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综合治疗神经内分泌寡转移前列腺癌一例报道

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摘　要　回顾性分析一例寡转移前列腺腺癌伴有神经内分泌分化病例：患者为63岁的男性，前列腺穿刺活检为Gleason评分5+4=9分，伴神经内分泌分化的寡转移性前列腺癌，予以雄激素剥夺疗法联合根治性前列腺切除术，术后予以体外放射治疗，随访血清PSA降至非常低的水平。

关键词　前列腺癌；神经内分泌前列腺癌；神经内分泌分化；寡转移；骨转移；雄激素剥夺疗法；前列腺癌根治术

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Case report: systemic therapy combined with prostate-directed therapy of oligometastases of prostatic adenocarcinoma with neuroendocrine features

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Abstract　We report a case of a 63-year-old man who presented with oligometastases of $pT_2N_0M_{1b}$, Gleason score 5+4 prostatic adenocarcinoma and neuroendocrine differentiation. Patient underwent systemic therapy (Androgen deprivation therapy, ADT) combined with radical prostatectomy, with subsequent reduction of serum PSA to very low levels. The patient is currently on radiotherapy. This is a rare case of primary prostatic cancer (PCa) with oligometastatases.

Key words　Prostate cancer; Neuroendocrine prostate cancer; Neuroendocrine differentiation; Oligometastatases; Osseous metastasis; Androgen deprivation therapy; Radical prostatectomy

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Prostate cancer is a very common form of cancer worldwide, with millions of new cases every year, accounting for 1/4 of all cancer cases in men. It is the second most common cause of cancer-related mortality among men[1-2]. The overwhelming majority of prostate cancers (PCa) are adenocarcinomas, most of which are low-risk cases with excellent long-term survival rates. In contrast, neuroendocrine differentiated (NED) prostate adenocarcinoma is rare entity. Less than 400 cases have been reported worldwide in the past 20 years[3]. Emanuele Zaffut identified 309 individuals with NED prostate cancer diagnosed from 510, 913 cases of prostate cancer between 2004 and 2013 within the Surveillance, Epidemiology, and End Results (SEER) database. Metastatic disease was identified in 198 (64.1%) cases.The most common histologic subtype (n=186; 60.2%) was small-cell carcinoma (SCC). The age-adjusted incidence of NED prostate cancer significantly increased over the study span: from 0.13/1, 000, 000 person-years in 2004 to 0.30/1, 000, 000 person-years in 2013; P=0.001)[4].

1　Case Presentation

In 2018, a 63-year old male came to our observation center with 1 year history of dysuria and pain on right hip.Digital rectal examination indicated fairly enlarged prostate.The PSA level (2018-09) was 116.98ng/ml. Prostate MRI (2018-09) showed the sized of enlarged prostate was about 6.6cm × 6.8cm × 9.6cm with slightly longer T1 signal shadow, see flaky liquefaction zone.Enhanced scan on solid region showed unevenly enhanced and the partial capsule was not complete.Considering the probability of prostate cancer, no invasion to rectum and no evidence of pelvic lymphadenopathy was found (Figure 1). Body bone imaging (2018-09) results: irregular form of aggregation of radioactivity on right iliac bone: bone neoplastic lesions, tumor bone metastasis (Figure 2). Prostate puncture biopsy: prostatic adenocarcinoma with neuroendocrine differentiation and Gleason's score of 5+4=9. Immunohistochemically, the tumor cells were CK (+); PSA (+); P504S (+); CD (+); Syn (-); CgA (-); P63 (-); GATA3 (-); Hi-ck (-); AR (+); ki-67 (30%) (Figure 3). Clinical TNM classification was $T_{3a}N_0M_{1b}$.

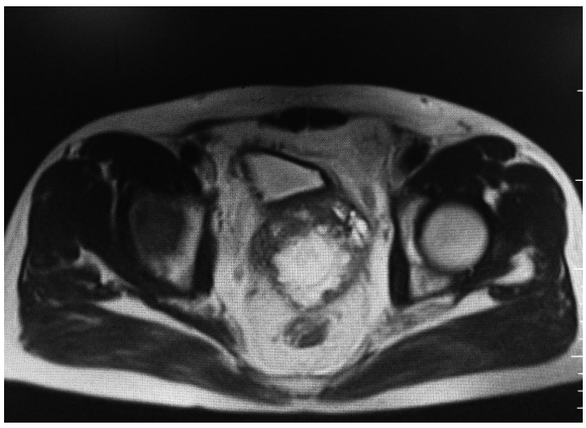

Figure 1　Prostate MRI

2　Treatment

The recommendation of ADT with Bicalutamide 50mg per day Triptorelin 3.75mg per month and Zoledronic acid 4mg per month was given, which the patient could afford.4 weeks later, Serum PSA sharply declined (10.196 ng/ml), dysuria and pain relieved. After 6 months treatment, serum PSA declined to 0.168ng/ml.Prostate MRI (2019-03) showed the size of prostate gland was reduced and no swelled lymph nodes were seen in the pelvic cavity.

