Case Report:

Adult Granulosa Cell Tumor with amyloid like stroma of Ovary

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Abstract:

Granulosa cell tumor accounts for 1.5% of all ovarian neoplasms. It is an estrogen producing neoplasm. It is of two types, an adult type that occurs mainly in postmenopausal women and a juvenile type that usually occurs in prepubertal girls and women younger than 30 years. The common presenting symptoms are abnormal vaginal bleeding in postmenopausal woman and menorrhagia, metrorrhagia or amenorrhea in those who are premenopausal. Complete surgical resection of the tumor is the treatment of choice. Recurrent disease tends to occur many years after the initial diagnosis so long-term follow up is needed. We report a case of adult granulosa cell tumor in a 55 year old woman.

Keywords: Granulosa cell tumor, ovarian tumor, ovary, tumor

Introduction :

Granulosa cell tumor (GCT) is an ovarian neoplasm showing differentiation towards follicular granulosa cells. It is the most common malignant sex cord stromal tumor comprising 1.5% of all ovarian tumors[1].There are two types of granulosa cell tumor, an adult type that occurs mainly in postmenopausal women and a juvenile type that usually occurs in prepubertal girls and women younger than 30 years. These tumors secrete estrogen. The common presenting symptoms include postmenopausal bleeding and menorrhagia, metrorrhagia or amenorrhea in those who are premenopausal. Complete surgical resection of the tumor is the treatment of choice [2].Recurrent disease tends to occur many years after the initial diagnosis so long-term follow up is needed. We report a case of adult GCT in a 55 year old woman.

Case Report :

We reported a case of 65 year old, para 4, woman with 4 living children. She was 10 years post-menopausal. She presented with a three week history of vaginal bleeding which was sudden in onset and profuse, with occasional passage of blood clots. She had associated intermittent lower abdominal pain that was dull, with no relieving or aggravating factors. She had no history of post-coital bleeding, weight loss, anorexia, urinary symptoms, abdominal mass, vaginal discharge, or dyspareunia. The vaginal examination revealed an atrophic, blood stained vulvo-vagina. A speculum examination showed an apparently healthy-looking cervix. The cervical os was found to be closed on digital examination. A bimanual examination revealed a bulky uterus that was about 8 week's gestational size. It was freely mobile and anteverted. There was no adnexal mass or tenderness. USG abdomen and pelvis was normal. All other findings in general and physical examination were normal. All hematological and biochemical investigations were also normal. As patient was postmenopausal, total abdominal hysterectomy with bilateral salpingo-oophorectomy

was performed for abnormal uterine bleeding. On gross examination uterus, cervix, and left fallopian tube and left ovary were unremarkable. The right ovary was 3.5x2.5x 1.5 cm with smooth outer surface. The cut section showed solid gray white to yellowish area with few papillary excrescences. Microscopically the ovarian tissue was partially replaced by a tumor showing island of neoplastic cells in fibrous stroma.(Figure 1) The tumor islands are composed of round to oval cells having vesicular nuclei and scant cytoplasm arranged in microfollicular pattern showing call exner bodies. Few of the nuclei show longitudinal grooves. (Figure 2) There was also presence of homogenous dense eosinophilic material mimicking amyloid. (Figure 3) Congo red stain was negative. So diagnosis of adult GCT with amyloid like stroma was given.

Discussion :

Ovarian GCT is classified as a sex cord-stromal tumor. Rokitansky in 1859 was the first to describe GCT of the ovary [3]. Granulosa cell tumors account for approximately 1.5% of all ovarian tumors [1]. 95% of granulosa cell tumors are of adult type and remaining 5% are of juvenile type [4].The WHO defined this tumor as a neoplasm composed of a pure or at the least a 10% population of granulosa cells often in a fibrothecomatous background. The etiology of these tumors is unknown. Several studies suggest that infertile women and those exposed to ovulation induction agents have an increased risk for granulosa cell tumors [5]. While most common in postmenopausal women these tumors occur over a wide age range, from teenagers to the elderly. The average age is 50-55 years. These tumors typically secrete estrogen which stimulates the endometrium to proliferate. The usual presenting symptom is postmenopausal bleeding in older women and menorrhagia, metrorrhagia or amenorrhea in those who are premenopausal. Endometrial biopsy reveals hyperplasia in 30-40% of patients and endometrial adenocarcinoma in 5-10% [6].Rare adult type granulosa cell tumors, most occurring in young women (15-35 years of age) secrete androgen and induce virilization [7].The typical symptoms include hirsutism, enlargement of the clitoris, deepening of the voice and amenorrhea. A rare unilocular thin-walled cystic variant is often androgenic when functional [7].About 25% of patient present with non-specific symptoms such as palpable abdominal mass, abdominal distention and pain. Rupture or torsion of the tumor and intratumoral hemorrhage can cause acute abdominal symptoms. Cross sectional imaging, i.e. computed tomography and magnetic resonance imaging is of value in the surgical planning and preoperative determination of resectability of patients with granulosa cell tumors [8].GCTs are typically unilateral (95%) with an average size of 12.5 cm and are commonly encapsulated with a smooth or lobulated surface. The sectioned surface of the tumor is yellow to tan with a variable admixture of cystic and solid areas [9]. Haemorrhage is seen in larger tumors. A small percentage is totally cystic, either uniloculated or multiloculated [9].A solid or cystic tumor with a combination of yellow tissue and haemorrhage is highly suggestive of a granulosa cell tumor. Microscopically the tumor cells resemble normal granulosa cells. They are small and round, cuboidal or spindle – shaped with pale cytoplasm and ill-defined cell borders. The nuclei are round to oval with fine chromatin and a single small nucleolus. The stroma is fibrous. In our case also the stroma was predominantly fibrous but in certain areas we get homogenous dense eosinophilic material similar to amyloid. But congo red stain was negative. Even

