Germ Cell Tumors of the Ovaries

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Abstract

The basic classification of ovarian germ cell tumors has largely remained unchanged for several decades. Ovarian germ cell tumors develop from primordial germ and stem cells that differentiate into extraembryonal and somatic tissues. In most cases, benign and malignant ovarian germ cell tumors can be correctly diagnosed due to their characteristic morphologic profiles. Several immunohistochemical (IHC) markers are widely available and can significantly facilitate tumor typing of germ cell tumors, especially in high grade tumors or in atypical clinical scenarios. In this chapter, the clinicopathologic features of ovarian germ cell tumors will be reviewed, with emphasis on morphology and diagnostically useful IHC markers.

Keywords

Germ cell tumors • Mature teratoma • Immature teratoma • Struma ovarii • Dysgerminoma • Yolk sac tumor • Embryonal carcinoma • Choriocarcinoma

Contents

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1 Introduction

Ovarian germ cell tumors (OGCTs) are derived from neoplastic transformation of the ovarian primordial germ and stem cells. These tumors are unique because they form imperfectly formed "normal" human body tissues (Nogales et al. 2014). Germ cell tumors (GCTs) can be classified into: (1) tumors with mature elements which include mature cystic teratoma (MCT), (2) tumors with immature elements exhibiting range of differentiation and include dysgerminoma, embryonal carcinoma (EC), choriocarcinoma (CC), yolk sac tumor (YST), and immature teratoma (IT), and (3) malignant transformations such as squamous cell carcinoma (SCC), carcinoid, malignant struma ovarii and other rare neoplasms arising in a preexisting mature teratoma (Table 1) (Prat et al. 2014). Most GCTs are benign with straightforward pathologic diagnosis. Only rarely these tumors present diagnostic issues especially when occur in unusual clinical scenarios. On the other hand, malignant ovarian germ cell tumors (MOGCTs) or malignant transformation in an existing MCT account for a small fraction of OGCTs (Nogales et al. 2014).

2 Epidemiology and Clinical Presentation

While OGCTs constitute 20–25% of all ovarian neoplasms, only <3% are malignant. The prevalence is significantly higher (15%) in Asian and black populations as compared to Caucasian populations (5%) (Low et al. 2012). Clinical information including patient age, elevated serum markers, and presentation are important to report to the pathologic laboratory when specimens are being submitted, as they constitute a component of the pathologic evaluation and assessment. For example, benign MCTs predominate in reproductive-age women, immature teratomas and malignant GCTs predominate at young age (below 20), and somatic malignant transformation, e.g., SCC is more common in postmenopausal women (Nogales et al. 2014).

Patients are either asymptomatic with the tumor discovered incidentally on clinical or radiologic examinations or present with abdominal pain and/or a palpable abdominal mass. The mass may grow rapidly in a fraction of cases (~10%) resulting in acute abdominal pain due to capsular distention, ischemic necrosis, hemorrhage, rupture, or torsion (Nogales et al. 2014). MOGCT may present with metastases. Alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG), and cancer antigen 125 (CA-125) titers are some serum tumor markers used mainly for follow-up after treatment (Prat et al. 2014).

Table 1 World Health Organization (WHO) classification of ovarian germ cell tumors[a]

Mature teratoma
Immature teratoma
Monodermal teratoma
Struma ovarii
Carcinoid
Somatic tumors arising from dermoid cyst
Squamous cell carcinoma and others
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Choriocarcinoma

[a]Only the most commonly encountered tumors in practice are included (Prat et al. 2014)

3 Mature Teratoma

Ovarian teratomas differentiate to mature tissues derived from the three germ layers. On the other hand, monodermal teratomas such as struma ovarii differentiate to one germ layer. Mature teratomas are the most common OGCTs accounting for ~20% of all ovarian tumors, more than 90% of OGCTs, and are the most common tumors seen in children (de Silva et al. 2004; Nogales et al. 2014).

