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Rare Ovarian Tumors

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Abstract: Ovarian cancer is the eighth most common cancer among women globally. There are currently no feasible screening strategies for this disease. Diagnosis, treatment, surveillance, and survival of patients have improved over the years with advancements in radiology, pathology, genomics, and molecular biology. Individualized care incorporates precision surgery to limit morbidity. Germline genetic analysis and identification of somatic mutations in tumor tissue provide data for the use of targeted agents and immunotherapy. High grade serous carcinomas comprise 70% of diagnoses, but rare ovarian cancers affect women characterized by a wide spectrum of ages and risk factors. This chapter discusses the pathologic and molecular features of these cancers. The text also highlights the evolution of treatment to modern-day standards and the landmark trials that contributed to these changes.

Keywords: clinical management of ovarian tumors; epithelial ovarian carcinoma; ovarian sex cord-stromal tumors; rare ovarian tumors; sex-cord stromal ovarian germ cell tumors

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INTRODUCTION

Rare ovarian tumors present as clinical complexities for clinicians around the world. The World Health Organization categorizes ovarian cancer into three groups: epithelial, germ cell, and sex-cord stromal (1). Tumors in each of these categories have distinct epidemiology, pathophysiology, and molecular biology. In this chapter, we discuss the intricacies of diagnosis, prognosis, and clinical management of these tumors.

OVARIAN GERM CELL TUMORS

Ovarian germ cell tumors (OGCT) are derived from totipotent gonadal germ cells. The histologic subtypes in this category of tumors are similar to those from the male testes, such as the analogous relationship between ovarian dysgerminoma and testicular seminoma. OGCT are staged similarly to epithelial ovarian carcinomas but have a bimodal distribution of age groups. About 58% of tumors in patients under age 20 are identified as OGCT (2). Fertility preservation is an important consideration during surgical staging. Although there are fewer studies compared to their seminomatous counterparts, the advancements in adjuvant therapy, pre-operative imaging, and molecular testing have improved patient-tailored care.

Dysgerminoma

According to a SEER database study from 1973 to 2002, dysgerminomas comprise about 33% of OGCT (3). Bilaterality occurs in 10–15% and is more common compared to non-dysgerminoma tumors. Clinical presentation includes an enlarged, palpable abdominal mass with abdominal distension. About 75% of women present with stage I disease (4). Lactate dehydrogenase (LDH) is a commonly used tumor marker. LDH is expressed on chromosome 12p, which has been found to be mutated in 81% of dysgerminomas through over-representation or isochromosome formation (5). Approximately 3–5% of patients can have elevation of human chorionic gonadotropin (hCG) due to the presence of syncytiotrophoblast cells (6).

These tumors can arise out of a gonadoblastoma, which are commonly benign tumors that are composed of sex-cord and stromal cells. Gonadal dysgenesis is also seen in these patients that can be categorized into two groups: 46XY pure gonadal dysgenesis (Swyer syndrome) and 45X/46XX mixed gonadal dysgenesis (7). Oophorectomy should be performed prior to puberty due to the high risk of contralateral dysgerminoma, except in the case of complete androgen insensitivity syndrome.

c-KIT is a tyrosine kinase that initiates cell growth in a variety of cells and is mutated in 25–50% of dysgerminomas (8). However, current immunotherapeutic targeting of this marker is unlikely to produce effect since mutations are most commonly expressed on exon 17, and drugs such as imatinib target actionable driver mutations on exon 11 (9).

These masses manifest as fleshy tan to white masses with areas of focal necrosis or hemorrhage. Histopathology shows sheets of polygonal cells with eosinophilic cytoplasm. Nucleoli are prominent and the nuclear membrane features angulated edges. Lymphocyte-containing fibrous septations are characteristic of this tumor. The lack of necrosis suggests the origin of the tumor from an underlying gonadoblastoma. Membranous and cytoplasmic immunohistochemistry (IHC) markers include placental alkaline phosphatase (PLAP) and D2–40 (podoplanin), while nuclear staining can stain positive for transcription factors octamer-binding transcription factor 4 (OCT-4), NANOG, and sal-like protein 4 (SALL4) (10–12).

Yolk sac tumor

Yolk sac tumors are the second most common subtype and make up 14–20% of OGCT (3). These malignant cells derive from the mesenchyme of the primitive yolk sac and are associated with elevations of serum alpha-fetoprotein (AFP) (13). A SEER database study from 1973–2003 demonstrated that the median age of diagnosis was 19 years with a bimodal distribution (14). They present as large (average 15 cm), gray-yellow tumors with areas of hemorrhage and cystic degeneration. Tumor histology is often mixed, and usually involves a dysgerminoma component. They have rare presentations in older patients with origins from an epithelial endometrioid ovarian tumor. Histologic characteristics include a labyrinth of channels lined by primitive cells and a hypocellular, myxoid stroma. Other patterns include festoon and papillary (15, 16). The least common subtypes include solid, glandular, cribriform-tubular, polyvesicular vitelline, parietal, and hepatoid (17–19). Schiller-Duval bodies, central blood vessels surrounded by tumor cells, are pathognomonic for the classic subtype. IHC is notable for AFP focally, glypican-3 (non-specific), and SALL4, the latter of which is a transcription factor in embryonal cells (11, 20). Endodermal elements can have IHC staining based on their tissue they represent.

