The Morphologic Spectrum of Metastatic Prostatic Adenocarcinoma to the Lung

Special Emphasis on Histologic Features Overlapping With Other Pulmonary Neoplasms

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Abstract

We undertook a detailed histologic study to identify specific morphologic features that may aid in distinguishing prostatic adenocarcinoma with lung metastases (PALM) from other pulmonary tumors with similar histologic features. In 16 cases, we found 3 predominant architectural patterns: microacinar (n = 10), tubulopapillary (ductal; n = 4), and carcinoid-like (n = 2). Characteristic features of PALM included small acinar and/or cribriform growth, frequent lymphangitic permeation, lack of stromal response, uniform round nuclei with prominent nucleoli, intraluminal blue mucin, and prominent cell borders. By immunohistochemical staining, prostate-specific antigen and prostate-specific acid phosphatase were present in 13 of 14 and 13 of 13 cases, respectively. Metastatic prostatic duct adenocarcinoma exhibited morphologic features similar to metastatic colonic adenocarcinoma. Two cases had a carcinoid-like appearance with nested or solid architecture, parachromatin clearing, and prominent nucleoli, but lacked the finely stippled chromatin pattern of carcinoid tumors. Several features that may result in misinterpretation or lack of association of the neoplasm in the lung with a prostatic primary include lung metastasis preceding the detection of a prostatic primary tumor, solitary pulmonary nodule, tubulopapillary (ductal) or carcinoid-like pattern, scant material in which histologic features of metastatic prostate carcinoma are not fully appreciated, and frequent necrosis. Attention to specific discriminating histologic features, supported by immunohistochemical staining, may be useful in the differential diagnosis, which is therapeutically and prognostically critical.

Pulmonary metastasis from a primary prostatic adenocarcinoma without involvement of other metastatic sites is quite uncommon.[1-5] There are a relatively few reports in the literature on prostatic adenocarcinoma with lung metastases (PALM), and they lack detailed information on its histopathologic features. The various histopathologic patterns of PALM may simulate a pulmonary adenocarcinoma, neuroendocrine lung tumors, or other metastatic carcinomas. Given the potential overlap in microscopic appearance, we sought to review our experience with PALM through a detailed study of its morphologic patterns, the distribution of lesions, and the extent of overlap with primary pulmonary adenocarcinoma. Although other series of PALM have focused on the radiologic, clinical, or postmortem findings, there is no series of PALM from the surgical pathology perspective. Our aim was to identify specific histologic features of PALM that might be useful for reaching an accurate diagnosis, thus permitting the most appropriate therapy provided in a timely fashion.

Materials and Methods

We retrieved 16 cases of PALM from the surgical pathology files of 3 tertiary medical centers: Emory University Hospital (n = 7), Atlanta, GA: Barnes-Jewish Hospital (n = 4), St Louis, MO; and the University of Texas M.D. Anderson Cancer Center (n = 5), Houston. This search covered a period of 21 years (1977-1998). For each case, all available H&E-stained slides (range, 1 to 17; median, 3) from the pulmonary metastases were reviewed.

Available clinical information included age at time of diagnosis of the primary prostatic carcinoma and at diagnosis

of the pulmonary metastases, location (laterality and lobe) of pulmonary involvement, and the type of surgical intervention for the pulmonary metastases. Detailed information regarding serum prostate-specific antigen (PSA), Gleason score, and chest radiographic findings were not available in several cases. The pathologic data evaluated in each case included growth pattern (lymphangitic or parenchymal), the histologic pattern of PALM (microacinar, tubulopapillary [ductal], or carcinoid-like), focality, tumor necrosis, stromal response, nuclear pleomorphism, prominence of nucleoli, nuclear chromatin pattern, mitotic rate, cytoplasmic features, presence of glandular intraluminal blue mucin, tumor cell shape, and prominence of tumor cell borders. Immunohistochemical stains for PSA and/or prostate-specific acid phosphatase (PSAP) had been performed in 14 cases, and chromogranin and synaptophysin were used in 1 of 2 cases exhibiting a carcinoid-like pattern at the time of original diagnosis. Mitotic counts were obtained by identifying mitotic figures in 10 consecutive high-power fields using a Nikon Eclipse E400 microscope with a Nikon Plan 40×/0.65 objective lens and a 10× ocular lens (Nikon, Tokyo, Japan). The degree of nuclear pleomorphism was established based on a 4-tiered scale: absent, mild, moderate, or marked. Nuclear pleomorphism was considered absent if the size and shape of tumor nuclei were uniform, mild if the largest tumor cell nuclear diameter was twice that of the smallest, moderate if the largest was 3 times greater, or marked if there was a 4-fold or greater variation in nuclear size.

