Metastatic Ductal Adenocarcinoma of the Prostate

Cytologic Features and Clinical Findings

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Abstract

We retrospectively reviewed the cytologic features of metastatic prostatic ductal carcinoma (PDC) in 23 cases, clinical manifestations, and clinical outcomes. Cytologic smears typically showed tumor cells with abundant cytoplasm and oval nuclei arranged in papillary groups or flat and folded sheets, some of which showed peripheral nuclear palisading. However, these features could be focal, subtle, and even indistinguishable from those of acinar carcinoma, particularly when the ductal component was predominantly of a cribriform and solid pattern or coexisted with acinar carcinoma. A determination of a prostatic origin of a metastatic PDC, based on cytomorphologic features alone, could be difficult. Immunostaining for prostate-specific antigen and prostatic acid phosphatase proved helpful in reaching a definitive diagnosis. The median follow-up of patients was 82 months, the median overall survival was 77 months, and the 5-year overall survival rate was 72%. Tumor growth pattern did not correlate with prognosis, but visceral metastasis conveyed a poor prognosis. The correlation with clinical and radiologic findings, a high index of suspicion, and the use of immunoperoxidase studies are important in making an accurate diagnosis.

Prostatic ductal carcinoma (PDC) is an unusual morphologic variant of prostatic adenocarcinoma. Characterized by tall columnar cells with abundant cytoplasm, this tumor originally was named endometrioid carcinoma because of its histologic similarity to uterine endometrial carcinoma.[1] On the basis of immunohistochemical staining results, ultrastructural findings, and its favorable response to androgen-deprivation therapy, it is believed that PDC is of prostatic duct orgin.[2-8] Although controversy exists regarding the clinical behavior of PDC,[1,5,9-11] most studies have found that this variant is more aggressive than ordinary acinar carcinoma, with a more advanced clinical and pathologic stage at presentation, a shorter time to progression, and a worse 5-year survival rate.[2-4,6-8]

Histologically, PDC displays a spectrum of architectural patterns: papillary, cribriform and solid, with or without central (comedo) necrosis.[1,2,4,6-8,11-13] These patterns tend to coexist and merge into each other and frequently are associated with an ordinary acinar component. To date, fine-needle aspiration (FNA) findings in PDC are scant; we found only 3 single case reports in the literature.[14-16] All 3 cases were primary PDC that had been sampled via transrectal FNA. Given the rarity of this tumor and the potential for its morphologic characteristics to overlap with those of other adenocarcinomas, it is conceivable that diagnosis of a metastatic PDC on FNA samples may be challenging. In this retrospective study, we reviewed the cytologic features, clinical and radiologic findings, and patients' outcomes in 23 metastatic PDCs diagnosed on FNA samples.

Materials and Methods

By using the pathology files of The University of Texas M.D. Anderson Cancer Center, Houston, we retrospectively

identified 23 FNA specimens of metastatic PDC obtained from 23 patients from January 1995 through December 2005. At the time of sampling metastatic tumors, 22 patients had a known history of PDC (pure or mixed with ordinary acinar carcinoma), and 1 patient had no known history of malignancy and the diagnosis of metastatic PDC was made based solely on the FNA findings. Clinical and radiologic information for all patients was reviewed.

All metastatic tumors were aspirated using a 20- or 22-gauge biopsy needle under image guidance, either computed tomography (n = 14) or ultrasound (n = 9). An average of 3 FNA passes was made per case. Direct smears were air dried for Diff-Quik staining (StatLab, Lewisville, TX) or fixed in modified Carnoy fixative (a 6:1 ratio of 70% ethanol to glacial acetic acid) for Papanicolaou staining. Smears were assessed immediately by a cytopathologist for specimen adequacy. Cells obtained from the needle rinse were subjected to centrifugation, and the sediment was fixed in a 50:50 mixture of 95% ethanol and 10% formalin and embedded in paraffin to make cell blocks (available in 20 cases). The cell blocks were sectioned and stained with H&E.