Embryonal carcinoma

Embryonal carcinomas represent 4% of OGCT and are diagnosed at an average age of 15 years. Patients usually present with abdominal pain, complaints of a pelvic mass, and abnormal uterine bleeding (AUB). Serum AFP and hCG are often elevated with these tumors, and an elevated estradiol level is associated with precocious pseudopuberty, a gonadotropin-independent process, in children (17). However, elevated estradiol levels cause menstrual abnormalities in postmenarchal individuals. Tumors are often large with an average diameter of 15 cm. Tumor cells exhibit well-defined, amphophilic cytoplasm with numerous mitotic figures. Syncytiotrophoblastic cells are often present and responsible for hCG elevation (17). IHC is positive for CD30, OCT4, SALL4, and glypican 4 (1). Embryonal carcinomas can be associated with gonadoblastoma and associated gonadal dysgenesis.

Non-gestational choriocarcinoma

These tumors are of the rarer form of OGCT and comprise 2% of the ovarian cancer group (21). They are highly aggressive compared to their placental counterpart. Short tandem repeat DNA testing can be used to differentiate these tumors

from gestational choriocarcinoma as the latter would contain paternal DNA (22). Intermediate trophoblastic cells, which express human placental lactogen (hPL), are arranged in a plexiform pattern with syncytiotrophoblastic cells (21).

Teratoma

Ovarian teratomas are derived from two of the three primary embryonic germ layers (ectoderm, mesoderm, endoderm). Monodermal teratomas are characterized by the tissue of origin, such as thyroid (struma ovarii) or gastrointestinal tract (carcinoid). A dermoid cyst is a particular type of teratoma composed only of ectodermal elements. The theory regarding the origin of teratomas involves parthenogenesis of an oocyte from the germ cell population (23). Teratomas are divided into mature and immature subgroups, the latter exhibits malignant characteristics based on the amount of neural differentiation on histology. The incidence of malignant degeneration is 0.3–2%, and squamous cell carcinoma is the most common histology (24, 25). Anti-NMDAR encephalitis, a rare paraneoplastic syndrome associated with this neoplasm, is thought to arise from autoantibodies targeting NMDAR in neuroectodermal components of the tumor (26).

Mature cystic teratomas account for 95% of ovarian teratomas and compose 20% of ovarian neoplasms in general. Patients present with abdominal pain with a pelvic mass about 5–10 cm in size. About 10% of these tumors are bilateral. Rokitansky protuberances are nodules of solid material that often contain adipose, dental, hair, or sebaceous products (26). These locations act as the nidus for carcinomatous degeneration. There are rare cases of predominantly solid teratomatous neoplasms. On histologic studies, ectodermal components include brain tissue, cerebellum, and ependymal tubules. Mesodermal structures include bone, cartilage, and smooth muscle. Endodermal findings include gastrointestinal/respiratory epithelium and thyroid tissue (1).

Immature teratoma

Immature teratomas comprise about 36% of OGCT and most commonly occur within the first three decades of life (3). Clinical presentation includes an elevated serum AFP level if associated with a yolk-sac component. These masses are usually unilateral, gray-tan in color, and contain areas of hemorrhage and necrosis. The immature neuroepithelial histologic components are the driving characteristic for malignancy and were originally graded into a 3-tiered system by Norris et al (27). Currently, the triple tiered grading is dependent on the presence of neuroepithelium in <1 (grade 1), 1–3 (grade 2), or >3 (grade 3) low power fields (LPF). Immature elements present as neuroectodermal tubules or rosettes and are surrounded by hyperchromatic and highly mitotic cells. Similar to dysgerminomas, teratomatous elements associated with mixed germ cell tumors harbor 12p isochromosomes or amplifications (28). These genetic findings suggest different molecular mechanisms behind pure and mixed teratomas.

Peritoneal spread is a phenomenon known to teratomas and are divided into two groups: gliomatosis peritonei and growing teratoma syndrome (GTS). The former is a rare condition originally described by Robboy et al. where mature glial elements are found in the peritoneal cavity (29). They are typically benign in nature and do not require additional therapy. Two theories regarding its origin

includes the implantation of cells from the teratomatous neoplasm and a "field effect" of cells that originate from Mullerian stem cells (30). GTS is the presence of mature teratomatous lesions after treatment for immature teratoma. Originally described as "chemotherapeutic retroconversion" by DiSaia et al. and later renamed by Logothetis et al., the manifestation of these tumors is generally regarded as benign and they are treated with surgical resection (31, 32). Three criteria should be met for this diagnosis: normalization of tumor markers during original treatment (AFP, hCG), new growth of masses during or after original treatment, and the identification of mature teratomatous elements in the newly found mass.

OVARIAN SEX CORD-STROMAL TUMORS

Sex-cord stromal tumors (SCST) are rare tumors that comprise about 8% of ovarian neoplasms (33). The sex cords embryologically derive from the gonadal ridges and develop into ovarian follicles. The stroma arises from the mesenchyme and differentiates into connective tissue, vasculature, and cells with endocrine function. Granulosa cells in the follicle aromatize androgens, produced from the mesenchymal-derived theca cell, to estradiol. Granulosa and Sertoli cells originate from the same gonadal precursor cells. Theca and Leydig cells are analogous and originate from two locations: primordial gonadal progenitor cells and the mesonephros (34). Steroid hormone production is the hallmark of these tumors, and precocious puberty, AUB, and virilization are clinical attributes. This group of tumors follow the same FIGO (International Federation of Gynecology and Obstetrics) staging system for ovarian epithelial carcinomas. A SEER database study demonstrated that 72% of cases are early-stage, and therefore have a favorable prognosis. About 57% of cases are in the age 30–59 age group, and an additional 12% are diagnosed in individuals younger than 30 years (35).

