Penile metastasis from prostate cancer with CDK12 mutation: A case report and literature review

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Received July 24, 2025; Accepted January 14, 2026

DOI: 10.3892/ol.2026.15492

Abstract. There are few reported cases of penile metastasis from prostate cancer. Its clinical presentation can be non-specific, posing diagnostic challenges. A 65-year-old man presented with dysuria in July 2016. Initial evaluation revealed a prostate-specific antigen (PSA) level >500 ng/ml, and magnetic resonance imaging findings suggested advanced metastatic acinar adenocarcinoma (T4N1M1). Pathological examination of a tissue specimen confirmed prostate adenocarcinoma, with a Gleason score of 4+3=7. The patient was started on androgen deprivation therapy with goserelin (10.8 mg every 3 months) and bicalutamide (50 mg once daily), and stable disease was achieved for 66 months. In April 2022, an increased PSA level and a growing penile mass were observed. Prostate-specific membrane antigen positron emission tomography/computed tomography revealed penile metastasis from prostate cancer (PCa). The mass was surgically removed, and pathological examination confirmed infiltrating poorly differentiated PCa. Bicalutamide was replaced by enzalutamide (160 mg once daily) in the treatment regimen. Subsequently, based on the identification of *CDK12* mutations by genetic testing, treatment with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (300 mg twice daily) was initiated. To date, the patient has remained clinically stable with low PSA levels. This case highlights the potential utility of molecular profiling and combined PARP inhibition and androgen receptor-targeting therapy in *CDK12*-mutated metastatic castration-resistant PCa with rare penile metastasis.

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Key words: prostate cancer, penile metastasis, olaparib, enzalutamide, CDK12, PARP inhibitor

Introduction

Penile metastasis from prostate cancer (PCa) is exceptionally rare, reportedly occurring in <0.5% of PCa cases, and is associated with a poor prognosis (1). While the bones and lymph nodes are common metastatic sites, penile involvement can also arise by mechanisms including retrograde venous spread due to anatomical connections between the pelvic venous plexuses and penile dorsal veins (2). The clinical presentation of penile metastases is often non-specific (3), making differentiation from primary penile lesions or other benign conditions difficult without sophisticated imaging and histopathological confirmation. This diagnostic ambiguity underscores the need for heightened clinical suspicion in patients with advanced PCa presenting with new penile abnormalities.

A key aspect in managing advanced PCa, including rare metastatic presentations, is to understand the molecular characteristics of the tumor. The mechanism by which *CDK12* regulates homologous recombination repair (HRR) genes is linked to intronic polyadenylation (IPA) (4). IPA can lead to aberrant mRNA splicing and the emergence of mRNA isoforms characterized by alterations in the 3'untranslated regions and coding sequences, thereby affecting the stability, translation efficiency and coding potential of HRR-related mRNAs (5).

The present case report describes a patient with *CDK12*-mutated metastatic castration-resistant PCa (mCRPC) who developed a rare penile metastasis after a prolonged period of response to initial androgen deprivation therapy (ADT). The study details the diagnostic workup, which utilized prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT), and the subsequent therapeutic strategy guided by molecular profiling. This case underscores the clinical challenge of penile metastasis, illustrates the pivotal role of comprehensive genomic testing in guiding personalized therapy for mCRPC, and presents a novel and sustained response to a combination of enzalutamide and the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib in this specific genetic context.

Case report

A 65-year-old man was admitted to Nanfang Hospital (Guangzhou, China) in July 2016 with progressive difficulty in urinating. The patient had a history of type 2 diabetes. The

Table I. Summary of selected reported cases of penile metastasis from prostate cancer.

