



Enteric Type - Adenocarcinoma of the Prostate Associated with Atypical Intestinal Metaplasia of the Prostate: Report of First Case and Review of Literature

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Case Study

An 85-year-old white male complained initially of pain while sitting, which shortly progressed to pain, referred to rectal, groin and pelvic regions. A CT scan of pelvis with contrast showed markedly enlarged prostate with no evidence of lymphadenopathy, ascites or visible bone lesions. His PSA was 3.5 ng/dl for which he underwent a Trans Rectal Ultrasound Prostate (TRUSP) biopsy at an outside institution, which showed what was diagnosed as Gleason 5+5=10 carcinoma of prostate in cores from right apex and target cores from what was labeled as peri-prostatic mass. The patient was referred to our institution. Urologic exam noted gross extension of a prostate mass into the rectum consistent with cT4 prostate cancer and recommend bone scan, chest CT, pathology review of the outside prostate biopsy slides, and referral to medical oncology for Androgen Deprivation Treatment (ADT) initiation.

Review of his prostate biopsies revealed a poorly differentiated adenocarcinoma with sheets of large cells with high grade nuclei and extensive "dirty" necrosis, abortive gland formation and no mucin in the cores from the right prostate apex and the peri-prostatic mass (Figure 1). The cores from the right side of prostate showed mainly benign prostate tissue with foci of atypical glands with intestinal metaplasia with goblet cells and paneth cell-like cells with eosinophilic granular cytoplasm (Figure 2) and occasional small extracellular mucin pools. IHC revealed that the poorly differentiated carcinoma was negative for PSA, PSAP GATA3, p63, chromogranin, and synaptophysin but positive for CK20, villin, and CDX2 (Figure 1). CK7 was positive in few cells. The foci of intestinal metaplasia were strongly positive for CK7 (Figure 2) but negative for CK20. PIN4 and p63 stains showed intact basal cell layer with mild over expression of AMACR in the luminal cells of the intestinal metaplasia. Synaptophysin and chromogranin were positive in the paneth cell-like cells (Figure 2). Some of the luminal cells were also positive for CK5 and/or CK14 components of the PIN4 cocktail as they showed brown cytoplasmic reaction (Figure 2). Based on pathologic examination the list of differential diagnoses included; metastatic colorectal carcinoma, primary prostate carcinoma with enteric differentiation; although never reported but was considered due to the accompanying intestinal metaplasia, high grade urothelial adenocarcinoma of prostatic urethra with features mimicking colorectal adenocarcinoma, and because of the anatomic location of the tumor, adenocarcinoma of the bulbourethral/Cowper's gland. The bone scan and the chest CT scan revealed no evidence of metastatic disease. The patient underwent colonoscopy, which was essentially normal revealing no colorectal masses. A rectal biopsy from an area with external compression revealed a small focus of adenocarcinoma in the sub mucosa of an intact normal colon mucosa. This focus was positive for CK20, CDX2, and villin and negative for PSA, PSAP, P63, CK7, and GATA3 similar to the mass in the prostate.

Cancer TYPE ID[®] testing performed at Biotheranotics, Inc, San Diego, CA on the peri-prostate mass biopsy material ruled out prostate adenocarcinoma, but was indeterminate between gastro esophageal adenocarcinoma (55%) and intestinal (either colon or small intestine adenocarcinoma, 41%). The patient was also found to have elevated serum CEA.

Given that the tumor IHC profile is most consistent with a colorectal type tumor the medical oncologist treated the patient similar to rectal cancer using capecitabine, which would also be active in a gastro esophageal adenocarcinoma. Given the patient is quite symptomatic with severe pain

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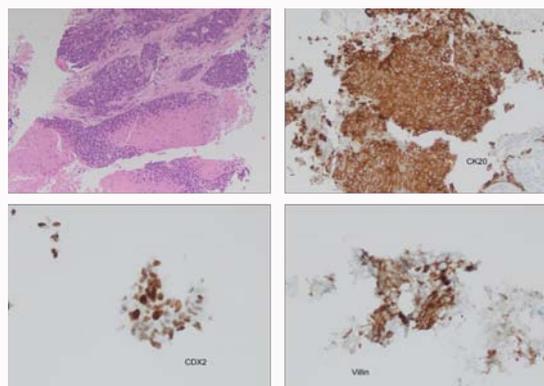


Figure 1: Biopsy of prostate apex showing poorly differentiated adenocarcinoma with extensive dirty necrosis and some abortive gland formation. The tumor cells are positive for CK20, CDX2 and villin.