Fibroma

Ovarian fibromas are pure stromal tumors with an average age of diagnosis at 48 years, and account for 4% of ovarian neoplasms (36). Fibromas can range from small lesions during pathologic ovarian evaluation to a large pelvic mass. They are commonly unilateral. Ascites is more often noted in masses greater than 10 cm in diameter. Meigs syndrome, which includes the combination of pelvic ascites and pleural effusion, occurs in 1% of cases (37). Another rare clinical presentation is in patients with nevoid basal cell carcinoma syndrome (Gorlin syndrome) (38). These masses have a smooth capsule that range from white to yellow. There can be areas of cystic degeneration, hemorrhage, and necrosis. Nuclei have an ovoid appearance with minimal cytoplasm. Other histologic characteristics include collagen bands, hyalinized plaques, and cytoplasmic globules of lipid (36). Mitotic activity is generally not visualized. A subset called cellular fibromas, that comprise about 10% of these neoplasms, exhibit 4 or more mitoses per 10 high power field (HPF) (39). These neoplasms are not hormonally active. Trisomy and tetrasomy 12 can be found in these tumors. Cellular fibromas have been reported to have loss of heterozygosity with PTCH (9q22.3) and STK11 (19p13.3) (40).

Thecoma

Thecomas are pure stromal tumors that have the potential to be large pelvic masses of up to 40 cm, but usually about 5–10 cm. They are generally unilateral (97%), diagnosed at an average age of 59 years, and have a benign clinical course (41). They grossly present as a yellow mass with focal white areas. Histologic imaging shows oval to round nuclei with pale pink cytoplasm with ill-defined borders. Mitotic activity is not a common occurrence. These neoplasms are hormonally active and associated with postmenopausal bleeding (PMB) and endometrial hyperplasia/carcinoma (41). Positive IHC markers include inhibin and calretinin (42). Luteinized thecomas associated with sclerosing peritonitis are rare tumors that present in premenopausal women (average age 28 years) with bilateral localization and significant ascites (43). They are hormonally inert tumors that have a tan to red appearance on sectioning. Cells are spindle shaped, and there are interspersed rounded cells with pale cytoplasm that represent luteinization. Although benign, these neoplasms have exhibited associated morbidity secondary to complications from bowel obstruction.

Fibrosarcoma

Fibrosarcomas are pure stromal tumors that present as a lobulated, pelvic mass in unilateral fashion. They are malignant tumors with aggressiveness that is dependent on the level of anaplasia. Histologic evaluation reveals mitotic figures and pleomorphism. Associations with trisomies 8 and 12 are described in the literature (44). There is a rare association with Maffucci and Gorlin syndromes (45).

Leydig cell tumor

These pure stromal tumors account for 20% of steroid cell tumors. They are diagnosed at an average of 58 years and commonly secrete androgens (46). Clinical signs of virilization include hirsutism, clitoromegaly, male pattern baldness, and breast atrophy. These tumors are relatively small compared to the other tumors denoted in the SCST with an average diameter of 2.4 cm. Reinke crystals are characteristic for identification and these cells usually originate from the ovarian hilus, but stromal, non-hilar forms also exist (46). Because of the lack of mitoses or nuclear atypia, these tumors generally have a benign clinical presentation. IHC is positive for inhibin, calretinin, and steroidogenic factor-1 (SF-1) (47, 48).

Steroid cell tumor

Steroid cell tumors are pure stromal tumors and are usually specified as “not otherwise specified” (NOS). Approximately 50% have androgenic clinical symptoms (49). These tumors must be differentiated from stromal luteomas, which are neoplasms in the ovarian cortex with eosinophilic pale cytoplasm that contain lipochrome pigment and degenerative pseudovascular spaces without the presence of Reinke crystals (50). Tumor cells are polygonal with cytoplasm that ranges from eosinophilic (lipid-poor) to vacuolated (lipid-rich). Mitotic activity and atypia are rare but are present in 33% of neoplasms considered malignant. In addition to nuclear atypia, other malignant findings include tumor size greater than 7 cm,

greater than 2 mitoses per 10 HPF, necrosis and hemorrhage (49). IHC is positive for inhibin, calretinin, and SF-1 (47, 48).

Adult granulosa cell tumor

Adult granulosa cell tumors (AGCT) are pure sex cord tumors that comprise 95% of GCT and about 1% of all ovarian neoplasms (51). Clinical symptoms upon presentation include a pelvic mass and AUB. The sensitivity and specificity of tumor markers inhibin B and antimullerian hormone is 89%/100%, and 92%/81%, respectively (52, 53). Long-term surveillance is needed as 47% of recurrences are identified more than 5 years from diagnosis (54, 55). A concurrent endometrial biopsy or dilation and curettage is recommended for endometrial evaluation as 29% of patients exhibit endometrial hyperplasia and 5–7.5% are diagnosed with carcinoma (56). Poor prognostic factors include advanced stage, large tumor size (greater than 15 cm), bilaterality, and capsular rupture (1). Tumor cell nuclei have coffee-bean shapes that represent nuclear grooves, and the cytoplasm is eosinophilic due to luteinization. Nuclear atypia is seen in 2% of cases. Tumor growth patterns include diffuse, insular, microfollicular, and macrofollicular (1). Diffuse pattern exhibits tumor cells laid out in sheets and the insular pattern has tumor cell growth in cords and trabeculae. The microfollicular pattern is identified with Call-Exner bodies, which are eosinophilic spaces surrounded by granulosa cells. The cystic component of these tumors has granulosa cells that are undermined by theca cells, and some tumors have spindle cells that can be mistaken for a cellular fibroma. IHC is positive for inhibin, calretinin, SF-1, FOXL2, CD56, and Wilm's Tumor 1 (WT1). They are usually negative for cytokeratin 7 (CK7) and epithelial membrane antigen (EMA) (42, 57). Genetic aberrancies include trisomy 14 and monosomy 22 (58). FOXL2 is a nuclear transcription factor that exhibits a C402G point mutation in these tumors (59).

