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A RARE CASE REPORT ON SYNCHRONOUS TUMOUR: ADULT GRANULOSA CELL TUMOUR COEXISTING WITH SEROUS CYSTADENOMA WITH FOCAL PAPILLARY PROLIFERATION

Pathology

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ABSTRACT

Background: Synchronous tumors of the ovary refers to the simultaneous occurrence of multiple distinct types of tumours within one or both ovaries. These tumours can be either benign or malignant and can originate from different cell types within the ovary. Synchronous ovarian tumours are relatively rare but can present with unique challenges in diagnosis and management. Granulosa cell tumours (GCT) belong to the group of sex cord and stromal tumours of the ovary. Adult granulosa cell tumours account for approximately 1% of all ovarian tumours and 95% of all granulosa cell tumours. They are found more often in postmenopausal than premenopausal women, with a peak incidence between 50 and 55 years of age. **Case detail:** We present the case of a 57-year old female, Para 2/Living 1 with Bilateral ovarian cyst with ventral hernia and type II DM . Serum tumour markers were within normal range. One ovary shows large cyst measuring 9x7x 5.3cms. Other ovary shows cyst measuring 4x3.5 cms. She underwent total abdominal hysterctomy with bilateral salpingoophorectomy and cystectomy. Histopathological report showed one ovary with sex cord tumor suggestive of adult granulosa cell tumor and other ovary showing features of benign serous cystadenoma with focal proliferation. **Conclusion:** Given the rarity and complexity of the synchronous tumor, a multidisciplinary approach is essential for accurate diagnosis and appropriate treatment planning. Collaboration between gynaecologists, radiologists and pathologists is essential throughout the diagnostic and treatment process to ensure comprehensive evaluation and management of synchronous tumors.

KEYWORDS

Total abdominal hysterectomy with bilateral salphingo ophorectomy, Adult Granulosa cell tumour, Synchronous tumors, focal papillary proliferation

INTRODUCTION

Synchronous tumors of the ovary refers to the simultaneous occurrence of multiple distinct types of tumours within one or both ovaries(1). Though these types of tumors are often seen in various organs, their concurrence in the ovary is rare. About 0.5 -1.7% of gynecological malignancies have synchronous primary cancer of female genital tract(2). Amongst the synchronous gynecological malignancies endometrioid carcinoma is most common and has good prognosis(3).

These tumors are distinct and independent of each other, they do not represent metastasis from one site to another but arise independently in different locations or different types of tissue. The concept was first introduced by Theodor Billroth, a renowned Austrian surgeon, in 1889(4).

The ovary can develop tumors from three main types of tissues: epithelial, germ cell, and stromal. Each category includes various subtypes of tumors, each with distinct characteristics and clinical implications. Epithelial tumors are the most common type of ovarian tumors, arising from the surface epithelium of the ovary making up to about 90% of malignant ovarian tumors. The subtypes include serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas. Non-epithelial ovarian tumors which make up the remaining 10% of malignant ovarian tumors include sex cord stromal ,germ cell tumors and metastatic or miscellaneous tumors(5).

Granulosa cell tumors (GCT consist of only 5% of all ovarian cancers. However, they are the most common subtype of ovarian sex-cord tumors (70%)They were first reported by Rokitanski in 1855(6) . Although there is no consensus on the pathogenesis of these tumors, most investigators believe that they originate from early ovarian mesenchyme and they are composed of granulosa cells, theca cells, and fibroblasts in different degrees.

Adult granulosa cell tumor (GCT) of the ovary is often a hormonally active, stromal cell neoplasm that is distinguished by its ability to secrete sex steroids such as estrogen. The highest prevalence is observed in the seventh decade of life.

They are rare neoplasms of heterogenous group originating from the ovarian matrix, and nearly 90% of the hormone-producing tumors are SCSTs. Hence, patients with SCSTs are known to present with signs and symptoms of excess estrogen and androgen. Patients can present with vaginal bleeding caused due to endometrial hyperplasia or carcinoma as a result of prolonged exposure to tumor-derived estrogen. The simultaneous occurrence of surface epithelial tumors of the ovary with other types of ovarian tumors is indeed rare, but there have been a few documented cases. In 10% of cases, a juvenile granulosa cell tumor may rupture and as the result acute abdominal pain may be the first presenting symptom mimicking an ectopic pregnancy in younger patients(7). Ascites is present in 10% of the patients.

Bilateral granulosa cell tumors account for 3% of patient and most commonly are limited to the ovaries at the time of diagnosis, stage I according to FIGO classification(8). GCT usually presents with a mass on pelvic examination which is then confirmed on ultrasonography. Many SCSTs are known for their indolent course and tendency to affect the unilateral ovary. Additionally, it's noteworthy that granulosa cell tumors can recur even several decades after the initial diagnosis, emphasizing the importance of long-term follow-up and surveillance in managing these patients.

