Comprehensive treatment for metastatic castration-resistant prostate cancer with neuroendocrine differentiation: a case report

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Zeng-Feng Han is responsible for writing original draft, conceptualization and data curation. Bin-Xu Sun is responsible for conceptualization and data curation. Tian-Qi Chen is responsible for review & editing, data analysis. Jin-Ming Liu, Jun-Qi Sun and Ya-Di Shi are responsible for data analysis and figure structure. Rui-Yu Mou and Shan-Qi Guo are responsible for supervision and revision. All authors contributed to the development of the manuscript and the care of the patient presented. All authors have read and agreed to the final manuscript.

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Abbreviations
CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NED, neuroendocrine differentiation; CT, Computed tomography; MRI, magnetic resonance imaging; PSA, Prostate-Specific Antigen; PET-CT, Positron Emission Tomography-Computed Tomography; ALP, Alkaline Phosphatase; NSE, Neuron Specific Enolase; AR, Androgen Receptor; PCA, prostate cancer; CGA, Chromogranin A; Syn, Synaptophysin; NTS, Neurotrophins; BRCA, Breast Cancer; PARP, Poly (ADP-ribose) Polymerase; ADT, Androgen Deprivation Therapy; ONECUT, One-Cut Homeobox; Hnf, hepatocyte nuclear factor.

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Abstract
Retrospective analysis of the progression of a case of metastatic castration-resistant prostate cancer with neuroendocrine differentiation: the patient was a 65 year old man with prostate adenocarcinoma on prostate biopsy, Gleason 4+4 score = 8, 70%, ISUP4 group, localized invasion of nerves. Progressed to metastatic castration-resistant prostate cancer after 8 months of novel endocrine therapy, persistent elevated PSA after endocrine therapy, chemotherapy, and radiation, abdominal metastasis, brain metastasis, gastric metastasis, and staging as neuroendocrine differentiation after second prostate biopsy, which is a highly malignant subtype and has been considered as a mechanism of resistance to targeted therapies. We discuss how to choose a more optimal treatment plan and outline the patient’s diagnostic and therapeutic course. We provide a reflection for the clinical study of metastatic castration-resistant prostate cancer with neuroendocrine type.

Keywords: metastatic castration-resistant prostate cancer; neuroendocrine differentiation; neoplasm drug resistance; distant metastasis; secondary puncture
Introduction

Castration-resistant prostate cancer (CRPC), especially metastatic castration-resistant prostate cancer (mCRPC) is one of the most prevalent malignancies and is the main cause of cancer-related death among men in the world. In addition, it is very difficult for clinical treatment because of the natural or acquired drug resistance of CRPC [1]. mCRPC with neuroendocrine differentiation (NED) is frequently resistant to drug therapy, it is a highly malignant subtype of prostate cancer and it mostly occurs in castration-resistant prostate cancer patients after androgen ablation therapy. The process of cell differentiation to obtain neuroendocrine phenotypes is called with neuroendocrine differentiation (NED). It is thought to be a mechanism of resistance to androgen-deprivation therapy, ultimately leading to a poor prognosis [2].