Juvenile granulosa cell tumor

Juvenile granulosa cell tumors (JGCT) are pure sex cord tumors that account for 5% of GCT and are diagnosed at an average of 15 years. Clinical symptoms include isosexual precocity in children and AUB in post-menarchal patients (60). About 95% of these tumors are FIGO stage I. Risk factors for recurrence include capsular rupture, ascites, and extra-ovarian spread. Unlike the recurrence pattern for AGCT, JGCT recur sooner within 3 years. Gross examination reveals solid and cystic components that are yellow to tan in color. Nuclei are round and exhibit mitotic figures with nuclear atypia in 10–15% of cases. Cellular cytoplasm is usually eosinophilic and the stroma is not as apparent compared to that of AGCT (60). IHC is positive for inhibin, calretinin, SF-1, CD56 and CD99. A small portion of cases exhibit staining for FOXL2. The genetic profile is associated with trisomy 12. These tumors can be associated with enchondromas including Maffucci syndrome and Ollier disease (61, 62).

Sertoli cell tumor

Sertoli cell tumors (SCT) are pure sex cord tumors that present at an average 30 years and are benign in clinical course. A clinicopathologic study of 54 cases demonstrated that most tumors were stage I and ovary-confined (63). They are

hormonally active with estrogen and can manifest clinical symptoms of isosexual precocious puberty or menstrual abnormalities in women of reproductive age. Rare cases of virilization and progestational decidual reaction of the peritoneum were noted in another case series (64). Cut surfaces are tan to yellow with areas of hemorrhage and necrosis (64). The tubular pattern is the most common histologic finding, and other visual cues include trabeculae surrounded by cuboidal to columnar cells with lipid rich, eosinophilic cytoplasm. Other less common patterns include alveolar, diffuse, pseudopapillary, retiform, and spindled. Risk factors for aggressive behavior include tumor size greater than 5 cm, necrosis, nuclear atypia, and increased mitotic index (greater than 5 per 10 HPF) (63). IHC is positive for WT-1, inhibin, SF-1, calretinin, and CD99 (65–67).

There have been isolated case reports of associated renin and aldosterone production (64, 68). There have also been documented cases in patients with Peutz Jeghers syndrome (PJS), an autosomal dominant disorder from a mutation in the serine-threonine kinase, STK11, that is characterized by GI hamartomatous polyps, melanocytic macules, and increased risk of certain cancers (69). The most common mutation is loss of heterozygosity in chromosome 19p13.3 (70). Although 5–15% of women with PJS have ovarian sex cord tumors, they are most commonly sex cord tumors with annular tubules (SCTAT).

Sex cord tumor with annular tubules

SCTAT are pure sex cord tumors that comprise less than 1% of SCST and are classified according to its association with PJS. The average age of diagnosis of sporadic SCTAT is 36 years and that of SCTAT associated with PJS is 27 years. The association with PJS was first elucidated by Scully et al. and further studied by Young et al. in a review of 74 cases of SCTAT where 27 were linked with PJS. Hyperestrogenism was noted as 25 patients exhibited isosexual precocity, AUB, or PMB. Endometrial hyperplasia was identified in sporadic and PJS specimen. Four cases associated with PJS had evidence of adenoma malignum of the cervix (71, 72). PJS is associated with 33% of cases (1). Sporadic tumors are grossly larger (greater than 3 cm) and unilateral. Tumors associated with PJS are usually microscopic to 3 cm in size, multifocal, and bilateral. PJS-associated tumors are benign with rare cases of malignancy. About 20% of sporadic cases have evidence of metastasis and are associated with malignancy (73–75).

Histopathology is notable for annular tubules that are simple or complex in architecture. Simple annular tubules are associated with sporadic SCTAT and are ring-shaped with nuclei located peripherally around a hyalinized central body (71). Complex annular tubules are associated with PJS and have rings involving multiple hyalinized cores with calcifications. Cells have a columnar shape with round hyperchromatic nuclei. Nuclear atypia and mitotic figures are rare. Sporadic SCTAT can exhibit areas of Sertoli cell or granulosa cell differentiation (72).

Sertoli-Leydig cell tumor

Sertoli-Leydig cell tumors (SLCT) are mixed sex cord-stromal tumors that represent less than 0.5% of ovarian neoplasms. This tumor was previously known as arrhenoblastoma and androblastoma because of structural and histologic similarities to testes. The DICER1, a gene that codes for a ribonuclease (RNase)

III endoribonuclease protein important in protein translation, is mutated in 60% of SLCT (76). The average age of diagnosis is 25 years, but patients with DICER1 mutations have an earlier diagnosis at 13 years (1, 77). Clinical manifestations include a palpable pelvic mass, pelvic pain due to capsular distension, tumor rupture, and hormonal manifestations. Between 40–60% present with virilizing symptoms, and the remaining exhibit estrogenic or no hormonal symptoms (78). A clinicopathologic study of 23 patients with SLCT demonstrated that 91% of patients presented with stage I disease (78). The size of these tumors is 12–14 cm. SLCT can recur in up to 33% of patients with 95% of relapsing patients presenting within 5 years from diagnosis. Brown et al. demonstrated that a majority of recurrences were in the abdominopelvic cavity, and none of these patients had nodal disease at recurrence (79).