Results

In most cases (n = 15), the pulmonary metastases were identified after the primary prostatic tumor was identified. However, in 1 case, the prostatic primary tumor was diagnosed 2 years after a solitary pulmonary metastasis seen on computed tomography scan had been diagnosed as a poorly differentiated adenocarcinoma. The time interval between the diagnosis of the prostatic primary tumor and the lung metastases ranged from 0 to 14 years (median, 2 years). Age at diagnosis of pulmonary metastases ranged from 52 to 80 years (for 16/16 cases; median, 70 years) and at diagnosis of prostatic adenocarcinoma from 50 to 82 years (available for 10/16 cases; median, 69).

For the pulmonary lesions, the surgical procedures included lobectomy (n = 1), open lung biopsy (n = 6), transthoracic needle aspiration biopsy (n = 4), and transbronchial biopsy (n = 5). Information about laterality and lobe involvement by pulmonary metastases were available for 10 of 16 cases: right upper lobe (n = 2), right middle lobe (n = 1), right lower lobe (n = 3), left upper lobe (n = 2), and left lower lobe (n = 2). In the remaining patients, tumor was localized to the left lung, unspecified site (n = 3), or the location was not given (n = 3). No tumors were endobronchial.

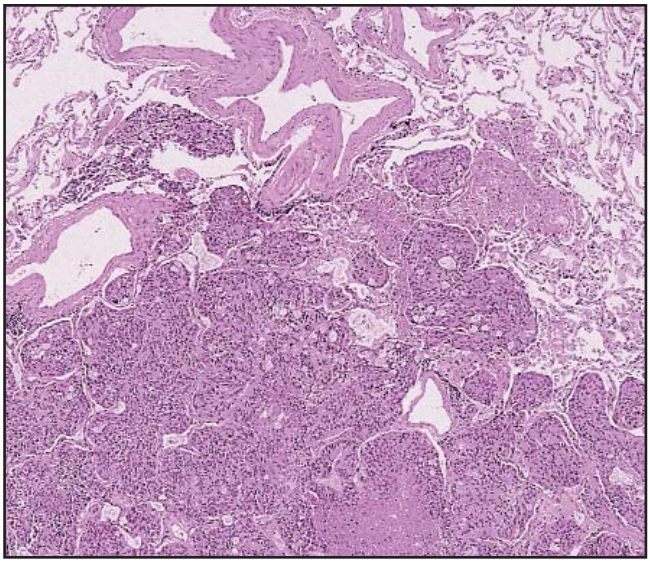

Image 1 Microacinar pattern of prostatic adenocarcinoma with lung metastases. At low magnification there is an interlobular and perivascular distribution of tumor (H&E, ×10).

In 11 cases, there was a solitary pulmonary metastasis that ranged from 0.1 to 2.5 cm. Five cases exhibited multiple metastatic lung nodules within the same lobe of lung. The multiple lesions were most commonly identified in the subpleural region and ranged from 0.1 to 4 cm in greatest dimension.

Pathologic Findings

Three histologic patterns of PALM were identified: microacinar with or without cribriform gland formation (n = 10) **Image 1**, **Image 2**, and **Image 3**; tubulopapillary (ductal) with cribriform glandular architecture and comedonecrosis (n = 4) **Image 4**, **Image 5**; and carcinoid-like (n = 2) **Image 6**, **Image 7**. Tumor cell necrosis was present in 14 cases. The predominant distribution in the lung was lymphangitic (n = 10) or parenchymal (n = 2). However, 4 of 16 cases could not be assigned a predominant distribution pattern because of the lack of orientation or paucity of material in the paraffin-embedded cell block from transthoracic fine-needle aspiration biopsies. Stromal desmoplasia was absent in all cases. Nuclear pleomorphism was absent (n = 6) or mild (n = 10); moderate or severe nuclear pleomorphism was not observed. The cytoplasm was eosinophilic (n = 12), amphophilic (n = 2), or clear (n = 2). Eosinophilic nucleoli were prominent in 11 cases. The nuclear chromatin pattern was coarse or hyperchromatic (n = 9) or vesicular (n = 7). The mitotic rate ranged from 0 to

