The Utility of PSMA and PSA Immunohistochemistry in the Cytologic Diagnosis of Metastatic Prostate Carcinoma

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*The diagnosis of metastatic prostate carcinoma frequently requires the use of immunohistochemical adjuncts. Immunohistochemistry for prostate-specific antigen (PSA) is commonly used for this purpose but can be of limited utility. Recently, prostate-specific membrane antigen (PSMA) has been shown to be a promising marker for the identification of metastatic prostate carcinoma in surgical specimens. The utility of this marker has yet to be reported for cytology specimens. We sought to compare the sensitivities of PSMA and PSA immunohistochemistry and investigate the specificity of PSMA by utilizing cell block preparations from cytologic cases of metastatic prostate carcinoma (*n = *19) and carcinomas of nonprostatic origin (*n = *33). The sensitivity of PSMA immunohistochemistry was higher (16/19; 84%) in detecting metastatic prostate carcinomas than that of PSA immunohistochemistry (11/19; 58%). Strong, diffuse staining for PSMA was seen in 13 (81%) of 16 PSMA-positive cases whereas strong, diffuse staining for PSA was observed in six (55%) of 11 PSA-positive cases. Positivity for either PSMA or PSA was seen in 17 of 19 cases of metastatic prostate carcinoma for a combined sensitivity of 89%. PSMA immunohistochemistry was completely negative in 32 of 33 cytology cases of nonprostatic carcinomas. Therefore, the specificity of this marker was 97% in this study. In conclusion, our results indicate that PSMA is a highly sensitive and specific immunomarker for the detection of metastatic prostate carcinoma in cytology specimens.* Diagn. Cytopathol. 2014;42:570–575.

Key Words: prostate-specific membrane antigen; prostate-specific antigen; carcinoma; cytology; immunohistochemistry

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INTRODUCTION

Prostate cancer is the most common noncutaneous malignancy in adult men. In 2013, it is estimated that there will be 238,590 new cases of prostate cancer and 29,720 prostate cancer-related deaths.[1] Although most men are diagnosed with localized disease, a significant subset of patients is diagnosed with locoregional disease spread and/or distant metastases or will develop metastasis later in the course of their disease.[2] Although surgery for localized prostate cancer can be curative, the treatment for metastatic disease involves antiandrogen therapy, chemotherapy, immunotherapy, and/or radiation.[3–7] Accurate diagnosis of metastatic prostate carcinoma is essential for the timely management of patients with metastatic disease.

Cytologic samples, including fine-needle aspiration (FNA) and effusion specimens, represent a rapid, minimally invasive, relatively inexpensive means to identify and diagnose metastatic prostate cancer. Although the diagnosis of well-differentiated metastatic prostate cancers can be straightforward, the diagnosis of higher-grade, poorly differentiated tumors can be challenging.[8] Compounding this problem, studies have shown that metastatic prostate carcinoma can present in a different morphologic pattern compared to that of the primary tumor.[9–12] Thus, immunohistochemistry can serve as a useful adjunct in this regard. Traditionally, antibodies directed against prostate-specific antigen (PSA) and prostate acid phosphatase (PAP) are used for this purpose. Nonetheless, negative immunoreactivity for both of these markers in a significant subset of metastatic prostate carcinomas, especially higher-grade tumors, can contribute to diagnostic difficulties.[13,14]

Prostate-specific membrane antigen (PSMA) expression is present in both benign and neoplastic prostatic tissue,[15–24] and its expression is stronger in the latter.[17,21,22] Expression has also been shown to be