The gross appearance can range from solid to cystic with areas of hemorrhage and necrosis. Prognosis is dependent on the level of differentiation (well, moderate, poor). The gradient from well-to-poorly differentiated depends on the decreasing differentiation level of the Sertoli cell component and the increasing quantity of primitive gonadal stroma. A clinicopathologic study of 207 cases demonstrated that 11%/54%/13% were well/moderately/poorly differentiated upon initial exam. Additionally, 22% contained heterologous elements and 15% exhibited a retiform pattern. Eleven percent with moderate differentiation, 59% with poor differentiation, and 19% with heterologous elements were identified as malignant (77). Histology is notable for Sertoli cells shaped in a tubular fashion and Leydig cells in small clusters or cords in the stroma. Leydig cells can exhibit vacuoles, lipofuscin, and Reinke crystals. Moderately differentiated tumors have mitotic figures at an average of 5 per 10 HPF. Poorly differentiated tumors have mitotic figures up to 20 per 10 HPF and contain a sarcomatoid (spindle-shaped) stroma. Retiform tubules are areas of anastomosing, slit-like spaces that resemble the rete testis, and this retiform component is seen in moderately- and poorly-differentiated SLCT (77). Tumors with heterologous elements comprise 20% of SCLT. The most common epithelial heterologous elements are enteric type mucinous epithelium and carcinoids (80). The most common mesenchymal heterologous elements are cartilage or skeletal muscle. About 20% of tumors cause serum AFP elevation, which is attributed to hepatocytic heterologous elements from Leydig cells. Well- and moderately-differentiated SLCT can resemble endometrioid adenocarcinoma. IHC is positive for vimentin, keratin, alpha-inhibin, calretinin, CD56, SF-1, and WT-1. About 50% of tumors are positive for CD99 and FOXL2 (42, 81, 82).

EPITHELIAL OVARIAN CARCINOMA

Epithelial ovarian carcinoma (EOC) represents 95% of ovarian cancers. Histologic subtypes include borderline, high grade serous (HGSC), low grade serous (LGSC), endometrioid, clear cell, mucinous, seromucinous, and Brenner tumors. HGSC represents 70–80% of EOC. We discuss all the above except for HGSC. Tumor classification has evolved to include histology, immunohistochemistry, molecular pathology, and genomics. Epidemiologic risk factors for EOC include early menarche, nulliparity, late menopause, hereditary factors, and endometriosis. Protective factors include breastfeeding and oral contraceptive pills (OCP).

Clinical presentation includes an adnexal mass, pelvic pain, vaginal bleeding, atypical cells on cervical cytology, early satiety, abdominal distension due to ascites, bowel obstruction, shortness of breath due to pleural effusion, and venous thromboembolism (VTE). Cancer antigen 125 (CA 125) is elevated in 80% of non-mucinous EOC, and is clinically relevant for assessment of treatment response when it is found to be elevated during initial evaluation (83). While germ cell tumors have a predilection for lymphatic spread, EOC metastasizes through the lymphatic, hematogenous, and transcoelomic routes (84). Patients initially present with advanced stage at the time of clinical symptoms due to peritoneal carcinomatosis. Hematogenous spread of tumor cells to the parenchyma of the lung and liver is stage IV classification (85).

Borderline tumors

Borderline tumors were first classified by Howard Taylor in 1929 as tumors with "semi-malignant" characteristics. These tumors were officially recognized as a histologic subtype of EOC by the FIGO in 1971 and the World Health Organization (WHO) in 1973. Previous names for these neoplasms include atypical proliferative tumors and tumors of low malignant potential. They comprise 15% of ovarian neoplasms. Borderline tumors are categorized into histologic types that include serous (50%), mucinous (40%), endometrioid (2–10%), clear cell (<1%), seromucinous, and Brenner tumor. Approximately 71% of borderline tumors are diagnosed as FIGO stage I/II disease (86). About 4–7% of these tumors can progress to invasive carcinoma, usually LGSC with rare instances of HGSC. Ten-year survival outcomes range 96–99% with FIGO stage I-III cancers, and 77% with stage IV cancers (87).

Serous borderline tumors (SBT) present at a median age of 50 years (88). Tumor bilaterality can range from 33–55%. These tumors exhibit KRAS and BRAF mutations (89, 90). Gross pathology reveals that these tumors are cystic with papillary projections that often involve the tumor surface. Histology reveals tumor cells with heterogenous nuclei and eosinophilic cytoplasm that form clusters and branching papillae with stromal cores. The micropapillary/cribriform subtype is devoid of fibrovascular cores and exhibit papillae 5 times longer than wide (88). This subtype is characterized by the classic "Medusa head" appearance. Tumor microinvasion is considered stromal invasion greater than or equal to 5 mm and does not negatively impact survival outcomes (91). Extraovarian disease associated with borderline tumors are usually in the form of non-invasive implants, and these can be classified into epithelial and desmoplastic types (92, 93). The former contains papillary proliferation in a hierarchical branching pattern, while the latter is characterized by cellular clusters enmeshed in fibrous, inflammatory infiltrate with psammoma bodies. Any implant with greater than 5 mm of invasion is considered extraovarian LGSC (94). Epithelial implants can be identified in the retroperitoneal lymph nodes, and is associated with endosalpingiosis, which is the ectopic proliferation of fallopian-tube epithelium. Lymph node involvement is not considered metastatic deposits and does not change the survival outcomes of these patients. Risk factors for recurrence include micropapillary/cribriform subtype, bilateral tumors, extraovarian disease, and residual disease after primary cytoreduction (95).

