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Case reports in prostate cancer

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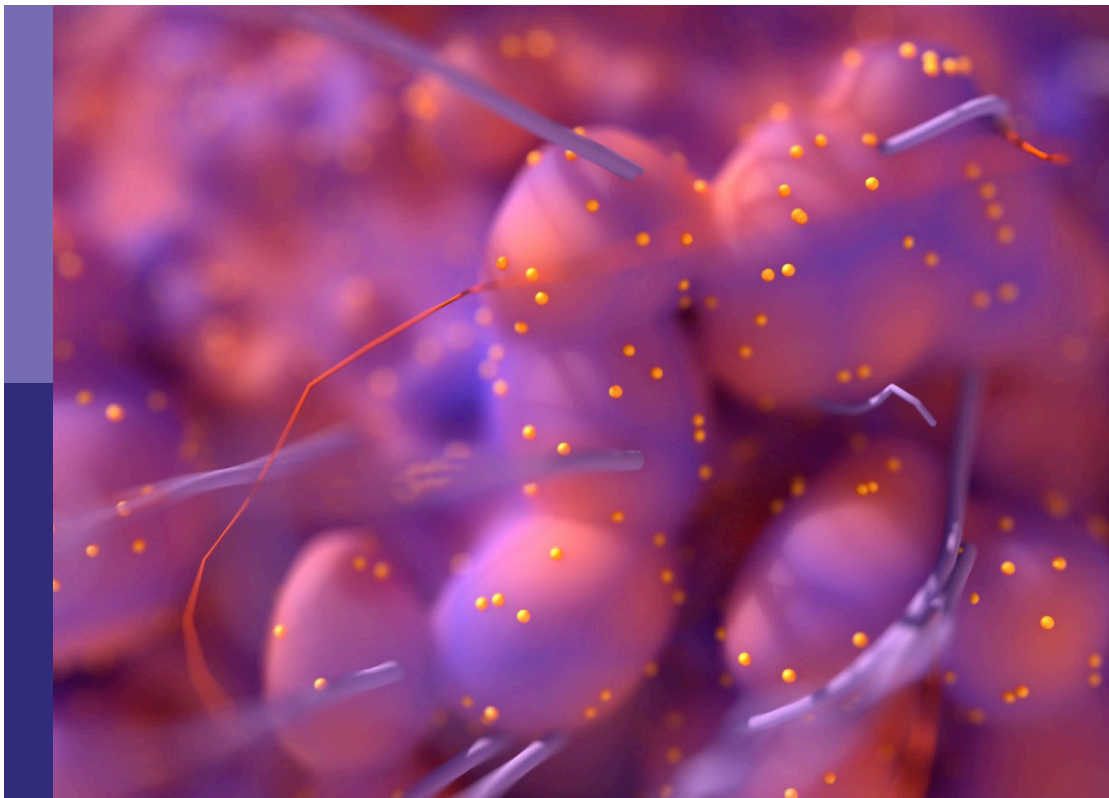

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Case reports in prostate cancer

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CASE REPORT
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An Unusual Case of Metastatic Basal Cell Carcinoma of the Prostate: A Case Report and Literature Review

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Background: Primary basal cell carcinoma (BCC) is a rare prostate cancer. Currently, a standard treatment regime for BCC of the prostate is lacking and most patients have a poor prognosis. We reported on a patient with BCC of the prostate whose cancer metastasized after undergoing a radical prostatectomy and whose prognosis improved after treatment with etoposide.

Case Presentation: A 62-year-old male with a history of seminoma was admitted complaining of intermittent gross hematuria for 1 month. Following a prostate biopsy, the patient was diagnosed with BCC of the prostate and received radical prostatectomy and radiotherapy. Initially, the patient's symptoms improved; however, 2 years later, a chest computed tomography (CT) scan revealed lung nodules. The patient did not exhibit any symptoms of BCC of the prostate; however, pathological examination and immunohistochemical staining of the nodules confirmed metastatic BCC of the prostate. Chemotherapy with docetaxel and cisplatin was well-tolerated but did not slow disease progression. Next-generation sequencing revealed mutations in the ataxia telangiectasia-mutated (*ATM*), SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily b-member 1 (*SMARCB1)*, and phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) genes. The patient did not receive targeted therapy owing to financial limitations and instead, etoposide was administered. A 9-month follow-up chest CT scan showed an 80% reduction in existing lung nodules and no new nodules had developed.

Conclusion: Our patient, diagnosed with recurrent prostate BCC after receiving a radical prostatectomy, responded to treatment with etoposide. Radical prostatectomy and radiotherapy should remain first-line therapy; however, etoposide may be an alternative second-line therapy when other options are not available. Consensus regarding treatment plans, and the molecular mechanisms behind prostate BBC, must be elucidated.

Keywords: basal cell carcinoma, prostate, metastasis, case report, therapy

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INTRODUCTION

Basal cell carcinoma (BCC) is most frequently observed in areas of the body that receive sun exposure, including the skin, and BBC of the prostate is extremely rare. Until recently, only 99 cases of primary BCC of the prostate had been reported (1). Typically, BCC of the prostate possesses low malignancy potential; however, there are reports of aggressive BBC leading to metastasis and recurrence (2–5). Owing to the limited number of cases, proper management strategies are still lacking for prostate BCC. We reported on a 62-year-old male who showed a partial response to etoposide, according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

CASE DESCRIPTION

Approximately 2.5 years ago, a 62-year-old male who presented with intermittent gross hematuria and a prostate-specific antigen (PSA) level of 2.42 ng/mL was admitted to the Tianjin Baodi hospital. A digital rectal examination did not reveal any masses or nodules. Ultrasound examination revealed an enlarged prostate ($3.4 \times 4.6 \times 3.3$ cm) and the bladder is normal. He did not present any psychosocial disorders and no one in his family had been diagnosed with a tumor. A 12-core prostate biopsy revealed BCC in one-half of the prostate. A pathology report was obtained from the hospital where the patient was initially diagnosed. The prostate biopsy was immunohistochemically negative for PSA, alpha-methyl acyl-coenzyme A racemase, chromogranin A, and synaptophysin; and positive for cytokeratin-903 (34βE12), p63, and Ki67 (<1%). An abdominal computed tomography (CT) scan was normal indicating there had not been metastasis. This was confirmed by whole-body bone scintigraphy. Based on these findings, the patient was diagnosed with non-metastatic prostate BCC and was treated with a radical prostatectomy. The pathology report indicated local invasion of the nerve and thrombosis of tumor vessels; however, the margin and seminal vesicles were negative. Immunohistochemical analysis was negative for PSA, alpha-methyl acyl-coenzyme A racemase, P53, cytokine 7 (CK7), and CK20 and positive for 34βE12, p63, and Ki67 (<1%).

The patient's TNM classification was pT2NxMx. To reduce the risk of metastasis, our patient received image-guided radiotherapy. The serum PSA level remained unchanged at 0.00 ng/mL before and after radiotherapy. The patient showed no evidence of disease progression until he was medically examined 2 years later. A chest CT scan revealed multiple lung nodules (**Figure 1**); however, bone scintigraphy showed no metastasis. A biopsy was performed on the nodules, and the patient was diagnosed with metastatic BCC of the prostate. Immunohistochemical analysis was negative for PSA, chromogranin A, synaptophysin, androgen receptor, thyroid transcription factor-1, CD117, CD30, and octamer-binding transcription factor-4 and positive for 34βE12, P40, CK5/6, low molecular weight cytokeratin, and Ki67 (20%) (**Figure 2**).

Information regarding the management and outcomes for BCC of the prostate is limited, and there is currently no standard treatment. We reviewed relevant literature to determine the optimal diagnostic and treatment methodology. Hormonal therapy is commonly administered; however, outcomes are poor. Considering that basal cells do not exhibit secretory activity, the patient received three cycles of chemotherapy with docetaxel, but the tumor continued to grow, albeit slowly. Subsequently, we added cisplatin for another three cycles of chemotherapy. This treatment failed and the number of nodules in the patient's lungs increased. Therefore, next-generation sequencing of the patient's sample from a lung nodule was performed free of cost at Foundation Medicine, which revealed mutations in the ataxia telangiectasia-mutated (*ATM*), SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily b-member 1 (*SMARCB1*), and phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) genes. The patient did not receive targeted therapy owing to his financial limitations and there were no clinical trials in which he could enroll. The patient's Zubrod/ECOG/WHO score was 1; therefore, following approval by the ethics committee, the patient received nine cycles of chemotherapy with etoposide (100 mg/day for 10 days, 4 weeks/cycle) after disease recurrence to prolong survival. A 9-month follow-up chest CT scan revealed a nearly 80% reduction in the size of lung nodules (**Figure 3**).

DISCUSSION

Owing to the rarity of BCC of the prostate, when this type of prostate cancer is detected, physical examinations, abdominal CT scans, and magnetic resonance imaging should be performed to exclude the possibility of metastasis. The 2016 WHO classification of tumors of the urinary system and male genital organs categorizes adenoid cystic hyperplasia carcinoma and basaloid variants as malignant basal cell tumors. A basaloid pattern is characterized by irregular solid clumps, trabeculae, and large cellular masses of basaloid cells. Tumor cells contain small, dark, often angulated nuclei, and a scant cytoplasm forming small nests in a peripheral palisading pattern (4). Infiltrative permeation, extraprostatic extension, perineural invasion, necrosis, and stromal desmoplasia are characteristic of BCC and these characteristics may assist in differential diagnosis. Immunohistochemical analyses revealed that most BCC cells were positive for B-cell lymphoma-2, 34βE12, p63, and CK5/6 (6). Previous studies reported mutations in the MYB proto-oncogene (*MYB*), phosphatase and tensin homolog (*PTEN*), epidermal growth factor receptor (*EGFR*), and erb-b2 receptor tyrosine kinase 2 (HER-2) genes (7–10). Simper et al. demonstrated that PTEN expression is downregulated and EGFR is overexpressed in BCC cells (8). Of the 99 cases of prostate BBC reported (mean age: 67.1 ± 12.2 years), clinical data were available for only 88 cases. Of these 88 patients, 33 (37.5%) patients whose cancer had not metastasized underwent radical prostatectomies, including 3 receiving pelvic exenterations;

Abbreviations: BBC, basal cell carcinoma; *ATM*, ataxia telangiectasia-mutated; *SMARCB1*, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily b-member 1; *PIK3R1*, phosphoinositide-3-kinase regulatory subunit 1; PSA, prostate-specific antigen; *PTEN*, phosphatase and tensin homolog; *EGFR*, epidermal growth factor receptor.

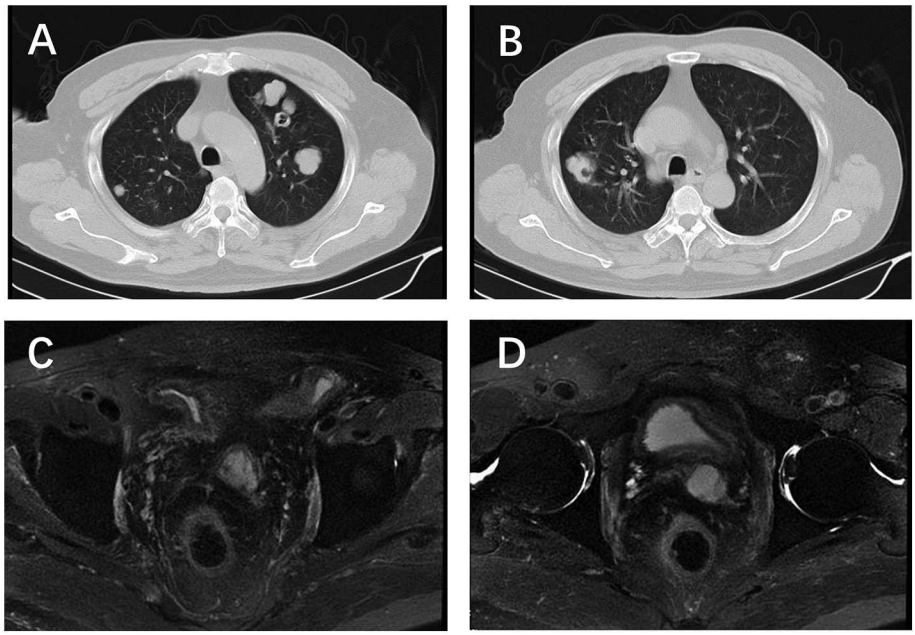

FIGURE 1 | Chest CT and pelvic MRI before etoposide chemotherapy. **(A,B)** Multiple nodules located in both sides of the lung; **(C,D)** no visible recurrence shown on the pelvic MRI.

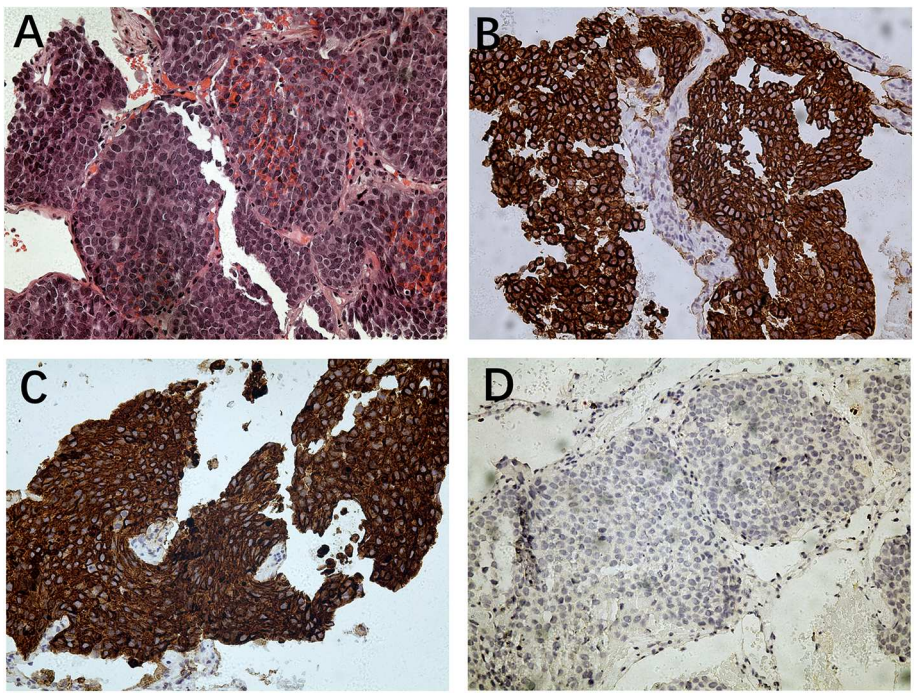

FIGURE 2 | Histopathology of lung metastesis. **(A)** Hematoxylin and eosin staining (magnification: ×200); **(B)** immunohistochemistry for 34βE12 (magnification: ×200); **(C)** immunohistochemistry for CK5/6 (magnification: ×200); **(D)** immunohistochemistry for PSA (magnification: ×200).

metastasis occurred in 17 patients and was undetermined in 52, whereas cancer in 19 patients remained localized. Eight of the 17 patients showed metastasis after surgery and 9 showed metastasis when diagnosed. Locations of metastases included the liver, lung, bone, penis, colon, and seminal vesicles. The liver (64.7%) was the most common area for metastasis. The percentages of lung

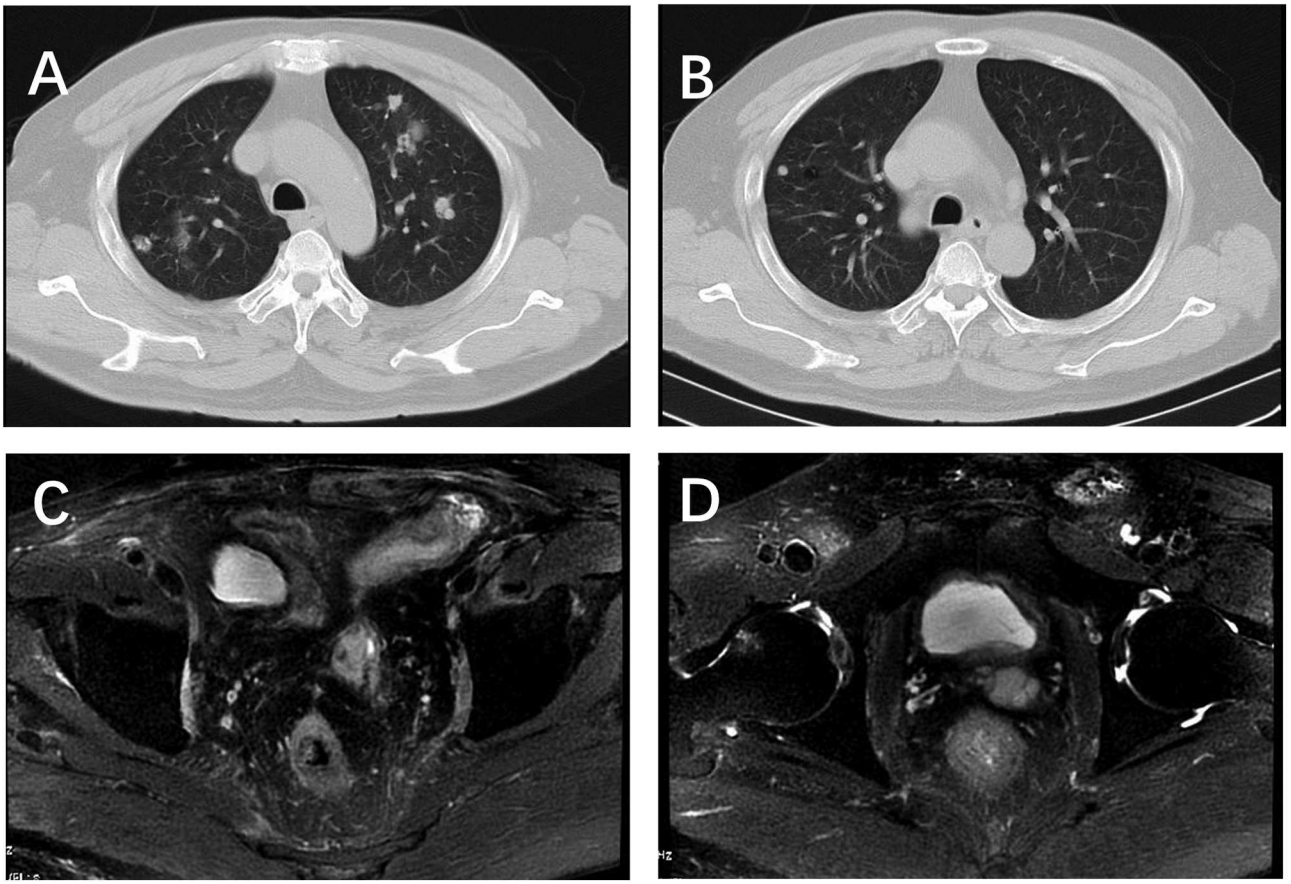

FIGURE 3 | Chest CT and pelvic MRI after 5 circles etoposide chemotherapy. **(A,B)** 80% decrease in size of measurable lung nodules; **(C,D)** no visible recurrence shown on the pelvic MRI.

and bone metastasis were 58.8 and 35.3%, respectively. Of the 71 patients for which follow-up data were available, 15 (21.1%) lived $\leq$1 year and only 20 (28.2%) lived $\geq$5 years.

When next-generation sequencing was performed, mutations in *ATM*, *SMARCB1*, and *PIK3R1* were revealed. ATM is a serine/threonine-protein kinase that plays a critical role in DNA damage responses. Mutations in *ATM* can lead to a defective DNA damage response and homologous recombination-mediated DNA repair. *ATM* mutations induce sensitization to PARP inhibitors such as olaparib, the only PARP inhibitor approved by the National Medical Products Administration of China for epithelial ovarian cancer, dermal ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (11–13). Loss or inactivation of ATM may increase the sensitivity to PARP inhibitors or inhibitors of DNA-dependent protein kinase subunit (14). Sun et al. demonstrated that inhibition of the ATM pathway can increase p53 activation, apoptosis, and accumulation of DNA damage (15). *SMARCB1* encodes the SNF5 protein (also known as INI1), which is one of the three core subunits of the SWI/SNF family of chromatin remodeling complexes (16). Preclinical evidence suggests that the loss of *SMARCB1* can increase the sensitivity to the enhancer of zeste 2 polycomb repressive complex 2 subunit inhibitors (17), inhibitors of the Hedgehog pathway (18), CDK4/6 inhibitors (18), and inhibitors of the fibroblast growth factor receptor (19). *PIK3R1* encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K) (20). The loss of PIK3R1 can result in increased PI3K signaling and promote tumorigenesis and hyperplasia in PTEN-deficient cells (21). Preclinical studies have shown that mutations in *PIK3R1* may increase sensitivity to the PI3K-AKT-mTOR pathway inhibitors, specifically inhibitors of PI3K-alpha or AKT. Moreover, PIK3R1 plays an important role in conferring resistance to cisplatin (22). Drugs targeting SMARCB1 and PIK3R1 are still being evaluated in clinical studies.

Therapeutic treatment options for patients with BCC of the prostate are limited because of the rarity of this disease. Most patients with primary BCC of the prostate are treated with hormone therapy, radiotherapy, radical prostatectomy, or a combination of these treatments. However, outcomes remain poor. Our patient initially received a radical prostatectomy and radiotherapy. His progression-free survival over a 17-month period between initial treatment and reoccurrence was monitored. Six cycles of chemotherapy with docetaxel and cisplatin did not reduce the number or size of the lung nodules. Following this treatment failure, nine cycles of chemotherapy

with etoposide were administered, producing a partial response resulting in an 80% decrease in the size of existing lung nodules and no development of new nodules. During etoposide treatment, the patient showed only mild nausea and vomiting. Thus, although some studies have shown that etoposide is ineffective in patients with BCC of the prostate (6, 23); in certain case like the present one, etoposide may be the most suitable option. The mechanism of action of etoposide in patients with prostate BCC should be further studied. A CT scan of the patient with BCC of the prostate revealed his condition was stable 9 months after commencing treatment with etoposide.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SD: manuscript writing. QL: data collection. ZX: data collection. HW: project development and data collection.

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CASE REPORT
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Case Report: Prostate Adenocarcinoma With Mucinous Features of Normal-Level Serum PSA, Atypical Imaging, Biopsy-Negative, and Peculiar Urethrocystoscopic Manifestation

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Background: Mucinous tumors of the prostate are seen as rare morphological variants of prostate carcinoma. Misdiagnosis and missed diagnosis are frequent clinically, especially when the clinical performance appears atypical. Furthermore, there has not been reported about the urethrocystoscopic performance of mucinous adenocarcinoma growing into the prostatic urethra so far.

Case Presentation: The current case report describes a 48-year old Asian male who was hospitalized because of intermittent gross hematuria for more than two months. The patient was diagnosed as prostatic space occupying lesions and an examination of needle biopsy was conducted on him, which did not indicate a definite malignancy. Transurethral plasma kinetic resection of the prostate (TUPKP) was performed for the patient, but the postoperative pathology revealed prostatic adenocarcinoma with mucinous features. Specifically, two cord-like neoplasms, extending to the bladder neck, were found through urethrocystoscopy in the prostatic urethra, both of which grew pedicles. The pedicles were situated on the right side of the parenchyma of the prostate. Finally, the patient underwent radical prostatectomy three weeks later.

Conclusion: Here, we reported a case that prostatic adenocarcinoma with mucinous features was diagnosed after TUPKP. The patient had normal serum prostate-specific antigen levels with atypical images and negative biopsy result. This report lays stress on the vigilance of clinicians in prostate mucinous adenocarcinoma and makes a description of its peculiar urethrocystoscopic manifestation, typical imaging, and unique growth pattern for the first time.

Keywords: prostate cancer, mucinous adenocarcinoma, PSA, urethrocystoscopic manifestation, transurethral resection of the prostate, MRI, needle biopsy

INTRODUCTION

The primary mucinous tumors of the prostate include mucinous adenocarcinoma of the prostate (MCP), prostatic adenocarcinoma with mucinous features (PCMF), and mucinous adenocarcinoma of the prostatic urethra (MCPU) (1, 2). MCP is extremely rare, with an incidence rate ranging from 0.21–1.10%. Mucinous adenocarcinoma of the prostate is defined as a primary prostatic acinar tumor, characterized by the presence of more than 25% of the tumor composed of glandular tissue with extraluminal mucin. This diagnosis can only be made in radical prostatectomy specimens. Other prostate specimens, including biopsy and transurethral resection, are able to at best confirm the diagnosis of PCMF (3–7). Clinicians and pathologists are often likely to misdiagnose or miss the diagnosis of this disease due to the deficiency in due awareness of its uncommon presentation (8). The results and prognostic significance of it have not been fully understood. Moreover, to the author's knowledge, urethrocystoscopy of these kinds of adenocarcinoma, which grow into the prostatic urethra, has not been previously reported.

CASE PRESENTATION

A 48-year old male patient from Asia was admitted to the author's hospital, complaining for more than two months about intermittent gross hematuria accompanied by bulky and dark red clots. The patient also suffered from hemospermia without painful ejaculation during this period and there was no special family or social-related history. A rectal examination suggested a mild enlargement of the prostate, and the central groove was accessible. An irregular and hard mass of about 4 cm in diameter was palpable on the right prostate lobe.

Ultrasonographic examination indicated benign prostatic hyperplasia and a prostatic space occupying lesion (**Figure 1**). Magnetic resonance imaging (MRI) manifested a prostatic space occupying lesion, presenting mixed signals, with a strong signal around the periphery and cluster-like low signals in the right lobe, at a diameter of about 36 mm (**Figure 2**). The total value of prostate-specific antigen (tPSA) was 2.28 ng/mL, the value of free prostate-specific antigen (fPSA) was 0.267 ng/mL, and that of the carcinoembryonic antigen (CEA) reached 4.98 ng/mL. The values of CA-242, CA-50, and CA-199 were slightly higher than normal ones. The patient subsequently underwent a transrectal needle biopsy aimed at the low signal lesion of the prostate. The histopathological examination found no definite malignancy (**Figure 3A**).

Three weeks later, this patient was hospitalized with dysuresia and transurethral plasma kinetic resection of the prostate (TUPKP) was accordingly performed to relieve the symptoms and confirm the diagnosis. It was noteworthy that urethrocystoscopy examined two cord-like neoplasms in the prostatic urethra, extending to the neck of the bladder. Both of them had pedicles that were located at the prostatic apex on the right side of the verumontanum (**Figures 4A, B**). The cord-like neoplasm was first removed from the pedicle, and then the right lobe of the prostate was resected. This part of the prostate tissue was surrounded by a multi-chamber cystic mass. There were clear boundaries between the cysts and prostate tissue. In the process of the resection, it was found that the surrounding prostate tissue had a tough texture and no blood supply (**Figure 4C**). For the purpose of pathological diagnosis, the surgery aimed to remove the whole tumor with clean margins. Surprisingly, postoperative pathology indicated multifocal mucinous adenocarcinoma with a Gleason score (GS) of 4 + 3 = 7 (**Figure 3B**). Further immunohistochemical staining showed sections were tested positive for PSA and prosaposin (PSAP) (**Figures 3C, D**), and negative for caudal type homeobox 2 (CDX-2), cytokeratin-20 (CK20), alpha-methylacyl-CoA racemase (AMACR, P504S), cytokeratin-5/6 (CK5/6), cytokeratin-7 (CK7), high molecular weight cytokeratin 34βE12, and transformation-related protein 63 (P63), and Mucin-2 (MUC2) staining revealed ∼20% positivity (**Figure 3E**).

Radical prostatectomy was performed one month after it was confirmed that the bone scan and colonoscopies demonstrated no abnormality and a follow-up visit was made for the patient for three years to date. The latest examination showed the patient had no biochemical recurrence and all tumor markers remained at normal levels. The MRI indicated the signal of the anastomosis area was normal and no enlarged lymph node was detected in the pelvic cavity.

DISCUSSION

MCP, also known as colloid adenocarcinoma, is considered as one of the rarest morphological variants of prostate cancer (PCa;

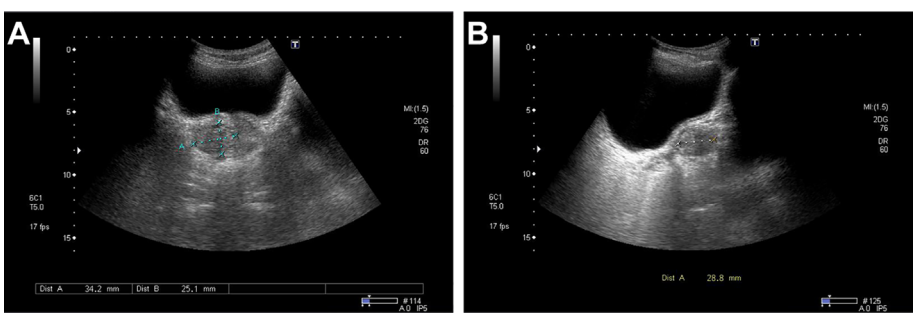

FIGURE 1 | Ultrasound detected a non-uniform hypoechoic nodule, about 34 mm × 25 mm × 29 mm in size, in the right lateral lobe of the prostate with the obscure boundary. No marked color flow signal was observed within the lesion upon Color Doppler flow imaging. **(A)** Transverse position. **(B)** Sagittal position.

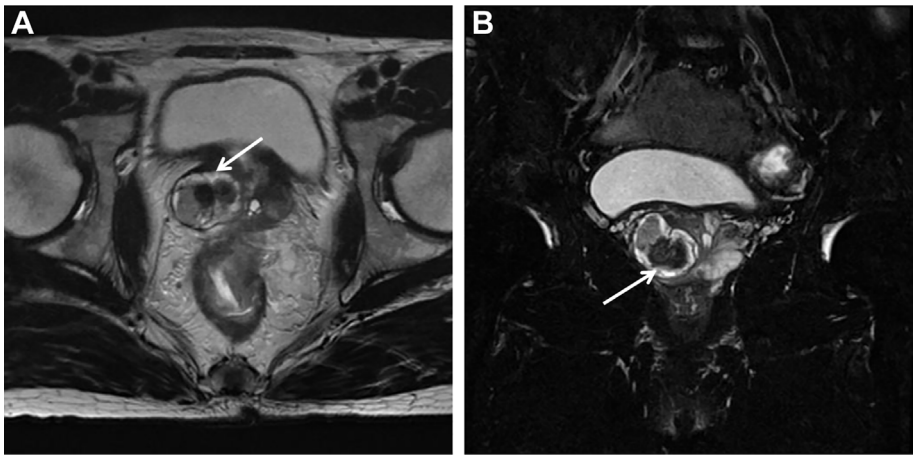

FIGURE 2 | MRI detected a round-like mixed signal lesion in the right lobe of the prostate. T2WI showed mixed signal, with high signal around the periphery and a cluster-like low signal in the center. The lesion boundary was clear, with visible capsule, and the diameter was about 36 mm. The right peripheral zone of the prostate was compressed. **(A)** Axial T2-weighted Image. **(B)** Coronal Fat-suppressed T2-weighted Image.

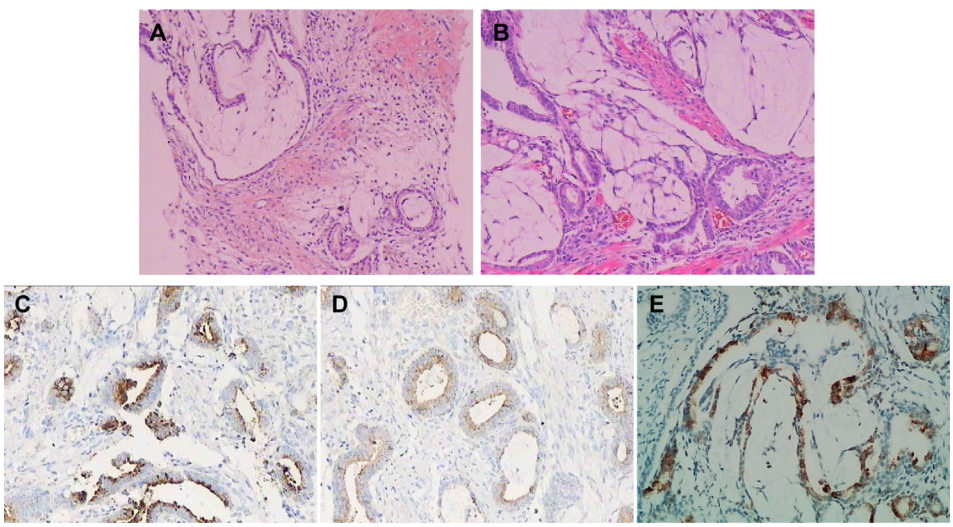

FIGURE 3 | Histopathological and immunohistochemical findings of the tumor. **(A)** Hematoxylin and Eosin stained section of needle biopsy found prostate tissue with interstitial edema around the acinar, part of which showed mucus edema-like changes. **(B)** Hematoxylin and Eosin stained section of TUPKP specimen manifested multifocal mucinous adenocarcinoma with diffuse infiltration. GS was 4 + 3 = 7. Immunohistochemical staining showed positive for PSA **(C)** and PSAP **(D)**, and MUC2 staining showed ~20% positivity **(E)**.

