

**Case Report**

# Metastatic Prostate Adenocarcinoma in Primary Lung Adenocarcinoma: An Unusual Case Report and Literature Review

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**Tumor-to-tumor metastasis (TTM) is a rare condition in which one tumor metastasizes into another tumor. Based on the literature, the most common donor of TTM is lung and the most common recipient is kidney. Here we reported a rare case that has the metastatic prostate adenocarcinoma in primary lung adenocarcinoma. According to our knowledge, it is the first report in the English literature in the last 20 years. The patient is a 74-year-old male with the history of prostate cancer, which was treated by external beam radiation and androgen deprivation therapy. Nine years after treatment, he was found to have multiple metastatic bone lesions and androgen deprivation therapy was given again. Eleven years after initial diagnosis, the patient present with short of breath and CT showed a right upper lobe nodule and an enlarged right hilar lymph node. Both the lung nodule and the hilar lymph node were biopsied. The hilar lymph node was positive for metastatic prostate adenocarcinoma. Interestingly, the lung nodule showed two different histological components intermixed with each other. The majority of tumor cells formed glandular structure and were immunostained positive for CK7, TTP-1 and Napsin A, compatible with primary lung adenocarcinoma. Some individual and small cluster of cells were negative for the above markers, but highlighted by PSA, PSAP and racemase (AMACR/P504S) immunostain, which were consistent with metastatic prostate adenocarcinoma. The patient was scheduled to be treated with stereotactic body radiation therapy (SBRT), but he declined. His current condition is stable at the most recent follow-up.**

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**Key Words:** tumor-to-tumor metastasis, lung adenocarcinoma, prostate adenocarcinoma

## INTRODUCTION

Tumor-to-tumor metastasis (TTM) is an uncommon manifestation which is defined by the coexistence of two histologically distinct neoplasms at the same location. The exact incidence of this phenomenon remains unknown due to the rarity. The first case was reported by Dr. Fried in 1930 in which the metastasis of a bronchiogenic carcinoma in a meningioma was described.<sup>1</sup> Based on the available case reports and serial studies, the most frequent donor in TTM is lung cancer, followed by breast cancer.<sup>2-4</sup> The recipient or host tumor of TTM can be a malignant neoplasm or a benign tumor.<sup>5</sup> Renal cell carcinoma (RCC) is the most frequent recipient in malignancy<sup>6</sup> and meningioma is the most common intracranial neoplasm to harbor metastasis.<sup>7,8</sup>

Primary lung cancer as recipient tumor of TTM is extremely rare. We reviewed the past twenty years of publications and found total eight cases have been reported. Five cases are lung carcinoma harboring metastasis of papillary thyroid carcinoma.<sup>9-13</sup> one case is the metastasis of colon cancer to

the primary lung cancer.<sup>14</sup> one case is a tumor consisting of non-small cell lung cancer and metastatic adenoid cystic carcinoma of maxillary sinus.<sup>15</sup> the last case is a primary lung adenocarcinoma containing the metastatic endometrioid adenocarcinoma.<sup>16</sup> To our knowledge, we report the first case of a metastasis of prostate adenocarcinoma into a primary lung adenocarcinoma.

## CASE REPORT

The patient is a 74-year-old Caucasian male with remote history of prostate adenocarcinoma diagnosed 11 years ago, with a Gleason score 4 + 4 = 8. He was treated with external beam radiation and androgen deprivation therapy, Casodex followed by Zoladex, for two years. The patient had poor clinic follow-up after treatment. Nine years after the initial diagnosis, the patient had severe obstructive lower urinary symptoms and he received transurethral resection of the prostate (TURP). Specimen from TURP showed residual prostatic adenocarcinoma with Gleason score 5 + 4 = 9, involving 90% of submitted tissue. Periprostatic fat invasion and extensive perineural invasion were also identified. At the same time, bone scan showed multiple metastatic lesions. No bone biopsy was obtained. It was recommended that he

