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SCIENCE DIRECT

Gynecologic Oncology 96 (2005) 865–869

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Case Report

Hormonal treatment of a recurrent granulosa cell tumor of the ovary: case report and review of the literature

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Received 28 August 2004
Available online 13 December 2004

Abstract

Background. Granulosa cell tumors of the ovary are rare, primarily treated surgically. In advanced or recurrent disease, data are inconclusive regarding the benefit of either primary or adjuvant chemotherapy. Hormonal therapy has been suggested as an alternative treatment.

Case. Our patient had three recurrences of estrogen receptor negative and progesterone receptor positive GCT, the first two treated by surgery with or without adjuvant chemotherapy. For the third recurrence, the patient received alternating biweekly cycles of megestrol and tamoxifen. Computed tomography showed stable disease at 6 months, partial response at 18 months, and complete response at 22 months. The patient continues on hormonal therapy and has been disease-free for 5 years.

Conclusion. This study and others suggest that hormonal therapy may provide another option for treating these relatively rare tumors.

Keywords: Granulosa cell tumors; Estrogen/progesterone receptors; Hormone therapy; Medroxyprogesterone acetate

Introduction

Granulosa cell tumor (GCT) of the ovary is a relatively rare cancer, accounting for only 3–5% of all ovarian malignancies. Histologically, these neoplasms belong to the category of sex-cord stromal tumors, comprising 70% of tumors in this group [1]. Unique features of these tumors are their capacity to secrete estrogens (less commonly androgens and progestins) and their tendency to recur many years after the initial excision, sometimes 10–20 years later. Because of tumor-derived estradiol, these tumors may present early with abnormal vaginal bleeding. The majority of these patients (78–91%) have stage I disease at diagnosis and surgery alone achieves survival rates of 84–95% for 10 years [1]. In contrast, advanced-stage disease has a considerably worse prognosis for 10-year survival: 50–65% for stage II and 17–33% for stages III and IV [1]. Surgery is the primary treatment for advanced or recurrent disease, and data are limited as to whether adjuvant chemotherapy confers any survival advantage. Cisplatin-based regimens have shown the best activity in advanced or recurrent disease but no standard treatment has evolved. Consequently, some authors have advocated continued research for new treatment options [2]. A growing number of case reports have described hormonal treatment of recurrent GCTs.

We report a case of a GCT with an impressive response to hormonal therapy, and review the literature on hormonal treatments. In addition, we report the progesterone and estrogen receptor status in our series of GCTs and discuss implications of receptor status in these tumors.

Case report

A 56-year-old multiparous woman presented 20 years status post-hysterectomy with a 13-cm ovarian mass. Laparotomy at another institution revealed at least stage II

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doi:10.1016/j.ygyno.2004.10.042

disease based upon gross tumor implants present in the pelvis; a complete staging operation was not performed. After bilateral salpingo-oophorectomy (BSO), omentectomy, and tumor debulking of undocumented extent, the patient received four cycles of doxorubicin and cyclophosphamide. Retrospective immunohistochemical analysis on tissue blocks from this original tumor showed it to be estrogen receptor (ER) negative and progesterone receptor (PR) positive.

Eight months after completing her chemotherapy, she presented with a 20-cm septated pelvic mass without evidence of ascites or adenopathy. A second laparotomy confirmed recurrent GCT and achieved complete cytoreduction The patient again received adjuvant therapy but, due to toxicity, she completed only two cycles of cisplatin, bleomycin, and etoposide. Again, retrospective immunostaining demonstrated negative ER and positive PR.

The patient suffered a second recurrence 2 years later, 3 years after her original diagnosis. A third operation successfully removed a 15-cm lobulated pelvic mass, leaving no gross residual disease. The patient declined any further adjuvant chemotherapy. This tumor also showed the same pattern of ER-negative and PR-positive staining.

Within 4 months of her last operation, the patient developed a recurrent 6 × 5 cm mass in her pelvis that was biopsy confirmed GCT. The patient remained opposed to further chemotherapy and surgery but accepted the option of hormonal therapy. She received megestrol 40 mg b.i.d. for 2 weeks alternating with tamoxifen, 10 mg b.i.d. for 2 weeks. After 6 months of hormonal therapy, the patient's disease remained stable. By 18 months of therapy, the tumor measured 3 × 2 cm by computed tomography (CT), demonstrating a partial response. At 22 months, a CT scan showed no evidence of disease, documenting a complete response. Now 8 years from her original diagnosis, the patient is doing well with a 5-year disease-free interval on tamoxifen and megestrol. She continues on hormonal therapy.

Methods

To investigate the incidence of hormone receptors in GCTs, we searched the pathology database for all granulosa cell cases over the last 10 years at our institution (older specimens were unavailable, as tissue blocks had been discarded). A single pathologist reviewed all slides to confirm the diagnosis of GCT. The tissue blocks from each specimen were re-cut and immunohistochemically stained using the Techmate 1000 automated immunohistochemistry stainer after microwave pretreatment to enhance retrieval of formalin-fixed epitopes. The antibody for estrogen receptors was Immunotech 1D5; the antibody for progesterone receptors was Novocastra 1A6. Controls were run with each staining. The same pathologist interpreted the staining using a scoring system for receptors in breast cancers [3]. The proportion of nuclei that stained with estrogen or progesterone receptors was scored on a scale of 1 to 5. The intensity of staining was scored on a scale of 1 to 3 (3 = strong intensity). The proportion and intensity scores were then added, and a total score of 3 or greater was considered positive for hormone receptor.

Results

Review of our institution's records identified 22 specimens of GCTs from 18 patients: 18 primary and 4 recurrent specimens. Table 1 summarizes the data on hormone receptors in these tumors. All 22 cases were positive for PR, all showing strong intensity. Estrogen receptor staining was positive in 32% of the specimens.

Follow-up information on our patients was limited, because our cancer registry does not track GCTs unless the pathology report specifically states "malignant" GCT. Five patients had 2 or more years of documented follow-up. Of these, two had recurrences (one being our case report), and all five are alive and well. In both patients with recurrences, the ER was negative and PR positive in both the primary and the recurrent tumors.

Discussion

This case demonstrates a remarkable response of a recurrent ovarian GCT to alternating hormonal therapy with

Table 1
Nuclear estrogen and progesterone receptors

Patients	Age	Stage	ER	PR
1	59	IA	–	+
		1st recurrence	–	+
		2nd recurrence	–	+
2	47	IC	+	+
3	49	IC	+	+
4	46	IA	+	+
5	60	IA	–	+
6	24[a]	IA	–	+
7	66	IA	+	+
8	30	IA	+	+
9	43	IA	–	+
10	53	IA	–	+
11	46	IA	–	+
12	66	IA	–	+
13	50	IC	–	+
14	26[a]	IA	–	+
15	74	IA	+	+
16	65	IA	–	+
17	NA	NA	+	+
18[b]	56	IIIA	–	+
		1st recurrence	–	+
		2nd recurrence	–	+

Intensity + proportion = score: Negative (–) if score < 3; Positive (+) if score 3 or greater.
[a] Juvenile GCT.
[b] Same patient as case report.