Educational Case

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Educational Case: High-Grade Serous Carcinoma of the Ovary

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, female reproductive system, ovary, ovarian neoplasia, high-grade serous carcinoma, cytology, peritoneal fluid

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Primary Objective

FO1.2: Causes of Ovarian Neoplasm: Describe the risk factors, genetic associations, and molecular basis, including hereditary cancer syndromes, for ovarian neoplasms, including those derived from epithelium, sex-cord stromal as well as germ cell neoplasms.

Competency 2: Organ System Pathology, Topic: Female Reproductive—Ovary (FO), Learning Goal 1: Ovarian Neoplasia

Secondary Objectives

N3.1: Morphologic Features of Neoplasia: Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanism and Processes, Topic: Neoplasia (N), Learning Goal 3: Characteristics of Neoplasia

SP1.2: Differential Diagnosis: List the major differential diagnoses for each type of cytology or surgical pathology specimen derived from a lesion or mass and describe appropriate further studies, both special stains and immunohistochemistry.

Competency 3: Diagnostic Medicine and Therapeutic Pathology, Topic: Surgical Pathology (SP), Learning Goal 1: Role in Diagnosis

CYP1.4: Use of Cytology for Staging of Neoplasm: Describe how cytologic specimens can add valuable information for tumor staging.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: Cytopathology (CYP), Learning Goal 1: Cytologic Diagnosis

Patient Presentation

A 72-year-old postmenopausal woman presents to her primary care physician for gradual onset of abdominal discomfort, bloating, and fullness of the abdomen over last several months.

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She has no significant past medical history, and she is up-to-date with her screening pap tests and mammograms. She has never been pregnant nor taken oral contraceptives. She denies a history of cigarette smoking. She has a family history of a paternal first cousin with breast cancer in her early 40s and a paternal aunt with ovarian cancer in her 50s. Her menarche was at age 12, and she reached menopause in her 50s.

Diagnostic Findings, Part 1

On physical examination, she is found to have moderate symmetric distension of the abdomen and a positive fluid wave. Her abdomen is nontender to palpation with normal bowel sounds. Pelvic examination reveals a painless, nonmobile left adnexal mass. There is no hepatosplenomegaly.

Questions/Discussion Points, Part 1

What Additional Workup Should These Physical Examination Findings Prompt?

The presence of a distended abdomen with a positive fluid wave along with a painless nonmobile left adnexal mass warrants further workup. These findings, especially in the postmenopausal age-group, raise the possibility of a malignant ovarian neoplasm. Ultrasound would be helpful to further characterize the adnexal mass; however, due to the presence of concurrent obscuring ascites, abdominal and pelvic computed tomography (CT) maybe a more helpful diagnostic tool. Imaging characteristics concerning ovarian malignancy include cystic masses with septations, multiloculation, or a mass with both solid and cystic components. Also, measurement of serum tumor markers such as cancer antigen-125 (CA-125), lactate dehydrogenase, alpha–fetoprotein, and beta-human chorionic gonadotropin can be helpful as some ovarian tumors may cause an elevation in one or more of these markers.

Diagnostic Findings, Part 2

Given the concern for malignancy due to her presentation with an adnexal mass and ascites, the patient is referred for abdominal and pelvic CT. The imaging shows an irregular, multilocular 10-cm left adnexal mass, abdominal ascites, and omental caking; all 3 features concerning metastatic malignancy. Blood work indicates a CA-125 of 641 U/mL (reference range 0-35 U/mL).

Questions/Discussion Points, Part 2

What Is the Differential Diagnosis Based on the Clinical, Imaging, and Laboratory Findings?

The differential diagnosis of a postmenopausal woman with a unilateral adnexal mass and ascites with imaging features suggestive of metastatic malignancy includes high-grade ovarian neoplasms. The most common high-grade ovarian neoplasm, which often presents with metastatic disease, is high-grade serous carcinoma (HGSC). Other primary ovarian neoplasms usually present earlier and without the involvement of extrapelvic organs. The other possibility to consider is a high-grade malignant neoplasm of the gynecologic tract that secondarily involves the ovary, which is often not possible to clarify with clinical and imaging characteristics. The presence of high CA-125 favors a primary ovarian malignancy over metastasis. Cancer antigen-125 is a serum marker used for screening ovarian cancer but lacks sensitivity for disease detection before advanced stage. Serum levels between 500 and 1000 U/mL are abnormal and may be associated with ovarian malignancy. Unfortunately, this marker has not proven to be a useful screening tool, as it is often elevated in non-neoplastic conditions like pregnancy and is normal in a significant proportion of women found to have ovarian cancer. Furthermore, CA-125 is not entirely site-specific and can be raised in a fallopian tube, endometrial, and primary peritoneal carcinoma as well. Therefore, the harm of surgery and psychological distress for patients with false-positive screens outweighs any mortality benefit from screening for elevated CA-125 in clinical decision-making. However, serum levels of CA-125 are used clinically to evaluate for potential recurrence following surgical resection and chemotherapy in women with high-grade serous ovarian cancer.[2-4]