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underwent 12-18 month of androgen deprivation therapy by Zoladex injection. However, after two injections, the patient elected to discontinue therapy due to the side effects. He was started on daily Casodex as an alternative. Eleven years after the initial diagnosis of prostate cancer, the patient presented with shortness of breath. Chest CT showed a 1.7 cm spiculated lesion in the right upper lobe of lung and mild mediastinal lymphadenopathy, suspicious for primary lung neoplasm. The patient had a biopsy of lung mass and fine

needle aspiration (FNA) of right hilar lymph node. Cytology of FNA showed clusters and singly dispersed malignant epithelial cells with thin cytoplasm, round to oval nuclei and prominent nucleoli. These cells were stained positive for prostate specific antigen (PSA) and prostate specific acid phosphatase (PSAP). Morphology and immunohistochemical staining (IHC) were consistent with metastasis of prostatic adenocarcinoma.

**Table 1.** Cases of lung cancer as the recipient of TTM.

Case	Age/sex	Donor tumor	Recipient tumor	History	Symptoms	Imaging studies
(1). <sup>13</sup>	82/M	PTC	Squamous cell carcinoma	PTC, S/P thyroidectomy 6 years ago	Postoperative follow-up	Abnormal lung shadow on CXR
(2). <sup>9</sup>	64/F	PTC	Moderately differentiated adenocarcinoma	Simultaneously	Hoarseness of voice	RUL lung mass and hypermetabolic focus of thyroid
(3). <sup>10</sup>	44/F	PTC (pT4N1)	Adenocarcinoma in situ	PTC, S/P thyroidectomy 8 years ago	Postoperative follow-up	Nodules of bilateral lower lobe
(4). <sup>11</sup>	65/M	PTC (pT3N1b)	Adenocarcinoma	PTC, S/P thyroidectomy 7 months ago	Postoperative follow-up	LUL lung mass
(5). <sup>12</sup>	56/M	PTC	Adenocarcinoma	Simultaneously	Cough and sputum for three months	LUL lung mass and increased uptake of left thyroid
(6). <sup>14</sup>	70/M	Colonic adenocarcinoma	Non-small cell carcinoma	Colonic adenocarcinoma 20 years ago, non-small cell lung carcinoma 10 years ago	Postoperative follow-up	Right apical lung nodule
(7). <sup>16</sup>	72/F	Endometrioid adenocarcinoma (grade 1)	Adenocarcinoma	Follicular lymphoma 6 years ago	Clinical follow-up	Thick endometrium and right lung mass
(8). <sup>15</sup>	56/M	Adenoid cystic carcinoma	Poorly differentiated adenocarcinoma	Adenoid cystic carcinoma of right maxillary sinus 11 years ago	Postoperative follow-up	RML nodule

Note: PTC: papillary thyroid carcinoma; S/P: status post; CXR: chest X ray; RUL: right upper lobe, LUL: left upper lobe, RML: right middle lobe

