



Bimodal Therapy for Prostatic Metastasis of Pulmonary Poorly Differentiated Adenocarcinoma: A Case Report

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Abstract

Secondary solid prostate neoplasms are rare conditions commonly diagnosed as incidental findings at autopsy. Melanoma and small cell carcinoma are the most common histotypes which metastasize at prostate. We report a rare case of prostatic metastasis of a poorly differentiated pulmonary adenocarcinoma, treated with bimodal therapy including surgery and systemic immunotherapy. A 68-year-old man with a history of a stage IB lung adenocarcinoma developed urinary symptoms which did not improve despite medical therapy. The patient underwent a Transurethral Prostatic Resection (TURP) followed by systemic administration of Nivolumab, a monoclonal antibody used to treat several sub-types of solid neoplasm including, melanoma, lung and kidney cancer. The patient remained asymptomatic and progression-free at 2 years after the start of immunotherapy.

Keywords: Prostate adenocarcinoma; Lung cancer; Metastasis; Immunohistochemistry; Transurethral resection of the prostate; Targeted therapy

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Introduction

Prostate Cancer (PCA) is the one of the most frequently diagnosed cancer among men with an incidence of 449,800 cases per 100,000 inhabitants [1]. Approximately 6% of new PCA cases present with metastatic disease, with a 5-yr survival rate of only 29% [2]. No improvement has been noted in overall or cause-specific survival for men presenting with metastatic PCA over the last 2 decades [3]. Furthermore, recent forecasts estimated an additional 15,891 metastatic cases from 2015 to 2025, with an increasing incidence of 1.03% per year [4]. In a recent autoptic series, a metastatic spread to the prostate was diagnosed in 5.6% of cases [5]. Secondary PCA in surgical specimens is even more exceptional [6]. In particular, lung cancer metastases to the prostate are uncommon, and mostly caused by small cell or poorly differentiated large cell carcinomas [6-8]. We report here a case of prostatic metastasis from pulmonary adenocarcinoma.

Case Presentation

A 68-year-old man with a history of a stage IB (pT1bG3N0) lung adenocarcinoma, treated with right upper lobectomy and no chemotherapy two years before, presented to our clinic with dysuria and urinary urgency. He was a heavy smoker (50 pack years), but his family history was negative for cancer. His medical history included type-2 diabetes mellitus, chronic obstructive pulmonary disease and anxiety-depressive syndrome. The patient was in home therapy with repaglinide 1 mg t.i.d., venlafaxine 150 mg q.d., Bupropion 150 mg b.i.d., Alprazolam 0.5 mg q.d.

The oncological follow-up after surgery was reported to be negative. He was initially treated by his general practitioner with daily tamsulosin, which did not lead to any clinical improvement of the urinary symptoms (IPSS 25). A Serum PSA was 2.15 ng/ml and at the ultrasound prostate size was 60 ml.

Six months after the onset of urinary symptoms, the patient was admitted urgently to another community hospital due to symptoms related to urinary retention. The laboratory parameters revealed acute renal failure (creatinine level of 3.71 mg/dl). Kidney function recovered after the

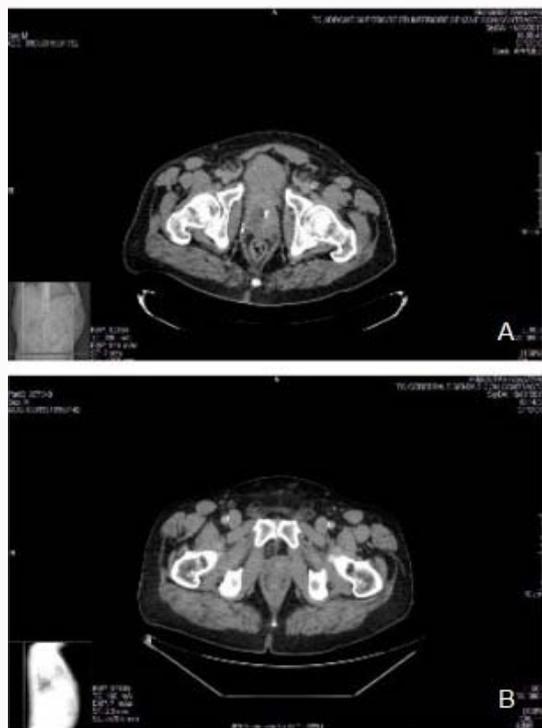


Figure 1: Radiological findings **1a** CT scan, performed before the first TURP, showed a hypodense mass of about 4 cm x 2.6 cm at the right prostatic lobe. **1b** CT scan performed about 1 year after the start of the immunotherapy revealed an inhomogeneous prostate without focal nodularity.

placement of a urinary catheter and the creatinine levels returned to a normal range within few days.