Diagnostic Findings, Part 3

Given her extensive disease with omental caking and ascites, a diagnostic biopsy of her omental tissue is performed to confirm the nature of the malignant neoplasm. (Needle biopsy of ovarian masses is generally avoided due to the risk of seeding malignant cells in the abdomen in the process of obtaining tissue. However, recent studies have reported the risk of peritoneal needle track seedling to be very minimal.[5]) The histologic and immunohistochemical characteristics of the omental tissue biopsy are most consistent with an HGSC.

The patient then undergoes surgical cytoreduction and staging, including visual assessment of her abdominal organs and peritoneal surfaces, hysterectomy with bilateral salpingo-oophorectomy, and omentectomy. The ascitic fluid is also submitted for cytologic evaluation, as this is an important part of staging ovarian neoplasms.

Questions/Discussion Points, Part 3

What Are the Different Types of Primary Ovarian Tumors?

Tumors of the ovary can arise from one of the 3 cell types found in the ovary: surface epithelial cells, germ cells, or sex cord-stromal cells (Figure 1). The most common type of primary ovarian tumor is epithelial, and the most common malignant epithelial tumor is serous carcinoma. Other types of malignant epithelial carcinoma include mucinous, clear cell, and endometrioid. Serous carcinomas are further categorized as high and low grade depending on histologic appearance and architecture. High-grade serous carcinoma accounts for up to

