Case Report

Immunotherapy in the treatment of rectal invasion by prostate cancer with focal neuroendocrine differentiation: a case report and literature review

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Background: Incidences of rectal infiltration by prostate cancer (PCa) are reported to affect up to 12% of patients studied. PCa invading the rectum is prone to cause difficulty in defecation, bloody stool and pain, leading to a decline in patients' quality of life. Unfortunately, the prognosis for these patients is poor and the survival period is short. Total pelvic exenteration (TPE) has been demonstrated to mitigate pain and improve symptoms such as defecation difficulty, dysuria, and hematuria. However, most patients still harbor residual tumor and fail to exhibit any improvement in long-term survival.

Case Description: Here, we present a case of PCa invading the rectum with focal neuroendocrine differentiation, characterized by clinical presentations of defecation difficulties and rectal bleeding. A TPE procedure was performed, with a whole exome sequencing (WES) assay indicating that the patient exhibited a high tumor mutation burden (TMB) and high microsatellite instability (MSI-H). Subsequently, the patient received androgen deprivation therapy (ADT) combined with adjuvant immunotherapy following the procedure. At the subsequent six-year follow-up, no local or systemic recurrence was observed, and the prostate-specific antigen (PSA) level remained undetectable.

Conclusions: This disease entity remains relatively rare in the literature. Accurate differential diagnosis is important. TPE combined with immunotherapy may improve the prognosis. It is of utmost importance to achieve an accurate differential diagnosis, which necessitates the collaboration of multiple disciplines and the performance of requisite tests, including immunohistochemistry and genetic testing.

Keywords: Prostate cancer (PCa); total pelvic exenteration (TPE); neuroendocrine differentiation; immunotherapy; case report

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Introduction

Prostate cancer (PCa) is a prevalent solid malignancy, ranking as the second leading cause of cancer-related mortality among men in the United States. The unique anatomical location of the prostate often facilitates cancer invasion into neighboring organs, such as the rectum (1). Locally advanced pelvic tumors without distant metastases can cause severe local problems, such as pain, voiding, and defecation problems, which may result in a decreased

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quality of life (1-3).

It has been demonstrated that total pelvic exenteration (TPE) is an effective treatment for perineal pain and other symptoms associated with pelvic floor dysfunction, including bloody stools, fecal incontinence, hematuria, ureteral obstruction, urinary incontinence, and retention (3). However, TPE combined with radiotherapy or androgen deprivation therapy (ADT) did not improve the patient's prognosis (4). The median life expectancy for these patients typically ranges from 12 to 24 months. Here, we present a case of a patient with pathological stage T4 PCa invading the rectum, who underwent TPE combined with immunotherapy, and whose quality of life and prognosis were significantly improved. Clinical presentation, surgical technique and pathological examination were described. We present this case in accordance with the CARE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-223/rc).

