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Case report

Serous borderline tumor of the ovary with isolated cardiophrenic lymph node spread at diagnosis

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1. Introduction

Borderline ovarian tumors are epithelial neoplasms with the capacity for intraperitoneal spread, whose indolent nature renders them distinct entities from low-grade serous carcinomas. The subcategory of serous borderline tumors makes up approximately 10% percent of all ovarian neoplasms. Serous borderline tumors show more epithelial proliferation and hierarchical branching than benign serous cystadenomas, but lack the stromal invasion, cytological atypia, and increased mitotic index seen in low-grade serous carcinomas. Despite lack of invasion, serous borderline tumors have the propensity to spread within the peritoneal cavity. (Chamberlin et al., 2001) They are commonly diagnosed at a younger age than low-grade serous carcinoma, with a mean age at diagnosis of 42, and at an earlier stage, with 75% of tumors diagnosed at FIGO stage I. (Chamberlin et al., 2001; Tan et al., 1994) The prognosis of serous borderline tumors is generally excellent. Survival of patients with stage I disease is no different than the general population and survival of patients with extra-ovarian implants is over 95%. (Chamberlin et al., 2001)

Spread of serous borderline tumors, when present, is primarily intraperitoneal. Interestingly, involvement of regional lymph nodes has been described as a relatively common finding. In one study of 169 patients, 9% of pelvic and paraaortic staging lymph node biopsies were positive for borderline tumor. (McKinnon et al., 1998) However, spread to distant lymph nodes is far less common with less than 1% of cases diagnosed as stage IV at the time of surgery. (Morice et al., 2001; Seidman and Kurman, 2000) Previous reports have documented recurrences of borderline serous tumor in the cervical, scalene and internal mammary lymph nodes. To our knowledge, supradiaphragmatic lymph node involvement by serous borderline tumor at the time of initial surgery has not been previously reported. (Lesieur et al., 2011; Abu-Hijleh et al., 1995) Cardiophrenic lymph node involvement has been previously documented in two cases of low-grade serous carcinoma, but never in association with borderline serous tumors. (Zanetta et al., 2001) Here we report the first case of serous borderline tumor with cardiophrenic lymph node involvement at the time of initial surgery.

2. Case summary

A 44-year-old G0 presented to a new gynecologist reporting 6 months of increasing urinary frequency and pelvic pressure. Her medical and surgical history are notable for a body mass index of 26, 12 years of oral contraceptive use, and no prior surgeries. Her family history is notable for two maternal aunts with breast cancer and maternal ovarian cancer at age 60. A pelvic ultrasound was obtained given her symptoms and family history showing bilateral adnexal masses. A subsequent pelvic magnetic resonance imaging demonstrated bilaterally enlarged adnexa, with the left measuring 9.5 × 6.1 × 7.4 cm and right measuring 9.6 × 5.1 × 7.6 cm (Fig. 1A).

She was referred to a gynecologic oncologist and tumor markers were notable for a CA-125 of 1,053 U/mL, CA-19–9 of 64 U/mL, and CEA of 2.6 ng/mL. Repeat pelvic ultrasound showed multiseptated cystic masses on both adnexa, each with abundant solid areas and color flow (Fig. 1B). Computed tomography (CT) scan of the abdomen and pelvis re-demonstrated bilateral cystic and solid pelvic masses as well as

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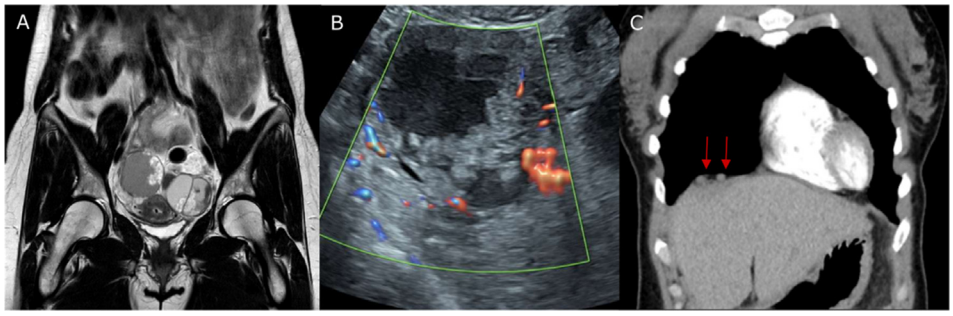