after extensive literature review we didn't found a case of adult GCT with amyloid stroma. So this might be the first case of this entity and it needs further study to find out the significance of this amyloid like material in adult GCT. Patterns of growth include microfollicular (with call exner bodies), macrofollicular, trabecular, insular, watered – silk, solid and diffuse (sarcomatoid).The theca cell component may also be present. Focal luteinization of either the granulosa or the theca cell component may occur which is particularly prominent in those tumors associated with pregnancy. An important diagnostic feature is the presence of folds or grooves in the nuclei resulting in 'coffee-bean' appearance [9]. Granulosa cell tumors are immunoreactive for CD99, alpha-inhibin, vimentin, cytokeratin (punctate), calretinin, S-100 protein and smooth muscle actin. The tumor cells are negative for cytokeratin 7 and epithelial membrane antigen [10,11]. All granulosa cell tumors have a potential for aggressive behaviour. A quarter of GCT patients will have recurrences, and the mean time to their detection is 5–10 years [12]. 10–20% of patients may develop recurrences as late as twenty to forty years after the primary diagnosis [13]. Frequent sites of recurrence include the upper abdomen (55–70%) and the pelvis (30–45%) [14]. In early-stage patients, risk factors for relapse include large tumor size, high mitotic index, and tumor rupture; therefore, these features may indicate the need for postoperative adjuvant chemotherapy [12]. Additional postsurgical risk factors include advanced stage of presentation, lymphovascular space invasion, bilaterality, and Ki67/p53 overexpression. The overall ten-year survival rates in patients with GCT range between 60 to 90% [12]. Approximately 80% of females with advanced GCT die due to the disease, which is partly related to the tendency for delayed recurrence [15]. This unpredictability of the time interval for recurrent and/or metastatic disease indicates the requirement for a long-term clinical follow up in all cases [12]. The most important prognostic factor is the stage of the tumor [11]. Nearly 90% of patients with granulosa cell tumor have stage I disease. Factors related to a relatively poor prognosis include age over 40 years at the time of diagnosis, large tumor size (>5cm), bilaterality, mitotic activity and atypia [16].Among adults, survival is adversely affected by tumor rupture. The differential diagnosis includes endometrioid carcinoma, endometrioid stromal sarcoma, undifferentiated carcinoma, poorly differentiated adenocarcinoma and thecoma. The insular and trabecular patterns of granulosa cell tumor may be mistaken for a carcinoid and vice versa. Carcinoids have uniform round nuclei with coarse chromatin, lack nuclear grooves and show chromogranin positivity. Furthermore, primary carcinoids of the ovary are usually associated with other teratomatous elements, whereas the metastatic ones are generally multi-nodular and bilateral. The surgical procedure for patients with GCT has traditionally been similar to that used for epithelial ovarian cancer. In a young patient desiring to preserve fertility, unilateral salpingo-oophorectomy should be performed and a total abdominal hysterectomy with bilateral salpingo-oophorectomy should be performed for patients whose fertility is not an issue and for postmenopausal women [17]. Omentectomy is also performed. Adjuvant chemotherapy and/or radiotherapy should be reserved for advanced or recurrent disease. In our study, as the patient was postmenopausal woman and tumor was in stage I, total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed.

Conclusion :

GCT is best considered an unusual indolent neoplasm of low malignant potential with late recurrences .The multifaceted clinical presentations coupled with the unpredictable biological behavior with late relapses are diagnostic pitfalls necessitating a high degree of suspicion for accurate clinical and pathological diagnosis. Surgery continues to be the primary cornerstone of initial treatment with chemotherapy and/or radiotherapy being reserved for advanced or recurrent disease states. Long-term lifelong follow up including physical/pelvic examination, abdominal/pelvic CT scan, and/or tumor markers is recommended in all patients with GCTs as delayed tumor recurrences beyond 5 years are characteristic of this disease. It needs further study to find out the significance of amyloid like material in adult GCT.