Case presentation

A 66-year-old man presented to a general surgeon with a history of increasing defecation difficulties and rectal bleeding. During the rectal examination, it was observed that the patient had a tight rectal stricture that did not allow for the insertion of the examining finger. A urological opinion was sought. Colonoscopy revealed a mucosal elevated lesion in the rectal lumen 8 cm from the anal verge, occupying 2/5 of the lumen, with ulcer formation on the surface, and the rectal biopsy specimen showed poorly differentiated adenocarcinoma. Combined with immunohistochemical inspection: prostate-specific antigen (PSA) (+), P504S (3+), androgen receptor (AR, 3+), it is considered to be a poorly differentiated infiltrating prostatic carcinoma. Total PSA was 13.5 ng/mL. Transperineal biopsy of the prostate showed infiltrating poorly differentiated adenocarcinoma of the prostate: International Society of Urological Pathology (ISUP) grade group 5, Gleason score of 5+5=10. According to winter's clinical classification (5), the patient belongs to type III: anterior rectal mass with ulceration of the intestinal mucosa. This may result in a fungating ulcerating mass. Subsequent radiographic investigations, including whole-body emission computed tomography (ECT) and prostate-specific membrane antigen (PSMA)-positron emission tomography-computed tomography (PET/CT), yielded negative indications of systemic metastasis. Magnetic resonance imaging (MRI) findings indicate the presence of PCa, with evidence of extracapsular extension, and invasion into the bilateral seminal vesicles, bladder, and rectum. Additionally, there are signs of metastatic disease to the pelvic lymph nodes. Based on imaging findings, the patient belongs to stage T4N1M0. On the advice of the multi disciplinary team, the patient decided to undergo TPE (involving *en bloc* resection of the rectum, bladder, and prostate/seminal vesicles combined with cutaneous ureterostomy and colostomy). Postoperative pathology confirmed a poorly differentiated follicular adenocarcinoma with focal neuroendocrine differentiation (ISUP grade group 5, Gleason score of 5+5=10), with cancer invading the muscular layer of the bladder and the wall of the rectum, and that the tumor had extended through the prostatic capsule the seminal vesicles bilaterally, pathological stage: pT4N0Mx (vascular invasion +, rectal margin +). *Figure 1* shows the immunohistochemical findings that synaptophysin (Syn) and chromogranin A (CgA) were positive. The patient's PSA level decreased to 0.013 ng/mL two weeks after the operation. ADT, comprising bicalutamide and goserelin acetate, was initiated three weeks postoperatively, achieving an undetectable PSA level (0.003 ng/mL) one month later. Whole exome sequencing (WES) assay suggested that the patient exhibited high tumor mutation burden (TMB, 76.72 muts/Mb) and high microsatellite instability (MSI-H). The patient began continuous ADT combined with postoperative adjuvant

Highlight box

Key findings

- Patients with prostate cancer (PCa) exhibiting neuroendocrine differentiation and a high tumor mutation burden (TMB) or microsatellite instability (MSI) may benefit from immunotherapy.

What is known and what is new?

- Neuroendocrine PCa (NEPC) is a rare and aggressive variant of PCa that is known to be somewhat resistant to conventional androgen deprivation therapy (ADT).
- Immunotherapy is an effective treatment for NEPC with high TMB or MSI.

What is the implication, and what should change now?

- The findings suggest the importance of immunotherapy in the treatment of NEPC with high TMB or MSI. It is recommended that genetic testing be conducted on these patients in order to ascertain whether they have an intentional gene mutation or an immunotherapy target. In addition, for these patients with complex medical conditions, we advocate for a multidisciplinary approach, enlisting the expertise of urologists, oncologists, pathologists, and radiologists, to collaboratively devise treatment strategies.

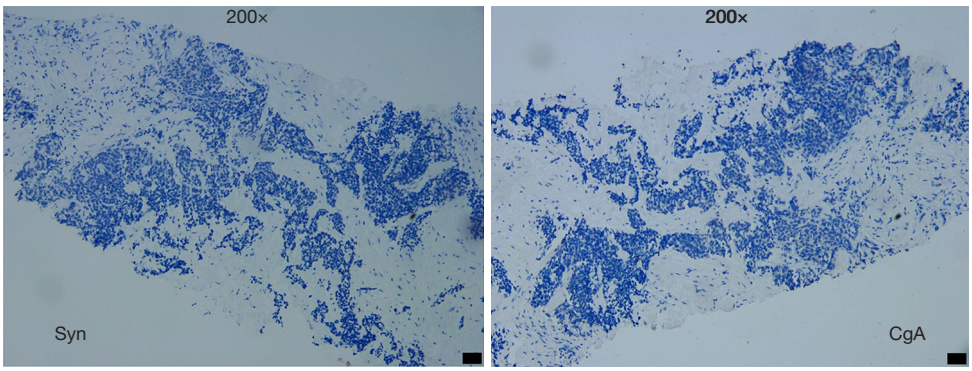

Figure 1 Immunohistochemistry for chromogranin A (CgA) and synaptophysin (Syn), ×200 magnification.