The FNA features of metastatic PDC were analyzed retrospectively for background content, cellularity, smear pattern and architecture, cell shape, and cytoplasmic and nuclear features. To facilitate making a diagnosis, immunoperoxidase studies were performed with 15 cases (on cell-block preparations or destained smears) at the time of diagnosis. The antibodies, sources, and dilutions were as follows: prostate-specific antigen (PSA; dilution 1:3,000; DAKO, Carpinteria, CA), prostatic acid phosphatase (PAP; dilution 1:50; DAKO), cytokeratin 7 (dilution 1:100; DAKO), cytokeratin 20 (dilution 1:40; DAKO), and thyroid transcriptional factor-1 (dilution 1:25; DAKO).

Statistical Analysis

Overall survival (calculated from the time of diagnosing the primary PDC until death or the last follow-up date) and the 5-year overall survival rate were estimated by using the Kaplan-Meier product-limit method. The 2-sided log-rank test was used to test the association between ductal component (pure vs mixed) and survival outcome. *P* values of less than .05 were considered statistically significant. Statistical analyses were carried out using Splus 6.0 (Insightful, Seattle, WA).

Results

The pathologic findings of primary and metastatic tumors and the clinical outcome of the 23 patients are summarized in **Table 1**. The mean age at the time of diagnosis of the primary prostatic carcinoma was 61.7 years (range, 53-76 years). The mean interval between diagnosis of the primary prostatic carcinoma and sampling of the paired metastatic tumor was 38.3 months (range, <1-180 months; median, 28.5 months). Synchronous metastasis (interval <1 month) was found in 3 cases. The mean serum PSA level at the time of sampling metastatic tumors was 87 ng/mL (range, 0.3-698 ng/mL; median, 26 ng/mL). In 3 patients (13%), the value was within normal limits (<4 ng/mL), and in 20 patients (87%), the value was elevated. The serum PSA levels did not correlate with the site or size of the metastatic tumor.

In the 22 patients with a history of prostatic adenocarcinoma, the histologic diagnosis of the primary PDC was made by using specimens obtained via core needle biopsy (n = 8), transurethral resection (n = 11), or radical prostatectomy (n = 3). Seven cases showed pure ductal carcinoma, and 15 cases showed mixed ductal and acinar carcinoma (defined as mixed PDC) (Table 1). The ductal component of these 22 primary carcinomas showed patterns of papillary (n = 2), papillary and cribriform (n = 6), cribriform (n = 5), cribriform and solid (n = 4), and not specified (n = 5). The only patient (case 23) who had no known history of malignancy was an 85-year-old man with a large, destructive pelvic bone lesion with soft tissue extension. He had undergone a prostatectomy 30 years earlier for "benign prostatic hypertrophy."[17] Based on cytomorphologic features and immunocytochemical stains, the pelvic lesion was diagnosed as metastatic PDC with papillary features. Subsequent testing of this patient revealed a markedly elevated serum PSA level (Table 1).

The metastatic sites aspirated were lymph nodes (n = 7), bone (n = 5), liver (n = 8), and lung (n = 3) (Table 1). The mean size of the metastatic tumors, as measured by computed tomography or ultrasound, was 3.06 cm (range, 1-10 cm; median, 3.0 cm). The median follow-up duration from the time of primary carcinoma diagnosis to the last follow-up date in 22 patients with a history of PDC was 82 months. Modalities of treatment included transurethral resection of the prostate, total prostatectomy, hormonal therapy, chemotherapy and radiotherapy, or a combination of these treatments. Twelve patients were alive, of whom 9 were doing well (defined as a decline in the serum PSA level and improvement in performance status without detectable new metastasis) and 3 patients had disease progression. Eleven patients had died; 1 died of an unknown cause, and 10 died of PDC. Among the latter group, 9 had visceral metastases (7 in the liver, 1 in the lung, and 1 in the brain with coexisting iliac bone metastasis [case 8]) and 1 had sternal bone metastasis. For the 22 patients with a history of PDC, the median overall survival time was 77 months, and the 5-year overall survival rate was 72% (95% confidence interval, 58.7%-99.7%). The distributions of overall survival were not different between patients with pure PDC and patients with mixed PDC, and the 5-year overall survival rates were 87% and 71%, respectively (*P* = .53).

