Neuroendocrine prostate cancer treated with multimodal examination and therapy: A case report

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ABSTRACT

Neuroendocrine prostate cancer (NEPC) is rare, with short overall survival, and no established standard therapy. Therefore, the management of NEPC is often challenging. We report a case of a 63-year-old male diagnosed with NEPC and treated with multimodal examinations and therapies. Chemotherapy of cisplatin and etoposide for 6 months had a certain effect. However, his cancer progressed, and he took genetic screening exams. It revealed that his tumor mutational burden was high, and pembrolizumab was started. In this report, we suggested several new treatments.

1. Introduction

Neuroendocrine prostate cancer (NEPC) is rare, accounting for only about 0.2–1% of whole prostate cancers. On the other hand, it has been reported that 17–40% of the castration-resistant prostatic cancers under anti-androgen therapies changed into NEPC. The longer anti-androgen therapy continues, the more likely NEPC occurs. As the level of prostate specific antigen (PSA) in NEPC is often in the normal range, NEPC is overlooked until more severe clinical symptoms occur. The median overall survival is short in NEPC and a standard therapy has not been established yet. Thus, the management of NEPC is challenging, and several examinations and therapies are needed frequently. Herein, we report a case of NEPC treated with multimodal examinations and therapies.

2. Case presentation

A 63-year-old male was presented to our hospital for diagnosis of prostate cancer. After the transrectal ultrasound-guided prostate biopsy, computed tomography (CT), and bone scintigraphy, prostate cancer with invaded seminal vesicles and multiple bone metastases was diagnosed. Initially, his PSA was 234.8 ng/mL, had poorly differentiated adenocarcinoma, and a Gleason score of 5 + 4 was detected. We started combined androgen blockade with bicalutamide and degarelix. After a year, the PSA level declined to 0.032, and bone scintigraphy showed no bone metastasis.

After two months, magnetic resonance imaging revealed metastasis of pubis, and the levels of PSA gradually increased, so antiandrogen drug was switched from bicalutamide to abiraterone acetate. Although the levels of PSA decreased to 0.003, fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT and somatostatin receptor scintigraphy revealed multiple metastases of lymph nodes, bones, and lungs (Fig. 1). Considering the existence of small cell carcinoma of the prostate, tumor markers associated with small cell carcinoma were examined and it was determined that their levels were high (carcinoembryonic antigen [CEA] 177 ng/ml, nerve specific enolase [NSE] 76 ng/ml, and gastrin discharge peptide precursor [ProGRP] 36,800 pg/ml) while PSA was still at a lower level (Fig. 2). We performed a prostate biopsy again and immunohistochemical staining revealed positive expression of chromogranin A and synaptophysin, so a diagnosis of NEPC was made (Fig. 3A and B). Because direct invasion into the rectum and bladder were detected through CT, colostomy and cystostomy were constructed. We started chemotherapy comprising 80 mg/㎡ of cisplatin and 100 mg/㎡ of etoposide (EP therapy). After six cycles, tumor shrinkage of the prostate, lymph nodes, bones, lungs and the liver was seen through FDG-PET/CT (Fig. 2B).
However, multiple brain metastases appeared, and we decided to perform whole-brain radiation therapy. Although we did four more cycles of EP therapy, the disease progressed. Following this, we checked genetic screening exams by FoundationONE CDx and found that the tumor mutational burden (TMB) was high. Although we performed pembrolizumab one time, he unfortunately died due to tumor progression.

3. Discussion

Although the actual cellular derivation of NEPC is still uncertain, there are several similarities between NEPC and other neuroendocrine tumors such as the lung. For example, both include bustling mitotic figures, sheets of uniform cells with high nuclear-to-cytoplasmic ratio and diffuse infiltration, and chemotherapy with cisplatin and etoposide has been chosen for primary treatment according to the standard therapy for small cell lung cancer. However, the response is just in some cases and the duration is mostly short. In this patient, we concerned partial response after several cycles of chemotherapy; however, the
disease progressed. Thus, treatment option for NEPC except for this chemotherapy is required.

For patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line therapy, it is reported that treatment with 177Lu-Dotatae called peptide receptor radionuclide therapy (PRRT) showed remarkably longer progression-free survival and a significantly higher rate than standard therapy. Some neuroendocrine cells have somatostatin receptors. A somatostatin analogue with 177Lu attaches to the somatostatin receptors on the neuroendocrine cells, and its radioactive substance damages the inside of the cells. Octreotide scans can easily check whether the neuroendocrine tumors have somatostatin receptors. Because PRRT was not covered by insurance in Japan at that time, we could not use PRRT. As some cases of NEPC with positive results of somatostatin receptor scintigraphy might benefit from PRRT, we speculated that PRRT might be an option for NEPC treatment.

Our patient had high TMB as a result of genetic screening exams, and we used pembrolizumab at the last stage. TMB is defined as the number of somatic, coding, and indel mutations per mega base of interrogated genetic sequence. In the KEYNOTE-158 study, 30% of patients with TMB-high had a robust response to pembrolizumab monotherapy. Recently, genetic screening exams for prostate cancer has been rapidly spreading and increasing for precision medicine. Because NEPC is aggressive and there are no standard effective therapies, we thought that genetic screening exams should be conducted at an earlier stage with a search for the appropriate drugs.

4. Conclusion

NEPC is an aggressive variant of prostate cancer, and there is no standard effective therapy. Several new treatments and genetic screening exams have the potential to improve the management.

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Declaration of competing interest

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