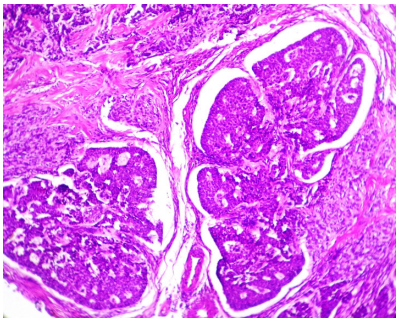

Figure 1: Island of neoplastic cells in fibrous stroma. (H & E, 10X)

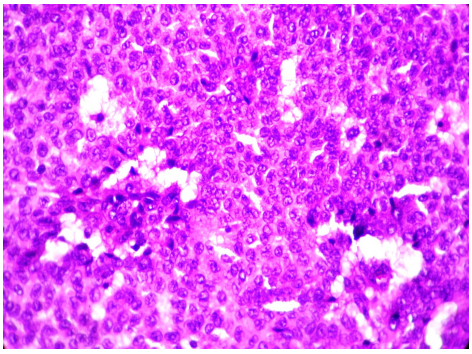

Figure 2: Round to oval cells having vesicular nuclei and scant cytoplasm arranged in microfollicular pattern showing call exner bodies. Few of the nuclei show longitudinal grooves. (H & E, 40X)

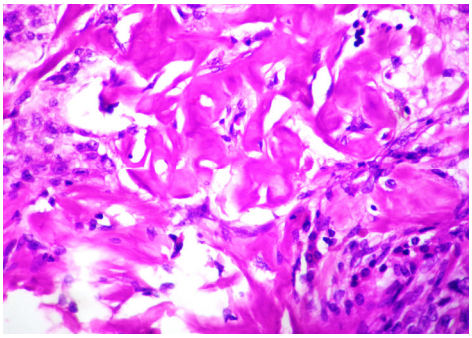

Figure 3: Amyloid like stroma

References :

1. Stage AH, Grafton WD. Thecomas and granulosa-theca cell tumors of the ovary. An analysis of 51 tumors. Obstet Gynecol 1977; 50: 21-7.
2. Savage P, Constenla D, Fisher C, Shepherd JH, Barton DP, Blake P, Gore ME. Granulosa cell tumors of the ovary: Demographics, survival and the management of advanced disease. Clinical Oncology 1998;10: 242-5.
3. Rokitansky CV. Über Abnormalitäten des Corpus Luteum. Wien Med Ztc 1859;4: 253-4.
4. Scully RE. Juvenile granulosa cell tumor. Pediatr Pathol 1988;8:423-7.

5. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994; 331: 771-6.
6. Aboud E. A review of granulosa cell tumors and thecomas of the ovary. Arch Gynecol Obstet 1997; 259 : 161-5.
7. Nakashima N, Young RH, Scully RE. Androgenic granulosa cell tumors of the ovary. A clinicopathologic analysis of 17 cases and review of the literature. Arch Pathol Lab Med. 1984; 108 : 786 – 91.
8. Morikawa K, Hatabu H, Togashi K, Kataoka ML, Mori T, Konishi J. Granulosa cell tumor of the ovary: MR findings. J Comput Assist Tomogr 1997; 21: 1001-4.
9. Norris HJ, Taylor HB. Prognosis of granulosa-theca tumors of the ovary. Cancer 1968; 21: 255-63.
10. Choi YL, Kim HS, Ahn G. Immunoexpression of inhibin alpha subunit, inhibin/activin betaA subunit and CD99 in ovarian tumors. Arch Pathol Lab Med 2000;124: 563-9.
11. McCluggage WG, Maxwell P. Immunohistochemical staining for calretinin is useful in the diagnosis of ovarian sex cord-stromal tumors. Histopathology 2001;38: 403-8.
12. Pectasides D, Pectasides E, Psyrri A. Granulosa cell tumor of the ovary. Cancer Treatment Reviews 2008; 34(1): 1–12.
13. East N, Alobaid A, Goffin F, Ouallouche K, Gauthier P. Granulosa cell tumor: a recurrence 40 years after initial diagnosis. Journal of Obstetrics and Gynaecology Canada 2005; 27(4): 363–4.
14. Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. Journal of Clinical Oncology 2007; 25(20) : 2944–51.
15. McNeilage J, Alexiadis M, Susil BJ, Mamers P, Jobling T, Laslett G, et al. Molecular characterization of sarcomatous change in a granulosa cell tumor. International Journal of Gynecological Cancer 2007;17(2): 398–406.
16. Miller BE, Barron BA, Dockter ME, Delmore JE, Silva EG, Gershenson DM. Parameters of differentiation and proliferation in adult granulosa cell tumors of the ovary. Cancer Detect Prev 2001; 25: 48-54.
17. Koukourakis GV, Kouloulias VE, Koukourakis MJ, Zacharias GA, Papadimitriou C, Mystakidou K, et al. Granulosa cell tumor of the ovary: tumor review. Integr Cancer Ther 2008;7:204-15.

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