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Table 1
Clinical and Pathologic Findings for 23 Patients With Prostatic Ductal Carcinoma

	Primary Tumor (Histologic Diagnosis)			Metastatic Tumor (Cytologic Diagnosis)						
Case No./ Age (y)	Diagnosis	Pattern of Ductal Component	Immunohisto-chemical Analysis	Interval (mo)	Serum PSA	Location	Size (cm)	Immunocyto-chemical Analysis	Follow-up (mo)	Disease Course
1/63	ACA, ductal	Papillary	ND	61	Normal	Lung	2.0	PSA+, PAP+, CK7–, CK20–	82	Alive, well
2/57	ACA, ductal	Papillary	ND	<1	↑	Retroperitoneal LN	2.0	ND	52	Alive, well
3/56	ACA, ductal	Papillary/cribriform	PSA+, PAP–	5	↑	Lung	1.5	PSA+	51	DOD
4/54	ACA, ductal	Papillary/cribriform	ND	43	↑	Rib	3.0	PSA+, PAP+	71	Alive, well
5/65	ACA, ductal	Papillary/cribriform	ND	180	↑	Inguinal LN	3.5	PSA–, PAP+	206	Alive, disease progression
6/73	ACA, ductal	Papillary/cribriform	ND	36	↑	Sternal bone	4.0	ND	69	DOD
7/72	ACA, ductal	Papillary/cribriform	ND	61	↑	Liver	2.5	PSA+	70	DOD
8/60	ACA, mixed	Papillary/cribriform	PSA+, PAP+	28	↑	Iliac bone	1.0	PSA+, PAP+	53	DOD*
9/59	ACA, mixed	Cribriform	ND	59	↑	Iliac bone	3.0	PSA+, PAP+	64	Alive, disease progression
10/59	ACA, mixed	Cribriform	ND	40	↑	Liver	1.5	ND	76	DOD
11/63	ACA, mixed	Cribriform	PSA+, PAP+	92	↑	Liver	3.2	PSA+	98	DOD
12/55	ACA, mixed	Cribriform	PSA–, PAP+	18	↑	Liver	1.5	PSA–, PAP+	49	DOD
13/58	ACA, mixed	Cribriform	ND	13	↑	Liver	8.0	ND	28	DOD
14/61	ACA, mixed	Cribriform/solid	ND	2	↑	Iliac LN	1.2	ND	14	Alive, well
15/59	ACA, mixed	Cribriform/solid	ND	93	Normal	Lung	1.0	PSA+, PAP+, TTF-1–	96	Alive, well
16/59	ACA, mixed	Cribriform/solid	PSA+, PAP+	2	↑	Liver	3.5	PSA+, PAP+	119	DOD
17/66	ACA, mixed	Cribriform/solid	PSA+	56	↑	Liver	4.0	PSA+	77	DOD
18/76	ACA, mixed	NOS	PSA–, PAP+	<1	↑	Liver	1.0	PSA–, PAP+	18	Alive, disease progression
19/53	ACA, mixed	NOS	ND	29	↑	Retroperitoneal LN	1.0	ND	71	Alive, well
20/63	ACA, mixed	NOS	PSA+	2	↑	Pelvic LN	5.0	ND	8	Alive, well
21/65	ACA, mixed	NOS	ND	<1	↑	Pelvic LN	3.0	ND	34	Alive, well
22/61	ACA, mixed	NOS	ND	19	Normal	Pelvic LN	4.0	PSA+	35	Died†
23‡/NA	BPH	Papillary§	ND	NA	↑	Pelvic bone and soft tissue	>10	PSA+, PAP+, CK7–, CK20–, TTF-1–	NA	Alive, well

ACA, ductal, adenocarcinoma, pure ductal type; ACA, mixed, adenocarcinoma, mixed ductal and acinar type; BPH, benign prostatic hypertrophy; CK, cytokeratin; DOD, died of disease; LN, lymph node; NA, not available because it was not clear when the primary cancer developed; ND, not done; NOS, not otherwise specified; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; TTF-1, thyroid transcriptional factor 1; +, positive; –, negative; ↑, elevated.
* Died of coexisting brain metastasis.
† Died of unknown cause.
‡ Case reported previously.[17]
§ Although a primary tumor was not documented, a cell-block section of the metastatic tumor showed pure prostatic ductal carcinoma with a papillary pattern.

