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Review article

Durable response to BRAF inhibitor monotherapy in recurrent metastatic low grade serous ovarian cancer

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ABSTRACT

Low grade serous ovarian cancers (LGSOC) in an advanced setting have limited systemic treatment options. In this paper we report a case of metastatic LGSOC harboring a BRAF mutation, treated with dabrafenib. We discuss the clinical, pathologic and molecular characteristics as well as surgical considerations and ongoing investigations in LGSOC.

1. Case presentation

A 39-year-old nulligravid woman initially presented with abdominal pain, and abdominal imaging revealed a large multicystic pelvic mass with solid components. Serum CA-125 level notably was elevated to 14,073 units/mL. She underwent an exploratory laparotomy which found the left ovary to be replaced by a 25 × 25 × 25 cm sized multilobulated tumor that was densely adherent to the posterior pelvis and fallopian tube. This mass was fully resected, and the frozen intraoperative pathology section reported a 'papillary serous neoplasm of low malignant potential (borderline tumor)'. Apart from a left salpingo-oophorectomy, she also underwent two cystectomies on the right ovary to remove two 15 cm sized cystic masses. A 6 cm × 2 cm sized right ovary was preserved to maintain fertility. Final pathology report confirmed borderline serous tumors of both the resected left ovary and the cysts from the right ovary. No ovarian surface involvement or definite invasion was reported for the ovarian specimens and no implants were identified. She was then followed with serial pelvic ultrasounds every 6 months, which, except for transient right ovarian cysts, were unremarkable.

Three years after her initial surgery she reported a new lump in her axilla. She underwent an excisional biopsy of this right axillary lymph node which showed metastatic papillary serous carcinoma consistent with a Mullerian tract primary. Immunohistochemistry showed the tumor cells to be positive for CK-7, WT-1, and negative for TTF-1, compatible with a metastatic papillary serous carcinoma of tubo-ovarian or primary peritoneal origin. A PET scan to assess disease burden, showed slight attenuation in the level II neck lymph nodes, a right axillary 1.2 × 1.0 cm node with maximum SUV of 7.22, an unchanged, fluid attenuating lesion in the superior aspect of the lateral segment of the left hepatic lobe, and a 3.9 × 5.2 cm sized mixed attenuated, complex, right adnexal mass with a focal segment of metabolic activity within the solid component. The patient underwent an exploratory laparotomy with total abdominal hysterectomy, right salpingo-oophorectomy, and omentectomy. The right ovary measured 6 × 4 cm, and on gross inspection was visibly concerning for malignancy. Despite these concerning gross findings, the pathology on the mass only showed an ovarian endometrioma. The remaining specimens showed benign changes, including endosalpingiosis of the right fallopian tube. A repeat CT scan post-surgery showed the hepatic cyst to be unchanged, expected post-operative changes, and no other new concerning lesions. She was then referred to medical oncology to discuss systemic therapy options given the discovery of metastatic disease in her right axilla. At this point, the patient had a family friend, also a pathologist, who offered to review her initial biopsies from 3 years prior. This unofficial repeat review by an independent pathologist was interpreted as showing that the right ovarian capsule was ruptured with borderline serous tumor; whereas, the left ovary showed invasive serous carcinoma arising from borderline serous tumor with numerous foci of microinvasion. The right axillary node was also felt to be consistent with serous carcinoma

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of the ovary. She underwent 6 cycles of carboplatin and paclitaxel with CA-125 levels decreasing to 10 units/ml at the end of treatment from 14 units/mL prior. She was monitored thereafter and was not offered any endocrine therapy at this timepoint.

Two years later, she again developed a new right axillary mass. Mammogram and ultrasound this time showed multiple, newly enlarged right axillary lymph nodes. Core biopsy of these lymph nodes confirmed low-grade papillary serous carcinoma of the ovary (LGSOC) which was found to be 90 % estrogen receptor-positive and 10 % progesterone receptor-positive. CT scan at this time point revealed the previously described right axillary nodes, along with scattered sub-centimeter lung nodules mostly confined to the right lower lobe, which were too small to biopsy. This case was reviewed by a multi-disciplinary tumor board who reached a consensus opinion that the patient had local recurrence of a low-grade serous tumor to the right axilla with indeterminate pulmonary nodules. Aggressive local control was recommended. A complete right axillary radical lymph node dissection of all three levels was performed with pathology revealing metastatic papillary carcinoma involvement in 6 of the 21 level-1 lymph nodes, and none of the level 2 or 3 nodes. Altogether, 6 of 30 nodes were involved with disease. Following surgery, adjuvant radiation therapy with a total dose of 5,000 cGy was administered over the course of 5 weeks.

After surgery adjuvant tamoxifen therapy was discussed given the presence of concerning pulmonary nodules and an accompanying high estrogen receptor positivity on tumor pathology. Though the patient was given a prescription she ultimately chose not to begin therapy. Four months later, a follow-up chest CT scan showed persistent nodules demonstrating slight interval growth still too small to biopsy. She began tamoxifen therapy and continued for over one year with a CT chest performed every 6 months. Baseline CA-125 during tamoxifen therapy fluctuated between 23–25 units/mL. At 12 months of endocrine therapy, a repeat CT chest showed an interval increase in pulmonary nodules with a right upper lobe nodule increasing from 8 mm to 14 mm and the left upper lobe nodule increasing from 7 mm to 11 mm. CA-125 level

