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Case report

Direct evidence on the efficacy of GnRH agonist in recurrent steroid cell tumor-not otherwise specified

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ABSTRACT

Background: Steroid cell tumor (SCT) not otherwise specified (NOS) is rare and recurrence and metastasis rarely occurs; therefore, reports regarding its treatment are limited. We report a case of recurrent SCT-NOS treated with gonadotropin releasing hormone agonist (GnRHa) and successful.

Case: A 50-year-old woman underwent a staging laparotomy and diagnosed as SCT-NOS. Multiple liver tumors and intraperitoneal dissemination were detected 5 years 10 months after the initial surgery. As the immunohistochemical analysis showed positive staining for GnRH receptor, GnRHa was attempted. After the first cycle the serum testosterone level was normalized and after six cycles CT scan confirmed reduction of the tumor size.

Conclusion: Some ovarian SCT-NOS have GnRH receptors; thus, GnRHa may have a reducing effect for these tumors without major adverse event.

1. Introduction

Steroid cell tumor (SCT) accounts for 0.1% of ovarian neoplasms and classified as a type of sex cord-stromal tumor. Approximately 80% of SCT fall into the "not otherwise specified (NOS)" category (Hayes and Scully, 1987), and approximately half of patients present with androgenic symptoms. Pathologically, the cells are found to be most commonly arranged in a diffuse pattern, but can grow in nests or cords. Tumor cells are polygonal and have an abundant cytoplasm that ranges from eosinophilic (lipid-poor) to pale and vacuolated (lipid-rich). The nuclei are typically round with a prominent central nucleolus, usually accompanied by increased mitotic activity. SCT-NOS exhibits malignant behavior in approximately one-third of cases (Kurman et al., 2014). Hayes et al. reported that malignant behaviors were noted in 18 out of 63 cases, and its predicting features included tumor size of > 7 cm, > 2 mitoses/10 high power field, necrosis, hemorrhage, and significant nuclear atypia (Hayes and Scully, 1987). Since an early stage SCT-NOS is primarily treated with surgery, no consistent effective treatment was available for its metastatic or recurrent tumors. Recurrence and metastasis rarely occurs; therefore, reports regarding its treatment are limited.

Here, we report a case of recurrent SCT-NOS unsuccessfully treated with chemotherapy; therefore, gonadotropin releasing hormone agonist (GnRHa) treatment was initiated and successful.

2. Case

A 50-year-old gravida 3, para 3 woman presented with hirsutism. On physical examination, a solid tumor in the left ovary was found in the pelvic cavity, and thus, she was referred to our hospital. Magnetic resonance imaging (MRI) T2-weighted images showed a mixture of low- and high-intensity left ovarian tumor measuring 90 mm × 65 mm. Her serum testosterone level was 882 ng/dl, leading to a diagnosis of testosterone producing ovarian tumor. The patient underwent a staging laparotomy, including total abdominal hysterectomy, bilateral salpingo-oophoprectomy, pelvic lymph node sampling, and omental biopsy. The tumor comprised diffuse sheets of steroid cells with lipid-rich cytoplasm, polygonal with central round nuclei, and abundant eosinophilic cytoplasm in the pathological examination. Immunohistochemical staining showed a diffuse strong cytoplasmic staining for inhibin (Fig. 1). Nucleic atypia was not strong, and necrosis or hemorrhage was not observed. The ovarian tumor was diagnosed as SCT-NOS (pT1c2 N0 M0). Because the tumor was completely resected and the effective adjuvant chemotherapy was not evident, the patients

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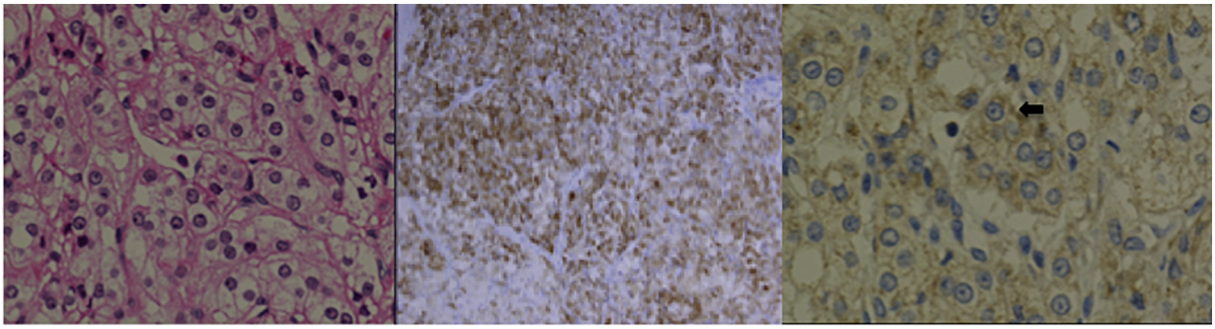

Fig. 1. Hematoxylin and eosin staining (×400) (left) and immunohistochemical staining of inhibin (middle) and GnRH receptor (right) of the surgical specimen. Positive staining for GnRH receptor in the cytoplasm (arrow) and diffuse strong cytoplasmic staining for inhibin are observed.

was discharged without postoperative adjuvant treatment.

