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CASE REPORT

Primary Extra-Uterine Endometrial Stromal Sarcoma and Synchronous Breast Cancer: A Double Whammy: A Case report

Pavneet Kohli[1] · Prasanth Penumadu[1] · Neelesh Srivastava[1] · Bheemanathi Hanuman Srinivas[2] · Vidyalakshmi Rangarajan[2]

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Abstract
Endometrial stromal sarcoma is an uncommon gynecological tumor. Extra-uterine endometrial stromal sarcoma (EESS), the extra-uterine variant of its relatively more common counterpart, is even rarer with only few documented case reports. We report a case of a 40-year woman with bilateral adnexal tumors and synchronous invasive ductal breast carcinoma (IDC) posing a diagnostic challenge. The histopathology of specimen confirmed the diagnosis of EESS in the absence of florid endometriosis and synchronous hormone-positive infiltrating duct cancer in the breast. Patient was started on adjuvant endocrine therapy and is disease free at the end of 2 years.To the best of our knowledge, this is the first documentation of synchronous presentation of IDC and EESS, highlighting the possible role of hyper-estrogenemia as an etiological factor.

Keywords Extra-uterine endometrial stromal sarcoma · ESS · Uterine sarcoma · Uterine rare tumors

Introduction

Endometrial stromal sarcoma (ESS) is a rare malignancy constituting less than 1% of all uterine malignancies. The extra-uterine endometrial stromal sarcoma (EESS) is an even rarer entity and poses a diagnostic dilemma due to its non-uterine origin and uncharacteristic histological profile and pattern of invasion [1]. Absence of tumor within the uterus is perhaps the most essential criteria for diagnosing EESS. As the name suggests, the etiology of EESS is attributed to underlying endometriosis, with more than 60% reported cases of EESS associated with foci of endometriosis [1, 2].

We report this case of an EESS with a synchronous hormone-positive invasive ductal breast carcinoma (IDC). To the best of our knowledge, this is the first case of synchronous presentation of these two tumors and can shed some light on an underlying hyper-estrogenemic state as the causative factor for EESS.

Case Presentation

A forty-year-old nulliparous woman, with polycystic ovarian disease (PCOD), presented with the complaints of abdominal pain for ten days duration along with history of vomiting and loose stools. She complained of shortness of breath on exertion and bilateral lower limb swelling. She gave history of a painless, gradually progressing 2 cm lump in the breast for the past two years. She attained menarche at the age of 11 years and had irregular cycles subsequently.

Breast examination revealed a 1.5-cm firm mobile mass in the right lower inner quadrant. An abdominal examination revealed a firm abdomino-pelvic mass. Per vaginal examination revealed a normal cervix and fullness in the left lateral fornix. On per rectal examination, a hard mass was palpable over the anterior wall of the rectum.

Dr. Pavneet Kohli is an Assistant professor, Department of Surgical Oncology, JIPMER, Puducherry, India; Dr. Prasanth Penumadu is an Associate professor, Department of Surgical Oncology, JIPMER, Puducherry, India; Dr. Neelesh Srivastava is a senior resident, Department of Surgical Oncology, JIPMER, Puducherry, India; Dr. Bheemanathi Hanuman Srinivas is an Additional Professor, Department of Pathology, JIPMER, Puducherry, India; Dr. Vidyalakshmi Rangarajan is a senior resident, Department of Pathology, JIPMER, Puducherry, India.

✉ Prasanth Penumadu
drpenumadu@gmail.com

[1] Department of Surgical Oncology, JIPMER, Puducherry 6050006, India

[2] Department of Pathology, JIPMER, Puducherry 605006, India

A contrast-enhanced CT scan (CECT) revealed a heterogeneously enhancing 8.5 x 9.7 cm well-defined circumscribed solid cystic lesion in right adnexa and 8.2 x 8.4 cm solid cystic lesion in the left adnexa. Both ovaries were not separately visualized and the lesion in the pelvis showed a loss of fat planes with uterus, bladder and sigmoid colon. The lesion was compressing the ureters and causing bilateral hydrouretronephrosis. (Fig 1.). A bilateral mammogram revealed diffuse microcalcifications present over the entire right breast.