Case Report

A 65-year-old man sought medical attention at another hospital with urinary frequency and dysuria. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed abnormal signals in the inner and outer glands of the prostate, leading to a suspicion of prostate cancer. His laboratory prostate-specific antigen (PSA) level was 104.18 ng/mL, prompting a prostate biopsy. The biopsy results showed adenocarcinoma of the prostate with a Gleason score of 4 + 4 = 8, 70% involvement, and classified as ISUP4 group with local nerve invasion. Immunohistochemistry results showed p504s (+) and 34be12 (-). Further investigation with positron emission tomography-computed tomography (PET-CT) revealed: 1. Consistent with the diagnosis of prostate cancer, with possible involvement of the bladder; 2. Enlarged lymph nodes in the paragastric aorta and bilateral iliac vessels, indicating possible metastasis; 3. Multiple nodules in both lungs, with a high likelihood of metastasis; 4. Abnormalities in the right carotid artery sheath, left suprachial vessels, and trachea, as well as increased lymph nodes in the hilus of the lungs, suggesting possible metastasis; 5. Multiple bone metastases throughout the body. After a comprehensive evaluation of the patient’s condition, a treatment plan consisting of subcutaneous goserelin and oral apalutamide was administered for a period of 5 months. However, upon review, an increase in PSA levels was observed, prompting a change in the treatment plan. This included the use of oral abiraterone for 2 months, followed by two rounds of docetaxel and carboplatin chemotherapy, as well as two sessions of prostate cancer arterial interventional chemotherapy perfusion and embolization (using lobaplatin 40 mg). Despite these interventions, the patient’s PSA levels continued to slowly rise. Taking into account the patient’s preferences, the treatment plan was modified to include subcutaneous administration of goserelin and oral enzalutamide. The patient was experiencing mental weakness, fatigue, frequent urination, urinary urgency, difficulty urinating, bilateral lumbosacral pain, poor appetite, poor sleep, and weight loss. After receiving symptomatic treatment with traditional Chinese medicine, the patient’s clinical symptoms, including fatigue, poor appetite, poor sleep, and urination disorder, showed improvement compared to their previous state. At the same time, due to the patient's bone metastasis, which was causing discomfort in their hip, sciatric nerve, and lower leg, he underwent 15 sessions of local palliative radiotherapy. Upon reevaluation, laboratory tests showed elevated levels of PSA (196.8 ng/mL), low levels of testosterone (0.0 ng/dL), high levels of alkaline phosphatase (ALP) (852.4 U/L), and neuron specific enolase (NSE) (28 ng/mL). Prostate MRI (Figure 1) and PET-CT (Figure 2) were also performed, revealing the following findings: 1. After comprehensive treatment of prostate cancer, the calcification of prostate gland and the mild radioactive concentration showed by PET time-delay imaging showed the change after treatment. 2. PET imaging showed high-density bone masses throughout the body, indicating bone metastasis, with possible involvement of the spinal canal. 3. The patient also had thickening of the gastric wall near the cardia area, which was confirmed as malignant through PET imaging and endoscopy. The patient was recommended to undergo radium-223 treatment, but this was not possible due to the presence of visceral metastasis. The head CT scan revealed a left deviation of the pituitary gland and an abnormal slope signal, indicating the presence of occupying lesions. Immunohistochemistry (Figure 3) confirmed that the patient now has neuroendocrine tumors. Genetic testing did not show any changes in BRCA1 and BRCA2, ruling out the use of PARP inhibitors. The patient’s PSA level was re-evaluated: 541.34 ng/mL (Figure 4). Given the neuroendocrine nature of the lesions, as well as the latest examination results showing disease progression with multiple bone and abdominal metastases, not excluding brain and gastric metastases, the patient’s prognosis is extremely poor. The patient’s current health status is also poor, with severe anemia and a platelet count of 56 × 10^9/L, unable to undergo chemotherapy. Currently, he is receiving traditional Chinese medicine injections and oral decoctions to maintain his treatment status. We are closely monitoring his progress and following up on his prognosis. Our goal is to not only help the patient survive his tumor, but also improve his overall quality of life through traditional Chinese medicine treatment. Before writing this manuscript, we obtained permission from the patient and his family and ensured their privacy would be protected.

Figure 1 Prostate MRI. (A). White arrow shows the tumor lesion in prostate; (B). Lateral projection shows the tumor lesion in prostate.
Figure 2 PET-CT. (A). After comprehensive treatment of prostate cancer, the calcification of prostate gland and the mild radioactive concentration showed by PET time-delay imaging showed the change after treatment. (B)–(F). PET imaging showed high-density bone masses throughout the body, indicating bone metastasis, with possible involvement of the spinal canal; (G)–(H). The patient also had thickening of the gastric wall near the cardia area, which was considered as malignant through PET imaging.

Figure 3 Immunohistochemistry. Immunohistochemistry shows positive change in NTS. Chromogranin A, CGA, Synaptophysin, Syn, Neuron Specific Enolase, NSE, Neurotrophins, NTS. Bar = 100μm.

Figure 4 PSA changing and treatment flowchart. The flowchart indicate the treatment of this patient and the change of PSA.
Discussion

The introduction of novel therapeutic agents for advanced prostate cancer has led to a wide range of treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC). In the past decade, new treatment options for mCRPC, including abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, radium-223, 177Lu-PSMA-617, and Olaparib, have demonstrated a survival benefit in phase 3 trials [3]. However, cross-resistance may occur between these treatments, and the optimal treatment sequence must be considered [4]. This patient underwent multiple treatment regimens over a period of more than 1 year, but despite this, the PSA levels continued to rise and the disease progressed with an increase in metastatic lesions. Despite the availability of multiple therapies to prolong survival, mCRPC remains an incurable and fatal disease. The majority of prostate cancer-related deaths are caused by distant metastases. The large number and uncommon location of distant metastatic lesions in this patient also contribute to the poor prognosis.

mCRPC with NED typically develops after prolonged androgen deprivation therapy (ADT). This type of castration-resistant prostate cancer (CRPC) has a very poor prognosis [5]. It is crucial for clinicians to be vigilant about the potential transformation of prostate cancer into NED and to recommend a second biopsy of the prostate for patients suspected of having NED as soon as possible. Failure to do so may result in delays in diagnosis and treatment. Unfortunately, the incidence of NED is often underestimated due to the infrequency of second biopsies in clinical practice. Given its aggressive biological behavior, it is imperative that we give mCRPC with NED the attention it deserves.