6, 9, 10). Most of patients with MCP are sensitive to androgens (9–11). The most common site of metastases is the bone (usually osteoblasts), followed by lymph nodes and lungs (5, 6). Diagnostic criteria for MCP were established in 1979, and then extended in 2000 and 2008: 1) Only radical prostatectomy specimens can be used for diagnosis, and it requires the presence of at least 25% of the original tumor composed of glandular tissue with extra luminal mucin. 2) Primary non-prostatic mucinous carcinoma must be excluded. 3) The growth pattern of the tumor should not be papillary. 4) Gleason score grading should be based on the underlying architectural pattern. 5) The involvement of urothelial type prostatic adenocarcinoma must be minimal or only secondary (2, 12–14). Although the original tumor should be composed of at least 25% glands with extra-luminal mucin to confirm the diagnosis, the clinical significance of this cut-off point is unclear (15). Furthermore, the volume and proportion of the mucinous component have no impact on prognosis (5, 7). Herein, the MCP and PCMF will be touched upon.

Significant changes have taken place in the criteria for grading mucinous adenocarcinoma (9, 12, 16, 17). Many pathologists were

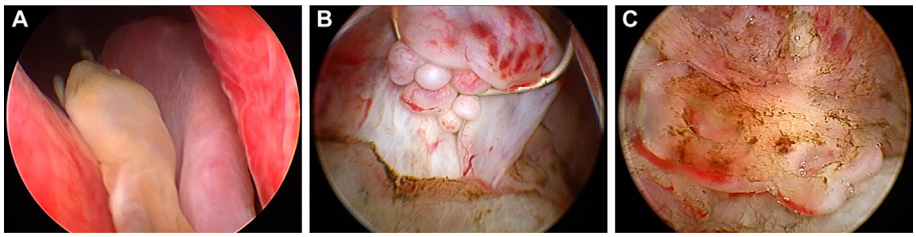

FIGURE 4 | Urethrocystoscopic performance of the tumor. **(A)** Two cord-like neoplasm located at the apex of the prostate and extended from the right of verumontanum to the neck of the bladder. **(B)** A multi-chamber cystic mass surrounded a region of the prostate gland that lacked blood supply. **(C)** Mucous substance can be observed on the cut surface.

inclined to assign GS = 8 to all prostate mucinous adenocarcinoma (14). Nevertheless, on the 2014 International Society of Urological Pathology Consensus Conference reached a consensus, stating that the underlying structure of a tumor should serve as the basis for determining GS (18). Even so, it is a must for us understand that the hypothetical prognostic significance of grading derived in this way has insufficient evidence. The relationship between GS and the prognosis of mucinous adenocarcinoma has not been comprehensively elucidated (14). The GS assigned for mucinous adenocarcinoma is usually high, while its prognosis seems to be analogous to non-mucinous adenocarcinoma with the same GS. The average 5-year biochemical recurrence-free survival for patients with MCP was reported to be 87.5-100% (4, 7, 14).

The morphology of the mucus components is usually variable and has multiple forms in most cases. Common forms of the glands consist of cribriform, poorly formed, unitary well-formed, and fused one, whereas isolated cells, strings of cells, papilliform structures, and solid bunches are observed less often (7, 16). The immunohistochemical presentation of prostatic mucinous adenocarcinoma is similar to that of regular acinar prostate adenocarcinoma, often tested positive for PSA and prostatic acid phosphatase (PAP) (19). Only a minority of cases are negative for PSA and PAP, yet positive for CEA (2, 5). Most patients with prostate mucinous adenocarcinoma have the improved serum tPSA, with an average level of 9.0 ng/mL (14). Another study evaluated 143 samples with a mucinous component of 5–100% and found an average preoperative tPSA value of 7.8 ng/mL (7).

MUC2, a known suppressor of breast, pancreas, and colon adenocarcinoma tumor, was also detected in all MCP patients (20–22). Nevertheless, it remains unknown whether it will play a role in the behavior where the cancer seems relatively indolent. Similar to non-mucinous PCa, studies have found that the ETS-related gene (ERG) is tested positive in approximately half of MCP and PCMF patients (23, 24). While TMPRSS2-ERG fusion was identified in 83% of mucinous adenocarcinomas, its prognostic value has aroused controversy (25, 26). Some suggest that the fusion of these genes is associated with a worse prognosis (27, 28), while others have found a correlation between the fusion status and tumor stage, and it is not linked with recurrence or mortality (29, 30). Some studies have even indicated that there is no correlation with the tumor stage, GS, or biochemical recurrence-free survival (24, 31). Considering the prognosis of mucinous PCa, these studies may further confirm that TMPRSS2-ERG fusion fails to predict the prognosis of PCa.

The conventional interpretation method of MRI for non-mucinous PCa may fail to be applied to mucinous adenocarcinoma (32, 33). Typically, on T2-weighted (T2WI) MRI, almost all types of mucinous carcinomas in other organs display a high signal intensity and are therefore confused with necrotic tumors, effusions, and cysts (34). A study on four cases of mucinous adenocarcinoma found that all lesions appeared highly intense on T2WI MRI. This situation was especially so when the tumor was confined to the peripheral zone (PZ) where it was difficult to identify, under the circumtance of being isointense with the surrounding normal PZ tissue (35). A previous study manifested that mucinous prostate adenocarcinoma metastasis, which could not be detected by 18F-sodium-fluoride (Na-F) positron emission tomography/computed tomography (PET/CT) or 18F-fluciclovine PET/CT, could be identified by 68Ga-PSMA-11 PET/CT successfully, which might be utilized for differential diagnosis in the future (36).

MCPU is another variant of primary mucinous prostate gland tumor, arising from the prostatic urethra and commonly progressing rapidly (37). The tPSA value of these patients has never increased. Tumors are generally positive for CEA, CK7, and CK20 and negative for PSA and PSAP (38). It is worthwhile noting that mucinous carcinoma with signet-ring cells and signet-ring cell carcinoma also have mucinous features, making it particularly essential to distinguish these from mucinous adenocarcinoma, since these tumors are extremely aggressive, with no response to endocrine therapy, and there is zero rate of survival for 5-year patients (11, 39).

In this report, the tPSA level of the patient remained normal and the biopsy result revealed no definite malignancy. Non-mucinous PCa are often represented by hypointensity on T2WI MRI, whereas this lesion showed high signal in the periphery and low signal internally on T2WI MRI, which has greatly puzzled the authors. Accordingly, the low-signal shadow was targeted for needle biopsy and no malignancy was detected. For further diagnosis, TUPKP was subsequently performed and it could be observed under urethrocystoscopy that the surrounding mucus-rich tissue had a clear boundary with the internal one. Actually, mucinous carcinomas usually demonstrate hyperintensity on T2WI MRI. Coupled with the urethrocystoscopic manifestation and the pathological features, it was acknowledged that the

periphery of the lesion was mucinous adenocarcinoma, while the low-signal internal tissue on T2WI MRI was prostate tissue lacking blood supply. This peculiar growth pattern of cancer has never been reported before. The lesion's periphery was thin and contained much mucus, thereby making it difficult to get a specimen through puncture.

For lesions with highly suspected malignancy but negative results of needle biopsy, it is believed that transurethral resection specimen pathological examination can be employed for diagnosis, if the tumor is located in the central zone or transitional zone of the prostate. Prostatic mucinous adenocarcinoma seems to differ in the origin, growth pattern, and biological behavior from non-mucinous adenocarcinoma. Given the difficulty in diagnosing prostate mucinous adenocarcinoma, we hope this report could be conducive to clinicians, radiologists, and pathologists' further understanding of this disease.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YZ, HS, JL, and HY collected and analyzed the patient's clinical data and designed the research. ZY, KL, and HW performed the review of literature and drafted the manuscript. HS, WW, and ZW supervised the report and the publication process. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Which Way to Choose for the Treatment of Metastatic Prostate Cancer: A Case Report and Literature Review

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Background: Prostate cancer (PCa) is the second most common cancer among males in the world and the majority of patients will eventually progress to the metastatic phase. How to choose an effective way for the treatment of metastatic PCa, especially in the later stage of the disease is still confusing. Herein we reported the case of a patient diagnosed with metastatic PCa and conducted a literature review on this issue.

Case Presentation: A 57-year-old man with metastatic PCa had been managed by Dr. J.P. since April 2012 when the patient was admitted to the Third Affiliated Hospital of Sun Yat-sen University by aggravating frequent urination and dysuria. The prostate-specific antigen (PSA) concentration was 140 ng/ml, and the diagnosis of PCa was confirmed by prostate biopsy, with Gleason score 4 + 5 = 9. Chest CT and bone scan indicated multiple metastases in the lungs and bones. Triptorelin, bicalutamide, zoledronic acid, and docetaxel were then administered, six cycles later, the metastatic tumors in the lungs disappeared and those in the bones lessened significantly, along with a remarkable reduction in PSA level (< 2 ng/ml). Intermittent androgen deprivation was subsequently conducted until August 2018, when the serum PSA level was found to be 250 ng/ml, again docetaxel 75 mg/m^2 was administered immediately but the patient was intolerant this time. Instead, abiraterone was administered until March 2019 because of intolerable gastrointestinal side-effects and increasing PSA level. In October 2019, the patient came to our center, a modified approach of docetaxel (day 1 40 mg/m^2 + day 8 35 mg/m^2) was administered. Luckily, the PSA level decreased rapidly, the bone pain was greatly relieved, and no obvious side effects occurred. However, four cycles later, docetaxel failed to work anymore, the metastatic tumor in the liver progressed. We proposed several regimens as alternatives, but they were soon denied due to the high prices or unavailability or uncertain effect of the drugs. In addition, the patient's condition deteriorated speedily and can no longer bear any aggressive treatment. Finally, the patient died of multiple organ failure in August 2020.

Conclusion: The experiences of this case provide valuable evidence and reference for the treatment choices of metastatic PCa, in some circumstances modified and advanced regimens may produce unexpected effects.

Keywords: prostate cancer, metastasis, treatment, case report, literature review

INTRODUCTION

Prostate cancer (PCa) was first described as a very rare disease by J Adams in 1853 (1). Now, however, PCa is the second most commonly diagnosed cancer and the fifth leading cause of cancer deaths among males, with the estimated occurrence of approximately 1.3 million new cases and 359, 000 deaths worldwide in 2018 (2). Early localized PCa can be effectively treated by radical prostatectomy or radiotherapy while most PCa will eventually progress to metastatic PCa, leading to a median survival time of approximately 3 years for patients (3, 4). Finding a best way of treatment and personalize strategies for metastatic PCa are worthy of consideration. Herein we reported on a 57-year-old man diagnosed with metastatic PCa in 2012, over the next eight years, various therapeutic methods were involved or considered, making the whole treatment process deserves to be shared and further discussed.

CASE DESCRIPTION

In April 2012, a 57-year-old man presented with aggravating frequent urination and dysuria was admitted to the Third Affiliated Hospital of Sun Yat-sen University, Dr. J.P. took charge of this patient. Digital rectal examination (DRE) revealed palpable hard nodules and the blood test showed prostate-specific antigen (PSA) concentration was 140 ng/ml. Further ultrasound examination suggested PCa with the right seminal vesicle invasion, chest computed tomography (CT) scan indicated metastatic tumors in bilateral lungs and enlarged lymph nodes in the mediastinum (**Figure 1A**), bone scan demonstrated multiple metastases in the scapulae, ribs, sacroiliac joints, hip joints, thoracic vertebrae, lumbar vertebrae, etc (**Figure 1B**). The diagnosis of PCa was further confirmed by transrectal ultrasound-guided prostate biopsy, with a Gleason score 4 + 5 = 9.

Androgen deprivation therapy (triptorelin) was administered immediately by intramuscular injection, together with anti-androgen (bicalutamide) orally and zoledronic acid intravenously. What's more, the chemotherapy regimen (docetaxel, 75 mg/m^2 every 3 weeks) was carried out synchronously, combined with prednisone 5 mg orally twice a day. After six cycles, chest CT and bone scan showed that the metastatic tumors in the lungs were surprisingly disappeared, and the metastatic tumors in the bones lessened significantly (**Figures 1C, D**), along with a remarkable reduction in PSA level (< 2 ng/ml).

Subsequently, namely November 2015, intermittent androgen deprivation (triptorelin combined with bicalutamide) was conducted until 2018, during this period, no regular follow-up was executed for various reasons. In August 2018, the patient was readmitted to hospital due to lumbar compression fractures in an accident fall, his serum PSA level was found to be 75 ng/ml, and rapidly increased to 250 ng/ml 2 months later, implying that the disease had progressed to castration resistance period. A second time he received docetaxel 75 mg/m^2 immediately but sadly he could not tolerate it, severe fatigue and poor appetite debilitated and troubled him in the extreme, he was much frailer than several years ago. Instead, oral abiraterone was administered, together with prednisone. Fortunately, the PSA level decreased to 15 ng/ml a few months later. However, good times don't last long, abiraterone was discontinued in March 2019 due to intolerable nausea and vomiting, abdominal pain, and diarrhea. Soon, the PSA level went up to 95 ng/ml, again abiraterone was administered but failed to work, and the PSA level increased to 150 ng/ml, suggesting that the disease was resistant to abiraterone.

In October 2019, the patient came to our center presenting with poor appetite, general fatigue, and broad bone pain. CT/MRI scan showed widespread metastases in the lungs, liver, bilateral adrenals, thoracic and lumbar vertebrae, and pelvis bones (**Figure 2**), the PSA level was higher than 400 ng/ml. Considering the poor performance status of the patient and the failure experience of abiraterone and standard chemotherapy regimen, we administered docetaxel in a modified approach (day 1 40 mg/m^2 + day 8 35 mg/m^2). Luckily, the PSA level decreased rapidly, the bone pain was greatly relieved, and no obvious side effect was observed, the patient regained satisfying appetite and mental status as a consequence.

Four cycles later, the PSA level decreased to 11.48 ng/ml, the metastatic tumors in the lungs, bones, and adrenals shrank except that in the liver. To determine the pathological type of the prostate cancer and the property of the metastatic tumors in the liver, we performed prostate biopsy and liver biopsy. Consequently, no tumor cell was observed in the specimen of prostate, immunohistochemical stains showed expression of P63 and 34BE12 surrounding the gland (**Figure 3**). In the specimen of liver tumor, prostate adenocarcinoma was observed and the expressions of AR, PSA, P504S, MLH1, MSH2, MSH6, PMS2 were observed in the immunohistochemical stains, with ERG, Syn, CgA, hepatocyte, arginase-1, and PSAP not observed (**Figure 3**). Docetaxel failed to work effectively any more, the PSA level elevated gradually. We took enzalutamide, apalutamide, cabazitaxel, olaparib, and metronomic chemotherapy into consideration as an alternative but soon the proposal was denied because of the high cost or unavailability, uncertain effects of these drugs. In June 2020 and July 2020, we took two more cycles of docetaxel when the patient was back to our center, the PSA level decreased to a certain extent but soon

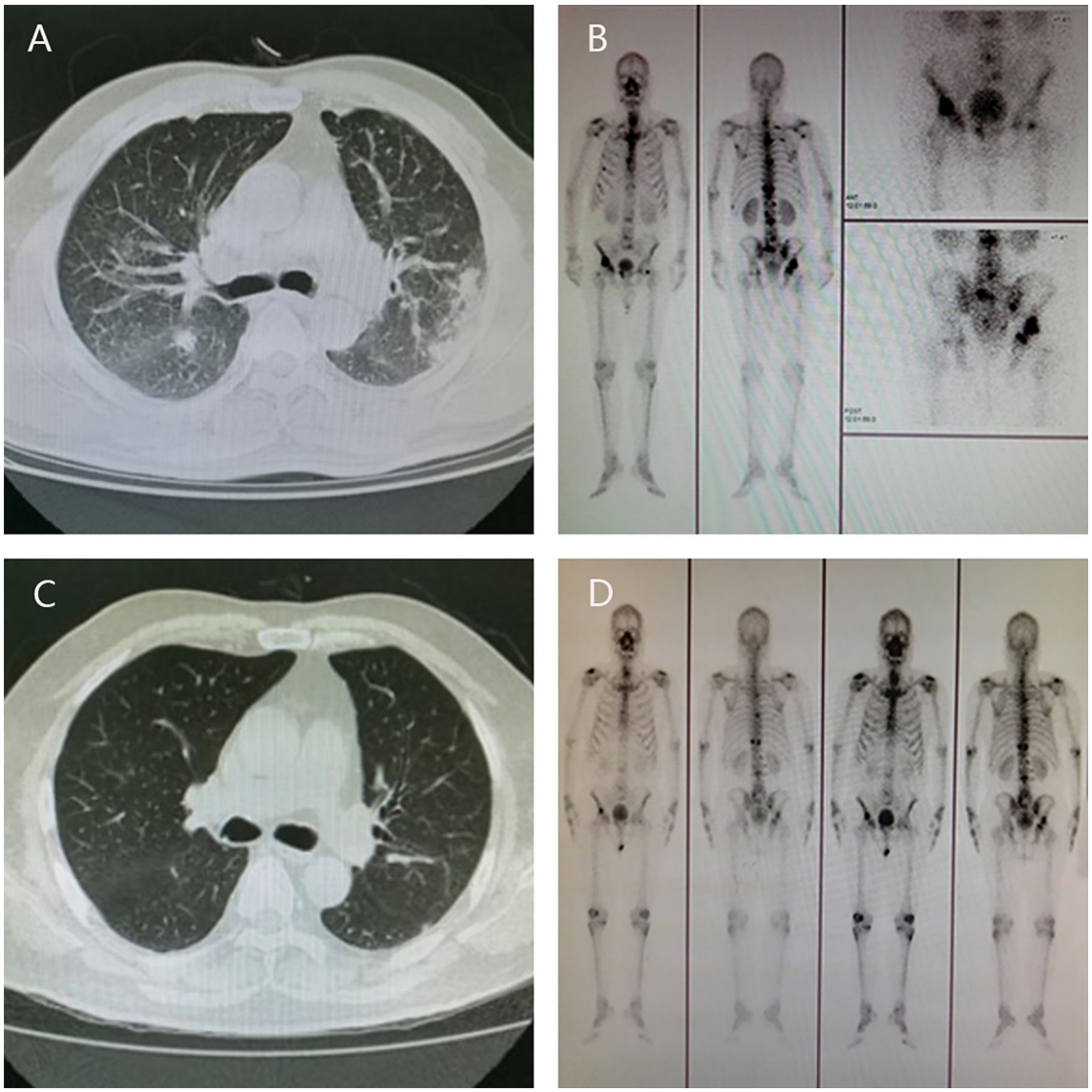

FIGURE 1 | Radiographic change pre- and post-therapy. The results of CT scan showed metastatic tumors in bilateral lungs at diagnosis **(A)** and no visible metastatic tumors in the lungs after androgen deprivation therapy and six cycles of chemotherapy **(C)**; Bone scan showed multiple metastases in the scapulae, ribs, sacroiliac joints, hip joints, thoracic vertebrae, lumbar vertebrae, etc at diagnosis **(B)** and the metastatic tumors in the bones lessened significantly **(D)**.

rebounded. At the meanwhile, the patient's performance status deteriorated speedily, and the total plasma bilirubin level elevated significantly, he could not tolerate any aggressive treatment. Finally, the patient died of multiple organ failure in August 2020. The overall process of disease progression, treatment course and changes of the PSA level were provided below in detail (**Figure 4**).

DISCUSSION

Improving the outcomes of the patients with PCa is a global health care challenge in recent years (5). In 1941, Charles Huggins and Clarence V. Hodges first introduced endocrine manipulation for metastatic PCa (6). Since then, androgen deprivation therapy (ADT) has been considered as the backbone of treatment for advanced and metastatic PCa (7). Usually, ADT consists of orchiectomy and long-acting luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Comparing the effect of LHRH agonists with orchiectomy, no significant difference was observed in terms of overall survival (OS), but the former was believed to be more acceptable and superior in lowering testosterone levels (8, 9). Even so, orchiectomy remains an effective, inexpensive alternative associated with lower risks of several clinically relevant adverse effects, such as fractures, peripheral arterial disease, venous thromboembolism, etc (10).

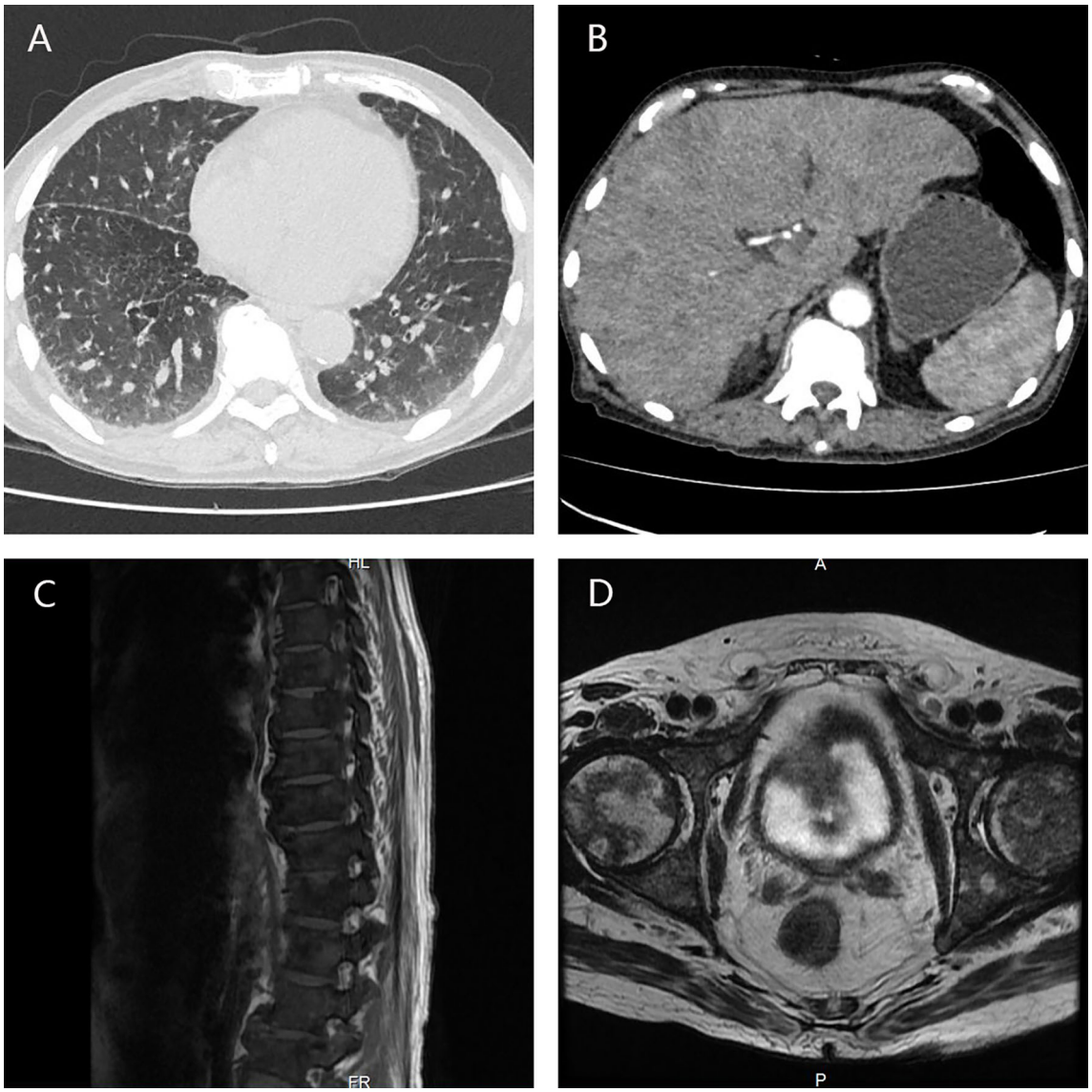

FIGURE 2 | CT/MRI scan showed widespread metastases in the lungs **(A)**, liver, bilateral adrenals **(B)**, thoracic and lumbar vertebrae **(C)**, and pelvis bones **(D)**.

In a phase III study, LHRH antagonists, a modified decapeptide competitively binding with LHRH receptors, was evaluated and proved to achieve a castrate level much faster than leuprolide in most cases without any flare, and PSA suppression was maintained throughout the whole follow-up period (11). Nevertheless, the definitive superiority of LHRH antagonists over LHRH agonists in OS seems difficult to be concluded (12), and the absence of long-term depot formulations limits the clinical use of antagonists, LHRH agonists are still the mainstream of ADT currently (13).

In terms of timing for ADT, immediate ADT and deferred ADT shared similar cancer specific survival (CSS) while the former was deemed to result in a remarkable increase in OS (14, 15). The latest European Association of Urology (EAU) guidelines recommend immediate ADT as mandatory in symptomatic patients whereas controversy still exists for asymptomatic metastatic patients due to the lack of quality studies (16), higher cost and more frequent treatment-related adverse effects of immediate therapy should be taken into consideration when decisions are made (15). Intermittent or continuous ADT is another concern discussed in several studies, no significant OS inferiority was observed in the intermittent androgen deprivation (IAD) group in contrast to the continuous androgen deprivation (CAD) group (17, 18). But IAD may be more favorable in terms of quality of life (QoL), sexual function, physical activity, cost savings, and treatment-related

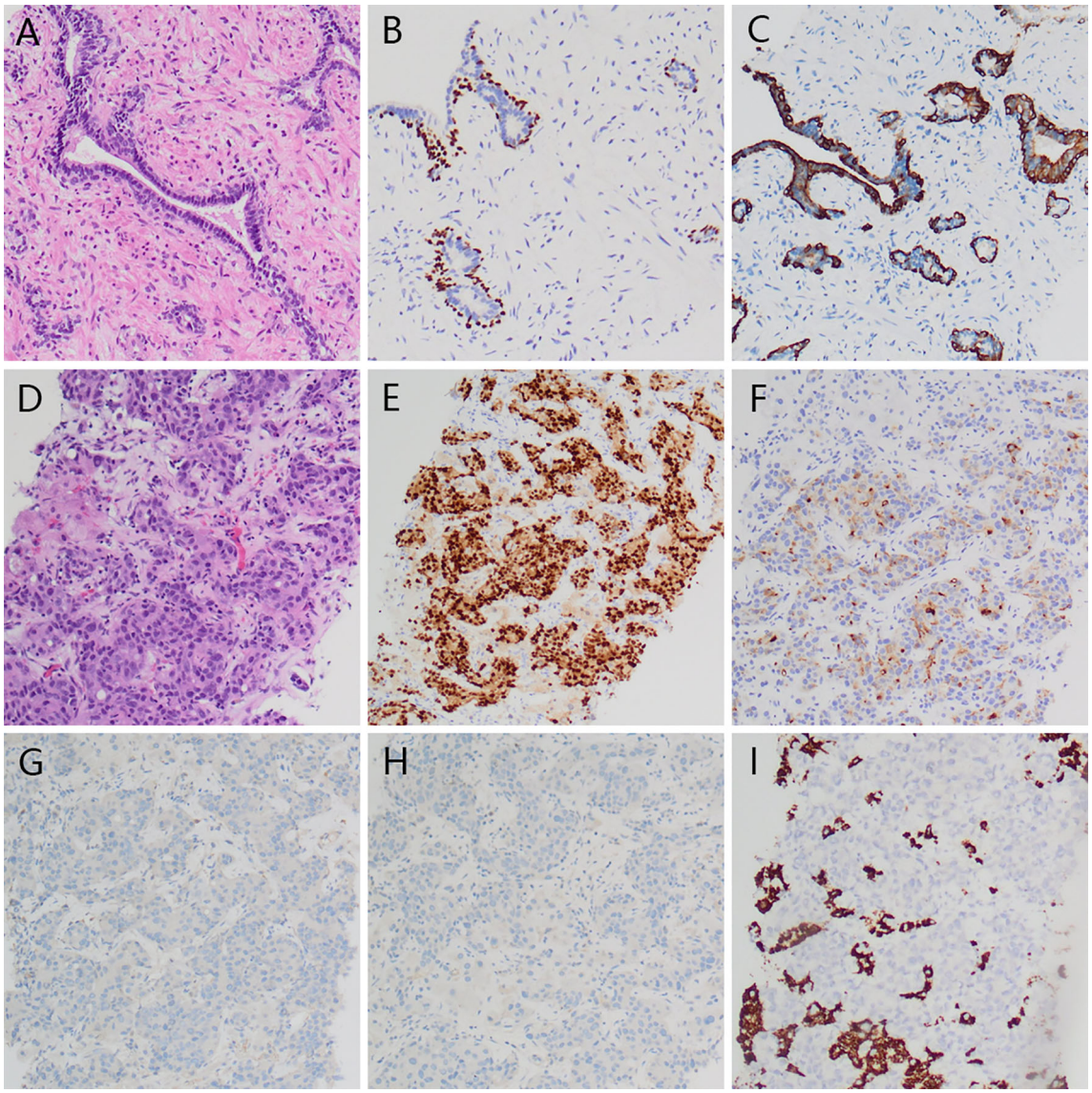

FIGURE 3 | Histopathology of prostate and liver tumor. No visible tumor cell in prostate specimen **(A)**, and expression of P63 **(B)** and 34BE12 **(C)** surrounding the gland. Visible prostate adenocarcinoma in liver tumor **(D)** with expression of AR **(E)**, PSA **(F)** and negative Syn **(G)** and CgA **(H)**, Hepatocyte **(I)**.

side-effects (17–19), suggesting that IAD perhaps be a preferred option in some cases, for instance, in the case we presented.

Complete androgen blockade (CAB), a combination of antiandrogen with ADT, has been proved to provide an OS benefit versus ADT monotherapy in a phase III randomized study and several systematic reviews (20–22). While on the other hand, CAB is associated with increased adverse events and reduced quality of life (22). Antiandrogens are often classified as steroidal anti-androgens such as cyproterone acetate (CPA), and non-steroidal anti-androgens (NSAA) such as nilutamide, flutamide, and bicalutamide (16). In a randomized controlled trial (RCT), participants treated with CPA showed similar OS, CSS, and time to progression compared with flutamide, but a lower risk of side effects was observed (23). However, more persuasive studies are currently absent and needed to be further conducted. Comparisons of the efficiency and safety of different NSAA are limited, but bicalutamide was found to show a more favorable safety and tolerability profile than flutamide and nilutamide (24). In our case, a combination of LHRH agonist with bicalutamide may be the most suitable regimen.

Chemotherapy had always been considered unresponsive to PCa until the 1980s. In 1981, Food and Drug Administration (FDA) approved estramustine as the first cytotoxic drug for the treatment of metastatic castration-resistant prostate cancer (mCRPC), followed by mitoxantrone in 1996 (25). Nevertheless, clinical benefits were limited to PSA response,

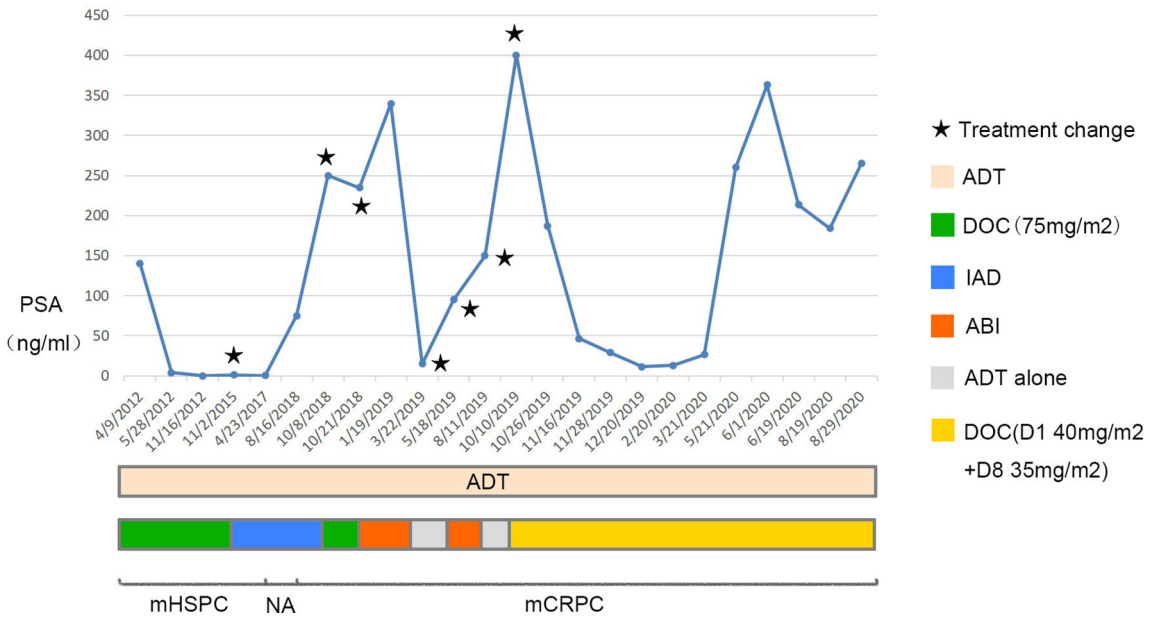

FIGURE 4 | Overall process of disease progression, related treatment and changes of the PSA level. The upper graph shows changes of the PSA level, the treatment course is in the middle and the progression of the disease is shown in the bottom. ADT, androgen deprivation therapy; DOC, docetaxel; IAD, intermittent androgen deprivation; ABI, abiraterone; NA, not available.

progression-free survival (PFS), and symptoms control, neither estramustine nor mitoxantrone showed OS benefit (26–28). In 2004, docetaxel replaced mitoxantrone as the standard of care based on two well-known phase III studies (TAX 327 and SWOG 9916), for its confirmed benefit on prolonging OS in patients with mCRPC (29, 30). Subsequently, docetaxel was proved to be effective in improving OS in patients with metastatic hormone-sensitive prostate cancer (mHSPC), especially those with high-volume metastatic disease, according to three phase III studies (CHAARTED, STAMPEDE and GETUG-AFU 15) and a systematic review and meta-analysis involved these three trials (31–34). As a consequence, ADT combined with docetaxel is strongly recommended by EAU guidelines as the first-line treatment for those who are initially diagnosed with metastatic PCa and fit for docetaxel (16). On the other hand, neutropenia, fatigue, nausea, and vomiting are common among patients receiving docetaxel (29), in our case, fatigue and poor appetite are the main manifestations in the first time of docetaxel rechallenge. Concerning those who are too frail to tolerate 75 mg/m^2 docetaxel, what Kellokumpu-Lehtinen P L did may provide an alternative that deserves to be referred to. In his dose-adjusted group, a similar oncological outcome was obtained while fewer adverse events were reported (35). In our case, we successfully proved the efficacy of docetaxel in the treatment of mHSPC (before guidelines), mCRPC, and the feasibility of modified chemotherapy regimen in frail patients, we also validated the benefit of docetaxel rechallenge in patients with mCRPC relapsing after an initial good response to docetaxel, which are consistent with previous studies (36, 37). In the later stages of the disease, docetaxel resistance occurred. The mechanisms of docetaxel resistance have not been explicitly illuminated, possible mechanisms include overexpression of P-glycoprotein, activation of androgen receptor, mutation of β-tubulin, aberrant angiogenesis, etc (38, 39). Therefore, biomarkers test may predict docetaxel response ahead of PSA change. Ploussard et al. proved the patients with the expression of βIII-tubulin had a significant shorter median OS than those with negative βIII-tubulin (40), other promising biomarkers include interleukin-6, macrophage inhibitory cytokine 1 and so on, but further studies are needed to confirm the clinical value (41, 42). The methods to overcome docetaxel resistance have also been discussed, alternative drugs such as cabazitaxel or enzalutamide are also good choices, nanotechnology mediated docetaxel delivery may also produce a surprising outcome (38, 39).