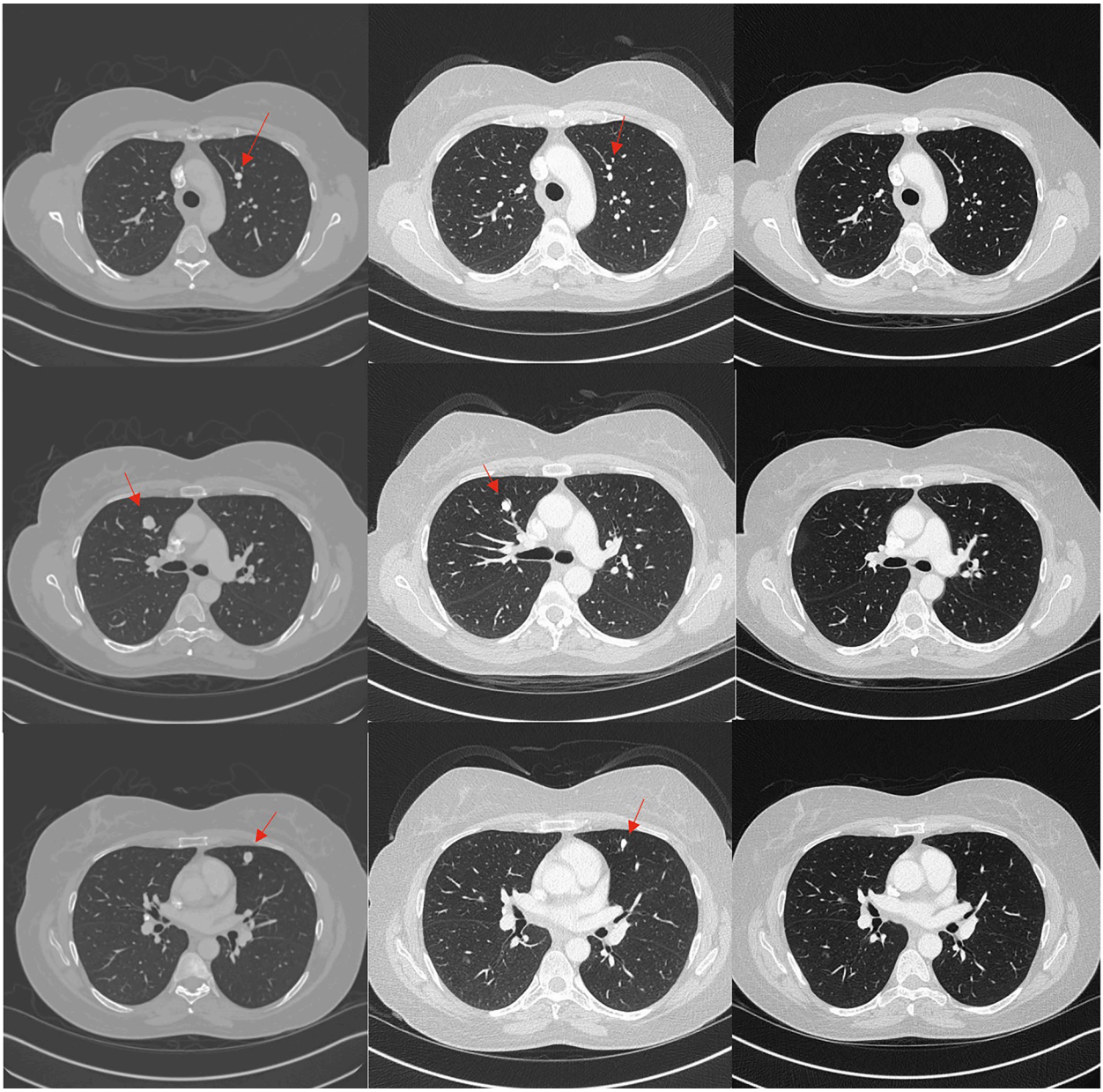

Fig. 1. Left: shows pulmonary nodules pre-BRAF inhibitor treatment measuring from top to bottom 7.4 mm, 14.1 mm, and 10.8 mm. Center: 2 months after initiation of BRAF inhibitor with nodules measured from top to bottom 4.1 mm, 9.4 mm, and 8.3 mm. Right: 9 months after initiation of BRAF inhibitor with complete resolution of nodules and no evidence of metastatic disease in the thorax, abdomen, or pelvis.

also increased to 32 units/mL. Of note, the patient reported occasional missed doses of tamoxifen during the preceding months.

At this point, her tumor had tested positive for the V600E BRAF mutation making her eligible for a phase I clinical trial with dabrafenib, a BRAF inhibitor, monotherapy. She was successfully enrolled on the trial and tolerated dabrafenib monotherapy without any dose limiting toxicities. A follow up CT chest, 2 months into dabrafenib monotherapy showed a decrease in the size of the pulmonary nodules along with a reduction in the CA-125 level from 32 units/mL to 15 units/mL (Fig. 1, Fig. 2). Within 9 months of starting dabrafenib, she no longer had any evidence of pulmonary nodules on CT imaging which was overall consistent with a complete response. Four years into the trial, given the outstanding persistent response she was transitioned off the trial to a compassionate use drug protocol in order to allow continued long-term access to dabrafenib therapy. At her most recent clinic follow up, she continues to remain in complete response with excellent tolerance to dabrafenib therapy for over 9 years.

2. Pathology case review

At initial surgical presentation, the patient's left ovarian mass and right ovarian cystectomies (received as two separate specimens) were originally diagnosed as serous borderline tumors (Fig. 3.A) with no definite invasion identified. The second pathology review described above reported multiple foci of microinvasion in the left ovary (Fig. 3.B, C). Notably, however, these foci demonstrated no cytologic features nor desmoplastic stromal response clearly diagnostic for low-grade serous carcinoma (Fig. 3.C). Additionally, these foci consisted of eosinophilic cells that, while present as small clusters and individual cells in the stroma, shared cytologic features with the background serous borderline tumor. Finally, all foci measured less than 5 mm in greatest dimension (Fig. 3.C). Per the WHO Classification of Female Genital Tumors (4th and 5th Editions) the findings were consistent with ovarian serous borderline tumor (SBOT) with microinvasion. While the right ovarian cystectomy was received fragmented, no overt capsular involvement or micropapillary features were noted in either ovarian specimen and no implants were identified in any of the specimens.

