Case Report

Carcinoid tumor of the ovary: A mysterious puzzle

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ABSTRACT

Carcinoid tumor of the ovary is a rare neoplasm that may present as a solid mass or combined with mucinous tumors or teratomas. Primary ovarian carcinoid represents <0.1% of ovarian malignancies. These tumors are often unilateral presenting as a solid mass and vary from microscopic to very large tumors. Metastatic ovarian carcinoid tumors are seen to be bilateral in most cases. Involvement of the ovary from gastrointestinal carcinoid is rare with no hepatic or peritoneal seedlings. Ovarian carcinoid tumors commonly occur in perimenopausal and postmenopausal women. Surgical removal of the tumor is the standard treatment modality. Tumor size and the presence of metastasis are necessary to plan the treatment modality. We herein report a case of carcinoid tumor of the ovary in a 55-year-old female, which we thought was a dermoid cyst of the ovary and turned out to be carcinoid after detailed immunohistochemical analysis.

Key words: Carcinoid, Metastasis, Ovary, Postmenopausal, Tumors

The term "Carcinoid" was coined by Oberndorfer in 1907 for the hormonally active tumors and carcinoma-like tumors having an insidious course than other malignancies. Carcinoids are rare neuroendocrine tumors accounting for 0.3% of all carcinoid tumors and 0.1% of all malignant ovarian tumors [1,2]. Neuroendocrine tumors are mostly found in the lung or gastrointestinal tract. Primary ovarian tumors especially carcinoid are extremely unusual [1]. Almost 40–45% of ovarian carcinoids are associated with carcinoid syndrome with a cluster of findings such as cutaneous flushing, cyanosis, diarrhea, abdominal cramps, bronchoconstriction, and carcinoid heart disease. The symptoms of carcinoid syndrome are due to the production of serotonin, histamine, tachykinin, kallikrein, bradykinin, motilin, substance P, corticotrophin, and prostaglandins [3,4]. Carcinoid tumor of the ovary generally shows a single layer of germ cells that are mostly seen to be associated with teratoma [5]. They originate from the enterochromaffin cells in mature cystic teratoma which arise from the epithelium of the gastrointestinal or respiratory tract. Carcinoids are frequently diagnosed in areas such as the ileum and appendix. Mature cystic teratomas are benign, but ovarian carcinoids are considered to be malignant and can occasionally metastasize [5].

We report a case of ovarian carcinoid in a 55-year-old female along with clinical history, histopathological findings, immunohistochemical analysis, and treatment done.

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CASE REPORT

A 55-year-old female was admitted for abnormal uterine bleeding for 1-month duration. She presented with the complaints of abdominal pain, on and off, for 1 month. There was no history of the passage of clots. Her past obstetric history was Para 2, Live 2, and Abortion 2. Her previous menstrual history was normal with a 3/30 days cycle. Both deliveries were normal full-term vaginal delivery. The last childbirth was 24 years back. She attained menopause 13 years back. The past obstetric history included 2 spontaneous abortions, for which she underwent dilatation and curettage at 2 months and 50 days, respectively. The products of conception were not sent for any genetic or pathological examination. She was a known diabetic for 18 years on insulin and under good glycemic control.

On examination, she was alert and oriented. There was no pedal edema or generalized lymphadenopathy. Her vitals were as follows: Blood pressure − 120/80 mmHg, pulse rate – 107 beats/min, respiratory rate – 16/min, temperature − 98.6°F, and oxygen saturation − 96% at room air. Cardiovascular, respiratory, and central nervous system examinations were all normal. Abdomen palpation was soft and non-tender. Per vaginal examination revealed normal size retroverted uterus, fornices were free and non-tender, and the cervix was bulky and non-tender. There were no ulcers on the external surface of the cervix.

The ultrasonogram of the abdomen and pelvis revealed a well-defined cystic lesion of size 9.1×7.5×8.5 cm with free-floating

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internal echoes and a few echogenic mural nodules with calcification noted in the left adnexa. No obvious demonstrable vascularity was noted within the mural nodules (Fig. 1). Ovarian parenchyma was not separately visualized which favored the diagnosis of dermoid cyst, suggesting further evaluation.

