Ureteral Metastasis: Uncommon Manifestation in Prostate Cancer

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Abstract. *Ureteral metastasis from a primary prostate cancer is a rare event in the initial diagnosis and progression of prostate cancer. We report here the case of a 72- year-old patient who was treated for castration-resistant metastatic prostate cancer involving bone, intra-abdominal lymph nodes, bilateral adrenal glands, and a small distal ureteral lesion with left hydronephrosis considered in remission, with a luteinizing hormone-releasing hormone analog plus abiraterone acetate (AA) and prednisone after initial docetaxel plus prednisone chemotherapy. After an episode of acute left flank pain, the previous left distal intraluminal ureteral mass appeared increased in volume on computed tomographic scan and was compatible with either a metastasis from prostate cancer, transitional cell carcinoma of the ureter, or a collision tumor. After left nephroureterectomy (NU), the mass was confirmed to be of prostatic origin on histopathological examination and the only site of metastatic progression of prostate cancer. Abdominal CT-scan and the operative specimen of the NU showed no direct extension of the abdominal lymph nodes into the ureteral lesion. We speculate that this unique ureteral prostate cancer metastasis was the result of hematogenic spread of prostate cancer, although microscopic spread through the lymphatic system could not be excluded. The transient anti-tumor effect of AA plus prednisone at the level of ureteral metastasis, as far as we are aware of, has never been documented before.*

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer-related death in men worldwide. Approximately 20% of patients with prostate cancer develop metastatic disease (1). In the largest autopsy study ever on a large number of patients with cancer of any kind between 1914 and 1943 before the advent of contemporary therapies reported in 2008, DiSibio *et al.* found that the most common sites of metastases from prostate cancer were confined to regional lymph nodes (26.2%), bone (19.7%), distant lymph nodes (18.4%), lung (12.8%) and liver (7.8%) (2). Metastasis to the ureter originating from primary prostate cancer was not reported in the former study and is extremely rare, with only 43 cases reported during the last century (3). It is not clear whether ureteral metastasis is the result of lymphatic or hematogenic spread. In contrast, bone, liver, lung and other organ-confined metastases are considered to result from hematogenic spread. The criteria for establishing true ureteral metastasis from any cancer type including that of the prostate have been defined and consist of one or more of the following features: a clear distance between the primary tumor and metastasis, an identical cellularity of the two tumors, and the presence of malignant cell emboli in the vasculature and lymphatic system of the ureteral wall (4). In the case reported here, the first two criteria were fulfilled. Therefore, the observation of a ureteral mass in the described case was considered as a true ureteral metastasis from prostate cancer. Abiraterone acetate plus prednisone is indicated as second-line treatment of metastatic castration-resistant prostate cancer after docetaxel plus prednisone (5). Although this drug has antitumor activity on metastases from any site for this disease, to our knowledge, this activity has never been documented in the setting of ureteral metastasis.

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Case Report

A 72-year-old-male presented with a history of prostatic adenocarcinoma (pT2N0M0, Gleason 4+4=8) treated with radical prostatectomy at another hospital in May 2006. The initial prostate-specific antigen (PSA) level was 5.4 ng/dl. Because of an increase in PSA and presumed local relapse in the prostate, external radiotherapy (70 Gy in 35 fractions of 2 Gy per fraction) was delivered to the prostatic bed in association with intermittent hormonal therapy [luteinizing hormone-releasing hormone (LHRH) agonist leuprorelin acetate] in December 2006. The latter was administered