The patient's subsequent axillary lymph node excisional biopsy 3 years later showed involvement by a serous neoplasm that showed more advanced cytologic atypia compared with the original serous borderline tumors and the microinvasive foci, but the nuclear features were still of low-grade atypia. The architectural growth pattern was confluent and destructive, consistent with metastatic low-grade serous carcinoma (Fig. 3.D-E). The subsequent total abdominal hysterectomy, right salpingo-oophorectomy and omentectomy did not show any pelvic or intraabdominal disease. Her right axillary recurrence two years later showed 6 of 30 lymph nodes involved by histologically similar low-grade serous carcinoma with extranodal extension present. No endosalpingiosis was identified in any of the lymph nodes.

3. LGSOC pathologic characteristics

Serous tumors of the ovary (serous neoplasia) include benign, borderline and malignant entities. (Moch, 2020) Serous carcinoma is further classified via a two-tiered grading system, high-grade and low-grade, considered to represent two histotypes given their distinct mechanisms of pathogenesis. High grade serous carcinoma originates from tubal-type epithelium, primarily from fallopian tube fimbriae, and develops via deleterious mutations in *TP53*. Histologic features include severe cytologic atypia and solid, pseudoendometrioid and papillary growth patterns. Low-grade serous neoplasms including serous borderline tumor and low-grade serous carcinoma are associated with mutations in *KRAS* or *BRAF*. Distinction between high-grade serous carcinoma and low-grade serous neoplasms is typically not a difficult diagnostic issue but can be facilitated by performing immunohistochemical staining on paraffin-embedded tissue. Demonstration of aberrant p53 expression (complete loss or diffuse strong staining) and WT1 positivity are characteristic of high-grade serous carcinoma; p53 wild-type pattern and WT1 positivity would support a diagnosis of a low-grade serous neoplasm.

Low-grade serous neoplasms encompass serous borderline tumor and low-grade serous carcinoma. Serous borderline tumors may be associated with extraovarian serous proliferations termed implants. Implants are non-invasive and classified as epithelial (no associated stromal reaction) or desmoplastic type (associated granulation tissue-type reaction or desmoplastic-type stroma without destructive stromal involvement). If implants are invasive, they should be classified as LGSOC. (Bell et al., 1988) An important histologic subtype of serous borderline tumor includes the micropapillary subtype. This morphologically distinct variant demonstrates non-hierarchical branching and is important to identify given its increased association with desmoplastic implants. (Longacre et al., 2005) Features complicating assessment of serous borderline tumors include identification and classification of 1) types of stromal invasion within the tumor, 2) presence and type of implants, and 3) lymph node involvement, if present.

Identification of low-grade serous carcinoma arising in the setting of serous borderline tumor can be quite challenging. Extensive sampling of primary ovarian low-grade serous neoplasms is essential to assess for

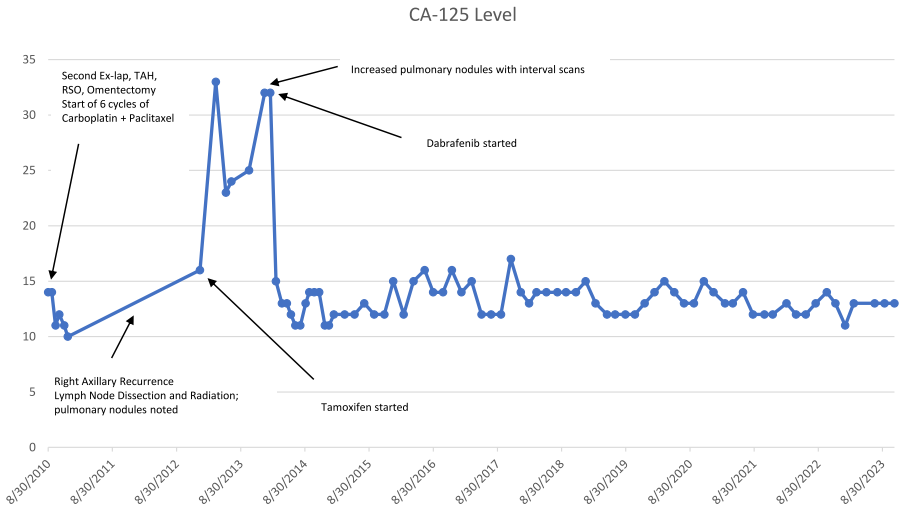

Fig. 2. CA-125 trend with clinical course. X axis: Time plotted. Y axis: CA-125 levels measured in units/mL.