To identify cytologic features that were specific to the ductal component, the morphologic features of the 7 metastases whose primary counterparts were pure PDC (cases 1-7) and the 1 tumor in which the cell block section showed unequivocal metastatic prostatic carcinoma with a pure ductal component (case 23) were first evaluated. On direct smears, tumor cells tended to have abundant cytoplasm and an oval nucleus and were arranged in papillary configurations or large, cohesive, flat or folded sheets, some of which exhibited peripheral nuclear palisading along a smooth luminal border **Table 2**, **Image 1**, and **Image 2**. In tumors with mixed ductal and acinar components (cases 8-22), these features were found less frequently and more focally (Table 2), diluted by the intermingled acinar pattern. In addition, when the ductal component was predominantly cribriform or solid, these ductal features tended to be subtle (ie, increased number of small crowded cell groups and dyshesive cells with loss of nuclear polarity and less abundant cytoplasm). On the smears of 1 tumor, a cribriform pattern was identified focally (case 12, Image 2D). Generally, papillary fronds and large glandular patterns on tissue sections correlated with large sheets of cells in smears, and columnar cell morphologic features correlated with abundant cytoplasm. In 4 metastatic tumors whose primary counterparts were mixed PDC, features suggestive of ductal components were not readily identified.

Table 2
Ductal Component–Related Cytologic Features in Pure and Mixed Metastatic Prostatic Ductal Carcinomas*

	Pure (n = 8)	Mixed (n = 15)
Papillary	5 (63)	0 (0)
Flat sheet	8 (100)	7 (47)
Peripheral palisading	6 (75)	5 (33)
Abundant cytoplasm	7 (88)	8 (53)

* Data are given as number (percentage).

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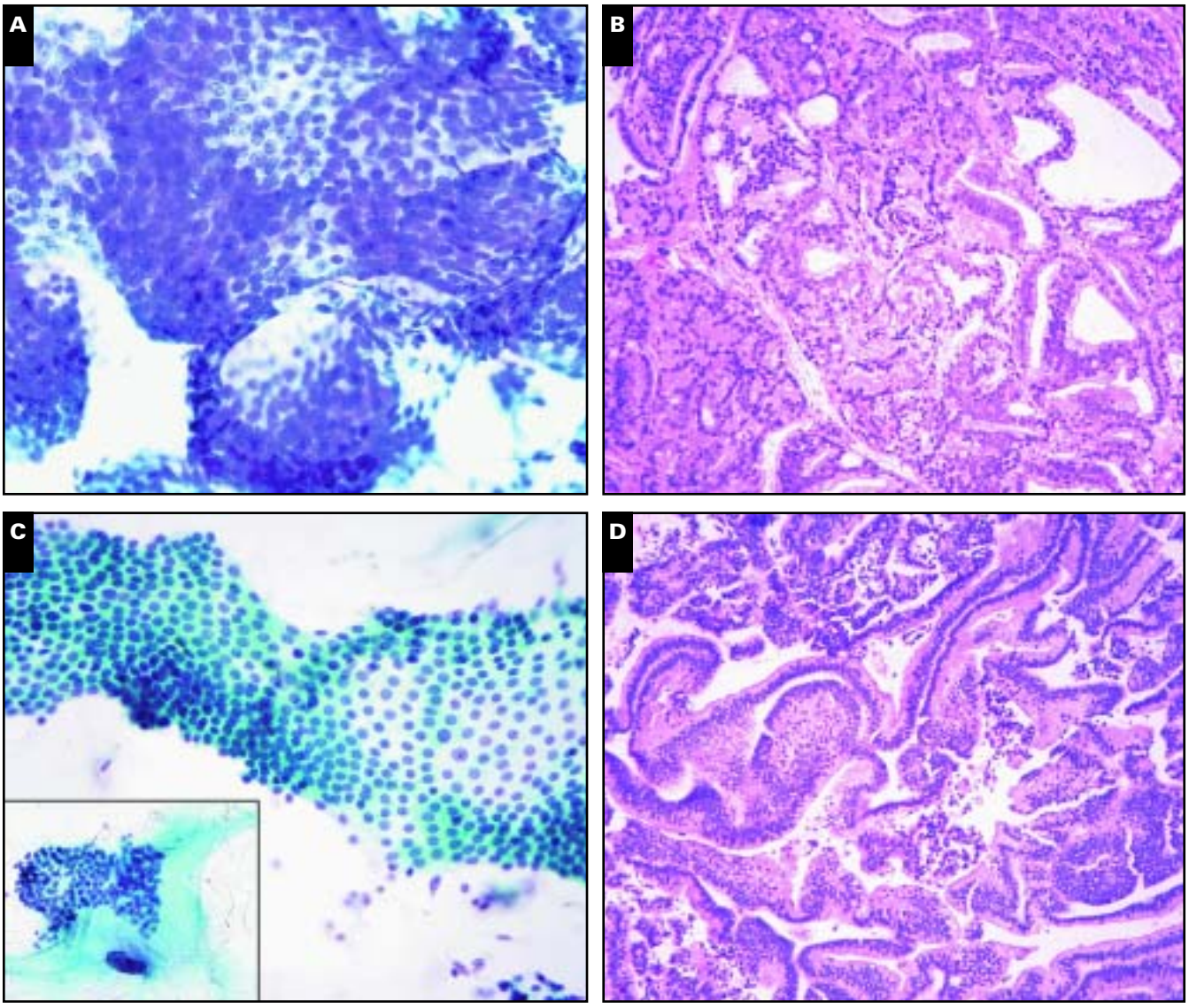

