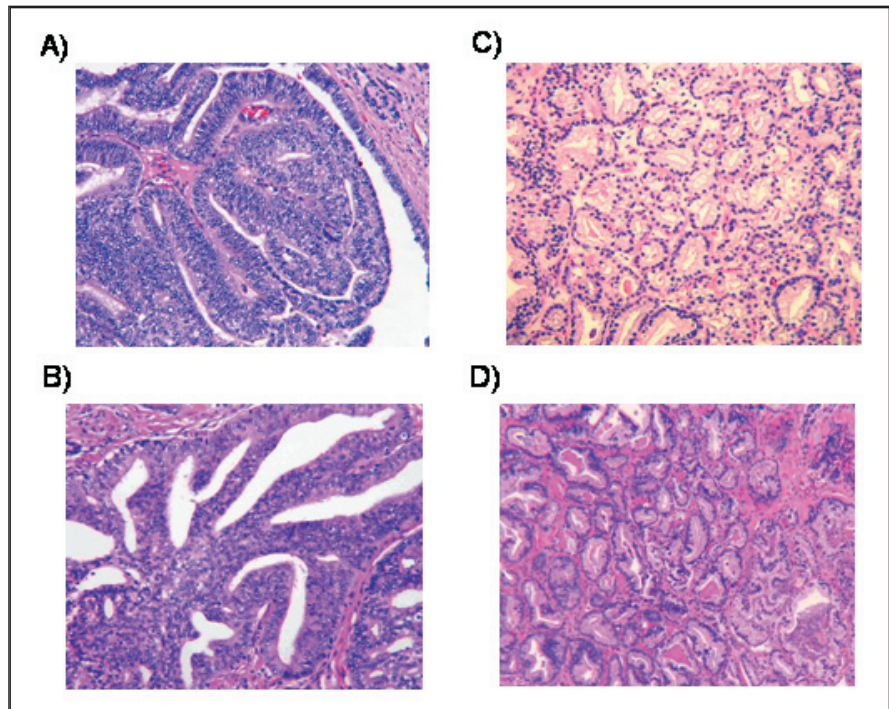


Figure 1. Examples of ductal and acinar adenocarcinoma of the prostate. Standard hematoxylin and eosin staining of samples representing papillary (A) and cribriform (B) ductal carcinoma. Sections of typical acinar adenocarcinoma pattern, Gleason pattern 3 (C and D), are shown for comparison.

positive. An abdominal and pelvic computed tomography scan revealed multiple enlarged pelvic lymph nodes (the largest measured at 1.6 × 1.2 cm) and an enlarged prostate (5 × 4.5 × 4.4 cm) with a volume estimated at 50 g. A bone scan showed no evidence of metastatic disease. The final pathologic diagnosis was ductal adenocarcinoma of the prostate.

Discussion

This case of prostate cancer presenting less than 2 years after a large volume of prostate tissue was removed for benign disease highlights a number of important considerations in the diagnosis and treatment of patients with this variant form of prostate cancer.

Prostatic ductal adenocarcinoma is a rare histologic subtype with a reported incidence of less than 1% of all prostate cancers.^{1,2} Morphologically, prostatic ductal cancers are described as malignant glandular structures lined by stratified columnar epithelium with either a papillary or cribriform pattern (Figure 1).^{1,3,4} Both patterns may be present in the

same tumor (as in this case), but usually one pattern predominates. Occasionally, luminal necrosis is observed. Ductal carcinomas typically have high-grade histology and are centrally located in large ducts near the intraprostatic urethra.^{1,3,5-10} In contrast, typical (acinar) prostatic carcinomas manifest with varying degrees of gland/acinar formation and a lower-grade cytologic appearance. As acinar carcinomas typically arise from the lateral regions of the prostate, stromal elements are often closely associated with the cancerous glands. The acinar pattern is notable for various degrees of abortive gland formation with admixed stromal tissue (Gleason 3 or 4) or a diffuse, infiltrative process (Gleason 5).¹¹

The tissue of origin for ductal adenocarcinoma of the prostate has been a source of controversy since its first reported description in 1967.⁵ Melicow and colleagues^{5,12} described tumors arising from the area of the prostatic verumontanum (prostatic utricle) which appeared histologically similar to endometrial adenocarcinoma of the uterus. Ductal adenocarcinomas often appear as a tumor mass which protrudes into the urethral lumen from ducts at or near the utricle on cystoscopy and located centrally in prostatectomy specimens. As the verumontanum is an embryologic remnant of the müllerian ducts, Melicow and Pachter hypothesized that cancer arising from the area of the prostatic utricle were derived from malignant degeneration of the remnant müllerian tissue, which was supported by some case reports.^{2,13-15} However, more sophisticated examination of ultrastructural characteristics and additional refinements in histochemical techniques have led to a consensus opinion that ductal adenocarcinoma of the prostate is a morphologic variant of the more common acinar adenocarcinoma.^{6,7,16-20} As in this case, ductal carcinomas typically express immunohistochemical markers of prostatic tissue including cytokeratin 7, PSA, PAP, and AR.