The prognosis of the malignancy depends on the subtype of SCST, the stage of the tumor, and age. Surgery is required for definitive tissue diagnosis, staging, and tumor debulking(9). In older women, a total abdominal hysterectomy and bilateral salpingo-oophorectomy are preferred. While women of childbearing age,surgery performed is a more conservative unilateral salpingo-oophorectomy, taken into account that careful staging reveals that the disease has not extended outside of the involved ovary and that there is no concomitant uterine carcinoma. For advanced disease, surgery has to be combined with platinum based chemotherapeutic agents.

We report one such rare case of a adult granulosa cell tumor of left ovary, occurring simultaneously with serous cystadenoma with focal papillary proliferation in the right ovary (10).

CASE DETAILS

A 59 year old female came with chief complaints of intermittent abdominal pain, near paraumbilical region and nausea since one year.

Pain was dragging type and increased after food intake which was relieved after taking analgesics and antacids. She attained menopause 4 years ago. On examination, the patient is conscious ,co-operative and well-oriented, afebrile. Vitals are stable. Abdominal examination showed distension of lower abdomen. A cystic mass of approximately 7x7 cm was felt on palpation occupying left iliac fossa, umbilical and hypogastric region with smooth surface and ill-defined borders. On percussion, dullness was present over the mass and tympanic notes over the flanks. On bimanual examination, uterus anteverted to 10 weeks size, firm in consistency and non-tender. On rectovaginal examination rectal mucosa was free. No deposits in rectovaginal septum. Bilateral parametrium was supple and no nodularity was felt in pouch of Douglas. All routine blood investigations were within normal limits. Ultrasound abdomen and pelvis showed a ventral hernia with bilateral complex adnexal cyst measuring 4x3 cms on the left side and 9x8cms on right side with internal septations . No vascularity was noted. CA-125 level was 12U/ml.

Risk of Malignancy Index(RMI) is computed by ultrasound score x menopausal score x CA 125 levels. RMI score of this patient was 36.
Patient was taken up for laparotomy proceeded with trans abdominal hysterectomy, bilateral salphingoophorectomy, bilateral cystectomy and hernioplasty . Specimens were sent to histopathological examinaton.

PATHOLOGICAL FINDINGS:

Received uterus with cervix with bilateral ovarian cysts (Figure 1) On gross examination, uterus with cervix appears unremarkable.Endometrial thickness was0.2cm, myometrial thickness was 1.5-2 cms with trabeculations.We separately received two ovarian cysts .One ovary showed large cyst measuring 9x7.5x3cms with grey white and glistening external surface. No breech was identified. On cut opening it extruded serous fluid and hemorrhage of about 5-6 ml . Cut surface showed 40% of solid and 60% cystic component. The solid area measured 5.5 x4 cms. Cut surface shows friable, variegated grey white to grey yellow tumor, soft to firm in consistency. Cystic areas measures 6.6 x 6 cms, with multiloculation. No papillary excrescence was noted. Cyst wall thickness was 0.4 cm(Figure 2) Attached tube measured 0.5 cm in length and the cut surface showed lumen .Other ovary showed a cyst measuring 4x3.5cms with no breech or papillary areas. On cut opening extruded serous serous fluid (2-3 ml). Cut surface showed multiloculated cyst. No solid or papillary areas noted. Residual ovarian parenchyma seen which measured 2x1.5cms.Other tube measured 0.4cm in length and its cut surface showed lumen.

Figure 1 Uterus with cervix with bilateral ovarian cysts and tubes

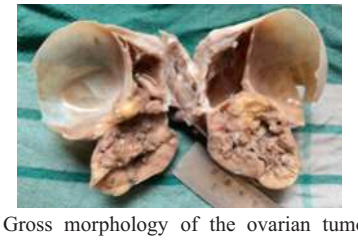

Figure 2 Gross morphology of the ovarian tumor with a large multilocular cystic component and a smaller variegated solid component Microscopy of the section studied shows cervix with chronic cervicitis and squamous metaplasia. Section studied from endometrium shows endometrial glands and stroma in disorderly proliferative phase.Myometrium shows adenomyosis. Sections from solid and cystic areas left ovary shows a well encapsulated tumour with tumor cells arranged predominantly in microfollicular, trabecular (Figure 5) , show call-exner bodies(figure 4).The individual cells are medium sized with eosinophilic cytoplasm round to ovalnuclei with vesicular chromatin, some of them showing longitudinal coffee-bean grooving psuedopapillary , insular and solid pattern(figure 3). Some microfollicular areas. Mitosis count is 6/10 HPF. No areas of necrosis were noted.Both fallopian tubes show normal histology.Sections from the right ovary shows cyst wall lined by ciliated columnar epithelium with focal papillary proliferation (Figure 6). It also shows scattered inflammatory infiltrates with congested blood vessels. No evidence of Serous tubal intraepithelial carcinoma(STIC)/maliganancy.