Image 1 Fine-needle aspiration features of 2 metastatic ductal carcinomas. **A** (Case 5), Smears showing large, flat, and folded cohesive sheets of tumor cells with moderate nuclear atypia (Papanicolaou, ×200). **B** (Case 5), Cell-block section showing complex large glands with a focal cribriform pattern lined mostly by a single layer of columnar cells (H&E, ×100). **C** (Case 23), Smears showing large, flat, cohesive sheets of fairly bland columnar epithelium in a clean background containing focal mucin (Papanicolaou, ×200; inset, Papanicolaou, ×100). **D** (Case 23), Cell-block section showing complex papillary fronds and ramifying glands lined by a single layer or variably stratified columnar cells, reminiscent of uterine endometrial carcinoma (H&E, ×100).

Cytologic features found in most tumors that did not seem related to a specific histologic pattern were moderate to high cellularity, clear to slightly granular cytoplasm with ill-defined cell borders, and variable nuclear enlargement and hyperchromasia. Bland nuclear features with mild nuclear pleomorphism were found in 4 tumors. Chromatin was granular and evenly distributed in 18 tumors, coarse in 4 tumors, and clumped in 1 tumor. Nucleoli were conspicuous to prominent in 14 tumors and inconspicuous in 9 tumors. Mitotic figures and necrotic background were found more commonly in tumors with a solid or cribriform histologic pattern. Focal mucin was found in 1 tumor (case 23, Image 1C inset).

Cell-block preparations were obtained in 20 metastatic tumors (87%). Of these, 12 showed morphologic patterns comparable to those of their primary counterparts. However, cell block sections from 2 metastatic tumors with a pure ductal component in their primary counterparts showed small foci of an acinar component in addition to a ductal component, and 4 tumors with mixed PDC in their primary counterparts showed an acinar component only. The cell blocks of the