Mucinous borderline tumors (MBT) are the second most common borderline tumor in North America, but account for 70% of borderline tumors in Asia (1, 96). About 70% of these tumors are diagnosed as FIGO stage I and have an excellent prognosis. KRAS mutations are found in 30–75% of tumors (97, 98). They can arise from mucinous cystadenomas when the borderline component is greater than 10% of the specimen. A small subset originates from mature teratomas or Brenner tumors. Patients present with a pelvic mass, and gross examination reveals a large (average 20 cm), unilateral mass with a smooth capsule (99). The cystic spaces within the tumor are filled with mucinous fluid. They are not associated with pseudomyxoma peritonei (PMP). Histology reveals stratified gastrointestinal-type epithelium with tufting and a cribriform pattern. Mitotic activity is confined in the crypts (1). Microinvasion can be present based upon the same principles as SBT. Unlike the serous subtype, MBT do not have peritoneal implants. MBT can contain mural nodules of various types that include sarcoma-like, anaplastic carcinoma, or sarcoma (100, 101). IHC is positive for CK7, CK20, and CDX2 and is negative for estrogen/progesterone receptors (ER/PR) (1).

Endometrioid borderline tumors (EBT) are diagnosed in the fifth to sixth decade, and are associated with endometrial hyperplasia and endometrioid endometrial adenocarcinoma (102). Therefore, endometrial evaluation is recommended to rule out associated uterine pathology. Molecular studies are notable for mutations in CTNNB1 (103). Up to 3% of patients present with disease greater than FIGO stage I (104). Average tumor size is 6.4 cm and ranges from solid to cystic in appearance (102). These tumors can be histologically divided into adenofibromatous and intracystic subtypes. Neoplasms with adenofibromatous characteristics exhibit stromal fibrosis, glandular crowding with squamous metaplasia, and mild-to-moderate nuclear atypia. Tumors with an intracystic pattern have papillary growth and involves an endometriotic cyst (102).

The remaining subtypes of borderline tumors are rare and are associated with endometriosis (exception: borderline Brenner tumors). Clear cell borderline tumors (CCBT) are diagnosed at a median age of 68 years (105). They usually accompany clear cell adenocarcinoma and express similar genetic mutations in PIK3CA and ARID1A (106). A clinicopathologic study of 19 cases of CCBT demonstrated that all cases were FIGO stage I and that two instances of recurrence were associated with intraoperative tumor rupture (107). Histology is notable for cells with clear or eosinophilic cytoplasm embedded in fibromatous stroma (108).

Seromucinous borderline tumors (SMBT) were previously considered an endocervical subtype of MBT. Unlike MBT, SMBT have positive IHC stains for ER, PR, and vimentin (109). Because they are another type of endometriosis-associated ovarian tumor, the incidence of endometrioid/clear cell-associated ARID1A and KRAS mutations are 33% and 69%, respectively (110, 111). Histologic findings include papillary branching with fibrous stromal cores infiltrated by neutrophils. These tumors exhibit Mullerian cellular heterogeneity (endometrioid, mucinous, clear cell). Hada et al. demonstrated recurrence in 2 out of 11 patients at 83 months for a patient that underwent bilateral cystectomy and at 65 months for a patient who underwent a unilateral salpingo-oophorectomy (USO) (112).

Borderline Brenner tumors (BBT) are rare tumors that resemble transitional (urothelial) epithelium, and are thought to arise from Walthard cell nests, which are clusters of transitional epithelia embedded in the fallopian tube serosa (113). These tumors are cystic in gross appearance with a median diameter of 12 cm (105).

These cells exhibit cytologic atypia with elongated nuclei and increased mitotic activity. Mutations in CDKN2A (p16), KRAS, and PIK3CA have been reported with these tumors (114).

Low grade serous carcinoma

LGSC are indolent neoplasms that are the carcinogenic progression of SBT as evidenced by the shared mutation in KRAS and BRAF. The median age of diagnosis is 43 years, which differs from the typical diagnosis of HGSC in the sixth decade of life (115). They are typically diagnosed at an advanced stage and are commonly bilateral at the time of primary cytoreduction. The mean OS for stage I disease is 123 months (116). A single-institution study by Gershenson et al. demonstrated a median PFS of 28.1 months and median OS of 101.7 months in a study population of 350 patients where 83.4% of the participants had FIGO stage III disease (117). The authors concluded that poor prognostic factors included age less than 35 years and persistent disease after primary treatment (117, 118). The gross appearance of these tumors demonstrates papillary projections with areas of cystic and exophytic growth. The presence of Psammoma bodies causes a gritty texture upon palpation. Histologic findings include mild-to-moderate nuclear atypia, a lack of nuclear pleomorphism, and a mitotic index less than 12 per 10 HPF (119). Invasive growth patterns can include a few clusters of cells, a micropapillary pattern, and an inverted macropapillary pattern characterized by fibrovascular cores (120). A component of SBT is commonly observed with these neoplasms. Unlike non-invasive implants associated with SBT, any invasive implant in the peritoneal cavity are considered metastatic deposits of LGSC (94). IHC studies are diffusely positive for ER, CK7, PAX8, and WT1 (121). Although LGSC and HGSC share histological features, molecular studies demonstrate that LGSC lack p53 mutations, hereditary factors (e.g., BRCA 1/2 mutation), homologous recombination deficiency, and other chromosomal aberrations that characterize HGSC and its increased chemosensitivity.