First author, year	Age, years	Gleason Score	Initial PSA, ng/ml	Treatment of penile metastasis	Follow-up period, months	Outcome	(Refs.)
Martz *et al*, 2021	61	4+4=8	1.57	MHB	6	Alive	(1)
Fiaschetti *et al*, 2016	84	NA	8.07	ADT	30	Dead	(2)
Kamaleshwaran *et al*, 2018	79	3+4=7	>100	ADT + RT	NA	NA	(8)
Fujita *et al*, 2021	80	4+4=8	48	ADT + RT	62	Alive	(9)
He *et al*, 2012	78	5+5=10	0.09	ADT + surgery	7	Dead	(11)
Present case	65	4+3=7	9.84	ADT + enzalutamide + olaparib	41	Alive	-

MHB, multicatheter interstitial high-dose rate brachytherapy; ADT, androgen deprivation therapy; RT, radiotherapy; NA, not available.

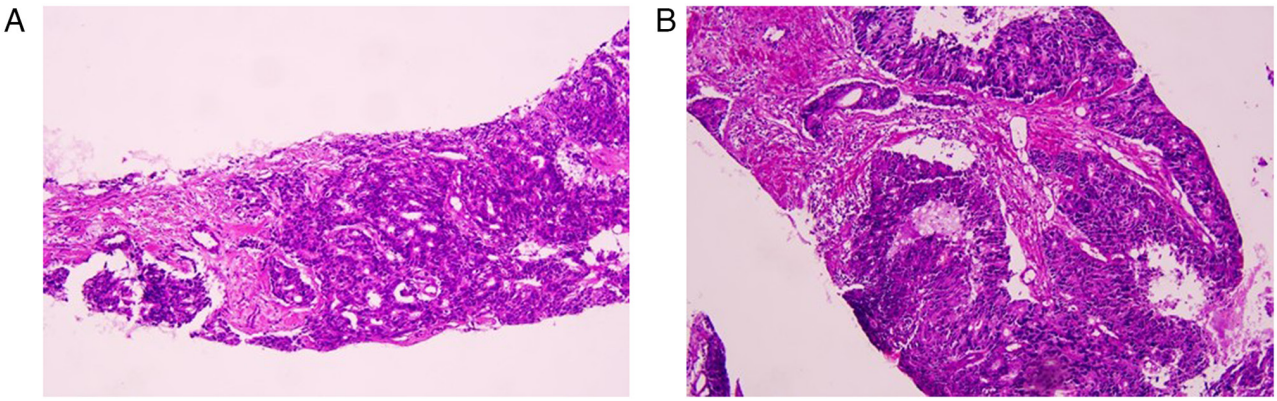

Figure 1. Histological examination of the prostate biopsy tissue specimen. (A) The predominant component consists of fused cribriform glands, consistent with a Gleason pattern 4. The minor component comprises individual, discrete glands of varying sizes with increased inter-glandular spacing, consistent with a Gleason pattern 3. (B) Characteristic features of Gleason patterns 4 and 3, including fused glands and glands with infiltrative growth (hematoxylin and eosin staining; magnification, x10).

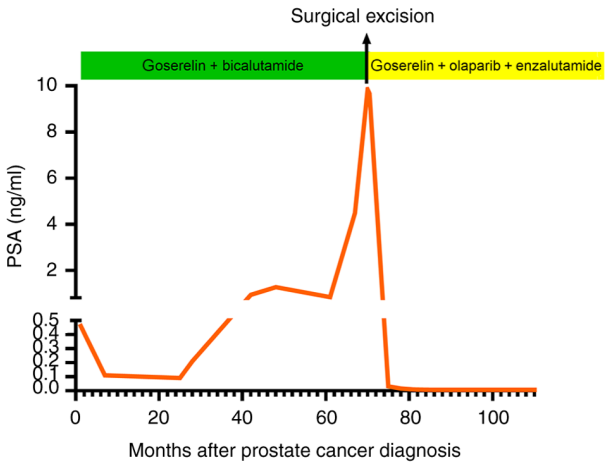

Figure 2. Changes in PSA level over the clinical course following the diagnosis of prostate cancer. The lowest limit of detection of the PSA assay is 0.006 ng/ml. PSA, prostate-specific antigen.