In patients with mHSPC, abiraterone, enzalutamide, and apalutamide are another first-line treatment choices according to EAU guidelines (16), all of which have shown significant improvements in OS and PFS than standard ADT in previous studies (43–45). In terms of abiraterone and docetaxel, existing evidence shows that abiraterone is comparative or even superior to docetaxel on oncological outcomes (46–50), and the former might be associated with higher QoL and less treatment-related toxicity (49, 50). Even though, as we reported, abiraterone may also produce severe side-effects, such as vomiting, abdominal pain, and diarrhea (50). Further contrastive data among different available first-line regimens are currently insufficient, several factors should be taken into

account when making a treatment decision, including disease volume, comorbidities, patient preference, toxicity profile, availability, and cost, etc (51).

Similarly, in patient with mCRPC, abiraterone, and enzalutamide were proved to significantly prolong OS and PFS in several randomized double-blind phase 3 studies and therefore were listed on the first-line treatment regimens (16, 52, 53). Apalutamide showed a significant metastasis-free survival (MFS) benefit among men with nonmetastatic castration-resistant prostate cancer (54), and good safety and efficacy in patients with mCRPC according to several small-size studies (55, 56), while further randomized phase 3 studies are needed to draw a more persuasive conclusion. Sipuleucel-T is another comparative first-line choice, which has shown its efficacy in prolonging OS among men with mCRPC, accompanied with tolerable adverse events (16, 57). Usually, abiraterone and enzalutamide are used prior to docetacel, and abiraterone -to-enzalutamide sequence was more favorable in terms of PFS (58). Interestingly, though, abiraterone and enzalutamide were confirmed to significantly prolong the survival of men with mCRPC after docetaxel (59, 60). Detection of androgen-receptor splice variant 7 (AR-V7) was proved to be associated with resistance to abiraterone and enzalutamide (61), while the negative conversion of AR-V7 following docetaxel has been reported, the discovery may explain the benefit of abiraterone and enzalutamide following docetaxel, and consequently abiraterone rechallenge may function as usual (62). On the other hand, enzalutamide showed a modest response rate in castration-resistant prostate cancer patients progressing after the use of abiraterone, similar clinical outcomes were observed in the application of abiraterone after enzalutamide failure, which implied cross-resistance was not inevitable (63, 64).

Cabazitaxel, a second-generation taxane developed to overcome docetaxel resistance, was approved in 2010 for the treatment of patients with mCRPC who had previously received docetaxel-based regimens (25), for its superiority over mitoxantrone in terms of clinical responses and OS (65). However, in patients with chemotherapy-naïve mCRPC, cabazitaxel did not show superiority for OS compared with docetaxel (66), therefore, docetaxel remains the first-line chemotherapeutic option for this population (16). Regarding the adverse events, cabazitaxel and docetaxel demonstrated different toxicity profiles, cabazitaxel may offer additional flexibility in patients with neuropathy, edema, or other conditions that may preferentially be exacerbated by docetaxel (66). In addition, cabazitaxel 20 mg/m^2 was deemed to be as effective as 25 mg/m^2, while less toxicity was observed, which suggested a lower dose should be preferred to reduce adverse events (66, 67). In frail elderly patients, metronomic chemotherapy, which is based on more frequent and low-dose drug administrations, such as daily oral vinorelbine and cyclophosphamide, provides an interesting alternative (68, 69), yet much larger, controlled, and prospective clinical trials are needed to figure out the optimal regimens (70). In patients with DNA-damage repair mutations in genes such as BRCA1, BRCA2, and ATM, Olaparib, a PARP inhibitor, led to a high response rate (71, 72), considering the potential similar mechanisms between olaparib and platinum (73), platinum-based chemotherapy may also be sensitive to this population (71), genetic test may play a valuable guiding role. When bone metastases were confirmed, radium-223 may provide benefit in OS, prolong the time to first skeletal event and improve pain scores and QoL (74). Recently, PD-1 inhibitor pembrolizumab showed antitumor activity and good disease control ability with acceptable safety in patients with docetaxel-refractory mCRPC, regardless of PD-L1 status, which is an encouraging innovation (75).

Bone metastasis and skeletal-related events (SREs) were proved to be associated with poorer prognosis among PCa patients, especially when they occurred synchronously (76, 77). Zoledronic acid was the first agent shown to decrease SREs according to a randomized placebo-controlled trial and therefore was approved by the FDA in 2002, with the recommended regimen of 4 mg every 3 weeks (25, 78). In 2011, a novel agent named denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) was confirmed better than zoledronic acid for the prevention of SREs (79). Interestingly, both zoledronic acid and denosumab were associated with increased bone mineral density among men receiving ADT for nonmetastatic PCa (80, 81), and denosumab was showed to offer benefit of delaying bone metastasis *via* changing the bone microenvironment in a large randomized study (82). Nevertheless, hypocalcemia was more frequent with denosumab versus zoledronic acid, all serum calcium deficiency should be corrected before and during treatment with bone protective agents (83).

CONCLUSION

Some limitations exist in our treatment course, including the absence of genetic or biomarker test for drug selection, and the deficiency of regular follow-up data. While on the other hand, individual or practical factors could not be ignored, personalized strategies are needed, together with systematic regimens. On the premise of ADT, the efficacy, toxicity, cost, availability of treatment regimens, and patients' preference should be taken into consideration. For some peculiar patients, modified and advanced regimens may produce unexpected effects.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XY and DJ: manuscript writing and data collection. YL, TZ, DX, and XC: data collection. JP: project development and data collection. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.659442/full#supplementary-material

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CASE REPORT
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A Case Report of Metastatic Castration-Resistant Prostate Cancer Harboring a *PTEN* Loss

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The treatment landscape of metastatic castration-resistant prostate cancer (mCRPC) has dramatically improved over the last decade; however, patients with visceral metastases are still faced with poor outcomes. Phosphatase and tensin homolog (*PTEN*) loss is observed in 40%–60% of mCRPC patients and is also associated with a poor prognosis. Several PI3K/AKT/mTOR pathway inhibitors have been studied, with disappointing anti-tumor activity. Here, we present a case of a patient with heavily treated mCRPC who had a modest tumor response to concurrent carboplatin, abiraterone acetate/prednisone, and liver-directed radiation therapy. We discuss the potential rationale supporting the use of this combination therapy and its safety in mCRPC. While the underlying basic mechanism of our patient's anti-tumor response remains uncertain, we suggest that further prospective studies are warranted to evaluate whether this combination therapy is effective in this population of patients with pre-treated mCRPC and *PTEN* loss.

Keywords: metastatic castration refractory prostate cancer, PI3K/AKT pathway, carboplatin, abiraterone acetate, ATM/Chk2/p53 signal pathway

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INTRODUCTION

Visceral metastases in men with metastatic castration-resistant prostate cancer (mCRPC) occur at a very late stage of disease. One retrospective study showed that the rate of radiologically detected visceral metastases before death from prostate cancer was 32% (1). In the vast majority of patients with visceral metastases, there are also detectable metastases at other sites such as bone and regional lymph nodes (1). The site of metastases impacts the expected survival of a patient. A prior meta-analysis showed that the poorest overall survival is seen in men with liver metastases (13.5 months) followed by lung metastases (19.4 months), non-visceral bone metastases (21.3 months), and lymph node-only metastases (31.6 months) (2).

The treatment landscape of mCRPC has dramatically improved over the last decade. The development of potent androgen synthesis and receptor inhibitors (3, 4); chemotherapy with taxanes alone or in combination with a platinum (5–8); poly (ADP-ribose) polymerase (PARP) inhibitors in patients who carry DNA homologous recombination repair gene-mutations (9); immunotherapy in men with high microsatellite instability (10); and prostate-specific membrane antigen (PSMA) targeted radiopharmaceutical agents (11) have significantly prolonged overall survival and progression-free

survival in mCRPC. Still, the disease is incurable and patients with visceral metastases have a limited expected survival.

Loss of the tumor suppressor gene phosphatase and tensin homolog (*PTEN*) is identified in 15%–20% of primary prostate tumor samples. Upon progression to castrate-resistant disease, the incidence increases to 40%–60% (12). Loss of function of *PTEN* leads to an activation of the PI3K/AKT/mTOR pathway precipitating cell proliferation, growth, and survival. *PTEN* loss is associated with a poor prognosis and is an independent prognostic indicator of prostate-cancer-specific death (12). While several PI3K/AKT/mTOR pathway inhibitors have been studied in mCRPC, the majority of outcomes have been disappointing, with no significant anti-neoplastic activity (13–19). However, early-phase studies show that ipatasertib, a new oral small-molecule inhibitor of AKT (protein kinase B), has promising anti-tumor activity when combined with novel hormonal agents; the activity appears to be significantly increased in mCRPC patients with *PTEN* loss (20). A Phase III randomized study of ipatasertib plus abiraterone is currently ongoing (21). Currently, treatment of mCRPC patients with *PTEN* loss is challenging.

Here, we present the case of a patient with *PTEN* loss castration-resistant prostate cancer with liver-only metastases who failed multiple lines of treatment but demonstrated some modest response to the combination of abiraterone acetate/prednisone plus carboplatin and liver-directed radiation therapy.

CASE PRESENTATION

A 62-year-old gentleman with a family history of prostate cancer and a personal history of stage II chronic lymphocytic leukemia (CLL) under observation (not required any treatment) and a right nephrectomy for stage I clear cell renal cell carcinoma (not required any systemic treatment) was diagnosed with a localized, high-risk prostate adenocarcinoma. His pre-surgery prostatic specific antigen (PSA) was 19.7 ng/ml, and he had a Gleason score of 4 + 5 = 9 in all prostate biopsy cores. He underwent a radical prostatectomy with bilateral pelvic lymphadenectomy in September 2016. Final pathology confirmed prostate adenocarcinoma with a Gleason score of 4 + 5 = 9 with invasion of periprostatic fat and the seminal vesicle as well as perineural invasion: pT3bN0. The pathology also revealed positive surgical margins. Post-surgery PSA was 2.39 ng/ml. He received bicalutamide and androgen deprivation therapy (ADT) with leuprolide for 6 months from his local urologist but did not receive salvage radiation. His PSA became undetectable with ADT. Germline genetic testing was performed using the Ambry CancerNext® test and was negative.

The patient presented to our medical oncology clinic in January 2020 with a 2-month history of lower abdominal pain, anal spasms, constipation, and significant lower urinary tract symptoms with a severe International Prostate Symptom Score (IPSS) of 33. He denied loss of appetite and his weight had been maintained. His PSA had risen to 2.3 in December 2019 in a previous record, but at our initial visit, it was elevated to 11.70 ng/ml and further elevated to 41.78 ng/ml within 4 weeks. A computerized tomography (CT) scan of his chest and abdomen and pelvis demonstrated numerous liver lesions and extensive sub-centimeter supraclavicular, mediastinal, and bilateral axillary lymphadenopathy. A nuclear bone scan was negative for bony metastases. Subsequently, a whole-body positron emission tomography/CT scan was performed to evaluate for a Richter's transformation given his CLL history. The scan showed hypermetabolic changes in a left hepatic lesion with an standardized uptake value (SUV) of 10.2; a caudate lobe lesion with an SUV of 11; a right dome of the liver lesion with an SUV of 8.0; hypermetabolic bilateral iliac nodes with SUVs of 3.8 and 2.7; and no fluorodeoxyglucose avidity above blood pool in his supraclavicular, bilateral axillary, mediastinal, and bilateral perihilar nodes. There was no evidence of bone marrow infiltration. A liver biopsy was obtained given it demonstrated the highest uptake value and showed metastatic carcinoma that was strongly positive for the prostate-specific immunohistochemical (IHC) markers NKX3.1 and PSA and negative for the neuroendocrine markers chromogranin and synaptophysin (**Figure 1**).

In light of these findings, the patient was started on leuprolide 22.5 mg plus docetaxel 75 mg/m^2. He received six cycles of docetaxel from March 2020 to June 2020 and tolerated the treatment well with no major treatment-related side effects except some mild fatigue. PSA trends shown in **Figure 2**. Repeat CT scans after three cycles of docetaxel + ADT showed stable disease; however, the scans repeated after six cycles showed disease progression in the liver (**Figures 3A, B**).

A repeat liver biopsy was again consistent with metastatic prostatic adenocarcinoma with similar morphology and IHC profile to the previous biopsy (**Figure 4**). Molecular testing through Caris Life Sciences was performed, and it showed positive for androgen receptor, *PTEN* loss in exon 2c.164, CDKN1B exon 1p.p92fs, tumor mutation burden (5 mutations/Mb), and stable microsatellite instability, and negative for NTRK1/2/3, ATM, BRCA1, BRCA2, FANCA, PALB2, RAD51C, and RAD51D. Second-line therapy with enzalutamide 160 mg was started in July 2020, but in August 2020, he presented to the emergency department with intractable right upper quadrant pain and CT scans showed progression of the hepatic masses with small, new infiltrative lesions (**Figure 3C**). PSA trends are shown in **Figure 2**. Due to the rapid progression, we switched to cabazitaxel 20 mg/m^2 with G-CSF as third-line therapy; the patient received three cycles from September to October 2020. While on cabazitaxel, his PSA dramatically increased to 188 ng/ml and repeat scans again demonstrated worsening of his extensive hepatic metastases (**Figure 3D**). AR-V7 testing was sent and was negative. We initiated abiraterone acetate 1000 mg daily/prednisone 5 mg twice daily combined with carboplatin AUC 5 every 3 weeks in November 2020 given *PTEN* loss. He also underwent Y-90 embolization of the right lobe of his liver in December 2020 (**Figure 3E**) and a second Y-90 embolization of the left lobe of his liver in January 2021 (**Figure 3F**). He was instructed to continue his abiraterone acetate/prednisone regimen throughout his Yttrium-90 (Y-90) embolization. Y-90 embolization is a type of radiation using resin or glass microspheres containing ^{90}Y administered directly into the hepatic arteries. However, the carboplatin was held 2 weeks prior and 2 weeks after Y-90 embolization. He received continuous ADT as backbone. He

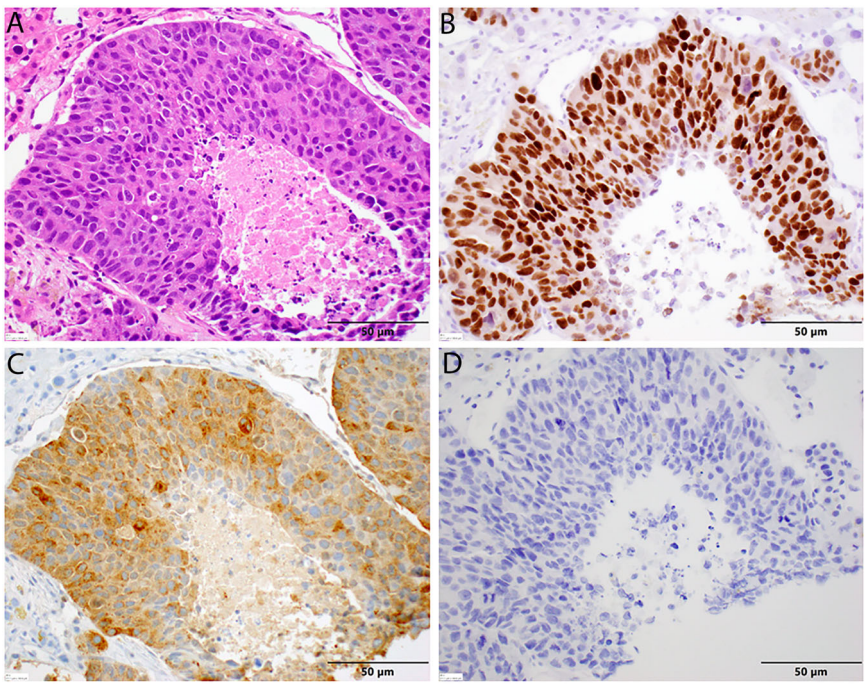

FIGURE 1 | Histopathology of liver biopsy. **(A)** Metastatic prostate adenocarcinoma displaying significant nuclear enlargement and pleomorphism, prominent nucleoli, mitotic figures, and comedo-type central necrosis in this representative field. Note the absence in neuroendocrine features and the surrounding benign hepatocytes [H&E stain, 40× magnification]. **(B)** Diffuse nuclear positivity with NKX3.1 in tumor cells [NKX3.1 stain, 40× magnification]. **(C)** Diffuse cytoplasmic positivity with PSA in tumor cells. **(D)** No cytoplasmic staining with chromogranin in tumor cells [chromogranin, 40× magnification].

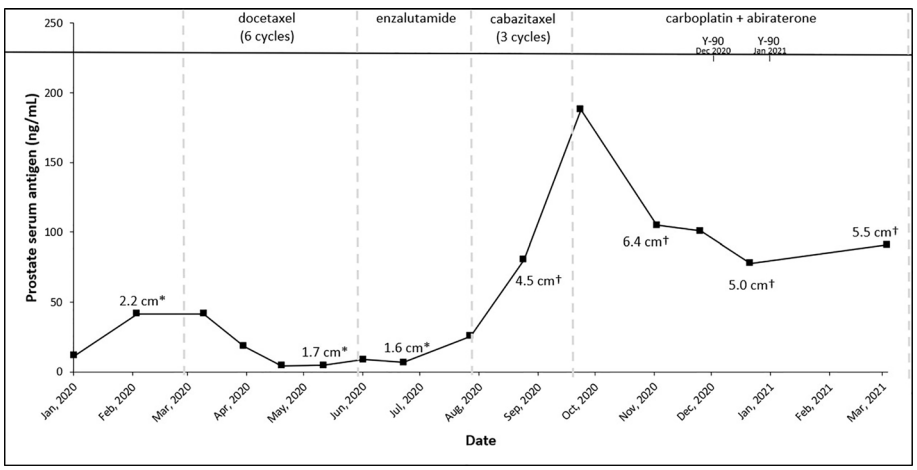

FIGURE 2 | Trends of treatment, prostate serum antigen, and tumor size across patient's treatment course. *Right inferior lobe lesion and †segment 7 lesion.

tolerated the treatment well without having any major side effects except grade 2 fatigue and grade 2 nausea/vomiting. His PSA slowly trended down and became stable, as shown in **Figure 2**. Repeat CT scans showed a partial response in the liver. He remains on the same chemotherapy/hormonal therapy combination at the time of writing with stable response (**Figure 3G**).

DISCUSSION

To our knowledge, abiraterone acetate/carboplatin/radiation combination therapy has never been studied in mCRPC patients; we report the first case on this chemotherapy/hormonal therapy/radiation therapy combination. This case

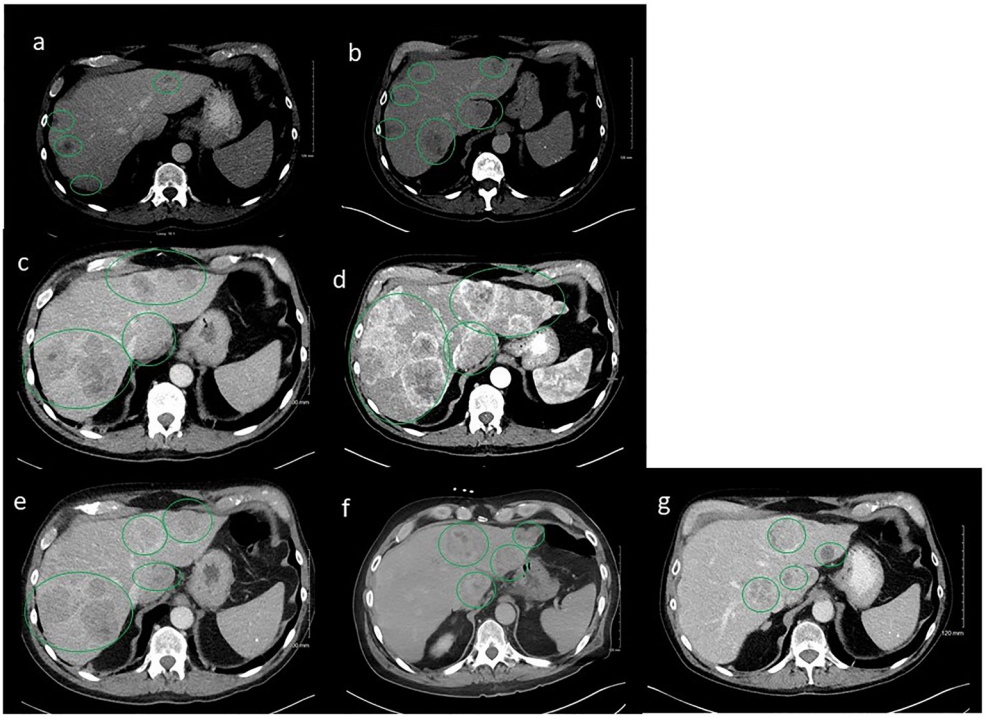

FIGURE 3 | Serial computerized tomography (CT) images of abdomen and pelvis with contrast of the patient's tumor after sequencing treatments. Green oval cycles represent tumors. **(A)** Prior to docetaxel, March 2020. **(B)** Six cycles after docetaxel, June 2020. **(C)** Two months after enzalutamide, August 2020. **(D)** After three cycles of cabazitaxel, October 2020. **(E)** After Y-90 embolization to the right lobe of liver concurrent with carboplatin/abiraterone acetate, December 2020. **(F)** After Y-90 embolization to the left lobe of liver concurrent with carboplatin/abiraterone acetate, January 2021. **(G)** On carboplatin/abiraterone acetate, May 2021.

demonstrates the clinical utility of the above combination therapy in patients with metastatic CRPC with *PTEN* loss.

Prostate cancer is a heterogenous disease and a small subset of the prostate adenocarcinoma population can present with aggressive clinical features like neuroendocrine origin. This subpopulation frequently carries some driver molecular alterations in retinoblastoma-associated protein 1 (*RB1*), tumor protein 53 (*TP53*), and/or *PTEN* (22). These alterations have been associated with abnormal cell proliferation and increased DNA damage response defects through activation of Akt signaling (23).

Loss of *PTEN* by mono- and biallelic deletions or mutations is among the most frequently observed molecular aberrations in localized and metastatic prostate cancer. *PTEN* loss is identified in 15%–20% of primary prostate tumor samples (12). Upon progression to castrate-resistant disease, the incidence increases to 40%–60% (12). *PTEN* loss is known to be associated with a poor prognosis (12). *PTEN* plays a crucial role as a tumor suppressor in cell cycle by controlling both G1/S and G2/M transitions (24). Loss of *PTEN* promotes activation of the PI3K/AKT/mTOR signaling pathway, which modulates several downstream pathways. This signaling pathway also causes abnormal cell proliferation and survival (25–27). *PTEN* regulates *p53* by modulating its DNA binding activity. *PTEN* and *p53* both regulate the DNA damage response pathway by promoting nucleotide excision repair (NER) following ionizing radiation damage (28). When *PTEN* function is lost, Akt signaling pathways are activated through inappropriate activation of Chk1 (29) and, thus, impairs DNA damage repair and the DNA damage response pathway (28).

Platinum compounds as monotherapy or combination therapy have shown promising activity in mCRPC (7, 8). Platinum-based agents cause mono-, inter-, or intra-strand crosslinking of DNA triggering DNA damage, which activates ATM/Chk2/p53 signaling, inducing apoptosis and cell cycle arrest (30). Interestingly, androgen receptor signaling also regulates DNA repair genes of both non-homologous end joining (NHEJ) and homologous recombination (HR) repair pathways (31). Preclinical studies (both *in vitro* and *in vivo* models) have demonstrated the synergistic combinations of radiation and novel androgen synthesis inhibitors (abiraterone acetate or enzalutamide) in both androgen-dependent and androgen-independent prostate cancer (31, 32). The rationale is that the ionizing radiation enhances DNA damage, which then activates the ATM/Chk2/p53 signaling pathway promoting cell cycle arrest (33, 34). Anti-androgen therapy further augments by decreasing DNA repair genes and, thus, inducing synthetic lethality and causing apoptosis of prostate cancer cells (31, 35). Recent early-phase studies further confirmed the clinical efficacy data of these synergistic combinations (36–38). Phase III studies are ongoing.

We hypothesize that a response was seen in this case because carboplatin and radiation both induce DNA damage through the

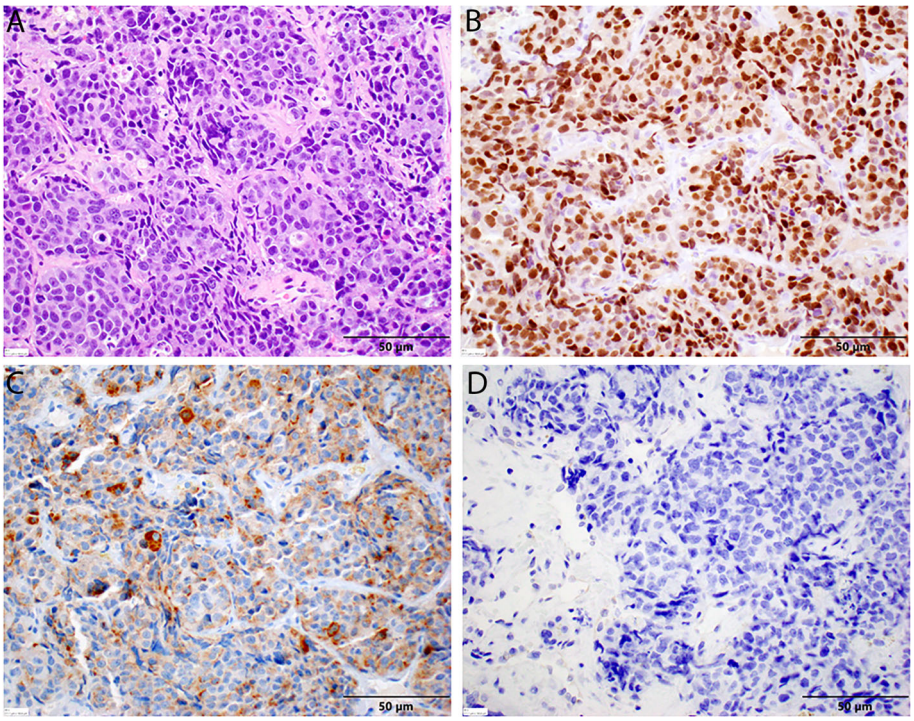

FIGURE 4 | Histopathology of second liver biopsy. **(A)** Metastatic prostate adenocarcinoma displaying similar features to the previous sample, including significant nuclear enlargement and pleomorphism, prominent nucleoli, mitotic figures, and single-cell necrosis in this representative field. Again, note the absence of neuroendocrine features [H&E stain, 40× magnification]. **(B)** Diffuse nuclear positivity with NKX3.1 in tumor cells [NKX3.1 stain, 40× magnification]. **(C)** Diffuse cytoplasmic positivity with PSA in tumor cells. **(D)** No cytoplasmic staining with chromogranin in tumor cells [chromogranin, 40× magnification].

ATM/Chk2/p53 pathway, and the loss of *PTEN* activates the PI3K/AKT pathway and causes DNA damage repair, which is further augmented by adding anti-androgen therapy. Therefore, the combination has some synergistic or additive benefits. While the underlying basic mechanism of our patient's anti-tumor response remains uncertain, our case highlights the possible benefit and safety of combination carboplatin/abiraterone acetate/radiation in treated mCRPC and suggests that further prospective studies are warranted to evaluate whether this combination therapy is effective in this population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ZM and CE: drafting of the article, acquisition of data, and final approval of the manuscript. DA: providing histopathology pictures and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Oncology

CASE REPORT
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Highlighting the Place of Metastasis-Directed Therapy in Isolated Liver Metastases in Prostate Cancer: A Case Report

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Metastatic prostate cancer remains a challenge for clinicians. Metastases involve mainly the bone compartment and can manifest as oligometastatic disease. In this setting, the role of metastasis-directed therapies (MDT) including surgery and/or stereotactic body radiotherapy is currently evaluated. Visceral metastases are less common and have very poor prognosis in mPC. Whether treating isolated visceral metastases such as liver metastases with MDT could increase the prognosis remains unknown. We report the management of a prostate cancer patient who progressed on androgen deprivation therapy with apparition of two liver metastases. We describe the feasibility of combining MDT with abiraterone acetate and prednisone in a patient with metastatic castration-resistant prostate cancer. MDT allowed the interruption of abiraterone acetate, preventing cumulative toxicity of this agent.

Keywords: metastasis-directed therapy, liver metastasis, oligometastatic, prostate cancer, abiraterone acetate, case report

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INTRODUCTION

Prostate cancer (PC) is, among men, the second common malignancy and the fifth cancer-related leading cause of death worldwide (1). Even if localized PC is treated with a curative intent and excellent outcome, the management of metastatic PC (mPC) remains a challenge for clinicians with a very poor outcome and limited therapeutic options. Metastases from prostate cancer involve mainly the bone compartment and lymph nodes (2). Between the localized and generalized metastatic statuses, oligometastatic disease represents a transition defined by a limited number of metastatic lesions that do not rapidly spread to other sites. Even if this transitional status naturally progresses into disseminated metastatic disease, it could represent a window of opportunity for localized radical treatment. Oligometastatic disease is usually defined by a maximum number of metastatic sites between 3 and 5 (3). However, this definition is largely based on conventional imaging such as bone scan and thoraco-abdominal computed tomography (CT); the increasing use of modern imaging such as PSMA-positron emission tomography (PET) and whole-body magnetic resonance imaging (MRI) will probably allow a better definition of this entity. There are no clear guidelines concerning

the management of oligometastatic disease in PC, but many trials are evaluating the role of metastasis-directed therapies (MDT) such as stereotactic body radiotherapy (SBRT) or surgery in this setting (4). Even if MDT could potentially increase progression-free survival (PFS) and delay the initiation of androgen deprivation therapy (ADT) in hormono-sensitive metastatic PC, the role of MDT remains controversial in castration-resistant PC (CRPC) patients with visceral metastases (5, 6). We report the case of a patient with isolated liver metastases progressing on ADT. Could MDT be an option in this patient?