Magnetic resonance imaging plain study of the abdomen and pelvis was done which showed the uterus anteverted and anteflexed and measuring 7.0×3.2×4.0 cm. There were no focal myometrial or endometrial lesions. A unilocular cyst was noted with predominant fatty components, dermoid mesh, and plug in the left adnexa measuring 8.4 cm×8.8 cm ×7.0 cm which was consistent with the left ovarian dermoid cyst. Few scattered calcifications were noted within the cyst. Other abdominal and pelvic organs appeared normal. With the above reports, the patient was advised total abdominal hysterectomy with a bilateral salpingo-oophorectomy procedure.

The patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The patient was positioned in a supine position under spinal anesthesia, Foley's catheter was placed under aseptic precautions, and clear urine was drained. The abdomen was opened in layers using Pfannenstiel incision. The uterus was normal in size. A cyst measuring 7×8 cm was identified involving the left ovary and was removed without disturbing the cyst wall. Bilateral fallopian tubes and the right ovary appeared to be normal. The bowel was adherent on the left broad ligament and the left infundibulopelvic ligament. Myoma screw was applied. The left ovarian cyst was clamped and removed in toto along with the intact pedicle. Pedicle was ligated. The right and the left infundibulopelvic ligaments were clamped, cut, and ligated. A bilateral uterine artery was identified, clamped, cut, and ligated. Uterovesicular fold was identified and incised. The urinary bladder was pushed down. The anterior peritoneum was incised. Bilateral uterosacral-Mackenrodt's ligament was clamped, cut, and ligated. A curved clamp was applied and incised. The uterus along with bilateral ovaries and the ovarian cyst was delivered out. The vault was closed using Vicryl no. 1. Hemostasis was achieved. The catheter was checked, and it drained clear urine. The abdomen was closed in layers. Rectus was closed by Vicryl no.1 and the skin was closed using monocryl followed by dressing. Vital signs were checked and were stable. Both intra- and postoperative periods were uneventful. The patient was discharged in clinically stable condition on the 4th postoperative day.

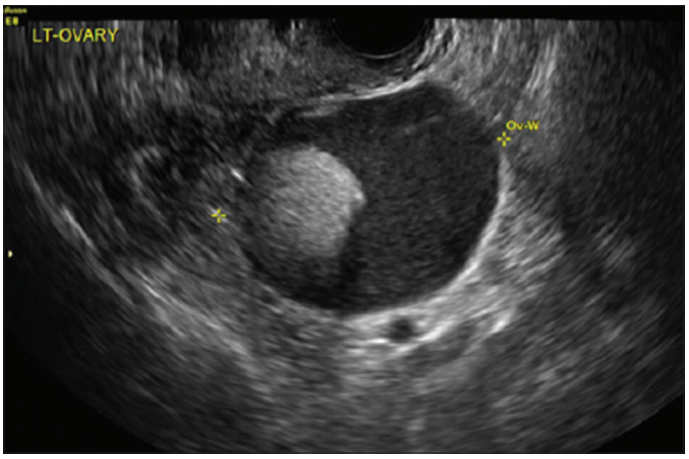

Figure 1: Ultrasonogram image of left ovarian cyst

The operated specimen was sent for histopathology examination. Gross examination revealed a hysterectomy with bilateral salpingo-oophorectomy specimen, the uterus with cervix measuring 8×4×2 cm. Ectocervix was hypertrophied with no visible ulcers or pigmentation. The endocervical canal measured 2.2 cm and the endometrial cavity measured 3.5 cm lined by pale brown endometrium of 0.4 cm. There were no polyps or myometrial lesions. The average myometrial thickness was 1.4 cm. The right fallopian tube measured 5 cm in length and the right ovary measured 2.5×1.5×0.5 cm. The left fallopian tube measured 4 cm in length and the attached ovary measured 3×1×0.5 cm with a cystic structure measuring 8×8×6.5 cm. The external surface of the cyst appeared smooth, gray-white with no solid proliferations. The cut surface of the cyst revealed white pultaceous material with a tuft of hair. The cyst was uniloculated with a focal solid gray-white area measuring 1.5×1 cm. Multiple sections were given from the specimen for histopathological examination.

On microscopy, sections from the uterus and cervix showed normal lining epithelium, muscle bundles, and congested blood vessels. The right fallopian tube showed intact epithelium and the attached ovary showed multiple corpora albicantia with many congested vessels. The left fallopian tube showed intact epithelium. Sections from the left ovarian tissue with cysts contained structures derived from the germinal epithelium. It showed skin with adnexal structures, hair follicles, adipose tissue, and glandular structure. Sections from the gray-white solid area showed papillary structure with central fibrovascular core and reticulated pattern of tumor cells (Fig. 2a and b). The tumor cells lining the papillae had round to oval pleomorphic, vesicular nuclei containing coarse chromatin and inconspicuous nucleoli with amphophilic to eosinophilic cytoplasm (Fig. 2c). Atypical mitotic activity of 2–4 mitosis per high power field was noted. There were no areas of necrosis. Impression for the left ovarian cyst was given as mature cystic teratoma with an insular pattern of carcinoid tumor.