Table I. PSMA and PSA Expression in Metastatic Prostatic Carcinomas

Case	*Source of cytologic sample*	*Gleason score of original tumor*	*Stage of original tumor*[a]	*PSMA staining result (score*[b]*)*	*PSA staining result (score*[b]*)*
1	Soft tissue, left T4-T5 paraspinal/epidural mass	Unknown	Unknown	Positive (5)	Positive (6)
2	Bone, right scapula lesion	7	Unknown	Positive (6)	Negative (0)
3	Lymph node, left cervical	Unknown	Unknown	Positive (6)	Positive (3)
4	Lymph node, left inguinal	9	T3b N0 Mx	Positive (6)	Positive (5)
5	Lymph node, left supraclavicular	9	T1c Nx Mx	Positive (4)	Negative (2)
6	Soft tissue, mediastinal mass	7	T3a N0 Mx	Positive (6)	Positive (6)
7	Bone, left posterior rib lesion	8	T3b N0 Mx	Positive (6)	Positive (6)
8	Lymph node, subcarinal	7	T1c Nx Mx	Positive (6)	Positive (6)
9	Lymph node, subcarinal	10	T2a N0 M0	Positive (5)	Positive (5)
10	Voided urine	7	T2a N0 M0	Positive (6)	Positive (6)
11	Lymph node, mediastinal 4R	7	Unknown	Positive (6)	Negative (0)
12	Lymph node, left cervical	9	T3a N1 Mx	Positive (6)	Positive (4)
13	Soft tissue, penis lesion	7	T1c Nx Mx	Positive (6)	Negative (0)
14	Bone, right inferior pubic ramus lesion	8	T1c Nx M1b	Negative (2)	Positive (3)
15	Right pleural fluid	9	T1c N1 M1b	Positive (6)	Positive (6)
16	Right pleural fluid	Unknown	Unknown	Positive (6)	Negative (0)
17	Lymph node, right inguinal	5	Unknown	Positive (6)	Negative (0)
18	Left pleural fluid	7	T1c Nx M0	Negative (0)	Negative (0)
19	Left pleural fluid	7	T2a N0 M0	Negative (0)	Negative (0)
	Sensitivity			84% (16/19)	58% (11/19)

[a]Stage was determined according to the American Joint Committee on Cancer (AJCC) Staging Manual, 7th ed.
[b]Refers to combined immunoreactivity score (see Materials and Methods section).
PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen.

greatest, with respect to immunostaining intensity and extent, in high-grade prostate carcinomas compared to low-grade carcinomas.[20,22] We are not aware of any reports in the literature, to date, that examine the utility of PSMA immunohistochemistry in the diagnosis of metastatic prostate cancer in cytology specimens. Therefore, the aims of this study were 2-fold. First, we sought to compare the performance of PSMA and PSA immunohistochemistry for the detection of metastatic prostate carcinomas. Next, we performed PSMA immunohistochemistry for cytologic specimens of nonprostate carcinomas to better understand the diagnostic specificity of this marker.

MATERIALS AND METHODS

The study was approved by the institutional review board at University of Michigan. The electronic pathology database was searched, using the search terms "prostate" or "prostatic," to identify reports of potential cytologic cases of prostatic carcinoma. A total of 21 cases, in which tumor cells were present in the cell block, were identified. Clinicopathologic evaluation utilizing the electronic medical record (clinical notes, radiology reports, and pathology reports) was performed and confirmed metastatic prostatic carcinoma in 19 of these cases (Table I). In two cases, nonprostatic origin was confirmed and these two cases were included in the nonprostatic carcinoma control cohort (cases 1 and 2, Table II). The control cohort also consisted of 4, 5, 12, and 10 consecutive cases of urothelial, gastrointestinal, lung, and renal carcinomas diagnosed in men, respectively, for which the cell blocks contained adequate material for immunohistochemical evaluation (cases 3–33, Table II). For these cases, the electronic medical records (clinical notes, radiology reports, and pathology reports) were reviewed in conjunction with the original diagnostic slides to confirm the primary site of malignancy. Unstained sections of 4-μm thickness were prepared from each of the formalin-fixed, paraffin-embedded cell blocks.