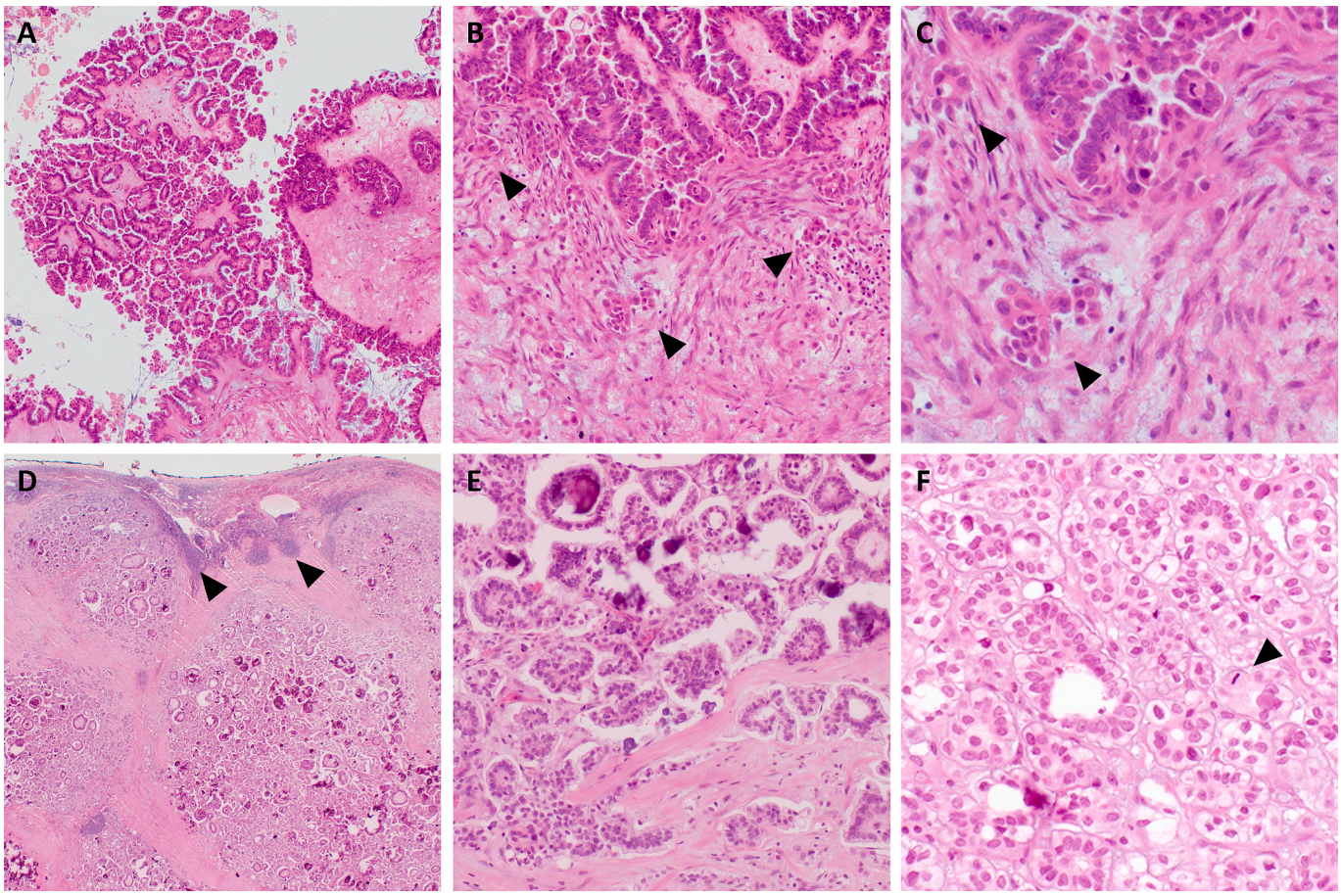

Fig. 3. Photomicrograph composite. Left ovary, serous borderline tumor: A. Low power magnification illustrating papillae with hierarchical branching (H&E, 100x) and scattered foci of microinvasion (arrowheads; B. 200x, C. 400x). Cytologic atypia is bland and no mitotic figures are present. Axillary lymph node with low grade serous carcinoma: D. Low power magnification demonstrating extensive destructive nodal involvement by tumor; lymph node capsule present at top and residual benign lymphoid tissue at arrowheads (20x). E. Intermediate power of area with destructive and confluent growth pattern (200x); higher magnification showing increased cytologic atypia including nuclear enlargement, nuclear membrane irregularity, variable hyperchromasia, nucleoli and occasional mitotic figures (arrowhead) (400x).

microscopic capsular implants, microinvasion (individual cells or cell clusters in stroma bearing increased eosinophilic cytoplasm < 5 mm in greatest dimension), microinvasive carcinoma (LGSOC < 5 mm in greatest dimension) and overt low-grade serous carcinoma. Of note, in the majority of studies, stromal microinvasion has not been demonstrated to have a negative impact on outcome. Finally, SBOT may be associated with lymph node findings ranging from benign endosalpingiosis, serous borderline tumor, and even low-grade serous carcinoma. Low-grade serous carcinoma exhibits several architectural patterns including small cell nests with a haphazard growth pattern, micropapillae, and macropapillae within unlined spaces. Cytologic atypia is mild to moderate. The tumor is associated with a destructive pattern of stromal invasion.

The pathologic presentation described herein raises interesting questions, namely the significance of the microinvasive foci in this patient's primary ovarian serous borderline tumor and subsequent axillary lymph node involvement by metastatic low grade serous carcinoma in the absence of abdominopelvic tumor involvement. Although the microinvasive foci were not initially reported as such for this patient, the tumors were well-sampled and no foci diagnostic for low-grade serous carcinoma were identified. Additionally, no overt microscopic surface involvement was noted, no micropapillary features identified in either ovarian tumor, and no implants seen in the other submitted specimens. Therefore, the patient would reasonably have been expected to demonstrate an indolent course. Her recurrence three years later with low grade serous carcinoma to axillary lymph nodes is quite unusual. Ovarian serous borderline tumor with nodal involvement by serous borderline tumor is well documented (Tan et al., 1994; Djordjevic and Malpica, 2010; Maniar et al., 2014) including supradiaphragmatic locations. (McKenney et al., 2006; Verbruggen et al., 2006) However, ovarian serous borderline tumor with nodal low-grade serous carcinoma has also been described. (Djordjevic and Malpica, 2012) Proposed mechanisms include transformation from pre-existing endosalpingiotic foci in pelvic and/or abdominal lymph nodes. (Djordjevic and Malpica, 2012) Of note, no endosalpingiotic foci were noted in any of these patient's axillary lymph nodes. However, clonal relationship between paired cases of serous borderline tumor and subsequent serous carcinoma has also been reported, implicating tumor progression. (Chui et al., 2019) The authors observed typical serous borderline tumors to be associated with *BRAF* mutations, including tumors with the pattern of microinvasion demonstrated in this patient's primary ovarian tumor. Treatment of this patient with a *BRAF* inhibitor with subsequent durable response contributes to promising evidence of efficacy of targeted therapy in this disease. (Tholander et al., 2020).

