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CASE REPORT PEER REVIEWED | OPEN ACCESS

A case of occult cancer of prostatic ductal adenocarcinoma in which urinary cytology and immunostaining led to identification of primary site

Yuki Kubo, Tomohiro Kanamaru, Yoshio Ichihashi, Naoko Nambu, Nobuyuki Terada, Shin-ichi Nakatsuka

ABSTRACT

Introduction: The diagnosis of prostatic occult cancer is often difficult. In particular, diagnosing ductal adenocarcinoma using pathological specimens sampled from metastatic sites is challenging because it has pathological features different from those of acinar adenocarcinoma, which is the most common histological subtype of prostate cancer. Here, we report a case of occult prostatic ductal adenocarcinoma in the lungs in which urine cytology first suggested primary prostate cancer.

Case Report: A man in his early 70s underwent lobectomy for a left-sided lung tumor. The initial pathological diagnosis was an enteric-type primary pulmonary adenocarcinoma (CDX2-positive and TTF-1-negative). The pathological diagnosis of recurrent lung tumors was the same as that of the initial diagnosis. During follow-up, urine cytology revealed prostatic adenocarcinoma, followed by a histological diagnosis of prostatic ductal adenocarcinoma by needle biopsy. Additional immunohistochemistry revealed that both the prostatic tumors and antecedent lung tumors demonstrated identical phenotypes (NKX3.1-positive, CDX2-positive, and TTF-1-negative); therefore, a final diagnosis of primary prostatic duct adenocarcinoma and pulmonary metastases was established.

Conclusion: Ductal adenocarcinoma of the prostate should be included in the differential diagnosis of tubulopapillary adenocarcinoma of unknown primary origin in elderly men, and the appropriate use of cytology and immunostaining can lead to a correct diagnosis.

Keywords: Ductal adenocarcinoma, Occult cancer, Prostatic cancer

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INTRODUCTION

Prostate cancer typically progresses slowly. Metastases are occasionally detected as bone fractures and back pain before the primary tumor grows, invades locally, and causes urological symptoms (occult cancer). In occult prostatic cancer, the primary site is identified by pathological examination of the biopsied or resected tissue of the metastatic tumor based on histological architecture

suggestive of prostatic acini and immunophenotypes for prostatic origin, such as prostate-specific antigen (PSA) and NKX3.1. However, because ductal adenocarcinoma, which is a minor subtype of prostatic cancer, shows a different histo/cytomorphology and immunophenotype from acinar adenocarcinoma, the correct diagnosis of metastasis from ductal adenocarcinoma may not be easy. Here, we report a case of occult prostatic ductal adenocarcinoma misdiagnosed as primary lung cancer, in which urine cytology first suggested primary prostate cancer and immunostaining confirmed the final pathological diagnosis.

CASE REPORT

A man in his early 70s was referred to our hospital after an abnormal shadow was observed in the left lung on radiography at his primary medical checkup. He smoked 20 cigarettes per day for 50 years. The patient underwent lobectomy for a solitary tumor in the upper lobe of the left lung and was histologically diagnosed with primary adenocarcinoma of the lungs. Recurrence was found in the lower lobe of the left lung three years after the initial diagnosis, and a second recurrence was found in the lower lobe of the right lung the following year, both of which were diagnosed as recurrences of lung adenocarcinoma after partial resection of each tumor. Six years after the first surgery, the patient complained of hematuria during follow-up and urine cytology revealed atypical cells suggestive of prostate cancer. Magnetic resonance imaging revealed a nodule in the right lobe of the prostate, and serum PSA level was mildly elevated (6.224 ng/mL). A subsequent prostate biopsy confirmed ductal adenocarcinoma of the prostate. A pathological review using immunohistochemistry revealed that the previously diagnosed lung tumors were metastases of prostatic ductal adenocarcinoma. Hormonal therapy was initiated, PSA levels decreased, and the prostate tumor shrunk markedly five months after diagnosis.