3.1 Gross Pathology

Most lesions are mature cystic teratomas (MCTs). Approximately, 15% of MCTs are bilateral. MCTs usually measure from 5 to 10 cm and contain a mixture of hair, skin, and malodorous sebaceous or keratinaceous material

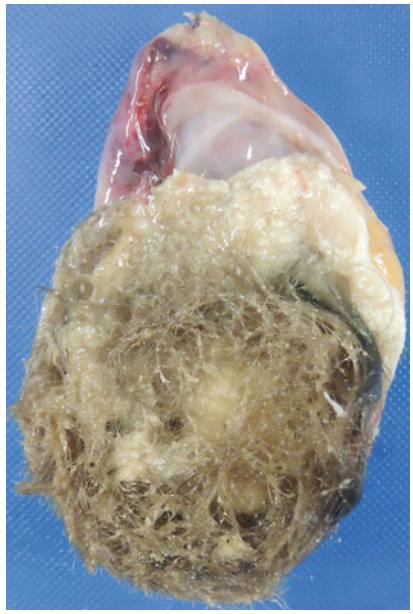

Fig. 1 Mature cystic teratoma containing hair tufts and sebaceous material

(Fig. 1). A raised protuberance (Rokitansky's tubercle) is often present and should be pathologically evaluated (Peterson et al. 1955). The cyst may be unilocular or multilocular, and the contents may appear hemorrhagic, similar to an endometriotic cyst. The more grossly complex the cyst is, the more likely the presence of other elements such as thyroid tissue (solid and brown mass).

3.2 Histopathology

Morphologically, MCTs are composed of various tissues derived from one or more germ layers. Ectodermal components, which are usually the most prominent, include skin with associated appendages (Fig. 2a) and mature neuroectodermal tissue (Fig. 2b), among others. Endodermal components include thyroid, salivary, and gastrointestinal tissues, among others (Fig. 2c, d). Mesodermal component includes muscle, cartilage (Fig. 2d), bone, and fat. MCTs may show minute neuroepithelial/ependymal areas which should not be reported as immature teratoma (Yanai-Inbar and Scully 1987). Gliomatosis peritonei (GP) is a teratoma associated with peritoneal nodules composed of mature glial tissue. Despite its advanced clinical stage (stage III), its behavior is benign if immature elements are absent. The origin for GP may be related to capsular rupture from the ovarian teratoma, although this is still largely speculative (Perrone et al. 1986; Peterson et al. 1955).

Ovarian mucinous tumors may be associated with mature cystic teratomas. These mucinous tumors display an IHC profile that is similar to gastrointestinal tract adenocarcinomas, including expression of CK20, CDX2, and villin and lack thereof for CK7 (Vang et al. 2007). These features would point toward a germ cell origin for the mucinous component rather than metastasis from a gastrointestinal primary. Rarely, the teratoma component is overgrown by the mucinous tumor (Vang et al. 2007).

4 Immature Teratoma

Immature teratoma is the second (after dysgerminoma) most common MOGCT (Fig. 3). Grossly, the tumors are large, solid, and fleshy with hemorrhage, necrosis, and cyst formation. Immature element (mainly primitive neuroectoderm) is the diagnostic feature of the lesion. Primitive neuroectodermal units are composed of tubules and rosettes. The tubules are lined by atypical, hyperchromatic, stratified cells with frequent mitoses. Immature cartilage, fat, bone, and skeletal muscles are often present but by themselves are not enough to qualify a MCT as immature. Embryoid bodies are the most primitive element in immature teratomas and consist of yolk sac epithelium and germ disk with cells resembling embryonal carcinoma. In rare instances, the immature element consists of mitotically active cellular glia admixed with ectodermal and endodermal elements (Yanai-Inbar and Scully 1987). Assessment of the degree of immaturity (grading) is a highly reliable prognostic and therapeutic factor (Gershenson 2012). Grading is performed by assessing the relative amount of the immature neuroectodermal component as assessed microscopically. Two-tiered (low