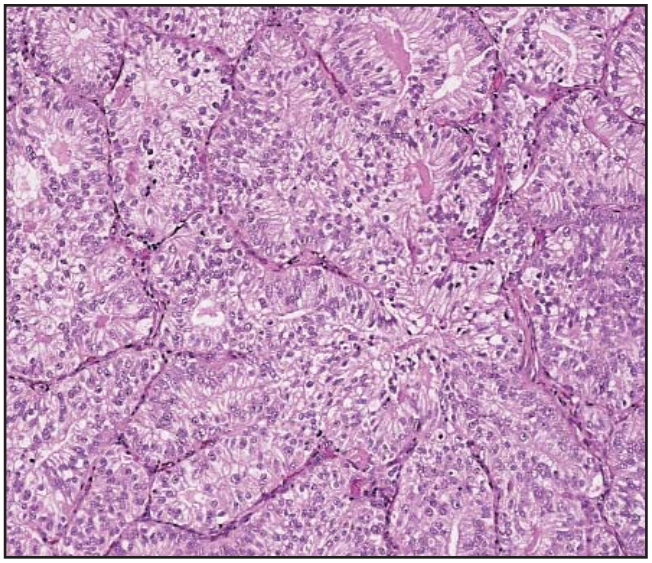

Image 2 Microacinar pattern of prostatic adenocarcinoma with lung metastases. There is a small acinar proliferation of tumor cells with minimal pleomorphism, eosinophilic cytoplasm, and conspicuous nucleoli (H&E, ×25).

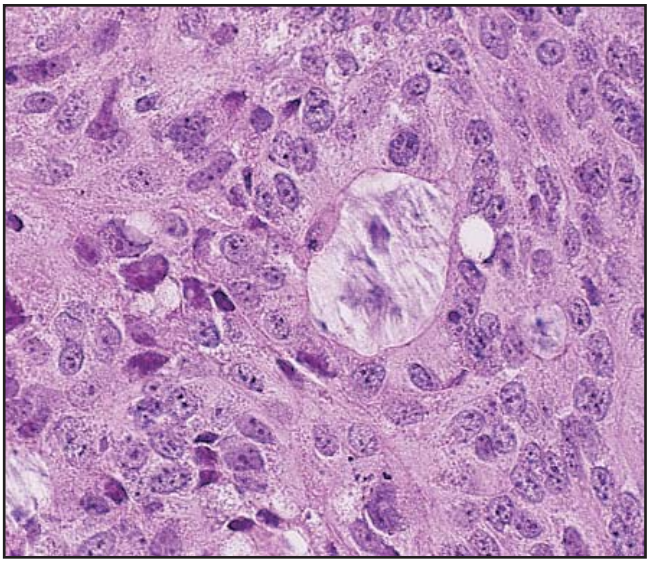

Image 3 Microacinar pattern of prostatic adenocarcinoma with lung metastases. Some of the tumor cells contain wispy intraluminal blue mucin (H&E, ×100).

58 (median, 9) per 10 consecutive high-power fields. Glandular intraluminal blue mucin was present in 3 cases (Image 3), but none of the tumors showed intracytoplasmic mucin. Tumor cell borders were distinct in 14 cases. The tumor cell shape was polygonal (n = 10), polygonal to columnar (n = 4), or predominantly cuboidal (n = 1) or columnar (n = 1).

Of 14 cases, 13 (93%) stained for PSA showed positive immunoreactivity in the tumor cells; all 13 cases that were stained for PSAP were positive. The case that showed negative immunoreactivity with PSA was positive for PSAP. Chromogranin and synaptophysin were negative in 1 of 2 cases with a carcinoid-like pattern.