The application of next-generation sequencing technology to mCRPC has laid the foundation for its development of precision medicine. According to years of basic and clinical research on prostate cancer, based on the heterogeneity and diversity of mCRPC and its multiple formation mechanisms, combined with second-generation sequencing technology, mCRPC is now typed etiologically, and precision medical treatment is adopted for different types of mCRPC to provide individualized treatment of mCRPC in clinics, especially drug-resistant mCRPC, which is more instructive. Therefore, three types of mCRPC formation mechanisms are proposed, namely (1) androgen receptor (AR)-related mechanisms, (2) stem cell formation mechanisms, and (3) neuroendocrine transformation mechanisms. Based on the heterogeneity and diversity of mCRPC and its multiple formation mechanisms, mCRPC were classified into three types, type I: androgen-AR signaling-dependent, with the molecular marker MKBPS; type II: tumor stem cell type, with the molecular marker YAP1; and type III: neuroendocrine type, with the molecular marker NTS. After the second histopathological biopsy of bone metastases, combined with immunohistochemical staining of biological molecular markers, the patient was typed as type III neuroendocrine type, and therefore the recommended treatment plan was platinum-based chemotherapy[6]. However, in the case of this patient, there have been two cycles of chemotherapy that have been stopped due to continued elevation of PSA and side effects of chemotherapy. It may be worth considering completing the remaining cycles of chemotherapy for reassessment and potential feedback.

mCRPC is not only a heterogeneous tumor, it changes over time developing neuroendocrine features or selection of clones resistant to hormonal maneuvers [7]. The majority of CRPC remain dependent on the AR signaling pathway, but approximately 15%-20% of CRPC tumors will lose their dependence on AR signaling at some point in their disease process and transform into neuroendocrine differentiation, and there is growing evidence that mCRPC with NED and CRPC in which no neuroendocrinization is detected have similar genomes but different transcriptomes, suggesting that the vast majority of mCRPC with NED may be the result of selective evolution under the pressure of therapeutic agents. mCRPC with NED is extremely malignant and is unequivocally associated with a poor clinical prognosis, often appearing late in the course of prostate cancer as a mechanism of treatment resistance, and its poor prognosis is primarily due to late diagnosis and lack of effective therapeutic agents.

mCRPC is caused by a variety of genomic and transcriptomic alterations. These changes contribute to the multifocal nature of prostate cancer [8]. Unfortunately, the majority of prostate cancer-related deaths are a result of distant metastasis [9]. In this case, the patient experienced rapid progression of the disease with multiple distant metastases, including rare occurrences of brain and gastric metastases, as well as neuroendocrinologic transformation.

This combination of factors leads to a very poor prognosis.

Choi et al. provided a perspective on the transcription factor ONECUT2, which mediates AR-independent cell growth and neuroendocrine differentiation in CRPC [10]. This factor plays a crucial role in the transition from adenocarcinoma to NED. The perspective highlighted the target genes of ONECUT1 and ONECUT2, including AR regulatory genes, FOXA1/2, and hepatocyte nuclear factor (Hnf). Specifically, ONECUT2 regulates the signaling of hypoxia-inducing factors, promoting prostate cancer differentiation and making it a potential therapeutic target in metastatic CRPC (mCRPC). In clinical studies, the incidence of RB1 and TP5 mutations or deletions was significantly higher in mCRPC with NED patients compared to those with prostate cancer (PCa). This suggests that the deletion of these oncogenes may be a contributing factor to the development of NED [11].

At the same time, a traditional Chinese medicine compound with astragalus as the main medicine was prescribed, including Astragulus, turmeric, radix curcumae. Astragulus has been used for centuries in traditional Chinese medicine in combination with other herbs. It is commonly combined with other herbs to improve fatigue, strengthen and regulate the immune system. In this case, this Chinese medicine had improved this patients’ quality of life, which is worthy of further research and clinical adoption.

Conclusion

mCRPC with NED is a very aggressive subtype of CRPC that appears in the terminal stage of CRPC. Currently, the effective therapies targeting the molecular features of NEPC have not been established. Although platinum-based chemotherapeutic regimens have shown better responses, the response time is short and the overall prognosis is poor. The incidence of NED is often underestimated due to the infrequency of second biopsies in clinical practice. Given its aggressive biological behavior, it is imperative that we give mCRPC with NED the attention it deserves. In the future, as we continue to understand the genomic, epigenetic and biological features of mCRPC with NED, the diagnosis and treatment of NED will be gradually improved. Inhibition and reversal of neuroendocrine differentiation from molecular mechanisms will become an important new therapeutic strategy.

References


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