Two weeks later, the patient was referred to our department due persistent macroscopic hematuria. An abdomino-pelvic computed tomography showed a 4 cm tumoral mass in the right lobe of the prostate (Figure 1A), while laboratory test revealed a slightly increased of serum PSA although in the normal range (3.42 ng/ml). Hemoglobin was 9.9 g/dl. Because of these findings, the patient was hospitalized. In view of the smoking status and normal PSA levels, an urothelial cancer of the bladder with prostate involvement was suspected and a cystoscopy with Transurethral Resection of the Prostate (TURP) performed in order to improve urinary symptoms. We decided to postpone an eventual prostate biopsy in order to avoid. We did not perform a prostate multi-parametric Magnetic Resonance Imaging (mpMRI) because of the need to resolve quickly the hematuria. During cystoscopy a bladder tumor could be not diagnosed.

Histological specimen showed a poorly differentiated carcinoma with glandular differentiation, with histological and immunophenotypical features of adenocarcinoma of pulmonary origin, involving the 90% of the resected tissue (Figure 2A). The tumor was characterized by immunoexpression for Thyroid Transcription Factor 1 (TTF-1) and aspartic peptidase Napsin A and by negativity for PSA (Figures 2B-2D). No EGFR mutations or ALK rearrangements were found; PD-L1 was negative.

Staging with 18F-FDG PET showed a pathologic uptake in the left iliac fossa and in the prostatic area, multiple millimetric bilateral lung nodules. A whole-body CT scan detected, besides the prostatic mass, an inhomogeneous area of contrast enhancement in the brain (at the level of left parietal lobe) and confirmed pulmonary bilateral micro

nodules. A brain MRI excluded the presence of brain metastases, diagnosing a cavernous angioma.

The patient was discharged on the 1st postoperative day with urinary catheter, which was removed one week after the surgical procedure. The patient started the first cycle chemotherapy with carboplatin (5AUC) and pemetrexed (500 mg/m²) 60 days after surgery but he developed macroscopic hematuria and pelvic pain 3 months after surgery with an increasing of IPSS of 27. A second surgical revision was required and the prostate adenoma was completely resected by preserving only the prostatic capsule.

Histological findings confirmed the diagnosis of metastatic adenocarcinoma of the lung. Subsequently, two additional cycles of chemotherapy were administered. CT re-staging revealed a disease progression with increase of the pulmonary nodules and appearance of two new hepatic metastases (the largest of 1 cm in maximum diameter). Moreover the patient developed a pancytopenia which required hospitalization and the use of granulocyte growth factors.

Because of failure and the toxicity of the first line therapy the patient started a second-line immunotherapy with nivolumab 10 mg/kg. After the third administration, the patient reported a symptomatic improvement, with decrease of pain and disappearance of macrohematuria, with consequent removal of the urinary catheter.

After 6 cycles, CT imaging showed a shrink of lung and liver metastases, with a numerical and dimensional increase of retrocrural and periaortocaval lymph nodes (Partial Response (PR) according to RECIST criteria). Due to the clinical benefit and according to the good radiological response according to RECIST criteria [9], the treatment with nivolumab was continued. Further CT assessments performed every 6 treatment cycles confirmed disease stability (Figure 1B).

After 18 cycles the patient showed another way a PR. Later the imaging showed disease stability until now. The patient is asymptomatic and progression-free at 2 years after the start of immunotherapy, which is ongoing. The patient didn't experience side effects related to the immunotherapy.

Discussion

Secondary prostatic tumors occur in less than 1% of all prostatic surgical specimens and they can be often detected as incidental findings at autopsy. In a series of 51 patients with secondary neoplasms of the prostate, 2/3 of them were caused by direct invasion and bladder cancer was the primary tumor in 85% of cases [5]. Metastatic involvement of the prostate by hematogenous or lymphatic spread is an uncommon event. Despite this fact, reported cases of prostatic surgical samples with metastatic involvement have increased in the last years [10-13].

Secondary involvement of the prostate by primary lung tumors is exceptionally rare. In the series of Bates at al. [5] only one autoptotic case of prostate metastasis from pulmonary adenocarcinoma was found, whereas in a recent review of the literature, no case was reported [7].

