



Oncology

Exceptional pathologic complete response achieved with androgen deprivation and docetaxel therapy in Gleason 10 prostate cancer



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ABSTRACT

Pathologic complete response is an exceptionally rare occurrence in prostate cancer, especially in the setting of poorly differentiated cancer, with high risk and poor prognostic features. Patient reviewed and signed an informed consent. The case details were collected.

Patient had PSA of 52.6 ng/dl and Gleason score 5 + 5 = 10 prostate adenocarcinoma with focal signet ring cell pattern. Genomic testing revealed pathogenic p53 and SPOP mutations. The patient received androgen deprivation therapy and six cycles of docetaxel. His PSA declined to undetectable, and radical prostatectomy (RP) showed no evidence of malignancy. The patient has discontinued all therapy and continues in remission 12 months after surgery.

Introduction

Pathologic complete response (pCR) is an exceptionally rare occurrence in prostate cancer, especially in the setting of poorly differentiated cancer, with high risk and poor prognostic features. Neoadjuvant androgen deprivation therapy (ADT) has been evaluated in multiple randomized trials and the results consistently showed downstaging of disease stage, decrease in positive margin rate, but no change in overall survival (OS).¹ In multiple randomized studies conducted, the incidence of pCR at radical prostatectomy, has been exceedingly low, and even rarer in Gleason 10 histology, which is considered extremely high risk disease. We report a unique case that demonstrated pCR after neoadjuvant ADT and docetaxel chemotherapy.

Materials and methods

Patient reviewed and signed an informed consent for clinical data collection from the medical record.

Results

Case history

The patient is a remarkably fit, pleasant 59-year-old gentleman, who was followed by urology for treatment of Peyronie's disease and was noted to have an elevated PSA of 52.6 in June 2017. The prior prostate specific antigen (PSA) was 3.5 ng/ml in July 2016. For the last

5 years the patient had annual PSA testing and his PSA level ranged from 1.9 to 3.7 ng/ml. The patient was on testosterone supplement injections since 2012 and his PSA level in July 2012 prior to starting on testosterone was 1.9 ng/ml.

A prostate biopsy was performed in June 2017 and the results showed 5 of 12 cores positive for prostate adenocarcinoma. The left lateral base and left base biopsies showed Gleason score 5 + 4 = 9 adenocarcinoma involving 80% and 45% of the specimens respectively. The left lateral apex, left mid and left apex biopsies revealed Gleason score 5 + 5 = 10 adenocarcinoma involving 5%, 40% and 10% of the cores respectively. The tumor cells demonstrated focal signet ring cell pattern. Prostate, right lateral base, right lateral mid and right lateral apex and left lateral mid biopsies were negative for prostatic adenocarcinoma (Fig. 1A). The contrast enhanced CT scan demonstrated mildly enlarged retroperitoneal and upper pelvic adenopathy about 1 cm in size with the largest node in the left common iliac region being 1.2 cm in short axis [Fig. 2]. Bone scan revealed no scintigraphic evidence of metastatic disease.

Genomic testing was conducted by Caris Inc, utilizing Next Gen sequencing on the biopsy specimens. The results revealed SPOP and TP53 mutations which appeared to be pathogenic (Table 1). No TMPRSS-ERG fusion was detected.

The patient was treated with ADT and 4 weeks later his PSA was < 0.1 ng/ml. Docetaxel chemotherapy was administered at a dose of 75 mg/m² intravenously every 21 days cycle for 6 doses. The toxicities noted were grade 1 alopecia and grade 1 fatigue. Patient had RP and a pCR was noted. The entire prostate was submitted for microscopic

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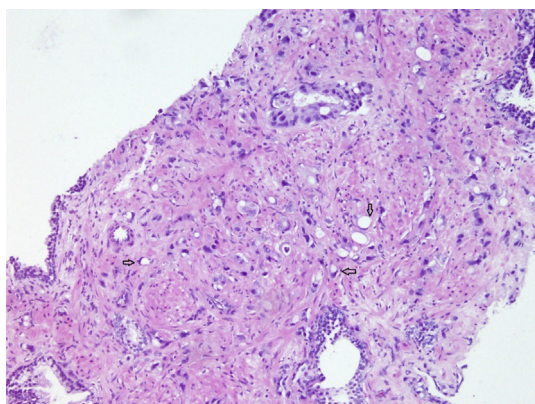


Fig. 1A. Prostate needle core biopsy shows Gleason score 9 (5 + 4) within tumor cells and ill-defined tumor glands. Signet cell features are also seen (arrow).

Table 1
Genomic results on prostate biopsy.

Biomarker	Testing	Result
Androgen Receptor/AR	IHC	Positive 2+, 90%
Androgen Receptor/AR	NGS	Mutation not detected
ATM	NGS	Mutation not detected
BRCA1	NGS	Mutation not detected
BRCA2	NGS	Mutation not detected
PDL-1	IHC	Negative 0%
MSI	NGS	Stable
TP53	NGS	Mutated, PL32fs
SPOP	NGS	Mutated, Pathogenic, pFI33V
PTEN	NGS	No loss detected
TMPRSS-ERG	Gene fusion testing	Not detected
ERCC1	IHC	Positive, 2+, 50%
TUBB3	IHC	Negative
Tumor Mutation burden	NGS	Megabase 9, intermediate

The clinically actionable mutations are shown in bold.