The diagnosis of ductal adenocarcinoma of the prostate generally depends on the histologic appearance of large glandular structures in association with stratified columnar epithelium in a centrally located tumor.¹ In many cases, the more common acinar carcinoma is found along with the ductal adenocarcinoma.^{1-3,6,15,16,18-24} This association supports the hypothesis that ductal adenocarcinoma is not a unique type of prostate cancer, but rather a morphologic variant of the usual acinar prostate carcinoma extending into the proximal prostatic duct tissue. Bock and Bostwick¹⁶ questioned if the typical histologic features of papillary and cribriform architecture were sufficient to diagnose ductal adenocarcinoma by studying a series of whole-mount prostatectomy specimens selected for a diagnosis of acinar adenocarcinoma. Foci with typical "ductal" features were found in the peripheral zone more commonly than expected (17 of the 338 cases). They conclude that cribriform and papillary architecture is not unique to ductal carcinomas and suggest that the term should be used only for tumors limited to the large periprostatic ducts.¹⁶

Other investigators propose that ductal carcinoma of the prostate should be considered as a distinct pathologic entity. Aside from the unique pathologic appearance, they cite the

observations that the standard grading system does not appropriately predict the clinical behavior of these tumors.^{3,4,8} Although many of these tumors may be classified with a Gleason score of 3 according to the original grading scheme, pathologists now generally assign a Gleason score of 4 to this pattern.¹¹ In addition, studies suggest that this variant may possess a unique biologic behavior. A recent report suggests that while most ductal adenocarcinomas secrete PSA, they may be more likely to produce unusual serum markers such as carcinoembryonic antigen (CEA).⁸ The significance of these observations are poorly understood due to the small numbers of cases reported from any one institution.

The present case also highlights the importance of the zonal anatomy of the prostate. Anatomically, the prostate may be divided into central, transition, and peripheral zones. The transition zone includes the glandular tissue proximal to the ejaculatory ducts of the intraprostatic urethra which comprises a small amount (5–10%) of the tissue in a normal-sized prostate.²⁵ The majority of prostate adenocarcinomas arise from the peripheral zone (70%), with a minority of cases arising from the transition (approximately 20%), or central zones (1–5%).²⁵ Benign prostatic hypertrophy is caused by the disproportionate growth of tissue from the transition zone. In this case, it is likely that the retropubic prostatectomy removed the enlarged tissue (adenoma) from the transition zone without sampling of the central and peripheral zones, which potentially may have harbored adenocarcinoma. It is not possible to determine if cancer was present at the time of retropubic prostatectomy or if it developed in the intervening 21 months. However, the high-grade histology and rapid increase in serum PSA implies that a small amount of adenocarcinoma was present at the time of retropubic prostatectomy which rapidly progressed to produce symptomatic obstruction less than 2 years after the procedure.

The clinical presentation of ductal carcinoma may also be differentiated from acinar carcinoma. As with acinar prostate cancer, ductal adenocarcinoma affects elderly men. However, ductal adenocarcinomas more commonly present with local obstructive or irritative symptoms such as acute urinary obstruction and hematuria.^{1,3,8} This is consistent with the central location of these tumors. In contrast, most patients with acinar carcinomas are diagnosed by asymptomatic increases in PSA or, less commonly, a nodule appreciated on exam.²⁶ The exophytic growth into the urethra accounts for the clinical presentation of obstruction and hematuria seen in some series.¹ The majority of patients also had enlarged or hardness of the prostate on digital rectal exam rather than nodularity, consistent with the deep central location of primary tumors. This case highlights the nature of the obstructive symptoms which are a hallmark of the ductal variant as both hematuria and urinary obstruction were noted within 2 years after the removal of a large amount of prostatic tissue.