Multiple liver tumors and intraperitoneal dissemination were detected on computed tomography (CT) scan performed 5 years and 10 months after the initial surgery. Her serum testosterone level was elevated to 497 ng/dl, and the patient complained of progressive hirsutism and virilization. The chemotherapeutic regimen with bleomycin (20 mg/m^2 on day 2, weekly), etoposide (100 mg/m^2 on days 1–5, triweekly), and cisplatin (20 mg/m^2 on days 1–5, triweekly) (BEP) was administered for the recurrent SCT-NOS. The Response Evaluation Criteria in Solid Tumors (RECIST) demonstrated a stable disease (SD) after three cycles of BEP. The chemotherapeutic agent was changed to paclitaxel (175 mg/m^2 triweekly), and carboplatin (AUC5 triweekly) (TC). After 8 cycles of TC, the chemotherapy was discontinued due to prolonged neutropenia and peripheral neuropathy. The serum testosterone level elevated to 448 ng/ml 1 month after the discontinuation. CT scan showed SD. As the immunohistochemical analysis of her primary tumor showed positive staining for GnRH receptor in the cytoplasm (Fig. 1), a GnRHa was attempted with reference to the previous case reports (Brewer and Shevlin, 1998; Wang et al., 1998; Lee et al., 1999) due to the lack of other effective alternatives after obtaining a written informed consent.

After the first cycle of GnRHa (leuprorelin 1.88 mg administered intramuscularly every month), the serum testosterone level was immediately normalized (Fig. 2), and after three cycles of GnRHa, CT scan confirmed a 28.6% reduction of the tumor size (Fig. 3). Adverse events were not observed and her hirsutism and virilization were improved. Tumor sizes (RECIST 34.3%) was further reduced after three additional cycles of GnRHa; therefore, it was discontinued after the 6 cycles of administration. However, testosterone was increased to 134.8 ng/ml 2 months after GnRHa discontinuation and CT scan showed increased tumor size. Then, GnRHa was readministered, which resulted in immediate normalization of the serum testosterone level and shrinkage of the recurrent tumors. Thus GnRHa was continued to administer thereafter (now, 22 months after first GnRHa and no symptom).

3. Discussion

We reported a case of recurrent SCT-NOS treated with GnRHa that demonstrated promising results. Recurrence and metastasis rarely occurs in SCT-NOS. Surgical cytoreduction should be performed in widely metastatic malignant disease, followed by adjuvant chemotherapy. Although a definitive chemotherapeutic regimen is not yet defined, BEP is favorably and frequently used. Kim et al. reported that intraperitoneal dissemination and liver metastases were completely

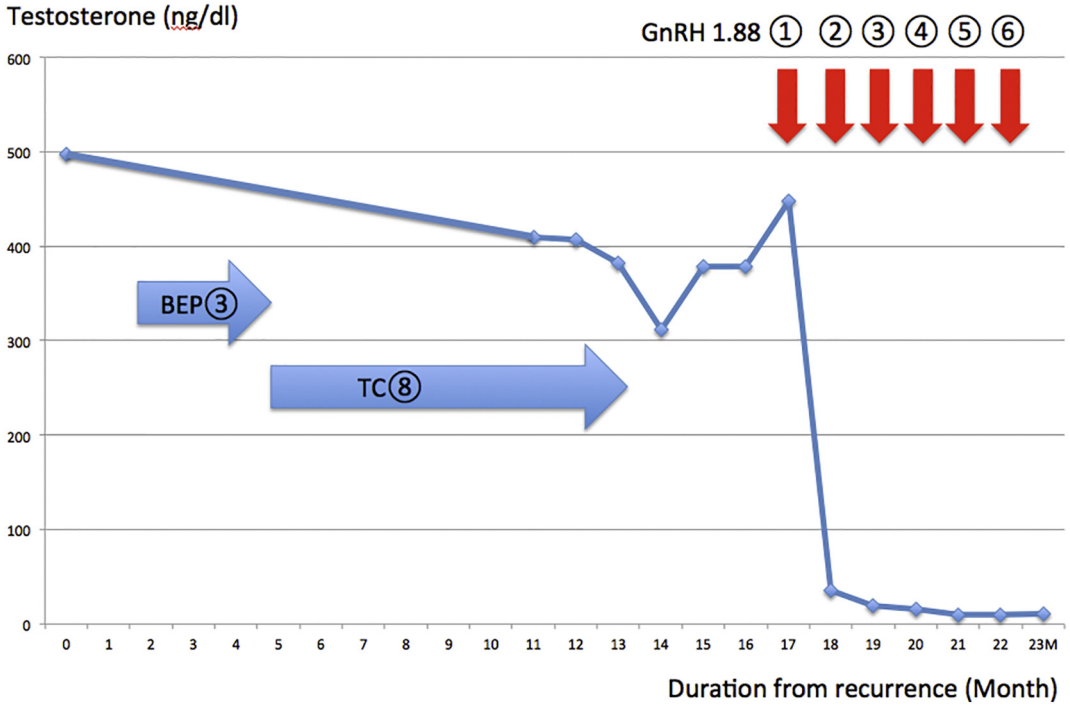

Fig. 2. Transition of testosterone during treatment course.