4. LGSOC clinical characteristics

4.1. Demographics

LGSOC represent 2 % of all epithelial ovarian carcinomas. (Slomovitz et al., 2020) When limiting to only serous ovarian carcinomas, LGSOC still account for only 3–10 %. (Slomovitz et al., 2020; Zwimpfer et al.,

2023; Kaldawy et al., 2016) This percentage is likely closer to 3 % as the prevalence of LGSOC has been decreasing of late, in contrast to the increasing prevalence of the LGSOC precursor Serous Borderline Ovarian Tumors (SBOT). This is in part accounted by the improved surveillance and treatment trends of SBOT. (Slomovitz et al., 2020) The mean age of onset for this subgroup is 55.5 years, which is notably younger than the mean age of onset of high grade serous ovarian cancers (HGSOC) at 62.6 years. (Kaldawy et al., 2016) LGSOC is also not usually clustered in families unlike HGSOC as the inherited mutations such as BRCA1 and BRCA2 are more closely associated with HGSOC while being rare in LGSOC. (Slomovitz et al., 2020; Kaldawy et al., 2016).

4.2. Pathogenesis and molecular characteristics

The pathogenesis of LGSOC is not completely understood at present but existing data suggests that SBOT are a precursor tumor. LGSOC has been shown to typically be characterized by an activation of the mitogen-activated protein kinase (MAPK) pathway, particularly through KRAS, BRAF, ERBB2, and NRAS. (Kaldawy et al., 2016; Hollis, 2023) Slomovitz et al. presented a model for LGSOC pathogenesis which begins with an epithelial progenitor cell of the fallopian tube that migrates to the ovary during ovulation, advancing to a benign serous neoplasm, then an SBOT, followed by a non-invasive LGSC (niLGSC), before ultimately transforming into an invasive LGSOC (Fig. 4). It is also thought that some SBOT can bypass these interim lesions and progress directly to invasive LGSC. (Slomovitz et al., 2020).

Both SBOT and LGSOC have elements of MAPK pathway activation which further supports the above model of SBOT as a precursor lesion existing on the same continuum with LGSOC, sharing a common pathogenesis driven by the MAPK pathway. (Hsu et al., 2004) However, there are some differences in the molecular makeup of SBOT and LGSOC, with mutations in the MAPK pathway gene BRAF being more common in SBOT when compared to LGSOC. If an SBOT has accumulated a BRAF mutation, it is perhaps less likely to progress to a LGSOC and if it does, the disease is felt to typically present in early stages. (Slomovitz et al., 2020; Hollis, 2023) KRAS mutations rates on the other hand are about equal between SBOT and LGSOC. (Kaldawy et al., 2016).

Overall, the high prevalence of MAPK mutations in LGSOC are a notable contrast to HGSOC which are characterized by an almost universal presence of TP53 mutation. Over 96 % of HGSOC harbor a TP53 mutation versus only 8 % in LGSOC. (Kaldawy et al., 2016).

4.3. Clinical markers

Estrogen receptor (ER) is expressed in the majority of those with LGSOC and progesterone receptor (PR) is expressed in just over half of cases. (Slomovitz et al., 2020; Voutsadakis, 2021) Studies suggest that the high levels of ER and PR positivity are significantly associated with improved overall survival in LGSOC. (Fernandez et al., 2020).

The majority of LGSOCs have elevated CA-125, but have a lower median pretreatment CA-125 compared to HGSOCs, (119.1 vs 246.7 in Fader et al). (Fader et al., 2014) Although the CA-125 levels tend to trend in response to combination platinum based and taxane chemotherapy combinations in LGSOC with one study showing 50 % of patients with CA-125 having a greater than 50 % decline from pretreatment baseline, this often does not correlate with radiographic response. (Slomovitz et al., 2020) The normalization of CA-125 does not appear to correspond to a reduced likelihood of recurrence. The utility of CA-125 appears to be at the initial debulking surgery and chemotherapy, as it is those with an elevated pretreatment CA-125 level reduced to below 35 U/mL that have been shown to have improved overall survival. (Kaldawy et al., 2016).

4.4. Survival and prognostic factors

LGSOC overall survival is 99 months for all stages as compared to HGSOC at 57 months. (Kaldawy et al., 2016) The location of the primary tumor appears to have some prognostic significance. LGSOC arising primarily in the peritoneum is typically associated with older patients, those with a higher BMI, a higher pretreatment CA-125, and a higher rate of gross residual disease following primary cytoreduction. Progression-free survival and overall survival was found to be more favorable for peritoneal versus ovarian primaries. (Slomovitz et al., 2020).

The deviating pathways in tumorigenesis of LGSOC appear to have little importance on prognosis, as those with SBOT which progressed to LGSOC versus LGSOC that appeared de novo were found to have equitable progression free survival and overall survival. (Slomovitz et al., 2020).

Of the demographic factors, age and BMI have been identified to have prognostic significance. Those who are older than 35 years have a longer progression free survival, overall survival, and lower likelihood of progression or recurrence. BMI equal to or greater than 35 and smoking both carried a greater risk of mortality. (Slomovitz et al., 2020).

