

Clinical case

The management of granulosa cell tumor of the ovary — a case history

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Introduction

Granulosa cell tumors comprise 3% to 10% of all malignant ovarian tumors. They are diagnosed at all ages, but usually occur after the menopause [1]. The most common presenting symptom is abnormal uterine bleeding due to hormonal activity of the tumor. Complete surgical removal is the management of choice for these tumors. The stage at the initial operation appears to be the most important prognostic factor for cancer-related survival. The management of metastatic disease or inoperable loco-regional relapse has yet to be defined for this uncommon ovarian tumor. The following case history illustrates a number of management problems in a patient with granulosa cell tumor of the ovary. Therapeutic options for the different stages of the disease will be discussed.

Case history

A 59-year-old woman presented with a history of abdominal discomfort and dysuria of six months' duration, with additional symptoms of dyspareunia and anal tenesmus. There was no history of vaginal discharge or bleeding. She was multiparous and had been postmenopausal for eight years. On examination the only abnormal finding was a mobile mass in her lower abdomen. Laboratory investigations including full blood count, plasma electrolytes, serum creatinine and liver function tests all showed normal results apart from an elevated lactate dehydrogenase of 369 U/L (normal \leq 250) and 17-beta-estradiol of 250 pmol/L (postmenopausal woman normal \leq 60). A cervical smear showed no abnormalities except for an absence of atrophy of epithelial cells. The chest X-ray picture was normal. Intravenous pyelography showed an impression on the bladder but no urethral obstruction and ultra-sound confirmed a solid mass originating in the right ovary.

An exploratory laparotomy was performed. Apart from adhesions of the enlarged right ovary to the small

intestine, no abnormalities were found. After washout of the peritoneal cavity an infracolic omentectomy and total hysterectomy was performed with bilateral salpingo-oophorectomy including the adherent part of the small intestine. Histological examination showed a granulosa-cell tumor of the right ovary confined within the capsule (FIGO stage IA) and a carcinoma in situ of the endometrium of the uterus. The patient's post-operative recovery was uneventful and her serum beta-estradiol level returned to normal postmenopausal levels.

During follow-up the patient complained of disabling flushes which were treated successfully with conjugated estrogen 1.25 mg daily.

After two years the patient again experienced abdominal pain. On examination no tumor was found but ultra-sonography revealed an abdominal mass. Determination of her estradiol levels was not helpful due to the estrogen medication. Laparotomy was performed and in addition to extensive adhesions, two peritoneal lesions of 1.0 and 4.0 cm diameter were found. Both lesions proved to be granulosa cell tumor and could be completely resected. No adjuvant therapy was given.

Six months later a routinely performed CT scan of the abdomen showed a local recurrence and liver metastases. The endogenous 17-beta-estradiol level (after cessation of the estrogen medication) was elevated to 180 pmol/L. Palliative poly-chemotherapy was started with PVB courses; cisplatin (20 mg/m² day 1–5), vinblastine (0.15 mg/kg days 1 and 2) and bleomycin (30 mg/24-hour infusion on day 2 and 15 mg short infusion day 15) every four weeks. After two courses there was a reduction in tumor size. After four courses early signs of bleomycin lung toxicity were detected on the chest X-ray and bleomycin was discontinued. After six courses the patient developed polyneuropathy and chemotherapy was stopped. A partial response was obtained with normalization of estradiol levels and elevation of luteinizing hormone (LH), follicle-stimulating hormone (FSH) levels to postmenopausal values.

One and a half years later, four years after the initial presentation, abdominal pains recurred due to growth of the liver metastases. Elevation of her serum estradiol levels (156 pmol/L) had preceded clinical manifestations four months earlier. Chemotherapy was re-instituted with carboplatin (day 1, 340 mg adjusted to creatinine clearance of 50 ml/min) and etoposide (120 mg/m² days 1–3) every three weeks. Again a partial response was seen after four courses, with normalization of estradiol to postmenopausal levels. No further tumor regression could be achieved and treatment was stopped after the sixth course. The response lasted only six months. A third attempt with polychemotherapy (carboplatin and etoposide) was less successful and stabilization of the tumor was the best response achieved with a total dose of six courses.

No further treatment was given and slow progression of the tumor advanced to end-stage disease one year later. At that time the patient was completely bed-ridden, complained of abdominal pain, loss of appetite, night-sweats and tumor-related fever. The enlarged liver extended into the pelvis and the patient became dependent on blood transfusions at 10-day intervals. Palliative therapy with dexamethasone orally 3 mg daily was started, with considerable benefit. Her subjective symptoms disappeared and the massive liver mass shrank to only a small palpable rim just below the right costal margin. The patient became transfusion-independent and was able to resume her normal daily activities. This unexpected objective response on dexamethasone lasted for one year. Fifteen months later, eight years after her initial diagnosis, the patient died of progressive disease.