Immunohistochemistry was suggested for confirmation. Immunohistochemistry was done using various markers, and it revealed alpha-fetoprotein - Negative, Cytokeratin 7 - Negative, Glypican-3 - Negative, Synaptophysin - Positive (Fig. 3b and c), Chromogranin A - Positive in <5% cells (Fig. 3d), Cytokeratin 20 - Negative, cluster differentiation 56 (CD56) - Positive (Fig. 3a), and Ki 67 labeling index (proliferation marker) – 5–7%. Impression was given as a neuroendocrine tumor of the ovary.

DISCUSSION

Carcinoid tumor of the ovary originates from the germ cells and are well-differentiated neuroendocrine tumors resembling the neuroendocrine tumors arising from the pulmonary and gastrointestinal tracts [3,6]. Ovarian carcinoids arising as a primary tumor from the ovary are very rare and they represent 0.3–1% of all carcinoid tumors and <1% of all ovarian tumors [2,3,6,7].

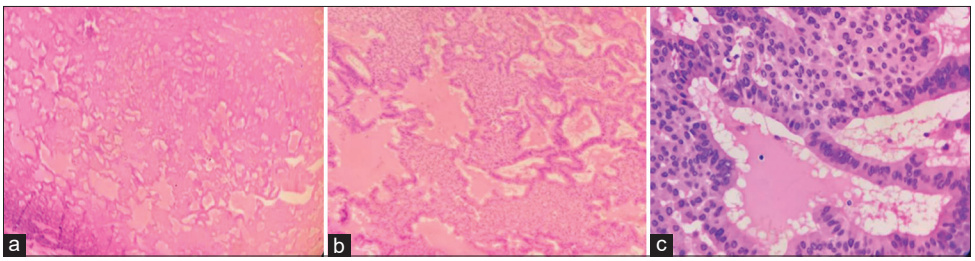

Figure 2: (a) Photomicrograph showing scanner view of the ovarian tumor cells (H&E stain, 4x); (b) arranged in papillary architecture (H&E stain, 10x); (c) tumor cells are large with oval nuclei, coarse granular chromatin and inconspicuoud nucleoli (H&E, 40X)

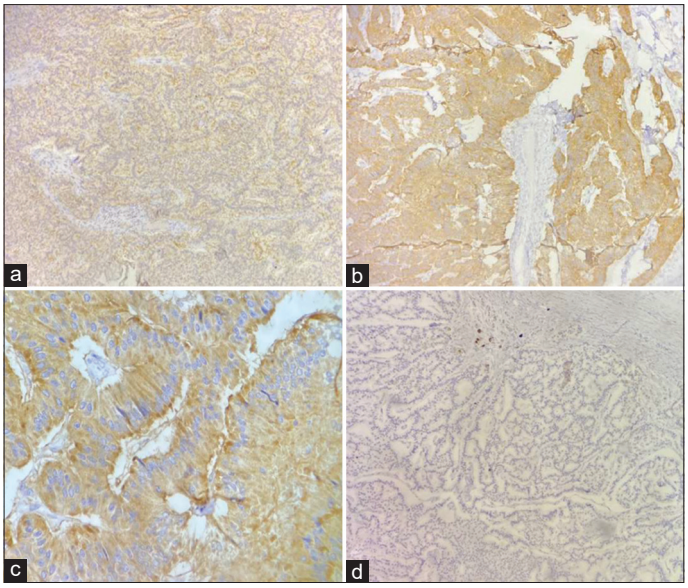

Figure 3: Photomicrograph showing (a) cluster differentiation 56 (CD56) positive tumor cells (CD56 marker, ×10); (b) synaptophysin-positive tumor cells (synaptophysin, ×10); (c) synaptophysin-positive tumor cells (synaptophysin, ×40); (d) chromogranin positivity in <5% of tumor cells (chromogranin, ×10)

Ovarian cancers are the fifth cause of cancer death in women and have similar genetic pathways as in breast cancer [6]. These tumors are invariably unilateral and affect perimenopausal and postmenopausal women [2,7].