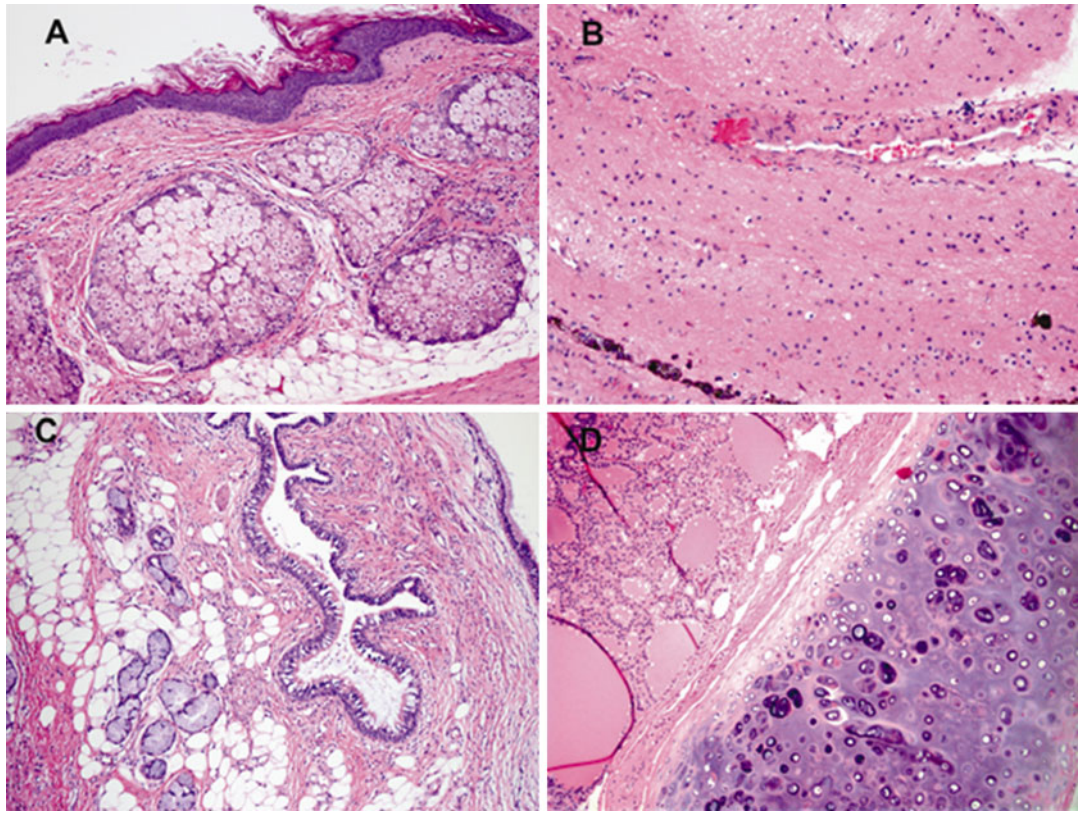

Fig. 2 Mature cystic teratoma containing tissues from all three germ lines. (**a**) Dermoid cyst lined by keratinized squamous epithelium with sebaceous glands in the dermis. (**b**) Mature glial (brain) tissue. (**c**) Glandular type epithelium. (**d**) Cartilage and variable sized colloid filled thyroid follicles (struma ovarii)

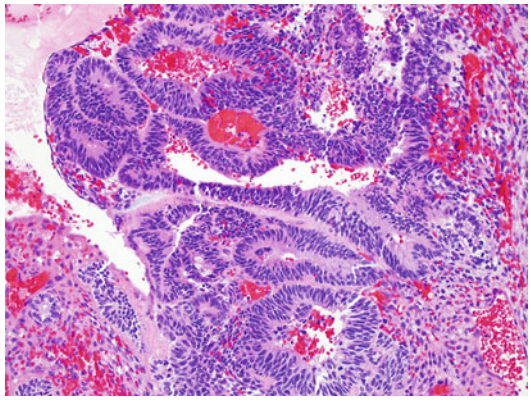

Fig. 3 Immature teratoma containing the diagnostic immature primitive neuroepithelium forming gland-like pseudo-rosettes with palisaded nuclei

and high grade) and three-tiered grading systems are in use (O'Connor and Norris 1994).