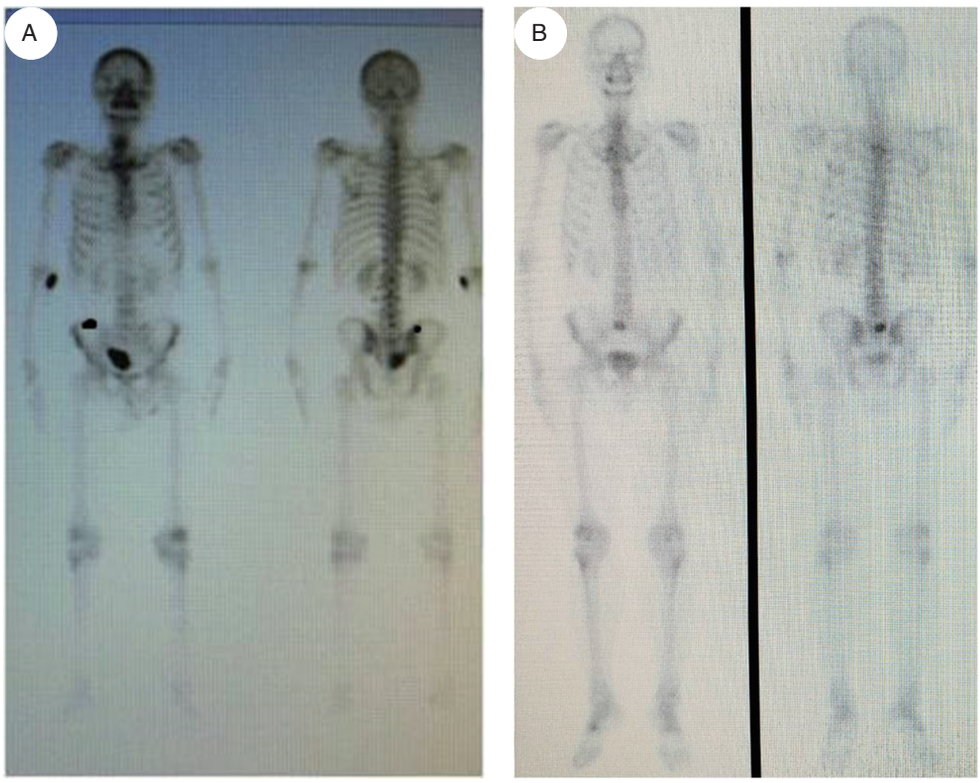

Figure 2　Whole body bone imaging

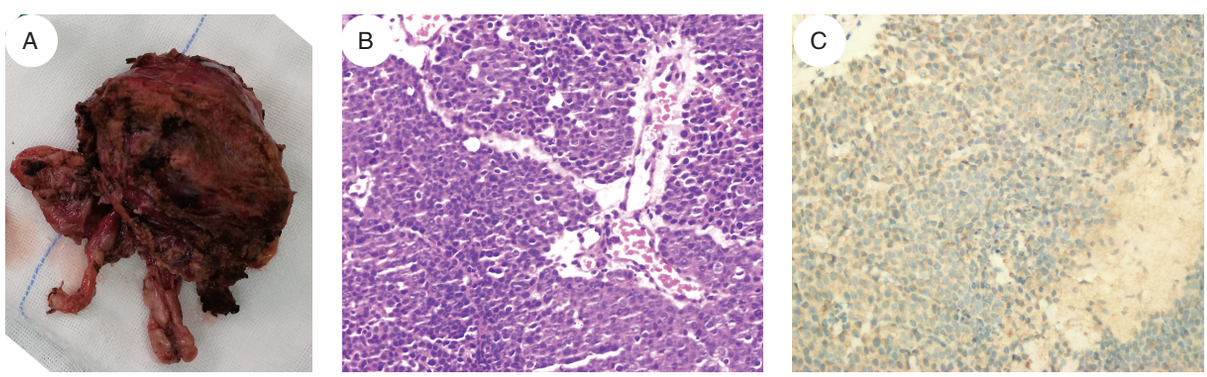

Figure 3　Prostate puncture biopsy

A. Prostate surgical specimen; B. Neuroendocrine differentiated (NED) prostate cancer with HE staining (200 × magnification); C. Positive immunostaining for CD56 (200 × magnification)

Whole body bone imaging (2019–03) indicated no new bone metastases were found.