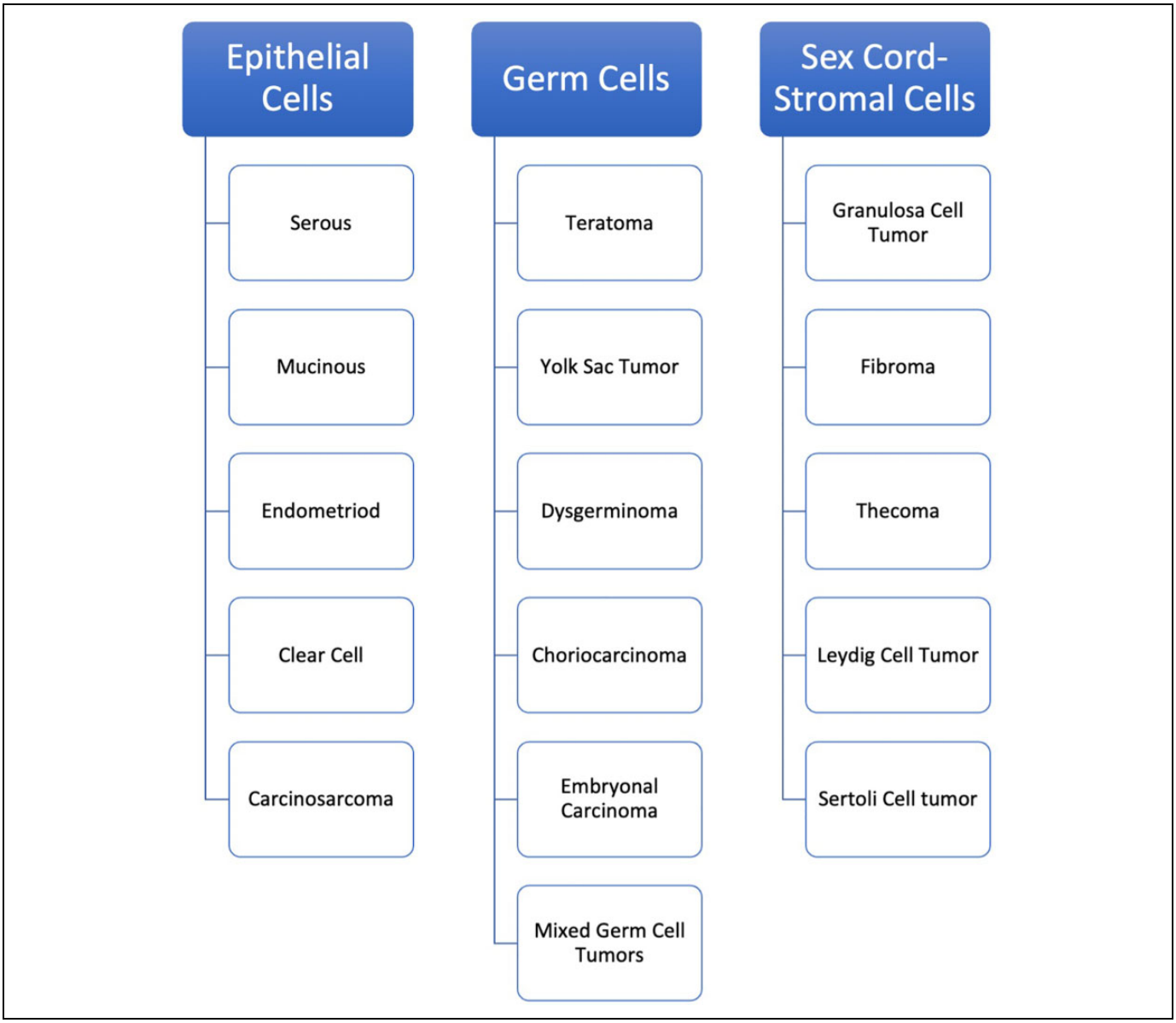

Figure 1. Primary ovarian tumors can be categorized by likely tissue of origin: epithelial, germ, or sex cord-stromal cells.

70% of all ovarian cancers and is associated with the highest mortality.[3]

Germ cell tumors are proliferations of different germ cell lines: oocytes give rise to dysgerminomas, extraembryonic yolk sac cells give rise to yolk sac tumors, and placental cells give rise to choriocarcinoma. Teratomas, the most common germ cell tumor, occur in women of reproductive age and are derived from germ cell lines. Grossly, these tumors are cystic structures that contain hair, sebaceous material, and calcified material resembling teeth. These tumors can be categorized as immature or mature. Malignant immature teratomas are distinguished from benign mature teratomas by the presence of neuroepithelium and are associated with more rapid growth and spread.[6]

Sex cord-stromal tumors can be hormonally active, as they are derived from cells related to gonadal hormone regulation. Ovarian stroma is embryonically derived from the embryonic gonad, which is undifferentiated until hormonal signaling during fetal sex cord development. Due to this, neoplasms representing both male and female sex cord stroma can occur in ovaries. Sertoli and Leydig cell tumors are composed of cells that resemble sex cord-stromal cells of testes, thus these tumors are associated with the production of testosterone and virilization. Conversely, granulosa cell tumors are known to produce a large, pathologic amount of estrogen. This excess estrogen can present clinically as precocious puberty in children or endometrial hyperproliferation or estrogen-sensitive breast proliferation in adult women. Sex cord-stromal tumors derived from fibroblasts (fibromas), lipid droplets (thecomas), or a combination of the 2 and are less commonly hormonally active.[6]