Discussion points

1. Presenting symptoms, diagnosis and prognosis of granulosa-cell ovarian tumor

A minority of granulosa cell stromal tumors occur in children before their fifth year and may present with sexual pseudo-precocity. The majority of the tumors occur after the menopause (55%) or during reproductive life (40%) [2]. A higher incidence has been reported after ovarian stimulation with clomiphene citrate and/or gonadotrophins in patients with primary and secondary infertility [3]. Abnormal uterine bleeding due to hormonal activity of the tumor is a presenting symptom in more than one-half of the adult victims. The endometrium may show cystic hyperplasia (60%) and adenocarcinoma is reported in 3% to 13% of cases [4, 5]. Abdominal discomfort and distension is noted in one-third of the patients, of whom 8% may present with acute symptoms due to torsion or rupture of the ovarian tumor [4, 6]. Virilization is a rare complication of androgen production by the tumor.

Granulosa-cell tumors are diagnosed at an early stage more often than other ovarian tumors due to their

hormonal activity; they account for 70% of all feminizing ovarian tumors. Precocity in young girls, estrogen-stimulated vaginal smears and cervical mucus or endometrial hyperplasia may alert the gynaecologist to the possible existence of a granulosa cell tumor. Laboratory tests may show an elevated estrogen level and low FSH and LH levels in menopausal women, but one-third of these tumors are not steroid-producing and investigations will be hampered by premenopausal status or the use of exogenous estrogens. Inhibin, a polypeptide produced by granulosa cells, is stimulated by FSH and itself inhibits the release of FSH from the pituitary gland. Elevated levels of inhibin may also act as a marker for this tumor [7], but not specifically, as other ovarian cancers may also be associated with elevated levels of inhibin [8]. Histology is therefore necessary to prove the nature of the tumor. Thecomas must be differentiated from granulosa cell tumors and mixed granulosa–theca cell tumors. Pure thecomas are benign tumors of stromal origin, and only rarely do they recur after complete surgical removal [5]. Mixed tumors and pure granulosa-cell tumors are both malignant and have the same, less favourable prognosis. The tumors may show different histological patterns, but the pattern does not correlate with survival [9].

Advanced clinical stage (FIGO II–IV), presence of tumor rupture, large tumor (>5 cm) and high number of mitotic figures are all associated with poor prognosis [4–6, 9, 10]. The majority of patients (78%–92%) present with FIGO stage I with five-year survival rates of 92%–98% and at 10 years of 86%–92%. The five-year survival of FIGO stage II is reported to be 57%–76%, and at 10 years 30%–61%. Survival in FIGO stages III and IV at 5 and 10 years is 11%–22% and 6%, respectively, but the total number of patients with advanced disease is very low in most series. The overall survival with granulosa cell tumor is more favourable than with epithelial cell cancer of the ovary. This may be at least partially due to the earlier stage at diagnosis of granulosa cell cancer, as stage for stage survivals are comparable for the two tumor types. Tumor relapses occur on an average six years after initial diagnosis, but late recurrences of more than 20 years have been reported [2].

2. Initial management according to FIGO stage of granulosa-cell tumor of the ovary

The initial treatment for granulosa-cell tumor of the ovary should be a bilateral oophorectomy with hysterectomy and removal of as much metastatic disease as possible. Incomplete surgical removal is associated with a poorer overall prognosis [5, 11, 12].

There is no general consensus concerning the advisability of a conservative unilateral oophorectomy in younger patients with limited disease and a strong wish for preservation of fertility. The available retrospective studies are inconclusive. Conservative surgery was acceptable to Malkasian [2] only for patients with

FIGO stage IA disease. In contrast, Kietlinska [11] has pointed out that although the five-year survival in stage I disease is not compromised by conservative surgery, longer follow-up revealed that it carries a much less favourable prognosis than the one following radical surgery. Conservative surgery must also deal with the possibility of associated endometrial cancer and the occasional bilateral occurrence of the tumor. Although bilateral tumors are uncommon, with a reported incidence usually of 2%–5% of cases [4–6, 9], a much higher incidence was noted by Ohel (26%) [10]. Unilateral oophorectomy should be preceded by dilatation and curettage of the uterus, and biopsy of the remaining ovary has been advocated.

Radical surgery is therefore probably preferable in terms of overall prognosis, and the loss of child-bearing potential must be weighed carefully against the increased chance of an incurable relapse after conservative surgery. Initial-presentation FIGO stage IV is very rare for granulosa-cell tumor and experience with management is sparse. The role of primary or secondary debulking in these patients is unclear. Palliative chemotherapy with cisplatin containing regimens may be advisable [13].