Fig. 1. A) Pelvic MRI showing bilateral complex masses with solid and cystic components B) Transvaginal ultrasound demonstrating a multiseptated cystic mass of the right ovary with abundant solid areas and color flow C) Chest CT showing several prominent cardiophrenic lymph nodes measuring up to 14 × 9 mm.

omental stranding and trace ascites. CT scan of the chest demonstrated several prominent cardiophrenic lymph nodes measuring up to 14 × 9 mm (Fig. 1C). Her physical examination was unremarkable. She was counseled that these imaging findings were concerning for malignancy and a surgical procedure was recommended.

The patient was taken to the operating room for a diagnostic laparoscopy with a plan for surgical staging based on intraoperative frozen section results. Laparoscopy revealed a normal upper abdomen with mild granularity of the omentum. Assessment of the pelvis revealed bilaterally enlarged adnexa (up to 10 cm) with abundant surface papillary projections. A frozen section biopsy of the right ovary was consistent with serous borderline tumor. The decision was then made to proceed with laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and *trans*-diaphragmatic removal of enlarged cardiophrenic lymph nodes. In order to remove the cardiophrenic lymph nodes, a *trans*-diaphragmatic incision was made 2 cm right lateral to the falciform ligament and 2 cm dorsal to where the diaphragm starts at the costal margin. The anterior packet of cardiophrenic lymph nodes was then palpated and excised completely with a LigaSure device. The packet of lymph nodes contained a least 3 firm and enlarged lymph nodes. The defect in the diaphragm was then closed with several 0 Ethibond sutures, which were placed in a horizontal mattress fashion. At the time of closing the final suture, the patient was in Trendelenburg positioning and all air was evacuated from the chest using a red rubber catheter with the tip immersed in saline during a prolonged positive pressure breath. The catheter was removed as the final stitch was tied down. The closure was airtight, and the lung parenchyma was not injured during the procedure. The superficial part of the closure was performed with 3–0 Vicryl suture. Surgery was uncomplicated and the patient had an unremarkable postoperative recovery.

Final pathology revealed bilateral serous borderline tumors of the right and left ovaries measuring 11 cm and 10 cm, respectively, with surface involvement and non-invasive implants along the fallopian tubes (Fig. 2A-B). The endometrium was uninvolved by tumor and showed an altered gland and stromal pattern consistent with IUD use. There were also non-invasive implants of serous borderline tumor on the uterine serosa and microscopic foci within fibroadipose tissue of the omentum. All five cardiophrenic lymph nodes were positive for serous borderline tumor (Fig. 2C-D). Immunohistochemistry performed on the cardiophrenic lymph nodes revealed that the tumor was positive for estrogen receptor (ER) (moderate to strong staining in 60% of tumor cells), progesterone receptor (PR) (weak to moderate staining in 20% of tumor cells), and PAX8, and negative for calretinin, supporting the diagnosis and excluding a mesothelial proliferation. A custom, previously described, targeted next-generation sequencing assay (Garcia et al., 2017) was performed on tissue from both the patient's primary ovarian tumor and cardiophrenic lymph nodes, and revealed identical canonical activating mutations in *KRAS* (c.35G > A, p.G12D) in both specimens.

The patient was diagnosed with stage IVB serous borderline tumor and she was counseled for close observation after her case was reviewed at an interdisciplinary tumor board and consultation with a gynecologic medical oncologist. She underwent genetic testing at the recommendation of genetic counseling and was found to have variants of unknown significance in *CDH1* (c.1375G > A, p.V459M) and ESR1 (c.1346A > G, p.K449R). The patient's CA-125 normalized 5 weeks post-operative. At the time of last follow up 4 months post-operatively, our patient's CA-125 was 13 U/mL. Given the ER and PR positivity of the tumor, she was recommended to avoid hormone replacement therapy (HRT) and she will continue to follow up in the survivorship clinic for management of her menopausal symptoms. A plan was made to monitor CA-125 levels and obtain imaging if she becomes symptomatic.