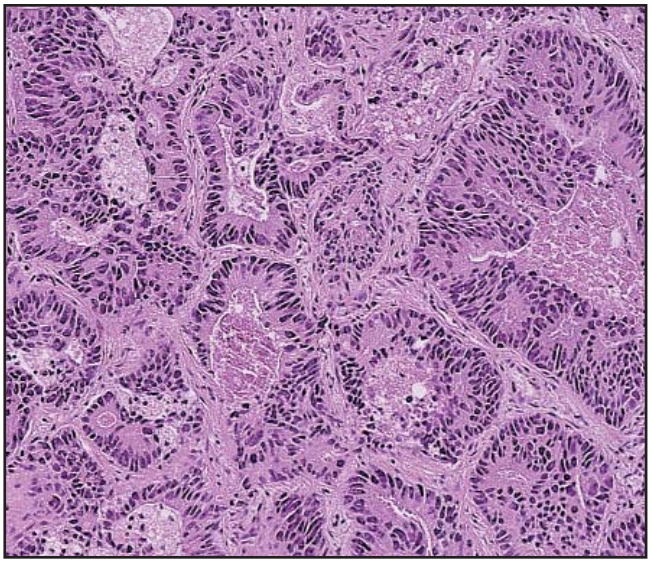

Image 4 Tubulopapillary (ductal) pattern of prostatic adenocarcinoma with lung metastases. The tubulopapillary structures are associated with prominent comedonecrosis, reminiscent of intestinal type adenocarcinoma (H&E, ×25).

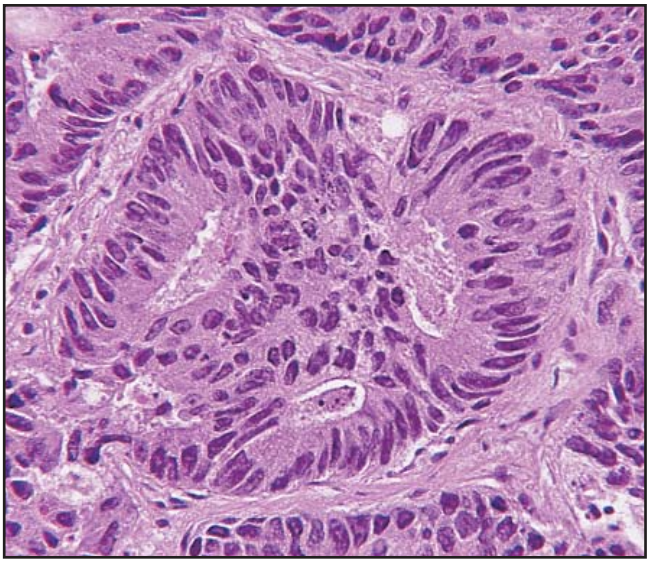

Image 5 Tubulopapillary (ductal) pattern of prostatic adenocarcinoma with lung metastases. At higher magnification, the cuboidal, stratified tumor cells have irregular nuclear chromatin and prominent nucleoli. These features are distinctly different from the microacinar pattern (Image 2) (H&E, ×63).

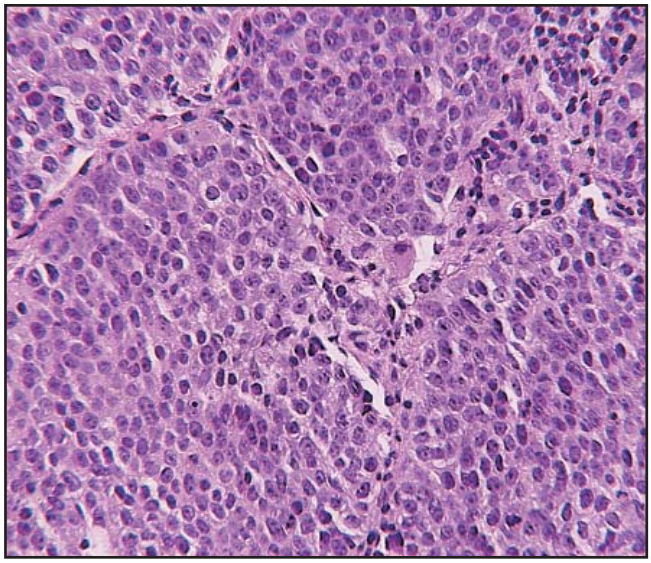

Image 6 Carcinoid-like pattern of prostatic adenocarcinoma with lung metastases. There is a prominent nested arrangement of tumor cells at low magnification (H&E, ×63).