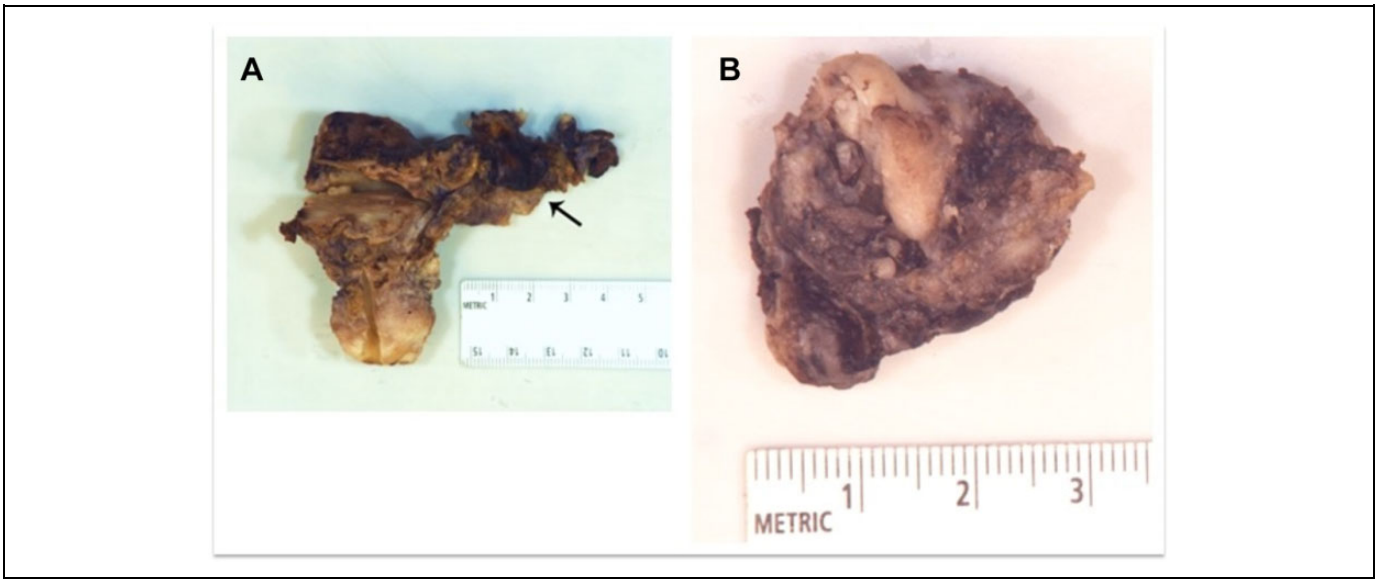

Figure 2. Gross images. (A) Uterus with left adnexa (black arrow) and para-adnexal soft tissue. The fallopian tube has a red shaggy serosal surface and a fimbriated end with multiple tan-red adhesions. Sectioning of para-adnexal soft tissue reveals a diffusely hemorrhagic cut surface. (B) Left ovary. The ovarian surface displays hemorrhagic serosal adhesions. Sectioning of the ovary reveals a yellow-white mottled cut surface. The entire ovarian parenchyma is replaced by a hemorrhagic friable mass.

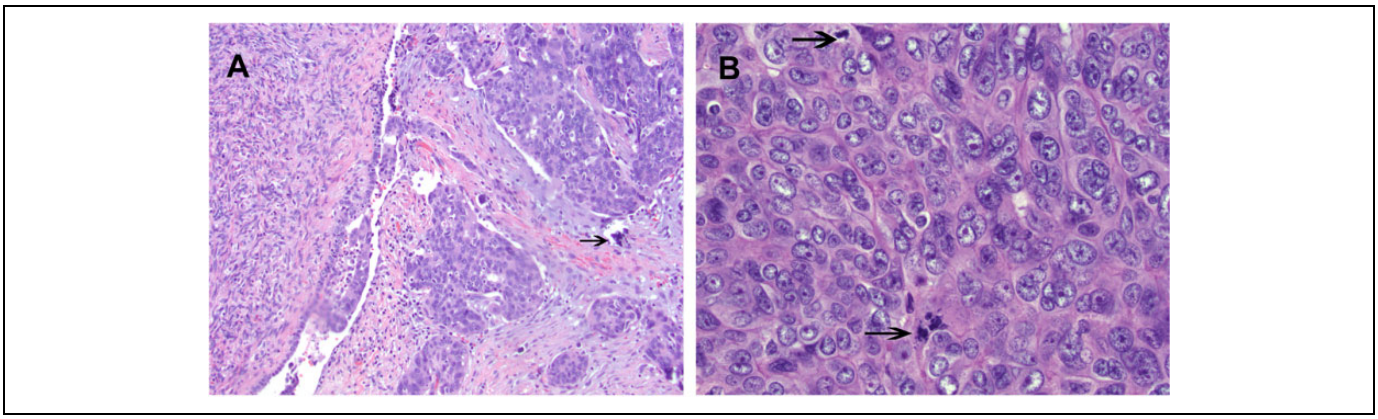

Figure 3. Serous ovarian carcinoma: nests of invasive tumor cells involve the left ovary (black arrow on associated calcifications) (A), uterine serosa and myometrium (B) shows moderate to severe pleomorphism, increased nuclear to cytoplasmic ratio, prominent nucleolus, and atypical mitotic figures (black arrow; hematoxylin and eosin, ×400).

Describe the Gross and Microscopic Features of High-Grade Serous Carcinoma

On gross examination, HGSC of the ovary can be unilateral or bilateral (Figure 2). They typically present as complex cystic structures with the cyst walls comprised of papillary epithelium. Irregular shape, nodularity on the tumor capsule, and capsular adherence to other pelvic structures are gross features associated with malignant serous tumors. Malignant and borderline serous tumors also frequently involve the surface of the ovary[6] (Figure 2B). This tumor also displays hemorrhagic and friable cut surfaces. Frequently, HGSC extends beyond the ovary into the fallopian tube, para-adnexal soft tissue, uterine serosal surface, peritoneal cavity, and omentum.

The microscopic examination revealed sheets and trabeculae of tumor cells in solid configuration (Figure 3). The tumor cells have a high nuclear to cytoplasmic ratio, prominent nucleoli, moderate pleomorphism, and associated calcifications. Microscopically, tumor cells are seen infiltrating the uterine serosal surface and myometrium.

What Grading Schema Is Used to Grade Ovarian Carcinoma? If the Entire Tumor Resembles That Represented Here, What Grade Would You Give This Tumor?