initial prostate-specific antigen (PSA) level was recorded as >500 ng/ml (normal range, 0-4ng/ml). Magnetic resonance imaging (MRI) suggested advanced metastatic PCa [8th American Joint Committee On Cancer (AJCC) Staging, AJCC T4N1M1] (6) with invasion of the left seminal vesicle, bladder and rectum, pelvic lymph node involvement, and right iliac acetabular bone metastasis. Histological examination of a biopsy tissue specimen confirmed acinar adenocarcinoma with a Gleason score of 4+3=7 (Fig. 1). The patient was started on endocrine therapy with goserelin (10.8 mg every 3 months) and bicalutamide (50 mg once daily) in July 2016. The PSA levels subsequently decreased and reached a nadir of 0.09 ng/ml in July 2018 (Fig. 2), accompanied by an improvement in urinary symptoms.

Beginning in January 2022, the PSA levels exhibited a progressive increase, reaching 9.84 ng/ml in April 2022. During this period, a gradually enlarging mass was noted on the right side of the penis. PSMA PET/CT (Fig. 3A) showed increased PSMA uptake in the left seminal vesicle and the left anterior wall of the rectum, suggesting the PCa had invaded these areas. Based on the PET/CT, there is increased PSMA uptake in the penile mass on the right side, which is considered malignant. No abnormal uptake was observed in previously involved lymph nodes, and no other metastatic foci were identified. Therefore, the patient was considered eligible for surgery to remove the penile mass. In April 2022, the penile mass was removed under local anesthesia.

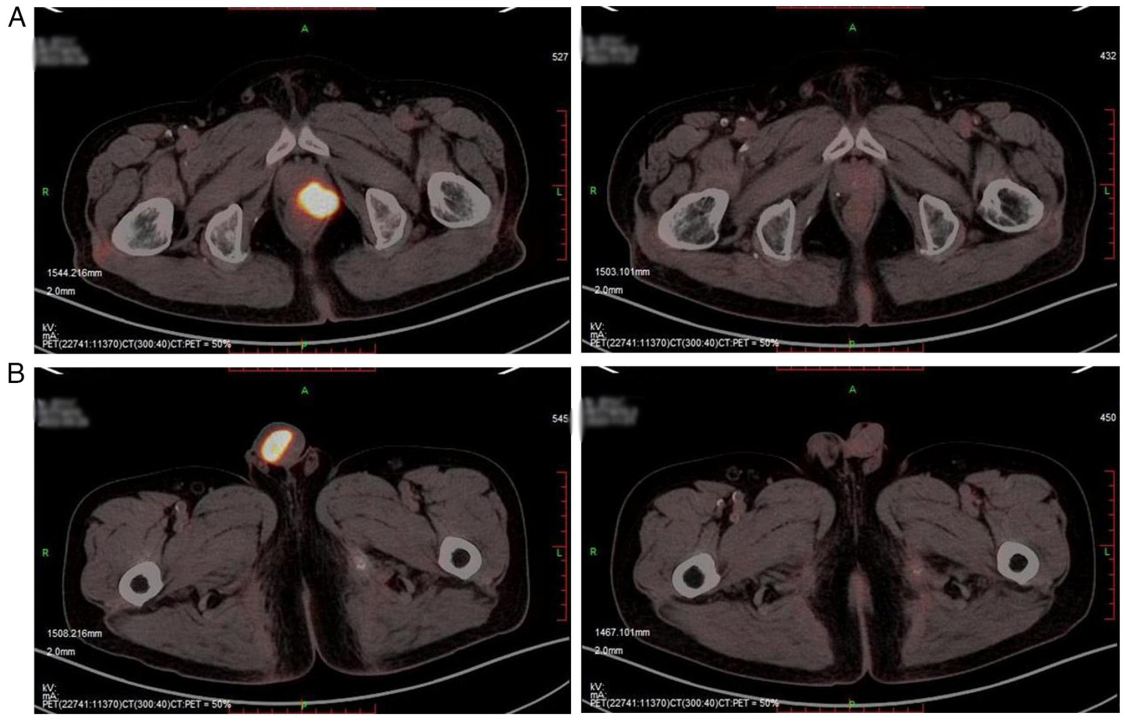

Figure 3. Prostate-specific membrane antigen PET/CT images of the (A) prostate and (B) penis before and after treatment. The PET/CT images on the left were taken before treatment and those on the right were taken after treatment. PET/CT, positron emission tomography/computed tomography.