Immunohistochemistry for PSMA was performed using the Ventana Benchmark Ultra (Ventana, Tucson, AZ) using 3,3′-diaminobenzidine as the chromogen. Following deparaffinization, antigen retrieval was

Table II. PSMA Expression in Metastatic Carcinomas of Extraprostatic Origin

Case	*Primary malignancy*	*Source of cytologic specimen*	*PSMA staining result (score[a])*
1	Invasive extramammary Paget's disease	Lymph node, left inguinal	Negative (0)
2	Esophageal squamous cell carcinoma	Lymph node, right supraclavicular	Negative (0)
3	Urothelial carcinoma	Lymph node, left inguinal	Negative (0)
4	Urothelial carcinoma	Lymph node, left inguinal	Negative (0)
5	Urothelial carcinoma	Lymph node, mediastinal station 7	Negative (0)
6	Urothelial carcinoma	Right pleural fluid	Negative (0)
7	Rectal adenocarcinoma	Colon, rectal mass	Negative (0)
8	Gastric cardia adenocarcinoma	Ascites fluid	Negative (0)
9	Gastroesophageal junction adenosquamous carcinoma	Soft tissue, periportal mass	Negative (0)
10	Colonic adenocarcinoma	Soft tissue, retroperitoneal nodule	Negative (0)
11	Esophageal adenocarcinoma	Pericardial fluid	Negative (0)
12	Pulmonary adenocarcinoma	Lymph node, mediastinal station 7	Negative (0)
13	Pulmonary adenocarcinoma	Lymph node, mediastinal station 4R	Negative (0)
14	Pulmonary adenocarcinoma	Soft tissue, peribronchial mass	Negative (0)
15	Pulmonary adenocarcinoma	Lymph node, mediastinal station 10L	Negative (0)
16	Pulmonary adenocarcinoma	Lymph node, mediastinal station 4R	Positive (3)
17	Pulmonary adenocarcinoma	Lymph node, mediastinal station 4R	Negative (0)
18	Pulmonary adenocarcinoma	Lymph node, mediastinal station 7	Negative (0)
19	Pulmonary adenocarcinoma	Lymph node, mediastinal station 4R	Negative (0)
20	Pulmonary adenocarcinoma	Lymph node, mediastinal station 11R	Negative (0)
21	Pulmonary adenocarcinoma	Lymph node, mediastinal station 4R	Negative (0)
22	Pulmonary adenocarcinoma	Lymph node, mediastinal station 2R	Negative (0)
23	Pulmonary adenocarcinoma	Lung, left upper lobe mass	Negative (0)
24	Renal cell carcinoma	Pericardial fluid	Negative (0)
25	Renal cell carcinoma	Lymph node, pararenal	Negative (0)
26	Renal cell carcinoma	Lymph node, paratracheal	Negative (0)
27	Renal cell carcinoma	Lymph node, paratracheal	Negative (0)
28	Renal cell carcinoma	Pancreas, pancreatic head mass	Negative (0)
29	Renal cell carcinoma	Lymph node, mediastinal station 4R	Negative (0)
30	Renal cell carcinoma	Kidney, left renal mass	Negative (0)
31	Renal cell carcinoma	Kidney, right renal mass	Negative (0)
32	Renal cell carcinoma	Left pleural fluid	Negative (0)
33	Renal cell carcinoma	Bone, T6 vertebral lesion	Negative (0)

[a]Refers to combined immunoreactivity score (see Materials and Methods section).
PSMA, prostate-specific membrane antigen.

performed on unstained cell block sections using CC1 buffer, pH 8.5 (Ventana, Tucson, AZ). Subsequently, immunohistochemistry was performed using the mouse monoclonal anti-PSMA antibody (3E6; 1:25 dilution; DAKO, Carpinteria, CA) along with appropriate controls. The UltraView Universal DAB Detection Kit (Ventana, Tucson, AZ) was used for detection of mouse primary antibodies.

Immunohistochemistry for PSA was performed using the DAKO Autostainer (DAKO, Carpinteria, CA) using 3,3′-diaminobenzidine as the chromogen. Immunohistochemistry was performed using the rabbit polyclonal anti-PSA antibody (1:3000 dilution; DAKO, Carpinteria, CA) following antigen retrieval in 0.01*M* citrate buffer, pH 6.0 (DAKO, Carpinteria, CA) along with appropriate controls. The EnVision+ System for use with rabbit primary antibodies (DAKO, Carpinteria, CA) was used as the secondary antibody.