There have been multiple systems previously proposed to grade serous ovarian tumors. The World Health Organization grading

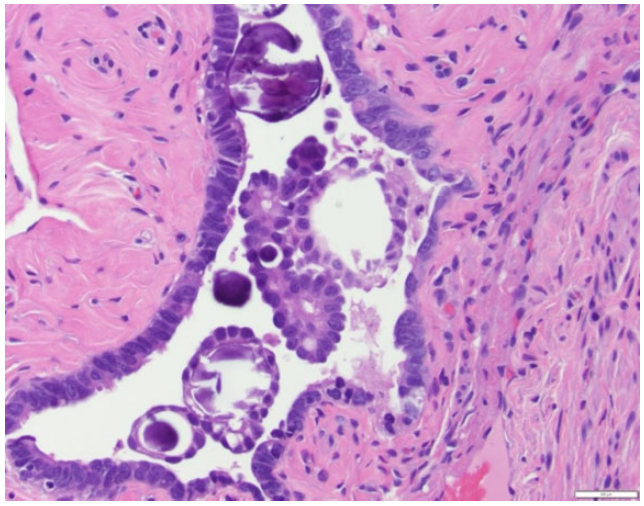

Figure 4. Low-grade serous neoplasm involving fallopian tube epithelium shows monotonous round to oval nuclei, few papillary structures, and psammomatous calcifications (hematoxylin and eosin, ×400).

system considered the cytology of the tumor. However, the cytologic parameters for each grade were not concretely described, and therefore, the system was not widely adopted. The International Federation of Gynecology and Obstetrics (FIGO) system considers architecture and the percentage of solid tumor compared to glandular or papillary structures out of the total tumor volume to determine a 3-tiered grade: grade 1 is equivalent to less than 5% solid tumor, grade 2 is 5% to 50% solid growth, and grade 3 is greater than 50% solid growth in proportion to the total tumor volume.[7] The Shimizu/Silverberg system mirrors the Nottingham system of breast carcinoma evaluation, considering architecture, cytologic atypia, and mitotic index.[8]

The only recommended grading system adopted as the standard of care is the 2-tiered grading system (high grade vs low grade) due to its better reproducibility and prognostic value in the initial evaluation of patients with serous ovarian carcinoma. This system considers nuclear features and mitotic activity.[7] The histology of HGSC is not reliably uniform, though tumors typically form in solid masses of malignant cells with some areas of necrosis. Architecture can be varied to include papillary or cribriform configurations. High-grade serous carcinoma is typically associated with nuclear atypia with hyperchromatic and pleomorphic nuclei with eosinophilic nucleoli. Mitotic figures are common[4] (Figure 3). Using this 2-tiered system, this patient's tumor would be HGSC based on the findings of nuclear atypia, increased nuclear-cytoplasmic ratios, prominent nucleoli, and atypical mitotic figures. Low-grade serous carcinoma (LGSC), on the other hand, usually shows a papillary pattern with fibrovascular cores, and psammoma bodies are frequently observed. Low-grade serous carcinoma typically has uniform appearing nuclei with less than 3-fold variation in nuclear size (Figure 4), which is key to differentiate it from HGSC.[8]

Beyond histologic differences, HGSC and LGSC have distinct molecular pathways associated with their development. High-grade serous carcinomas are characterized by somatic *TP53* mutations, and the LGSC are characterized by somatic mutations in *BRAF* and *KRAS* (MAP-kinase pathways). The key morphologic, immunophenotypic, and molecular differences between the 2 subtypes are listed in Table 1. Recent studies have revealed that HGSC may originate from the fallopian tube epithelium rather than the ovarian surface; carcinoma originating from these cells has been designated as "serous tubal intraepithelial carcinoma" (STIC). Studies have further demonstrated that primary peritoneal HGSC and fallopian tube HGSC originate from STIC of fallopian tube fimbriae in up to 60% of cases and are often lumped together with ovarian HGSC for the purpose of staging of tumors beyond stage III. On the contrary, LGSC is believed to follow a different pathway and usually progress from serous borderline tumors.[8]

Describe the Cytologic Findings of the Peritoneal Fluid Cytology and Importance of Its Evaluation in Staging of Ovarian Neoplasms

Cytologic evaluation of the peritoneal fluid in a negative sample shows benign sheets of mesothelial cells, scattered inflammatory cells, and absence of epithelial cells. Peritoneal fluid cytology in this patient reveals tight 3-dimensional clusters of tumor cells with increased nuclear to cytoplasmic ratio and prominent nucleoli (Figure 5). Increased cytoplasmic eosinophilia, papillary configuration, and psammomatous calcifications can also be seen in a cytologic analysis of ascites in patients with HGSC.[9] If the primary malignancy is unknown during peritoneal fluid cytology evaluation, immunohistochemical profiles often help determine the site of origin of gynecologic tract.[10] Involvement of peritoneal fluid confers a higher stage than disease confined to the adnexa. Hence, peritoneal lavage fluid/ascitic fluid is routinely sent for cytologic evaluation while performing surgical cytoreduction and staging.