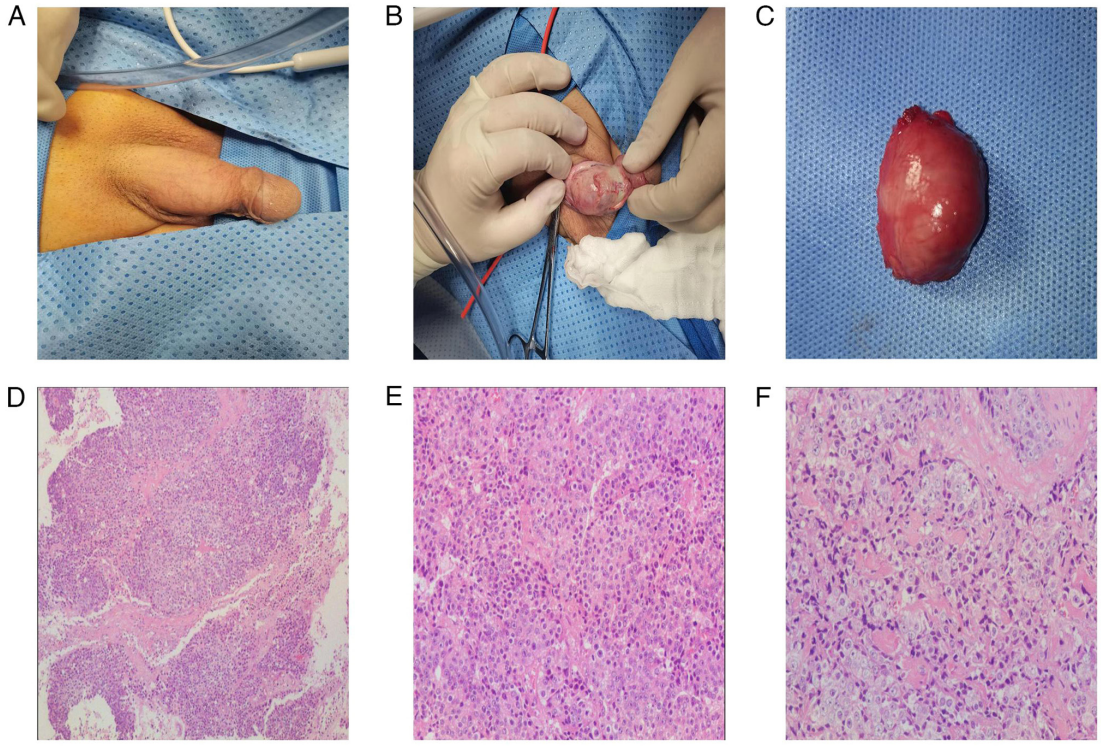

Figure 4. Macroscopic and microscopic characteristics of the metastatic penile tumor. During the preoperative (A) and intraoperative (B) periods,a mass is visible on the right side of the penis. (C) Completely resected penile mass. (D-F) Microscopic examination of the penile mass. Tumor cells are arranged in irregular sheets and nests and exhibit infiltrative growth. Hematoxylin and eosin staining. (D) Magnification, x40; (E) magnification, x100; (F) magnification, x200.