Carcinoembryonic antigen was 0.5 ng/ml and CA 125 was 390.3 U/ml. An ultrasound guided biopsy from the pelvic mass revealed a spindle cell tumor with immunohistochemistry (IHC) strongly positive for vimentin and negative for inhibin and calreticulin of the ovary. A biopsy of the right breast lump revealed a luminal A infiltrating ductal carcinoma.

Colonoscopy revealed a fleshy friable mass seen at 10 cm from anal verge. Biopsy was suggestive of an endometrial stromal sarcoma. The tumor cells were positive for IHC with CD10, ER, cyclin-D1 and negative for Pan CK.

Patient was discussed in a multidisciplinary tumor board and was planned for surgery.

Intraoperative findings revealed a 1.5-cm lump in the right lower inner quadrant of the breasts with few enlarged level 1 axillary nodes. Laparotomy revealed bilateral solid cystic adnexal masses adherent to rectum with dilated bilateral ureters. The left ureter was infiltrated by tumor. Peritoneal deposits were present on the ileo-colic mesentery infiltrating the ileum. Deposits were also noted in transverse mesocolon infiltrating the colon.

Patient underwent a total abdominal hysterectomy, bilateral salpingo-oopherectomy, infra-colic omentectomy, anterior resection of the rectum, limited resection of ileo-colic segment of the bowel with ileo-ascending colon anastomosis, partial excision of left ureter and Boari flap repair and bilateral ureteric stenting and a right modified radical mastectomy.

Histopathology assessment of the intraoperative specimen revealed features of bilateral low-grade extra-uterine endometrial stromal sarcoma. Multiple sections from bilateral ovarian cysts showed features of low-grade endometrial sarcoma. The endometrium of the uterus showed normal proliferative epithelium and the myometrium revealed of adenomyosis. Eleven regional lymph nodes were free of tumor. Serosal aspect of appendix and rectum showed infiltration by low-grade ESS. Deposits over the right colon, transverse colon, mesocolon and omentum showed tumor deposits (Fig. 2). Microexamination of breast revealed a 1.5-cm IDC with 90% comedo DCIS and no lymph node spread was noted when evaluation of 16 lymph nodes was carried out. She was started on adjuvant letrozole and is disease free at the end of two years.

Discussion

EESS is an extremely rare diagnosis with only a few cases reported till now. The extra-uterine location, non-gynecological symptoms and signs at presentation, and confounding histologic features can pose a diagnostic challenge. The