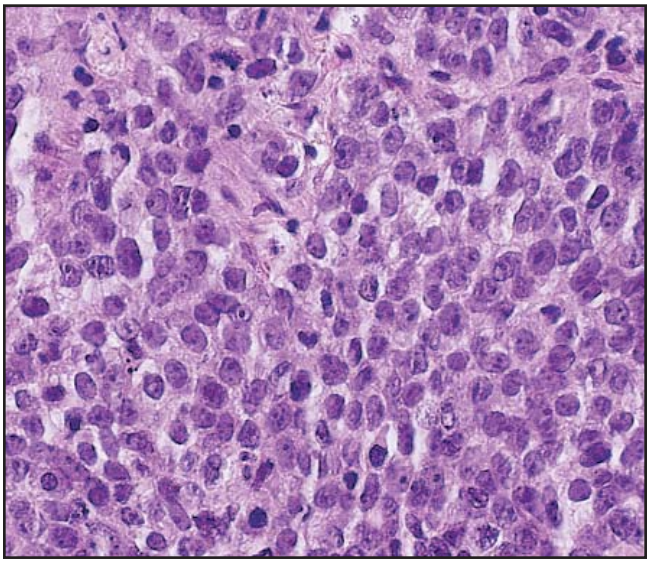

Image 7 Carcinoid-like pattern of prostatic adenocarcinoma with lung metastases. The finely stippled chromatin pattern of neuroendocrine lung tumors is lacking (H&E, ×100).

Discussion

Several clinicopathologic studies have addressed PALM, but the histologic features or the extent to which they mimic or differ from primary pulmonary neoplasms has not been described in detail. Clinical detection of PALM is infrequent because patients usually are asymptomatic, except in cases with pulmonary lymphangitic carcinomatosis.[6,7] In a retrospective review of chest radiographs from patients with stage D prostatic adenocarcinoma (advanced metastatic prostatic carcinoma involving bone, lymph nodes, or parenchymal organs), Apple et al[8] found radiographic abnormalities suspected to represent intrathoracic metastases in 24% of cases. Lindell et al[9] retrospectively reviewed the chest radiographs at initial diagnosis of 1,435 patients with prostatic carcinoma and identified 75 (5.2%) with mediastinal nodal and/or pulmonary parenchymal metastases. At diagnosis, 60 of these patients had a nodular pattern of PALM, 12 had mediastinal adenopathy and/or pulmonary nodules, and 3 had a lymphangitic pattern.[9] In an autopsy study of the metastatic patterns of prostate cancer by Bubendorf et al,[10] 556 (35.0%) of 1,589 patients showed hematogenous metastases, and the prevalence of lung metastases in these cases was 45.7%. In contrast with this high percentage seen at autopsy, the frequency with which the general surgical pathologist encounters PALM in biopsy or resection specimens is quite uncommon because the lesions are asymptomatic, the presence of metastases may be clinically obvious based on multifocality of pulmonary lesions and the rise in the serum PSA level, the patient might not be a candidate for surgical intervention, or metastases may not be detected on routine chest radiographs. Radiographic studies have shown the detection rate of PALM to be approximately 5%.[5,7,11]

We set out to define specific morphologic features of PALM to help facilitate a correct diagnosis and to alert pathologists to consider it in the differential diagnosis in appropriate cases. In most of our cases (n = 15), the pulmonary metastases were discovered after the diagnosis of a prostatic primary tumor, and in the majority (n = 11) the lesions were solitary, heightening clinical suspicion of a pulmonary primary neoplasm. One case of a solitary lung metastasis, which was diagnosed initially as a poorly differentiated adenocarcinoma on scant material from a transthoracic needle aspiration biopsy, was detected 2 years before the identification of the prostatic primary neoplasm. This patient did not receive additional surgery for the pulmonary lesion. However, a recent case report of solitary PALM without osseous or nodal metastases indicated that the patient underwent unnecessary lobectomy.[4] Other pitfalls that might lead to misinterpretation of PALM as a primary pulmonary neoplasm include the presence of only a limited amount of tumor in biopsy or fine-needle aspiration specimens, a tubulopapillary (ductal) or carcinoid-like histologic pattern that does not readily permit the association of the pulmonary tumor with prostatic carcinoma histologic features, and the frequent presence of necrosis in PALM, which is unusual in primary prostatic carcinomas.