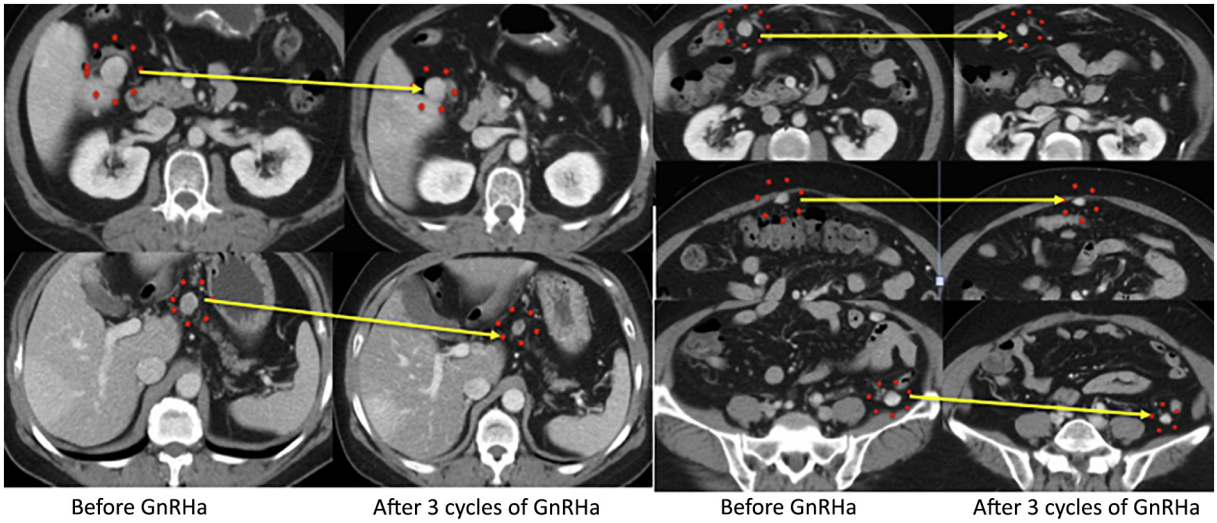

Fig. 3. Size reduction of measurable tumors by computed tomography after three cycles of GnRHa (RECIST 28.6%).

removed with debulking surgery, radiofrequency ablation to the liver metastasis and adjuvant BEP (follow up, 43 months) in a recurrent case occurring 5 years after the initial surgery (Kim et al., 2014). However, the effectiveness of chemotherapeutic regimes has not been established due to the rarity of SCT-NOS.

GnRHa has been used to treat recurrent malignant diseases due to its suppressive effect on ovarian steroidogenesis. There are several reports that GnRHa is effectiveness for SCT-NOS. Brewer et al. reported that GnRHa administration showed a remarkable response in recurrent SCT-NOS with lymphoadenopathy (Brewer and Shevlin, 1998). Wang et al. demonstrated the effectiveness of GnRHa in a patient with SCT-NOS, whose elevated serum testosterone level after the complete tumor removal returned to normal after one cycle of GnRHa and was maintained for 32 months (Wang et al., 1998). Lee et al. reported that elevated serum testosterone levels returned to normal after one cycle of GnRHa in a 70-year-old patient with presumed testosterone-secreting ovarian tumor (Lee et al., 1999). In our case, multiple measurable recurrent tumors were found and the administration of GnRHa successfully shrunk the tumor. The primary tumor was confirmed to be positive for GnRH receptor in immunohistochemistry. To our knowledge, this is the first report that demonstrates the definite response and direct evidence of GnRHa's effectiveness in managing measurable lesions in recurrent SCT-NOS.

Although the mechanism of tumor reduction remains unclear, various ovarian testosterone-secreting tumors are not autonomous but apparently depend on continuous gonadotropin stimulation (Pascale et al., 1994). Androgen's action on GnRH is reported to be similar to that of estrogen, which possibly lowers the testosterone level and may lead to effective tumor shrinkage. GnRHa therapy can suppress the receptor activity and may be suggested as treatment for progressive ovarian tumors. Several reports demonstrated the antitumor effect of GnRHa, but its precise mechanism remains unknown. Several studies in the past few years have shown that many gynecologic cancers express the GnRH receptor (Aguilar-Rojas et al., 2016); hence, GnRHa may directly inhibit these gynecologic cancers.

In conclusion, some ovarian SCT-NOS have GnRH receptors; thus, GnRHa may have a reducing effect for these tumors without major adverse event.

Author contribution

The work presented here was carried out in collaboration among all authors.

TN, and YA designed methods, analyzed the data, interpreted the results, and wrote the manuscript. AM is a pathologist and made pathological diagnosis of the case. TN, TN, HN, and YA are chief doctors and treated the patient.

Declaration of Competing Interest

We have no conflict of interest to declare.

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