Histopathological examination of the penile mass revealed infiltrating poorly differentiated PCa (Fig. 4). Tissue specimens were fixed in 10% formalin, embedded in paraffin and sectioned into 4-μm serial slices. The sections were mounted on APES-coated slides (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), baked at 60˚C for 1-2 h and stored at 4˚C for later

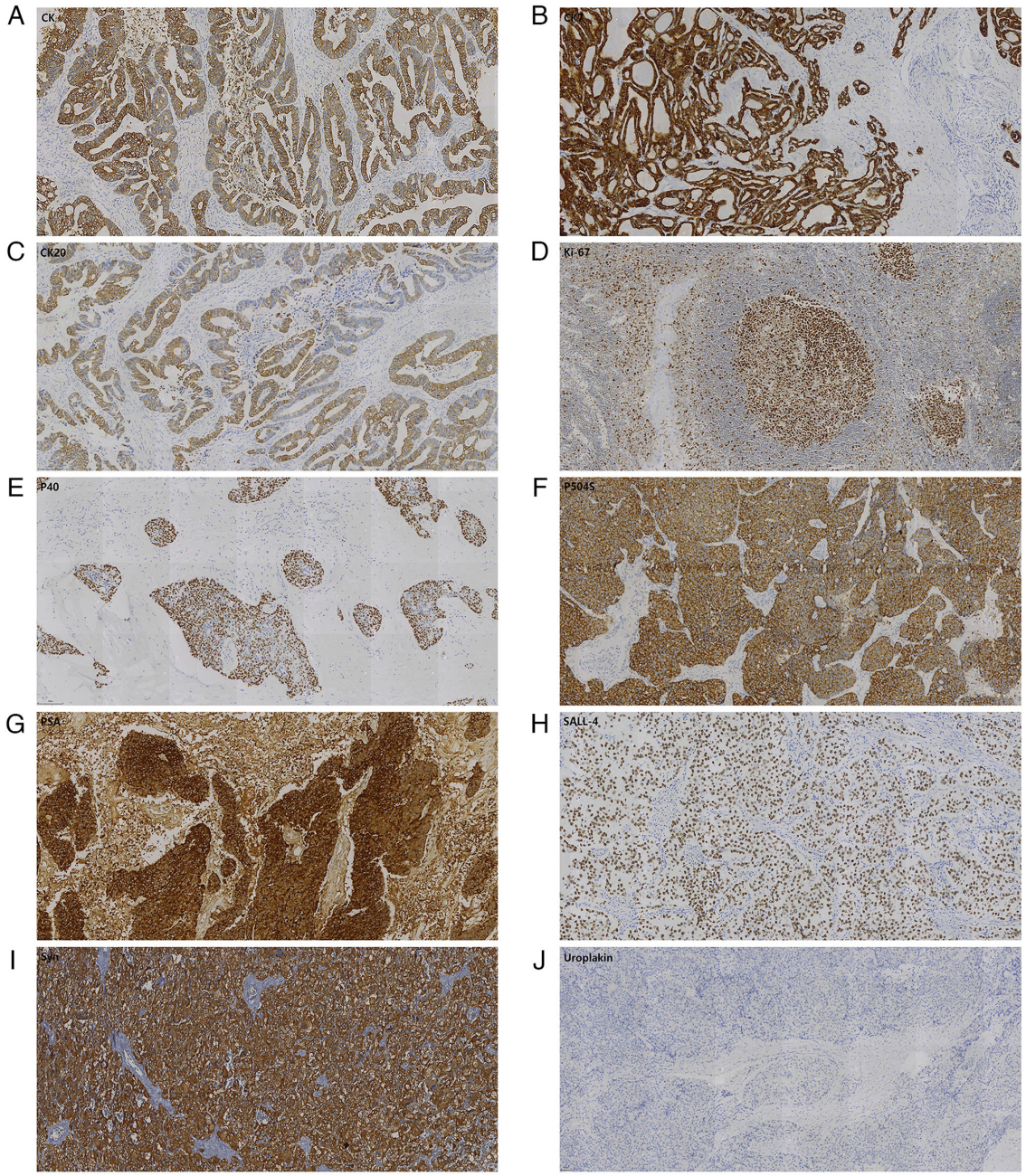

Figure 5. Immunohistochemical staining of the penile tumor. Staining results are (A) CK-positive, (B) CK7-negative, (C) CK20-focally positive, (D) Ki-67-positive, (E) p40-negative, (F) P504S-positive, (G) PSA-positive, (H) SALL4-negative, (I) Syn-negative and (J) uroplakin-negative. Magnification, x200. (For negative markers, staining is limited to non-neoplastic tissue components). CK, cytokeratin; P504S, α-methylacyl-CoA racemase; PSA, prostate-specific antigen; SALL-4, Spalt-like transcription factor 4; Syn, synaptophysin.

