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Multiple Recurrence of Granulosa Cell Tumor of the Ovary: A Case Report and Review of the Literature

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ABSTRACT

Granulosa cell tumors comprise approximately 5% of all ovarian malignancy and account for 70% of malignant sex cord stromal tumors. Granulosa cell tumors have been diagnosed from infancy, the peak incidence being perimenopausal age. The potential of malignancy of these tumors is low, recurrence are often late and found in 10-33% of cases. A 32-year-old female para 1 live 1 presented with large abdominal mass fourth time in her lifetime for which she underwent staging laparotomy with debulking surgery. Histopathology of mass collected which was suggestive of granulosa cell tumor. She had three laparotomy for same region in the past. At 13 year of age she was diagnosed with a stage IA granulosa cell tumor (GCT) of the ovary first time. For which she underwent surgical staging and removal of adnexal mass, after that she was asymptomatic for 7 years. In 2003 she again presented with lump abdomen for which she underwent a resection of adnexal mass, histopathology was consistent with recurrent GCT. After second surgery she also received two cycles of chemotherapy. Despite adjuvant chemotherapy treatment the patient presented again after three years in 2006 with adnexal mass and was found to have a third recurrence. For which she received 6 cycles of chemotherapy and mass was regressed. After four year in 2010 she again presented with lump abdomen for which she underwent surgical staging total abdominal hysterectomy with right salphingo oophorectomy with removal of mass. After five year in 2015 she again presented with lump abdomen for which surgical management was done. So over the 20 years this patient had multiple recurrences and progressive disease despite surgical and targeted treatment. In conclusion the long history of granulosa cell tumor highlights the importance of extended follow up of the patient.

Keywords: Granulosa cell tumor, Recurrent disease, Chemotherapy, Surgical staging

Introduction

Granulosa cell tumors (GCT) are derived from the granulosa cells of the ovary. They constitute approximately 5% of the ovarian tumors and more than 70 % of the sex cordstromal tumors. Two distinct histological types—adult GCT (AGCT) and juvenile GCT (JGCT) are there which display different clinical and histopathological features. AGCTs are more commonly seen in perimenopausal and postmenopausal women, with a peak incidence at 50–55 years while JGCTs are rare tumors, representing 5 % of all GCTs and occurring in pre menarchal girls and young women [1]. Granulosa cell tumours arise from granulosa cells that are hormonally active stromal elements and responsible for production of estradiol. Adult granulosa cell tumor are usually stage 1 at the time of diagnosis,

but it may recurs in 5 to 30 years after initial diagnosis while most juvenile granulosa cell tumors are clinically benign and only 10% recurs within 5 year after the initial diagnosis. FOXL2 gene encodes the transcription factor which required for the normal development of the granulosa cell. Shah et al. in their study they found that somatic missense mutation in FOXL2 (c.402C > G; p.C134W) in GCT. These mutations was seen in 86 of 89 (97%) adult GCT, 1 of 10 (10%) juvenile GCT. The high frequency of these mutations suggests this mutation may be pathognomic for AGCT, and the absence of this mutation in JGCT shows that JGCT may be an entirely different tumor [2,3]. Chromosomal abnormalities have also been recently evaluated in these tumors. Detected abnormalities of chromosome include trisomy 12, monosomy 22, and deletion of chromosome 6. Among juvenile granulosa cell tumors it has been identified by cytogenetic studies that trisomy 12 and a deletion in chromosome 6q plays a major role. BRCA1 and BRCA

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2 mutations are not associated with these tumors. Few syndromes are associated with predisposition of GCT as Peutz Jeghers syndrome and Potters syndrome. While Ollier disease and Maffucci disease are associated with juvenile GCT [4].

Case Report

A 32-year-old female para 1 live 1 presented with large abdominal mass for 2 year for which she was admitted and evaluated. In past the patient had three laparotomies and two chemotherapy cycles for granulosa cell tumor. She was diagnosed with a granulosa cell tumor (GCT) of the right ovary in 1996 for which she underwent left salphingo oophorectomy at our institution. No further treatment was given. The patient remained disease free for 7 years; however, in April 2003 she again noticed a lump in abdomen. A second exploration was performed and removal of the mass done along with staging and multiple biopsies were taken. This time again histopathology of mass consistent with recurrent GCT; however, the lymph nodes and biopsies were negative. The patient was treated with chemotherapy for two cycle (ICE regime constitutes ifophosphamide, cisplatin and etoposide). After chemotherapy patient was asymptomatic for two years.

In 2006 after two years of chemotherapy patient again presented with left adnexal mass for which CECT was done and USG guided FNAC was done and histopathology sent and found to be granulosa cell tumor. Patient wants conservative management this time so six cycles of chemotherapy was given. After chemotherapy patient was asymptomatic for three years.