immunotherapy, receiving programmed cell death protein 1 (PD-1) antibody pembrolizumab in three-week cycles at a dosage of 150 mg intravenous (IV). After 72 courses, the patient has been followed up for 70 months. The patient was regularly followed up, and no adverse reactions or side effects were observed during the treatment period. The PSA levels remained stable at around 0.003 ng/mL, and PSMA-PET/CT examination showed no signs of local recurrence or systemic metastasis.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Incidences of rectal infiltration by PCa are reported to affect up to 12% of patients studied (6-8). The autopsy findings indicate that approximately 0.095% (9/9,504) of patients with PCa presenting with a rectal mass are incorrectly diagnosed with rectal cancer (9). Given the distinct treatment protocols for PCa and rectal cancer, when considering a radical resection of the rectum in a man with a suspected primary rectal carcinoma, it is important to rule out the possibility of direct extension from PCa. As a special-stage tumor, PCa invading the rectum is prone to cause difficulty in defecation, bloody stool and pain, leading to a decline in patients' quality of life (2,3). Unfortunately, the prognosis for these patients is poor and the survival period is short (1,4,8,10). TPE has been demonstrated to mitigate pain and improve symptoms such as defecation difficulty, dysuria, and hematuria. Additionally, it has been shown to reduce tumor burden and enable precise pathological staging (3,11).

Therefore, some scholars believe that TPE should no longer be reserved exclusively for salvage therapy, but rather be considered a curative treatment tool due to the improvement of medical technology and the decrease in complications (12).

However, Guo *et al.* demonstrated that despite extensive resection, most patients still harbor residual tumor and fail to exhibit any improvement in long-term survival. They also found evidence of residual tumor, such as tumor cells at the margin of resection, lymphovascular invasion, or metastasis to the lymph nodes, in patients who underwent TPE. Besides, the study indicated that poorly differentiated PCa with heterogeneous differentiation might result in inadequate responses to radiation therapy (RT), ADT, and chemotherapy (1).

A study (13) conducted in Switzerland found that patients with T4 stage PCa had a high probability of postoperative recurrence, with 56% experiencing recurrence within one year after surgery. While postoperative adjuvant ADT extended the progression-free survival, it did not benefit the overall survival of the patient (14).

The current clinical practice guidelines lack a standardized treatment regimen for stage T4 PCa. Current European Association of Urology (EAU) guidelines recommend RT or radical prostatectomy (RP) as part of a comprehensive treatment (15). Moreover, there are insufficient data on stage T4 PCa cases in the references of existing guidelines (16,17).

Immunotherapy, as an emerging cancer treatment method, has not yet been widely used in PCa. Studies

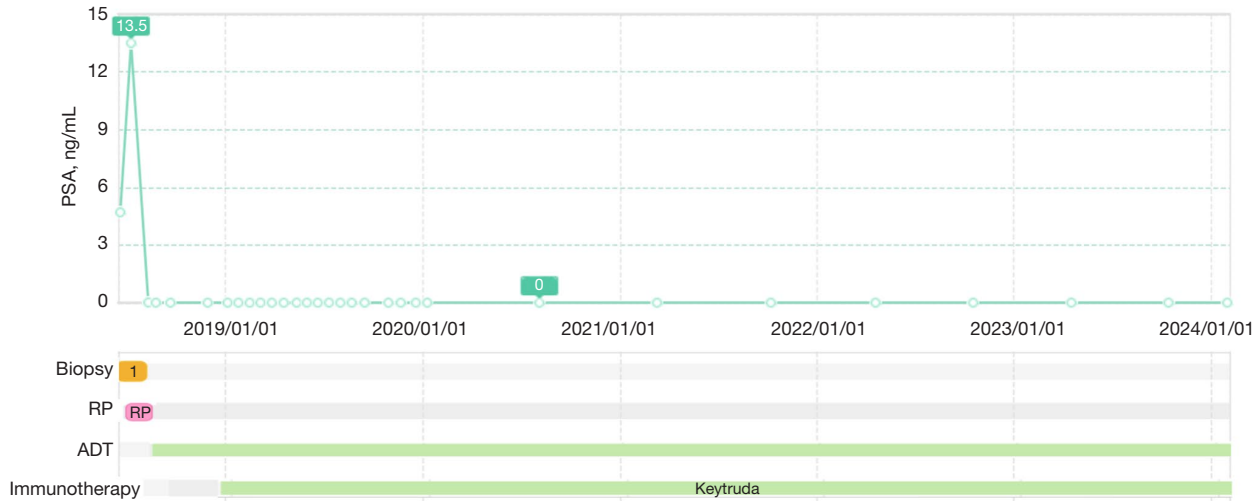

Figure 2 The patient's detailed treatment process, the condition change and the tumor marker change. PSA, prostate-specific antigen; RP, radical prostatectomy; ADT, androgen deprivation therapy.