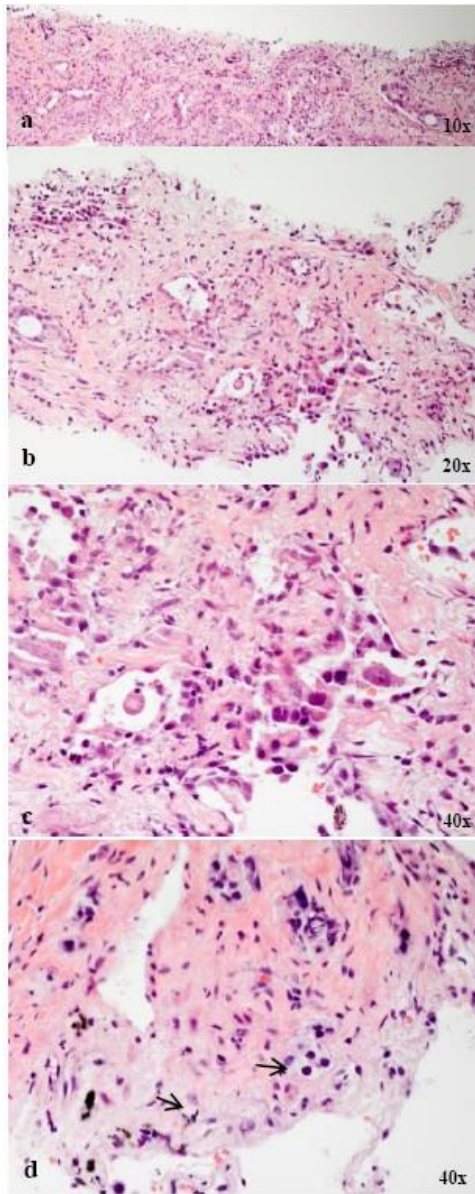
The core biopsy of lung mass showed the evidence of malignancy. Majority of infiltrative tumor cells formed glandular structure with focal cribriform pattern (**Figure 1a-1b**). These cells had increased nuclear/cytoplasm ratio and hyperchromatic nuclei. Mitotic figures were evident (**Figure 1c**). CK7, TTF-1 and Napsin A immunostaining were positive, which is compatible the lung primary adenocarcinoma (**Figure 2**). Interestingly, a portion of biopsy was negative for all the above markers (**Figure 2a-c**). Small cluster or individual tumor cells that did not form glands were noted in this area. They had round nuclei with prominent nucleoli and pale cytoplasm (**Figure 1d**). These cells were highlighted by PSA, PASP and racemase (AMACR/P504S) immunostaining, which is consistent with adenocarcinoma of prostatic origin (**Figure 3**). Therefore, the final diagnosis of right upper lung mass biopsy is metastatic prostatic adenocarcinoma mixed with invasive moderately differentiated primary lung adenocarcinoma. The patient was scheduled for stereotactic body radiation therapy (SBRT), but he declined due to the concern of side effects. His condition is stable according to the most recent follow-up.

## DISCUSSION

Although the first case was described more than 80 years ago, TTM remains as a rare phenomenon. The diagnostic criteria of TTM proposed by Campbell, et al. in 1968 was widely cited in the literature.<sup>17</sup> It requires: 1) more than one histologically distinct neoplasm; 2) benign or malignant

neoplasm as recipient; 3) true metastatic growth pattern of donor neoplasm excluding tumor embolism or contiguous growth; 4) exception of metastatic neoplasm into the lymphatic system that are already involved by hematopoietic malignancy. However, when patients do not have known history of malignancy and the donor tumor resembles primary neoplasm, the diagnosis of TTM may pose a challenge to pathologists, especially when limited sample is provided. IHC staining and imaging studies are helpful tools to seek out the origin of metastatic tumor. In our case, although metastatic component presents as single or small clusters of cells with relatively bland morphology, the IHC panel (positive for PSA, PSAP and racemase; negative for CK7, TTF-1 and Napsin A) clearly indicates the prostatic origin.