CASE PRESENTATION

In July 2008, based on a prostate-specific antigen (PSA) increase (8.5 ng/ml), a 69-year-old man without relevant medical history was diagnosed with a localized prostate adenocarcinoma Gleason 7 (3 + 4). No distant lesion was seen on conventional work-up (bone scan and thoraco-abdominal CT). Radical prostatectomy was performed with lymphadenectomy, confirming Gleason 8 (4 + 4) prostate adenocarcinoma invading the seminal vesicles (cT3bN0M0) (**Figure 1**). Postsurgical PSA was undetectable. Six months later, PSA increased to 0.34 ng/ml and salvage pelvic radiotherapy (70 Gy in 35 fractions of 2 Gy according to the intensity-modulated radiotherapy (IMRT) and an 18-month duration of ADT was performed with a subsequent decrease of PSA (<0.02 ng/ml). In June 2014, PSA re-increased (1.05 ng/ml) with no visible lesion on bone scan and thoraco-abdominal CT; the testosterone level was within normal range (200 ng/dl). A ^{68}Gallium (Ga)-PSMA-PET-CT showed two infra-centimetric lymph node lesions (one in the para-rectal area and one in the pre-sacral area). ADT was initiated, and SBRT was performed on these lesions, with a delivered dose of 54 Gy (2 Gy per fraction). PSA decreased progressively with a nadir of 0.5 ng/ml in June 2015 (testosterone <20 ng/dl); ADT was maintained. In October 2015, PSA increased to 10 ng/ml on ADT (testosterone <20 ng/dl) and thoraco-abdominal CT showed one isolated liver lesion. ^{68}Ga-PSMA-PET, ^{18}Fluorodeoxyglucose (FDG)-PET, and liver magnetic resonance imaging (MRI) showed two liver lesions (lesion A = an 11-mm lesion located in segment VII and lesion B = a 20-mm lesion involving both segments V and VI) (**Figure 2**). Biopsy confirmed prostate adenocarcinoma without any neuroendocrine differentiation (**Figure 3**). Abiraterone acetate plus prednisone (AA-P) was added to ADT and resulted, at 6 months, in a PSA decrease (0.15 and 0.16 ng/ml at 6 and 9 months, respectively) and modest tumor shrinkage (-10% following RECIST criteria at 6 and 9 months, respectively). The limited number of liver lesions, the well-circumscribed aspect of these lesions, the absence of any other visible lesion, and the absence of a more pronounced radiological response led us to consider MDT in addition to ADT and AA-P; in August 2016, microwave needle ablation was performed on lesion A, and 4 weeks later, we performed SBRT (50 Gy in 5 fractions of 10 Gy) on lesion B that was less accessible to radiofrequency (**Figure 4**). This treatment was well tolerated. In November 2016, PSA was undetectable (<0.01 ng/ml) and liver MRI did not show any active lesion, which led us to consider interruption of AA-P and continuation of ADT alone. Nine months after AA-P arrest, PSA re-increased (0.6 ng/ml) and ^{68}Ga-PSMA-PET showed a new liver metastasis, close to the irradiated site, without any other distant lesion. AA-P was restarted in October 2017 (testosterone <20 ng/dl) but did not result in a PSA decrease (1.1 ng/ml) or radiological response (5% increase in tumor size, following RECIST criteria) after 9 months; no new lesion was detected on ^{68}Ga-PSMA-PET. In front of this maintained radiological stable disease, surgical liver segmentectomy was performed in September 2018; histopathology showed Gleason 8 (4 + 4) prostate cancer adenocarcinoma without neuroendocrine differentiation. Resection was complete, and there were no postoperative complications. AA-P was stopped after surgery while ADT was continued. PSA remained stable at 6 and 9 months (1.5 and 1.9 ng/ml, respectively), and thoraco-abdominal CT did not show any new metastatic lesion at 6 months. However, 12 months after surgery, PSA increased to 12 ng/ml and multiple liver lesions appeared on thoraco-abdominal CT and liver MRI. In September 2019, docetaxel (75 mg/m^2 every 3 weeks) was started without any radiological response after 3 cycles (progressive disease following RECIST criteria). Six cycles of cabazitaxel (20 mg/m^2 every 3 weeks) were administered, resulting in a 6-month lasting stable disease. After failure of docetaxel and cabazitaxel, we rapidly initiated platinum-based chemotherapy. After six courses, our patient presented a radiological partial response following RECIST criteria with maintained quality of life. In April 2021, clinical and radiological response was maintained and no treatment had to be reintroduced.

DISCUSSION AND CONCLUSION

Visceral metastases occur in up to 32% of CRPC patients during disease evolution, involving most commonly the liver and lungs (6, 7). This incidence could increase with time, due to improvement of patient survival and increasing selection of aggressive clones. Liver metastases are associated with poor outcome; in a meta-analysis evaluating 8,820 mCRPC patients treated with docetaxel, the median OS reached 31.6 months in men with lymph node-only disease, 21.3 months in men with non-visceral bone metastases, 19.4 months in men with lung metastases, and 13.5 months in men with liver metastases (2). However, these patients do benefit from conventional treatments including abiraterone, enzalutamide, and chemotherapy (8, 9, 5). MDT of isolated metastases, particularly bone metastases, is emerging as a potential option in PC treatment. Ost et al. showed in a phase II trial (STOMP trial) that MDT could delay CRPC-free survival and the ADT-free survival in hormonosensitive PC with bone or lymph node metastases (6). However, the benefit of MDT remains unclear in the CRPC setting and in liver metastases.

We highlight in this report the feasibility of combining MDT to AA-P in a CRPC patient with isolated liver metastases. The first MDT (SBRT) allowed AA-P interruption during 9 months.

Abbreviations: AA-P, abiraterone acetate prednisone; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; MDT, metastasis-directed therapies; mPC, metastatic prostate cancer; MRI, magnetic resonance imaging; PC, prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy.

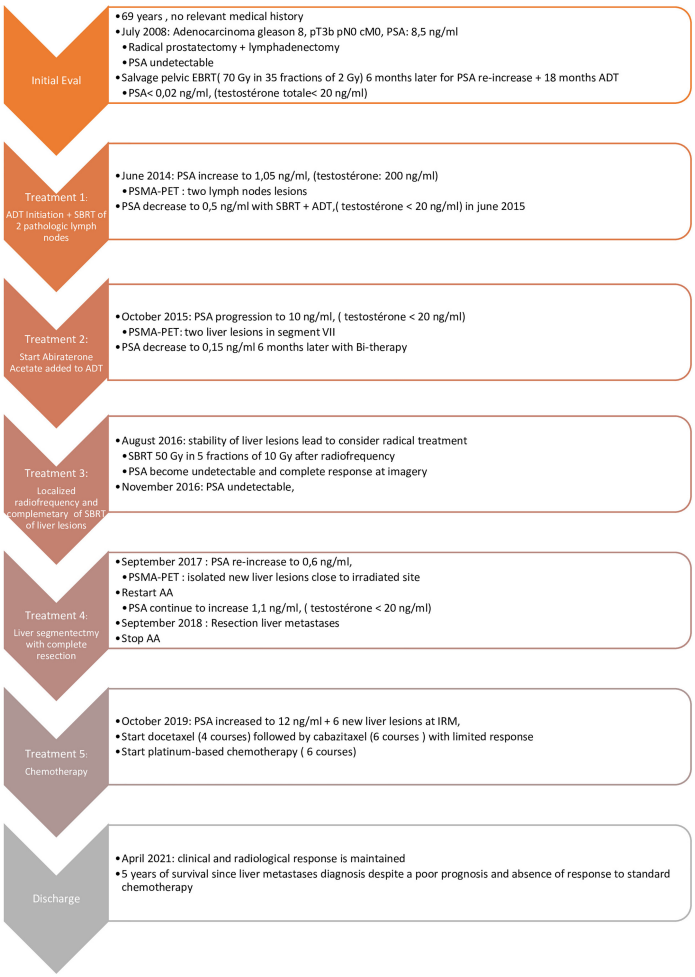

FIGURE 1 | Timeline.

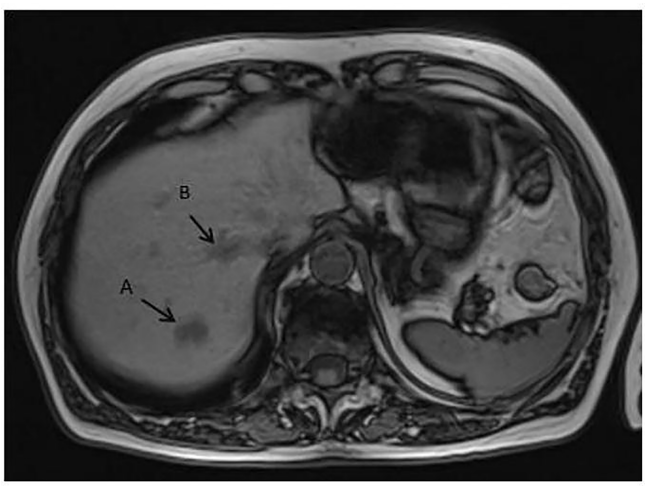

FIGURE 2 | MRI liver revealed two metastases: **(A)** in segment VII and **(B)** straddling segments V and VI.

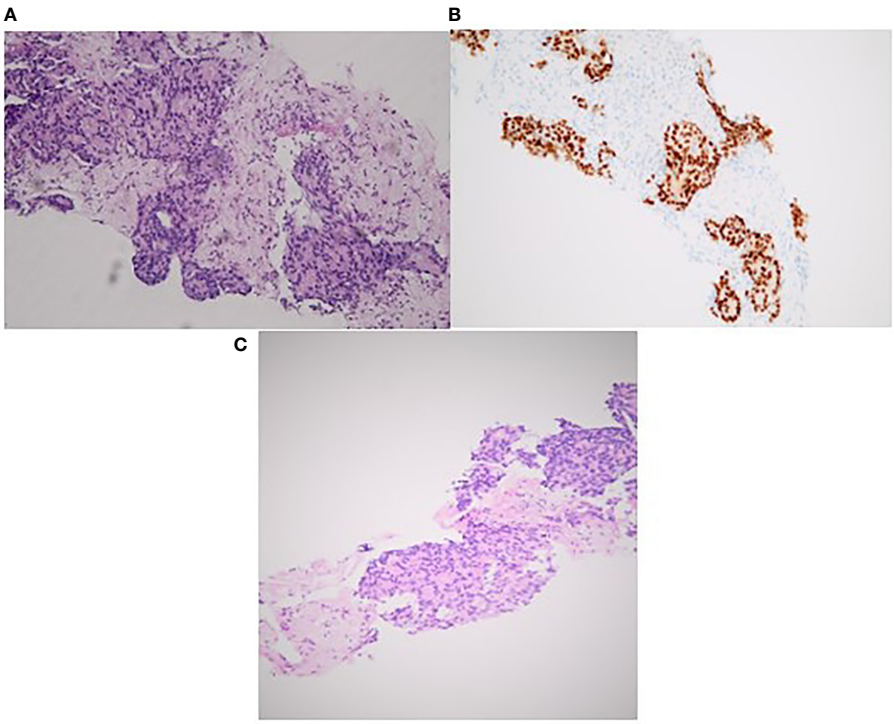

FIGURE 3 | Histopathology findings of liver biopsy lesions confirming prostatic origin with cribriform pattern **(A)**. Positive staining for PSA **(B)**. Hematoxylin and eosin stain (×20) **(C)**.

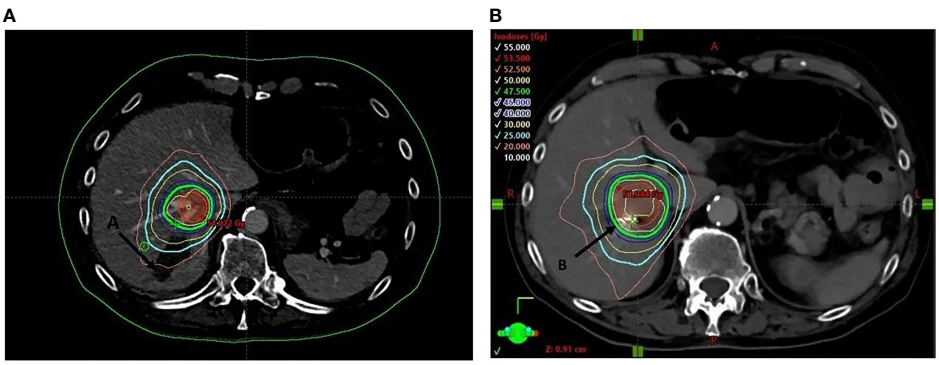

FIGURE 4 | Dose distribution of the stereotactic body of radiotherapy (50 Gy in five fractions) of lesion **(B)** (coils) post radiofrequency of lesion **(A)**.

At local resurgence, a new MDT strategy (surgery) allowed AA-P arrest and delayed the initiation of a new systemic treatment during 12 months.

We thus showed that, even in liver metastasis and CRPC settings, MDT was feasible and could be considered in order to interrupt systemic treatment and/or decrease cumulative toxicities related to the long use of AA-P. Furthermore, this strategy also delayed the initiation of chemotherapy that, in this case, appeared poorly efficient and that in other patient cases could not be appropriate (low-volume disease in the elderly population, in which docetaxel could deteriorate life quality).

This case highlights the feasibility of combining MDT to AA-P in a CRPC patient with liver metastases and the subsequent possibility to interrupt temporary systemic treatment. Two other options could have been proposed in this patient: the first one was to consider only AA until progression, as recommended by guidelines, and the second one was to continue AA after the first MDT. We do not know whether these options could have led to

similar or superior outcomes for our patient. The impact of intermittent AA-P is also not known as no clinical trial has evaluated this strategy. Another limitation is that we mainly based on PSA evolution to decide the MDT strategy or AA-P interruption; further biomarker or imaging tools are needed to correctly define a real oligometastatic status (9–11).

To our knowledge, there are only 10 case reports focusing on the efficacy of MDT in isolated non-lymph-node visceral metastatic lesions (three patients with liver lesions, one patient with cerebral lesions, three patients with testicular lesions, two patients with lung lesions, one patient with testicular and cerebral lesions). MDT consisted in surgical resection for these patients (**Table 1**) (11–20). The radical management of isolated metastases resulted in all these patients in a decrease of PSA; the PFS was equal or superior to 1 year in six patients (and not available in two patients), and OS reached 2 years in four patients (not available in three patients).

This case report suggests the feasibility to combine MDT to systemic treatment in poor prognosis mCRPC patients. Increasing evidence shows the efficacy of MDT in delay systemic treatment

TABLE 1 | Patient cases reported for metastasis directed therapy in visceral oligometastatic prostate cancer (January 2010–January 2020).

Authors	Initial tumor characteristics	Primary tumor treatment	Progression	Non-visceral metastases	Visceral metastases and clinical features	Metastases management (SBRT/ surgery)	Systemic treatment following VM diagnosis	- PSA response- PFS- Systemic treatment- Outcome
Tilmans et al., 2020 (12)	67 years PSA: unknown TNM: unknown Gleason: unknown	- RP - 8 years later: salvage prostatic EBRT + ADT	Metastatic progression on ADT 18 months after onset of EBRT-ADT	None	- 1 liver metastasis - PSA: 32 ng/ml - No neuroendocrine	- Extended left hepatectomy	- ADT - Docetaxel (6 courses every 3 weeks) Before hepatectomy	- PSA < 1 ng/ml - PFS = 1 years - Enzalutamide - OS = 32 months
Ishizaki et al., 2019 (13)	63 years PSA: 9.95 ng/ml T4N1M0 Gleason 5 + 5	- Neo adjuvant ADT + docetaxel (6 courses every 3 weeks) - Prostatic EBRT	Metastatic progression on ADT 22 months after docetaxel	None	- 1 cerebellar metastasis - PSA: 1.34 ng/ml - No neuroendocrine	- Surgical resection + WBRT	- Unknown	- PSA < 1 ng/ml - PFS = 23 months - No systemic treatment - OS = 23 months
Kawai et al., 2017 (14)	55 years PSA: unknown TNM: unknown Gleason: unknown	- RP - Adjuvant ADT - Salvage EBRT 11 years later + ADT (not interrupted since diagnosis)	- Metastatic progression on ADT (never interrupted) 4 years after EBRT	None	- 1 liver metastasis - PSA = 13.77 ng/ml - No neuroendocrine	- Surgical segmentectomy	None	- PSA= 0.54 ng/ml - PFS: 9 months - Docetaxel - OS: NA
Chang et al., 2017 (15)	80 years PSA: unknown TNM: unknown Gleason 4 + 4	- Prostatic EBRT	Metastatic progression 3 years after EBRT	None	-Right testicular metastasis and 1 cerebral metastasis PSA: 319 ng/ml - No neuroendocrine	- Orchiectomy and - 5 fractions of stereotactic brain radiotherapy	None	- PSA decreased to undetectable - PFS = NA - OS = NA
Bonetta et al., 2017 (16)	58 years PSA: 7.6 ng/ml pT3bN0M0 Gleason 4 + 5	- RP - Adjuvant RT - ADT declined by the patient	Metastatic Progression 32 months after RT	None	- Left testicular metastasis - PSA: 0.61 ng/ml - No neuroendocrine	- Orchidectomy	None (ADT declined by the patient)	- PSA decreased to 0.01 ng/ml. - PFS ≥ 5 years - No new systemic treatment - OS ≥ 5 years
Wang et al., 2016 (17)	68 years PSA: 7.6 ng/ml pT3aN0M0 Gleason 3 + 4	-EBRT+ 18-month ADT	Metastatic Progression 6 years after end of ADT	None	- 1 liver metastasis - PSA: 48 ng/ml - No neuroendocrine	- Left hepatic lobectomy	ADT	- PSA decreased to < 0.01 ng/ml - PFS ≥ 1 year - No new systemic treatment - OS ≥ 1 year
Peres Gago et al., 2016 (18)	55 years PSA: 4.5 ng/ml pT3aNX Gleason 4 + 3	- RP - Salvage EBRT 2 years later (No ADT)	Progression 22 months after EBRT	None	- Lung nodules - PSA: NA - No neuroendocrine	- Surgical resection	ADT	- PSA decreased to < 0.01 ng/dl - PFS ≥ 4 years - No new systemic treatment - OS ≥ 4 years

(Continued)

TABLE 1 | Continued

Authors	Initial tumor characteristics	Primary tumor treatment	Progression	Non-visceral metastases	Visceral metastases and clinical features	Metastases management (SBRT/ surgery)	Systemic treatment following VM diagnosis	- PSA response- PFS- Systemic treatment- Outcome
Wallis CJD et al., 2011 (19)	46 years PSA: 14.7 ng/ml pT3aN0M0 Gleason 4 + 5	- Neo-adjuvant ADT - RP - Salvage EBRT 6 years later (no ADT)	Metastatic progression 6 months after EBRT	None	- 3 lung nodes - PSA: NA - No neuroendocrine	- Surgical resection	Unknown	- PSA decreased to 0.28 ng/ml - PFS: 9 months - No new systemic treatment - OS > 1 years
Kwon et al., 2011 (20)	66 years PSA: unknown pT3N0M0 Gleason 4 + 5	- RP - Adjuvant EBRT + ADT	Metastatic progression on ADT 4 months after EBRT	None	- Testicular metastasis - PSA: 0.347 ng/ml - No neuroendocrine feature	- Orchidectomy	ADT continuation	- PSA decreased to 0.03 ng/ml - PF = NA - OS = NA
Janssen et al., 2010 (21)	68 years PSA: 7.66 ng/ml pT3bpN0M0 Gleason 3 + 3 Cribriform feature	- Neo adjuvant ADT - RP - Salvage EBRT 2.5 years later	Metastatic Progression 1 month after end of RT	None	- Testicular metastasis - PSA: 3.08 ng/ml - No neuroendocrine feature	- Orchiectomy	None	- PSA decreased to 0.07 ng/dl - PFS ≥ 2 years - No new systemic treatment - OS ≥ 2 years

EBRT, external beam radiotherapy; RP, radical prostatectomy; HT, hormone therapy; ADT, androgen deprivation therapy; PND, pelvic node dissection; LFT, liver function test; Pca, prostate cancer; PFS, progression-free survival; WBRT, whole-brain radiotherapy; OS, overall survival.

onset in the early mPC stage (metastatic hormonosensitive PC). We suggest that this strategy could also be considered very early in CRPC patients particularly if MDT could allow systemic treatment interruption, prevent cumulative toxicities, and delay subsequent line of treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s)' and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

A-EY analyzed all the data and was a major contributor in writing the manuscript. AH performed the oncologic treatment and contributed to the writing manuscript. CC performed the oncologic treatment and contributed to the writing of the manuscript. NC performed the SBRT treatment and contributed to the writing of the manuscript. BM performed the liver surgery and contributed to the writing of the manuscript. GP performed the histopathology analysis and contributed to the writing of the manuscript. ES performed the oncologic treatment and was a major contributor in writing the manuscript. All authors contributed to the article and approved the submitted version.

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PI-RADS v2.1 Combined With Prostate-Specific Antigen Density for Detection of Prostate Cancer in Peripheral Zone

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Purpose: To evaluate the diagnostic performance of combining the Prostate Imaging Reporting and Data System (PI-RADS) scoring system v2.1 with prostate-specific antigen density (PSAD) to detect prostate cancer (PCa).

Methods: A total of 266 participants with suspicion of PCa underwent multiparametric magnetic resonance imaging (mpMRI) in our hospital, after at least 4 weeks all patients underwent subsequent systematic transrectal ultrasound (TRUS)-guided biopsy or MRI-TRUS fusion targeted biopsy. All mpMRI images were scored in accordance with the PI-RADS v2.1, and univariate and multivariate logistic regression analyses were performed to determine significant predictors of PCa.

Results: A total of 119 patients were diagnosed with PCa in the biopsy, of them 101 patients were diagnosed with clinically significant PCa. The multivariate analysis revealed that PI-RADS v2.1 and PSAD were independent predictors for PCa. For peripheral zone (PZ), the area under the ROC curve (AUC) for the combination of PI-RADS score and PSAD was 0.90 (95% CI 0.83-0.96), which is significantly superior to using PI-RADS score (0.85, 95% CI 0.78-0.93, P=0.031) and PSAD alone (0.83, 95% CI 0.75-0.90, P=0.037). For transition zone (TZ), however, the combination model was not significantly superior to PI-RADS alone, with AUC of 0.94 (95% CI 0.89-0.99) vs. 0.93 (95% CI 0.88-0.97, P=0.186).

Conclusion: The combination of PI-RADS v2.1 with PSAD could significantly improve the diagnostic performance of PCa in PZ. Nevertheless, no significant improvement was observed regarding PCa in TZ.

Keywords: mpMRI, prostate neoplasm, diagnostic performance, PSAD; PI-RADS

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INTRODUCTION

PCa is the most common malignancy among males in Northern America and Europe, where one in nine men will be diagnosed with prostate cancer at some point during their lifetime (1, 2). Compared with conventional examinations such as serum prostate-specific antigen (PSA) and digital rectal examination (DRE) (3, 4), mpMRI has demonstrated more accuracy in localizing,

diagnosis, and staging of PCa. Previous studies showed MRI-targeted fusion biopsy is superior to the conventional standard transrectal ultrasonography (TRUS)–guided biopsy (5–8). Besides, a rencently published study demonstrated that MRI-targeted fusion biopsy could significantly reduce the risk of Gleason Score (GS) 3 + 4 upgrading at radical prostatectomy compared to standard biopsy (9). In 2019, the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR) updated the Prostate Imaging-Reporting and Data System (PI-RADS) to version 2.1, which is a standardized scoring system for performing, interpreting, and reporting the PCa with mpMRI (10–12). Despite this guideline having been widely applied in clinical practice, the inter-reader agreement is not very high and the reported diagnostic performance varied widely (13). Furthermore, using PI-RADS alone may result in a moderate diagnostic accuracy for PCa (14), a recent study revealed that the pooled sensitivity and specificity for version 2.1 were 0.87 and 0.74, respectively (15). Therefore, a combination of MRI with other clinical parameters and biomarkers should be considered to improve the diagnostic performance. Among several potential factors, PSAD was considered as a promising predictor for the presence of PCa (16–18).

The National Comprehensive Cancer Network (NCCN) guidelines suggest a PSAD value below 0.15 ng/ml/ml for very low-risk cancer (19), and several studies have demonstrated that PSAD could be regarded as an independent predictor or in conjunction with other clinical information for staging or evaluation of PCa (16, 18, 20, 21). Thus, the objective of our study was to evaluate whether the diagnostic performance of PI-RADS v2.1 could be improved by adding PSAD.

METHODS AND MATERIALS

Study Population

This retrospective study was approved by our institutional review board who waived the requirement for informed consent and was conducted in accordance with the Declaration of Helsinki. We searched the electronic database of our institution for consecutive 309 patients who underwent mpMRI and subsequent systematic TRUS-guided prostate biopsy and/or MRI-TRUS fusion targeted biopsy between July 2017 and June 2020. We excluded 43 patients for reasons as follows: 1) history of biopsy or treatment; 2) the images were fuzzy or with artifacts; and 3) missing clinical data. The patient selection process is described in **Figure 1**.

Image Acquisition

All mpMRI examinations were performed on a 3.0 T MRI scanner (Philips Ingenia, The Netherlands) before biopsy, with a 32-channel body phased-array coil. The imaging acquisition protocol was in compliance with the PI-RADS v2.1 criteria, which includes high-resolution axial and sagittal T2-weighted imaging (T2WI), and axial diffusion-weighted imaging (DWI). The DWI sequences were obtained with multiple $\boldsymbol{b}$ values ($\boldsymbol{b}$=0, 100, 1,000, 2,000 s/mm^2), in which the values of 100 and 2000 s/mm^2 were used to visually evaluate and analyze the apparent diffusion coefficient (ADC) map.

Image Analysis

All examinations were independently reviewed by two fellowship-trained radiologists (***W.J.***, with 8 years of experience and ***T.T.T.***, with 3 years of experience) in prostate cancer imaging, who were blinded to clinical information and pathologic findings. The PI-RADS v2.1 guidelines were used to score each lesion based on the DWI and T2WI sequences, and the highest overall PI-RADS score of each mpMRI scan was used.

Prostate Biopsy

All patients underwent a 10-core systematic TRUS-guided biopsy after at least 4 weeks of the MRI examination, and MRI-TRUS fusion targeted biopsy was performed for lesions with PI-RADS 2.1 score ≥3. The MRI-TRUS fusion targeted biopsy was performed with ESAOTE Mylab Twice color Doppler ultrasound device, which was equipped with real-time virtual sonography (RVS) imaging fusion system. The prostate biopsies were performed by a qualified urologist who with experience of at least 200 MRI-TRUS fusion biopsies.

Pathology

All specimens were assessed by an experienced pathologist (with 6 years of experience) in our institution according to the International Society of Urological Pathology (ISUP) 2014 updated Gleason score grading system (22, 23). The PSAD was calculated by serum total PSA divided by the prostate volume, which was estimated according to PI-RADS v2.1 recommends that the maximum anteroposterior diameter and longitudinal diameters measured on midsagittal T2WI, while the maximum transverse diameter measured on the axial T2WI.

Statistical Analysis

All statistical analyses were conducted by using STATA 16.0, and a *P* value of less than 0.05 was considered statistically significant. The inter-reader agreement of the PI-RADS v2.1 score was evaluated by weighted Cohen's kappa (κ) statistic: a κ value of <0.20 indicates slight agreement, a κ value between 0.21 and 0.40, fair agreement, a κ value between 0.41 and 0.60, moderate agreement, a κ value between 0.61 and 0.80, substantial agreement, and a κ value of between 0.81 and 1.00, almost perfect agreement.

We performed univariable logistic regression analysis for each variable to investigate the significant predictors of PCa, which included age, PSA level, MRI prostate volume, PSAD, and PI-RADS v2.1 score. Afterward, multivariable binary logistic regression analysis was performed to explore the significant clinical factors for PCa. The AUC was calculated and used to determine the diagnostic performance of variables, and the best combination was defined as the one with the largest AUC. The diagnostic sensitivity and specificity with their 95% confidence intervals (95% CIs) were calculated. A nomogram for the best combination in the multiple logistic regression analyses was generated using "nomology" command in STATA 16.0.

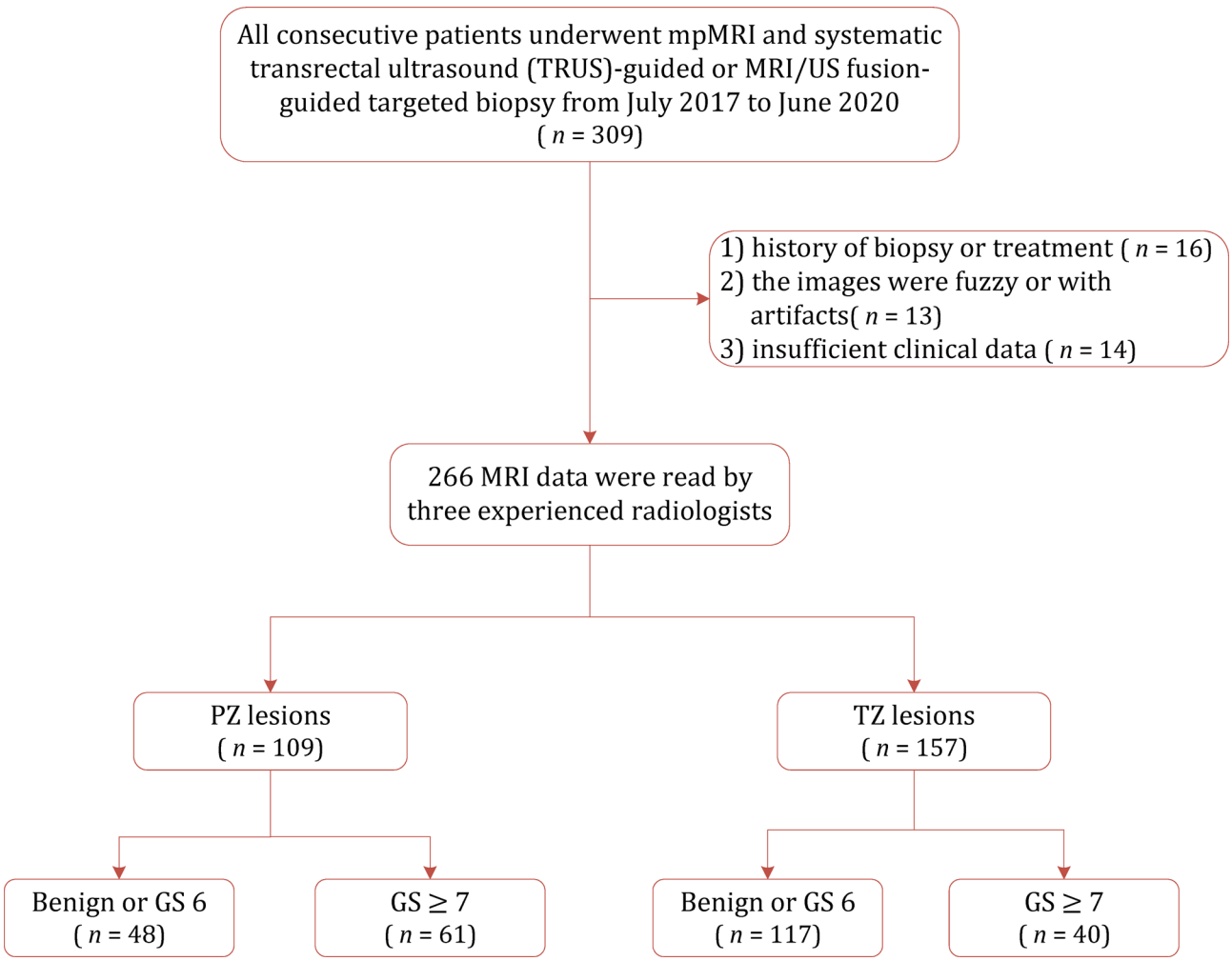

FIGURE 1 | Flowchart of the study population with the exclusion criteria. GS, gleason score; PZ, peripheral zone; TZ, transition zone.

RESULTS

Patient Characteristics

The patient characteristics are summarized in **Table 1**. The median age of 266 patients included was 71.3 years, with a median PSA level of 11.33 (interquartile range [IQR] 6.85-21.4) and median PSAD of 0.21 (IQR 0.12-0.49). A total of 119 patients (39.3%) were diagnosed with PCa in the biopsy, of whom 101 patients were diagnosed with clinically significant PCa (GS ≥ 7 or tumor size ≥ 0.5 mL), and the remaining 18 patients were diagnosed with clinically insignificant prostate cancer (GS=3+3).

Diagnostic Performance of PI-RADS v2.1

The sensitivity and specificity of PI-RADS v2.1 category ≥3 for diagnosing PCa of the whole gland were 96.2% (95% CI 90.5%-98.5%) and 61.3% (95% CI 52.5%-69.4%), respectively. For 157 lesions located in the TZ, a cutoff threshold ≥3 yielded a sensitivity of 94.4% (95% CI 84.9%-98.1%) and specificity 69.9% (95% CI 60.5%-77.9%). Regarding 109 lesions located in the PZ, a cutoff threshold ≥3 yielded a slightly higher sensitivity (98.7%, 95% CI 93.0%-99.8%) but significantly lower specificity (18.6%, 95% CI 8.9%-35.3%). When used PI-RADS category ≥4 as the cutoff threshold, the sensitivity and specificity for diagnosing PCa of the whole gland were 89.4% (95% CI 82.0%-94.0%) and 84.7% (95% CI 77.3%-90.0%), respectively. Regarding TZ, this cutoff yielded a sensitivity of 90.7% (95% CI 80.1%-96.0%) and 89.3% (95% CI 81.9%-93.9%). As for PZ, a cutoff threshold ≥4 yielded slightly higher sensitivity (92.2%, 95% CI 84.0%-96.4%) but lower specificity (65.6%, 95% CI 48.3%-79.6%). The weighted κ value of 0.52 (95% CI 0.50-0.56) suggested that the inter-observer agreement was moderate for PI-RADS v2.1. **Table 2** shows the detailed diagnostic accuracy.

Concerning PSAD, a cutoff value ≥0.15 ng/mL/mL yielded sensitivity of 96.3% (95% CI 87.3%-99.5%), with specificity of 53.4% (95% CI 43.3%-63.3%) in TZ. Whereas for PZ, the generated sensitivity and specificity for this cutoff threshold were 90.9% (95% CI 82.2%-96.3%) and 53.1% (95% CI 34.7%-

TABLE 1 | Patient characteristics. Clinical Characteristics of Patients Analyzed in This Study.