use. Immunohistochemistry was performed using the streptavidin-peroxidase (SP) method: After dewaxing, rehydration and antigen retrieval with citrate buffer (pH 6.0) via microwave heating, endogenous peroxidase activity was blocked with 3% H_2O_2 (Reagent A of Ultra-Sensitive™ S-P kit; Fuzhou Maixin Biotechnology Development Co., Ltd.) at room temperature for 10 min; non-specific binding was blocked with 10% goat serum (Reagent B of the same kit) at room temperature for 10 min; the primary antibody against Cripto-1 (diluted 1:75) was applied and incubated overnight at 4˚C; this was followed by sequential incubation with biotin-labeled goat anti-mouse/rabbit IgG (Reagent C) and streptavidin-peroxidase solution (Reagent D), each at room temperature for 10 min; color development was performed using diaminobenzidine (DAB) chromogen solution (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 1-3 min; sections were counterstained with hematoxylin for 5 min, then dehydrated, cleared and mounted. All antibodies and kits were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., DAB reagent and APES-coated slides were obtained from Beijing Zhongshan Jinqiao and the HRP-labeled secondary antibody was sourced from Wuhan Boster Biological Technology, Ltd. Stained sections were examined under a BH-2 light microscope (Olympus Corp.). Control experiments were performed by replacing the primary antibody with PBS while keeping all other steps identical. Immunohistochemical examination revealed the mass was

positive for cytokeratin (CK), PSA, α-methylacyl-CoA racemase (P504S) and Ki-67 40%, and focally positive for CK20. In addition, the mass was negative for CK7, p40, synaptophysin (Syn), uroplakin and spalt-like transcription factor 4 (SALL4). CK positivity indicates that the mass is of epithelial origin. PSA and P504S supports a prostatic origin. P40 negativity confirms basal cell loss and verifies malignancy. Meanwhile, CK7 negativity and uroplakin negativity rule out urothelial carcinoma; Syn negativity rules out neuroendocrine tumors; and SALL4 negativity rules out germ cell tumors (7) (Fig. 5). Therefore, the diagnosis was progression to mCRPC.

As the disease progressed, bicalutamide was discontinued and the patient was switched to a next-generation antiandrogen. Meanwhile, considering the patient's history of diabetes and the fact that abiraterone can affect blood glucose levels, enzalutamide (160 mg once daily) was selected. A total of 99 genes (Xiangxian™-Prostate Cancer 99-Gene Panel; AcornMed) associated with prostate cancer were tested, covering those related to hereditary tumors, endocrine therapy, targeted therapy, chemotherapy drugs and prognosis. Eventually, *CDK12 p.L636fs* and *CDK12 p.D1004fs* were identified. Based on these findings, olaparib (300 mg twice daily) was added to the treatment regimen in May 2022. Following this combination therapy, PSA levels decreased markedly, reaching 0.03 ng/ml in September 2022, which was substantially lower than the nadir prior to the development of penile metastasis. PSA levels have since remained stable and are consistently at <0.006 ng/ml (Fig. 2). In October 2024, follow-up PET/CT (Fig. 3B) showed no increased PSMA uptake in the left posterior lobe of the prostate, suggesting sustained tumor suppression following treatment. No evidence of local recurrence was observed at the site of the resected penile metastasis, and no lymph node metastases were detected in the pelvic or retroperitoneal regions. The patient has been followed up every three months, and no new abnormal symptoms or discomfort have been observed.

