Cystic Prostatic Ductal Adenocarcinoma: An Unusual Presentation and Cytological Diagnosis

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Abstract. Prostatic ductal adenocarcinoma (PDA) is an uncommon histological variant of prostatic adenocarcinoma that may present clinically as a cystic mass [1-3]. We report a case of cystic PDA presenting as a cystic perirectal mass in a 61 year old male. Fine needle aspiration cytology showed malignant cells with round-oval to focally elongated nuclei, conspicuous nucleoli, and amphophilic cytoplasm with focal acinar formation. Tumor cells were positive for prostate-specific antigen; however, the cytology was non-specific for site of origin. The radical cystoprostatectomy specimen revealed the true site of origin and showed a cystic PDA adjacent to conventional prostatic acinar adenocarcinoma. Our objective is to describe the common cytological features of PDA and to analyze the differential diagnoses associated with cystic masses of the prostate.

Key words: cystic prostatic ductal adenocarcinoma, immunohistochemistry, cytology, histology, prostatic cysts

Introduction

Prostatic ductal adenocarcinoma (PDA) usually arises in large primary periurethral ducts and grows as an exophytic polypoid or papillary lesion into the urethra around the verumontanum [2, 4]. Patients typically present with either urinary obstructive symptoms or gross/microscopic hematuria [1-5]. Generally, this variant is thought to behave in an aggressive manner with a more advanced clinical and pathological stage at presentation. It has a poor 5-year survival rate when compared to prostatic adenocarcinoma of acinar morphology [1, 2, 4, 6, 7]. Histologically, PDA is characterized by tall columnar cells with abundant amphophilic cytoplasm which form a single or pseudostratified layer configured into a papillary or cribriform architecture. They may show a range of cytological atypia ranging from very bland to markedly pleomorphic [2]. Frequently, PDA is associated with an acinar component [1, 4].

Fine needle aspiration (FNA) of PDA has rarely been described and may cause diagnostic difficulty when presenting as a mass of indeterminate origin because the cytological features do not readily point to an adenocarcinoma of prostatic origin (Table 1). Its cytomorphological characteristics overlap with that of other adenocarcinomas. Here, we describe a case of cystic PDA with emphasis on the cytological features and discuss the differential diagnoses with the aid of adjunct studies.

Case Presentation

The following case was evaluated and reported in compliance with the University of South Florida’s Institutional Review Board Policy #311.
A 61 year-old male patient presented with complaints of alternating constipation and diarrhea for 6 months and gross hematuria and hematospermia for 2 weeks. In addition, he experienced dysuria, urinary frequency, and urinary urgency. Digital rectal examination revealed a large cystic mass extending to the prostate apex toward the anal verge. The total serum prostate-specific antigen (PSA) concentration in the peripheral blood was 18.1 ng/mL, while the serum carcinoembryonic antigen (CEA) level was 104 ng/mL. Computerized tomography (CT) and magnetic resonance imaging (MRI) revealed a large, nearly midline, cystic lesion measuring 6.6 x 6.5 cm, intimately associated with the prostate gland and rectum (Figures 1-2). An irregular solid nodularity was noted along the internal wall of the cyst. Overall, it was unclear whether the origin of the lesion was the prostate, seminal vesicle, or rectum. There was external iliac lymphadenopathy. Bone scan revealed no bone metastases.

Subsequently, cystoscopy was performed and showed a 3 to 3.5 cm bilobar obstructing the prostate gland with no evidence of malignancy. The mucosa of the urinary bladder was unremarkable. Urine cytology was negative, as was the Urovysion analysis (Chicago, IL).

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<td>FNA</td>
<td>Single case report</td>
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<td>Males</td>
<td>1-10 cm range (median, 3.0 cm)</td>
<td>FNA</td>
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A transrectal ultrasound-guided FNA of the cystic lesion was performed. It was noted that the cyst fluid CEA level was 3370 ng/mL. Smears had moderate to high cellularity showing large, flat, and 2-/3-dimensional cohesive sheets of overlapping tumor cells with round to oval to focally elongated nuclei exhibiting hyperchromasia and mild to moderate nuclear atypia (Figure 3). The tumor cells also possessed moderate to abundant amphophilic, slightly granular cytoplasm. The chromatin was finely granular and evenly distributed. Nucleoli were conspicuous. Mitotic figures and necrotic debris were not identified. There were numerous histiocytes and blood in the background. The cell block preparation showed scattered groups of malignant cells forming gland-like and cribriform structures lined mostly by a single layer of columnar cells with hyperchromatic nuclei (Figure 4). Focally, papillary structures were identified. Immunohistochemical stains performed on additional sections of the cell block with appropriate controls revealed the tumor cells to be diffusely and strongly positive for CAM5.2, polyclonal CEA, and PSA while negative for cytokeratin 5/6, cytokeratin 7, cytokeratin 20, and p63 (Figure 5). An adenocarcinoma of the prostate was favored based on the elevated serum PSA and the results of the PSA immunohistochemical stain. However, it was not clinically determined whether the cystic mass was arising from the prostate to confirm this. In addition, although CEA levels were non-specific, levels were elevated in the cyst fluid, leading to the inclusion of other primary tumors as part of the differential diagnosis, in addition to a prostate etiology.