The three-tier grading system has been adopted by the most recent World Health Organization (WHO) classification of gynecologic tumors (Prat et al. 2014). Grade 1 tumors contain rare foci of immature elements occupying <1 low power field (x4) in any slide. The immature elements in grade 2 tumors occupy 1–3 low power field in any slide. On the other hand, the primitive neuroectodermal immature elements occupy >3 low power fields in grade 3 tumors (Norris et al. 1976). Any tumor with immature elements occupying more than one low-power field per any slide is a high-grade tumor in the two-tier grading system (i.e., all grade 2 tumors

are high grade) (O'Connor and Norris 1994). The two-tier grade system may be more practical since most grade 2 tumors are more comparable in clinical behavior to grade 3 tumors than they are to grade 1 tumors in a three-tiered system. Additionally, unlike grade 1 tumors which are treated conservatively, grade 2 and 3 tumors are treated similarly with recommended chemotherapy (Patterson and Rustin 2006). A point of caution is the occasional presence of normal neuroepithelium in mature teratomas which should not be confused with immature neuroectodermal elements.

4.1 Serum Markers and Immunophenotype

One third of immature teratomas produce AFP. Positive markers include SOX2, SALL4, Glypican-3 (focal), and OCT3/4 (focal) (Liu et al. 2010).

5 Monodermal Teratomas

5.1 Struma Ovarii

Struma ovarii is a monodermal teratoma composed predominantly of thyroid tissue. The tumor occurs most frequently in the fifth decade of life. Clinical hyperthyroidism occurs in <5% of cases. Grossly, the tumor characteristically appears as greenish brown, firm to slightly gelatinous. Microscopically, struma ovarii varies from a classic macro- and microfollicles with abundant colloid to a cyst with small tubules (Fig. 2d). Solid patterns with hurthle or clear cells may be present and occasionally form trabecular configurations that may mimic carcinoid (Loughrey et al. 2003). The presence of morphologically benign thyroid tissue in the peritoneum (peritoneal strumosis) is now being recognized as a metastatic low-grade follicular neoplasm (Roth and Karseladze 2008).

5.2 Carcinoid Tumor

Carcinoid tumor is a well-differentiated neuroendocrine tumor that arises in MCTs. Grossly, these tumors are brown to tan masses. Microscopically, primary ovarian carcinoids exhibit insular, trabecular, strumal (see below), and goblet cell variants. Insular carcinoids are characterized by tubular glands arranged in garland-like patterns separated by fibrous stroma and sharply defined central lumina with uniform rounded nuclei with fine chromatin stippling (salt and pepper) (Figs. 4 and 5). Trabecular carcinoids display discrete linear cords and trabeculae. The rare

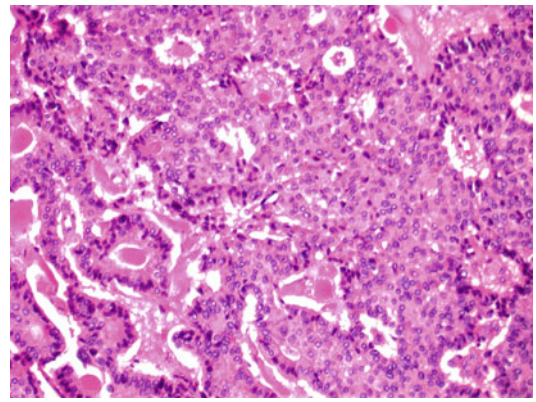

Fig. 4 Insular carcinoid forming broad interconnected sheets of cells

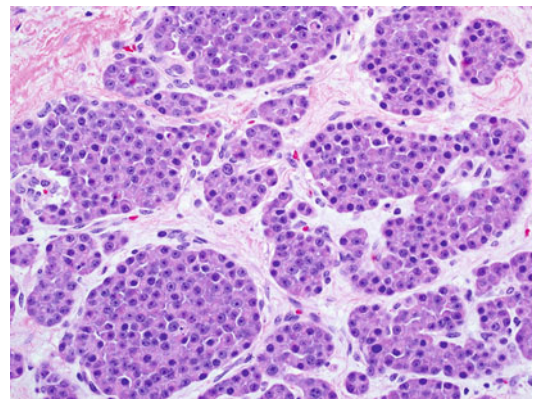

Fig. 5 Insular carcinoid forming sheets of cells with the characteristic granular (salt and pepper) chromatin