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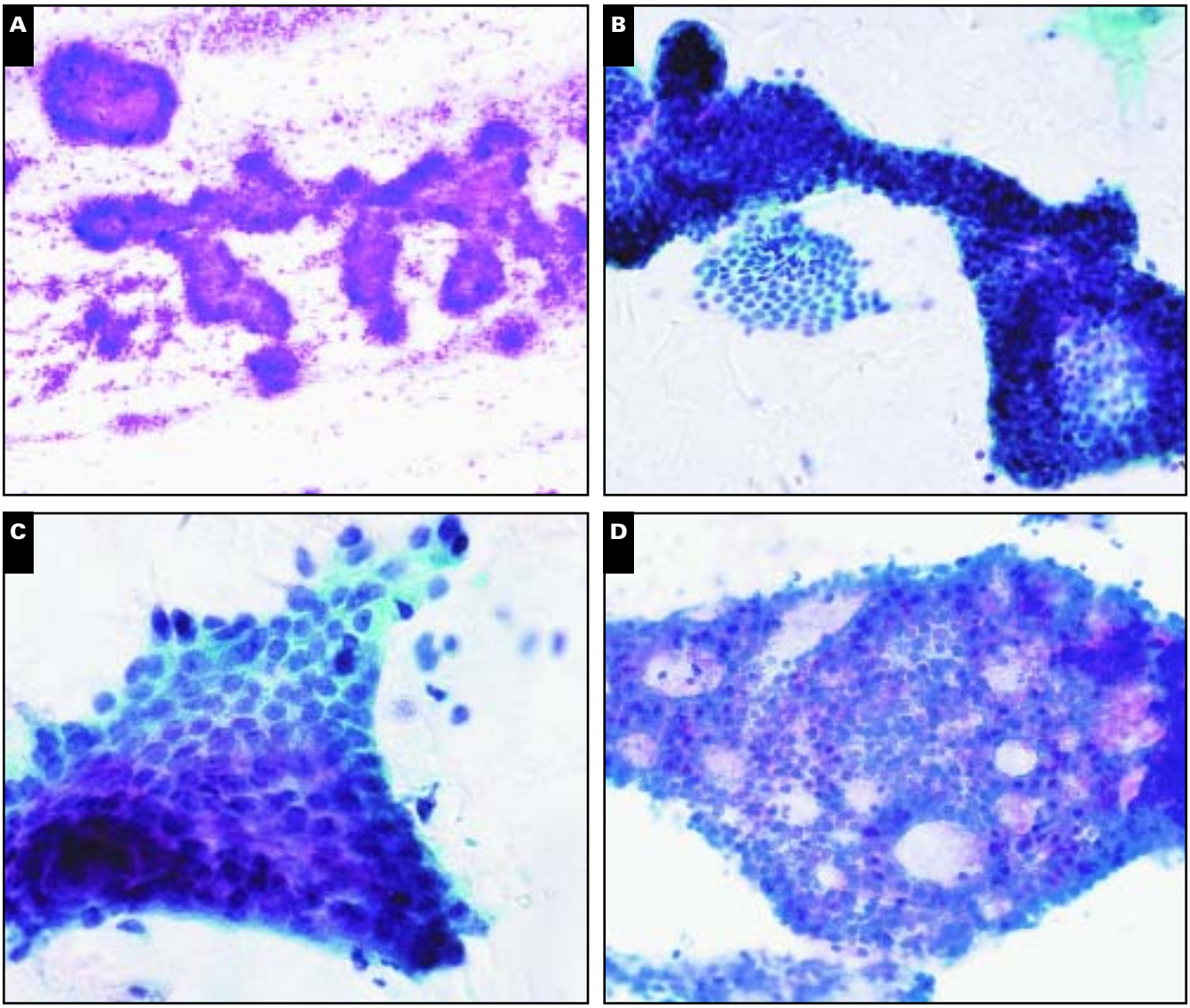

Image 2 **A** and **B** (Case 2), Fine-needle aspiration (FNA) smears of a metastatic ductal carcinoma showing papillary configuration (**A**, Diff-Quik, ×100; **B**, Papanicolaou, ×200). **C** (Case 1), FNA smear showing a cohesive, flat sheet of tumor cells with peripheral nuclear palisading along a smooth luminal border (Papanicolaou, ×400). **D** (Case 12), FNA smear demonstrating a well-formed cribriform pattern (Papanicolaou, ×200).

remaining 2 tumors contained too few cells to determine a morphologic pattern. Ductal components seen in cell-block sections varied from complex papillary fronds, ramifying glands, and anastomosing bands with infolding and pseudopapillary formations to epithelial sheets punctuated by multiple lumens (cribriform) and solid groups. They were lined mostly by a single layer or variably stratified columnar cells with basally located nuclei and abundant apical cytoplasm. Tumor cells in cribriform and solid areas tended to be cuboidal or polygonal. Nuclei were crowded and variably hyperchromatic and often demonstrated prominent nucleoli.

Of the 15 metastatic tumors with immunoperoxidase study results, PSA staining was positive in 12 (80%) (including 3 tumors from patients with normal serum PSA levels) and negative in 3 (20%) tumors. PAP staining was positive in all 10 tumors tested. The 3 PSA-negative tumors showed immunoreactivity to PAP. The staining results of the metastatic tumors were compared with the available results of their primary counterparts (including 2 of 3 metastatic tumors that were PSA– and PAP+) and were consistent (Table 1).