have shown that patients with high TMB respond more favorably to immunotherapy, as evidenced in various tumor types such as lung cancer (18) and melanoma (19). An early study has shown that immune checkpoint inhibitors (ICIs) demonstrate limited anticancer activity (20). It is widely acknowledged that selecting patients with deficiencies of mismatch repair (dMMR) genes is crucial because this group of patients may respond positively to ICIs (21). In addition, MSI-H/dMMR is currently the only indication approved by the U.S. Food and Drug Administration (FDA) for the use of PD-1 immunotherapy in solid tumors (22). Our patient presented with both MSI-H and high TMB. Without standard treatment, although EAU guidelines at the time recommended ADT combined with radiotherapy for locally advanced PCa. Based on the results of the patient's postoperative tissue genetic testing, and after MDT, the patient ultimately decided to have adjuvant immunotherapy first and delay the timing of radiotherapy. Our patient received regular follow-up appointments. The PSA levels remained stable at around 0.003 ng/mL (*Figure 2*), and the PSMA-PET/CT examination showed no signs of local recurrence or systemic metastasis. However, the responses of ICIs in MSI-H/dMMR PCa are not universal. In addition, it remains unclear. Despite these results, interest in combining ICIs with other therapies remains high due to the observed encouraging outcomes (23).

Interestingly, in our case, the patient's postoperative pathology revealed a diagnosis of PCa with focal neuroendocrine differentiation. The neuroendocrine subtype of PCa is characterized by the expression of specific neuroendocrine markers, including chromogranin and Syn, which are generally not present in the conventional adenocarcinoma form of the disease.

This shift towards a neuroendocrine phenotype is increasingly recognized as a critical adaptive mechanism that confers resistance to standard treatment modalities, particularly ADT (24,25). The presence of neuroendocrine features in PCa cells is a significant prognostic factor, often associated with a more aggressive disease course and poor treatment outcomes (26). As such, these cells are often less responsive to conventional treatments, highlighting the need for novel therapeutic approaches tailored to combat this aggressive and treatment-resistant form of PCa. In the context of PCa with neuroendocrine features, immunotherapy may be beneficial due to the immunosuppressive tumor microenvironment often found in these tumors (27). Recent advancements have revealed that immunotherapy may be particularly effective in this subset of patients. In this study, Bhinder *et al.* (28) found that PD-L1 was identified as the only checkpoint gene with significantly higher expression in neuroendocrine PCa (NEPC) compared to other PCas. A clinical trial (29) has demonstrated the potential of immunotherapy in one NEPC patient with complete response to the programmed cell death 1 ligand 1 (PD-L1) inhibitor avelumab. In a case, Yoshida *et al.* (30) found that metastatic castration-resistant PCa with neuroendocrine differentiation and MSI-H that responded significantly to pembrolizumab