Immunostained slides were reviewed (K.D.B. and M.H.R.) and scored for both intensity of staining (0, negative; 1, weak intensity; 2, moderate intensity; 3, strong intensity) and extent of staining (0, 0% of cells; 1, <10% of cells; 2, 10–50% of cells; 3, >50% of cells). The combined immunoreactivity score was recorded by taking the sum of the scores for intensity and extent of staining. A combined immunoreactivity score of 3 or greater was considered as a positive result. Completely negative staining or weak, very focal staining (combined immunoreactivity score of 2) were both considered as negative results.

RESULTS

Cytology cases of metastatic prostatic carcinoma, obtained from 19 patients, were examined in this study. The anatomic sites from which the cytologic samples were obtained are listed in Table I. Sixteen (84%) of the 19 metastatic prostatic carcinoma cases were scored as positive for PSMA (Table I). Staining intensity in all 16 PSMA-positive cases ranged from moderate to strong. Notably, strong, diffuse staining in the tumor cells (combined immunoreactivity score of 6) was observed in 13 of 16 PSMA-positive cases. Of the three cases that were scored as PSMA-negative, two had complete absence of staining and

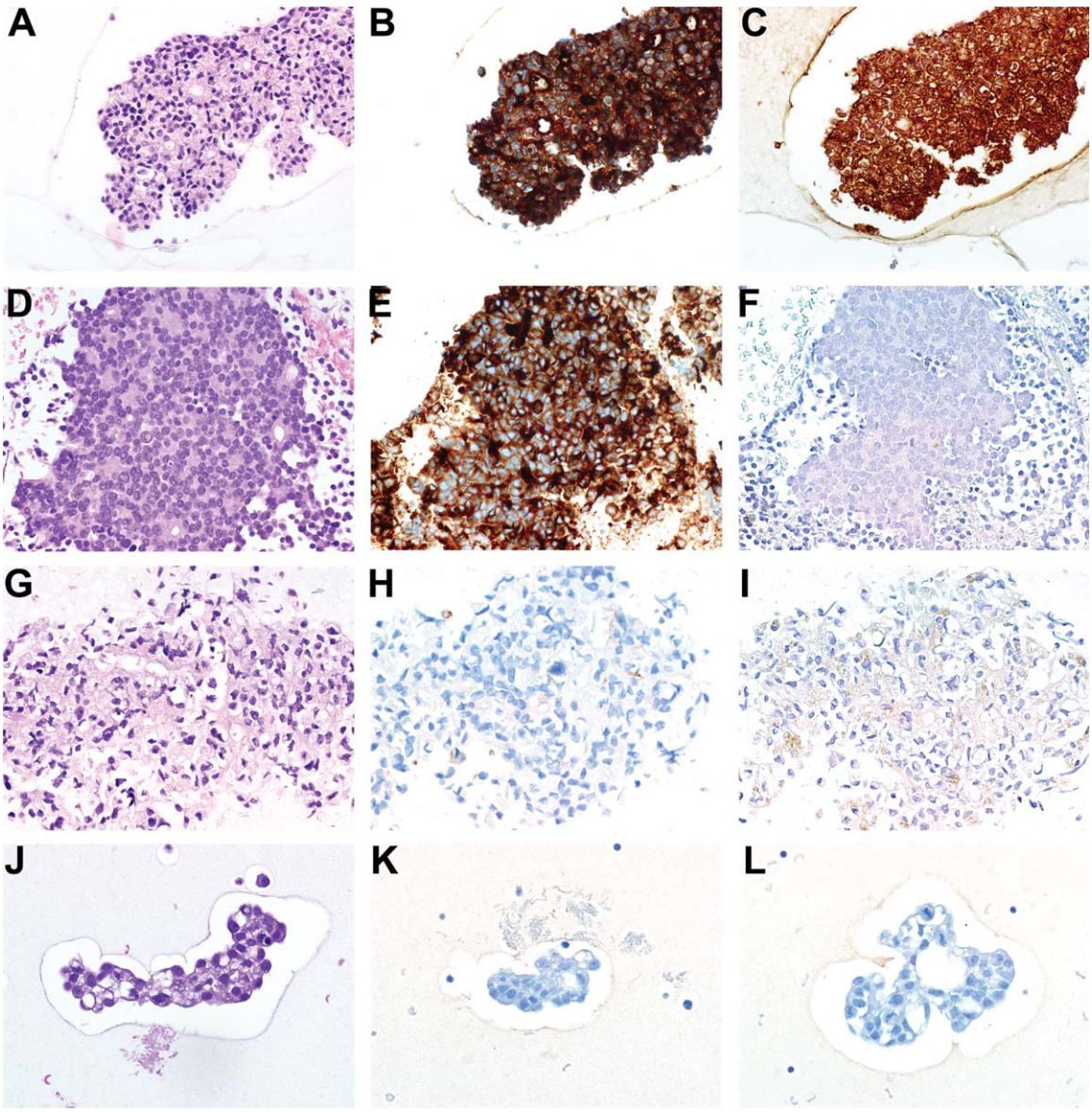

Fig. 1. Immunohistochemistry for PSMA and PSA for cases of metastatic prostate carcinoma**.** (**A**, **D**, **G**, **J**) Representative photomicrographs obtained from hematoxylin and eosin (H&E) stained cell block sections derived from cases of metastatic prostate carcinoma (cases 6, 11, 14, and 19, respectively). (**B**, **E**, **H**, **K**) Corresponding immunohistochemical stains for PSMA expression. In panels B and E, strong diffuse staining for PSMA is demonstrated (combined immunoreactivity score of 6). PSMA immunostains in panels H and K were interpreted as negative. (**C**, **F**, **I**, **L**) Corresponding immunohistochemical stains for PSA expression. In panel C, strong diffuse staining for PSA is demonstrated (combined immunoreactivity score of 6). The PSA immunostains in panels F and L were interpreted as negative. The PSA immunostain for case 14 (panel I) was interpreted as positive; weak staining intensity was noted in greater than 10% but less than 50% of the tumor cells (combined immunoreactivity score of 3). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

