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Recurrent low grade serous ovarian cancer in a 20 year old woman: A case from the Ohio State University College of Medicine

David E. Cohn [a,*], Floor J. Backes [a], John J. Wallbillich [a], Kristin Bixel [a], Sarah M Crafton [a], Robert Neff [a], Adam C. ElNaggar [a], Blair Smith [a], Adrian A. Suarez [b]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ohio State University College of Medicine, Columbus, OH, United States
[b] Department of Pathology, Ohio State University College of Medicine, Columbus, OH, United States

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SUMMARY

A 20 year old with recurrent low-grade serous carcinoma (LGSC) is discussed. The differential diagnosis, pathology, epidemiology, treatment options are discussed. Focus on the molecular pathways of LGSC and the implications of the diagnosis on fertility are highlighted.

Presentation of case

A 20-year-old nulligravid woman presented to an emergency department with acute abdominal pain; a contrast enhanced CT scan of the abdomen and pelvis demonstrated a 13 × 9 cm left pelvic mass with calcifications and small-volume omental disease. A chest CT showed a small right pleural effusion. At that time the CA-125 was 159, where the normal range is <35. Other tumor markers – including LDH, AFP, HCG and inhibin – were all normal. Two days later in an outside hospital she underwent a midline laparotomy where diffuse carcinomatosis with innumerable small bowel serosal and mesenteric nodules were noted. In the pelvis a left ovarian mass was noted to be densely adherent to the uterus and rectum. A decision was made at that time to perform only an ovarian cystectomy for diagnosis. Additional samples from the abdominal wall demonstrated what was described as low-grade serous carcinoma arising from the left ovary. A complete cytoreduction was not attempted due to the disease distribution. Her postoperative course was complicated by a pulmonary embolism diagnosed on postoperative day 2 and was treated with low-molecular-weight heparin. She declined consultation with a reproductive endocrinologist to discuss options regarding the preservation of fertility prior to undergoing adjuvant therapy. She was initially treated with neoadjuvant intravenous carboplatinum (area under the curve 5) and paclitaxel (175 mg/m^2 over 3 h), beginning 24 days after her laparotomy. After four cycles of neoadjuvant chemotherapy her CA-125 decreased to 135. A contrast-enhanced CT scan of the chest, abdomen, and pelvis demonstrated stable disease. Five weeks after completing neoadjuvant chemotherapy she underwent a laparotomy with the goal of interval cytoreduction. At that time diffuse disease in the omentum, splenic hilum, ascending colon and rectum was noted, with adherence of the left and right ovaries to the uterus and sigmoid colon. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, total colectomy, end ileostomy, splenectomy, partial hepatectomy of segment 6, and caudal cystectomy were performed. She had no residual disease following surgery, and pathologic evaluation confirmed low-grade serous carcinoma. Her cancer was found to have no identifiable genomic alterations. Adjuvant letrozole 2.5 mg daily was started on postoperative day 60. At 12 months following her complete cytoreduction, she experienced a symptomatic recurrence in her peritoneal cavity. A biopsy confirmed low grade serous carcinoma, and genomic analysis of this specimen again did not reveal any reportable alterations. She was then enrolled on a trial investigating MEK (mitogen-activated protein kinase (MAPK) extracellular signal–regulated kinase (ERK) kinase) inhibition, which has led to stabilization of her disease over 6 months of therapy.

Pathology and grading of ovarian cancer

The ovaries measured 8.7 cm and 5.7 cm on the right and left respectively (largest diameters), and grossly showed a solid and cystic neoplasm. Low power microscopic examination showed a serous epithelial neoplasm with different histologic patterns; focally, there were areas in which the tumor featured non-hierarchical branching with cells arranged in long papillae or in cribriform formations around relatively large fibrovascular cores [Fig. 1A]. In these areas there was no evidence of stromal invasion and higher power examination showed monotonous cells with high nuclear to cytoplasmic ratio. These areas are reminiscent of borderline tumors with micropapillary architecture or the so-called non-invasive low-grade micropapillary carcinoma. However, in other very extensive areas there was obvious invasion of the stroma as evidenced by infiltrative architecture and desmoplastic reaction. The latter areas had abundant psammomatous calcifications

* Corresponding author at: 320 West 10th Avenue, M-210 Starling Loving Hall, Columbus, OH 43210, United States.
E-mail address: david.cohn@osumc.edu (D.E. Cohn).