Pathological findings

The initial lung tumor in the left upper lobe was a grayish–white mass with a diameter of 18 mm (Figure 1A). Histologically, atypical cuboidal-to-columnar cells had proliferated in an acinar and glandular arrangement, suggesting an adenocarcinoma (Figure 1B). The first and second recurrences in the left and right lower lobes, respectively, showed an adenocarcinoma with a histological appearance similar to that of the initial tumor. Both primary and recurrent tumors showed a histological intestinal phenotype: tumors consisted predominantly of glandular proliferation of tall columnar tumor cells rich in mucin, and were CDX2(+), TTF-1(−), cytokeratin 7(−), and cytokeratin 20(focal+), as determined by immunohistochemistry. This histology was different from that of prostatic acinar adenocarcinoma, which accounts for more than 90% of prostate cancers. Therefore, we could not assume that the lung tumors were prostate cancer metastases. Based on the histomorphology and immunophenotype, we considered enteric-type primary pulmonary adenocarcinoma and gastrointestinal primary (especially lower gastrointestinal primary) as differential diagnoses and ruled out the latter because no abnormalities were found in the gastrointestinal tract on endoscopy and computed tomography.

Urine cytology revealed small clusters of atypical cells with eccentric round nuclei, small distinct nucleoli, and foamy cytoplasm (Figure 2A). Immunocytochemistry revealed the presence of NKX3.1 (Figure 2B). These findings suggested a diagnosis of prostatic adenocarcinoma.

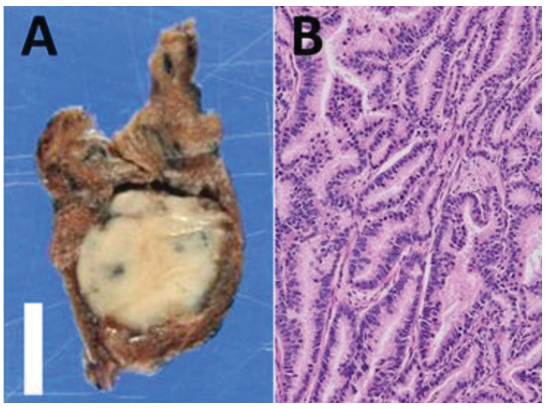

Figure 1: The initial lung tumor of the left upper lobe. (A) A grayish–white mass is identified. White bar 1 cm. (B) Hematoxylin and eosin (H&E) stain, original magnification ×200. Cuboidal to columnar atypical cells proliferate in acinar to glandular arrangements.

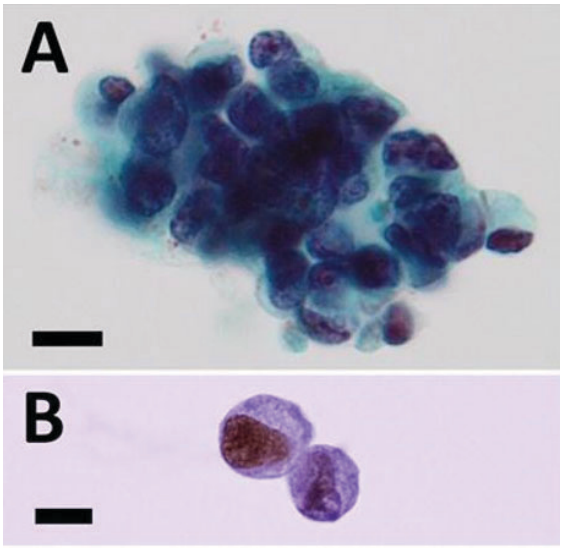

Figure 2: Urine cytology. Black bar 10 μm. (A) Papanicolaou stain. Clustered atypical cells are seen, with a high nucleo-cytoplasmic ratio, increased amounts of fine granular chromatin, eccentric oval nuclei, small distinct nucleoli, and foamy cytoplasm. (B) Immunocytochemistry of NKX3.1. The nuclei of the tumor cells are positive for NKX3.1.

Prostatic biopsy, performed for a definitive diagnosis, revealed that columnar atypical cells formed fused glands, and ductal adenocarcinoma was diagnosed (Gleason score 4 + 4 = 8/GG4) (Figure 3A). The histological findings of the prostatic tumor were similar to those of the previously identified lung tumors (Figure 4A). Additional immunohistochemistry revealed that both prostatic and lung tumors were positive for NKX3.1 and CDX2, and negative for TTF-1 (Figures 3B–D and 4B–D). Therefore, we concluded that ductal adenocarcinoma of the prostate was the primary tumor and that the lung tumors had metastasized to prostatic cancer.