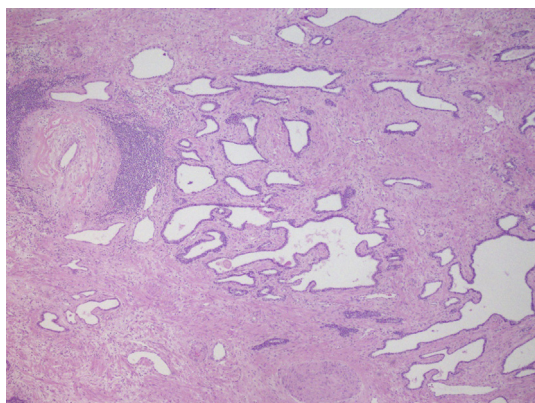


Fig. 1B. Prostatectomy specimen shows atrophic prostatic glands, patchy chronic inflammation and basal cell hyperplasia.

examination and revealed benign prostatic glands with atrophic changes and basal cell hyperplasia (Fig. 1B). Prominent stromal fibrosis with patchy chronic inflammation and focal acute inflammation was noted. One year post RP the patient continues to be in remission.

Tissue testing

Next-generation sequencing

Tumor tissue slides from prostate biopsy were submitted to Caris Life Sciences, a Clinical Laboratory Improvement Amendments (CLIA),



Fig. 2. Contrast enhanced axial CT scan image through the upper pelvis demonstrates morphologically rounded mildly enlarged common iliac lymph nodes (arrows).

the College of American Pathologists (CAP) and the International Organization for Standardization (ISO) 15189-certified/accredited laboratory (Phoenix, AZ, USA) for molecular profiling aimed to provide molecular-guided treatment options. The molecular profiling included next-generation sequencing and immunohistochemistry. Direct sequencing was carried out on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq platform (Illumina Inc., San Diego, CA, USA). A custom-designed SureSelectXT assay (Agilent Technologies, Santa Clara, CA, USA) was used for targeting 592 genes that were selected based on the COSMIC database (<http://cancer.sanger.ac.uk/cosmic/browse/genome>).

Gene fusion testing

Gene detection and fusion testing was performed on mRNA isolated from a formalin fixed paraffin embedded tumor sample using the Archer FusionPlex Solid Tumor Panel and the Illumina MiSeq. This assay id designed to detect fusions occurring at known breakpoints within tested fusion genes. Fusions occurring outside of known breakpoints in these genes may not be detected. Analytical validation of this test shows sensitivity and specificity of 98.3% and 100% respectively.

Comment

Neoadjuvant therapy has the benefits of controlling the dissemination of disease earlier and of evaluating response rates at RP. It also allows patient selection for consolidative local therapy depending on the extent of response attained on systemic therapy. It enables better prognostication, saves costs and helps avert significant toxicities of long term therapies continued until progression. The impact of perioperative chemotherapy on clinical outcomes has been disappointing. SWOG 9921 showed that addition of chemotherapy with mitoxantrone and prednisone did not confer any OS benefit over that seen with adjuvant ADT.¹ RTOG 0521 showed a small long term benefit favoring the use of neoadjuvant ADT and docetaxel with 4 year OS of 93% and 89% respectively in the arms with or without docetaxel.¹ CALGB 90203 is evaluating the results of neoadjuvant ADT and docetaxel chemotherapy followed by RP as compared to RP alone in high risk localized prostate cancer. The clinical results of this study are still awaited and will likely shed light on the overall role of contemporary chemotherapy.²

Genomic testing enables delivery of personalized therapy and is gradually gaining importance in therapeutic decisions for high risk localized prostate cancer. The case presented here demonstrated an

exceptional response which is seen in 0–3% of patients in most neoadjuvant trials reported to date.³ The TMPRSS-ERG gene is androgen regulated and has demonstrated higher likelihood of response to ADT and abiraterone.⁴ SPOP gene mutations may predict for a likely response to docetaxel and is worthy of exploration in larger patient cohorts.⁵ In addition the patients with TMPRSS-ERG mutations (85% of patients with prostate cancer) almost never harbor SPOP mutations. Further investigation of the role of SPOP mutations in predicting therapeutic outcomes in prostate cancer is required.

Conclusion

Genomic medicine has the potential to categorize an overarching clinical stage and diagnosis of prostate cancer into subtypes defined by patterns of therapeutic sensitivity or resistance. Exceptional responders such as this case will pave the way for defining therapeutic outcome prediction.

Author contribution

UV is the medical oncologist and the primary person writing and coordinating the manuscript, DS and EA were responsible for pathology review, HA was responsible for radiology review and JW was the urologist on the case. All authors have contributed to the manuscript content and reviewed and approved it.

Data availability statement

The datasets generated during and/or analysed during the current

study are available from the corresponding author on reasonable request.

Disclosures

All authors declare that there are no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eucr.2019.01.018>.

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