one exhibited faint staining in less than 10% of the tumor cells (combined immunoreactivity score of 2).

Eleven (58%) of the 19 metastatic prostatic carcinoma cases scored positive for PSA (Table I). Six of the 11 PSA-positive cases exhibited strong, diffuse staining (combined immunoreactivity score of 6). The remaining five PSA-positive cases varied in staining intensity and extent with combined immunoreactivity scores of 3–5. Of the eight cases that were scored as PSA-negative, seven exhibited a complete absence of staining, and one demonstrated faint staining in less than 10% of the tumor cells (combined immunoreactivity score of 2).

Overall, the sensitivity of PSMA immunohistochemistry was higher than that of PSA immunohistochemistry (84 vs. 58%, respectively). For 10 cases, both immunostains were scored as positive (Figs. 1A–C). Seventeen of

19 cases were positive for either PSMA or PSA for a combined sensitivity of 89%. Six of the eight PSA-negative cases were PSMA-positive (Figs. 1D–F). One case was scored as PSMA-negative and PSA-positive (Figs. 1G–I). Two cases of metastatic prostate carcinoma were negative for both PSA and PSMA (Figs. 1J–L).

Finally, we sought to investigate the specificity of PSMA as a diagnostic immunomarker by examining, in parallel, cytology specimens obtained from 33 male patients with carcinomas of extraprostatic origin. The primary malignancy and anatomic sites from which the cytologic samples were obtained are indicated in Table II. In this cohort, PSMA positivity was only seen in one case of a metastatic pulmonary adenocarcinoma (Table II, case 16). In this case, PSMA immunoreactivity of moderate intensity was observed in less than 10% of the tumor cells (not shown). The remaining 32 cases of nonprostatic carcinoma were completely negative for PSMA. Therefore, in our study, the specificity of PSMA positivity for identifying metastatic prostate carcinoma was 97%.