Discussion

PDC accounts for fewer than 1% of prostatic adenocarcinomas.[2,4] Although PDC usually involves the prostatic urethra and large periurethral prostatic ducts, it may arise from more

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peripheral prostatic ducts admixed with conventional acinar carcinoma.[1,2,4,6-8,11-13] Depending on the size and location of the involved ducts and their growth propensities, the ductal component may display a variety of histologic patterns (ie, papillary, complex glandular and cribriform, and solid) that often are intermingled.

Few studies of metastatic PDC have been reported, and all were conducted on histologic tissue samples. Metastatic tumors can be morphologically identical, similar or dissimilar to their primary counterparts,[18] and may show pure ductal, acinar, or both components.[4,6] These findings could be attributable to the difference in metastatic propensity between ductal and acinar components when primary PDC contains mixed acinar and ductal components[6] or simply may result from inadequate sampling. In our study, metastatic tumors were sampled via FNA, and most of them showed features (in cell-block sections) comparable to those of the primary tumors. However, 2 metastatic tumors whose primary counterparts were pure PDC (based on histologic findings from core needle biopsy specimens) also showed small foci of acinar component, and 4 metastatic tumors whose primary counterparts were mixed PDC (based on core needle biopsy specimens and transurethral resection) failed to reveal an unequivocal ductal component.

The cytologic features of metastatic PDC have not been described. In light of the wide spectrum of histomorphologic features in PDC, considerable variation of cytologic findings in metastatic PDC sampled via FNA can be anticipated. Our study indicates that pattern recognition may be the key to identifying this entity. In smears, cytologic features indicative of ductal morphology were papillary groups, flat or folded sheets, and peripheral nuclear palisading along a luminal border. Tumor cells typically had abundant cytoplasm. These features on smears were identified readily in tumors with a papillary or large glandular histologic pattern lined by columnar cells and were more subtle in tumors with a cribriform or solid histologic pattern. This difference was due to a tendency of tumor cells within a cribriform or solid pattern to be cuboidal or polygonal,[6] thereby forming smaller, crowded cell groups with a loss of polarization and cohesion. The subtlety of the ductal component on smears can be compounded further by the frequently coexisting acinar carcinoma. These factors may have contributed in part to the lack of unequivocal ductal features in the 4 metastatic tumors in our study whose primary tumors were mixed PDC.

The cytologic features of PDC in our study were similar to those described in 3 reported primary PDCs sampled via transrectal FNA.[14-16] All 3 cases showed papillary fragments of various sizes; in 2 cases, sheets of tumor cells also were found. Abundant cytoplasm was noted in 2 cases. Bland cytologic features with mild nuclear pleomorphism were described in 2 cases. Nuclear enlargement, crowding and overlapping, hyperchromasia, and nucleoli were noted variably.[14-16]

Although tumors with papillary or large glandular patterns are recognized readily as "ductal" in cytologic smears, these are the types of tumors that cause diagnostic difficulty in the metastatic setting because the cytologic features do not readily permit an association with a prostate origin. Similar morphologic features can be found in adenocarcinomas of many other origins, such as the gastrointestinal tract, pancreaticobiliary tract, lung, and urinary bladder.[8,12,19] When PDC metastasizes to the lung and liver, primary adenocarcinoma of these 2 organs needs to be excluded. A broad differential diagnosis including metastatic PDC should be considered. Correlation with clinical information and radiologic findings usually gives clues about the true nature of the lesion. Immunoperoxidase staining for PSA and PAP (with or without other markers) and measurement of serum PSA levels can further elucidate the primary origin. It is important to note that although nuclear palisading, necrotic debris, and mucin in the background frequently suggest a colorectal origin, they are not incompatible with a prostatic origin. Mucin production has been described in prostatic carcinoma, including PDC.[6,11,20-23] When more than 25% of the tumor component contains lakes of extracellular mucin, it is defined as mucinous carcinoma of the prostate. In our study, scant mucin was found in the smears of 1 case (case 23) but was not evident in corresponding cell-block sections.