Characteristics	Value
Patients (n=266)	
Age (year, mean±SD)	71.34±8.23
PSA (ng/ml, IQR)	11.33 (6.85-21.4)
PSAD (ng/ml/ml, IQR)	0.21 (0.12-0.49)
Volume (ml, IQR)	52 (36.22-72.38)
Gleason score	
3+3	18
3+4	19
4+3	19
4+4	27
4+5	12
5+4	11
5+5	13
Location	
PZ	109
TZ	157

IQR, interquartile range; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; SD, standard deviation.

70.9%). The optimal cutoff using PSAD for TZ was ≥0.33 ng/mL/mL, at which the sensitivity and specificity were 77.8% (95% CI 64.4%-88.0%) and 86.4% (95% CI 78.2%-92.4%). The optimal cutoff using PSAD for PZ was ≥0.25 ng/mL/mL, at which the sensitivity and specificity were 72.7% (95% CI 61.4%-82.3%) and 81.3% (95% CI 63.6%-92.8%).

Logistic Regression Analyses of PCa

The univariate logistic regression analysis revealed that the variables of PSA, prostate volume, PSAD, and PI-RADS were significant independent predictors for PCa. However, PSA and prostate volume were excluded because they were strongly correlated with PSAD. Eventually, only PSAD and PI-RADS score were included in the multivariable logistic regression analyses. **Table 3** shows the details of logistic regression analyses.

For the whole gland, the predictive power of the combination of PI-RADS and PSAD (AUC 0.94, 95% CI 0.91-0.97) was significantly superior to each of them alone (AUC 0.92, 95% CI 0.88-0.95, P=0.018, and 0.83, 95% CI 0.77-0.88, P<0.001, respectively). We performed analyses according to the location of the lesions. Regarding PZ, PI-RADS in conjunction with PSAD yielded AUC of 0.90 (95% CI 0.83-0.96), which is substantially superior to PI-RADS (AUC 0.85, 95% CI 0.78-0.93, P=0.037) and PSAD (AUC 0.83, 95% CI 0.75-0.90, P=0.031) alone, which is demonstrated in **Figure 2**. As for TZ, however, the improvement of combination (AUC 0.94, 95% CI 0.89-0.99) was not significant as compared to PI-RADS (AUC 0.93, 95% CI 0.88-0.97, P=0.186), but substantially better than PSAD (AUC 0.88, 95% CI 0.82-0.94, P=0.007). The detailed AUC analyses are presented in **Table 4**. A nomogram was generated for predicting PZ PCa, which is based on the combination of PI-RADS score and PSAD (**Figure 3**).

DISCUSSION

Our study demonstrated that both PI-RADS v2.1 and PSAD had a high diagnostic performance for the detection of PCa. The optimal cutoff threshold of PI-RADS score for both PZ and TZ was ≥4, at which the sensitivities were 92.2% and 90.7%, with specificities of 65.6% and 89.3%, respectively. The AUC of PI-RADS v2.1 score for TZ and PZ were 0.85 and 0.93, respectively. According to our analyses, the cutoff threshold of PSAD ≥0.15 ng/mL/mL yielded high sensitivity (90.9% and 96.3% for PZ and TZ) but low specificity (53.1% and 53.4%), with corresponding AUC were 0.83 and 0.88 for PZ and TZ. While in conjunction of PI-RADS score with PSAD, we noted that the diagnostic performance was superior to using these two predictors alone, especially for PZ lesions. The AUC for the combination was 0.94, compared with 0.92 for PI-RADS (P=0.018) and 0.83 for PSAD (P<0.001) alone. We performed analyses according to zonal location, and the combination of AUC 0.90 suggested that the diagnostic accuracy was significantly improved in PZ, where AUC for PI-RADS and PSAD were 0.85 (P=0.031) and 0.83 (P=0.037), respectively. In TZ, however, no significant improvement in diagnostic performance was observed while adding PSAD to PI-RADS, with AUC improved from 0.93 to 0.94 (P=0.186), but it was significantly superior to using PSAD as an independent predictor (AUC 0.88, P=0.007).

Several previous studies have demonstrated that the diagnostic performance was significantly improved as the combination of PI-RADS and PSAD (16, 20, 24). To our knowledge, however, there was no published study on the combination of PI-RADS v2.1 with PSAD for PCa PZ lesions. Distler et al. demonstrated that the NPV of PI-RADS can be improved by including PSAD, with an AUC of 0.79 (95% CI 0.76-0.82) (24). Another study performed by Washino et al.

TABLE 2 | Diagnostic accuracy of PI-RADS and PSAD.

Cutoff	Zonal	Sensitivity	95% CI	Specificity	95% CI
PI-RADS 2.1 ≥ 3	PZ	98.7%	93.0%-99.8%	18.6%	8.9%-35.3%
	TZ	94.4%	84.9%-98.1%	69.9%	60.5%-77.9%
PI-RADS 2.1 ≥ 4	PZ	92.2%	84.0%-96.4%	65.6%	48.3%-79.6%
	TZ	90.7%	80.1%-96.0%	89.3%	81.9%-93.9%
PASD ≥ 0.15 ng/ml/ml	PZ	90.9%	82.2%-96.3%	53.1%	34.7%-70.9%
	TZ	96.3%	87.3%-99.5%	53.4%	43.3%-63.3%
Optimal PSAD (ng/ml/ml)	PZ (0.25)	72.7%	61.4%-82.3%	81.3%	63.6%-92.8%
	TZ (0.33)	77.8%	64.4%-88.0%	86.4%	78.2%-92.4%

CI, confidence interval; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PZ, peripheral zone; TZ, transition zone.

TABLE 3 | Univariate and multivariate logistic regression analyses. Logistic Regression Analysis.

Variable	β Coefficient	Odd Ratio	95% CI	*P* Value
Univariable logistic regression model for PZ				
Volume	-0.004	1.0	0.98-1.01	0.517
PSAD	3.63	37.66	3.3-429.1	0.002
PI-RADS	1.80	6.05	3.1-11.9	<0.001
Age	0.09	1.09	1.03-1.16	0.003
PSA	0.06	1.06	1.01-1.1	0.014
Univariable logistic regression model for TZ				
Volume	-0.3	0.97	0.96-0.99	<0.001
PSAD	2.68	14.57	4.64-45.76	<0.001
PI-RADS	1.92	6.82	4.05-11.49	<0.001
Age	0.02	1.02	0.98-1.06	0.46
PSA	0.03	1.03	1.02-1.05	<0.001
Multivariable logistic regression model for PZ				
PSAD	2.33	10.3	1.01-105.4	0.006
PI-RADS	1.56	4.78	2.26-10.09	<0.001
Multivariable logistic regression model for TZ				
PSAD	1.39	4.03	1.13-14.36	0.032
PI-RADS	1.75	5.76	3.64-9.12	<0.001

PI-RADS, Prostate Imaging Reporting and Data System version 2.1; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PZ, peripheral zone; TZ, transition zone.

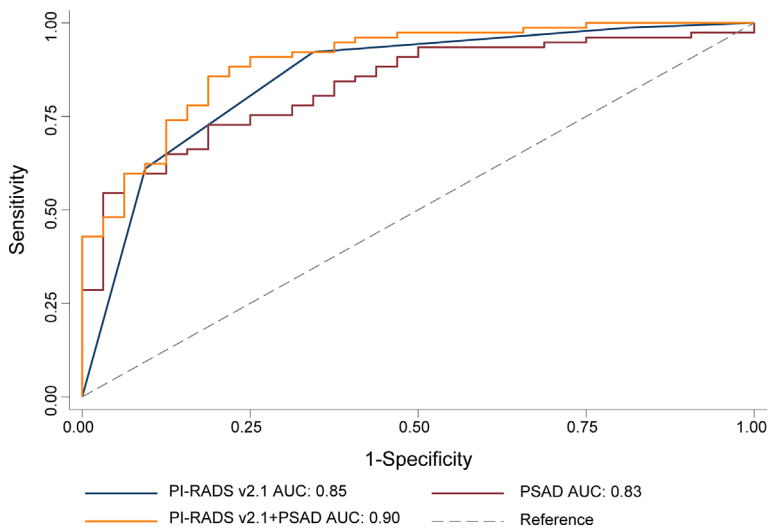

FIGURE 2 | ROC for the comparison of PI-RADS+PSAD with PI-RADS and PSAD alone for the diagnosis of the prostate cancer. PI-RADS, Prostate Imaging Reporting and Data System version 2.1; PSAD, prostate-specific antigen density; AUC, area under the ROC curve.

TABLE 4 | ROC curve analysis for predicting prostate cancer.

Variable	AUC (95% CI)	P Value
Whole Gland		
PSAD	0.83 (0.77-0.88)	<0.001
PI-RADS	0.92 (0.88-0.95)	0.018
PI-RADS+PSAD	0.94 (0.91-0.97)	–
PZ		
PSAD	0.83 (0.75-0.90)	0.037
PI-RADS	0.85 (0.78-0.93)	0.031
PI-RADS+PSAD	0.90 (0.83-0.96)	–
TZ		
PSAD	0.88 (0.82-0.94)	0.007
PI-RADS	0.93 (0.88-0.97)	0.186
PI-RADS+PSAD	0.94 (0.89-0.99)	–

AUC, area under the ROC curve; CI, confidence interval; PI-RADS, Prostate Imaging Reporting and Data System version 2.1; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PZ, peripheral zone; TZ, transition zone.

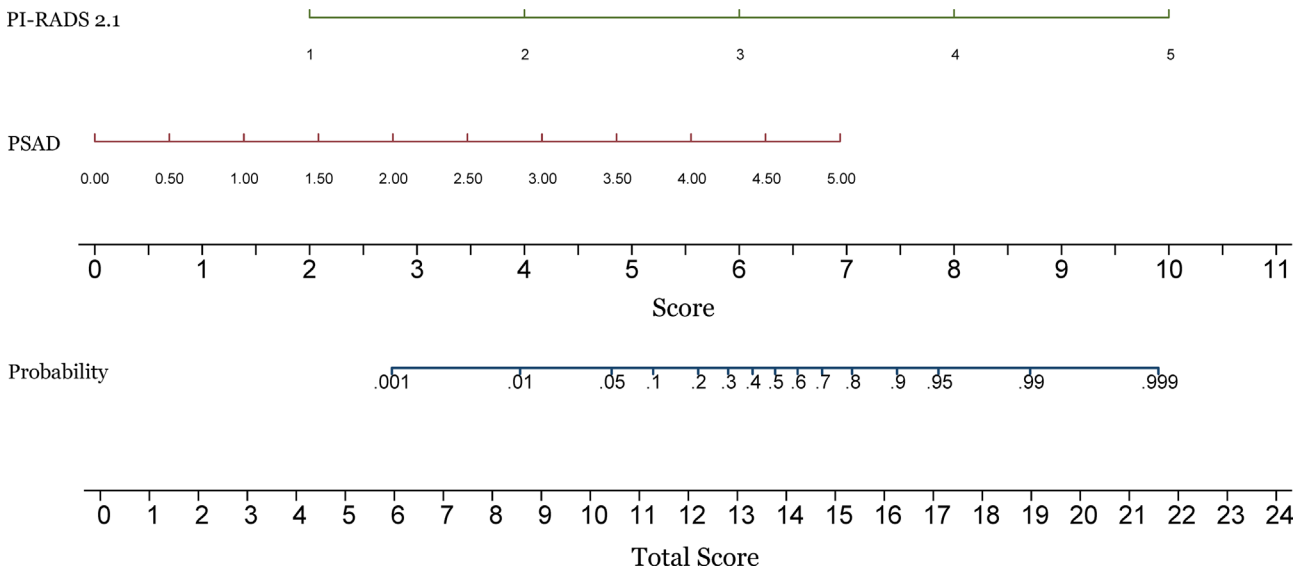

FIGURE 3 | Construction of a nomogram for predicting the probability of prostate cancer in the peripheral zone. PI-RADS, Prostate Imaging Reporting and Data System version 2.1; PSAD, prostate-specific antigen density.

showed that patients with a PI-RADS v2 score of ≤3 and PSA density of <0.15 ng/mL/mL may avoid unnecessary biopsies (16). In our study, however, the optimal cutoff threshold was slightly higher, with 0.25-0.33 ng/mL/mL. Our study demonstrated that the combination of PSAD and PI-RADS was benefitted for detection of any PCa in PZ. In several recent studies, Roscigno et al. demonstrated that that mpMRI is not accurate enough during the AS follow-up, and it is still necessary to combine mpMRI with other clinical variables to improve the predictive accuracy (25, 26).

As a standardized reporting system, the PI-RADS has been validated and widely applied in clinical practice. Two meta-analyses demonstrated that the pooled sensitivity for PI-RADS v1 and v2 were 0.78 and 0.89, with the specificity of 0.79 and 0.73, respectively (27, 28). A more recent study including 14 head-to-head comparisons showed that PI-RADS v2 has slightly higher sensitivity but at the expense of minor decreased specificity (29). To address the problem of variability across institutions and readers, especially for lesions in the transition zone, the ESUR updated PI-RADS to v2.1 in 2019 (12). However, a study revealed that there was no significant difference in diagnostic performance between PI-RADS v2 and v2.1 (15).

Although PI-RADS v2.1 demonstrated good overall performance for the diagnosis of PCa, the specificity for PZ is still lower and thus leads to unnecessary biopsy. Moreover, the sensitivity may vary widely and depend on radiologists' own experience (30–32). As a promising predictor, PSAD has shown promising potential for the detection of PCa. However, using PSAD as independent predictor alone results in lower diagnostic performance, moreover, the cutoff value varied widely (21, 33). A prior study showed that with a cutoff of 0.15 ng/ml/ml the sensitivity and specificity for csPCa were 0.70 and 0.70, respectively. In that study, the highest Youden's index was at PSAD of 0.20 ng/ml/ml, which yielded a sensitivity of 0.70 and specificity of 0.79. According to our results, however, the optimal cutoff thresholds for distinguishing PCa were 0.25 ng/ml/ml for PZ and 0.33 ng/ml/ml for TZ. Therefore, the PSAD should be employed with other methods for the detection of PCa in clinical practice. In summary, the combination of PI-RADS v2.1 score and PSAD could be helpful during the decision-making process before prostate biopsy. Over the past few years several new technologies have been developed for the management of PCa. The implementation of robotic surgery allowed an unprecedented refinement of surgical techniques, moreover, the robot-assisted radical prostatectomy procedure is constantly evolving (34). Additionally, artificial intelligence can help physicians to build personalized predictive models, and a recent study demonstrated that with clinical characteristics, their algorithm can improve the prediction of MRI-TRUS fusion targeted biopsy results, which was superior to PSA, its derivates and mpMRI alone (35).

Our study has some limitations. First, this was a single-center retrospective study, and patient selection bias may limit the generalizability. Therefore, the present results may need further validation in prospective multi-center studies with a larger number of patients. second, the PI-RADS v2.1 score was assessed based on T2WI and DWI sequences. However, the PI-RADS performance based on these two sequences was comparable with those studies that have incorporated dynamic contrast-enhanced, which was considered to play a minor role in the diagnosis of PCa. Thirdly, the reference standard was MRI-TRUS fusion targeted biopsy, which may miss potential lesions with a negative MRI but positive pathology.

CONCLUSION

Adding PSAD to PI-RADS v2.1 score could significantly improve the diagnostic performance of PCa in PZ. Nevertheless, no substantial improvement in accuracy was observed regarding PCa in TZ.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Jiangsu Vocational College of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Guarantor of the article: ZY. Conception and design: WJ and TT. Collection and assembly of data: JY, TT. Data analysis and interpretation: WJ and ZY. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: ^{18}F-PSMA-1007 PET/CT Avid Solitary Penile Metastasis of Castration-Resistant Prostate Cancer With a PSA of 0.072 ng/ml

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Penile metastasis of prostate cancer is rare, with a poor prognosis, and only a limited number of relevant cases have been reported so far. With the application of ^{18}F-PSMA-1007 PET/CT, the biochemical recurrence of prostate cancer can be detected at an early stage for providing important evidence, facilitating clinical decision-making. Here, we have reported a case of solitary penile metastatic recurrence in the context of mild PSA progression (PSA: 0.072 ng/ml). This case highlights the preferable sensitivity of ^{18}F-PSMA-1007 PET/CT imaging in prostate cancer.

Keywords: penile metastasis, ^{18}F-PSMA-1007 PET/CT, prostate cancer, PSA, castration resistance

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BACKGROUND

Secondary penile tumors are rare and have a poor prognosis, with a mortality rate of 80% within 6 months, 28% of which is accounted for by prostate cancer (1–3). Previous literature has reported that penile metastasis occurs mainly secondary to primary prostate cancer without any medical treatment (4, 5) or occurs during an androgen-deprivation therapy (ADT) without surgery (6, 7). However, the present case represents a biochemical recurrence of prostate cancer in the penis during ADT after radical prostatectomy with a PSA of 0.072 ng/ml, which has not been reported in the literature so far.

CASE PRESENTATION

A 60-year-old man visited the hospital with the complaint of intermittent urethralgia and urine arrest. The preliminary screening revealed an elevated PSA of 40.688 ng/ml. Accordingly, prostate cancer was suspected and needle biopsy was performed, followed by confirmation of the adenocarcinoma of the prostate with a Gleason score of 3 + 4 = 7 (**Figure 1**). Considering the patient's unwillingness to undergo surgery and external beam radiotherapy (EBRT), the ADT was adopted with bicalutamide and leuprorelin. PSA decreased significantly at the beginning of treatment, but increased gradually as the treatment progressed, to reach 4.86 ng/ml in October 2018. Prostate magnetic resonance imaging (MRI) confirmed prostate cancer with bladder invasion (**Figure 2**). The patient's condition was evaluated comprehensively, and radical prostatectomy and

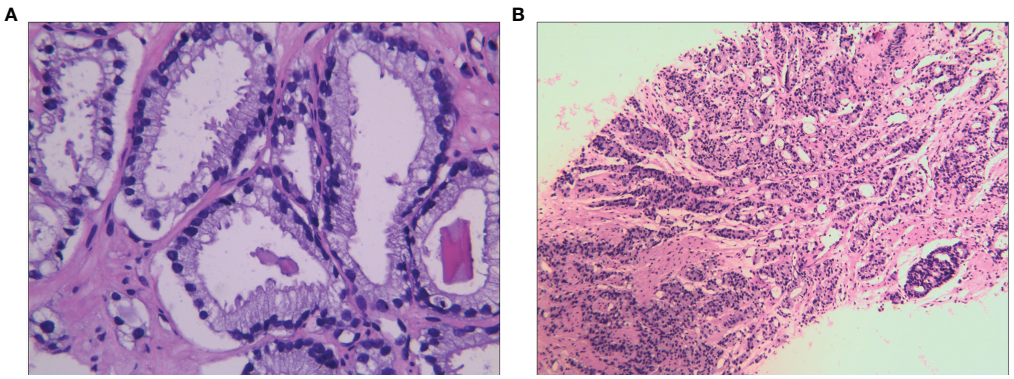

FIGURE 1 | Adenocarcinoma of the prostate with a Gleason score of 3 + 4 = 7 **(A, B)**.

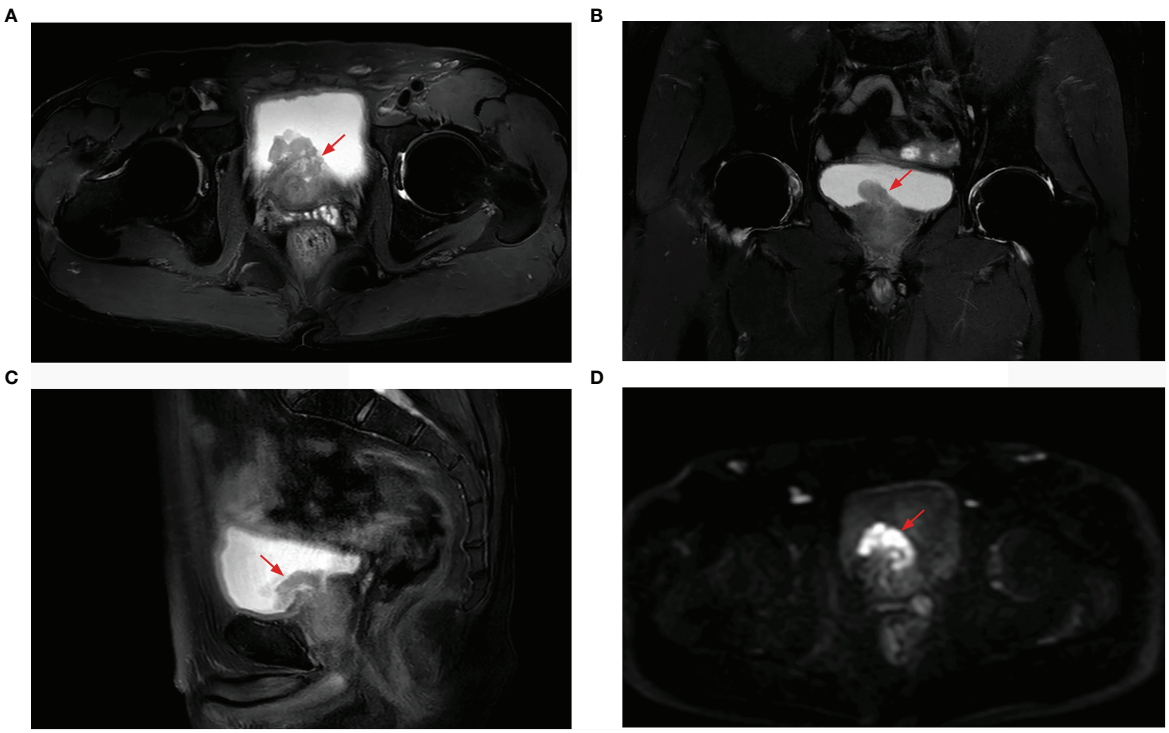

FIGURE 2 | Prostate MRI revealing prostate cancer with bladder invasion, a marked hyperintensity on T2-weighted imaging [**(A)** axial, **(B)** coronal, **(C)** sagittal], and hypointensity on diffusion-weighted imaging **(D)**.

cystectomy were conducted. Adenocarcinoma of prostate cancer combined with nerve and vascular invasion was confirmed with an elevated Gleason score of 5 + 5 = 10, and tumor invasions of the bladder neck, bladder mucosa, and submucosal muscularis were also observed. For the reconstruction of the urinary excretory system, ileocystoplasty was performed (**Figure 3**). A stable serum PSA level (PSA ≤ 0.03 ng/ml) was maintained to reveal a favorable prognosis within a year of surgery. However, a slightly elevated PSA level was noted with a value of 0.035 ng/ml in October 2019, for which ADT with bicalutamide and leuprorelin was undertaken. Biochemical recurrence was suspected, and PET/CT was performed after injection with 11.95 mCi (442.1 MBq) ^{18}F-PSMA-1007 in August 2020 on the recommendation of the patient's physician with a PSA of 0.072 ng/ml. Surprisingly, no other PSMA-avid foci were located in the prostatic bed and the pelvis, except for an intense uptake in the corpus cavernosum with a SUV_{max} of 6.4 (**Figure 4**). Considering the poor efficacy of ADT, abiraterone was applied; meanwhile, the usage of bicalutamide and leuprorelin was

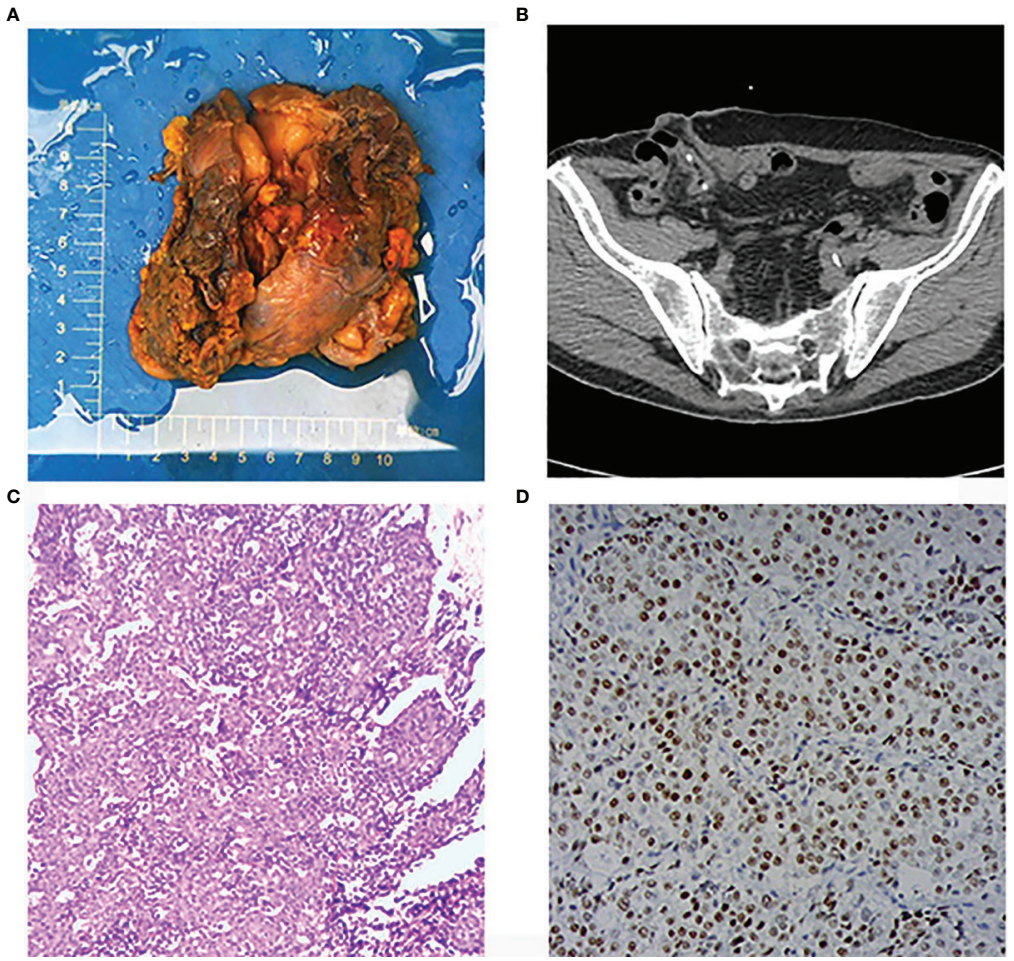

FIGURE 3 | **(A)** Gross specimen of the prostate with a small bladder tissue. **(B)** Ileocystoplasty was performed and a new urinary excretory system was reconstructed. **(C)** H&E staining of bladder invasion lesions showing poorly differentiated prostatic adenocarcinoma with a Gleason score of 5 + 5 = 10. **(D)** Immunohistochemical staining result, NKX3.1(+).

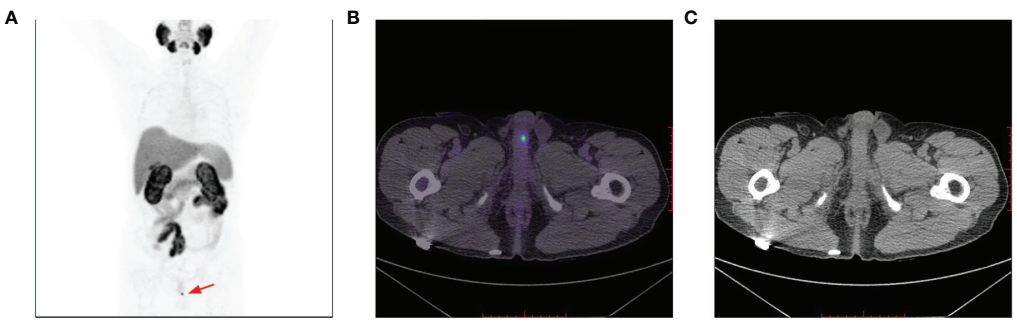

FIGURE 4 | A ^{18}F-PSMA-1007 PET/CT avid solitary penile lesion with a SUV_{max} of 6.4 **(A, B)**; no morphological abnormalities of the penis detected on CT imaging **(C)**.

discontinued. Subsequently, an elevated PSA level was recorded (0.547 ng/ml) in March 2021 and in July 2021 (6.79 ng/ml) (**Figure 5**). Enzalutamide combined with denosumab was applied, but abiraterone was discontinued. After several months, the patient showed a marked increase in PSA value (>100 ng/ml), combined with penile bleeding. ^{18}F-PSMA-1007 PET/CT revealed that the uptake of penile lesions was significantly higher (SUV_{max} 7.4) and that the range of lesions was enlarged than earlier; meanwhile,

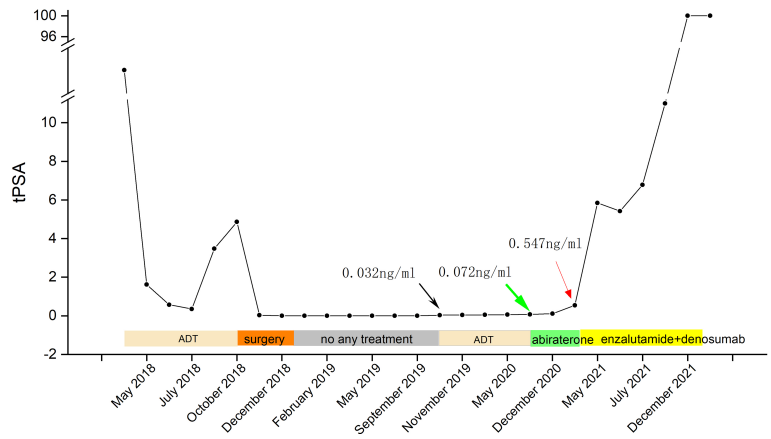

FIGURE 5 | Timeline of the PSA level and treatment (green arrow—a positive result of ^{18}F-PSMA-1007 PET/CT imaging with a PSA of 0.072 ng/ml; black arrow—an elevated PSA of 0.032 ng/ml; red arrow—an elevated PSA of 6.79 ng/ml).

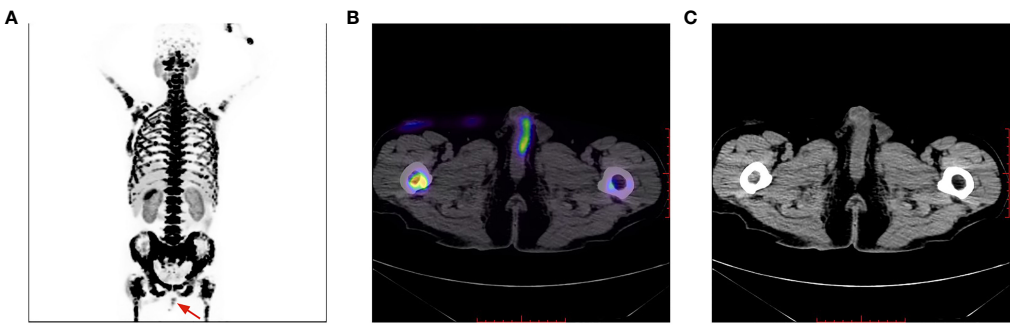

FIGURE 6 | Penile lesion was enlarged with a higher SUV_{max} of 7.4 **(B)**; meanwhile, systemic bone metastasis was certified **(A)**. No morphological abnormalities of the penis detected on CT imaging **(C)**.

systemic bone metastasis was detected (**Figure 6**). Considering the poor prognosis, the patient refused to undergo penectomy, and hence palliative chemotherapy was adopted.

DISCUSSION AND CONCLUSION

Penile metastasis of prostate cancer is rare (8, 9), with only a few PSMA-targeted imaging presented in the literature (7, 10, 11), none of which underwent radical prostatectomy, and only ADT and external beam radiotherapy were performed in these cases. Castration resistance develops over time and the tumor can recur. However, in the present case, a solitary biochemical recurrence of prostate cancer occurred in the penis during ADT after radical prostatectomy, while no recurrence was noted in the prostate bed and pelvis. The patient progressed to systemic bone metastasis despite undertaking a full course of androgen deprivation, which indicated castration resistance (12). Because the patient underwent ileocystoplasty surgery, urine was not excreted through the urethra, and hence the possibility of false-positive results contributed by penile radioactive retention can be ruled out. Unfortunately, due to the extensive metastasis and poor prognosis, the patient did not undergo further biopsy and penectomy. The case of biochemical recurrence after prostatectomy with a relatively low serum PSA level of 0.072 ng/ml may have been affected by a sequential ADT, which possibly reduced the activity of a recurrent lesion. However, owing to the high sensitivity of ^{18}F-PSMA-1007 PET/CT imaging, biochemical recurrence lesions could be detected at an early stage. As Giesel et al. (13) reported, ^{18}F-PSMA-1007 PET/CT detected biochemical recurrence with a PSA level of 0.08 ng/ml, which, in turn, provided important evidence for clinical decision-making.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific Research Ethics Committee of Ningxia Medical University General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Case Report: Reversal of Hyaluronic Acid Rectal Wall Infiltration with Hyaluronidase

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Peri-rectal spacers provide protection to the rectum for patients receiving radiation therapy treating prostate cancers. Commonly used hydrogel spacers hold the disadvantage that they cannot be readily reversed should inadvertent injection outside of the target area occurs, potentially leading to ischemia of the rectal mucosa leading to severe pain and ulceration, which can then lead to superinfection and pelvic abscess formation, and subsequently recto-prostatic fistulas. This could require major surgical intervention. New hyaluronic acid spacers are readily reversible with hyaluronidase and provide a valuable means to correct any misinjected spacer. We present a patient with prostate cancer who was planned for radiation therapy and required a rectal spacer. The hyaluronic acid rectal spacer was injected in part into the rectal wall. The patient was asymptomatic, and a sigmoidoscopy confirms healthy bowel mucosa only. The misinjected hyaluronic acid was successfully treated with targeted injection of hyaluronidase into only the rectal wall portion. Serial follow-up imaging demonstrated rapid dissolution of the misinjected hyaluronic acid with the well-positioned hyaluronic acid remaining. The patient did not experience any side effects of the hyaluronidase.