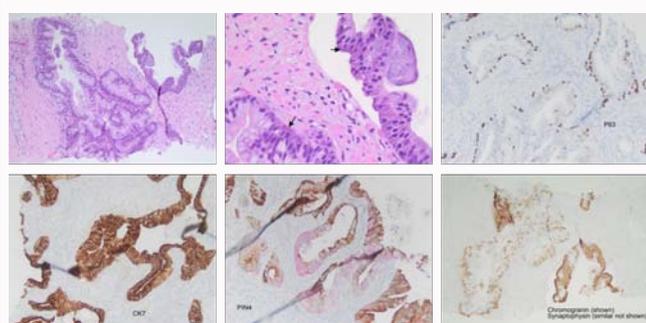


Figure 2: Intestinal metaplasia of prostatic glands with goblet cells and paneth cell-like granular cells (arrows in top row middle panel). The glands with intestinal metaplasia show intact basal cells on p63 (top row right panel). The meta-plastic cells are positive for CK7 (lower row left panel), AMACR (red) and HMWCK (brown) in the PIN4 stain (lower row middle panel). The granular cells are positive for chromogranin (shown) and synaptophysin (not shown) (lower row right panel).

he also received radiation. After completion of chemo radiation, CT of chest, abdomen, and pelvis (CT C/A/P) showed treatment response to the pre rectal soft tissue mass but new metastatic disease was noted in the liver and likely in the lung. Foundation Medicine ACT cell Free DNA[®] testing at Foundation Medicine, Cambridge, MA revealed mutations in KRAS G12R 33.0% and PIK3CA Q546E 21.8%. The patient was then started on 10 cycles of capecitabine and bevacizumab. CT C/A/P after 3 cycles showed response but doses were reduced because the patient developed rash, diarrhea and sever fatigue. After completing chemotherapy the patient was transferred to hospice, where he later passed away.

Discussion

The differential diagnosis of this case included metastatic colon carcinoma, adenocarcinoma of prostatic urethra, adenocarcinoma of Cowper's gland, and adenocarcinoma of prostate with enteric phenotype.

Metastatic colon carcinoma was ruled out by a negative colonoscopy.

Urothelial adenocarcinoma with features mimicking colorectal carcinoma arising from prostatic urethra was also excluded. Although the lining of the urethra was not sampled in any of the core biopsies, this possibility was not favored because of the presence of intestinal metaplasia of the prostatic ducts and acini. These foci were found in

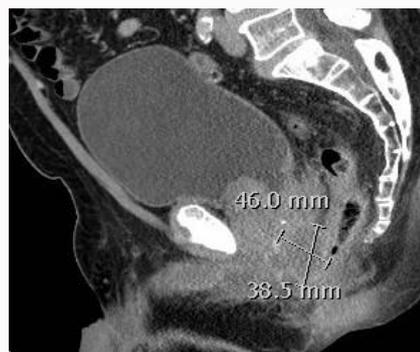


Figure 3: Sagittal CT image of pelvic mass 46.0 mm x 38.5 mm involving right apex of prostate and region of the right bulbourethral gland and abutting the penile bulb and the anterior wall of the low rectum.

cores from the right side of the prostate and they were seen under the capsule of the prostate rather than towards the innermost tip of the core. Additionally the tumor was negative for GATA3, p63 and the high molecular weight keratins CK5 and CK14 components of the PIN4 cocktail. Adley et al. [1] published a case of prostatic urethra urothelial adenocarcinoma with high-grade cells and abundant dirty necrosis with no mucin production mimicking colorectal carcinoma. The tumor was positive for CK7 and high molecular weight cytokeratins and negative or focally positive for CK20. This IHC profile is opposite to the IHC profile in our case as described in the pathologic review above. Also of note, neither urinary bladder nor urethral tumors or suspicious lesions were identified on cystoscopy performed at the time the TRUS prostate biopsy procedure was performed.

Adenocarcinoma of Cowper's (bulbourethral glands) is an exceedingly rare tumor with only about 20 cases in the world literature [2-17]. Almost all reported cases are adenoid cystic carcinoma [2,3,5,6,8,9,15]. However, Syvänen et al. [4] reported a case of bulbourethral gland adenocarcinoma in a 25-year-old male in which the cells were high grade and were strongly positive for CK20 and CDX2 similar to colorectal adenocarcinoma. The tumor was organ confined and predominantly in situ adenocarcinoma with foci of early invasion. A second look at the CT images of our case by our radiology could not resolve this conflict and could not exclude a possible origin in the right bulbourethral gland (Figure 3). Although origin from the right bulbourethral gland with secondary involvement of the prostate is possible, the opposite of a tumor arising from the apex of the prostate, extending to, and destroying the bulbourethral gland is also a possible scenario. The presence of atypical glands with intestinal metaplasia with goblet cells and paneth cell-like cells in prostate cores close to the tumor and restricted to right side of the prostate, which is the side of the tumor favors the prostate as the source of origin of this tumor. The intriguing point; however, is the divergent immunohistochemical profile of the intestinal metaplasia (upper GI profile) from that of the tumor, which is a lower GI profile.

Conclusion

Overall, this is a very unusual case with a tumor that appears anatomically to arise from the right apex of prostate or the right bulbourethral gland, but with an IHC profile matching that of primary colorectal carcinoma. The tumor at the primary and metastatic sites showed response to a colorectal cancer treatment regimen; however, the patient did not tolerate the full dose of treatment and developed

debilitating complications. He was then transferred to Hospice care where he later passed away.

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