The histologic findings that usually are encountered in pulmonary adenocarcinoma that are not seen in PALM include marked nuclear pleomorphism with irregular nuclear

contours, indistinct tumor cell borders, intracytoplasmic mucin, stromal desmoplastic reaction to tumor, and a lepidic pattern of growth.[12] Features of PALM that may aid in distinguishing it from pulmonary adenocarcinoma are lymphangitic distribution, absent to mild nuclear pleomorphism, abundant eosinophilic cytoplasm with conspicuous round nucleoli, and distinct cell borders. Wispy intraluminal basophilic mucin, without intracytoplasmic mucin, was present in a relatively small proportion of the cases, but this finding should alert the pathologist to the possibility of PALM because of its strong association with prostatic adenocarcinoma.[13]

The tubulopapillary (ductal) pattern corresponds to the histologic features that when present in a predominant or pure form are designated as prostatic duct adenocarcinoma and account for approximately 1% of prostatic adenocarcinomas.[14-16] In addition, this variant may be seen in conjunction with conventional or the usual type of prostatic adenocarcinoma in varying proportions in up to 40% of cases (prostatic adenocarcinoma with ductal features). In our series, the tubulopapillary (ductal) pattern was the second most frequent form of PALM. The overrepresentation of this pattern in PALM provides further support to the aggressive nature of this variant of prostatic adenocarcinoma.[17-20] Moreover, it could be easily confused with a metastatic colonic adenocarcinoma or a pulmonary adenocarcinoma because of its tubulopapillary and/or cribriform appearance and frequent comedonecrosis.[14] The cells are cuboidal to columnar and invariably stratified and contain irregular nuclear chromatin and prominent nucleoli.

On low-power examination, 2 of the cases had a striking carcinoid-like appearance; however, neither showed the finely stippled chromatin pattern characteristic of carcinoid tumors or other pulmonary neuroendocrine neoplasms.[12] This feature of carcinoid-like tumor appearance also has been noted, on occasion, in primary prostatic adenocarcinomas and may be focal or extensive.[21] Some authors have suggested that previously reported cases of "prostatic carcinoid tumors" most likely represent adenocarcinoma of the prostate with neuroendocrine features.[14,21,22] Anton et al[23] reported 3 cases of PALM mimicking carcinoid tumor in which an initial diagnosis of primary pulmonary or mediastinal carcinoid tumor had been made. The problem is further compounded if the cases are analyzed by immunohistochemical analysis, as up to 47% of conventional or the usual type prostatic adenocarcinomas show evidence of neuroendocrine differentiation.[24] Therefore, caution is warranted while interpreting immunohistochemical stains in this setting, as neuroendocrine markers (chromogranin or synaptophysin) alone will not exclude a prostatic adenocarcinoma.

Other entities in the differential diagnosis of PALM include malignant melanoma, non-Hodgkin lymphoma, acinic cell carcinoma, and adenoid cystic carcinoma. When the histologic features are equivocal, immunohistochemical staining for PSA or PSAP is of utmost importance and should be used along with a panel of other antibodies for the diagnosis of pulmonary adenocarcinoma, such as the presence of thyroid transcription factor-1 and cytokeratin 7 and absence of cytokeratin 20.[25,26]

We have detailed the major histologic features of PALM and emphasized its varied appearances. Distinction from pulmonary adenocarcinoma, neuroendocrine lung tumors, and other tumors can be achieved by careful observation of morphologic detail and with clinical correlation. In selected cases, the use of immunohistochemical stains, including PSA and/or PSAP, along with other markers may help make this distinction. Proper recognition of PALM may prevent unnecessary surgery and may prompt the use of other therapeutic modalities, including hormonal therapy or chemotherapy.