Immunostaining for PSA and/or PAP is reported as invariably positive, at least focally, in primary PDC.[2,4,6,7,10,12,19] The metastatic tumors in our study showed positive PSA staining in 12 (80%) of 15 tumors tested and positive PAP staining in all 10 tumors tested. The 3 PSA–tumors showed immunoreactivity for PAP. Negative staining could stem from the intrinsic nature of a tumor, but also could result from insufficient sampling when the distribution of positively stained cells is focal and patchy. These factors justify inclusion of both antibodies in the diagnostic workup of metastatic PDC. Compared with immunostaining findings, serum PSA levels at the time of sampling of metastatic tumors are more variable and less reliable as an indicator of prostatic origin: despite a normal serum PSA value in 3 patients, PSA staining in the metastatic tumors was positive.

Controversy remains regarding the clinical behavior of PDC. Melicow and Pachter[1] and Melicow and Tannenbaum[9] originally believed that this tumor usually manifested as a low-stage lesion and behaved less aggressively than the usual acinar carcinoma. Similarly, Millar et al[5] reported that 5 of 8 patients with pure PDC were alive after 11, 8, 7, 3, and 1 years; the remaining 3 patients died of an intercurrent disease, of which 1 patient survived 12 years without treatment. These authors concluded that PDC could be regarded as having a good prognosis. Survival up to 12 years also was reported in another patient with pure papillary PDC.[13] Recently, however, most studies have found that PDC is more aggressive than

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usual acinar carcinoma**,** with a poor 5-year survival rate ranging from 15% to 43%.[2-4,6-8] Some reports have indicated that 25% to 40% of cases show metastases at the time of diagnosis. In addition to lymph node and skeletal metastases, as seen in ordinary acinar carcinoma,[2,4,6] PDC tends to spread to unusual sites, including the penis, testis, and visceral organs (eg, liver, lungs, and brain).[12,18] In our study, visceral metastases were found in 11 cases (48%) and bone and lymph node involvement in 12 cases (52%). In 1 patient with bone metastasis, brain metastasis developed eventually.

Although the prognostic data for our study were derived from patients who had metastatic disease sampled via FNA rather than from all patients with PDC, the study is important because it used a relatively large number of cases with relatively long follow-up periods. The median overall survival time for 22 patients was 77 months, and the 5-year overall survival rate was 72%, which is better than results from most reports.[2-4,6-8] Remarkably, 1 patient with metastatic PDC in his pelvic bone (case 23) had a history of prostatectomy for benign prostatic hypertrophy 30 years earlier. This metastatic tumor showed extremely bland cytologic features. It was unclear whether the primary PDC arose from residual prostatic tissue after surgery or an occult PDC was overlooked at the time of prostatectomy owing to bland cytologic features. Previous studies have demonstrated that bland cellular features have contributed considerably to the misinterpretation of primary PDC as benign prostatic tissue, prostatic urethral polyp, or papillary adenoma of the utricle.[2,8] In a study by Brinker et al,[8] morphologic features of malignancy, such as prominent nucleoli, nuclear hyperchromasia, and nuclear enlargement, were absent in a number of primary PDC cases. If primary PDC existed at the time of prostatectomy for our patient, then this patient (case 23) is the longest survivor (365 months) ever described in the literature.

We found no evidence that tumor growth patterns correlated with prognosis. No significant difference in the 5-year overall survival rate was found between patients with pure PDC and those with mixed PDC, although the number of cases in each group was small. It is possible that prognosis is similar stage for stage and grade for grade among prostatic carcinomas with different growth patterns. Visceral metastasis is a reliable indicator of poor prognosis: 9 of 10 patients in our study who died of disease showed visceral metastasis. Whether PDC is an inherently aggressive tumor remains to be determined.

We described FNA findings of metastatic PDC in 23 cases. A spectrum of cytologic features in correlation with histologic findings exists. Owing to the rarity of this variant and the fact that morphologic features overlap with adenocarcinomas of other primary sites, a diagnostic dilemma may occur in the metastatic setting in regard to the primary origin. Correlation with clinical and radiologic findings, a high index of suspicion, and adjunct immunoperoxidase studies are important for making an accurate diagnosis.

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