Keywords: hyaluronic acid, hyaluronidase, prostate cancer, radiation therapy, rectal spacer

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INTRODUCTION

Peri-rectal spacers have been shown to be effective in reducing toxicities resulting from radiation therapy for prostate cancer (1). The goal of rectal spacing is to position the rectal wall temporarily away from the prostate, keeping it safely distant from the high-dose region. The spacer is implanted using a transperineal approach under trans-rectal ultrasound (TRUS) guidance, together with the placement of fiducial markers in the prostate. In rare occasions, it is possible to inadvertently puncture part of the rectal wall, which may cause misplacement of a portion of the implant. This could cause potential ischemia to the rectal wall, ultimately leading to severe complications if left unnoticed.

For spacers composed of hyaluronic acid (HA), the resorption process naturally occurs slowly *via* the enzyme hyaluronidase (HAS). In dermal applications, HA implants (fillers) are reversed more quickly by injecting exogenous HAS (2). This is the first known case of reversing a HA peri-rectal implant with the use of HAS.

CASE PRESENTATION

The patient was a 69-year-old man with a newly diagnosed Gleason 4 + 4 = 8 prostate cancer who was scheduled for high-dose intensity modulated radiation therapy (IMRT). A prostate-specific membrane antigen positron emission topography (PSMA PET) scan showed localized disease. The prostate and seminal vesicles were planned to receive hypofractionated radiation therapy to a dose of 60 Gy in 20 fractions. The patient was started on androgen deprivation therapy with leuprorelin. In further preparation for his treatment, three gold fiducial markers were implanted into his prostate under a general anesthetic for image-guided radiation therapy. Additionally, a rectal spacer (Barrigel®, Palette Life Sciences, Santa Barbara, California, USA) was also implanted into the peri-rectal fat between Denonvillier's fascia and the anterior rectal wall. The goal of the implant was to create approximately 1 cm of symmetrical separation between the prostate and rectal wall, from the base to the apex of the prostate.

The technique involved the use of a midline 18G needle inserted transperineally into the perirectal fat using a freehand approach under sagittal TRUS guidance. The patient was observed to have a large rectal hump (arising from the rectourethralis muscle), which required a challenging angle of entry for the needle into the perirectal fat. Approximately 9 cc of HA was inserted along a length of 4.5 cm extending from the base to the apex of the prostate. Upon routine review of the post-implant MRI images 2 weeks after HA insertion, a portion of the HA implant at the level of the prostate apex was determined to have infiltrated the rectal wall into the muscularis propria layer (**Figure 1**). **Figure 1B** shows the low-density anterior border of the misinjected HA, with the low-density area corresponding to the muscularis propria layer of the rectal wall. This volume of HA was estimated at 5 cc out of a total of 10 cc of HA delineated on MRI. It extended from the midline to the right of the prostate for 2 cm, starting at the apex and extending superiorly for 3 cm. Using the grading scale initially described by Fischer-Valuck et al., our case would constitute grade 3 rectal wall infiltration (3). The needle had inadvertently penetrated the rectal wall during its entry into the perirectal fat at the level of the rectal hump, and as the needle was withdrawn while injecting HA, this resulted in a portion of HA in the intramural location. The patient was asymptomatic, denying any pain, bleeding, or tenesmus. A sigmoidoscopy was performed, which confirmed an intact rectal mucosa. As a significant portion of the HA was determined to be within the rectal wall, the patient's IMRT was withheld to prevent any potential spacer-related toxicity. However, to avoid any prolonged delays with commencement of his IMRT, a decision was made to dissolve the portion of HA that had infiltrated the rectal wall.

A sub-dermal patch test was done on the patient before his GA to check for any rare allergic reaction. Twenty units of HAS was injected intra-dermally in the forearm with a 25 G needle, and after 30 min, the injection site was assessed for any weal, itching, or erythema. No reaction was observed. As we had planned to dissolve 5 cc of HA within the rectal wall, at least 30 U of HAS per 0.1 cc of HA was required (4). HAS (3000 U) in 6 ml of sterile saline was prepared for injection. The equipment used is shown in **Figure 2**.

The patient underwent general anesthesia and was positioned as for the original HA procedure and imaged with TRUS confirming the location of the HA within the rectal wall (**Figure 3**). The HA was clearly visible on TRUS. A 20 G Chiba biopsy needle was inserted transperineally using a freehand approach into the middle of the HA bleb and advanced towards its superior extent. HAS (2000 IU) was injected into the HA bleb as the needle was withdrawn to its inferior extent. The HA bleb became hyperechoic on TRUS after the injection. No immediate dissolution was noted (**Figure 3B**). We were also unable to extract any part of the HA bleb by aspirating with an 18 G rigid BP needle. The entire procedure lasted approximately 20 min and was considered straightforward.

During follow-up, the patient remained asymptomatic immediately post procedure, at day 2, day 7, and day 14. MRI scans on day 2, day 7, and day 14 post HAS injection demonstrated complete reabsorption of the intramural HA at day 2 (**Figure 1**). There was some reabsorption of the HA within the peri-rectal fat at day 2 but only minimal additional reabsorption was seen at day 7. By day 14, no further ongoing changes were seen. The patient has since been scheduled to undergo radiation therapy planning with the goal of resuming his planned IMRT within 4 weeks. There were no changes to the dose of IMRT planned.

DISCUSSION

Prior to the development of HA, hydrogels and balloons were available for use as rectal spacers in prostate cancer. Balloon spacers may significantly reduce the radiation dose to the rectum (5) but have been associated with rectal perforation (6, 7). This in turn may lead to delays in radiation for the primary issue of prostate cancer (7) and require further intervention. Hydrogel spacers sustained less volume loss throughout the treatment period (5); however, they cannot be reversed and need to be surgically removed if they were infiltrated into the rectal wall.

HA was first approved for use as a cosmetic filler by the United States' Food and Drug Administration (FDA) in 2003, and since then, it has experienced exponential growth in

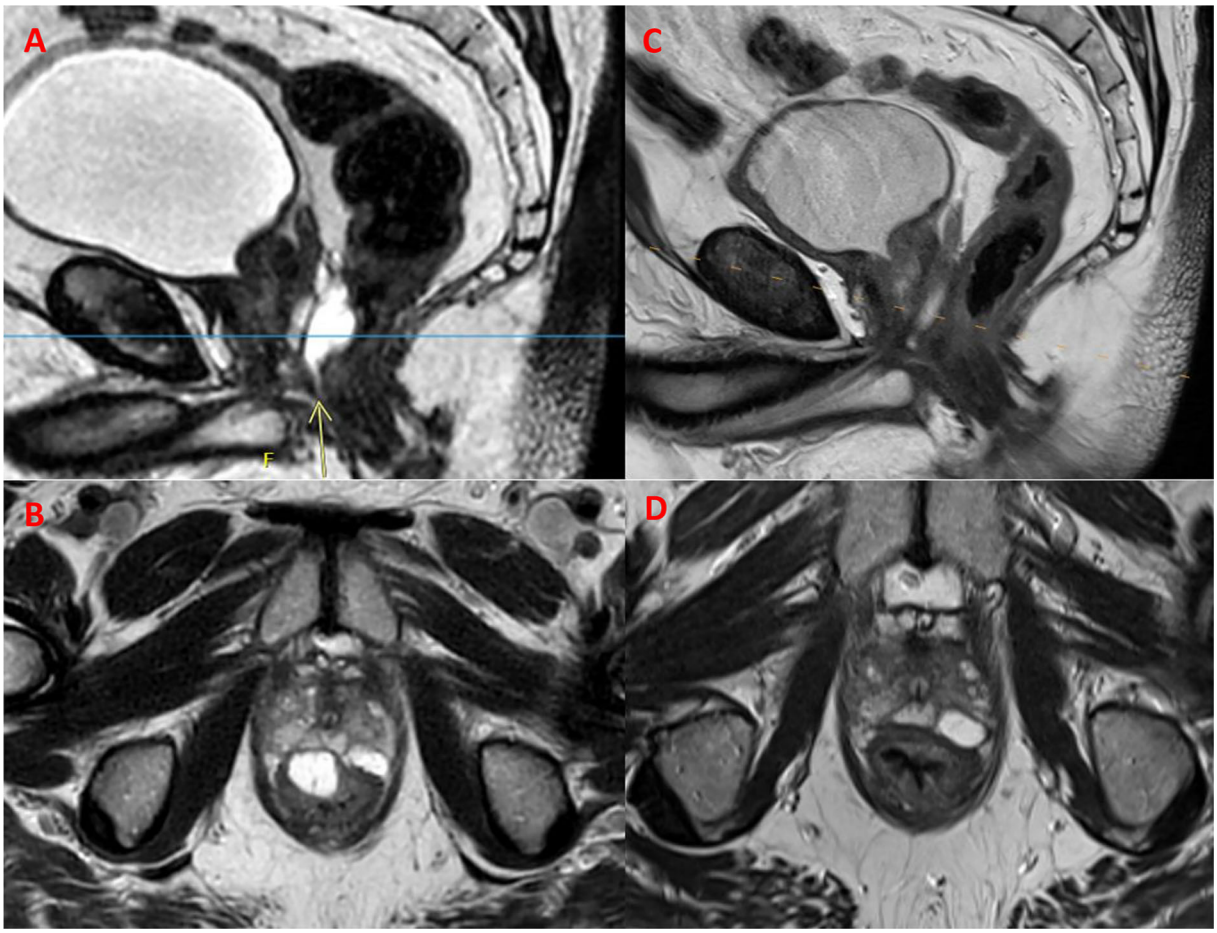

FIGURE 1 | Magnetic resonance images demonstrating intramural non-animal stabilized hyaluronic acid (NASHA) in **(A)** sagittal and **(B)** axial views denoted by*. Two days post hyaluronidase injection, the intramural NASHA is no longer visible in the same views **(C, D)**.

popularity and use (2). A unique property of HA, including HA that is misplaced or overfilled, is that it can be reversed with HAS (8). This ability to reverse and remodel hyaluronic acid is advantageous as it allows correction of any inaccurately placed product and can minimise adverse events, as in our case. Other rectal spacers such as hydrogel cannot be reversed and would need to be surgically removed. Some degree of rectal wall infiltration was found to occur in 6% of cases in the randomized hydrogel spacer trial (3), none of which required further intervention. However, the potential consequences of more severe gross rectal wall infiltration may include ischemia of the rectal mucosa leading to severe pain and ulceration, which can then lead to superinfection and pelvic abscess formation, and subsequently recto-prostatic fistulas requiring major surgical intervention such as a defunctioning ileostomy/colostomy or even pelvic exenteration (9, 10). Notably, McLaughlin et al. described a patient receiving high-dose stereotactic body radiation therapy. The radiation dose may have contributed to the formation of a rectourethral fistula ultimately managed with pelvic exenteration (10). Nevertheless, we have now demonstrated that this risk can be mitigated by early recognition and the use of HAS to rapidly reverse portions of the implant, preventing subsequent downstream severe complications.

Although HAS has been used routinely to dissolve dermal and breast HA fillers (see below), this is the first report of the use of HAS in reversing a peri-rectal HA implant. The dose of HAS recommended has ranged between 5 and 30 IU for every 0.1 cc of HA to be dissolved. At these doses, multiple HAS injections may be necessary to completely dissolve any undesired HA. As such, we decided to increase the dose, beyond the upper end of the recommended dose of HAS in order to ensure we did not require a second procedure. In addition, there is no known upper limit for the amount of HAS that can be injected safely. While the maximal dose of HAS is not documented, up to 200,000 IU has been given, demonstrating an increase in allergic-type reactions (11). Our patient received well under this dose, and thus the risks of adverse reactions are minimized. We used approximately 50 IU per 0.1 cc of HA and saw rapid dissolution of the HA that

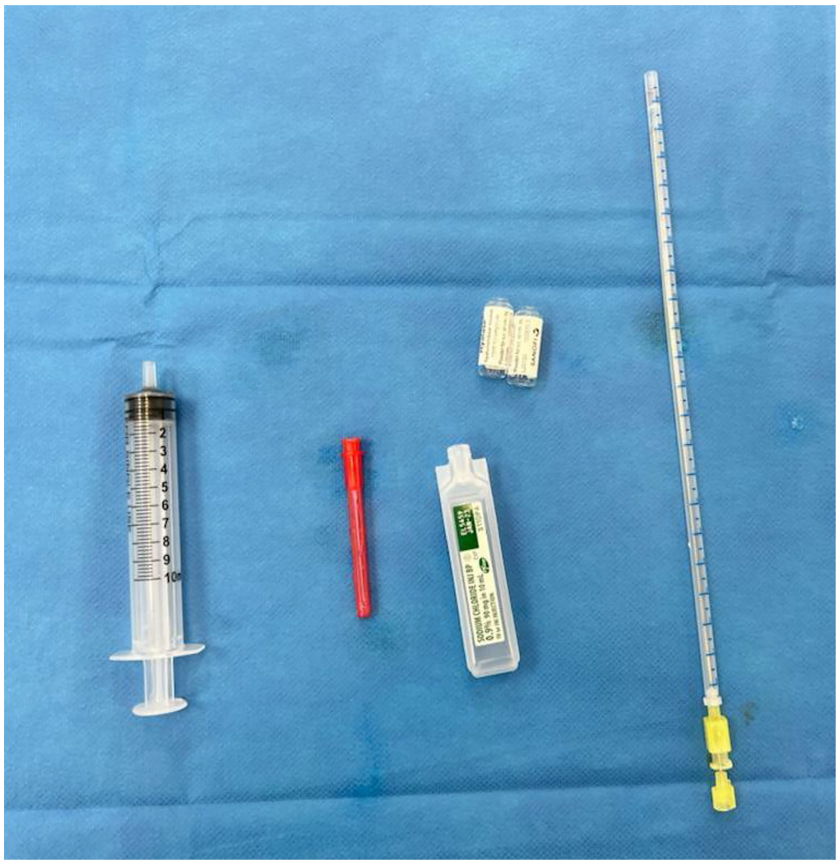

FIGURE 2 | Equipment required for preparing hyaluronidase (left to right)—10 cc syringe, blunt drawing needle, normal saline, hyaluronidase, and spinal needle.

had infiltrated the rectal wall. This had quickly dissolved within 48 h. If the patient had been symptomatic with severe pain, this would have resulted in rapid resolution of his symptoms. In addition, it would have averted potentially prolonged clinical symptoms as it may take 1 year for HA to resolve naturally. This procedure also allowed us to reschedule the start of the patient's IMRT with minimal delay.

Additionally, HA is clearly visualized on several imaging modalities including ultrasonography and MRI, and to a lesser extent computer tomography. This allows clinicians to precisely assess the position and volume of any inaccurately placed HA and can help facilitate the calculation of the HAS dose required. During HAS injection, visualization under ultrasound can guide the accurate placement of HAS. Using this guidance, we have shown that it is possible to target only the misplaced portion of the implant with HAS, while leaving the remaining portion of the implant in the correct position.

Complications of HAS in the cosmetic surgery setting are well documented. These include allergic reactions, which ranges from 0.05% to 0.69% in frequency; the majority of these are reported to be localized injection site reactions (12). Systemic reactions such as angioedema and urticaria can occur at a lower frequency (<0.1%). Higher dose (more than 100,000 IU) and intravenous route of administration are more likely to produce allergic reactions (12). Specific to urology, the injecting needle could injure the surrounding organs. Inadvertent placement of HAS into the correctly placed HA could lead to over-dissolution of the rectal spacer leading to increased toxicity from their IMRT due to loss of the protective rectal spacer. However, once adequate time has passed, there is the potential to insert additional HA into the peri-rectal space if this was deemed important.

Several learning points arise from our case. During transrectal ultrasonography with the sagittal view, the rectal wall is tented by the rectourethralis muscle near the apex of the prostate. When injecting HA, the needle should always pass above rather than through the rectal wall to minimize the risk of injury to the rectal wall. In addition, HA should always be inserted when the needle tip is in clear view during the entire procedure. As HA does not polymerize, there is no time constraint with the insertion process. HA is also clearly visible on TRUS imaging, and it does not distort or degrade the rectal or prostate images, allowing us to accurately track the insertion to minimize the risk of rectal wall infiltration. We would also recommend performing an MRI scan to help delineate the location of the HA and identify any patients

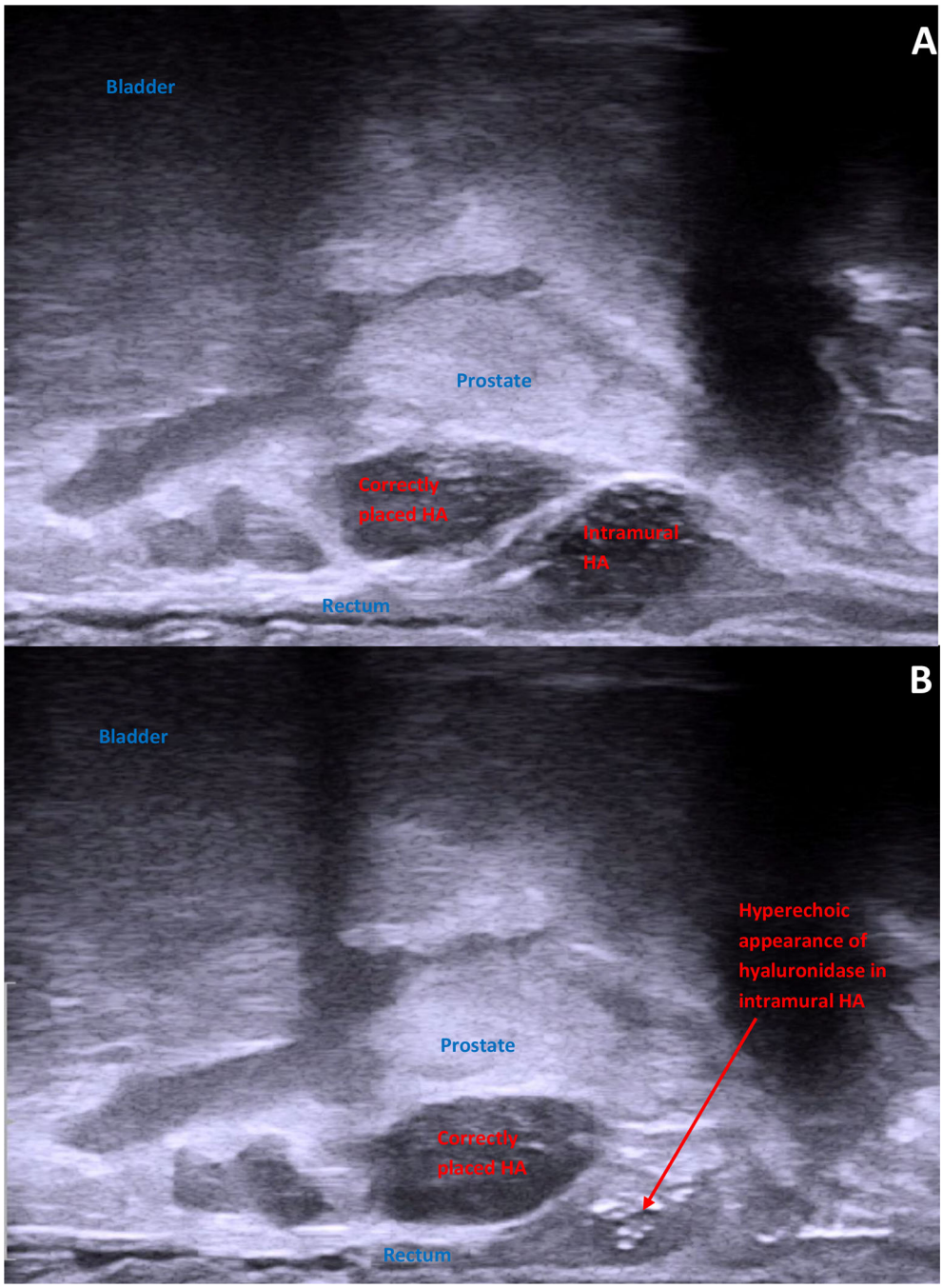

FIGURE 3 | Intraoperative transrectal ultrasound images demonstrating **(A)** the misinjected HA in the rectal wall and **(B)** the hyaluronic acid immediately after injection into the intramural NASHA (now hyperechoic).

who may have gross rectal wall infiltration. This would be difficult to identify on a CT scan. Furthermore, onset of action of HAS is within minutes and effects last up to 48 h (4, 11). Therefore, it is expected that patients with painful symptoms due to rectal wall infiltration could experience rapid relief after HAS injection. A repeat MRI can be performed at 2 days post HAS injection to demonstrate the resolution of the HA. No further changes were noted at 2 weeks post HAS injection, allowing us to repeat the planning images for radiation therapy. This translates to a small and clinically insignificant delay in initiation of their IMRT as opposed to many months delay in the case of non-reversible preparations.

CONCLUSION

HA use as a rectal spacer is safe and can reduce the toxicity of radiation therapy to the prostate. In the event of rectal wall infiltration, HA can be simply and readily reversed with HAS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JI was the treating clinician of the patient. JI and MC provided supervision for this body of work. AH drafted the manuscript that was edited by all authors. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Absence of PSA Flare With Apalutamide Administered 1 Hour in Advance With GnRH Agonists: Case Report

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Objective: To examine the effects of apalutamide on endocrine function and flare prevention in metastatic hormone-sensitive prostate cancer (mHSPC) patients administered GnRH agonists.

Methods: The first newly diagnosed mHSPC patient took apalutamide for 2 weeks followed by combination with GnRH agonist, as recommended by clinical guidelines. Serum luteinizing hormone (LH), testosterone, and PSA were detected during the oral administration of apalutamide before and after ADT. Eight newly diagnosed mHSPC patients innovatively took apalutamide 1 hour before GnRH agonist administration; LH, testosterone and PSA were detected before and after ADT.

Results: In the first patient, LH and testosterone levels were increased during apalutamide monotherapy, and serum PSA levels decreased rapidly, demonstrating apalutamide effectively blocked AR signaling. In patients on the 1-hour regimen, combined treatment with apalutamide and GnRH agonists led to peak level of testosterone on day 3 and castration level on day 28, while PSA decreased continuously. No one experienced dysuria or bone pain worsen after ADT.

Conclusion: Taking apalutamide 1 hour in advance may effectively prevent the flare-up effect in prostate cancer patients treated with GnRH agonists. Compared with the 2-week regimen, the 1-hour regimen could simplify the treatment process and bring testosterone to castration levels in advance.

Keywords: hormone-sensitive prostate cancer, ADT, GnRH agonist, flare, apalutamide

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INTRODUCTION

For metastatic hormone-sensitive prostate cancer (mHSPC), androgen deprivation therapy (ADT) is the cornerstone of systemic therapy, while GnRH agonists are the mainstream choice for ADT (1, 2). Several guidelines recommend the use of androgen receptor (AR) antagonists for 1 to 4 weeks prior to GnRH agonist injection to prevent initial flare effects (3–5). Apalutamide is a new

generation of AR antagonists. Compared with first-generation AR blockers such as bicalutamide, apalutamide can block AR more efficiently and should have more advantages in preventing the ignition effect of GnRH agonists (6–8).However, the effects of apalutamide monotherapy on hormone secretion and the prevention of ignition effects have not been fully studied in clinical studies. Among the 9 newly diagnosed mHSPC patients, 1 took apalutamide for 2 weeks, then injected GnRH agonist, while 8 took apalutamide 1 hour before GnRH agonist administration. The report is as follows.

CASE PRESENTATION

The baseline data of all patients were shown in **Table 1**. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJH-IRB20211246).

2-Week Regimen

Patient 1

A 55-year-old man was hospitalized for lower extremity deep vein thrombosis and pulmonary embolism in December 2020. Screening for tumor markers found that serum PSA was 269.5ng/ml. Abdominal CT scan: Slightly enhancing low-density nodule in the left lobe of the prostate, enlarged lymph nodes adjacent to the iliac vessels on both sides (the largest one 34*30mm). Bone scan showing increased activity in right scapula, the axillary side of the right sixth rib, and the left fifth anterior rib. Prostate biopsy showed: prostate adenocarcinoma, Gleason score 4 + 3 = 7. TNM staging was considered as T2cN1M1b, stage IV. The patient had dysuria and frequent urination. Referring to the AUA guidelines and NCCN guidelines, the patient received GnRH agonist injections after 2 weeks of apalutamide treatment and continued oral apalutamide. Serum luteinizing hormone (LH) and testosterone levels at admission were 6.9mIU/ml and 3.43ng/ml, respectively. When apalutamide monotherapy for 3 days, PSA decreased by 34%. Taking into account the half-life of PSA (about 3 days), newly generated PSA in the third day is only about 16% of the original (**Supplementary Figure 1**). After 2 weeks of apalutamide treatment, LH and testosterone levels increased to 14.67 mIU/ml and 4.98 ng/ml, and PSA level decreased from 269.5 ng/mL at admission to 27.649 ng/mL (see **Figures 1–3** and **Supplementary Table 1**). The

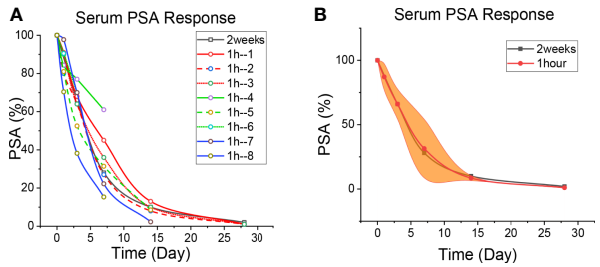

FIGURE 1 | Patient's PSA level. **(A)** The level of PSA reduction in each patient. The black line is the 2-week regimen; Red, green and blue are patients with 1H regimen. **(B)** Median reduction of PSA levels in patients with 1H regimen. The black line is the 2-week regimen; The red line is the patients with 1h regimen; The yellow areas are interquartile spacing.

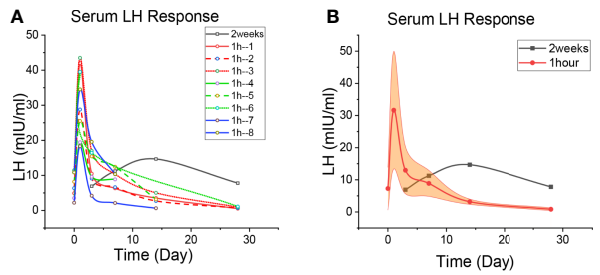

FIGURE 2 | Patient's LH level. **(A)** The level of LH change in each patient. The black line is the 2-week regimen; Red, green and blue are patients with 1H regimen. **(B)** Median changes of LH levels in patients with 1H regimen. The black line is the 2-week regimen; The red line is the patients with 1h regimen; The yellow areas are interquartile spacing.

significant effects of apalutamide on LH, testosterone, and PSA demonstrate the high AR-binding affinity of apalutamide. After GnRH agonist (Goserelin) treatment in this patient, PSA declined steadily, while testosterone reached castration levels (41 ng/dl) after 28 days of ADT. The testosterone reached the lowest value (22 ng/dl) after 40 days of ADT. The delay in the decline of testosterone is associated with the increase in LH during apalutamide administration. Dysuria and bone pain resolved during treatment.

TABLE 1 | Basic patient information.

No.	Age	Gleason score	TNM stage	PSA (ng/ml)	LH (mIU/ml)	Testosterone (ng/ml)	Timein advance
1	55	4+3 = 7	T2cN1M1b	269.541		3.43	2 week
2	64	4+5 = 9	T4N1M1b	437.42	4.9	3.43	1h-1
3	65	4+5 = 9	T3bN1M1b	269.26	6.36	4.48	1h-2
4	65	5+4 = 9	T4N1M1b	897.51	11.45	2.45	1h-3
5	79	4+5 = 9	T3bNxM1b	77.534	3.53	3.89	1h-4
6	68	4+5 = 9	T4NxM1b	86.732	8.2	2.35	1h-5
7	75	5+4 = 9	T3bNxM1b	200.71	10.86	5.56	1h-6
8	55	4+5 = 9	T4N1M1b	98.062	2.2	2.25	1h-7
9	68	4+5 = 9	T3bN1M1b	132.22	10.85	5.1	1h-8

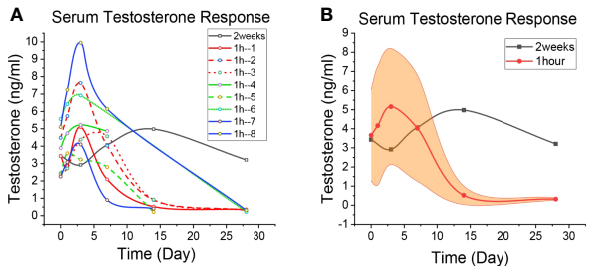

FIGURE 3 | Patient's Testosterone level. **(A)** The level of Testosterone change in each patient. The black line is the 2-week regimen; Red, green and blue are patients with 1H regimen. **(B)** Median changes of Testosterone levels in patients with 1H regimen. The black line is the 2-week regimen; The red line is the patients with 1h regimen; The yellow areas are interquartile spacing.

1-Hour Regimen

The baseline data of Patient 2-9 were shown in **Table 1**. Given the higher AR-binding affinity of apalutamide, 1 hour after receiving apalutamide monotherapy, the patient was injected with GnRH agonist (Goserelin or Leuprorelin) (**Supplementary Tables 2–9**). The serum PSA, LH and testosterone levels were detected on day 0 (before treatment), 1, 3, 7, 14, and 28 (**Figures 1–3** and **Supplementary Tables** for details). PSA decreased steadily after ADT, while LH and testosterone rose to their peaks on day 1 and day 3, respectively. Testosterone reached the castration level on day 28, which was earlier than the two-week regimen. Two patients had dysuria, and four had bone pain, all of which were prostate cancer involvement. The patients had no biochemical or clinical "flare" during treatment. Symptoms such as bone pain and dysuria significantly improved in the first week of intervention.

Methods

2-week regimen: Patient was treated with apalutamide 240 mg on days 0-14; combined with a GnRH agonist from day 15.

1-hour regimen: GnRH agonist was given combined with oral apalutamide 240 mg for 1 hour. Then, apalutamide 240mg daily and GnRH agonist once monthly as usual.

All patients were hospitalized.

DISCUSSION

In 2020, the number of new prostate cancer cases in the world has reached 1.4 million, ranking second among men (9). About 30% of Chinese prostate cancer patients are in a metastatic state when firstly diagnosed. ADT combined with AR antagonist therapy is one of the main treatment options (10). Apalutamide, as a synthetic biaryl thiohydantoin compound, can inhibit AR nuclear translocation, DNA binding and transcription of AR target genes (11). The SPARTAN study (12) included 1207 nmCRPC patients, and the median metastasis-free survival (MFS) after apalutamide treatment increased from 16.2 months to 40.5 months. TITAN study (6) included 1052 mHSPC patients, and showed significantly advanced in OS when taking apalutamide. Moreover, apalutamide has been approved by the FDA and CFDA for the treatment of nmCRPC and mHSPC.

During the first week after GnRH agonist injection, due to its agonistic effect on the pituitary gland, the serum LH rebounded, followed by an increase in testosterone secretion. Some patients may experience aggravation of clinical symptoms such as bone pain, spinal cord compression, and dysuria (13). Testosterone can activate AR in prostate cancer cells (14) and promote its entry into the nucleus to regulate PSA transcription, eventually causing an increase in serum PSA levels, which is called PSA flare phenomenon (15, 16). Testosterone reduces to the castration level after 4 weeks of GnRH agonist injection (3). For hormone-sensitive prostate cancer, anti-androgen drugs should be used over 1 week before the initial application of GnRH agonists to fully block AR receptors and prevent the "flare" phenomenon (4). In a number of clinical trials, different anti-androgen drugs such as nilutamide (17), estramustine phosphate (ECT) (18), chlormadinone acetate or diethylstilbestrol diphosphate (19) etc. taken 1-4 weeks in advance are effective in preventing PSA flare. This is comparable to the result of apalutamide taken 1 hour in advance in our study. In another study, patients using both Long-term ECT and goserelin acetate depot showed a slow rise in PSA levels for at least 8 weeks. Furthermore, when treated with long-term and short-term chlormadinone acetate or diethylstilbestrol diphosphate, the PSA decreased by about 70% by the end of 2 weeks, slower than 1-hour regimen.