The natural history of ductal adenocarcinomas typically mirrors that of acinar carcinomas with a tendency to involve con-

tiguous lymph nodes and the axial skeleton. However, some series suggest that ductal adenocarcinomas exhibit a greater tendency to spread to unusual visceral sites such as lung, liver, and brain.^{1,8} In addition, a series of ductal adenocarcinomas have recently been reported which describes the unusual spread by local extension to the testes and penis.⁸ The treatment for ductal adenocarcinoma is generally no different than acinar prostate cancer.^{3,6-8,19,22} Some studies suggest that ductal adenocarcinoma displays a greater propensity for extracapsular spread and may be less responsive to standard systemic therapies.^{1,4,21,22,27} However, other studies observe increased responsiveness to local and systemic therapy (including androgen-deprivation therapy and cytotoxic chemotherapy), despite the high-grade cytologic appearance and the occurrence of locally advanced or systemic disease.^{2,3,7,12,28-30} Millar et al³ suggest that the differences in survival may be determined primarily by the coexistent acinar elements. This is consistent with the observation by Greene et al³¹ that malignancies arising in the transition zone may have less malignant potential than those that arise in the peripheral zone. Therefore, treatment recommendations typically do not change with the diagnosis of ductal adenocarcinoma. However, careful follow-up is needed for patients with ductal adenocarcinoma with particular attention directed for the development of early metastasis to bone or other visceral sites and the potential use of alternative tumor markers such as CEA.

Conclusion

Ductal adenocarcinoma of the prostate is an important variant form of prostate cancer. Historically, ductal carcinomas were thought to derive from müllerian remnant tissue, but the current consensus is that ductal carcinomas represent a distinct morphologic growth pattern of the common acinar carcinoma growing into the proximal prostatic duct tissue. Controversy exists as to the exact pathologic criteria for the diagnosis of ductal adenocarcinomas. However, the tissue of origin must be differentiated from other epithelial primary sites, most notably the urinary bladder. A pure ductal pattern is exceedingly rare as most cases occur with a coexistent acinar adenocarcinoma. The presentation of ductal adenocarcinoma is notable for the early occurrence of urethral obstructive and irritating symptoms owing to the central location of the tumors. A divergence of opinion exists as to the natural history of ductal adenocarcinomas. Some studies suggest ductal carcinomas exhibit a clinically aggressive phenotype. Other studies suggest that despite the high-grade histology, ductal carcinomas may be more responsive to standard treatments. There are a number of reports of ductal carcinomas exhibiting an unusual pattern of metastatic spread to visceral sites such as penis, testes, and lungs, in addition to the more common spread to bone. More specific criteria are needed to codify the pathologic diagnosis and outcomes for patients with ductal adenocarcinoma to better establish if treatment recommendations should be changed based on this variant of prostate cancer.