3. Discussion

Previous reports have documented findings of recurrent borderline serous tumor in the cervical, scalene and internal mammary lymph nodes. (Chamberlin et al., 2001; Tan et al., 1994) This is the first report of serous borderline tumor with involvement of supradiaphragmatic lymph nodes at the time of staging surgery.

In this case, imaging findings and CA-125 values were highly concerning for malignancy prompting a preoperative discussion with the patient to pursue full surgical debulking, which included removal of the enlarged cardiophrenic lymph nodes. In retrospective cohort studies, CA-125 levels are elevated in approximately 25% of borderline tumors. (McKinnon et al., 1998) The decision to remove the enlarged cardiophrenic lymph nodes was based on evidence that invasive implants or low grade serous carcinoma in distant sites confers a lower overall and progression free survival in patients with serous borderline tumors. (Longacre et al., 2005) Intraoperatively, three frozen histopathology samples were examined, including the cardiophrenic lymph nodes that were indeterminate for serous borderline tumor. Our patient underwent a complete debulking procedure including total abdominal hysterectomy, bilateral salpingo-oophorectomy, removal of cardiophrenic lymph nodes and omentectomy. Retrospective review of patients with advanced stage III and IV disease suggests radical surgery including a total hysterectomy and bilateral salpingo-oophorectomy may reduce the risk of recurrence and progression to invasive disease. (Morice et al., 2001)

The role of lymphadenectomy in management of serous borderline tumor of the ovary is controversial. Lymph node involvement is mainly confined to the pelvic and paraaortic lymph nodes, even in advanced disease. (Tan et al., 1994) Complete pelvic lymph node staging with or without paraaortic dissection has been shown to upstage patients, but not predict recurrence or survival. (Seidman and Kurman, 2000; Lesieur et al., 2011; Qian et al., 2018) There is little data to guide whether removal of just enlarged lymph nodes (i.e. debulking rather than staging) provides survival benefit. Retrospective review of selected lymph node biopsy suggests the identification of invasive implants or presence of microinvasive low grade serous carcinoma may predict lower