Discussion

Penile metastasis from PCa is rare, and a search for relevant literature on PubMed (https://pubmed.ncbi.nlm.nih.gov/) using the keywords 'prostate cancer' AND ('penile metastasis' OR 'penis metastasis') identified <100 reported cases. The condition has been reported to have a mean survival time after diagnosis of ~9 months (8). The longest reported survival duration to date is 62 months (9). By comparison, the patient described in the present case report has survived for 41 months since the diagnosis of penile metastasis. Although only five other cases were analyzed in the present review, they are highly representative in terms of both PSA level distribution and treatment strategy coverage. These cases include instances of both very low and very high PSA, demonstrating that penile metastasis can occur across different tumor burdens. They also encompass a range of treatment approaches, from traditional androgen deprivation therapy to novel combination regimens. By comparing prognostic differences among various strategies, this study particularly highlights the breakthrough efficacy achieved through genotype-guided precision combination therapy in key cases, thereby supporting the critical role of molecular testing in rare metastatic prostate cancer and the value of innovative combination strategies (Table I).

When PCa metastasizes to the penis, the metastatic lesions typically occur in the penile root, penile shaft or glans (10). Proposed mechanisms of penile metastasis include direct invasion, previous device implantation, retrograde venous flow, and arterial or lymphatic dissemination (11). Among these, retrograde venous flow is considered the most likely pathway for penile metastasis from PCa (2). He *et al* (11) reported tumor thrombi within the veins of the penile corpus cavernosum, supporting this mechanism.

Penile metastases can manifest as painless nodules, surface nodules, ulcers, erythema, urinary retention, irritative voiding symptoms, perineal pain, hematuria and/or priapism (3). Due to their low incidence and non-specific clinical manifestations, penile metastases must be differentiated from other conditions such as idiopathic priapism, sexually transmitted infections, tuberculosis, Peyronie's disease, primary tumors and non-specific inflammatory lesions (2,12-14). Various imaging techniques are valuable aids in the differential diagnosis. Color Doppler ultrasonography can detect uneven nodules in the penile corpora cavernosa, but lacks specificity for penile metastasis (3). CT is helpful for detecting secondary penile lesions (14), while MRI, with its high soft-tissue contrast, can reliably differentiate and accurately stage penile lesions (15). PSMA is an integral membrane protein located on the membrane of prostate glandular epithelial cells. In prostate cancer cells, including those from both primary tumors and metastatic lesions, the expression level of PSMA is significantly upregulated, leading to markedly increased radiotracer uptake on PET/CT images. Thus, PSMA PET/CT is particularly useful for diagnosing atypical penile metastases from PCa (16,17).

No standardized treatment strategy exists for penile metastases. Management should be individualized according to symptom burden, the extent of the tumor and patient performance status (3). Local treatment approaches include surgery or radiotherapy (18); however, the latter carries a risk of urethral stenosis or ulceration (19). ADT remains the cornerstone for the management of metastatic PCa (20). The addition of enzalutamide to ADT has been shown to improve outcomes in metastatic hormone-sensitive PCa (21,22). PARP inhibitors, including olaparib, have demonstrated efficacy in tumors with HRR gene defects (23). Preclinical and clinical studies suggest a synergistic effect may be achieved using PARP inhibitors and androgen receptor-targeted therapies (24). In particular, clinical trials, including the PROpel (25), MAGNITUDE (26) and TALAPRO-2 (27) trials, have reported improved outcomes with combination therapy among patients harboring HRR mutations. It is worth noting that the updated TALAPRO-2 study indicates that OS showed a statistically significant and clinically meaningful improvement regardless of HRR gene mutation status.

In the present case, treatment with ADT combined with enzalutamide and olaparib resulted in a marked decline in PSA levels and sustained radiographic disease stability. At 41 months, the survival time following a diagnosis of penile metastasis in the present case exceeds the median overall survival time reported for olaparib monotherapy (10.1 months) (28) and enzalutamide monotherapy (35.3 months) (29). Notably, this survival duration also exceeds

those described for multicatheter interstitial high-dose rate brachytherapy-based regimens (6 months) (1), ADT alone (30 months) (2), or surgery combined with ADT (7 months) (11) in men with PCa metastatic to the penis (Table I). Currently, the combination regimens involving novel endocrine drugs and PARP inhibitors include olaparib plus abiraterone, niraparib plus abiraterone, and enzalutamide combined with talazoparib. However, the combination of enzalutamide and olaparib has not yet been reported. Although limited by this being a single case, the present outcome suggests that a combination of olaparib and enzalutamide may be a viable option to promote the antitumor effect of PARP inhibitors and novel endocrine drugs. The present case may serve as a reference for the treatment of mCRPC with HRR mutations.