Finally, molecular characteristics of LGSOC have been shown to affect the aggressiveness of subtypes of LGSOC. It has been shown that LGSOC with MAPK pathway mutations such as KRAS and BRAF are among the least aggressive. (Köbel and Kang, 2022) Both KRAS and BRAF mutations have been demonstrated in small number studies to have better overall survival (78 months vs 47 months, $P = 0.28$) compared to wild-type KRAS and BRAF, although the data was not significant. (Kaldawy et al., 2016) This limited evidence does suggest that BRAF and KRAS may have positive prognostic significance in LGSOC apart from being a target for therapy.

5. LGSOC surgical considerations

Primary surgical cytoreduction with the goal of complete resection is

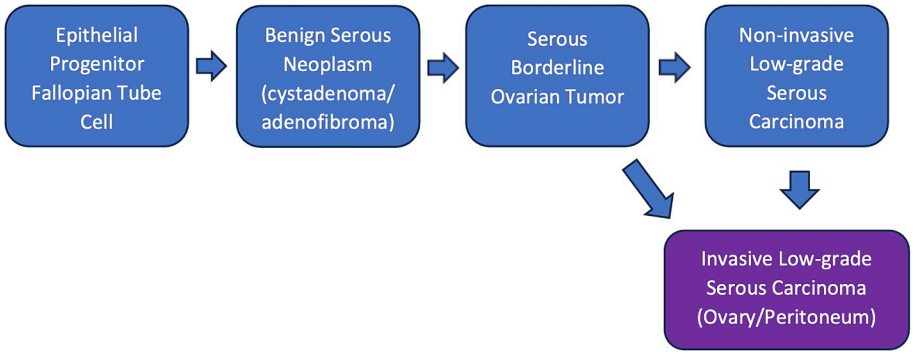

Fig. 4. Ovarian Tumorigenesis Model proposed by Slomovitz et al. with the progression of tumor characteristics culminating in invasive LGSOC of the ovary or the peritoneum.

the preferred treatment for LGSOC. (Network NCC) Residual disease is associated with poorer progression free and overall survival. (Grabowski et al., 2016; Vatansever et al., 2021; Fader et al., 2013) In a sub-analysis of Gynecologic Oncology Group (GOG) 182, 189 patients had a grade 1 tumor (a surrogate for LGSOC). Microscopic residual disease was associated with longer progression free survival (33.2 months) when compared to macroscopic disease of 1 mm-10 mm (14.7 months) and > 10 mm residual disease (14.1 months) of residual disease ($p < 0.001$). (Fader et al., 2013) Similarly, microscopic residual disease was associated with longer overall survival (96.9 months) compared to 1 mm-10 mm (44.5 months) and > 10 mm (42.0 months) residual disease ($p < 0.001$). Expert consensus is for consideration of an attempt at cytoreduction due to the tumor's lack of response to chemotherapy, and all patients with newly diagnosed LGSOC should be evaluated by a gynecologic oncologist for surgery. (Grisham et al., 2023) The role of hyperthermic intraperitoneal chemotherapy in LGSOC remains unknown and warrants further areas of research.

There is a paucity of data regarding fertility preservation due to the rarity of the tumor. Expert consensus supports fertility preservation for early stage (Stage IA-IC1) following comprehensive surgical staging in well counseled patients. (Grisham et al., 2023).

Several RCTs have evaluated the role of selective secondary cytoreduction in patients with ovarian cancer but these trials included a small number of LGSOC patients. In a systematic review and *meta*-analysis on the role of secondary cytoreduction in LGSOC, it was found that no gross residual disease at completion of surgery was associated with improved OS (HR = 0.4, 95 %CI = 0.23–0.7). Moreover, visible disease at completion of surgery was associated with significantly worse progression free survival (HR = 3.51,95 %CI = 1.72–7.14). (Goldberg et al., 2022) Secondary cytoreduction is generally reserved for surgical candidates with oligometastatic or limited recurrent disease. Expert consensus suggests that secondary cytoreduction may be an option in LGSOC with more extensive disease.

6. LGSOC systemic treatment options

As stated above, standard of care for LGSOC is upfront cytoreduction surgery, if eligible, with adjuvant chemotherapy for Stage IIC-IV disease. NCCN guidelines for recommended primary systemic therapy is an adjuvant taxane and platinum combination for an average of six cycles as tolerated with the option for additional bevacizumab. Unfortunately, LGSOC has been found to be fairly chemo-resistant when compared to HGSOC, and this is seen in both the *in vitro* as well as neoadjuvant, primary and recurrent settings. (Kaldawy et al., 2016; Grabowski et al., 2016) Chemoresistance was demonstrated in-vitro with data from patient samples showing an increased likelihood of drug resistance to typically cytotoxic agents as compared to HGSOC. (Santillan et al., 2007) One study demonstrated multidrug resistance to be almost twice as likely in LGSOC type cells. (Previs et al., 2015) In the adjuvant setting, disease free rates after platinum based chemotherapy were around 52 % for LGSOC as compared to around 80 % for HGSOC (Gershenson et al., 2006; Ozols, 2006), despite the increased rate of no residual disease after primary debulking surgery in LGSOC patients. (Grabowski et al., 2016) Studies evaluating the role of neoadjuvant chemotherapy are limited and retrospective, and highlight the chemoresistance of this disease process. (Schmeler et al., 2008; Scott et al., 2020) Cobb et al demonstrated a significant decrease in response rate in LGSOC as compared with HGSOC, 11 % vs 75 % respectively. (Cobb et al., 2020) In additional retrospective data there was a shortened progression free survival in patients receiving neoadjuvant chemotherapy thus delaying the cytoreductive surgery, supporting an attempt at upfront cytoreduction. (Scott et al., 2020).

In addition to taxane/platinum chemotherapy there is increasing use of targeted agents such as bevacizumab, a monoclonal antibody to VEGF in ovarian cancers. Sub-group analysis from AGO-OVAR 11/ICON 7 of LGSOC patients showed some favor to the addition of bevacizumab, however this was not powered for significance of that analysis. (Oza et al., 2015) The addition of bevacizumab to adjuvant chemotherapy is another preferred recommendation by NCCN guidelines.