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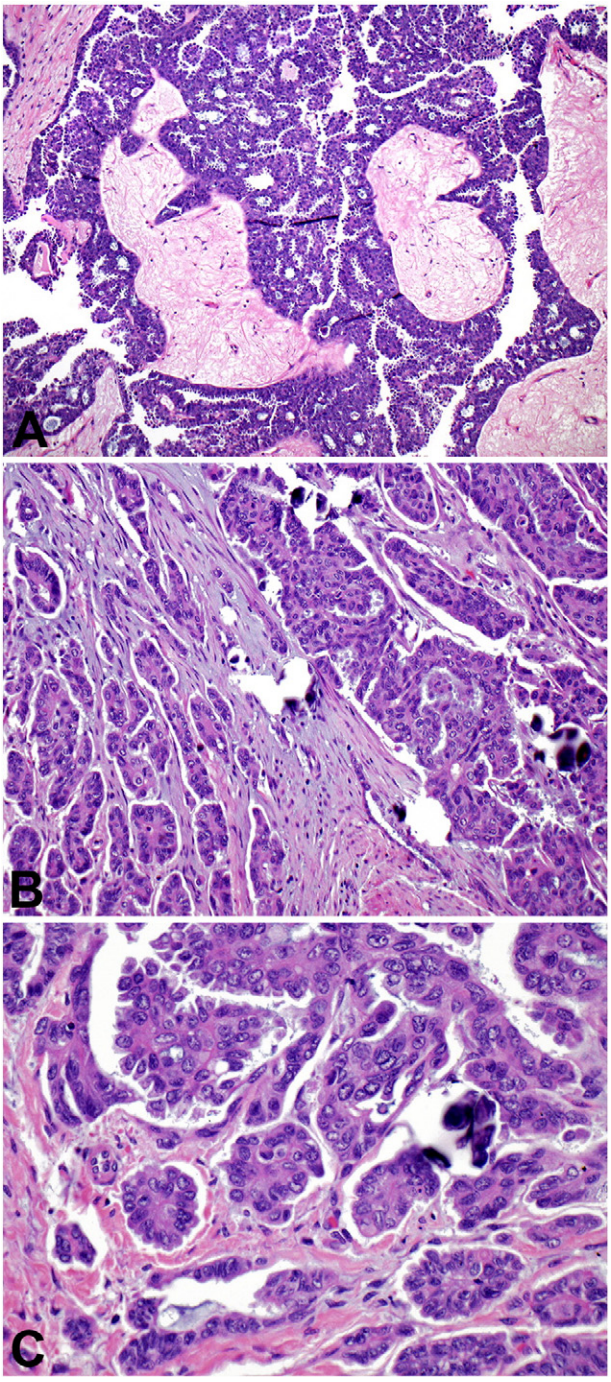

Fig. 1. Areas of the tumor with no evidence of stromal invasion showed monotonous cells growing in non-hierarchical long coalescing papillae giving the impression of cribriforming (A). Other areas had definite infiltrative architecture and desmoplastic stromal reaction indicating an invasive tumor; also seen are psammoma bodies (B). Invasive epithelial clusters showed only mild to moderate nuclear atypia (C).