In the clinical setting, secondary prostatic tumors mimic symptoms of primary prostate cancer or benign prostatic hyperplasia, with hematuria, dysuria and stranguria being most common events [8,10-13]. The patients have often widespread metastatic disease and the prostate metastases are detected at a late stage [13]. In 2014, Fu et al. [8] published an isolated case *in vivo*. The patient was treated with systemic chemotherapy and palliative radiotherapy on the

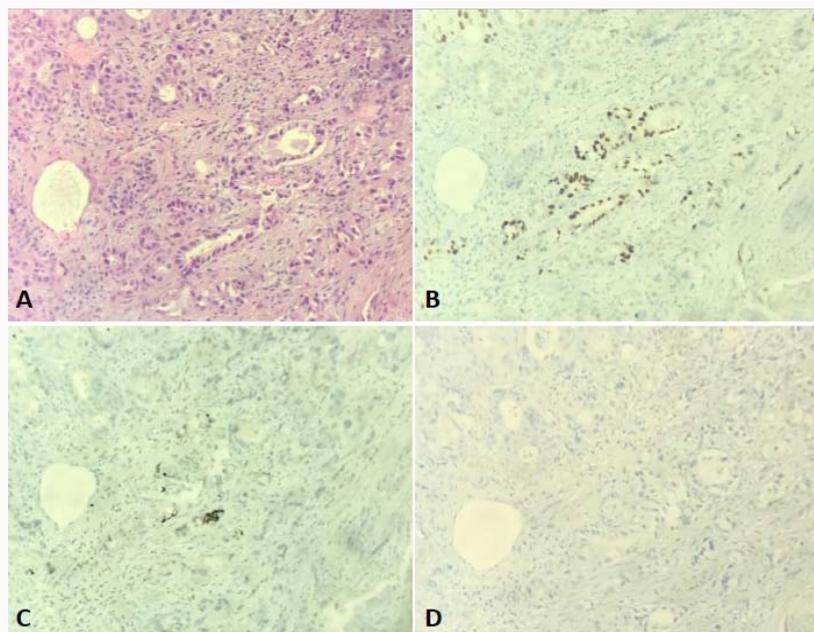


Figure 2: Pathological findings.

A) Hematoxylin/Eosin staining of lung adenocarcinoma in the prostate: note a clear glandular acinar differentiation of tumor which overlaps morphology of acinar carcinoma of the prostate.

B) Immunopositivity in the nuclei of tumor cells for TTF1 is helpful in the differential diagnosis between lungs and prostate because primary acinar and ductal adenocarcinomas of the prostate are typically negative.

C) Expression for Napsin A was documented in scattered cells with the typical granularity in the cytoplasm, highly specific of lung adenocarcinoma.

D) Note that tumor cells showed negativity for PSA.

(Original magnifications 20x)

prostatic lesion. Recently, Gilmour et al. [13] published a case report of a 55-year-old man affected by primary adenocarcinoma of the lung with metastatic progression to the brain, bone, lungs and adrenals and in treatment with second-line therapy with atezolizumab. Because of the onset of pelvic pain and severe dysuria, the patient underwent PET-TC which showed increased levels of metabolism in the prostate. Prostate biopsy reported a prostate metastasis by primary lung adenocarcinoma. The patient was treated with radiotherapy (39 Gy in 13 fractions) but the attempt of weaning off urinary catheter failed.

To date no validated specific treatment protocols for secondary tumors of the prostate are available [7]. Radiotherapy of the prostate could be suggested, considering that an improvement of overall-survival for lung adenocarcinoma in patients undergoing radiotherapy and TKIs was reported in literature [14]. In our case, we treated the patient with TURP and systemic therapy with Nivolumab after multidisciplinary discussion. Nivolumab was used in immunotherapy as indicated for the second-line immunotherapy in the metastatic disease, regardless of PD-L1 expression level, on the basis of CHECKMATE 017 clinical trial [15]. We decided to not consider radiotherapy as therapeutical treatment, because of its associated-risk to decrease urinary voiding [16], as also demonstrated by Gilmour's experience, where the bladder catheter could not be removed [13]. Basing on immunohistochemical analysis, adenocarcinomas of the lung express CK7 and more specific markers such as TTF1 and Napsin A, which results sensible for detecting prostatic metastasis from primary lung tumor but which are negative for adenocarcinoma of the prostate [7].

Conclusion

Secondary prostatic tumors, although rare, may pose serious

diagnostic challenges to both clinicians and pathologists. They must always be considered in differential diagnosis in patients with a previous history of another primary cancer and lower urinary tract symptoms. An accurate pathologic examination, including immunohistochemical and molecular analyses, may provide precise diagnosis and enable appropriate clinical management. A bimodal approach including a complete prostate resection up to prostatic capsule and immunotherapy such as nivolumab could improve 2-years CSS and OS in patient with lung adenocarcinoma regardless of PDL-1 expression.

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