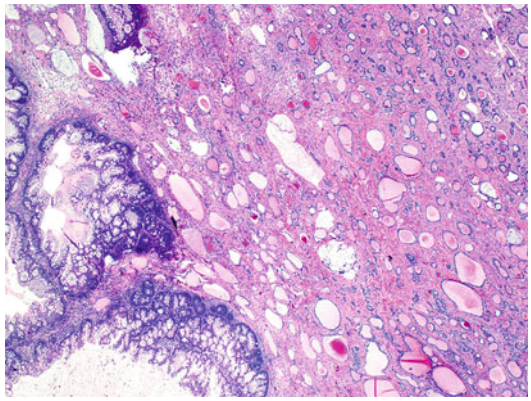

Fig. 6 Mucinous tumor (*left*) and goblet carcinoid (*right*). Notice the admixture of colloid-filled follicles of the thyroid stuma ovarii and the nests and cords of carcinoid component

goblet cell carcinoids exhibit range of differentiation, including well-differentiated tumors with glands lined by goblet cells in a mucinous background, confluent glands with cribriform or microcystic patterns, and frank carcinomas associated with the carcinoid (Baker et al. 2001).

5.3 Strumal Carcinoid

Strumal carcinoid is a mixed tumor composed of struma ovarii and carcinoid in a background of MCT elements. Grossly, strumal carcinoid exhibits both solid white-to-yellow appearance of carcinoid and fleshy brown areas of thyroid component. Histologically, the carcinoid merges abruptly with the thyroid follicles with variable colloid or both components may be morphologically indistinguishable (Fig. 6). TTF-1, PAX8, and thyroglobulin IHC stains will highlight the thyroid component (Prat et al. 2014).

6 Malignant Transformation in Teratomas

The reported incidence for an associated malignant tumor within an MCT is 1.2–14.2 cases per 100,000 more than 75–90% of which are squamous cell carcinoma (SCCs) (Fig. 7), especially in