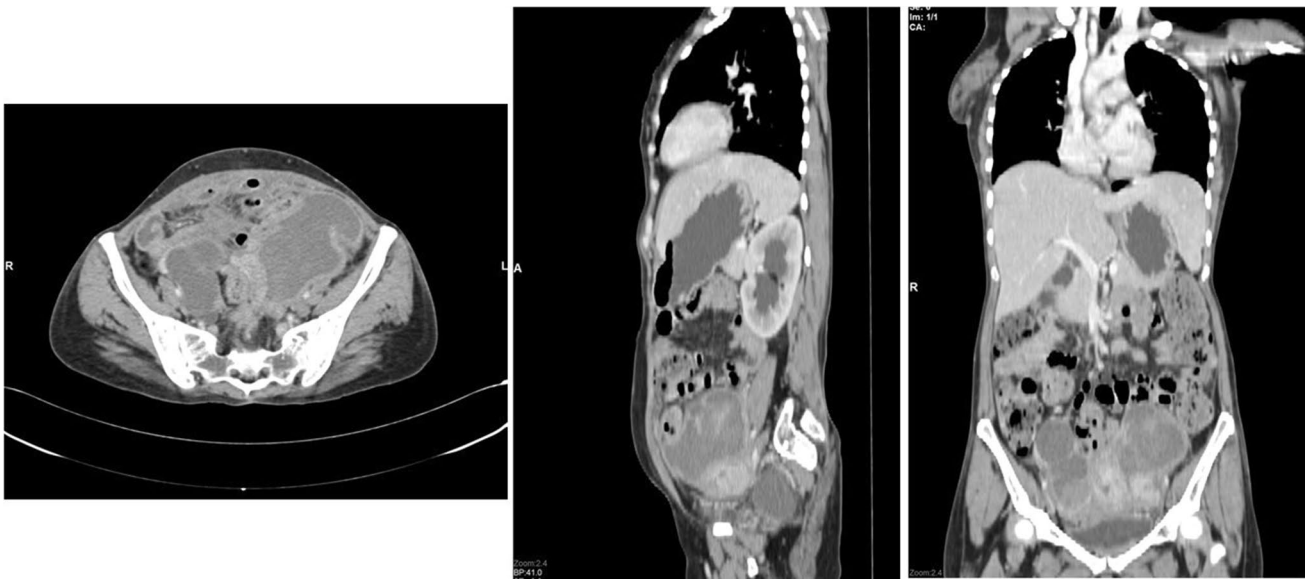

Fig. 1 CECT scan revealing a heterogeneously enhancing well defined circumscribed solid cystic lesion in bilateral adnexa. Both ovaries were not seen separately from the lesion in pelvis showed a loss of fat planes with uterus, bladder and sigmoid colon