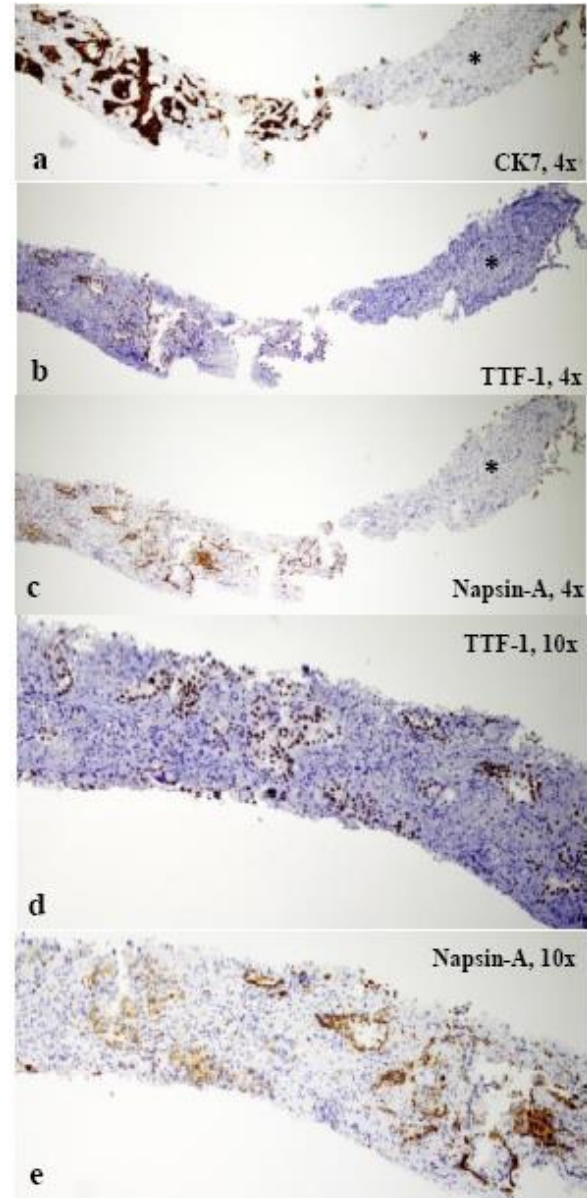
Although TTM is mostly found in advanced stage of cancer, identification of TTM may still affect the clinical staging and subsequent treatment. Therapy regimes may vary from case to case and depend on patient's age, other concomitant medical diseases, and histopathological features of malignancy. When the host tumor is a benign neoplasm, for example, meningioma, surgical resection is the primary treatment. It is still controversial whether adjuvant therapy will improve prognosis or not. For older patients with malignant host tumor, like our patient, usually chemotherapy or radiation is recommended. Surgical intervention can be considered if the patient's health condition allows.



**Figure 1.** Microscopic features of the right upper lobe of lung biopsy. Majority of the tumor cells form glands and grow in an infiltrative pattern (a, b). The glandular structures are lined by tumor cells that have increased nuclear/cytoplasm ratio, hyperchromatic nuclei and frequent mitotic figures (c). Individual tumor cells with rounded nuclei, prominent nucleoli and pale cytoplasm (arrow in d) are present.

RCC, especially clear cell RCC, is the most common malignant recipient and meningioma is the most frequent intracranial host tumor.<sup>6-8</sup> Lung and breast followed by thyroid cancer are the most common donor.<sup>2-4</sup> The mechanism underneath is poorly understood. The proposed theory is related to certain characteristics of recipient tumor including hypervascularity, high lipid and collagen content and slow growth rate, which provides a favorable environment for metastatic lesions.<sup>18,19</sup>

Lung carcinoma as a donor of TTM is extremely rare and only eight cases have been previously reported. We summarized the findings of these eight cases as shown in