CLINICAL MANAGEMENT OF OVARIAN GERM CELL TUMORS

Surgical staging is the cornerstone of initial management of OGCT and usually involves a midline laparotomy for adequate exposure of the peritoneal cavity. The principles of surgical staging are similar for epithelial, germ cell, and sex cord stromal tumors. If ascites is present, a sample is obtained and sent for cytologic evaluation. The surgeon should employ a systematic approach to evaluation, which usually starts from the diaphragm and continues toward the omentum, bowel, parietal peritoneum, and pelvic organs. Evaluation of the tumor should include an understanding of its gross origin, laterality, presence of capsular disease, and involvement of adhesions to adjacent structures. The role of lymphadenectomy varies depending on the type of neoplasm, as positive lymph node rates were 28%, 8%, 16% in dysgerminoma, malignant teratoma, and mixed germ cell tumors, respectively (122). Although lymph node evaluation can provide prognostic information, lymphadenectomy did not confer a survival benefit in clinical early-stage OGCT (123). Although there are no prospective trials regarding the

effectiveness of the extent of cytoreductive surgery, a GOG trial of 76 patients with malignant OGCT showed that adjuvant chemotherapy was ineffective for those patients with incomplete disease resection (124). Second-look laparotomy was previously performed for OGCT, but its effectiveness was disproven in patients who underwent complete tumor resection (125). Secondary surgeries are not part of standard care because of the inherent chemosensitivity. Clinicians should consider USO as a fertility-sparing measure in women suspected of early-stage disease, as conservative surgery with adjuvant chemotherapy provides optimal 5-year survival outcomes (98.2% stage I and 94.4% II-IV) and a 76% pregnancy rate (126, 127). Wedge resection or biopsy of a normal-appearing contralateral ovary is not recommended.

The early literature of adjuvant chemotherapy derived from that of testicular cancer. The VAC regimen (vincristine, actinomycin D, cyclophosphamide) was the initial adjuvant regimen of choice in the timeline, with an 86% remission rate in stage I patients, but with significantly poorer response in advanced-stage disease (128). Because of the success of platinum-based regimen in testicular cancer, the PVB regimen (cisplatin, vinblastine, bleomycin) was retrospectively evaluated and demonstrated a 96% remission rate up to 54 months from chemotherapy (129). This culminated in the prospective GOG #45 trial, where 97 patients received 3–4 cycles of adjuvant PVB with a 2-year PFS of 51% and a 2-year OS of 71%. Due to the neurotoxicity and constipation associated with vinblastine, the BEP regimen (bleomycin, etoposide, cisplatin) was evaluated in GOG #78, where patients underwent 3 cycles of BEP after complete resection (130). Of 93 patients, 89 were free of cancer, and recurrences were treated with alternate regimen. A major adverse effect with etoposide manifested as one patient developed acute myeloid leukemia (AML), but the BEP regimen had overall positive results. GOG #116 validated the use of carboplatin/etoposide as a substitute for the BEP regimen in stage IB-III dysgerminoma patients if treatment-induced adverse effects are of concern (131). Adjuvant chemotherapy is recommended for all stages and histology of OGCT, except for stage I dysgerminoma and stage IA grade 1 immature teratoma since the recurrence rate of these specific cancers are low enough to warrant observation (132, 133). However, the MITO-9 trial demonstrated that surveillance is feasible in adequately staged IB-C dysgerminomas, IA-IC grade 2–3 immature teratomas, and IA mixed malignant OGCT with a yolk sac component (134). This new data is yet to be incorporated into national guidelines for comprehensive care. Surveillance recommendations for OGCT are different in the pediatric population. Radiation therapy is a useful adjuvant treatment for dysgerminomas, but this is not often performed because of the efficacy and reduced toxicity with chemotherapy (135, 136).

Tumor recurrence is usually within 24 months of treatment, and treatment depends on platinum-sensitive or -resistant status, as a platinum-based regimen is recommended for the former. The benefit of secondary surgery is questionable, but there is the possibility of benefit in patients with immature teratoma (137). Patients with platinum-resistant or -refractory tumors should be referred to specialty centers for clinical trials. Treatment modalities include the TIP regimen (paclitaxel, ifosfamide, cisplatin) or high-dose chemotherapy (HDCT) with hematopoietic cell transplantation (HCT) as per the TIGER trial (NCT02375204).

CLINICAL MANAGEMENT OF OVARIAN SEX CORD-STROMAL TUMORS

The principles of surgical staging remain as mentioned previously for all types of ovarian cancers. Fertility-sparing surgery with USO should be considered in women of reproductive age with tumor clinically confined to one ovary, and complete staging surgery should be employed with all other patients (138, 139). Clinicians should provide minimally invasive surgery (MIS) as an option for fertility sparing treatment (140). An endometrial biopsy should be completed in patients who desire fertility and have hormonally active neoplasms. The role of systematic lymphadenectomy has less credence for SCST and should only be performed for clinically positive pelvic or para-aortic lymph nodes (79, 141).