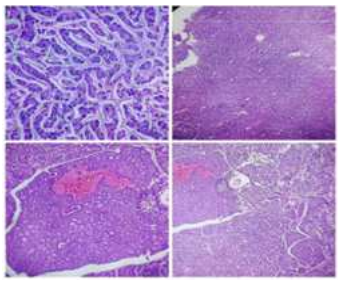

Figure 3 (a) Trabecular pattern (b)solid (c)micropapillary (d)insular

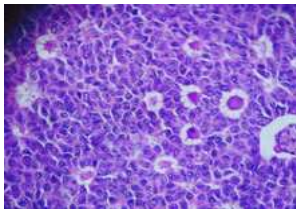

Figure 4 Call-exner bodies

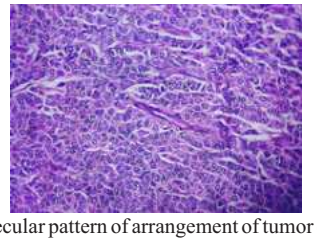

Figure 5 Trabecular pattern of arrangement of tumor cells

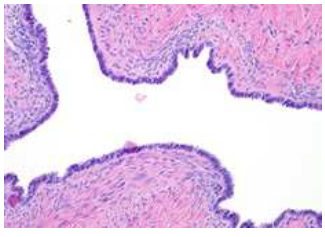

Figure 6 ovary showing cyst wall lined by ciliated columnar epithelium with focal papillary proliferation

DISCUSSION

Synchronous occurrence of primary cancers of the genital tract is rare and the incidence is reported to be approximately 1-2% .The majority of synchronous tumors occur in uterus and ovaries together. The significance of having synchronous tumors lies in the management and prognosis. Each type of tumor may require different treatment approaches, and the presence of multiple tumors can complicate the clinical course. Management decisions would typically involve a thorough evaluation of both tumors, including their size, location, histopathology, and any signs of malignancy.

The ovarian epithelial and stromal neoplasm are two different group of ovarian neoplasm described by World Health Organisation Classification of tumors(12). The surface epithelial tumors are the most common ovarian neoplasm ,whereas sex cord stromal tumors are relatively less commonly known.

Sex cord-stromal neoplasms of the ovary are a diverse group of tumors that arise from the ovarian stroma, which is the connective tissue that supports the ovary and includes the sex cords, structures involved in the development of ovarian follicles(11). They account for approximately 8% of all ovarian tumors and are relatively rare compared to epithelial ovarian tumors and have unique clinical and pathological features.

Ovarian GCTs are rare neoplasms characterized by their indolent behaviour and favourable prognosis. GCTs are derived from the granulosa cell layer of the ovarian follicles. They share many

morphological and and biochemical features with these cells. Additionally, theca cells, interstitial cells, and stromal fibroblasts have also been delegated as cells of origin for GCT. Normally, these cells proliferate in response to rising circulating gonadotropins and decline in response to circulating testosterone. They normally produce estradiol, sex steroids and peptides necessary for ovulation .

Serous cystadenoma of ovary represents 16% of all ovarian epithelial neoplasm.It is a benign entity, accounting for approximately two-thirds of benign ovarian epithelial tumors and occur in adult women of all ages with reported mean ages differing from 40-60 years. It is believed to arise from precursors derived from the ovarian surface epithelium or fimbriae. Serous cystadenoma of the ovary may occasionally show foci that meet the criteria for serous borderline tumor. If such foci represent <10% of the tumor volume , the tumor is designated as serous cystadenoma with focal epithelial proliferation(13).

On the basis of age of onset and clinicopathological characteristics, these tumours are subdivided into two distinct forms, the adult type and the juvenile type representing 95% and 5% of the tumours, respectively.

Approximately 97% of adult GCT harbour a somatic missense mutation in the FOXL2 gene (which is absent in juvenile). It represents an exciting advancement in molecular pathways of GCT. The deficiency of mismatch repair gene also contributes to the pathogenesis of GCT(14).

Most of the adult GCT present in post menopausal women, with a peak incidence between 50 and 55 years. However in our case, the patient was 59 years of age. Chromosomal abnormalities have been evaluated recently in granulosa cell tumors. These abnormalities include trisomy 12, monosomy 22, and deletion of chromosome 6, Peutz Jeghers syndrome and Potters syndrome which show a syndromic association with GCT of ovary. In the present case, chromosomal studies were advised to the patient at discharge(15).