References

- Bostwick D, Kindrachuk R, Rouse R. Prostatic adenocarcinoma with endometrioid features. Clinical, pathologic, and ultrastructural findings. *Am J Surg Pathol*. 1985;9:595-609.
- Tannenbaum M: Endometrial tumors and/or associated carcinomas of the prostate. *Urology*. 1975;6:372-375.
- Millar E, Sharma N, Lessells A. Ductal (endometrioid) adenocarcinoma of the prostate: a clinicopathological study of 16 cases. *Histopathology*. 1996;29:11-19.
- Brinker D, Potter S, Epstein J. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. *Am J Surg Pathol*. 1999;23:1471-1479.
- Melicow M, Pachter M. Endometrial carcinoma of the prostatic utricle (uterus masculinus). *Cancer*. 1967;20:1715-1721.
- Epstein J, Woodruff J: Adenocarcinoma of the prostate with endometrioid features. A light microscopic and immunohistochemical study of ten cases. *Cancer*. 1986;57:111-1119.
- Lee S. Endometrioid adenocarcinoma of the prostate: a clinicopathologic and immunohistochemical study. *J Surg Oncol*. 1994;55:235-238.
- Tu S, Reyes A, Maa A, et al. Prostate carcinoma with testicular or penile metastases. Clinical, pathologic, and immunohistochemical features. *Cancer*. 2002;94:2610-2617.
- Dube V, Farrow G, Greene L. Prostatic adenocarcinoma of ductal origin. *Cancer*. 1973;32:402-409.
- Bostwick D. *Neoplasms of the Prostate*. St. Louis, Ill: Mosby; 1997.
- Gleason DF. Histologic grade, clinical stage, and patient age in prostate cancer. *NCI Monogr*. 1988;7:15-18.
- Melicow M, Tannenbaum M. Endometrial carcinoma of uterus masculinus (prostatic utricle). Report of 6 cases. *J Urol*. 1971;106:892-902.
- Gillatt D, O'Reilly P, Reeve N. Endometrioid carcinoma of the prostatic utricle. *Br J Urol*. 1986;58:559-560.
- Stavropoulos N, Ioackim-Velogianni E, Sidoni K, et al. Endometrioid carcinoma of the prostate. The diagnostic value of Leu7 and prostatic specific antigen. *Br J Urol*. 1993;71:309-312.
- Carney J, Kelalis P. Endometrial carcinoma of the prostatic utricle. *Am J Clin Pathol*. 1973;60:565-569.
- Bock B, Bostwick D. Does prostatic ductal adenocarcinoma exist? *Am J Surg Pathol*. 1999;23:781-785.
- Oxley J, Abbott C, Gillatt D, et al. Ductal carcinomas of the prostate: a clinicopathological and immunohistochemical study. *Br J Urol*. 1998;81:109-115.
- Zaloudek C, Williams J, Kempson R. "Endometrial" adenocarcinoma of the prostate: a distinctive tumor of probable prostatic duct origin. *Cancer*. 1976;37:2255-2262.
- Wernert N, Luchtrath H, Seeliger H, et al. Papillary carcinoma of the prostate, location, morphology, and immunohistochemistry: the histogenesis and entity of so-called endometrioid carcinoma. *Prostate*. 1987;10:123-131.
- Walther M, Nassar V, Harruff R, et al: Endometrial carcinoma of the prostatic utricle: a tumor of prostatic origin. *J Urol*. 1985;134:769-773.
- Vale J, Patel A, Ball A, et al. Endometrioid carcinoma of the prostate: a misnomer? *J Royal Soc Med*. 1992;85:394-396.
- Ro J, Ayala A, Wishnow K, et al. Prostatic duct adenocarcinoma with endometrioid features: immunohistochemical and electron microscopic study. *Semin Diagn Pathol*. 1988;5:301-311.
- Aydin F. Endometrioid adenocarcinoma of prostatic urethra presenting with anterior urethral implantation. *Urology*. 1993;41:91-95.
- Samaratunga H, Singh M. Distribution pattern of basal cells detected by cytokeratin 34 beta E12 in primary prostatic duct adenocarcinoma. *Am J Surg Pathol*. 1997;21:435-440.
- Kabalin JN. Surgical Anatomy of the Retroperitoneum, Kidneys, and Ureters. In: Walsh P, ed. *Campbell's Urology*. 8th ed. Philadelphia, Pa: Saunders; 2002:57-70.
- Catalona WJ. Management of cancer of the prostate. *N Engl J Med*. 1994;331:996-1004.
- Cohen R, Chan W, Edgar S, et al. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. *Br J Urol*. 1998;81:413-418.
- Merchant RJ, Graham A, Bucher WJ, et al. Endometrial carcinoma of prostatic utricle with osseous metastases. *Urology*. 1976;8:169-173.
- Rotterdam H, Melicow M. Double primary prostatic adenocarcinoma. *Urology*. 1975;6:245-248.
- Young B, Lagios M. Endometrial (papillary) carcinoma of the prostatic utricle--response to orchiectomy. A case report. *Cancer*. 1973;32:1293-1300.
- Greene D, Wheeler T, Egawa S, et al. A comparison of the morphological features of cancer arising in the transition zone and in the peripheral zone of the prostate. *J Urol*. 1991;146:1069-1076.

Review

Bruce Montgomery, MD

Jeffrey Virgin, MD, PhD

University of Washington and VA Puget Sound Health Care System

Ductal adenocarcinoma (variously referred to as endometrial carcinoma of the prostate, adenocarcinoma with endometrioid features, or papillary carcinoma of the prostate) is a variant of “garden variety” acinar adenocarcinoma that has a confusing but interesting pathobiology. The case study by Shazer et al describes an elderly male who presents with hematuria after prior prostatectomy and is found at cystoscopy to have significant obstruction. TURP then documented the presence of high-grade carcinoma in the periurethral tissues with features suggesting cribriform growth pattern and immunohistochemical studies confirmed that the tumor was of prostatic origin.

Determining the prostatic or bladder origin of intraurethral and periurethral tumors is of paramount importance, as treatment options and expected prognosis differs substantially.