What Is the Utility of Additional Pathologic Analysis at This Point in Treatment?

Confirming the presence of tumor cells in samples taken from different sites (omentum, ovary, and uterus) as metastasis of a single malignancy rather than distinct processes has implications for prognosis and treatment. Morphologic comparison of the tumor cytology in different tissues often helps confirm metastasis.

The use of immunohistochemical stains helps characterize the tumor and its potential origin (Figure 6). Mutations in the tumor suppressor p53 are almost universal in HGSC; tumors might express null pattern or complete negative staining (resulting from a nonsense mutation) or strong diffuse positive or overexpression like in this case (resulting from a missense mutation and overexpression of the mutant protein). The overexpression of p53 observed in this case is usually due to a somatic mutation involving the *TP53* gene. High-grade serous carcinoma shows a high Ki67 positivity rate, higher than other serous tumor types (LGSC and borderline tumors), representing a higher rate of cell

Table 1. High-Grade Serous Carcinoma (HGSC) Versus Low-Grade Serous Carcinoma (LGSC).

Tumor Grade	Histologic features	Immunohistochemical profile	Genetic mutations	Proposed precursor lesion
HGSC	• Pleomorphic nucleoli (>3-fold variation in size) • Solid, papillary or cribriform architecture • High mitotic rate (>12 mitoses/10 HPF)	• WT-1 (80%) positive • ER; PR variable • High Ki-67 rate • Diffuse P53 nuclear Overexpression or null staining (complete loss of expression)	• Somatic *TP53* mutation in 95% • *BRCA1/2* somatic or germ line mutation in up to 50%	Serous tubal intraepithelial carcinoma (STIC)
LGSC	• Uniform nuclei (<3-fold variation in size) • Mostly papillary architecture • Low mitotic rate • Frequent psammomatous calcifications • Borderline component	• WT-1 (70%) positive • ER PR positive • Low Ki-67 index • P53 wild type	• No association with *TP53* Or *BRCA1/2* • Somatic mutation in *KRAS/BRAF* pathway	Borderline tumors

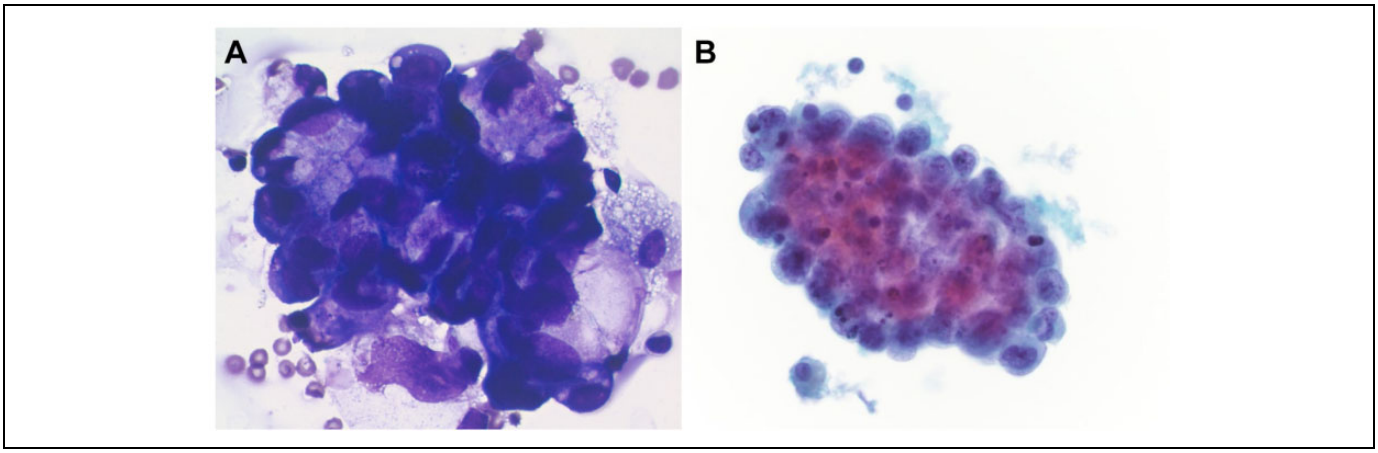

Figure 5. Peritoneal wash cytology: A-B: Three-dimensional tight clusters of atypical cells with increased nuclear to cytoplasmic ratio, moderate pleomorphism, coarse chromatin, and prominent nucleoli (thin prep, Diff-Quik (A) and papanicolaou stain (B), ×400).