DISCUSSION

To our knowledge, there are no reports, to date, that examine the utility of immunohistochemistry for PSMA in the evaluation of metastatic prostate carcinomas in cytology specimens. PSA and PAP immunohistochemistry have been traditionally utilized for this purpose; nonetheless, the efficacy of these markers is limited as a significant proportion of metastatic prostate carcinoma cases are negative for both markers. Our immunoperoxidase laboratory has validated the anti-PSMA antibody for clinical use. This marker is used routinely by our surgical pathology colleagues; they have observed a higher sensitivity of PSMA immunohistochemistry, compared to PSA, for confirming metastatic prostate carcinoma. In our study, the observed sensitivity of PSMA immunohistochemistry in highlighting metastatic prostate carcinoma tumor cells in cell block sections was 84%. This is consistent with previous studies that observed PSMA immunoreactivity ranging from 66 to 100% in surgical pathology samples.[15–22,25–28] Importantly, we compared the performance of PSMA immunohistochemistry to that of PSA immunohistochemistry and observed that the former is more reliable. Specifically, strong diffuse staining of tumor cells was seen at higher frequency on PSMA immunohistochemistry than on PSA immunohistochemistry. The overall sensitivity of PSMA immunohistochemistry (84%) was higher than that of PSA immunohistochemistry (58%).

The relatively high sensitivity of PSMA immunohistochemistry in metastatic prostate carcinoma samples is not surprising. Previous reports indicate that, on immunohistochemistry, PSMA expression is robust and observed for both low and high-grade prostate cancers.[20,22] In contrast, well-differentiated prostate carcinomas are more likely than higher-grade cancers to express PSA on immunohistochemistry.[13,14] High-grade carcinomas exhibit higher metastatic potential than their well-differentiated counterparts. Sensitivities ranging from 81 to 100% have been reported for the immunohistochemical detection of PSMA in metastatic prostate cancers.[16,17,19,20,23] Furthermore, PSMA expression was shown to be higher in cases of prostate cancers that metastasize to lymph nodes[17] and bone.[20] The biological mechanism underlying the increased expression of PSMA relative to PSA in higher grade, more aggressive prostate cancers is not exactly known. Although some have speculated that PSMA overexpression drives prostate cancer tumorigenesis, this has not been rigorously proven.[21] Thus, our results corroborate these previous reports and indicate that PSMA is a more efficacious immunomarker in the cytodiagnostic workup of metastatic carcinomas that originate from the prostate gland.

Highly sensitive immunomarkers raise concern with regards to the specificity of the marker being evaluated. We sought to investigate the specificity of this marker in our study by performing PSMA immunohistochemistry on cell block sections of nonprostatic carcinomas. We tested tumors of various primary sites such as lung, kidney, and gastrointestinal tract. These tumors especially metastasize to similar anatomic sites as prostate cancers, as evidenced by Tables I and II, and can represent cytomorphologic mimics of metastatic prostate carcinoma. Of these tumors, PSMA-negative results were obtained for all cases except for one case of lung carcinoma. Therefore, although the specificity of PSMA immunohistochemistry is not perfect, it remains very high (97%). Mhawech-Fauceglia et al. observed weak immunoreactivity for PSMA in a small proportion of various nonprostatic carcinomas such as gastric, colonic, gall bladder, pancreas, and lung.[18] Nonetheless, the specificity of strong, diffuse PSMA staining for metastatic prostate carcinomas was very high. Of note, Lane et al. observed that approximately 11% of bladder adenocarcinomas stained positively for PSMA in a diffuse fashion.[29] Therefore, despite the relative rarity of these tumors compared to prostate carcinomas, care should be exercised when adenocarcinomas of the bladder are considered within the differential diagnostic workup. In light of these reports, it is important to emphasize that in our cohort, strong diffuse PSMA staining was observed in the majority of our metastatic prostate carcinoma cases.

In conclusion, immunohistochemistry for PSMA is more sensitive than that for PSA in the cytodiagnostic workup of metastatic prostate cancers. Of note, the combination of PSMA and PSA immunohistochemistry was slightly more sensitive than the sensitivity of utilizing PSMA immunohistochemistry alone. As we now and others previously have demonstrated the high sensitivity and specificity for PSMA immunohistochemistry, we

believe that PSMA represents a valuable component to the immunohistochemical armamentarium for confirming prostatic origin for metastatic prostate carcinomas in diagnostic cytology.

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