Due to the common over-expression of ER and PR in LGSOC, (Wong et al., 2007) for patients that undergo adjuvant chemotherapy, NCCN guidelines do have category 2B recommendation for maintenance endocrine therapy. Although prospective data are needed, a retrospective study comparing maintenance endocrine therapy to standard of care observation demonstrated improved progression free survival of 64.9 months in those that received maintenance therapy compared to 26.4 months for those under observation. Improved overall survival was reported when adjusting for disease status. (Gershenson et al., 2017) Retrospective studies with adjuvant hormonal monotherapy instead of chemotherapy after optimal cytoreduction reported a 3-year progression free survival of 79 % and overall survival of 92.6 % at a median follow-up of 41 months. (Fader et al., 2017) Of note, most of the studies investigating hormonal therapy are in the recurrent setting. Retrospective analysis has demonstrated a response rate of 9 % with median progression free survival of 7.4 months, and sub-group analysis showed a longer time to progression in those patients with ER+/PR + tumors as compared to those with ER+/PR- tumors, 8.9 months versus 6.2 months, respectively. (Gershenson et al., 2012) Data from the international phase 2/3 trial GOG-0281/LOGS, which compared trametinib versus standard of care cytotoxic chemotherapy in patients with recurrent LGSOC demonstrated response rates of cytotoxic therapies ranging from 0-9 %, tamoxifen 0 % and letrozole 14 %. (Gershenson et al., 2022) Although there are promising responses, endocrine therapies remain a category 2B recommendation per NCCN guidelines.

Recurrence rates despite optimal frontline management remain high for LGSOC. Recommended management for eligible patients at recurrence would be secondary tumor debulking. (Crane et al., 2015) Current NCCN guidelines also recommend systemic treatment including chemotherapy with or without bevacizumab, hormonal therapies and targeted therapies that are selected based on patient exposures, fitness and targetable markers. There is no standard recommendation for therapy sequence and more trials are needed. Unfortunately, response rates for both hormonal therapies (Gershenson et al., 2012) and chemotherapies (Gershenson et al., 2009) are low in the recurrent setting. Additional studies have demonstrated improved response rates with bevacizumab-containing regimens and increased overall response rates to just below 50 %. (Schmeler et al., 2010; Dalton et al., 2017) Currently, multiple clinical trials are open, investigating various treatment regimens in the setting of recurrent LGSOC. (Grisham et al., 2023).

7. BRAF inhibitor therapy for LGSOC

Activation of MAPK pathway through mutations in KRAS or BRAF among others, is seen in over 60 % of SBOT and LGSOC in sharp contrast to their rarity in high grade ovarian serous tumors. (Hsu et al., 2004) BRAF mutations in particular are found in up to 33 % of all LGSOC. (Kaldawy et al., 2016) The high prevalence of these mutations makes targeting the MAPK pathway a particularly discerning strategy to circumvent the chemotherapy resistance of LGSOC. MEK as it lies downstream from both KRAS and BRAF makes an ideal target for such an approach and so MEK inhibition has been increasingly studied for LGSOC in recent times. The GOG 281/LOGS trial evaluated a MEK inhibitor trametinib in recurrent LGSOC, recording a 13-month (95 % CI 9.9–15) PFS with trametinib compared to 7.2 months (5.6–9.9) with a standard of care approach. (Gershenson et al., 2022) A subgroup analysis in this trial limited to only those treated patients carrying a KRAS/BRAF or NRAS mutation maintained a similar median PFS of 13.2 months. Based on these results trametinib is now listed within the NCCN guidelines as a viable systemic therapy option for recurrent LGSOC. Studies investigator alternative MEK inhibitors demonstrated PFS values of more than 9 months, with one such drug binimetinib, now being offered as a Category 2B recommendation in this setting. (Farley et al.,

2013; Monk et al., 2020).

When BRAF V600E mutation is the specified MAPK activating signal, instead of inhibiting MEK downstream, a combination strategy with a direct BRAF inhibitor has been studied in trials across multiple solid tumor types. Promising results in varied cancers has resulted in a rare tissue-agnostic indication FDA approval for dabrafenib and trametinib in BRAF V600E mutation positivity. (Gouda and Subbiah, 2023) The case presented in our paper demonstrates a complete response with BRAF inhibitor monotherapy in recurrent LGSOC which has been remarkably durable for over 9 years. This outcome is in line with prior case reports of similar BRAF inhibitor efficacy in BRAF V600E mutant LGSOC. (Tholander et al., 2020; Lima et al., 2022; Moujaber et al., 2018; Combe et al., 2015; Mendivil et al., 2018) These prior reports as summarized in Table 1, describe treatment responses which are sustained, lasting well beyond the 13 month PFS recorded with MEK inhibitor monotherapy in the GOG 281/LOGS trial. Three of these six prior cases record complete responses, with majority describing responses in heavily pre-treated settings of third line or higher. While some of these described reports utilized BRAF and MEK inhibitor combination therapy, Moujaber et al, and Combe et al reported treatment responses to BRAF inhibitor monotherapy similar to our case. (Moujaber et al., 2018; Combe et al., 2015) The rationale for combining BRAF inhibitors with MEK inhibitors is gathered from studies in other cancers such as melanoma where combination therapy has shown to have an improved response when compared to BRAF inhibitor monotherapy, as well as reduce development of resistance mechanism and propensity for secondary cancers through paradoxical activation of MAPK. (Long et al., 2014; Bowyer et al., 2015) The primary drawback with such a combination strategy however is the added drug related toxicity which can limit drug tolerability.