A radical cystoprostatectomy was performed and revealed a 7.5 cm in greatest diameter ovoid cystic mass involving approximately 80% of the prostate gland (Figure 6). The cyst was filled with blood and lined by multiple excrescences, ranging from 0.5 to 2.5 cm. Histopathological sections revealed a prostatic adenocarcinoma, Gleason’s score 4+4=8, consisting of prostatic ductal and acinar adenocarcinomas (Figure 7). The PDA had a papillary and cribriform architecture with focal extracellular mucin (Figure 8). The papillary fronds were lined by a single layer of columnar cells with focal stratification. The tumor cells had hyperchromatic nuclei with eosinophilic cytoplasm. Prostatic acinar adenocarcinoma was seen peripheral to the PDA. Both the prostatic ductal and acinar adenocarcinomas were confirmed by positive immunohistochemical
staining for PSA and AMACR and negative staining for basal cell markers (Ker903 and p63) (Figure 9). The tumor exhibited extraprostatic extension and involved the right seminal vesicle. Angiolymphatic and perineural invasion were noted. Ten of 28 regional lymph nodes were involved by tumor with extranodal extension (Pathological Stage: pT3bN1M1a).

After surgery, the patient received combined androgen deprivation therapy with bicalutamide and lupron. Twenty-four days status post-surgical resection, the patient’s PSA level was 0.64 ng/mL and within a month of androgen deprivation therapy his PSA level dropped by 50% to 0.16 ng/mL. Currently, the patient is 8 months post-surgical resection and continues to do well, with a PSA level of less than 0.01 ng/mL.

**Discussion**

Prostatic adenocarcinoma is a common form of cancer in men. Most prostatic adenocarcinomas are morphologically of acinar type [4]. However, unusual histological variants – such as prostatic ductal adenocarcinoma (PDA) – have been encountered. PDA exists in either a pure form or mixed with a conventional acinar adenocarcinoma [2-4]. It has a unique morphology and in some cases, such as in our case report, unique clinical features. Few studies have described the cytomorphology of PDA, and it is important to distinguish prostatic adenocarcinoma of any variant from other adenocarcinomas with similar features because patient prognosis and therapeutic options can differ.

Clinically, PDA presents with symptoms of urinary obstruction and/or hematuria, as in our patient. This malignancy commonly appears as an exophytic mass protruding into the urethra, but in rare occasions, this tumor may present as a cystic lesion [2-4, 8]. Cystic PDA occurs predominantly as a cystic mass in which the solid irregularities of the wall represent tumor [8]. At times, large cystic lesions in the area of the prostate and adjacent visceral organs, such as the rectum and bladder, make it difficult to discern the origin of the cystic lesion. In our case report, clinicians were confronted with this problem because the imaging studies could not definitively determine from where the cystic mass
Cystic Prostatic Ductal Adenocarcinoma originated. The mass appeared to be associated with the prostate, rectum, or seminal vesicle. The differential diagnoses for cystic lesions in this area encompass benign and malignant entities. Benign lesions to consider include a prostatic utricle cyst, cystic degeneration in benign prostatic hypertrophy, prostatic retention cyst, abscess, and congenital cyst/duplication cyst of gastrointestinal origin. Malignant lesions to take into consideration in this anatomic location include colorectal adenocarcinoma, urothelial carcinoma, prostatic adenocarcinoma, and metastatic lesions. Squamous cell carcinoma, particularly of the head and neck region, may present as a cystic metastasis before the primary tumor clinically manifests itself [9].

In evaluating cystic masses in this area, FNA may prove helpful. In our case, FNA of the cyst revealed cellular smears with large cohesive sheets of malignant cells, which tremendously helped to narrow our differential from benign entities to focus on malignant possibilities. Further evaluation of the smears demonstrated groups of tumor cells forming acini-like structures with lumina. The cells possessed slightly granular amphophilic cytoplasm and slightly variable nuclear enlargement with hyperchromasia and overlapping. Nucleoli were apparent. Similar cytomorphological features have been reported in FNA of metastatic PDA [1, 10, 11]. Gong et al reported that the cytological features indicative of ductal morphology were papillary groups, flat or folded sheets, and peripheral nuclear palisading along a luminal border [1]. Ramzy et al described the voided urine cytology of PDA and placed a strong emphasis on the presence of large, hyperdistended cytoplasmic vacuoles as a characteristic feature of this neoplasm while a case report by Vandersteen et al describing the cytology of PDA in bladder washings suggested that the presence of nuclear grooves may be important in the recognition of PDA [12, 13]. The smears in our case did not demonstrate peripheral nuclear palisading, nuclear grooves, or distended cytoplasmic vacuoles, which may be attributed to sampling or the method used for cytological sampling.