Adjuvant therapy in patients with AGCT is indicated for high-risk stage I (tumor rupture) and stage II-IV disease (142, 143). GOG #113 was a phase II trial that evaluated 4 cycles of the BEP regimen in women with stage II-IV or recurrent SCST where the primary endpoint was response during second-look laparotomy. The authors revealed that 37% of the population had negative findings during exam, patients with measurable residual disease exhibited the highest risk of death, and that BEP was a feasible regimen for treatment (144). The bleomycin-associated pulmonary toxicity was recognized, and the dose optimized to address this issue. An EORTC clinical trial exemplified the efficacy of the PVB regimen in patients with advanced or recurrent disease with a median PFS and OS of 19.3 and 41.1 months, respectively (145). Researchers at the M.D. Anderson studied the efficacy of taxanes in the SCST treatment regimen. After a median follow-up of 90–100 months for patients treated in the primary and recurrent setting, survival data was not yet mature. This corroborated the therapeutic potential of taxanes and demonstrated the need for long-term surveillance for SCST patients (146). Although GOG#187 did not verify taxane efficacy as a single agent, this ultimately led to GOG #264 that evaluated BEP vs carboplatin/paclitaxel in SCST(147). Preliminary results presented at the International Gynecologic Cancer Society 2020 annual meeting show a median PFS of 19.7 vs 27.7 months (95% CI 10.4–52.7) in favor of carboplatin/paclitaxel. Adjuvant radiation therapy does not provide substantial improvement in survival and can be considered for advanced disease in patients who are unable to undergo chemotherapy (148). Management of JGCT is best described in the pediatric literature.

The BEP regimen remains the standard of care chemotherapeutic regimen for SLCT, but other regimens including cisplatin/doxorubicin/cyclophosphamide and the VAC regimen have been published prior to BEP standardization (144, 149). Adjuvant chemotherapy is recommended for high-risk stage IC (tumor rupture, heterologous elements, moderate-to-poor differentiation) and stage II-IV disease (77, 142).

Recurrence usually manifests in the abdominopelvic cavity or in the retroperitoneum. The authors of the MITO-9 retrospective study found benefit with secondary cytoreduction in 94.2% of the study population undergoing surgery with or without adjuvant therapy (55). They reported that 33% of the secondary surgical group developed a second recurrence at a median of 38 months. However, data regarding surgery is sparse and systemic therapy is more commonly practiced. Treatment regimens in the recurrent setting for GCT encompass the

previous regimens as described above. Hormonal treatment in the form of tamoxifen, progestins, aromatase inhibitors (AI), and leuprolide have shown efficacy (150–152). Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), was demonstrated as an active regimen in the recurrent setting with a median PFS of 9.3 months, a 16.7% partial response rate, a 77.8% stable disease rate, and an acceptable toxicity profile (153).

CLINICAL MANGEMENT OF EPITHELIAL OVARIAN CARCINOMA

Surgical management for borderline tumors is in line with that mentioned previously in this chapter. Fertility-sparing treatment by way of USO for unilateral tumors and USO with contralateral cystectomy for bilateral tumors should be considered for women of reproductive age with ovarian-confined disease. Vasconcelos et al. evaluated cystectomy versus USO and reported a higher recurrence rate in patients with unilateral tumors who underwent a cystectomy along with a pregnancy rate of 45.4% with USO and 40.3% with cystectomy (154). The National Comprehensive Cancer Network (NCCN) guidelines recommend completion hysterectomy and contralateral USO after childbearing is complete (85). Chemotherapy is not indicated for stage I, and administration for advanced stage disease is usually not performed. Shih et al. showed that 3-year PFS for advanced-stage patients with and without chemotherapy was 70.6% vs 89.9%, respectively (155). This indicates that chemotherapy does not alter recurrence outcomes. Risk factors for recurrence include advanced stage, incomplete staging, residual disease after primary surgery, and ovarian preservation (156). Surgery is the mainstay treatment for pathologically-verified recurrent borderline tumor with the goal of complete resection for maximal survival outcomes (157).

Primary surgical management for LGSC remains the same as mentioned previously. A pre-operative CA 125 is usually obtained for baseline evaluation. Adjuvant chemotherapy is considered for stage IC disease and recommended for stage II-IV disease. The standard chemotherapy regimen is carboplatin/paclitaxel, but these indolent tumors are relatively chemoresistant compared to HGSC (158). Due to this tumor's proclivity for ER positivity, hormonal maintenance treatment after adjuvant chemotherapy improved PFS outcomes, but not OS in advanced-stage disease (159). A small retrospective study also validated the use of hormone therapy as monotherapy in place of chemotherapy in advanced-stage disease (160). GY-019 (NCT04095364) will provide level 1 evidence regarding this treatment modality by comparing platinum doublet therapy followed by maintenance letrozole to letrozole monotherapy in women with stage II-IV LGSC. Treatment for recurrent disease is limited due to the chemoresistance conferred by this neoplasm, as noted by a 4.9% response rate in the platinum-sensitive cohort of a retrospective study (161). The RAS/RAF/MEK/ERK pathway is paramount to pathogenesis, and MEK inhibitors have been extensively studied in various trials (162–164). Ongoing clinical trials with cyclin-dependent kinase 4/6 inhibitors in conjunction with hormonal treatment (NCT03673124, NCT03531645) will provide insight into further treatment options for patients in the primary and recurrent setting.

CONCLUSION

Rare tumors comprise all three major histotypes of ovarian neoplasms and can range from benign masses to aggressive carcinomas. Advancements in genomics and molecular biology have led to the development of targeted therapies for these cancers. Further research will provide data regarding the impact of patient-tailored surgery and molecular-based adjuvant therapy on survival outcomes.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this chapter.

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