The long term sustained responses with BRAF inhibitor monotherapy for LGSOC as in our case and the two other prior reports of Moujaber et al, and Combe et al, sharply contrasts with the rapid development of resistance with BRAF inhibitor monotherapy in melanoma. (Moujaber et al., 2018; Combe et al., 2015; Long et al., 2014) This suggests that resistance mechanisms to BRAF inhibitor monotherapy in LGSOC are different from those usually seen in other solid tumors, and perhaps BRAF inhibitor monotherapy could be a valid strategy in LGSOC setting. This finding could be especially pertinent given the sustained responses seen in these case reports that necessitates chronic BRAF inhibitor therapy over many years, which would be more tolerable with monotherapy as opposed to a combination strategy. Treatment interruptions of BRAF inhibitors have been attempted in three of the prior cases of LGSOC and in all of such instances there was eventual disease progression necessitating re-introduction of BRAF inhibitor therapy. (Tholander et al., 2020; Moujaber et al., 2018; Combe et al., 2015) Re-introduction of BRAF inhibitor therapy in all of the above cases promisingly regenerated a treatment response. Overall, the above reports suggest a reliable response to BRAF inhibitor therapy in BRAFV600E mutation carrying LGSOC and argue for routine and early testing for BRAF mutation in LGSOC.

Table 1
Compilation of existing case reports detailing treatment responses to BRAF inhibitor therapy. Abbreviations: BRAF inhibitor (BRAFi). MEK inhibitor (MEKi). Dabrafenib (Dab), Tramatenib (tram), Vemurafenib (vem). Encorafenib (enco). Binimetinib (bini). Partial response (PR). Complete response (CR). Stable disease (SD).

Paper	Age of patient	Line of systemic therapy	Single agent or combination	Best response	Response duration at time of censoring
Lima et al 2022[47]	59 30	4th line, 3rd line	BRAFi + MEKi (dab tram)	PR, CR	>18 months, >41 months
Moujaber et al 2018[48]	22 71	2nd line, 2nd line	BRAFi (dab) BRAFi	CR, PR	>11 months, >12 months
Combe et al 2015[49]	74	>5 line	BRAFi (vem)	PR	>21 months
Mendivil et al 2018[50]	47	6th line	BRAFi + MEKi	CR	>11 months
Tholander et al 2020[11]	50	4th line	BRAFi + MEKi (dab tram, later enco bini)	SD	>41 months

8. Future directions in LGSOC systemic therapy

Despite established consensus on the lower responsiveness of LGSOC to conventional cytotoxic chemotherapy, platinum-based chemotherapy remains the preferred first line systemic therapy in current clinical practice, followed usually by endocrine therapy in a maintenance setting. Efforts are currently underway to change this paradigm, with trials incorporating novel strategies which emphasize the role of endocrine therapy, either by using endocrine therapies upfront or in combination with CDK 4/6 inhibitors similar to their use in hormone receptor positive breast cancer. The ongoing NRG-GY019 study (NCT04095364) is a phase III trial investigating whether an aromatase inhibitor monotherapy with letrozole is non-inferior to the standard approach of carboplatin and paclitaxel followed by maintenance letrozole. The MATAO study (NCT04111978) is another endocrine therapy-based LGSOC trial which plans to investigate the efficacy of current standard of care letrozole as maintenance therapy by comparing outcomes against a placebo maintenance. (Heinzelmann-Schwarz et al., 2021) Results from a recent phase II study GOG 3026 (NCT03673124) which studied the combination of letrozole in combination with the CDK 4/6 inhibitor ribociclib in recurrent LGSOC has shown promise reporting an overall response rate of 23 % (90 % CI, 13.4 %-35.1 %) with an accompanying median PFS of 19.1 months. (OncLive, 2023) Another phase II study (NCT03531645) investigating the CDK4/6 inhibitor abemaciclib plans to evaluate the combination of fulvestrant with abemaciclib in a neoadjuvant approach for women with advanced low grade serous cancer. Preliminary results of this study published so far showed a clinical benefit rate of 80 % in 15 patients. (Cobb et al., 2022).

Apart from the above investigations into endocrine therapy, other investigational approaches in LGSOC include updated targeted therapy against the MAPK pathway. Avutometinib, a novel small molecule RAF/MEK clamp in combination with the small molecule focal adhesion kinase (FAK) inhibitor defactinib has shown to have encouraging response in an early phase 1 study and early results of the follow up phase II study (ENGOT-ov60/GOG-3052/RAMP 201) show promise with an overall response rate of 28 %. (Shinde et al., 2020; Banerjee et al., 2021; Banerjee et al., 2023) Finally, AcSé Pembrolizumab, a phase II basket study studying Pembrolizumab included 23 LGSOC patients, of which 12 patients showed disease control with immunotherapy in a platinum resistant setting. (Ray-Coquard et al., 2022) These results may warrant a deeper investigation of immunotherapy in LGSOC.

9. Conclusion

LGSOC tumors are relatively chemotherapy resistant with limited systemic treatment options for advanced disease in a recurrent setting. Our case reports a complete and durable response to BRAF inhibitor monotherapy in LGSOC harboring a BRAF V600E mutation after prior progression on chemotherapy and endocrine therapy. Optimal management of advanced LGSOC should incorporate early testing for actionable BRAF mutations routinely in clinical practice.

CRediT authorship contribution statement

Shashank Sama: Writing – review & editing, Writing – original

draft, Supervision, Conceptualization. **Sterling Rosqvist:** Writing – original draft, Data curation. **Talicia Savage:** Writing – original draft. **Lesley Lomo:** Writing – review & editing, Writing – original draft. **Kiera Sibbald:** Writing – original draft. **Alli Straubhar:** Writing – review & editing, Writing – original draft, Supervision. **Theresa L. Werner:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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