The patient underwent robot-assisted laparoscopic radical prostatectomy (RALRP) with pelvic lymph node dissection (PLND) in April 2019 (Figure 4). Postoperative pathological diagnosis: prostatic adenocarcinoma with neuroendocrine differentiation and Gleason's score of 5+4=9.Margin (–), seminal vesicle (–), regional lymph node (0/6): right closed-cell lymph node (–), left-handed obturator lymph node (–), left external iliac lymph node (–), right external iliac lymph node (–), left internal iliac

lymph node (–), right internal iliac lymph node (–), postoperative pathological stage: $pT_2N_0M_{1b}$. Urinary continence was well recovered one month after the surgery, PSA: 0.018ng/ml. (Figure 5).3 months later, external-beam radiation therapy (EBRT 30GY/5F) was given for bone metastasis based on ADT and Zoledronic acid.Pain was completely relieved, no side effects related to radiotherapy appeared.

3 Discussion

The pathological classification of neuroendocrine differentiated (NED) prostate cancer in the latest 2016 edition of *The WHO Classification of Tumours of the Urinary System and Male Genital Organs* is as follows: (1) prostate

Figure 4　T-type dissection for bladder neck (BN)

A. Once the optimal plane of dissection is visually identified, the first step starts with gently dissecting the midline BN fat down to the bladder muscle by the monopolar scissors with tip electrocautery for good surgical fields

B. The second step then is performed by a small longitudinal dissection of the anterior BN muscle fibers using the monopolar tip cauterization until the urethral catheter is identified. Stanch bleeding carefully with the bipolar instrument when necessary. The Foley catheter balloon is then deflated, and an inspection of the posterior BN is made in order to identify the interureteral crista. Remove the catheter, then transect bladder neck until it reaches the surface of the seminal vesicle.

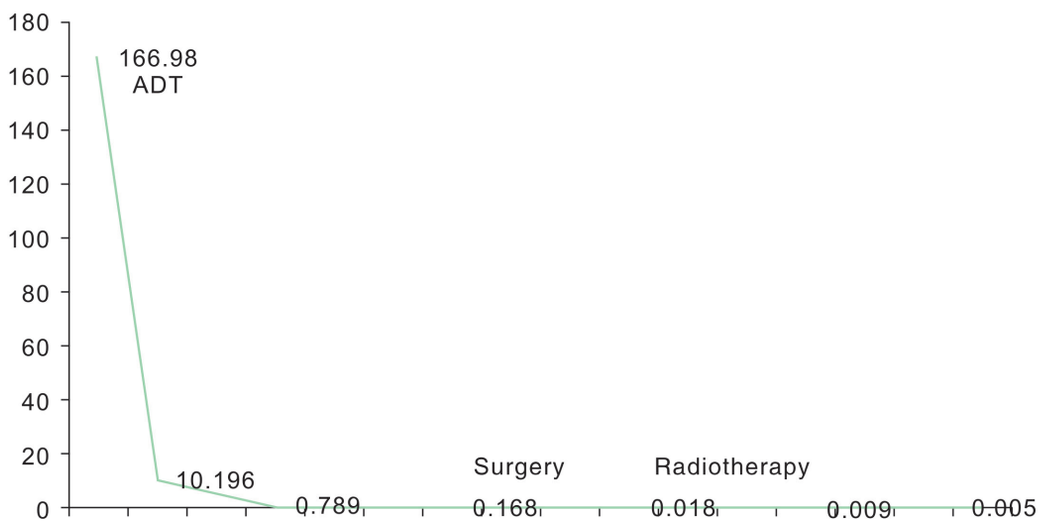

Figure 5　PSA level one month after the surgery

Note: PSA was 116.98 ng/ml before treatment. After 4 weeks ADT treatment, serum PSA sharply declined (10.196 ng/ml), dysuria and pain relieved. After RP and EBRT treatment, tPSA kept declining. tPSA was 0.005ng/ml in December 2019.

adenocarcinoma with NED; (2) well-differentiated neuroendocrine tumor; (3) small cell neuroendocrine carcinoma; (4) large cell neuroendocrine carcinoma[5]. NED prostate cancer mainly expresses NSE, Cg A, Syn, CD56, TTF-1 and other markers. The positive rates of the above markers in the literature are 85%, 80%, 85%, 92%, and 83%, respectively. NED prostate cancer can be diagnosed by pathological features and any expression of Cg A, Syn and CD56[6-7].

According to the American Society of Clinical Oncology, National Comprehensive Cancer Network for Prostate cancer, and the Cancer Care Ontario clinical practice guideline, the main option for patients with metastatic PCa is systemic ADT, with bone antiresorptive therapy with denosumab or zoledronic acid if bone metastases present, which is however supported by strong evidence[8-9]. At least 90% of prostate cancers are initially diagnosed as acinar adenocarcinomas[10], which are almost always androgen-dependent[3]. After 6 months treatment, serum PSA sharply declined, dysuria and pain relieved, the size of the prostate was reduced, and no evidence of new bone metastases was found.