CDK12 is a protein kinase that plays a crucial role in cell cycle regulation and gene transcription (30). *CDK12* mutations occur in ~7% of PCa cases, and patients with *CDK12* mutations have been shown to have a significantly shorter overall survival time and a shorter time to progression to castration-resistant disease compared with those patients with wild-type *CDK12* (31,32). A multicenter study reported similar findings, demonstrating that patients with *CDK12* mutations exhibited a shorter progression-free survival time and faster disease progression after receiving ADT than those with wild-type *CDK12*, and only one of seven patients achieved a reduction in PSA from a baseline of >50% (a PSA50 response) (33). In addition, patients with PCa harboring *CDK12* mutations have been shown to exhibit a shorter time to PSA progression following first-line androgen receptor signaling inhibitor compared with that exhibited by other patients (34). These findings suggest that *CDK12* mutations may result in PCa being intrinsically less responsive to ADT.

Alternative systemic therapeutic approaches for this molecular subtype are urgently needed and are currently being investigated. Wu *et al* (4) reported outcomes for four patients with mCRPC harboring CDK12 mutations treated with anti-programmed cell death protein-1 monotherapy, of whom 2 experienced marked reductions in PSA levels, thus benefiting from the treatment. However, in another retrospective study, only 2 out of 19 patients receiving immune checkpoint inhibitor therapy achieved a PSA50 response (35). Whether CDK12 mutations can serve as biomarkers to predict the potential response of PCa to ICIs remains unclear and requires further evaluation. In addition, Zhu *et al* (36) and Barata *et al* (37) reported that platinum-based chemotherapy can be effective for patients with CDK12 mutations. However, evidence supporting this is limited to only three case reports (36-38) and a clinical study in 2020 that reported patients with CDK12 mutations achieved a PSA50 response after receiving platinum-based chemotherapy, but specific data were not discussed (39).

In the present case, *CDK12 p.L636fs* and *CDK12 p.D1004fs* mutations were detected. It has been demonstrated that *CDK12* loss drives prostate cancer progression, and PARP inhibitors have some activity in patients with prostate cancer with biallelic inactivating *CDK12* alterations. In 2020, the U.S. Food and Drug Administration approved olaparib for the treatment of patients with mCRPC harboring HRR gene mutations. Based on these results, treatment with olaparib was selected, achieving a sustained response.

In conclusion, the present case highlights the diagnostic value of PSMA PET/CT in the identification of rare penile metastases and underscores the importance of molecular profiling in guiding therapy. The sustained response to enzalutamide and olaparib in a patient with *CDK12*-mutated mCRPC suggests that this combination may be a valuable option in similar genetic contexts. However, further studies are necessary to validate this approach.

Acknowledgements

Not applicable.

Funding

This study was supported by the Medical Scientific Research Foundation of Guangdong Province (grant no. C2023070) and the Special Clinical Research Program of Nanfang Hospital (grant no. 2022CR012).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QX and YW analyzed data, and wrote and edited the manuscript. QX and QD designed the study protocol. QD was the primary care physician of the patient and developed and implemented the treatment plan. QX, YW and BY performed the literature review and analyzed and interpreted the data in the paper. BY and HT obtained patient data and performed the histological examination of the tumor. HT and QD reviewed the manuscript. HT performed the analysis and interpretation of images. QX, YW, BY, HT and QD confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nanfang Hospital (Guangzhou, China; approval no. NFEC-202511-K26).

Patient consent for publication

Written informed consent for the publication of clinical details and images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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