[Fig. 1B]. On high power these areas are characterized by cells that have a fair amount of cytoplasm and relatively uniform nuclei with only mild to moderate atypia [Fig. 1C]. Mitotic figures were rare. There was diffuse nuclear labeling for estrogen receptor (ER) by immunohistochemistry. Collectively, the pathologic findings are those of low-grade serous carcinoma. We use a two-tier grading system which has been shown to provide a more precise prediction of clinical patterns [1] and to be reproducible [2]. This grading system was developed by M.D. Anderson and classifies serous carcinomas as low- and high-grade tumors [1]. It is based primarily on nuclear atypia with mitotic index as a secondary feature (≤12 mitotic index in low grade tumors vs >12 mitotic figures in high grade ones). High grade serous carcinomas are characterized by nuclear pleomorphism and anisonucleosis (≥3:1), irregular chromatin and prominent nucleoli. Low grade serous carcinomas have round to oval nuclei and evenly distributed chromatin. Two-tier grading of ovarian serous carcinomas is currently definitional in the WHO classification of tumors [3] and is in wide use in the United States. From the point of view of diagnostic pathology the distinction between low-grade and high-grade serous carcinomas is mostly a morphologic one and thus the diagnosis is typically made on H&E without recurring to special immunohistochemical stains. However, intense diffuse staining and complete absence of p53 are both consistent with mutations of this tumor suppressor gene, a characteristic early event in high-grade serous carcinogenesis infrequently seen in low-grade serous carcinomas and serous borderline tumors [4]. Similarly, differences in p16 staining (with intense nuclear and cytoplasmic staining in high-grade serous carcinomas and patchy staining in low-grade serous carcinomas) may be occasionally used to aid in the diagnosis [5].

Molecular events

The past decade has witnessed a rapid expansion in our understanding of the unique molecular profile of low-grade serous carcinoma of the ovary. The most commonly altered pathway in LGSC is the mitogen-activated protein kinase (MAPK) pathway. MAPK is a family of single-transduction enzymes that is involved in gene expression pathways. Activation of ERK1 and 2 leads to nuclear activity that leads to cell proliferation, survival and mobility. When the pathway (more broadly known as the RAS/RAF/MEK/ERK pathway) is dysregulated, cellular growth is inhibited (thus providing the rationale for MEK inhibition in cancer). Mutations in the genes in the RAS/RAF pathway have been documented in 20% of cancers overall, but are substantially more prevalent in specific malignancies like melanoma.

In 2003, Singer and colleagues reported that mutations in BRAF or K-RAS – which are upstream of MEK in the pathway – were found in over two-thirds of low-grade serous carcinomas, and are considered mutually exclusive (meaning, that no tumor had both a BRAF and K-RAS mutation) [6]. In contrast, none of the high-grade serous carcinomas evaluated contained a BRAF or K-RAS mutation. In general, 19–70% of low-grade serous tumors of the ovary have K-RAS mutations, while 2–14% have BRAF mutations [7]. A recent study addressed the issue of pathogenesis using genomic analyses of serous borderline tumors and low-grade serous carcinoma of the ovary and found two novel candidate genes – BIF1AX and USP9X – both of which appear to be mutated at much higher rates in low-grade serous carcinoma compared with serous borderline tumors [8]. Taken together, these findings suggest that specific oncogenic mutations may drive the development (or progression) of low-grade serous carcinoma from serous borderline tumors. The prevalence of alterations in this pathway in LGSC has provided the rationale for evaluating MEK inhibitors as a treatment option, and this is discussed in a separate section.

Epidemiology, the differential diagnosis and the role of tumor markers

The median age at diagnosis of low-grade serous ovarian cancer is 38 years, which is in contrast to high-grade serous ovarian cancer, in which the median age of diagnosis is 62. Low-grade serous carcinoma accounts for approximately 10% of serous ovarian cancers, whereas about 80% of high-grade ovarian cancers are of serous histology. Low-grade serous ovarian cancers likely arise de novo in conjunction with serous borderline tumors or as a recurrence in a patient previously diagnosed with a serous borderline tumor. In support of this theory, low-grade serous ovarian cancer is associated with a concurrent component of serous borderline tumor in about 60% of cases, yet only 2% of high-grade serous cancers are concurrently diagnosed with a serous borderline tumor.

Given the relatively young age at diagnosis for low grade serous ovarian cancer, the disease must be considered in the differential