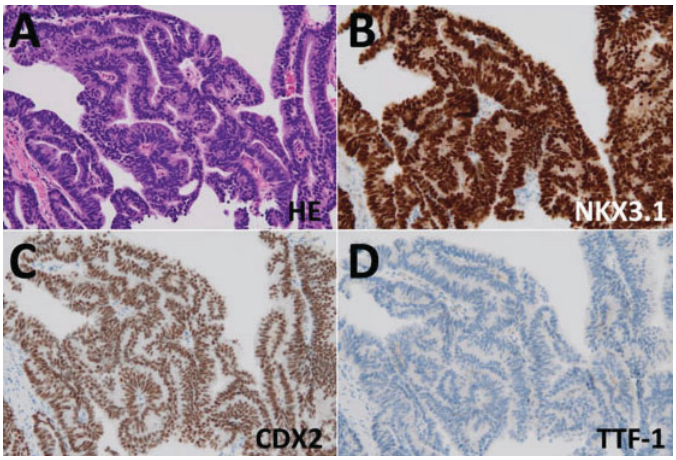

Figure 3: Prostatic biopsy. (A) H&E stain, ×200. Columnar atypical cells proliferate by forming fused glands, suggestive of ductal adenocarcinoma. Immunohistochemistry of NKX3.1 (B), CDX2 (C), and TTF-1 (D), all ×200. Tumor cells are positive for NKX3.1 and CDX2, and negative for TTF-1, which are compatible with the immunophenotype of primary prostatic ductal adenocarcinoma.

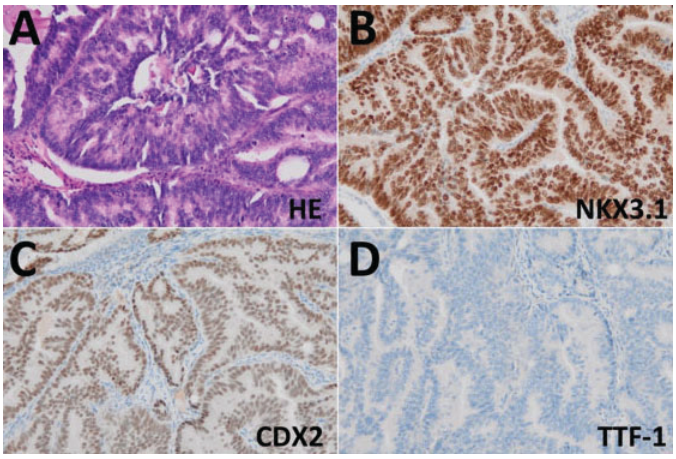

Figure 4: The lung tumor of the right lower lobe. (A) H&E stain, ×200. The histology of the lung tumor is similar to that of the prostatic adenocarcinoma. Immunohistochemistry of NKX3.1 (B), CDX2 (C), and TTF-1 (D), ×200. Tumor cells are positive for NKX3.1 and CDX2 and negative for TTF-1. These results coincide with the results of immunohistochemistry of the prostatic tumor, suggesting that both tumors are derived from the prostate.

DISCUSSION

The diagnosis of prostatic occult cancer is often difficult. The most common metastatic sites of clinically observed prostate cancer are the bones and lymph nodes. Although the lungs are the second most common site of metastasis of prostate cancer, and pulmonary metastasis of prostate cancer is detected in 46% of autopsy cases [1], clinical diagnosis of pulmonary metastasis before the detection of primary tumor metastasis to other organs is very rare (2%) [2]. The reasons for diagnostic difficulties include the fact that patients with metastatic prostate cancer do not always show elevated serum PSA levels and the absence of urological symptoms. Our patient showed neither urological symptoms nor abnormal urinalysis findings when the lung tumor was first noted, which may have delayed the correct diagnosis.

The histology of prostate cancer with ductal adenocarcinoma rather than acinar adenocarcinoma may have been a major factor in the difficulty in identifying the primary prostate in our case. Prostatic ductal adenocarcinoma is characterized by tubulopapillary proliferation of tall columnar cells with atypically elongated nuclei and occasional comedonecrosis. Seipel et al. stated that the pathological diagnosis of metastatic ductal adenocarcinoma of the prostate is often challenging because its histology differs from that of common acinar adenocarcinomas and often resembles non-prostatic adenocarcinomas, such as those of colon, stomach, pancreas, lung, and urinary bladder [3]. A case has been reported in which distinguishing pulmonary metastasis of prostatic ductal adenocarcinoma from that of colon cancer was challenging [4]. Ductal adenocarcinoma shows metastasis at diagnosis more frequently than acinar adenocarcinoma, and visceral metastases, such as those in the brain and lungs, occur more frequently in ductal adenocarcinoma than in acinar adenocarcinoma [5]. Therefore, ductal adenocarcinoma of the primary prostate should be included in the differential diagnosis of tubulopapillary adenocarcinoma of unknown primary origin in older men.