division. Other typical findings of HGSC distinguish stained cells as epithelial in origin ($CK7^+/CK20^-$) and derived from the gynecologic tract ($PAX8^+$). Positive staining for WT-1 and negative staining for HNF-1 help different HGSC from other ovarian tumor types. p16 is often positive in HGSC. Estrogen and progesterone receptors are variably expressed in HGSC as compared to LGSC.[8] This tumor is positive for ER and negative for PR. The immunostain findings in this case are consistent with an HGSC of the ovary.

What Risk Factors for Ovarian Carcinoma Are Present in This Patient's History?

Risk factors for the development of serous ovarian carcinoma are early age of menarche, older age of menopause, and nulliparity—all of which result in increased ovulatory cycles. Protective factors are those that decrease the number of ovulatory cycles, such as pregnancy, oral contraceptives, and breastfeeding.[11,12]

How Does the Patient's Family History Relate to Her Diagnosis? What Genetic Mutations Can Predispose Patients to Ovarian Carcinoma?

The patient's family history of 2 relatives with early onset breast carcinoma and ovarian carcinoma is concerning germ line mutations, such as mutations in *BRCA* genes. The patient's age and the fact that these relatives are second degree make a germ line *BRCA* mutation less likely in this case.

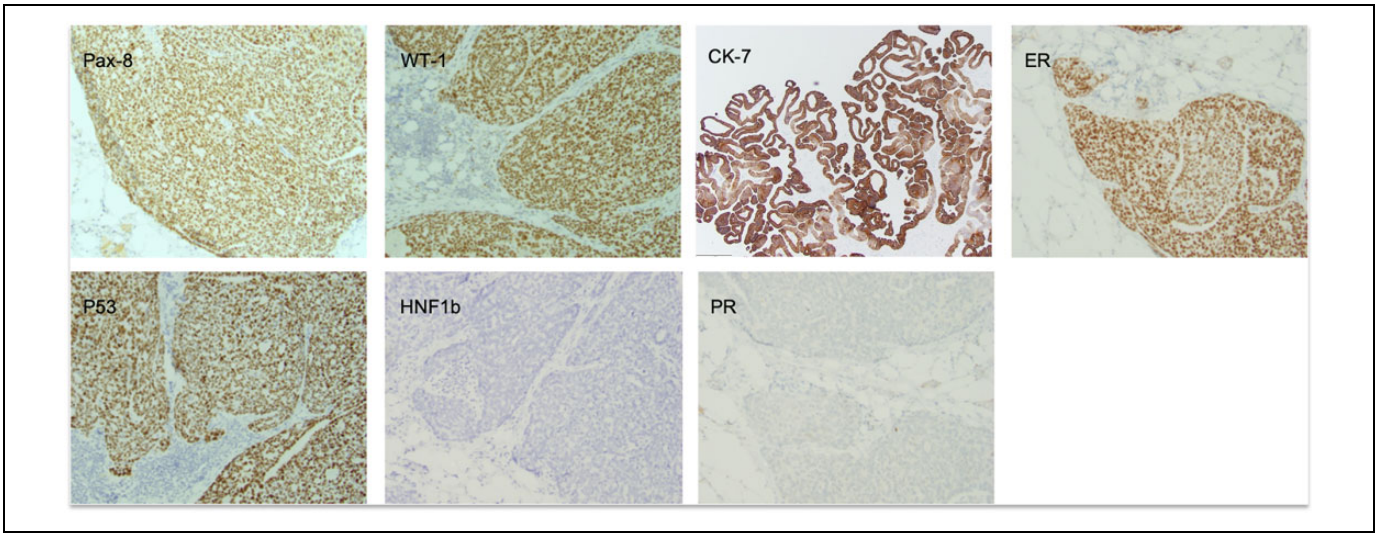

Figure 6. Serous carcinoma cells showing immunoreactivity for PAX-8, Wilms tumor-1 (WT-1), cytokeratin 7 (CK7), estrogen receptor (ER), overexpression of P53, and no immunoreactivity for HNF-1 beta subunit (HNF-1β) and progesterone receptor (PR; each ×100).