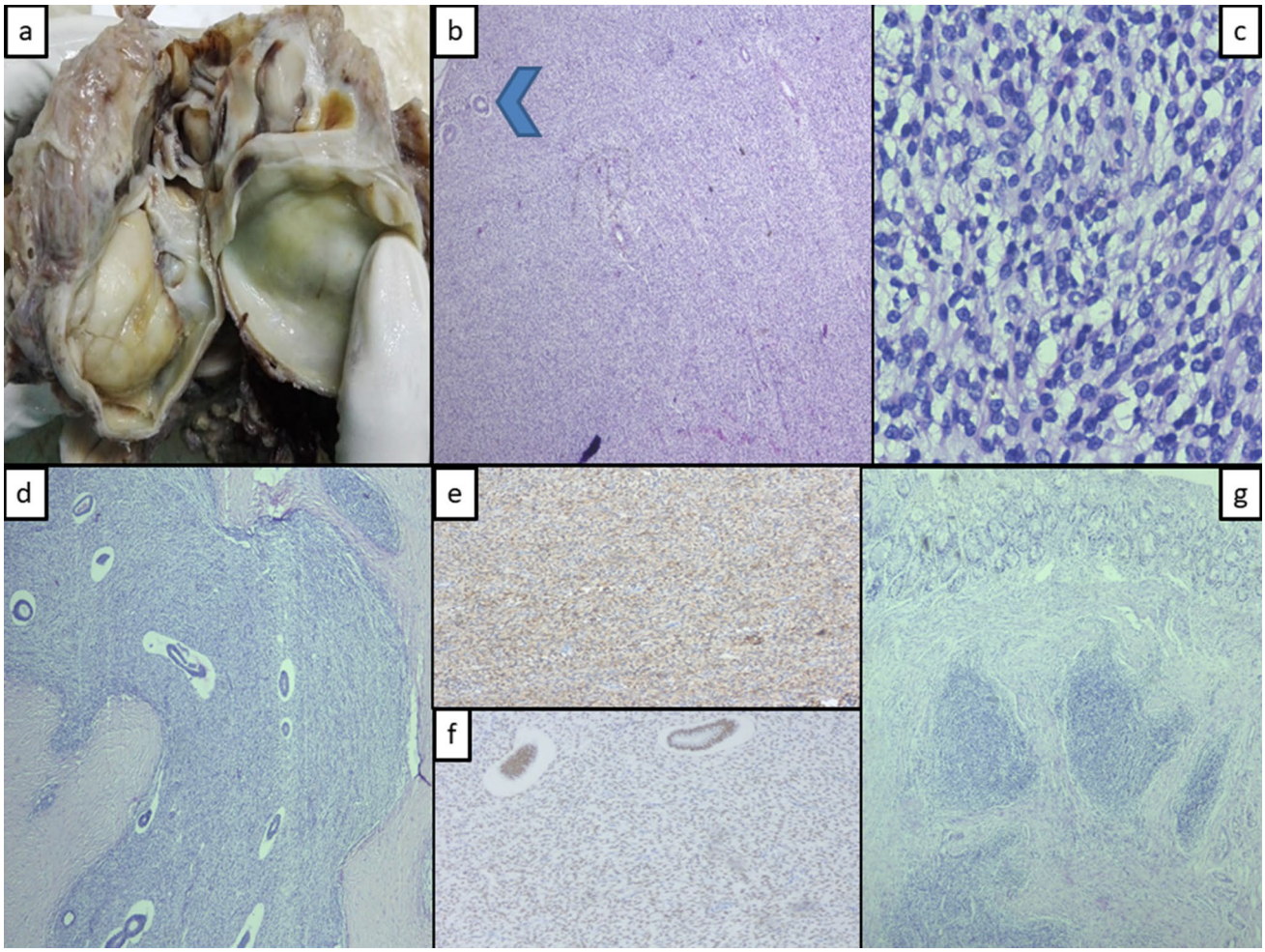

Fig. 2 Photomicrographs of **a** gross specimen of enlarged right ovary shows both solid and cystic areas: **b** Histopathology show tumor composed of sheets of spindle-shaped cells admixed with entrapped benign endometrial glands(arrow head)(H&EX100): **c** High power view reveals tumor cells with indistinct cytoplasm, oval nuclei with mild to moderate atypia(H&EX200): **d** tongue-like permeation of endometrial stroma and glands invading ovarian parenchyma (H&EX100): (e nd f) IHC with CD10 and ER show strong positivity in stromal and entrapped benign glands (DABX100 and DABX200): **g** sections from colon also show similar submucosal deposits (H&EX200)

ever evolving and changing terminology and classification system for ESS and related tumors adds to the confusion in diagnosis.

The age of the patients ranges from fourth to seventh decade with sixth decade being the median age [1]. Common presentations usually include abdominal/pelvic mass and pain, abnormal vaginal bleeding, altered bowel habits, urinary symptoms like hematuria and incontinence and occasionally small bowel obstruction [1, 2]. Masand et al. documented the most common site to be the peritoneum, (58.7%) ovaries (39.6%), bowel wall (44.4%), pelvis (31.7%) and vagina (9.5%) [1].

Previous reports have stated that almost 50% of EESS are associated with endometriosis, and these tumors may arise from stroma of ectopic endometrium [3]. Endometrial stromal sarcomas are mainly intrauterine; hence, the uterus should be thoroughly examined to exclude ovarian metastasis from the uterus. At times, differentiating a primary ovarian ESS from ovarian metastases can be challenging as both can present as bilateral involvement and in the background of ovarian endometriosis [3].

In reports where there is lack of associated endometriosis, origin of tumor is believed to be from gland-poor foci of endometriosis (stromal endometriosis) or de novo transformation from coelomic multipotent epithelium. Hyperestrogenemia is another etiological factor associated with EESS. Exogenous estrogen administration in the form of hormone replacement therapy has been associated with few case reports [1]. In our case, the patient had risk factors for hyper-estrogenemia like early menarche, nulliparity and PCOD. This may be responsible for synchronous

presentation of both the hormone-positive breast cancer and EESS in the absence of florid endometriosis.

The differential diagnosis varies depending on the location of the tumor and can include sex cord stromal tumors of the ovary, gastrointestinal stromal tumor in the abdominal cavity or solitary fibrous tumor.

Treatment guidelines are similar to the uterine counterparts. Cytoreductive surgery with R0 resection is the first line of treatment in these patients. The role of adjuvant hormonal therapy and the effective duration is still debatable. Although the evidence is weak, the overall response rate of endometrial stromal sarcoma to aromatase inhibitors is 67% [4]. Radiation and chemotherapy are usually reserved for recurrent disease.

Masand et al found that low-grade EESS was indolent and behaved similar to low-stage uterine ESS but had a greater chance of developing recurrences [1]. Other case reports also favor an indolent growth pattern of these tumors [3].

Various clinical and histologic features like primary tumor location, tumor size, vascular invasion, mitotic index, number of tumor sites (single/multiple) have been studied but do not show a detrimental effect on long term outcomes [1, 3]. The presence of high-grade cytological features or dedifferentiation is, however, associated with worse prognosis [1].

Conclusion

Extra-uterine low-grade endometrioid stromal sarcoma (EESS) is an exceedingly rare tumor with nonspecific presentation and can offer a diagnostic dilemma. Hyper-estrogenemia could be an etiological factor in the absence of endometriosis.

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About the Author

Pavneet Kohli is a Surgical Oncologist currently working as an Assistant Professor in Department of Surgical Oncology, JIPMER, Pondicherry, India. His interests include Gynecological and Breast Malignancies. He has extensive experience in advanced ovarian and endometrial malignancies with special interest in Cytoreductive Surgery and HIPEC in recurrent ovarian cancers. He has several publications in Pub Med indexed Journals and has presented various papers at several national and international conferences. He is passionate about Women Health and makes continuous efforts to engage with the community on the same.