3. *Adjuvant therapy in the management of granulosa-cell tumor of the ovary*

The majority of patients present with FIGO stage IA or IB disease, and surgery alone will be adequate primary therapy. Local recurrence and metastases occur especially in the higher stages. Compared with epithelial cancer of the ovary the role of adjuvant therapy in granulosa cell tumor FIGO stage IC and higher is less well understood. Prospective randomized studies are impracticable because of the low incidence of the tumor and the long interval during which relapses may occur. Results of treatment are derived from small non-randomized studies with short follow-up often not permitting meaningful conclusions.

Many retrospective series report the use of adjuvant radiotherapy. Adjuvant radiotherapy seemed to be associated with a better prognosis after long-term follow-up in the study of Kietlinska [11]. However, existing data are too incomplete for meaningful comparison of survival by stage of disease or other important prognostic factors. Retrospective analysis by Evans [5], Ohel [10] and Stenwig [4] did not document a possible positive effect of radiotherapy. At present there are no firm scientific arguments for adjuvant radiotherapy.

Colombo presented the results of cisplatin-containing polychemotherapy in 11 patients with advanced or recurrent disease [13]. In six patients (four with FIGO stage III and two with stage IV) adjuvant therapy was given after primary surgical debulking. In all five patients in whom surgery had been optimal, a surgically verified complete remission was subsequently obtained, while a patient who had sub-optimal surgery showed progression during polychemotherapy. During

follow-up lasting 6–36 months no signs of relapse have been noted. In addition to this small study, only anecdotal reports of adjuvant chemotherapy have been presented in the literature [14, 15]. Chemotherapy seems to be indicated for patients with FIGO stage IC–III tumors after surgical debulking, but the exact role of adjuvant chemotherapy in the management of granulosa cell tumor of the ovary remains speculative.

4. *Follow-up after initial therapy of granulosa-cell tumor of the ovary*

Because of the possibility of late recurrence even more than twenty years after initial treatment, follow-up for granulosa tumor of the ovary should be life-long [2, 11].

History, physical examination and biochemical markers will be included in the follow-up examination. Serum estradiol levels may be a marker in those patients in whom elevated levels were found before initial therapy. Serum inhibin, although not specific for granulosa-cell cancer alone [8], may be an alternative and sensitive marker for primary as well as recurrent disease and is less hampered by endogenous or exogenous estrogen. Elevation of the markers may precede clinical manifestations of recurrent disease by as long as 20 months [7].

The role of routine radiological diagnosis is not clear. Recurrence may occur intra-abdominally as in epithelial ovarian cancer. The first sites of metastases outside the peritoneal cavity are lungs, liver and even the brain, spread hematogenously. Although there are many recurrences within the first five years after initial therapy, the median interval is six years. The best approach is to perform radiological investigation in patients in whom there is suspicion of relapse, based on the symptoms, physical examination or laboratory results.

In addition to associated endometrial cancer, there is evidence of an increased incidence of breast cancer in patients with granulosa-cell tumor of the ovary [2, 10]. Incidences of 3.7% to 20% have been reported. Periodic examination of the breasts and mammography have been advocated.

5. *Management of inoperable advanced or relapsed granulosa-cell tumor of the ovary*

There is no consistently effective management in advanced or relapsed granulosa cell cancer of the ovary. Published experience with these patients is anecdotal. Although no cure is achieved, there have been reports of complete responses of long duration achieved by surgery, radiotherapy and chemotherapy, both alone and in combination.

Repeated surgical removal after recurrence has been reported to be successful in limited disease. Combination therapy of surgical debulking and radiotherapy or radiotherapy alone has been used [4, 5, 11, 12, 16]. The combination of surgery and radiotherapy was superior

in the opinion of Kietlinska [11], but comparative data are lacking.

Chemotherapy has been used in patients with large residual disease, metastases and inoperable recurrences. A twenty to twenty-five percent objective response rate has been reported in small groups of patients on monotherapy with melphalan and cyclophosphamide [16]. Anecdotal successes with L-phenylalanine mustard, adriamycin and actinomycin D have been published [14, 17, 18]. Combination chemotherapy with vincristine, adriamycin and cyclophosphamide (VAC), cisplatin, adriamycin and cyclofosfamide (PAC) or actinomycin D, 5-FU and cyclophosphamide (AcFuCy) has been used, yielding similar results [19, 20]. Colombo presented a successful combination with cisplatin, vinblastine and bleomycin (PVB) [13]. Five of six patients with residual disease after primary debulking surgery derived complete responses and four of five patients with recurrent disease responded, but two toxic deaths occurred. In his study only patients with residual disease <2 cm had a complete response with chemotherapy and longer-lasting responses. Until now reported studies have been too small to serve as a basis for conclusions regarding optimal combination chemotherapy or the number of courses to be given. Moreover, nothing is known of the possible activity of newer drugs such as taxol in granulosa cell tumor of the ovary.