In 2010 after three years of chemotherapy she again noticed huge abdominal mass for which patient underwent staging laparotomy with total abdominal hysterectomy with right salphingo oophorectomy with omentectomy. After third surgery patient was asymptomatic for 3 years.

Now in 2015 she again presented with large abdominal mass. On examination patient had 28 to 30 week gravid uterus size abdominopelvic mass which was firm in consistency and not mobile. Her tumor markers were in normal limits. USG and PET-CECT was done which was suggestive of a well defined heterogenous enhancing FDG avid complex (solid & cystic) mass lesion noted in the pelvis compressing the left ureter displacing the urinary bladder right anterolaterally and left kidney had hydrouretero nephrosis. This time patient underwent staging laparotomy and debulking of mass.

Peroperative findings – a large 15 x 15 cm encapsulated mass with increased vascularity was

present in the pelvic area arising from left side. This time patient underwent removal of adnexal mass along with infracolic omentectomy.

On cut section – tumor had variegated consistency. Solid portion of tumor was granular grey yellow in color.

Postoperative period was uneventful and patient discharged on 14 post operative day and referred to cancer center for chemotherapy

Discussion

GCTs are rare tumors which account for approximately 2–3% of all ovarian cancer. They are associated with a favorable outcome and prognosis, especially when they are diagnosed and treated in the early stages. Björkholm et al reported in 1981 that the 5 year survival rates were over 95% for stage I, 55% for stage II, and 25% for stage III tumors [5]. Lauszus et al., reported that the survival rates for stage I at 5, 10 and 20 years were 94%, 82%, and 62%, respectively [6]. These studies conclude that GCTs tend to be associated with late recurrence. Similar to epithelial ovarian cancers the presenting symptoms of granulosa cell tumors are usually nonspecific with abdominal pain (41.1 %) or distension (26.4 %) [1]. These patients present with a large ovarian mass Hyperestrogenic symptoms occur in all age groups. In prepubertal age group, precocious puberty will be seen. In the reproductive age group, menstrual patterns alteration (32.8 %) like menorrhagia, intermenstrual bleeding or amenorrhoea may be seen. Postmenopausal age group postmenopausal bleeding is the most common finding. Endometrial cancers, usually detected in the pathological specimens, are well differentiated early stage disease and have a good prognosis. Most of the women with early stage GCT require no further treatment and have good prognosis however, approximately 11%-37% of patients will relapse with a median time of 75 months (range 55-137 months) after diagnosis, with one report showing recurrence 40 years after initial diagnosis [7,8]. Extrapelvic recurrence of granulosa tumor has been reported in up to 52% of cases. Therefore long term follow up is required. The long term follow up should include physical exam as well as tumor marker studies including estradiol, inhibin, and mullerian inhibitory substance [9].

Patients had multiple recurrence of granulosa cell tumor associated with a poor prognosis. Most of the patient had recurrence within 10 years after the initial diagnosis, there are some case reports in which patient had recurrence of disease even after 10 years.

In our case, the patient had relapse multiple time after the initial diagnosis. In one case report patient

presented with retroperitoneal hemorrhage with recurrence after 4 year of initial diagnosis. Once the tumor recurs it's fatal approximately in 80 % cases. Park et al found in their study that, none of the patients with early stage disease who underwent optimal debulking had tumor recurrence and with advanced stage of GCT who received at least 6 cycles of BEP adjuvant chemotherapy none of the patient had tumor recurrence [10]. The longest time of recurrence reported in study is 40 years. Sun et al found in their study that about 21 % develop recurrence and the median time to relapse was 57.6 months (2–166 months) [11]. Aburustum et al [12] reported that local pelvic recurrence occurs in 70% cases, 9% recurrence occurs in pelvis and abdomen, 6% occurs in retroperitoneum, 6% pelvis and retroperitoneum and 3% had recurrence in pelvis, abdomen and retroperitoneum. It has been found that most recurrences of peritoneal is suggestive of possibility of missed peritoneal disease during primary surgery especially for early stage disease. According to a study by Fotopolou et al. dissemination of tumor patterns differed significantly between primary and recurrent patients, patient having significantly higher rates of diffuse peritoneal involvement and extraovarian tumor involvement of the middle and upper abdomen in the recurrent cases. It has been found in studies that only about 85 % of the relapsed patients could be operated without residual lesions compared to nearly 100 % in all primary patients. Multiple organ involvement with metastasis to liver, appendix and intestines are quite common while metastases to lung, bone, vagina, adrenal, spleen, pancreas, gall bladder, rectus muscle are rarely reported.

Conclusion

So due to high chance of recurrence even years after apparent clinical cure of the primary tumor, lifelong follow up of patient with clinical examination and tumor markers like inhibin B is recommended.

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