and produced a long duration of response. The pathology specimen of the biopsy yielded negative results for PSA and AR, while exhibiting positive findings for NEPC-related markers. Additionally, the patient's status is consistent with a post-combined androgen blockade (CAB) state, which strongly supports the diagnosis of treatment-emergent neuroendocrine PCa (T-NEPC). The presence of metastases in the lymph nodes and pancreas, along with the detection of a small cell carcinoma component on the prostate biopsy, is indicative of a poor prognosis in T-NEPC. However, following the confirmation of MSI-high, the patient demonstrated survival beyond 14 months, commencing after the administration of pembrolizumab, without evidence of progression. Neuron-specific enolase (NSE) and progastrin-releasing peptide (proGRP) were present at high levels at the first visit to our department with values of 24.3 ng/mL (<16.3 ng/mL), and 206 pg/mL (≤75 pg/mL), respectively. NSE and proGRP drops to lower levels as disease illnesses are controlled. Therefore, in neuroendocrine tumors, NSE and proGRP can be a reliable tool for monitoring disease changes. In our case, NSE was present at low level and remained stable in routine follow-up testing. This may be related to the fact that this patient had only focal neuroendocrine differentiation. Nevertheless, NEPC has been identified as exhibiting an immunologically "cold" tumor microenvironment (28). In a multi-institutional prospective study, the clinical and genomic features of NEPC emergent after AR-targeting therapy were characterized. The study found that genomic alterations in the DNA repair pathway were nearly mutually exclusive with the NEPC phenotype. This suggests that NEPC may encode a low number of neoantigens, leading to suboptimal responses to immunotherapy (31). These findings indicate that due to the highly immune-depleted tumor microenvironment and relatively lower mutation load in NEPC, extending the clinical success of immunotherapies to patients diagnosed with NEPC could be challenging (28).

Immunotherapy encompasses treatments beyond ICIs therapy. The gene expression pattern that distinguishes adenocarcinoma from NEPC may present opportunities to identify vulnerabilities specific to NEPC that can be targeted through immunotherapy. For instance, based on the pronounced expression of somatostatin receptors (SSTR), Yu *et al.* (32) administered ^{177}Lu-DOTA-TATE to a patient with NEPC. As a result, the initial lesions decreased in size, metastatic lesions disappeared, and there was a significant improvement, approaching complete remission. A study (33) profiling the systemic surfaceome identified FXYD domain-containing ion transport regulator 3 and carcinoembryonic antigen (CEA) cell adhesion molecule 5 (CEACAM5) as cell surface antigens enriched in prostate adenocarcinoma and NEPC, respectively. It was found that engineered chimeric antigen receptor (CAR)-T cells targeting CEACAM5-induced antigen-specific cytotoxicity in NEPC cell lines, suggesting that targeting NEPC-specific surface markers for cellular immunotherapies may pave the way for novel treatments for NEPC. The forkhead box protein A1 (FOXA1) mutation and overexpression may be a significant factor in PCa (34,35). A study identified FOXA1 single nucleotide variants in approximately 25% of the NEPC cases (36). Interestingly, our previous whole genome sequence study of PCa found that the rate of FOXA1 mutation in Asian populations (40%) is significantly higher than that in western cohorts (8%) (37). Furthermore, overexpression of FOXA1 has been demonstrated to suppress the immune response, resulting in therapeutic resistance of ICIs in PCa (38). Although targeting FOXA1 has proven to be a formidable challenge, proteolysis-targeting chimeras (PROTACs), including oligonucleotide-based PROTACs (39), offer a promising avenue for the development of new anticancer agents that target FOXA1 and its mutations.

These findings highlight the importance of accurately identifying neuroendocrine characteristics in PCa. As the field of immunotherapy advances, it is essential to objectively understand the complex interaction between cancer cells and the immune system. Identifying neuroendocrine differentiation in PCa is a crucial step towards more personalized and effective treatment strategies. Admittedly, this study is a single case report, and due to the limited number of cases, further clinical cases and studies will be necessary to explore this area more fully.

Conclusions

In conclusion, for patients with PCa invading the rectum, TPE represents a recommended treatment option, as it has the potential to significantly enhance their quality of life. However, given the elevated risk of surgical complications, the procedure should be conducted by an experienced surgeon.

The results of our study indicate that patients with PCa exhibiting neuroendocrine differentiation and a high TMB or MSI may derive greater benefits from immunotherapy. However, further validation and exploration of these

findings through rigorous fundamental research and clinical trials are necessary.

Furthermore, we advocate for a multidisciplinary approach, enlisting the expertise of urologists, oncologists, pathologists, and radiologists, to collaboratively devise treatment strategies. This comprehensive collaboration aims to optimize the health outcomes and quality of life for patients.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-223/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-223/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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