Figure 6. A radical cystoprostatectomy shows a 7.5 cm ovoid cystic mass filled with blood, involving approximately 80% of the prostate gland.

Figure 7 (A-B). Histopathological sections reveal a prostatic adenocarcinoma, Gleason’s score 4+4=8, consisting of prostatic acinar (A. H&E stained section, 20X) and ductal (B. H&E stained section, 10X) adenocarcinomas.
However, there were papillary groups seen on the cell block preparation. In addition, cytological features present in our case were similar to previously reported cases which included sheets of tumor cells, abundant cytoplasm, nuclear enlargement and crowding, and nucleoli [3, 14-16]. Fortunately, the cell block preparation contained malignant glandular structures and allowed the use of immunohistochemistry to determine the origin of the malignancy. The malignant cells were positive for CAM5.2 and polyclonal CEA which confirmed an epithelial malignancy, likely adenocarcinoma. Secondly, the type of adenocarcinoma needed to be determined (Table 2). Colorectal adenocarcinoma also has tall columnar hyperchromatic cells; however, a necrotic background is usually present. Urothelial carcinoma may also have papillary fragments with fibrovascular cores, but more often shows irregular cell clusters. In addition, the nuclei are typically more pleomorphic than one would see in prostatic ductal adenocarcinoma. Prostatic adenocarcinoma of acinar type forms microacini, and the tumor cells are round to oval with abundant cytoplasm and prominent nucleoli. Metastatic lesions should be considered as well. Adenocarcinoma of the lung may present as cohesive sheets, 3-dimensional clusters, or acini; however, the nuclei are irregular and eccentric with foamy cytoplasm, and large nucleoli. Pancreatobiliary malignancies may show cellular smears with increased nuclear to cytoplasmic ratio, chromatin clumping, nuclear crowding/overlapping, and loss of honeycombing. Poorly-differentiated squamous cell carcinomas can be difficult to distinguish from other poorly differentiated malignancies. Altogether, the cytomorphological features of the above types of adenocarcinomas are similar, so it is quite a difficult task to discern the origin of an adenocarcinoma relying on cytology alone.

Additional immunohistochemical studies showed that the tumor cells in our case were negative for cytokeratin 7, cytokeratin 20, cytokeratin 5/6, and p63. Negative results proved to be important in ruling out certain types of adenocarcinomas. It was highly unlikely that the mass was of lung, colorectal, or pancreatobiliary origin. It was certainly not a squamous cell carcinoma since the cytokeratin 5/6 and p63 were negative. The strong,
diffuse PSA positivity confirmed a prostatic origin. PDAs express PSA and prostatic specific acid phosphatase (PSAP) [2]. Although determining that the prostatic adenocarcinoma was also of ductal type could not be elicited on cytology, the FNA sample successfully discerned the origin of the cystic mass, which helped to select appropriate therapy.

Histologically, the PDA in our case had a distinctive papillary architecture lined by tall columnar cells showing focal nuclear pseudostratification mimicking endometrioid adenocarcinoma with moderate nuclear atypia. PDAs may have a more cribriform pattern or grow as solid nests with necrosis and rarely show extracellular or intracellular mucin [2]. Frequently, PDAs are found admixed with an acinar component. Most studies suggest that a ductal morphology connotes a more aggressive course [7]. The patient in this report had a resected specimen with extraprostatic extension, right seminal vesicle involvement, lymph node involvement, angiolymphatic invasion, and perineural invasion, all of which indicate a more aggressive tumor. Guidelines on management and treatment of this histological subtype do not exist, but reports suggest benefits from external beam radiotherapy and androgen deprivation and perhaps systemic chemotherapy with metastases [6, 17].

In conclusion, important FNA findings for cystic PDA are large sheets and clusters of cells, abundant cytoplasm, bland to marked nuclear atypia with crowding and hyperchromasia, and the presence of nucleoli, all of which can be seen in conventional prostatic acinar adenocarcinoma as well as in other types of adenocarcinomas. Clearly, it is significant to correlate cytological findings with clinical and radiological studies to narrow the broad differential and use immunohistochemistry as an adjunct when available to elucidate the diagnosis. FNA cytology can aid in the diagnosis of malignant cystic lesions of the prostate and promote timely intervention as well as improved management.

References