In general, exfoliated tumor cells in prostate cancer do not appear in the urine until the high clinical stage because prostate cancer usually arises from the peripheral zone of the prostate; therefore, screening for prostate cancer by urine cytology has not been established [6]. In rare cases, cancer cells detected by urine cytology provide the basis for the initial diagnosis of prostate cancer, as in our case [6]. In contrast to acinar adenocarcinoma, ductal adenocarcinoma preferentially shows an exophytic growth pattern involving the periurethral ducts, which allows tumor cells to be shed into the urine at an earlier stage [6]. A report by Lin et al., which described 28 cases of prostate cancer cells detected by urine cytology, stated that urine cytology was the first evidence of disease in 80% (4 of 5) of patients with ductal adenocarcinoma, whereas only 26% (6 of 23) had acinar adenocarcinoma [6]. In their report, ductal adenocarcinoma tumor cells

showed a papillary cluster and palisaded arrangement, columnar shape, and high nucleocytoplasmic ratio [6]. They had hyperchromatic nuclei with fine granular chromatin and often had prominent nucleoli [6]. These cytological characteristics do not always coincide with the tumor cell findings in our case, and we could not identify it as ductal adenocarcinoma, although we speculated that it was primary prostate cancer. High-grade urothelial carcinoma must be differentiated from ductal adenocarcinoma of the prostate, and immunostaining is often essential for the differential diagnosis.

Immunostaining is useful for identifying the primary tumor site, both histologically and cytologically. In our case, the demonstration of NKX3.1 by immunohistochemistry was the basis for the conclusion that the lung tumor was a metastasis of prostatic cancer. NKX3.1, a good marker of prostate cancer, is predominantly localized in the prostate epithelium [7]. Gurel et al. examined the sensitivity and specificity of immunohistochemistry for NKX3.1 and reported a sensitivity of 98.6% and a specificity of 99.7% [7]. In addition, NKX3.1, which is expressed in the nucleus, can be easily evaluated using cytological specimens. In addition to NKX3.1, PSA, PSAP, and prostein (P501s) were demonstrated to be useful and were detected in 100%, 100%, and 96.6% of ductal adenocarcinomas, respectively [3]. They also found that all patients with colon cancer tested negative for these markers [8].

However, the expression of CDX2 in our case led us to speculate gastrointestinal primary or primary lung adenocarcinoma of the enteric type. CDX2 is expressed specifically in normal and neoplastic intestinal epithelium; however, the expression of CDX2 in urinary bladder cancer, ovarian cancer, lung cancer, and neuroendocrine carcinoma has been reported [9]. Herawi et al. and Seipel et al. reported the expression of CDX2 in 5.7% (4 of 70) and 13% (14 of 104) of prostate cancer cases, respectively [3, 9]. CDX2 expression was described in 15% (9 of 60 cases) of prostatic ductal adenocarcinomas in Seipel's study [3]. Therefore, the specificity of CDX2 immunostaining as a gastrointestinal marker is limited, and the results of CDX2 immunostaining should be interpreted with caution when used for the differential diagnosis of gastrointestinal neoplasms.

CONCLUSION

Identifying the primary site may be difficult when prostatic ductal adenocarcinoma is detected as occult cancer at a metastatic site. Urine cytology may provide clues for the identification of primary prostate cancer. Immunostaining for prostatic markers, such as NKX3.1, is essential for identifying the primary site. CDX2 expression in prostatic ductal adenocarcinoma can lead to a false diagnosis at the primary site, especially when evaluated at the metastatic site.

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Author Contributions

Yuki Kubo – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Tomohiro Kanamaru – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically

for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yoshio Ichihashi – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Naoko Nambu – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nobuyuki Terada – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shin-ichi Nakatsuka – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.