The occurrence of postmenopausal bleeding in menopausal patients with granulosa cell tumors is a significant clinical finding. This bleeding is often attributed to the estrogenic activity of the tumor, which stimulates proliferative and hyperplastic changes in the endometrium. Consequently, the unopposed estrogen exposure may predispose these patients to develop Type 1 endometrial carcinoma.
Additionally, it's worth noting that a minority of granulosa cell tumors may secrete androgens. This can manifest clinically with symptoms such as clitoromegaly or hirsutism, although such presentations were not observed in the reported case series.

As evident in the presented cases, an array of histological morphologies is excibited by adult-type GCTs. Diffuse growth of oval cells with characteristic nuclear grooves ('coffee-bean' cells) are typical. Call-Exner body formation is typically seen in the microfollicular pattern of growth. The mitotic activity of these tumours is typically low, however increased mitotic activity of ≥ 4 MF/10 HPF is associated with a worse prognosis and increased risk of recurrence . Juvenile-type GCTs feature similar gross morphological features to their adult counterparts however typically lack the nuclear grooves seen in adult-type tumours and exhibit a higher mitotic rate . This relatively higher mitotic rate fits well with the apparent rapid cystic growth (and subsequent acute presentation) in the juvenile GCT cases of this series(16).

Granulosa cell tumors (GCTs) are indeed categorized as neoplasms of low malignant potential, distinguishing them from epithelial ovarian carcinomas. A variety of growth patters occur, most common pattern is diffuse in which tumor cells grow in sheets .Also often grow in cords, trabeculae , ribbon , gyriform ,nests. In microfollicular pattern (call-exner bodies) granulosa cells surround small spaces containing eosinophilic secretions. Occasionally large follicles (macrofollicular pattern)can be seen. One notable aspect of GCTs is their high detection rate, with approximately 80% of cases being diagnosed at stage I disease. This early detection contributes to a reported five-year survival rate exceeding 90%. Immunocytochemically, GCT is usually positive for vimentin, inhibin, calretinin, CD56 and WT1 (17).

Despite the favorable prognosis, recurrence following primary surgery can occur in approximately 25% of patients. Notably, recurrences can manifest even decades after the initial diagnosis, underscoring the need for long-term surveillance and follow-up care.

Additionally, staging procedures are typically performed during surgery to assess the extent of the disease and guide further management. This may include peritoneal washings, sampling of the omentum, and peritoneal biopsies. However, there is no consensus regarding the role of lymphadenectomy (removal of lymph nodes) in the management of GCTs.

Lack of evidence based predictive and prognostic factors continues to be a deterrent in accurately predicting the biological behaviour of individual GCTs. However long-term lifelong follow up including physical/pelvic CT scan and tumor markers as available is recommended in all patients with GCT as delayed tumor recurrences beyond 5 years are characteristic of this disease.

CONCLUSION

Female genital tract synchronous tumours are uncommon, comprising just 0.7% to 1.8% of all tumours in the female genital system. Synchronous ovarian tumours are rare, and majority of the cases reported are malignant. The management of synchronous ovarian tumors requires a comprehensive approach due to their rarity and the potential complexity involved. Early diagnosis and reporting of such cases helps in better understanding of synchronous ovarian neoplasms, which may impact in the management strategies and prevent complications.

Granulosa cell tumor of ovary is a rare ovarian entity that arises from the sex cord-stromal tissue of the ovary, with low malignant potential. Complete workup with the help of imaging and tumour markers can support the diagnosis. After histopathological report serum inhibin test as a tumor marker of granulosa cell tumor is usually run in retrospect. An endometrial assessment should be done once the diagnosis of granulosa cell tumors is confirmed. Though granulosa cell tumour is a tumour with low malignant potential, but it has a high chance of recurrence even years after apparent clinical cure of the primary tumor. So lifelong follow up with clinical examination and tumor markers like inhibin B is recommended. Other than stage of the disease, the other prognostic factors like age, tumor size, rupture of tumor, mitotic activity are not able to predict recurrences accurately. Adequate counseling followed by long-time follow-up with specialists in the multidisciplinary team is recommended to ensure thorough recovery and proper care. In patients with desire for fertility, a fertility preserving surgery with endometrial biopsy is safe and chemotherapy may be used if indicated without adversely affecting the chance and outcome of future pregnancies.

Serous cystadenoma ovary is a common benign ovarian tumor with an excellent prognosis that originates from epithelial cells. Due to rarity of such lesions, the knowledge of its actual etiopathogenesis and epidemiology is limited. Histopathological diagnosis of such neoplasms becomes very important, to provide appropriate treatment based on the individual biological characteristics of each component of synchronous tumors .

CONFLICTS OF INTEREST

There are no conflicts of interest.

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