intermittently based on increasing and decreasing PSA levels afterwards. In November 2012 and May 2013, because of objectivized progressive disease (PD) in retroperitoneal and para-aortic lymph nodes, a new mass in the right adrenal gland and right-sided hydronephrosis, enzalutamide (oral administration of 4×40 mg per day) was added to the LHRH agonist in the frame of a study and a double J stent inserted into the right ureter. Because of PD on this therapy, in July 2013, enzalutamide was stopped and 10 cycles of docetaxel (75 mg/m^2 intravenously every 3 weeks) plus prednisone (5 mg, twice a day continuously) was added to the LHRH agonist until February 2014. The PSA level decreased from 114.6 ng/dl to 4.60 ng/dl and a major partial response (PR) was observed for all metastatic sites on abdominal computed tomographic (CT)-scan. The right double J stent was removed. After a watchful waiting period of about 4 months, active treatment was restarted with abiraterone acetate (AA) 1,000 mg a day in one intake on an empty stomach in combination with prednisone 5 mg twice a day because of biochemical (PSA=57.9 ng/dl) and CT-scan relapse of the previous indicator lesions, including in a small mass in the distal left ureter accompanied by a grade two hydronephrosis (Figure 1A). No diagnostic procedure was undertaken to establish the nature of the left distal ureteral lesion. Under AA and prednisone, the PSA level dropped again to 5.04 ng/dl in September 2014 and increased slightly to remain around 8 ng/dl up to March 2015. Accordingly, the lymph nodes and other measurable/evaluable metastases, including the left distal ureteral lesion and hydronephrosis, had disappeared on the CT-scan in November 2014 (Figure 1B). On March 19, 2015, the patient complained of acute left back pain and the abdominal CT-scan showed a grade four hydronephrosis of the left kidney and ureter, with an intraluminal ureteral mass in the distal third of the left ureter (Figure 1C). The PSA was 7.95 ng/dl and no evolution was apparent in the other previous indicator lesions. The radiological differential diagnosis was transitional cell carcinoma (TCC) of the left ureter but because of the initial remission of this small mass after the initiation of AA plus prednisone, a metastatic lesion from prostate cancer remained probable. A left nephroureterectomy was performed on March 23, 2015 which indeed revealed a metastatic lesion from prostate cancer rather than TCC in the lumen of the ureter on histopathological examination. The tumor cells were negative for immunohistochemical staining with markers for TCC (p63, CK7 and CK 20), while they were focally positive for PSA (Figure 2). The macroscopic and microscopic histopathological examination revealed no continuity with any of the intra-abdominal lymph nodes. Because the section margins of the distal part of the ureter were free from cancer and the ureter was completely removed, no local consolidative therapy, *e.g.* radiotherapy, was initiated. No other lesions were detected on positron-emission tomography(PET)-CT scan performed after nephroureterectomy. As a consequence, AA plus prednisone, which seemed to control the lesions outside of the ureter was continued.

Discussion

Metastatic spread from prostate cancer is thought to occur through spread of cancer cells to regional lymph nodes, *via* lymphatic vessels, direct invasion of pelvic organs or systematically to the axial skeleton. Although the incidence of ureteral metastasis from any primary cancer is a rare event, in prostate cancer it is even rarer. In fact only 43 patients were reported to present this metastatic location from primary prostate cancer in the literature during the previous century (6). Seven additional cases were published from 2000 to 2013 (7). In some of the published cases, metastasis to the ureter was part of the primary presentation and initial diagnosis of prostate cancer, while in other cases, such as in the present one, it occurred during progression of the disease in patients in whom metastatic cancer was present (4). In the present patient, the ureteral metastasis was the only intra-abdominal manifestation of progression under systemic treatment with AA. Although AA was shown previously to produce antitumor effects in all metastatic sites (5), to our knowledge, the present case is the first documentation of response in the rare condition of ureteral metastasis. Remarkably, the response duration was apparently shorter than in patients with other documented localizations such as the lymph nodes or adrenal glands (normal PET-CT after nephroureterectomy). The proposed hypothesis to explain the mechanism of metastasis in the ureter includes implantation by instrumentation, arterial emboli and venous or lymphatic dissemination in a retrograde manner (8). The latter is the one most accepted. In our patient, no instrumentation took place at the left ureter. In the right ureter, a double J catheter was inserted two years before and removed more than one year later after achievement of a durable PR on docetaxel (February 2014). Induction of metastasis through instrumentation can therefore be excluded in the present case. The relapse in the ureter occurred in the absence of significant increase of PSA. Consequently and based on the radiographic imaging, TCC of the ureter was also suspected but because of the remission of the small mass induced by AA plus prednisone and not chemotherapy, the clinical preference was a metastasis from prostate cancer. Indeed, the anatomopathological findings together with the positive PSA staining in the operative specimen were indicative of prostate cancer. A 'collision' tumor of prostate cancer and TCC of the ureter was excluded in the absence of immunohistochemical staining for TCC markers (9). In summary, we believe that the reported patient suffered from a true metastasis from prostate cancer in the