BRCA1 and *BRCA2* are genes important for the repair of double-stranded DNA breaks via a process called homologous recombination repair. Homologous recombination repair uses a homologous template, unlike nonhomologous end joining, and is therefore less error-prone. In fact, although somatic and germ line mutations in *BRCA1* and *BRCA2* are implicated in only a proportion of serous ovarian cancers, some gene mutation, *BRCA* or otherwise, in the homologous recombination repair system is found in most epithelial ovarian cancers.[4,12,13] Genetic mutations in the homologous recombination DNA repair pathway are implicated in around half of cases, the most common being *BRCA1* and *BRAC2* (others include *CSMD3, NF1, CDK12, GABRA6, RB1*).[13]

It is believed that a proportion of HGSC in *BRCA* positive patients arise from STIC, prompting surgeons to routinely remove fallopian tubes in addition to ovaries in prophylactic procedures.[4] The American College of Gynecology recommends counseling patients on possible HGSC risk reduction with opportunistic salpingectomy in all patients undergoing hysterectomy for any indication.[14]

How Are Ovarian Carcinomas Staged?

Staging of ovarian carcinoma is done using FIGO guidelines. Stage I tumors are confined to the ovary and fallopian tube, and stage II tumors include spread to other peritoneal organs within the pelvis. Ovarian carcinoma commonly spreads to the peritoneal and pelvic cavity, and the extent of this involvement is used for staging purpose—Stage III includes peritoneal metastases outside the pelvis and stage IV includes distant metastases including liver metastases and malignant pleural effusions.[15] In this case, involvement of the fallopian tube, macroscopic lesions >2 cm on the omentum (outside the pelvic brim), and malignant cells found in the peritoneal fluid represents a stage IIIC serous carcinoma.

The majority of HGSCs of the ovaries are discovered late with advanced disease: only 13% of serous carcinoma are discovered in stages I or II.[4] This is most likely due to the ambiguity and late onset of symptoms. Neoadjuvant chemotherapy is sometimes used to make cytoreductive surgery more feasible in patients with advanced disease. Surgical resection after chemotherapy can make it challenging to determine the origin of cancer from different pelvic organs.

What Is the Recommended Management of Ovarian Epithelial Tumors?

Low-grade ovarian epithelial neoplasms with clinical stage of I to IIa are usually treated with debulking surgery. The treatment of HGSC is driven by the clinical and surgical stage. The stage predicts the likelihood of recurrence, distant metastases, and overall survival of the patient. Since the majority of HGSC presents with metastases to the peritoneal cavity and other organs (stage IIb-IV), their treatment regimen is comprised of a debulking surgery along with combination chemotherapy (paclitaxel and carboplatin). Ovarian epithelial tumors are largely chemoresponsive, and some higher stage tumors (stage IIC-IV) are treated with neoadjuvant chemotherapy followed by debulking surgery. Relapsed ovarian tumors after initial treatment are either treated with combination platinum-based chemotherapy or a single cytotoxic agent.[16]

Newer targeted therapeutic agents are also found to be helpful in treatment-resistant ovarian epithelial tumors. The newer agents include bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, and oral inhibitors of poly (ADP-ribose) polymerase. *BRCA* mutational analysis is also taken into consideration for treating treatment-resistant HGSC.[16]

Teaching Points

- An adnexal mass with ascites in a postmenopausal woman should be considered worrisome for a primary ovarian neoplasm.
- Ultrasound, abdominal, and pelvic CT scans are useful imaging modalities for the assessment and diagnosis of pelvic lesions and masses.
- CA-125 is not useful as a screening marker for ovarian cancer, but it can be used in the monitoring of recurrence for women with known ovarian cancer.
- Risk factors for the development of ovarian cancer include factors that increase the number of ovulatory cycles, including nulliparity, early menarche, and late menopause.
- Primary ovarian tumors can be grouped according to their tissue of origin: epithelial, germ, or sex cord-stromal cells.
- High-grade serous carcinoma is the most common ovarian epithelial neoplasm and has high rates of recurrence and metastatic disease.
- High-grade serous carcinoma is associated with germ line and somatic *BRCA* mutations, as well as other genetic mutations that may reflect defects in homologous recombination repair system.
- High-grade serous carcinoma and LGSC are 2 distinct serous carcinomas with different molecular pathway and morphologic and immunohistochemical characteristics.
- High-grade serous carcinoma is staged using the FIGO system, and the presence of malignant serous epithelium in cytological evaluation of peritoneal washings confers a more advanced stage.
- Immunohistochemical stains are often helpful in confirming the diagnosis of ovarian neoplasms.
- Management of HGSC is a combination of debulking surgery, peritoneal lavage fluid for staging, and adjuvant chemotherapy.

Declaration of Conflicting Interests

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