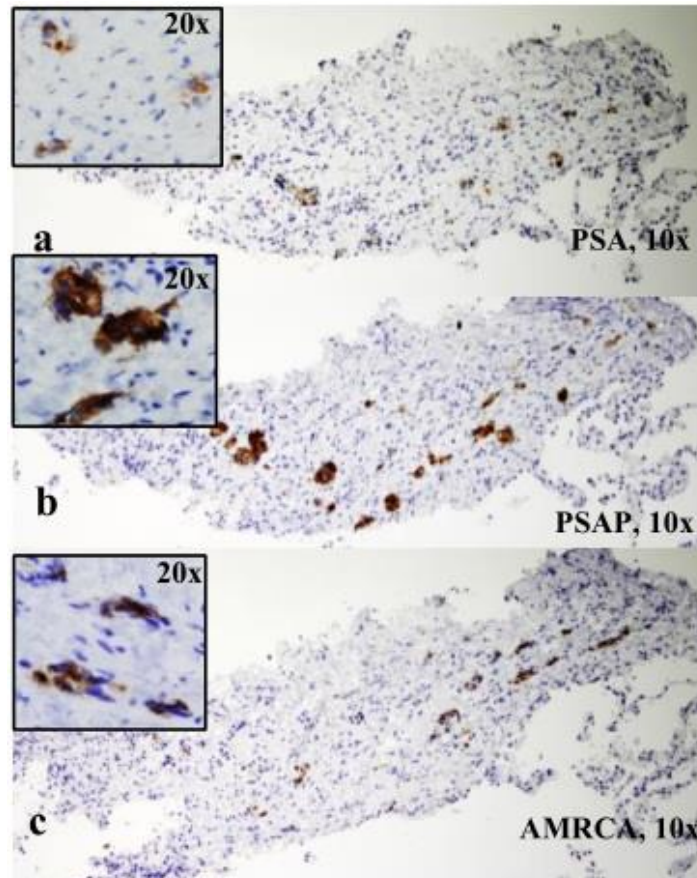


**Figure 2.** IHC staining of biopsy. The glandular tumor cells are stained positive for CK7, TTF-1 and Napsin A (a to e). A small portion of the biopsy is stained negative for all the above markers [\* in (a) to (c)].

**Table 1.** Most patients were asymptomatic and lung nodule/mass was identified during routine clinical follow-up. Five patients had known primary cancer history and the time between primary disease to clinically identified metastasis ranges from 7 months to 20 years. In three cases (case 2, 5 and 7), two distinct primary carcinomas were diagnosed at the same time. Majority of the recipient lung cancer (6 of 8) were lung adenocarcinoma and the rest two cases were squamous cell carcinoma (case 1) and non-small cell carcinoma (case 6). Interestingly, five out of eight cases were metastatic papillary thyroid carcinoma (PTC) to lung carcinoma (case 1-5). PTC has indolent behavior and mostly involves the regional lymph nodes. Distant metastasis is seen

in minority of PTC cases and the most common metastatic site is lung, followed by bone.<sup>20</sup> Lung is also a frequent site for distant metastasis of colonic and endometrioid adenocarcinoma. The reason why more cases of PTC-to-lung cancer metastasis have been reported is unclear. One of the reasons could be the mean age of PTC patients is relatively younger than patients with colon or endometrial cancer.

Therefore, more stage IV PTC patients undergo tumor resection (wedge resection or lobectomy) after the lung mass is identified. On the other hand, the older patients with advanced stage of colon or endometrial carcinoma mostly receive adjuvant therapy instead surgical intervention. Adequate sampling of the tumor mass helps to identify the foci of TTM.



**Figure 3.** Individual cells that are negative for CK7, TTF-1 and Napsin A are stained positive for PSA, PSAP and AMACR. Inserts show positively stained cells with higher magnification.

Based on our knowledge, the metastasis of prostatic adenocarcinoma to lung carcinoma has not been reported yet. Prostatic adenocarcinoma most often extends to regional lymph nodes or metastasizes to bone before the lung is involved.<sup>21</sup> Autopsy studies has shown 24%<sup>22</sup> to 38%<sup>23</sup> of prostate cancer have lung metastasis, and the majority of them following bone metastasis, only rare exceptions occur.<sup>24,25</sup> The clinical course of our case is compatible with the above finding. Also interestingly, among all nine cases listed in Table 1, only our patient was diagnosed by core biopsy. For patients who have previous cancer history, when a second tumor mass is identified, the possibility of TTM should be raised and sufficient sampling is critical for diagnosis. With the increased survival rate of cancer patients and the application of new diagnostic tools, more and more TTM cases will probably be reported.

In summary, we present a case of metastasis of prostatic adenocarcinoma in the primary lung adenocarcinoma. To our knowledge, this is the first case reported. Although TTM is rare, awareness of this phenomenon is important when morphology shows two distinct patterns. Imaging study and proper IHC will help identify the tissue origin. Correct diagnosis of TTM is critical for cancer staging and appropriate therapy.

#### CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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