During the treatment, we considered that what we can do more.Hellman proposed the concept of "Oligometastases".A state between the tumor confined to the primary lesion and extensive distant metastasis. The number of metastases is limited and the organ of transfer is specific: metastatic lesions confined to lymph nodes or bones (non-visceral metastases), and fewer than 5 metastatic lesions. At this stage, local directed treatment may be better effects[11-12].

Previous idea that locally advanced prostate cancer (T3) could not be cured by surgery, however, there are studies show that patients with advanced prostate cancer received radical prostatectomy (RP) may have survival benefit compared with patients with ADT only[13]. Comen et al[14]. believed that removing primary part of metastatic tumor reduce growth factor and immunosuppressive cytokines which could be the reasons for the benefits of prostate cancer patients. An article published in 2017 pointed out that the treatment of primary prostate lesions in metastatic prostate cancer can improve patient survival. In metastatic prostate cancer (mPCa), local therapy (LT) results in lower mortality relative to no local therapy (NLT).Within LT, lower mortality is recorded after radical prostatectomy (RP) than radiation therapy (RT), which means that individuals with prostate cancer that spreads outside of the prostate might still benefit from prostate-directed treatments, such as radiation or surgery, in addition to receiving androgen deprivation therapy[15].

So, after 6 months treatment, when PSA declined and size of the prostate was reduced, the patient underwent robot-assisted laparoscopic radical prostatectomy (RP) with pelvic lymph node dissection (PLND), with continuation of the ADT and Zoledronic acid treatment, and EBRT for bone metastases.

However, after an initial period of disease control through targeting the androgen axis, the disease almost inevitably progresses to castration-resistant prostate cancer (CRPC)[16].A neuroendocrine pattern is frequently observed in the cellular composition of CRPC, which was not present in the initial diagnosis[17].The emergence of this

Neuroendocrine (NE) pattern in CRPC has been attributed to the effect of androgen deprivation therapy and two main mechanisms have been hypothesized.The first hypothesis suggests that, under prolonged hormonal manipulation, the resistant neuroendocrine, like tumor cell populations are selected from an initially heterogeneous tumor. The second hypothesis suggests that prolonged androgen deprivation may activate a process referred to as neuroendocrine transdifferentiation, which enables prostatic adenocarcinoma cells to acquire neuroendocrine characteristics[3, 16, 18]. Neuroendocrine tumorigenesis does not result from the proliferation of prostate NE cells. Rather, this carcinoma arises from the differentiation of prostate adenocarcinoma into "NE-like" cells[3]. These cells do not express androgen receptors or PSA, elucidating why NE PCa is not responsive to aggressive Androgen Deprivation Therapy (ADT) and is not associated with an elevated PSA. In addition, several series have suggested that ADT, the standard treatment in men with advanced PCa, may induce NED[19]. Fortunately, ADT still works, which means that it is still Metastatic Hormone-Sensitive Prostate Cancer (mHSPC).Nicolas Mottet et al[20]. pointed out that early treatment with abiraterone plus ADT could prolong overall survival compared to ADT alone for patients with mHSPC, but no significant survival benefit for patients with Hormone-Sensitive Prostate Cancer (HSPC), which should help set the minimum the new Standard of Care (SOC) based on the best available evidence and for the benefit of the majority of patients. For men presenting with mHSPC and starting ADT, Abiraterone+Prednisone must be regarded as another standard therapy abreast docetaxel. Regrettably the patient did not receive abiraterone plus ADT because of Health Insurance Policy.

Combinatorial immunotherapy may be a new way for CRPC. A clinical pathway hypothesis of Immunologic Checkpoint Block (ICB) combined with Myeloid Derived Suppressor Cells (MD-SCs) targeted therapy for mCRPC is a new idea. Immune check-points are paired receptor-ligand molecules with interactions that suppress immune responses, the first to be found and identified as an immune checkpoint receptor, the cytotoxic T lymphocyte antigen 4 (CTLA-4), ICB produces a long lasting therapeutic response in important subsets of patients across multiple cancer types. However, mCRPC showed absolute resistance to ICB, but targeted therapy with agents that inhibit MDSC infiltration frequency and immunosuppressive activity can synergize with ICB to invigorate T cell immunity in the prostate tumor microenvironment thus impair CRPC progression, which gave us something new: inhibition of the activation of other inhibitory pathways after one immunologic checkpoint blocked may neutralize the anti-tumor effects, so the combination of two or more immune checkpoint inhibitors was expected to achieve better tumor inhibition[21].

4 Conclusion

We presented a case of oligometastatases of prostatic adenocarcinoma with NED.Efforts toward an enhanced understanding of the malignancy along with advancements in discoveries of the specific biochemical uniqueness are currently progressing. This patient benefits from comprehensive therapy (RALRP+ADT+EBRT). However, longer follow up

shall be made to confirm the long-term effect.

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