For newly diagnosed mHSPC patients, in order to avoid PSA flare, The AUA guidelines recommend 4 weeks of antiandrogen therapy to reduce the clinical risk of "testosterone surge"; the NCCN guidelines also suggest that antiandrogen therapy should be administered prior to or concurrently with LHRH agonists and continued for at least 7 days. The effect of single use of bicalutamide on endocrine *in vivo* has been reported: LH, FSH, testosterone and dihydrotestosterone all increased to varying degrees (20). After oral administration of flutamide and bicalutamide for 4 weeks (21), the testosterone level remained high, and the PSA level decreased by about 70%, which was comparable to that of apalutamide for 1 week (**Supplementary Table 1**), suggesting that the time can be shortened when apalutamide is used to prevent the flare-up effect of GnRH agonist. Taking into account the half-life of PSA (about 3 days), newly generated PSA in the third day is only about 16% of the original (**Supplementary Figure 1**), lower than administration of flutamide and bicalutamide for 4 weeks. Moreover, after oral administration, the serum concentration of apalutamide was close to the peak concentration at 1 hour and reached the peak at 2 hours in CRPC patients (22). Similar results were seen in another study (23). This is why the GnRH agonist is applied one hour after oral administration of apalutamide in Patient 2-9.

In study LACOG 0415, the patients were divided into goserelin + abiraterone acetate + prednisone group (ADT + AAP group), apalutamide + abiraterone acetate + prednisone group (APA + AAP group) and apalutamide alone group (APA group) (24). During the 25-week follow-up period, testosterone levels in the APA group continued to rise while the other two groups remained low. This may be related to the negative

feedback inhibition of testosterone on the hypothalamus and pituitary *in vivo* after the antagonist blocks AR (20). Similarly, it is shown that apalutamide can increase testosterone lastingly, but the effect on PSA and LH is still unclear, especially the changes of PSA and hormone levels within first week.

The results of a multicenter study aimed at investigating the efficacy of goserelin with or without antiandrogen drugs showed that patients on concomitant anti-androgen drugs had slower disease progression, better prognosis, and fewer PSA flares in early stages (25). Another clinical trial of leuprolide with or without nilutamide showed that patients had lower levels of prostatic acid phosphatase and lower levels of LH and testosterone elevations in combination with nilutamide (26). The above results show that GnRH agonists combined with anti-androgen drugs are more effective in controlling the levels of PSA, LH, and testosterone. As a new generation of anti-androgen drugs, apalutamide is more efficient in blocking AR receptors.

The PSA changes of the patients who underwent the 2-week regimen and the 1-h regimen are shown in **Figure 1**, and the specific values are shown in **Supplementary Tables 1–9**. It is seen that PSA decreased continuously in every patient. Taking apalutamide 1 hour in advance could efficiently prevent the PSA flare effect in prostate cancer patients treated with GnRH agonists. The declines on the third day are approximately 32% (the 2-week regimen) and 34% (the 1-h regimen), while on the 7th day, it was about 72% and 66%. The decrease in PSA on day 7 was consistent with 4 weeks of bicalutamide treatment (21), indicating a strong blocking effect of apalutamide. The half-life of PSA in human serum is approximately 3 days (27, 28). The serum PSA of the first patient on apalutamide alone for 3 days was about two-thirds of that before treatment. Given that the PSA at the beginning of treatment was reduced by half after 3 days, therefore, prostate cancer cells secrete PSA only one-sixth of the pre-treatment level after three days of oral administration of apalutamide (**Supplementary Figure 1**). This suggests that apalutamide can block AR and exert biological effects before peak serum concentration.

The LH changes of these three patients are shown in **Figure 2**, and the specific values are shown in **Supplementary Tables 1–9**. The LH of the patients in the 2-week regimen continued to rise after oral apalutamide monotherapy. One experiment showed peak LH concentrations (200% increase from baseline) on day 1 of GnRH agonist application and peak testosterone concentrations on day 3 (13). In **Figure 2**, every patient of the 1h regimen had a peak LH on day 1, which was mainly caused by the initial application of GnRH agonists; peak concentrations in 8 patients increased by approximately 408%, higher than 200%, suggesting the involvement of apalutamide. LH levels subsequently declined, and it was significantly faster for the patients of 1h regmen.

Changes in testosterone in patients who underwent the 2-week regimen and the 1-h regimen are shown in **Figure 3**, and the specific values are shown in **Supplementary Tables 1–9**. Similar to the LACOG 0415 study, patients on the 2-week regimen showed an overall upward trend within the first 14 days of apalutamide alone. But LACOG 0415 was studied on a weekly basis, ignoring data from the 3 days before the start of treatment. Patients in the 2-week regimen experienced a rapid decline in testosterone following combined GnRH agonists, reaching castration level (41 ng/dl) at day 28, then reached the lowest value (22 ng/dl) on day 40 day of ADT, showing the delay in the decline of testosterone. Meanwhile, testosterone in the 1h regimen reached castration levels on day 28 (34 ng/dl in average), indicating that the decline of testosterone was not significantly affect during ADT. Thus, the 1-hour regimen bring testosterone to castration levels in advance, compared with 2 weeks regimen.

Basic research shows that apalutamide can exert a strong AR receptor antagonistic effect in a short time, thereby reducing PSA levels. It has been reported in the literature that apalutamide can significantly inhibit the transcription level of PSA mRNA in prostate cancer cells for 16 hours *in vitro* (29). Apalutamide can effectively kill prostate tumor cells in 1 day (30). Adding excess testosterone to the 22Rv1 cell line mimics the "testosterone rebound phenomenon", apalutamide can significantly enhance the lethality of radiotherapy and has a concentration-dependent property (31), and also significantly up-regulate the expression of AR, PSA, TMPRSS2, etc., while there is no obvious response in CRPC cell lines such as PC3 and DU145 (14). Chris Tran, the inventor of apalutamide, has already reported (11): *In vitro* cell experiments, apalutamide significantly reduced PSA mRNA levels in LNCaP/AR cells for 8 hours. In *in vitro* animal experiments, the concentration of apalutamide in the serum reached the blocking effect of AR 24 hours after oral administration of mice. The strong AR blocking ability of apalutamide was demonstrated in the 1-hour regimen cases. One hour after oral administration of apalutamide, GnRH agonist was used, and the PSA decreased steadily, indicating that the use of apalutamide for one hour can effectively block AR receptors and avoid the flare effect caused by subsequent increases in LH and testosterone.

This study revealed for the first time that apalutamide monotherapy can rapidly lower serum PSA levels, while raise LH and testosterone in mHSPC patients. Absence of PSA flare with apalutamide administered 1 hour in advance in mHSPC patients treated with GnRH agonists. Furthermore, compared with the 2-week regimen, the 1-hour regimen can bring testosterone to castration levels earlier. This may have certain reference significance for simplifying the treatment process.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and

Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: CY. Data curation: ZH, ZW, and ZC. Formal analysis: ZH and CY. Funding acquisition: CY. Investigation: XZ and ZC. Methodology: ZH and CY. Project administration: ZH. Resources: CY. Software: XZ. Supervision: ZW. Validation: CY. Visualization: ZL. Writing – original draft: ZL and CY. Writing – review and editing: ZH. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.878264/full#supplementary-material

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CASE REPORT
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Case Report: Clinical Characteristics and Outcomes of HIV Positive Patients With Metastatic Prostate Cancer Treated With Immunotherapy: A Case Series and Literature Review

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Background: The treatment of metastatic prostate cancer has been revolutionized with the advent of many targeted therapies, including immunotherapy. Pembrolizumab has demonstrated benefit in the treatment of certain patients with docetaxel-refractory metastatic castrate-resistant prostate cancer (mCRPC). However, extrapolation of these data to patients with HIV is limited, as these patients are conventionally excluded from therapeutic clinical trials. This study aims to develop a better understanding of the clinical outcomes of HIV positive patients with prostate cancer treated with immunotherapy. A review of the literature is conducted on the use of immunotherapy in HIV positive patients with prostate cancer, and a summary is presented of two clinical cases from a single institution.

Methods: This is a retrospective case report of 2 patients diagnosed with prostate cancer and HIV who received treatment with pembrolizumab. Quantitative analysis was performed to summarize patient demographics, clinical history, and outcomes.

Results: Two patients with mCRPC and HIV on **highly active antiretroviral therapy** were identified. Both individuals had biochemical and radiographic response to treatment with pembrolizumab. The duration of response for individual 1 is >31 months and 14 months for individual 2. Neither patient had immune-related adverse events or decreased suppression of their HIV infection. One patient died from disease progression after 14 months of treatment and the other remains on treatment with pembrolizumab to date.

Conclusion: In this small case series, pembrolizumab appears to be a safe and effective treatment option for HIV positive patients with metastatic prostate cancer.

Keywords: HIV, immunotherapy, pembrolizumab, prostate cancer, PD-1 inhibitor, checkpoint blockade, mCRPC

INTRODUCTION

It is well established that HIV infection and the resulting immune suppression can lead to an increased risk of several cancers (1). People with HIV have about 500 times the risk of developing Kaposi sarcoma, 12 times the risk of developing non-Hodgkin lymphoma, and three times the risk of developing cervical cancer. HIV positive individuals are also at increased risk of developing other malignancies, including cancers of the anus, liver, head and neck, lung, and Hodgkin lymphoma (1, 2). Fortunately, with the substantial advancements in highly active antiretroviral therapies, the life expectancy of individuals with HIV is now effectively equal to those without HIV infection (3). Despite these advancements, however, persons with HIV continue to have increased risk of developing cancer compared to the general population. As these individuals live longer, the risk of developing malignancies that are common in the general population also increases.

Prostate cancer is now the second most common neoplasm among the elderly with HIV after lung cancer (4). Men with prostate cancer and well-controlled HIV seem to have clinical presentations and outcomes similar to those without HIV infection, including with regard to surgical and post-operative outcomes (4–6). Furthermore, HIV positive men with prostate cancer have recurrence-free survival outcomes similar to those of the general population (6). However, due to the frequent exclusion of HIV positive men from clinical trials, there has been a knowledge gap with regard to the efficacy of novel therapies, such as immunotherapy, in treating them.

Checkpoint inhibitors – such as inhibitors of cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death protein 1 ligand (PD-L1) – have revolutionized the approach to treatment of many cancers. For example, pembrolizumab has demonstrated efficacy in select men with docetaxel-refractory mCRPC (7). In general, checkpoint inhibitors work by inhibiting the immune escape mechanisms of cancer cells. In individuals who have underlying systemic conditions affecting the immune system, the efficacy of immunotherapy has not been well defined and extrapolation of these data to individuals with HIV has been limited due to their frequent exclusion from therapeutic clinical trials due to safety concerns. There has also been concern that immunosuppressed individuals may not have sufficient underlying T-cell immunity to benefit from immunotherapy. This has resulted in a paucity of data regarding the efficacy and tolerability of immunotherapy in HIV-positive individuals with prostate cancer.

Data shows that upregulation of PD-1 in CD8 T cells may mediate T-cell exhaustion and lead to progression of HIV (8). This suggests that PD-1 checkpoint inhibition may help control HIV infection, however to date this has not yet been formally studied. A retrospective analysis of 17 HIV individuals across two institutions evaluating the efficacy and safety of checkpoint inhibitors (9) included HIV positive individuals with lung cancer, hepatocellular carcinoma, anal cancer, renal cell carcinoma, non-Hodgkin's lymphoma, and advanced basal cell carcinoma. The authors of the study concluded that checkpoint inhibitors used to treat these malignancies had comparable efficacy and tolerability and did not adversely affect control of HIV.

The largest study to date on the use of checkpoint inhibitors for treatment of advanced malignancies in individuals with HIV is a prospective open-label, nonrandomized, phase 1 multicenter trial conducted across seven institutions (10). The trial enrolled 30 HIV positive individuals with the following malignancies: Kaposi sarcoma, non-Hodgkin lymphoma, anal cancer, squamous skin cancer, adenoid cystic carcinoma, bladder cancer, cholangiocarcinoma, hepatocellular carcinoma, non-small cell lung cancer, pancreatic cancer, papillary urothelial carcinoma, prostate cancer (only one patient), sarcomatoid lung cancer, and tonsillar cancer. Individuals on this trial were treated with pembrolizumab. The study demonstrated the safety of pembrolizumab in HIV positive individuals with cancer. All individuals from that trial were on ART and had controlled HIV infection as defined by the US department of health and human services. The CD4 positive T-cells remained stable throughout the treatment course. Clinical benefit was demonstrated in those with lung cancer, non-Hodgkin lymphoma, and Kaposi sarcoma.

To date, very little is known about the benefit and safety of PD-1 checkpoint immunotherapy specifically in the treatment of advanced prostate cancer among HIV positive patients. The case series presented here aims to describe the clinical outcomes of two HIV positive men from a single institution who were treated with pembrolizumab.

MATERIAL AND METHODS

A review was conducted of electronic medical records of patients who were diagnosed with metastatic prostate cancer and HIV at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center. Of the identified cases, a search was made for those who received treatment with pembrolizumab. Data were obtained from clinical notes, pathology reports, and molecular reports. Response evaluation criteria in solid tumors (RECIST) and Prostate Cancer Working Group 3 criteria were used to evaluate serologic and radiologic response to therapy. Patients were categorized as responders to therapy if they achieved complete response, partial response, or stable disease as per the RECIST criteria.

Study data were collected and managed using REDCap electronic data capture tools hosted at UCSF (11, 12). Small sample size precluded more granular stratification and regression analysis. All study procedures were approved by the UCSF Institutional Review Board.

RESULTS

Two men with HIV and mCRPC to bone and lymph nodes, who were treated with pembrolizumab were identified. Both individuals were heavily pretreated with each having received

seven or more prior lines of systemic therapy (**Figure 1**). The clinical characteristics of these men and their response to pembrolizumab are reported in **Table 1**. Individual 1 was diagnosed with HIV at age 36 and developed *denovo* metastatic prostate cancer at age 52. His family history was notable for colon cancer in a brother who died from complication related to this diagnosis at age 52. He also had a family history of unspecified type of cancer in a father and a brother. He had no known family history of prostate cancer. Individual 2 was diagnosed with HIV at age 58 and localized prostate cancer at age 63, which progressed to metastatic disease by age 70. His family history was notable for lung cancer in his father, diagnosed at age 62 and prostate cancer in his two of his brothers (age of diagnosis unknown). Information regarding germline testing of the family members was not available.

Both patients were receiving highly active antiretroviral therapy (HAART) for the entire duration of treatment with pembrolizumab. Individual 1 was on Atripla (efavirenz-emtrictabine-tenofovir) with Raltegravir and individual 2 was on Descovy (emtricitabine/tenofov alafenam) with dolutegravir. The median CD4 count at initiation of pembrolizumab was 261 cells/μl (range 170-353 cells/μl). The HIV RNA level was below detection threshold for both patients. Neither patient had known prior complications from the HIV infections and were on HAART for the duration of their prostate cancer therapy. Individual 1 did not have any known germline mutations and somatic next generation sequence (NGS) testing only showed a mutation in AR T878A with 1.3% allele frequency. The microsatellite instability (MSI) status and tumor mutational burden (TMB) was undetermined on their NGS testing. Individual 2 had a variance of unknown significance (VUS), c.2607+5G>A (intronic), in RET gene, a somatic BRCA2 T3310fs*17 mutation with 2.2% allele frequency, stable microsatellite status, low TMB of 4 mutations/mb, TP53 R248W, and TMPRSS2 fusion (TMPRSS(NM_005656)-ERG (NM_004449) mutations. Programmed cell death ligand 1 (PDL-1) testing by immunohistochemistry (IHC) was not performed for both patients.

At the time of this analysis, one of the two patients identified was alive. While on treatment with pembrolizumab, both patients responded to therapy with biochemical and/or radiographic response. Duration of response is summarized in **Figure 2**. Individual 1 had partial response for 31 months on treatment and remains on treatment to date. Individual 2 had stable radiographic disease for 14 months prior to disease progression with new brain metastasis, clinical decline, and ultimate death a month after his last dose of pembrolizumab. Neither patient had immune-related adverse events.

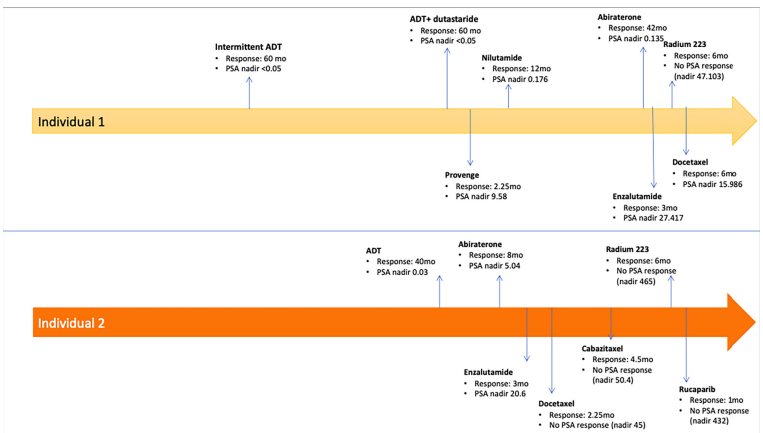

FIGURE 1 | Timeline of Treatments Received Prior to Pembrolizumab.

TABLE 1 | Patient Characteristics of Case Series of HIV Positive Patients with Metastatic Prostate Cancer Treated with Pembrolizumab.

Individual	Age at Prostate Cancer Diagnosis	Time to Prostate Cancer Diagnosis Post-HIV Diagnosis (years)	Prostate-specific Antigen at Start of Immunotherapy (ng/mL)	Prostate-specific Antigen Nadir on Immunotherapy(ng/mL)	RECIST v.1.1Response	Duration of Therapy (months)	Total number of Pembrolizumab cycles received
1	52	16	81	30	Partial	31	36
2	63	5	846	337	Stable	14	19

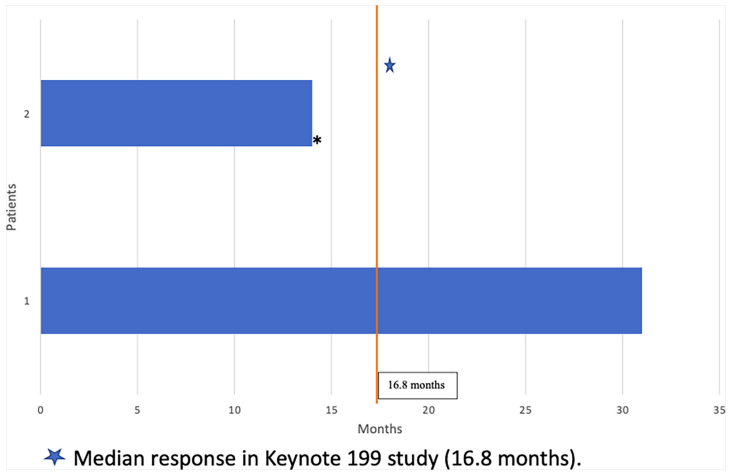

FIGURE 2 | Duration of Response to Pembrolizumab (months). Median response in Keynote 199 study (16.8 months).

DISCUSSION

Highly effective treatments for HIV have transformed what was once an incurable and frequently lethal condition. As the life expectancy of individuals with HIV now matches that of the general population, the cancer burden in this population will likely shift. By 2030, prostate and lung cancer are expected to emerge as the most common cancers in individuals with HIV (13). Therefore, it will be important to understand the effects of all available cancer therapies in this population.

Checkpoint inhibitors have revolutionized the treatment of many different cancers. For prostate cancer, the Keynote 199 study demonstrated the efficacy of pembrolizumab in select patients with docetaxel-refractory metastatic mCRPC (7). In that trial, the observed overall response rate was a modest 5%. However, the median duration of response among participants who achieved complete or partial response was durable at 16.8 months. Most of the participants on this trial (60%) had one or more treatment related adverse effects (TRAE), but only 15% had grade 3-5 TRAE and 5% discontinued treatment due to toxicity. Immune related adverse events (IRAE) were found in 17% of participants, with the most common iRAE being colitis, thyroid dysfunction, pneumonitis, and severe skin reactions. Notably, 2 patients died due to treatment related pneumonitis and sepsis (n=1 each) (7).

The limited case series presented here has demonstrated that some HIV positive patients can have prolonged response to pembrolizumab without increased toxicity. A prospective trial among HIV positive patients with different types of cancers has also demonstrated the safety of using pembrolizumab for this patient population (10). Because of the small sample size in this series it remains unclear whether patients with HIV and mCRPC are more likely to respond to checkpoint inhibition, and what underlying immunologic mechanisms may be operating to generate an anti-cancer immune response in these patients. Thus, it is important that future immunotherapy trials include HIV positive individuals in therapeutic clinical trials to better understand immunotherapy activity in patients who might have a lower CD4 count or higher HIV viral loads.

CONCLUSIONS

The small case series presented in this review adds to the accumulating evidence regarding the safety and efficacy of checkpoint inhibitors in patients with HIV. In individuals with mCRPC and HIV, Pembrolizumab result in a durable response, even among those who have been heavily pretreated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DI and HB designed the study and wrote the manuscript. TF, CP, and CR contributed to the design of the study and provided many edits to the manuscript. All authors approved the submitted manuscript

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CASE REPORT
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Case Report: 18F-PSMA PET/CT Scan in Castration Resistant Prostate Cancer With Aggressive Neuroendocrine Differentiation

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The development of a neuroendocrine phenotype as a mechanism of resistance to hormonal treatment is observed in up to 20% of advanced prostate cancer patients. High grade neuroendocrine prostate cancer (NEPC) is associated to poor prognosis and the therapeutic armamentarium is restricted to platinum-based chemotherapy. Prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET)/computed tomography (CT) imaging has recently emerged as a potential new standard for the staging of prostate cancer and PSMA-based radioligand therapy (RLT) as a therapeutic option in advanced metastatic castration resistant prostate cancer (mCRPC). PSMA-based theranostic is not currently applied in the staging and treatment of NEPC since PSMA expression on neuroendocrine differentiated cells was shown to be lost. In this case series, we present 3 consecutive mCRPC patients with histologically proven high grade neuroendocrine differentiation who underwent PSMA-PET/CT and surprisingly showed high tracer uptake. This observation stimulates further research on the use of PSMA-based theranostic in the management of NEPC.

Keywords: PSMA - prostate specific membrane antigen, neuroendocrine prostate cancer (NEPC), crpc, castration-resistance prostate cancer, small cell prostate cancer, theranostic PSMA radioligands

INTRODUCTION

Prostate cancer is the most frequent malignancy and the second leading cause of cancer death in Western male population (1). Cancer cells growth and proliferation strongly rely on androgen-androgen receptor (AR) axis. Therefore, androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer (2). The maintenance of ADT in association to taxane-based chemotherapy or next generation hormonal agents (NGHAs) in the castration resistant setting (CRPC) is currently recommended by international guidelines (3). Several mechanisms of resistance to hormonal treatments, such as genomic amplification, activating point mutations and

splice variants involving AR have been described (4–8). An increasingly recognized resistance mechanism occurring in up to 20% of advanced prostate cancer involves epithelial plasticity and divergent clonal evolution, in which tumor cells often acquire neuroendocrine features, showing low to absent AR expression (9, 10). Gene expression profiling studies suggest that CRPC following treatment with NGHAs is a heterogeneous disease continuum with distinct phenotypes, based on the expression of AR-regulated and neuroendocrine genes (11, 12). As a matter of fact, a subset of progressive CRPCs shows small-cell carcinoma or neuroendocrine features on metastatic biopsy (13–15).

Prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET)/computed tomography (CT) imaging has recently emerged as a potential new standard for the staging of prostate cancer (16). PSMA is a type II transmembrane glycoprotein highly expressed on prostate cancer epithelial cells (17, 18), especially in high-grade and metastatic castration-resistant disease (19). The expression of FOLH1 gene, encoding PSMA protein, is regulated by AR pathway (20). The induction of lineage plasticity by AR inhibition leads to the suppression of PSMA (21), implying that PSMA-targeted imaging could not effectively visualize neuroendocrine prostate cancers (NEPCs) (22–24). Immunohistochemical and systemic surfaceome profiling studies also indicate that treatment-induced neuroendocrine differentiation is associated with large changes in the repertoire of expressed cell surface proteins (25), with low expression of PSMA and higher expression of neuroendocrine markers, such as synaptophysin, DLL3 and CEACAM5 (14, 26–29). Moreover, PSMA suppression correlates with GLUT12 suppression and glucokinase upregulation, which is positively associated with higher glucose uptake in conventional 18F-fluorodeoxyglucose (FDG) PET imaging (20, 30, 31). These observations suggest a limited utility of PSMA-based theranostic in the management of NEPC (22–24, 32, 33).

On the other hand, a strong 68Ga-PSMA uptake was recently observed in all lesions of a newly diagnosed metastatic small cell prostate carcinoma (34). In addition, PSMA immunostaining positivity was observed in NEPCs after 6 months of neoadjuvant ADT plus enzalutamide (35).

Since May 2021, when PSMA radioligand therapy (RLT) became available in Italy as compassionate use, CRPC patients with disease progression to taxanes and at least one NGHA were offered to perform a PSMA-PET/CT imaging to establish their possible eligibility to treatment with PSMA RLT. In the present paper we report the results of PSMA uptake in 3 consecutive patients who developed a histologically documented high grade NEPC.

PATIENTS AND METHODS

From May 2021 to March 2022, 21 CRPC patients with progressing disease to NGHAs and chemotherapy were observed at the Medical Oncology Unit of the ASST Spedali Civili in Brescia (Italy). Three patients (14%) developed an aggressive neuroendocrine phenotype. Graphic timeline of events related to the three cases is displayed in **Figure 1**.

Case 1

A 58-year-old man presented with persistent cervical and back pain in July 2019. A spine magnetic resonance imaging (MRI) showed multiple lesions in the cervical, dorsal and lumbar tracts and following L1-L2 vertebral biopsies reported the diagnosis of metastatic prostate cancer. Serum prostate specific antigen (PSA) was 328 ng/ml and prostate biopsies confirmed the diagnosis of Gleason score 5 + 4 prostate adenocarcinoma. ADT with luteinizing hormone-releasing hormone (LHRH)-analogue was then introduced. In November, the patient was enrolled in the BonEnza randomized clinical trial (ClinicalTrials.gov Identifier: NCT03336983) and treatment with Enzalutamide and Zoledronic acid was added to ADT. Serum PSA decreased to 2,1 ng/ml, while CT and whole-body MRI showed a radiological response to therapy. However, in September 2020, due to back pain, a MRI of the spine was performed and showed the appearance of a new vertebral lesion (D5-D6) determining spinal cord compression and dislocation. A biopsy of the lesion was performed and the histological examination revealed metastasis from a combined small cell-large cell neuroendocrine carcinoma. The immunohistochemical staining resulted positive to TTF1 and synaptophysin, Ki67 expression was about 90% and PSA was not expressed. Although serum PSA further decreased to 1,31 ng/ml in response to hormonal treatment, a 18F-FDG PET/CT confirmed disseminated skeletal disease progression. From November 2020 to April 2021, eight Carboplatin plus Etoposide cycles were administered. After an initial partial response to therapy, in April 2021 a 18F-FDG PET/CT revealed several new bone lesions and higher tracer uptake in the pre-existing metastases. After four cycles of chemotherapy with Cyclophosphamide, Doxorubicin and Vincristine, 18F-FDG PET/CT showed skeletal disease progression and the occurrence of two tracer-avid foci in the liver. A next generation sequencing (NGS) according to FoundationOne® platform was performed on the specimen representing NEPC from vertebral lesion, showing RB1 and p53 mutations, TMPRSS2-ERG gene fusion and PTEN splice site alteration, whereas a low tumor mutational burden (TMB) and stable microsatellite status were observed (**Table 1**). Based on the NGS results, a third-line treatment for castration-resistant disease with Everolimus was attempted in August 2021. In order to explore the possibility to undertake PSMA-based RLT, a 18F-PSMA-PET/CT was performed in September 2021, which revealed an intense tracer uptake in the prostate and in several osteoblastic and mixed bone lesions (**Figure 2A2**). However, neither the hepatic metastases nor few of the 18F-FDG-avid bone lesions showed PSMA tracer uptake, suggesting a heterogeneous expression of PSMA across metastatic sites. In detail, the visceral localizations of disease, a typical feature of NEPC, showed high 18F-FDG avidity but no PSMA avidity, hinting at a possible clonal differentiation of disease induced by hormonal treatments. Given the evidence of exclusionary PSMA-negative lesions, the patient was not submitted to PSMA RLT. The following 18F-FDG PET/CT

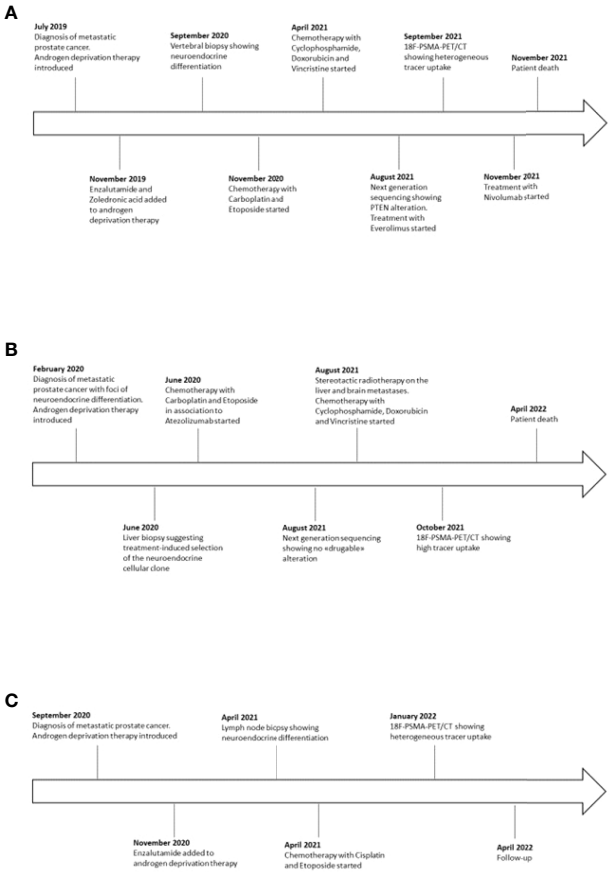

FIGURE 1 | Timeline with relevant data from case 1 **(A)**, case 2 **(B)** and case 3 **(C)**.

TABLE 1 | Patient 1 and patient 2 genomic signatures and gene alterations detected with next generation sequencing assay FoundationOne CDx.

	SPECIMEN	GENOMIC SIGNATURES	GENE ALTERATIONS
PATIENT 1	Para-vertebral tissue	**Tumor Mutational Burden**: 3 Muts/Mb **Microsatellite status:** MS-Stable	**PTEN:** splice site 165-2A>C **TMPRSS2:** TMPRSS2-ERG fusion **RB1:** loss exons 1-2 **TP53:** H179L
PATIENT 2	Liver	**Tumor Mutational Burden**: 5.04 Muts/Mb **Microsatellite status**: MS-Stable	**NKX2-1**: amplification **RB1**: loss **ERBB2**: amplification - equivocal **KEL**: R516* **TP53**: R283C

Muts, mutations; Mb, Megabase; MS, microsatellite.
**Translation termination (stop) codon.*

revealed hepatic and skeletal disease progression (**Figure 2A1**) and suggested the onset of secondary localizations of disease in the lungs, a finding subsequently confirmed by a CT examination. After a further line of treatment with Nivolumab inside a clinical trial, the clinical conditions deteriorated and the patient passed away in November 2021.