In this case history an unexpected response occurred on dexamethasone. Until now no such response has been reported in the literature. Clarification of the implications of this observation await publication of the experiences of others.

Conclusion

Many questions about the management of granulosa-cell tumor of the ovary remain unanswered. Its low incidence and long relapse interval preclude a rapid comprehension of the biology of the tumor and definition of the best treatment option in advanced or metastatic disease. The cornerstone of treatment remains surgery. In all studies patients with early-stage disease and optimal debulking proved to have the best prognoses even in recurrent disease. Patients with stage IC disease or worse may benefit from adjuvant therapy especially after optimal surgery, but there have been no well-designed studies to determine the role of radiotherapy or chemotherapy. Theoretically chemotherapy has the advantage of treating distant metastases as well, which do occur in granulosa cell tumors. Recurrent disease may respond to radiotherapy or chemotherapy, but the best results have been obtained after optimal surgery. Nevertheless individual patients may benefit from one treatment modality subsequent to the other after a long period has elapsed.

References

1. Young RH, Scully RE. Ovarian sex cord-stromal tumours: Recent advances and current status. *Clin Obstet Gynecol* 1984; 11: 93-134.
2. Malkasian GD. Tumors of granulosa-theca derivation. In Williams CJ (ed.): *Textbook of Uncommon Cancers of the Mayo Foundation*. Chichester: Wiley 1988; 3-13.
3. Willemsen W, Kruitwagen R, Bastiaans B et al. Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; 341: 986-8.
4. Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. *Gynecol Oncol* 1979; 7: 136-52.
5. Evans AT, Gaffey TA, Malkasian GD, Annegers JF. Clinicopathological review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol* 1980; 55: 231-8.
6. Malström H, Högberg T, Risberg B, Simonsen E. Granulosa cell tumors of the ovary: Prognostic factors and outcome. *Gynecol Oncol* 1994; 52: 50-5.
7. Lappöhn RE, Burger HG, Bouma J et al. Inhibin as a marker for granulosa-cell tumors. *N Engl J Med* 1989; 321: 790-3.
8. Cooke I, O'Brien M, Charnock FM et al. Inhibin as a marker for ovarian cancer. *Br J Cancer* 1995; 71: 1046-50.
9. Björkholm E, Silfverswärd C. Prognostic factors in granulosa-cell tumors. *Gynecol Oncol* 1981; 11: 261-74.
10. Ohel G, Kaneti H, Schenker JG. Granulosa cell tumors in Israel: A study of 172 cases. *Gynecol Oncol* 1983; 15: 278-86.
11. Kietlinska Z, Pietrzak K, Drabik M. The management of granulosa-cell tumors of the ovary based on long-term follow-up. *Eur J Gynaecol Oncol* 1993; 14 (Suppl): 118-27.
12. Pankratz E, Boyes DA, White GW et al. Granulosa-cell tumors a clinical review of 61 cases. *Obstet Gynecol* 1978; 52: 718-23.
13. Colombo N, Sessa C, Landoni F et al. Cisplatin, vinblastine and bleomycin combination chemotherapy in metastatic granulosa-cell tumor of the ovary. *Obstet Gynecol* 1986; 67: 265-8.
14. Camlibel FT, Caputo TA. Chemotherapy of granulosa-cell tumors. *Am J Obstet Gynecol* 1983; 115: 763-5.
15. Jacobs AJ, Deppe G, Cohen CJ. Combination chemotherapy of ovarian granulosa-cell tumor with cis-platinum and doxorubicin. *Gynecol Oncol* 1982; 14: 294-7.
16. Malkasian GD, Webb MJ, Jorgensen EO. Observations on chemotherapy of granulosa-cell carcinomas and malignant ovarian teratomas. *Obstet Gynecol* 1974; 44: 885-8.
17. Lusch CJ, Mercurio TM, Runyon W. Delayed recurrence and chemotherapy of a granulosa cell tumor. *Obstet Gynecol* 1978; 51: 505-7.
18. Disaia PJ, Saltz A, Kagan AR et al. A temporary response of recurrent granulosa-cell tumor to adriamycin. *Obstet Gynecol* 1978; 52: 355-8.
19. Slayton RE. Management of germ-cell and stromal tumors of the ovary. *Semin Oncol* 1984; 11: 299-313.
20. Slayton RE, Johnson G, Brady L et al. Actinomycin D, 5-fluorouracil and cyclophosphamide (AcFuCy) chemotherapy for ovarian stromal tumors; a gynecologic oncology group study. *Proc Am Soc Clin Oncol* 1980; 21: 430.

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