Neuroendocrine tumors are rare tumors arising from the amine precursor uptake and decarboxylation cells that originate from the neuroectoderm. Most commonly seen neuroendocrine tumors include pheochromocytoma, medullary carcinoma of the thyroid, Merkel cell carcinoma, carcinoid tumors, pancreatic islet cell tumors, and neuroendocrine tumor of the gynecological tract. Neuroendocrine tumors of the ovary include well-differentiated indolent tumors known as carcinoids and poorly differentiated high-grade tumors (small-cell and large-cell neuroendocrine tumors) [2,4,5]. Carcinoid tumors originate from the derivatives of the embryological primitive gut and are hence neuroendocrine tumors [7]. These tumors can be "functioning" or "non-functioning." The functioning type of carcinoid tumors presents with signs and symptoms which appear due to the secretion of biopeptides and the non-functioning types generally present as a mass [8,9].

World Health Organization has recognized four subtypes of ovarian carcinoid depending on the histopathological features, namely, stromal, insular, trabecular, and mucinous [1,2]. Insular and trabecular subtypes are the most commonly identified subtypes. In the insular type of ovarian carcinoid, the tumor cells appear as nests in a pseudo-cribriform pattern in the periphery, and the trabecular type shows tumor cells in parallel trabeculae and ribbons [1,6]. Insular subtype is often associated with carcinoid syndrome and only in 30% of cases [8]. The mucinous type, the most aggressive type, shows tumor cells arranged in a glandular pattern, and the glands are lined by goblet cells that float inside mucin pools [6,8,9]. Strumal type shows tumor cells arranged like thyroid follicles. Atypical carcinoid is the term used for carcinoid tumors that show confluent growth, crowded architecture with glandular pattern, and cribriform areas [6,9].

Immunohistochemistry aids in the diagnosis of primary ovarian carcinoid. The most common classic markers include synaptophysin and chromogranin. CD56 is positive but a non-specific marker. Caudal-related homeobox gene 2 and thyroid transcription factor-1 are important markers used to differentiate between primary and secondary carcinoid tumors. Estrogen and progesterone receptors are invariably negative [4,5,7].

Carcinoid tumors of the ovary secrete many neurohumoral substances such as histamine, serotonin, tachykinin, bradykinin, motilin, substance P, corticotrophin, kallikrein, and prostaglandins. Exposure to these substances regularly results in carcinoid syndrome which presents with a classic triad of wheezing, diarrhea, and flushing of the face and arms, mostly seen in functioning ovarian carcinoid. Large ovarian carcinoids are commonly seen to be associated with carcinoid syndrome. 5-hydroxyindoleacetic acid, a metabolite of serotonin can be measured in a 24-h urine sample and this biochemical test can be used as a marker for the diagnosis of carcinoid tumors [1,8,10].

Surgical treatment is the best and standard modality of treatment in these cases. Chemotherapeutic regimens help in palliation and reduction of symptoms only. The prognosis and survival of the patient depend on the primary site and size of the tumor, and the presence or absence of metastasis. In general, the prognosis of carcinoid tumors of the gastrointestinal tract is better than the carcinoid of the ovary. When there is an association with carcinoid syndrome, the prognosis is poorer. Invasion of cyst wall, disseminated tumor, and intraoperative rupture of the tumor dispose an unfavorable prognosis [4,5,7]. Yet, the tumor prognosis is highly unpredictable. The aggressiveness and malignant transformation of the tumor are indicated by the

presence of atypical mitotic activity and necrosis. Tumor size <1 cm requires regular follow-up, and the 5-year survival rate in case of metastatic disease is about 67%. In metastatic cases, the treatment is palliative as there is no therapy that found effective until date [1,4,8].

CONCLUSION

Carcinoid tumor of the ovary is a rare entity accounting for 0.1% of ovarian neoplasms and 0.8–5% of carcinoid tumors. Ovarian carcinoid tumors are challenging when there is multiple organ involvement. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the most common surgical treatment, with or without postoperative chemotherapy are available treatment options. Streptozocin and 5-fluorouracil are the most commonly used regimens for metastatic carcinoid tumors. Radiological and pathological workup along with the immunohistochemical analysis helps in the diagnosis of ovarian carcinoids. Surgical excision with or without chemotherapy is the mainstay of treatment. Extensive analysis and reporting of this entity is needed to dive into the study of newer therapeutic modules and the impact on prognosis in these patients.

AUTHOR'S CONTRIBUTORS

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