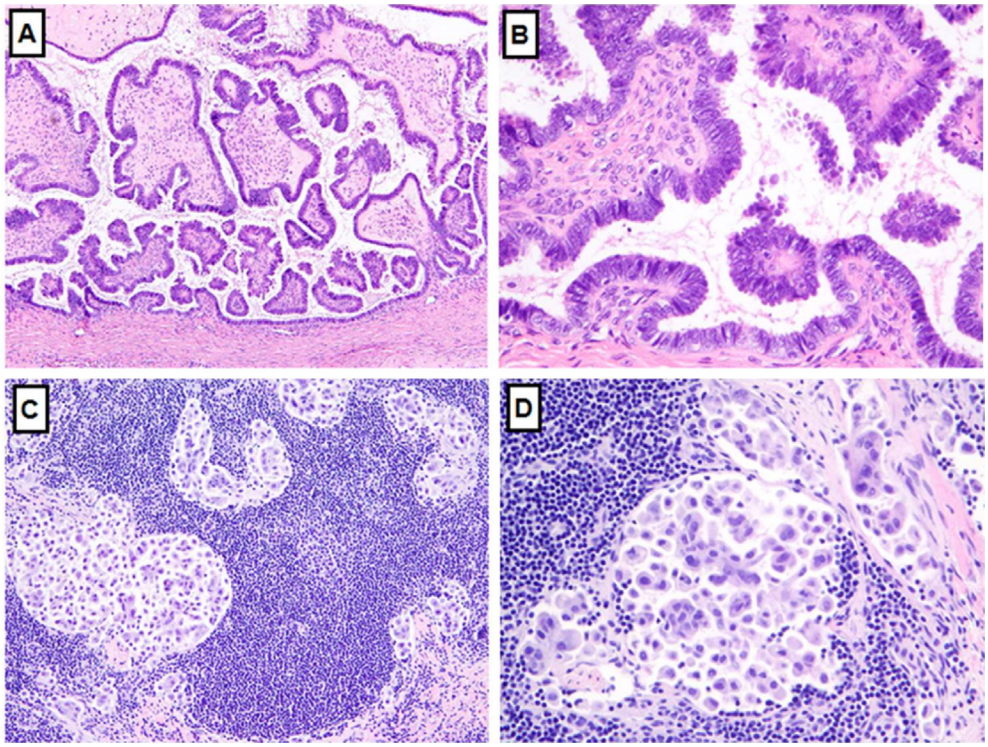

Fig. 2. Left ovarian serous borderline tumor showing hierarchical branching of variably sized papillae lined by moderately atypical cuboidal to columnar cells displaying characteristic budding and tufting (A and B). Serous borderline tumor involving a cardiophrenic lymph node (C and D).

disease-free survival. (McKenney et al., 2006) Current NCCN guidelines for management of advanced stage borderline tumors reflects the findings and uncertainty of these studies suggesting a cytoreductive surgery should be performed including removal of enlarged lymph nodes. (Armstrong et al., 2019)

All cases reported of recurrent serous borderline tumors of the ovary involving lymph nodes presented over 2 years after initial surgical management. (Lesieur et al., 2011; Abu-Hijleh et al., 1995) In our clinical case, given the lack of enlarged abdominopelvic lymph nodes on imaging, pelvic and paraaortic lymphadenectomy was not performed. Lack of systematic lymph node sampling limits our ability to interpret the mode of tumor dissemination to this patient's cardiophrenic lymph nodes, which classically are thought to drain the anterior abdominal wall and peritoneal cavity. (Abu-Hijleh et al., 1995) In cases of serous borderline tumors with lymph node involvement, the tumor in the lymph node is hypothesized to have originated by one of two possible mechanisms: 1) lymphatic spread from the ovarian primary, or 2) a synchronous primary arising from nodal endosalpingiosis. (Djordjevic and Malpica, 2010) The presence of identical *KRAS* mutations in both tumor specimens is supportive of a clonal relationship between the primary tumor, with secondary spread to the cardiophrenic lymph nodes, and not an independent neoplastic process arising from endosalpingiosis.

Prognosis of advanced stage serous borderline tumors of the ovary with distant nodal involvement is unclear. Stage IV borderline tumors have a 5-year overall survival of 77% with a low risk of malignant transformation of approximately 2%. (Zanetta et al., 2001) Predictors of recurrence and malignant transformation include classification of implants as invasive, higher stage at diagnosis, residual disease and micropapillary architecture. (Seidman and Kurman, 2000; Vang et al., 2017) Additionally, the presence of *KRAS* mutations have been associated with higher risk of malignant transformation. (Tsang et al., 2013) Management options reviewed with our patient at her follow-up visit included deferring HRT as this may be a risk factor for developing recurrent borderline tumor. (Mørch et al., 2012) Adjuvant aromatase inhibitor (AI) therapy was discussed but deferred. Current phase II and retrospective studies support use if AI in recurrent cases, but have not been studied in the adjuvant setting (Gershenson et al., 2012; Tang et al., 2019) The presence of a canonical KRAS mutation in this case, also highlights a potential role of MEK inhibitors as a treatment for recurrent disease. (Grisham et al., 2019)

This case highlights an unusual pattern of disease distribution at presentation of advanced-stage serous borderline ovarian tumor. The addition of chest CT to routine preoperative imaging may provide valuable information for both surgical planning and prognostication in these patients.

4. Consent

Informed patient consent was obtained prior to publication of this manuscript.

Author contributions

JDSL: This author participated in the design of the report, data curation, data analysis, writing and review of the manuscript

AAG: This author participated in the design of the report, data analysis, writing and review of the manuscript

AMC: This author participated in the writing and review of the manuscript

EB: This author participated in the data curation, data analysis and review of the manuscript

DLK: This author participated in the data curation, data analysis and review of the manuscript

MJW: This author participated in the design of the report, data analysis, writing and review of the manuscript

Declaration of Competing Interest

The authors declare no conflicts of interest.

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