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References

1. Bromberg WD, Gaylis FD, Bauer KD, et al. Isolated pulmonary metastases from carcinoma of the prostate: a case report and deoxyribonucleic acid analysis using flow cytometry. *J Urol.* 1989;141:137-139.
2. Eastham JA, Esensten ML, Wilson TG. Isolated pulmonary metastases from prostatic adenocarcinoma. *West J Med.* 1993;159:489-490.
3. Falkowski WS, O'Connor VJ. Long-term survival of prostatic carcinoma with lung metastases. *J Urol.* 1981;125:260-262.
4. Hofland CA, Bagg MD. An isolated pulmonary metastasis in prostate cancer. *Mil Med.* 2000;165:973-974.
5. Petras AF, Wollett FC. Metastatic prostatic pulmonary nodules with normal bone image. *J Nucl Med.* 1983;24:1026-1027.
6. Lome LG, John T. Pulmonary manifestations of prostatic carcinoma. *J Urol.* 1973;109:680-685.
7. Rockey KE, Graham TE. Prostate adenocarcinoma metastatic to the lung. *Postgrad Med.* 1990;87:199-208.
8. Apple JS, Paulson DF, Baber C, et al. Advanced prostatic carcinoma: pulmonary manifestations. *Radiology.* 1985;154:601-604.
9. Lindell MM, Doubleday LC, von Eschenbach AC, et al. Mediastinal metastases from prostatic carcinoma. *J Urol.* 1982;128:331-334.

10. Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1589 patients. *Hum Pathol.* 2000;31:578-583.
11. Arora VK, Bedi RS. Metastatic prostatic adenocarcinoma. *Indian J Chest Dis Allied Sci.* 1986;28:95-98.
12. Colby TV, Travis WD, Koss MN. *Tumors of the Lower Respiratory Tract.* Washington, DC: American Registry of Pathology; 1995. *Atlas of Tumor Pathology,* Third Series, Fascicle 13.
13. Ro JY, Grignon DJ, Troncoso P, et al. Mucin in prostatic adenocarcinoma. *Semin Diagn Pathol.* 1988;5:273-283.
14. Young RH, Srigley JR, Amin MB, et al. *Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra, and Penis.* Washington, DC: American Registry of Pathology; 2001. *Atlas of Tumor Pathology,* Third Series, Fascicle 28.
15. Dube VE, Farrow GM, Greene LF. Prostatic adenocarcinoma of ductal origin. *Cancer.* 1973;32:402-409.
16. Randolph TL, Amin MB, Ro JY, et al. Histologic variants of adenocarcinoma and other carcinomas of prostate: pathologic criteria and clinical significance. *Mod Pathol.* 1997;10:612-629.
17. Bostwick DG, Kindrachuk RW, Rouse RV. Prostatic adenocarcinoma with endometrioid features: clinical, pathologic, and ultrastructural findings. *Am J Surg Pathol.* 1985;9:595-609.
18. Christensen WN, Steinberg G, Walsh PC, et al. Prostatic duct adenocarcinoma: findings at radical prostatectomy. *Cancer.* 1991;67:2118-2124.
19. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features: a light microscopic and immunohistochemical study of ten cases. *Cancer.* 1986;57:111-119.
20. Ro JY, Ayala AG, Wishnow K, et al. Prostatic duct adenocarcinoma with endometrioid features: immunohistochemical and electron microscopic study. *Semin Diagn Pathol.* 1988;5:301-311.
21. Epstein JI. *Prostate Biopsy Interpretation.* Philadelphia, PA: Lippincott-Raven; 1995.
22. Ordonez NG, Ro JY, Ayala AG. Metastatic prostatic carcinoma presenting as an oncocytic tumor. *Am J Surg Pathol.* 1992;16:1007-1012.
23. Anton RC, Schwartz MR, Kessler ML, et al. Metastatic carcinoma of the prostate mimicking primary carcinoid tumor of the lung and mediastinum. *Pathol Res Pract.* 1998;194:753-758.
24. di Sant'Agnese PA. Neuroendocrine differentiation in human prostatic carcinoma. *Hum Pathol.* 1992;23:287-296.
25. Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. *Mod Pathol.* 2000;13:962-972.
26. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol.* 2000;7:123-127.

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