As described by Shazer et al, ductal carcinoma maintains the expression of all the hallmark proteins of acinar prostate carcinoma and yet appears histologically distinct. The term “endometrial” is a misnomer, as the tumor is clearly of prostatic origin, but it aptly describes the pattern of papillary or cribriform projections lined with stratified columnar epithelium which often fill the periurethral prostatic ducts. These tumors are often described as having a prominent intraurethral or periurethral component, leading to hematuria or obstructive symptoms. It is this propensity for an intraurethral component that likely leads to its recognition on pathologic evaluation as distinct from acinar carcinoma. Ductal carcinoma is said to be a rare variant, comprising 0.2–0.8% of prostate carcinomas.¹ Interestingly, Bock and Bostwick² studied 338 whole-mount radical prostatectomy specimens in which peripheral zone acinar adenocarcinoma had been found. They then searched specifically for a ductal carcinoma component, and found that 5% of all specimens contained a significant proportion of ductal adenocarcinoma, solely involving the periphery. The coexistence of ductal carcinoma with acinar adenocarcinoma in all specimens led these authors to argue that ductal adenocarcinoma is not distinct from acinar carcinoma but is a histologic variant with a greater propensity for papillary and cribriform growth patterns, and that its biology does not differ significantly from acinar carcinoma. Other authors have found that the prognosis associated with ductal carcinoma is either better, worse or similar to acinar carcinoma.³⁻⁵

Address correspondence to: Bruce Montgomery, MD, VA Puget Sound Health Care System, 1660 S. Columbian Way, Seattle, WA 98018. Tel: 206-764-2709; Fax: 206-764-2851; e-mail: rbmontgo@u.washington.edu.

The limited number of cases in most studies and the lack of correlation with patients matched for stage and tumor grade suggest that additional studies similar to those of Bock and Bostwick, with the addition of adequate risk stratification and long term follow-up, may be the only way to determine if ductal carcinoma carries any prognostic significance beyond its assignment of Gleason score of 4. An intriguing report from Tu et al⁶ raises the possibility that the ductal component may have a propensity for metastasis to the penis and testicle, as 7 of 8 patients with prostate cancer metastatic to those sites had ductal histology. Patients in this series had a median survival of 66 months after initiation of androgen deprivation, suggesting that survival was similar or better compared to patients with advanced acinar carcinoma treated with androgen deprivation. We do not know how the case study patient was subsequently treated for his apparent node-positive disease, but presumably androgen deprivation was the principal intervention. There are no case series discussing alternative approaches to the treatment of this disease that utilize more aggressive interventions such as early chemotherapy or adjuvant radiotherapy. Therefore, the standards of androgen deprivation, radiation therapy and prostatectomy for hormone-naive tumors and chemotherapy for androgen independent disease remain the principal means of treatment.

The majority of evidence presented by Shazer and others suggests that ductal carcinoma is a histologic variant of acinar carcinoma of the prostate rather than a distinct pathologic entity. In this context, the treatment for patients with this tumor should reflect the expected outcome for acinar adenocarcinoma based on PSA, Gleason score and clinical staging. Although these tumors may present with a higher likelihood of T3 or T4 disease, prostatectomy or radiotherapy are still reasonable treatment options for clinically localized disease and there is still significant potential for cure with local therapy. Numerous series have documented significant and prolonged responses to androgen deprivation, even in the face of atypical metastatic spread and locally aggressive disease. Therefore, our standard approaches to clinically localized and metastatic disease should continue to be considered for patients who are found to have ductal carcinoma of the prostate.

References

1. Bostwick DG, Kindrachuk RW, Rouse RV. Prostatic adenocarcinoma with endometrioid features. Clinical, pathologic, and ultrastructural findings. *Am J Surg Pathol.* 1985;9:595-609.
2. Bock BJ, Bostwick DG. Does prostatic ductal adenocarcinoma exist? *Am J Surg Pathol.* 1999;23:781-785.
3. Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. *Am J Surg Pathol.* 1999;23:1471-1479.
4. Millar EK, Sharma NK, Lessells AM. Ductal (endometrioid) adenocarcinoma of the prostate: a clinicopathological study of 16 cases. *Histopathology.* 1996;29:11-19.
5. Aydin, F. Endometrioid adenocarcinoma of prostatic urethra presenting with anterior urethral implantation. *Urology.* 1993;41:91-95.
6. Tu SM, Reyes A, Maa A, et al. Prostate carcinoma with testicular or penile metastases. Clinical, pathologic, and immunohistochemical features. *Cancer.* 2002;94:2610-2617.