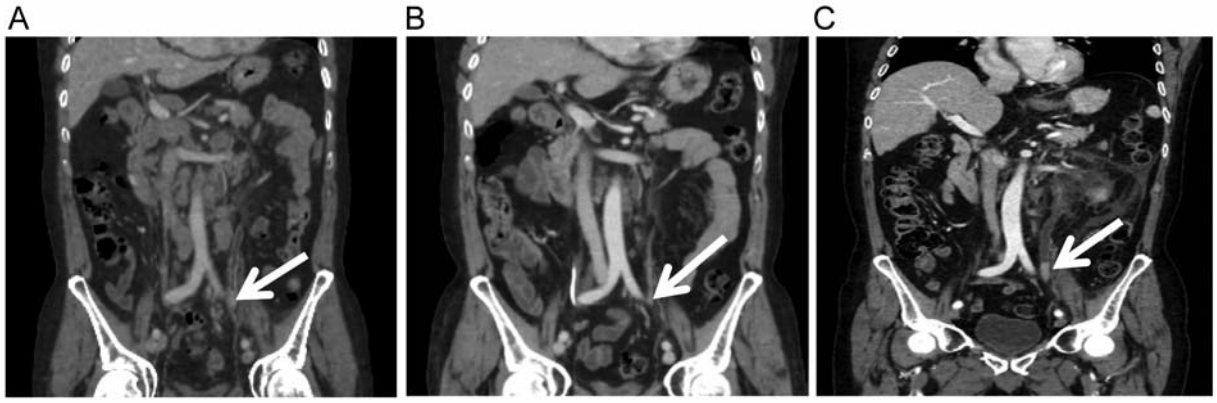

Figure 1. *Baseline abdominal computed tomographic scan before treatment with abiraterone acetate plus prednisone of prostate cancer metastasis in para-aortic and pelvic lymph nodes and left distal intraluminal ureteral mass with hydro-ureteronephrosis (arrow: A); remission (B) and recurrence (in absence of lymph node recurrence) (C) of left distal intraluminal ureteral mass and hydro-ureteronephrosis during AA plus prednisone (arrows).*

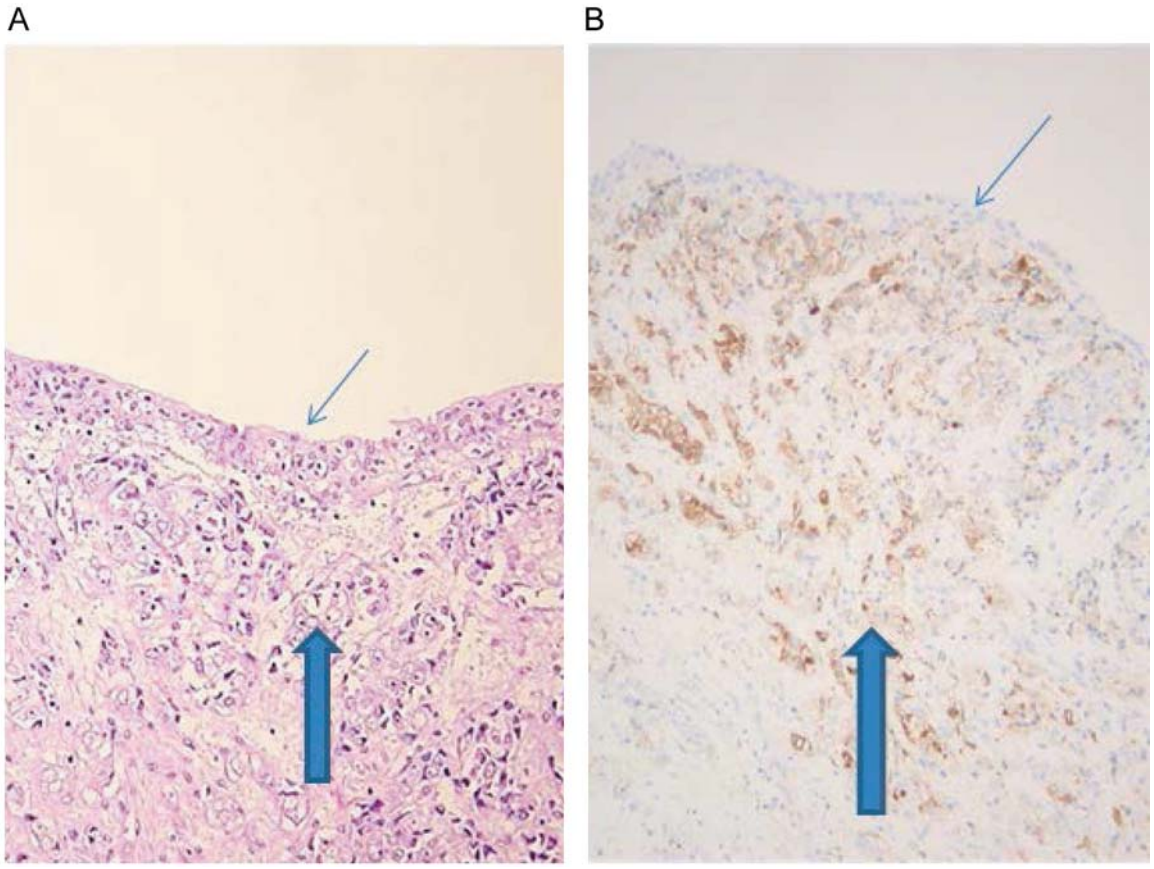

Figure 2. *Hematoxylin and eosin (A) and prostate-specific antigen (B) immunohistochemical staining of nephroureterectomy specimen showing ureteral mucosa (thin arrows) and tumor cells (thick arrows).*

left ureter which was proven to be the sole location of progressive disease under treatment with AA plus prednisone. We cannot rule-out that microscopic cancer in the involved lymph nodes in the pelvis in remission documented by CT scan was the origin of the metastasis. The present case is, to our knowledge, the first to show an anti-tumor effect of AA plus prednisone on ureteral metastasis of prostate cancer.

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