Case 2

A 64-year-old patient was submitted to transurethral resection of bladder (TURB) for a non-muscle invasive bladder neoplasm in 2010. A follow-up cystoscopy performed in February 2020 reported foci of infiltration in the bladder wall. The patient underwent TURB and prostate biopsies, both reporting a Gleason score 4 + 5 prostate adenocarcinoma (**Figures 3A–D**). Additional immunohistochemical staining showed foci of high grade neuroendocrine differentiation (**Figures 3E–H**). Given the nodal metastatic extent of the disease, ADT was introduced. Despite initial biochemical response and volumetric reduction of the lumbo-aortic and pelvic lymphadenopathies, CT and MRI examinations performed in June 2020 showed the appearance of

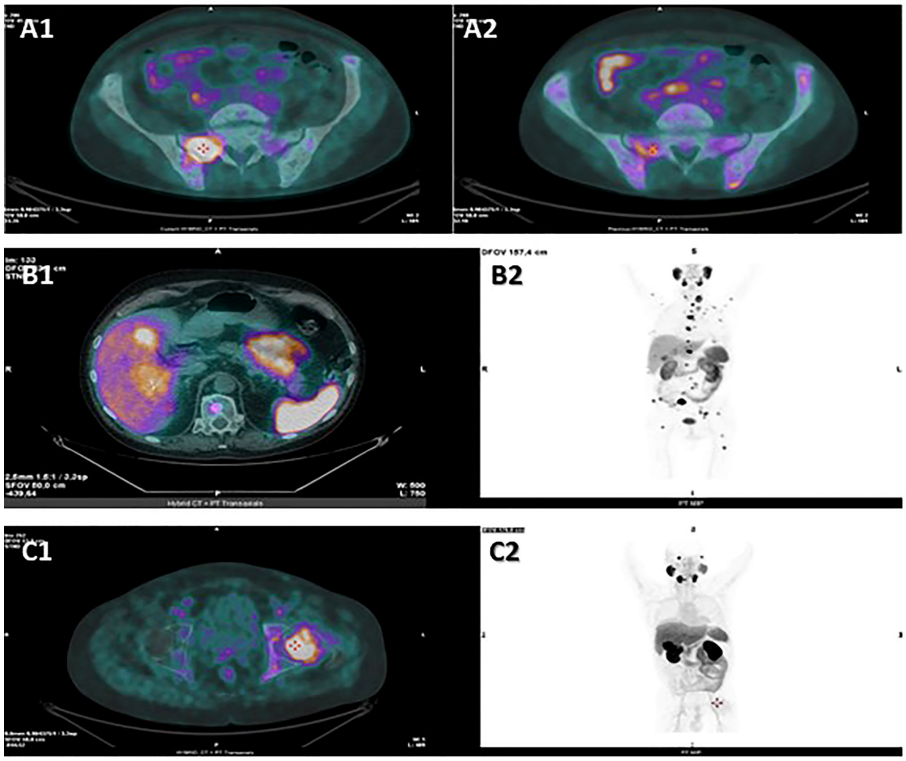

FIGURE 2 | Hybrid CT + PET transaxial images from 18F-FDG PET/CT **(A1)** and from 18F-PSMA-PET/CT **(A2)** examinations performed by patient 1 in September 2021, hybrid CT + PET transaxial **(B1)** and PET MIP total-body **(B2)** images from 18F-PSMA-PET/CT examination performed by patient 2 in October 2021, hybrid CT + PET transaxial **(C1)** and PET MIP total-body **(C2)** images from 18F-PSMA-PET/CT examination performed by patient 3 in January 2022. PSMA-PET scan performed by patient 1 revealed an intense tracer uptake in the prostate and in several bone lesions, such as in the right ala of the sacrum **(A2)**, while the hepatic lesions showed no tracer uptake. The following FDG PET scan revealed high FDG uptake in the liver and in several bone lesions, such as in the right ala of the sacrum **(A1)**. PSMA-PET scan performed by patient 2 revealed high tracer uptake in the liver **(B1, B2)**, bone **(B2)** and lymph nodes **(B2)**. PSMA-PET scan performed by patient 3 showed tracer-avid foci in the prostate and in several osteoblastic lesions, such as in the left femur head **(C1, C2)**, while no uptake was detected in the abdominal lymphadenopathies **(C2)**. CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose; PSMA,prostate-specific membrane antigen; MIP, maximum intensity projection.

hepatic hypodense lesions, which were histologically characterized as localizations of a TTF1+, synaptophysin+, chromogranin+, PSA-, NKX3.1- small cell neuroendocrine carcinoma (**Figures 3I–M**) with a Ki67 expression of 70%. The histological examination thus hinted at a treatment-induced selection of the neuroendocrine cellular clone previously described in the former prostate biopsy. Five cycles of chemotherapy with Carboplatin and Etoposide in association to Atezolizumab, followed by maintenance therapy with Atezolizumab, were then administered. In the following months, after an initial partial response to therapy, the liver lesions progressed and several new metastatic sites of disease were highlighted in the brain, in the vertebral spine, in the bone pelvis and in the femur. NGS according to FoundationOne® platform was performed on the specimen representing NEPC from hepatic metastasis. The assay revealed RB1 loss, p53 and KEL mutations and NKX2-1 and ERBB2 amplifications. Tumor microsatellite status was stable and the TMB was low (**Table 1**). Since no "druggable" alteration was found, the patient underwent stereotactic radiotherapy on the liver and brain metastases and, in August 2021, a second line of systemic treatment with Cyclophosphamide, Doxorubicin and Vincristine was required. After 6 cycles of chemotherapy, CT and MRI examinations performed in October 2021 showed a partial response on liver metastases. A 18F-PSMA-PET/CT performed in October 2021 revealed high tracer uptake in the bone, lymph node and liver sites of disease (**Figure 2B1, 2**), despite the previously histologically documented neuroendocrine differentiation. Unfortunately, the compassionate use of PSMA RLT had been discontinued pending the drug becoming commercially available and, at last, the patient developed a severe disseminated intravascular coagulation which led to his death.

Case 3

A 56-year-old man was referred to our Institution for pelvic pain and pollakiuria in September 2020. Serum PSA was 137 ng/ml and prostate biopsies demonstrated a Gleason score 4 + 5 ductal prostate carcinoma. Given the skeletal (pelvis and femur) and nodal metastatic extent of disease shown by bone and CT scan,

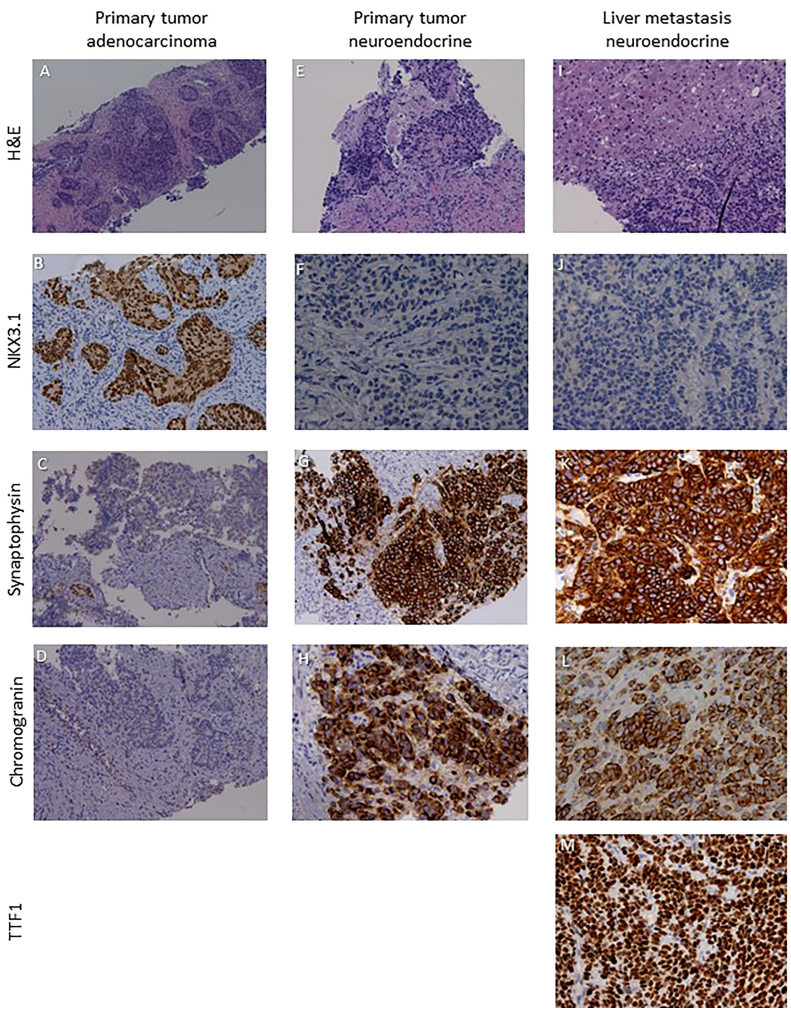

FIGURE 3 | Sections are from patient 2 prostate and liver biopsies and stained as labelled. Primary tumor was a NKX3.1+ synaptophysin- chromogranin-·prostate adenocarcinoma **(A–D)** with foci of NKX3.1- synaptophysin+ chromogranin+ high grade neuroendocrine cardnoma **(E–H)**. Liver metastases were characterized by a NKX3.1- synaptophysin+chromogranin+TTFl+ small cell neuroendocrine phenotype **(I–M)**. Original magnifications: 4X **(A)**, 10X **(B–D, G, I)**, 20X **(E, F, H, J–M)**. H&N, hematoxylin and eosin; TTF1, thyroid transcription factor 1.

ADT was introduced and, in November, Enzalutamide was added after the enrollment in the BonEnza clinical trial. A disease response to therapy was obtained and lasted 7 months. In April 2021 a CT examination showed the onset of several lymphadenopathies in the thoracic, abdominal and pelvic regions, although serum PSA levels did not increase (PSA: 0,07 ng/ml). An ultrasound-guided biopsy of an obturator lymph node was performed. The histological and immunohistochemical examinations showed a chromogranin+, synaptophysin+, PSA-, FAP-PSAP-, TTF1- high grade metastatic carcinoma, suggesting the diagnosis of NEPC. Serum neuron-specific enolase (NSE) was 141,9 ng/ml and chromogranin 60 IU/l, supporting the pathologic diagnosis. Eight cycles of chemotherapy with Cisplatin and Etoposide were then administered. Follow-up CTs indicated disease response in lymph nodes and stabilization of bone lesions. Of note, during the course of chemotherapy PSA values maintained undetectable despite the metastatic extent of disease, supporting the diagnosis of a neuroendocrine differentiation of former prostate cancer. In January 2022, a 18F-PSMA-PET/CT was performed, showing tracer-avid foci in the prostate and in several osteoblastic lesions, while no uptake was detected in the abdominal lymphadenopathies (**Figure 2C1, 2**). The heterogeneous expression of PSMA across different metastatic sites was regarded as a clinical contraindication to PSMA-based RLT. At the last visit in February 2022, CT scan showed stable disease and the patient was kept under follow-up.

DISCUSSION

Treatment induced neuroendocrine differentiation of mCRPC is associated with a deeply divergent transcriptional profile, as

compared to classic adenocarcinoma (14), including low-to-absent PSMA expression (24). In our small series, however, a clear positivity to 18F-PSMA radiotracer was observed in three consecutive patients with histologically proven high grade NEPC (with small cell histology in two cases). In two of these patients the heterogeneous PSMA uptake was regarded as a clinical contraindication to PSMA RLT. Instead, one patient showed an intense and homogeneous tracer uptake and was thus considered eligible for PSMA RLT. Unfortunately, the non-immediate availability of the drug and the onset of a serious complication linked to neoplastic progression prevented the RLT administration.

At the best of our knowledge, only rare cases of histologically proven high grade NEPC (34, 36) and one case of presumptive NEPC (37) that resulted PSMA positive at staging are described in the literature.

Derlin et al (38) assessed PSMA theranostic in prostate cancer patients who achieved a neuroendocrine phenotype as assessed by raising serum chromogranin A levels. In this series the outcome of RLT was not adversely influenced by neuroendocrine differentiation, while high PSMA uptake was confirmed to be crucial for achieving a tumor response.

It should be underlined that raising levels of circulating chromogranin A are frequent in patients with CRPC (39). This suggests the presence of a neuroendocrine phenotype which is associated with a worse prognosis (40, 41), but does not imply the development of a high-grade neuroendocrine phenotype, as the cases we have described.

In conclusion, even though the activity of PSMA RLT in high-grade NEPC is still to be documented, our case series suggests that in some of these patients PSMA membrane expression on neuroendocrine differentiated cells is preserved, hinting at a potential role of PSMA theranostic. Given the limited therapeutic options for patients with advanced high-grade NEPC, including potential molecularly driven treatments, we suggest that such patients should not be excluded *a priori* from PSMA-PET/CT testing, as the occasional evidence of high tracer uptake may open the door to PSMA RLT as an additional strategy upon progression to platinum-based chemotherapy.

DATA AVAILABILITY STATEMENT

All relevant data is contained within the article: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MarB, AD: conceptualization, paper writing IC, FV, SG: paper editing AB: conceptualization, tutoring, paper editing LB, SF, MarB, LP, FB: iconographic support, paper editing. All authors contributed to the article and approved the submitted version.

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Long response duration to pembrolizumab in metastatic, castration-resistant prostate cancer with microsatellite instability-high and neuroendocrine differentiation: A case report

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Background: The detection of microsatellite instability in urologic cancers is rare, especially in metastatic, castration-resistant prostate cancer with neuroendocrine differentiation.

Case presentation: This is a case of a 66-year-old Asian male patient with prostate adenocarcinoma who had metastases at initial presentation. Despite combined androgen deprivation therapy, his prostate-specific antigen (PSA) progressively increased, and prostate re-biopsy revealed small cell carcinoma. He was treated with platinum-based systemic chemotherapy, and his tumor markers, including PSA, remained negative; however, his local symptoms worsened. Subsequently, microsatellite instability-high was detected, and pembrolizumab was administered resulting in complete remission with the resolution of symptoms and continued therapeutic effect for more than 14 months.

Conclusion: Microsatellite instability testing should be considered, despite its low detection rate, because the response to pembrolizumab in metastatic, castration-resistant prostate cancer with detectable microsatellite instability is associated with a prolonged duration of response.

KEYWORDS

metastatic castration-resistant prostate cancer (mCRPC), neuroendocrine differentiation (NED), microsatellite instability-high (MSI-high), immune checkpoint inhibitor (ICI), pembrolizumab

Introduction

Small cell/neuroendocrine (NE) differentiation in prostate cancer can appear *de novo* in untreated patients but is relatively rare (<2%) (1). More commonly, NE differentiation occurs in castration-resistant patients after androgen deprivation therapy (ADT) (2). Recent studies have pointed to a model of divergent clonal evolution from castration-resistant prostate cancer (CRPC)-adenocarcinoma to CRPC with NE differentiation (CRPC-NE) with adaptation from an androgen receptor (AR)-driven state to an AR-independent state (3).

The limited therapeutic options for treating NE prostate cancer include cisplatin, carboplatin with etoposide (4), or docetaxel with a marginal median survival of 7–15 months (5–7).

Pembrolizumab, an anti-programmed cell death (PD)-1 monoclonal antibody, is known to exhibit antitumor activity in advanced non-small cell lung cancer (8), gastric cancer (9), urothelial carcinoma (10), and malignant melanoma (11). It has recently been considered to be an effective treatment for patients with microsatellite instability (MSI)-high and mismatch repair-deficient (dMMR) cancer (12). The frequency of MSI-high or dMMR in prostate cancer is not great ranging from 3% to 22% (13–18).

This report describes, to the best of our knowledge, the first case of metastatic CRPC-NE with MSI-high that responded significantly to pembrolizumab and produced a long duration of response.

Case presentation

A 66-year-old Asian male patient first presented to another hospital with complaints of a sense of residual urine and pollakiuria in March 2019. There was no family history of malignancy to the fourth degree of consanguinity, and the patient himself had no history of other malignancies. The prostate-specific antigen (PSA) was 50.2 ng/ml (<4.0 ng/ml), resulting in a suspicion of prostate cancer. Transrectal prostate needle biopsy was performed in April 2019 resulting in a Gleason score of 4 + 4 adenocarcinoma (Figure 1). The tumor proportion score (TPS) of PD-L1 was approximately 50% using

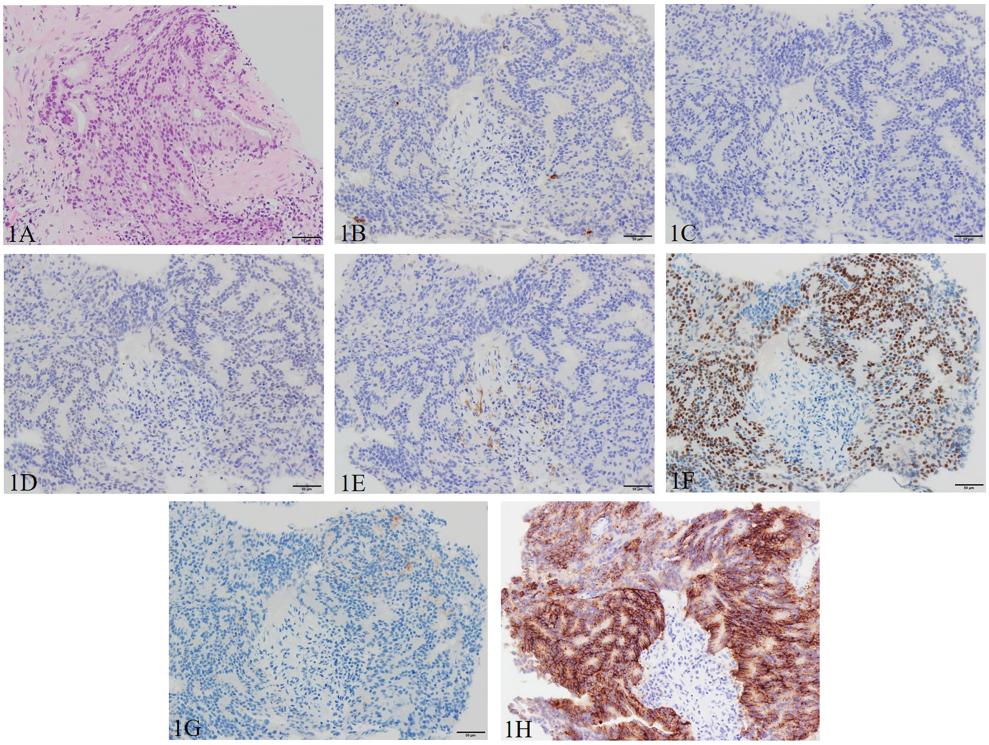

FIGURE 1
Pathological manifestations of initial prostate biopsy. Hematoxylin and eosin staining (magnification, ×200): **(A)** Gleason pattern 4 adenocarcinoma with nuclei unevenly distributed, cribriform, and growing in the form of fused glands is identified. Immunohistochemistry (magnification, ×200): **(B)** chromogranin A, **(C)** synaptophysin, **(D)** INSM1, and **(E)** SSTR2 are negative, and **(F)** AR, **(G)** PSA (focal), and **(H)** PD-L1 (focal) are positive. AR, androgen receptor; INSM1, insulinoma-associated protein 1; PD-L1, programmed death ligand-1; PSA, prostate-specific antigen; SSTR2, somatostatin receptor 2.

the clone 22C3 pharmDx kit (Agilent Technologies, Inc., Santa Clara, CA, USA) (Figure 1).

The patient was diagnosed with cT3aN0M1c (PUL) prostate cancer, and combined androgen blockade (CAB) with bicalutamide and degarelix was administered. In August 2019, the PSA decreased to 1.151 ng/ml, but it rose again to 3.800 ng/ml in November 2019, and the patient was referred to our hospital for further treatment. Serum PSA, neuron-specific enolase (NSE), and progastrin-releasing peptide (proGRP) were present at high levels at the first visit to our department with values of 4.220 ng/ml, 24.3 ng/ml (<16.3 ng/ml), and 206 pg/ml (≤75 pg/ml), respectively. Serum testosterone was at a castration level of 0.05 ng/ml. Contrast-enhanced computed tomography (CECT) showed an irregular contrast effect over the entire prostate, and somatostatin receptor scintigraphy showed mild accumulation in the prostate (Figure 2). After changing from degarelix to leuprorelin acetate, a prostate re-biopsy was performed in December 2019, and small cell carcinoma was detected (Figure 3). The patient had metastatic CRPC-NE and was treated with etoposide plus cisplatin (EP) (etoposide, 100 mg/m^2/day, days 1–3; cisplatin, 80 mg/m^2/day, day 1, repeated every 3 weeks). After the first EP course, renal function declined, so cisplatin was replaced by carboplatin (CBDCA) with a total of two courses of etoposide plus CBDCA (etoposide, 80 mg/m^2/day, days 1–3; CBDCA: AUC 5, day 1, repeated every 4 weeks). This was followed by irradiation of the prostate region (external beam radiation therapy, 70 Gy, 35 fractions). However, after completing irradiation, the patient complained of perineal pain and pain during urination, and CECT showed recurrent prostate staining, lymph node metastasis, and *de-novo* pancreatic metastasis. Two courses of single agent CPT-11 (100 mg/m^2/day, days 1, 8, and 15, repeated every 5 weeks) were administered as salvage chemotherapy, and concurrent MSI was investigated. MSI status was investigated using an approved kit (MSI-IVD kit, FALCO biosystems, Kyoto, Japan). The analysis of prostate re-biopsy specimens showed a high MSI status, and the patient was given pembrolizumab (200 mg/day, day 1, every 3 weeks). Following pembrolizumab administration, the local prostate, lymph node, and pancreatic metastases were all reduced, and complete remission was achieved with the resolution of symptoms (Figure 4). The patient is still undergoing treatment after more than 14 months of response without any immune-related adverse events. Supplementary Figure 1 illustrates the transient changes in his PSA, NSE, and proGRP levels and the treatment course received by the patient.

Discussion

MSI-high prostate cancer is rarely included as part of hereditary, non-polyposis colorectal cancer (HNPCC) also

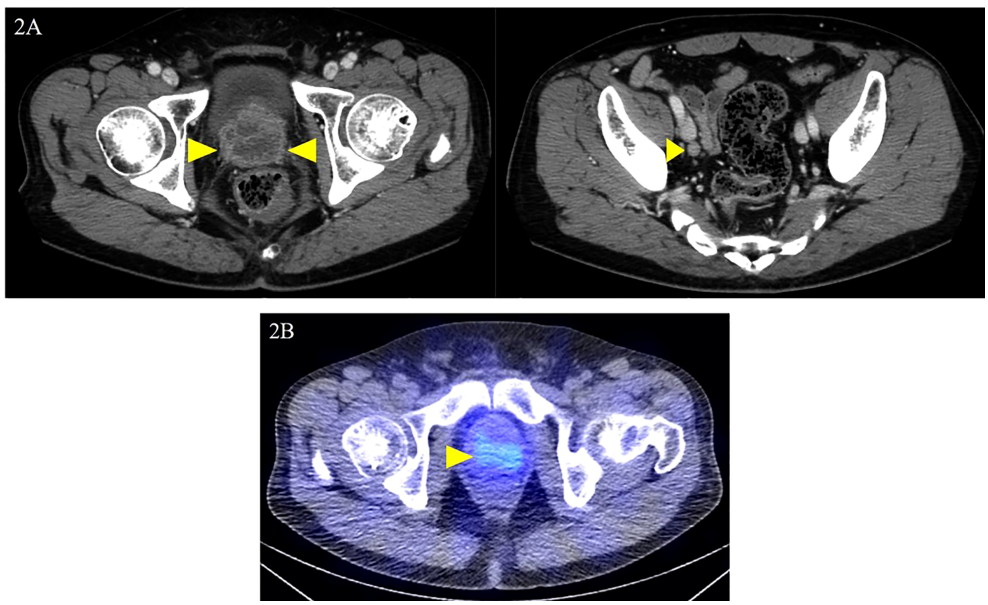

FIGURE 2
Local prostate lesion and involved lymph nodes on contrast-enhanced computed tomography and somatostatin receptor scintigraphy. Contrast-enhanced computed tomography examination at the first visit to the department: **(A)** dark staining throughout the prostate and enlarged right obturator lymph node was noted (yellow arrowheads); **(B)** somatostatin receptor scintigraphy shows mild accumulation in the local prostate lesion (yellow arrowhead).

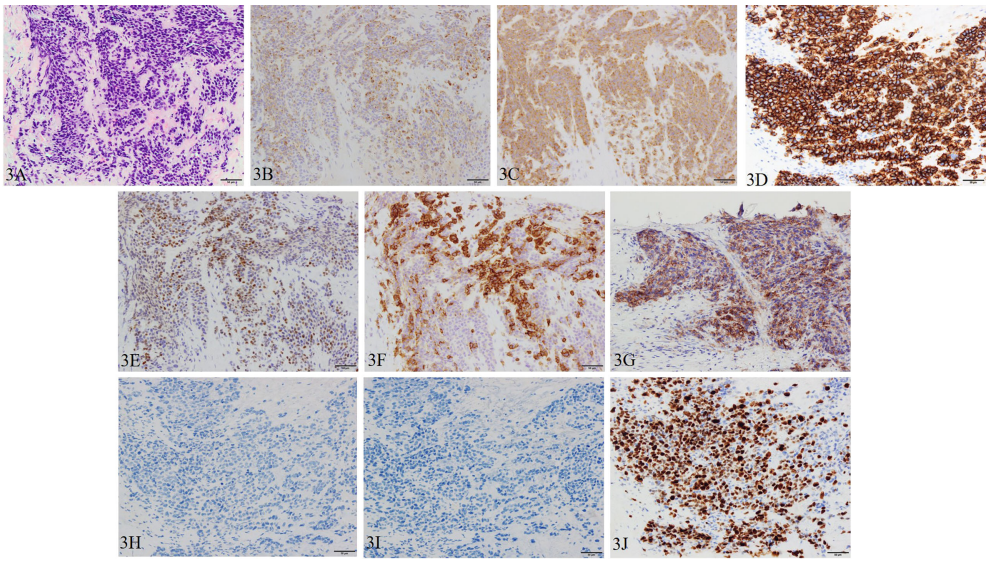

FIGURE 3
Pathological manifestations of prostate re-biopsy. Hematoxylin and eosin staining (magnification, ×200): **(A)** the tumor tissue is infiltrated with chromatin-rich, naked nucleated tumor cells with an increased nucleus/cytoplasm ratio of irregular nuclear shape. Immunohistochemistry (magnification, ×200): **(B)** chromogranin A, **(C)** synaptophysin, **(D)** CD56, **(E)** INSM1, **(F)** SSTR2, and **(G)** PD-L1 (focal) are positive, and **(H)** AR and **(I)** PSA are negative. **(J)** Ki-67 is also positive with a Ki-67 labeling index over 90%.

known as Lynch syndrome (19). However, the diagnosis of Lynch syndrome must meet Amsterdam criteria II, which at present requires at least three relatives with an HNPCC-related cancer, including cancers of the colon and rectum, endometrium, small bowel, ureter, or renal pelvis (20).

Although neuroendocrine-type prostatic adenocarcinoma with MSI-high in a patient diagnosed with Lynch syndrome has been reported previously (21), as described earlier, this patient does not meet Amsterdam criteria II, and he is, to the best of our knowledge, the first reported patient with non-hereditary CRPC-NE with MSI-high unrelated to Lynch syndrome worldwide.

In 2016, the World Health Organization reclassified prostatic NE tumors into five groups: standard adenocarcinoma with NE differentiation, adenocarcinoma with Paneth cell-like NE differentiation, carcinoid tumor, small cell

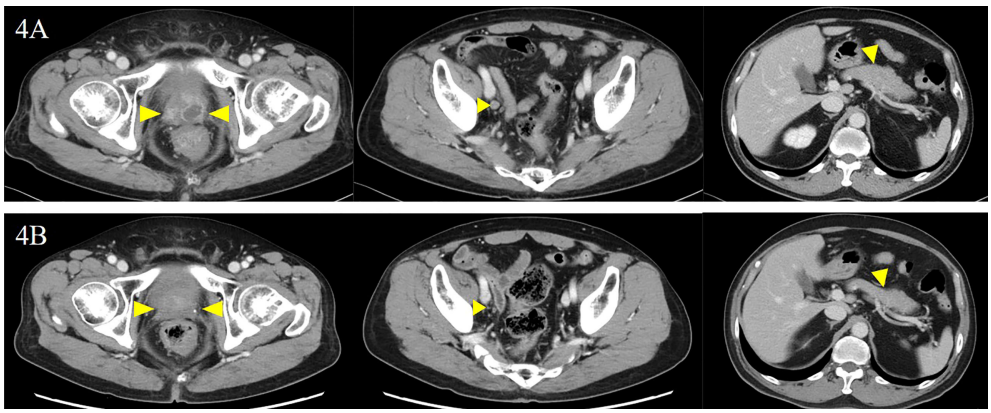

FIGURE 4
Local prostate lesion imaging including involved lymph nodes and pancreatic lesion before and after the administration of pembrolizumab. Contrast-enhanced computed tomography examination: **(A)** before the administration of pembrolizumab and **(B)** 5 months after the administration of pembrolizumab. There was complete remission of each lesion (yellow arrowheads).

NE carcinoma (SCNC), and large cell NE carcinoma (22). Following the classification of Hu et al., this case is consistent with what they designated SCNC (23). Additionally, *de-novo* SCNC is also rare, accounting for less than 1% of prostatic cancer cases (23).

However, in a multicenter prospective study, treatment-emergent SCNC was reported to account for 17% of the cases (24). Additionally, treatment-emergent neuroendocrine prostate cancer (T-NEPC) has been reported to occur primarily in advanced CRPC which is an alteration of normal prostate adenocarcinoma following ADT including CAB (25). Zhang et al. reported in a review of 94 cases of T-NEPC that 30.9% of AR and 47.9% of PSA were negative on immunohistochemical staining (26). Furthermore, T-NEPC has a median survival of 17.6 months. This is a significantly worse prognosis compared with normal CRPC patients (median survival of 23.6 months) with a reported median survival of 15.7 months for metastatic cases and 9.7 months for those with a small cell carcinoma component (26).

In this case, as shown in Figure 1, the pathology specimen of the initial prostate biopsy was weakly positive for PSA, strongly positive for AR, and negative for NEPC-related markers, but the pathology specimen of the re-biopsy turned negative for PSA and AR and positive for NEPC-related markers as shown in Figure 3. It is also a post-CAB state, and these facts strongly support that this case is T-NEPC. In addition, he had metastases in his lymph nodes and pancreas, and a small cell carcinoma component was detected on prostate re-biopsy which is consistent with a poor prognosis in T-NEPC. However, after confirming MSI-high, the patient survived more than 14 months, starting after pembrolizumab administration, without progression. It appears that even though it is infrequent, if MSI-high is present, a long-term survival benefit from pembrolizumab administration may be expected even in the poor prognosis group of T-NEPC. Furthermore, as noted previously, given that the detection rate of treatment-emergent SCNC is 17% (24), and the frequency of MSI-high in prostate cancer is rare, ranging from 3% to 22% (13–18), the frequency of cases with both MSI-high and T-NEPC is extremely rare. The patient in the present case had pancreatic metastasis. Although there are scattered reports of visceral metastases including bone, brain, liver, and lung in CRPC-NE (17, 26), we could not point to any pancreatic metastases as far as we could determine. There is a possibility that it is a feature of CRPC-NE with microsatellite instability-high, but this has not yet been confirmed and requires further investigation.

With regard to the patient's perspective, Japanese health insurance covered all genetic testing, so the patient accepted all the tests. Because the Japanese insurance system permits only an outpatient setting when using a next-generation sequencer such as FoundationOne CDx®, we investigated only MSI with a kit in this case, which is an inpatient setting. Since this patient was symptomatic and also post-irradiation, MSI investigation was performed during CPT-11 administration. The timing of the outpatient visit was very difficult due to the patient's ongoing symptoms and difficulty with chemotherapy withdrawal. Since next-generation sequencers (NGS) can detect many genetic mutations, the detection of mutations by NGS should be considered depending on the situation. However, if an outpatient visit is difficult during chemotherapy, MSI, which can be calculated separately from the NGS, may be considered first. Since the patient did not undergo a genomic test such as FoundationOne CDx® in this case, the patient accepted the test using the MSI-IVD kit without any problems. However, if the disease progresses in the future, the FoundationOne CDx® genomic test should be performed, and if the obtained results other than MSI-high indicate the hereditary nature of the disease, this fact should be explained to the patient after consultation with a physician specializing in genetic care.

It is necessary to discuss what treatment options will be available in the future if the disease progresses in the present case. First, a comprehensive cancer genome profiling using NGS will be done as it has not yet been performed. Depending on the results, there may be a therapeutic drug matching for the gene mutation. It has also been noted that Aurora kinase A inhibitor (27) and mammalian target of rapamycin inhibitor (28) may be effective against CRPC-NE although not in all cases. Next, immunohistochemical staining of the re-biopsy specimens showed expression of somatostatin receptor (SSTR) subtype 2. In addition, somatostatin receptor scintigraphy showed a mild accumulation of radionuclides in the prostate lesion. The usefulness of somatostatin receptor scintigraphy has been suggested not only in gastroenteropancreatic neuroendocrine tumors but also in CRPC-NE (29, 30). Furthermore, somatostatin receptor analogs such as octreotide have a high-binding affinity for SSTR subtypes 2 and 5 (31). These findings suggest that radionuclide therapy may be effective in this patient with SSTR subtype 2 positivity and somatostatin receptor scintigraphic accumulation.

The strength of the present case is that pembrolizumab, which was used in this case, is widely used in urologic malignancies and is relatively familiar with the management of immune-related adverse events. The limitation is that there are no other reports of durability of response in pembrolizumab in patients with CRPC-NE and MSI-high. Therefore, the optimal treatment for relapse after pembrolizumab treatment is still not well understood; however, the introduction of next-generation genome sequencers and positive immunostaining for SSTR subtype 2 in re-biopsy specimens should be used as a reference for treatment strategy.

Conclusion

This report discusses a patient with a long-term response to pembrolizumab in CRPC-NE with MSI-high. It is noteworthy

that while the patient had a small cell carcinoma component and metastasis to other organs and was in the poor prognosis group of T-NEPC, he still experienced long-term survival. If the presence of viable cells is suspected on radiological imaging, aggressive prostate re-biopsy should be performed. Furthermore, even if the results indicate a poor prognosis, MSI examination should be considered, even if its presence is infrequent.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Kanazawa University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TY and HIw treated the patient. TY and HY reviewed the literature and contributed to the preparation of the manuscript draft. TY and RT obtained the consent form from the patient. TY and HY drew the graph including the patient's data and contributed to the preparation of the manuscript draft. HY and HIk interpreted the imaging and pathological findings. TY, HY, and AM were responsible for the revision of the manuscript and important intellectual content. All authors agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.912490/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Transitive graph of serum PSA, NSE, and ProGRP with clinical course. CE, carboplatin plus etoposide; CRPC-NE, castration-resistant prostate cancer with neuroendocrine differentiation; EP, etoposide plus cisplatin; NSE, neuron-specific enolase; proGRP, progastrin-releasing peptide; PSA, prostate-specific antigen; RT, external beam radiation therapy.

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