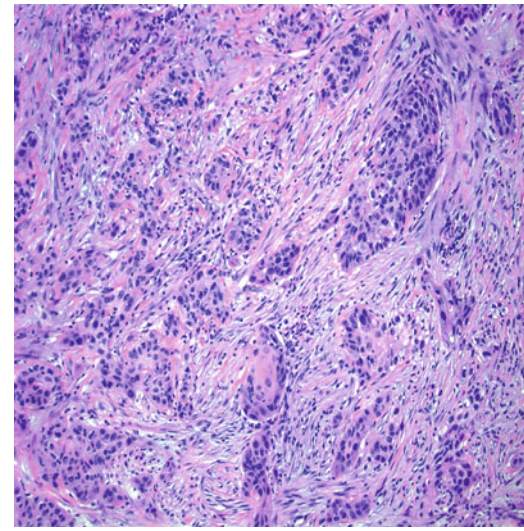

Fig. 7 Invasive squamous cell carcinoma arising in a mature cystic teratoma

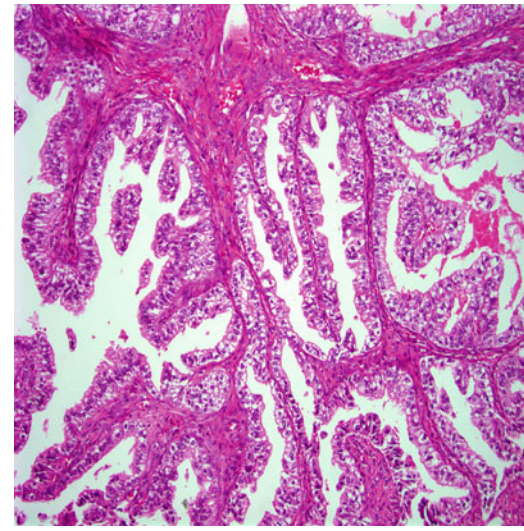

Fig. 8 Invasive adenocarcinoma arising in a mature cystic teratoma

postmenopausal patients (Hackethal et al. 2008). Wide varieties of other malignancies have been reported including adenocarcinomas (Fig. 8), lymphomas, melanomas, thyroid carcinoma (mainly papillary thyroid carcinoma), and YSTs. Advanced age and larger tumor size are some factors that have been significantly associated with malignant transformation (Desouki et al. 2015).

7 Dysgerminoma

The morphology of dysgerminoma is identical to the testicular counterpart, seminoma and the midline germinoma (Low et al. 2012).

7.1 Epidemiology and Clinical Features

Dysgerminoma comprises 1–2% of malignant ovarian tumors and is the most common malignant primitive GCT. The tumor occurs almost exclusively in children and young adults, with an average age of 22 years. Patients with gonadal dysgenesis with partial or complete Y chromosome are more commonly susceptible to dysgerminomas arising in a gonadoblastoma (Fig. 9). The overall survival for treated cases is >90%. Clinical stage and tumor size are the most important prognostic factors (de Silva et al. 2004; Prat et al. 2014).

7.2 Gross and Histopathology

The tumors are large with an average diameter of 10 cm. They exhibit solid, tan, or fleshy-white cut surfaces, occasional hemorrhage, necrosis, and cyst formation. Histologically, the neoplastic germ cells are usually arranged in sheets and sometimes grow in individual cords with rare microcysts or pseudoglandular spaces. The tumor is composed of large, clear, primitive germ cells showing no specific pattern of differentiation. The cells are polygonal with abundant eosinophilic cytoplasm and distinct cell borders. The nuclei are uniform with vesicular chromatin, prominent nucleoli, and numerous mitotic figures. The nests of neoplastic cells are surrounded by fibrous stroma with characteristic infiltrating lymphocytes (mostly T cells) (Hadrup et al. 2006; Fig. 9). A minority of cases show a prominent population of syncytiotrophoblasts. Cases with minimal lymphocytic infiltration or an epithelioid eosinophilic cytoplasm should be differentiated from EC and YSTs (Kao et al. 2012). Cases with granulomatous pattern composed of isolated cells embedded in an extensive fibrosis or chronic inflammatory matrix can also represent a diagnostic challenge. Additionally, clear cell carcinomas with solid growth pattern may display morphologic similarity to dysgerminomas (Nogales et al. 2014).

7.3 Serum Markers and Immunophenotype

A small fraction of dysgerminomas (3–5%) have elevated LDH or low levels of β-hCG. Tumor cells are positive for PLAP, CD117 (c-KIT) (Lau et al. 2007; Fig. 9), D2-40 which is a relatively specific marker (Lau et al. 2007), OCT3/4 (POU5F1), SOX2, and SALL4 by IHC (Liu et al. 2010; Table 2).

7.4 Genetic Abnormalities

Most cases show isochromosome 12p. *C-KIT* mutation has been reported in up to 50% of cases (Prat et al. 2014).

8 Yolk Sac Tumor

YST is a primitive GCT with multiple patterns ranging from primitive gut and mesenchyme to somatic tissue as intestine and liver. These tumors generally have a favorable response to contemporary chemotherapy regimens (de Silva et al. 2004; Nogales-Fernandez et al. 1977).

8.1 Gross and Histopathology

YST is usually a large, soft, encapsulated tumor with gray yellow cut surfaces. Areas of necrosis, hemorrhage, and cyst formation are common. These tumors show complex histologic characteristics comprising early endodermal differentiation into secondary yolk sac elements. Multiple

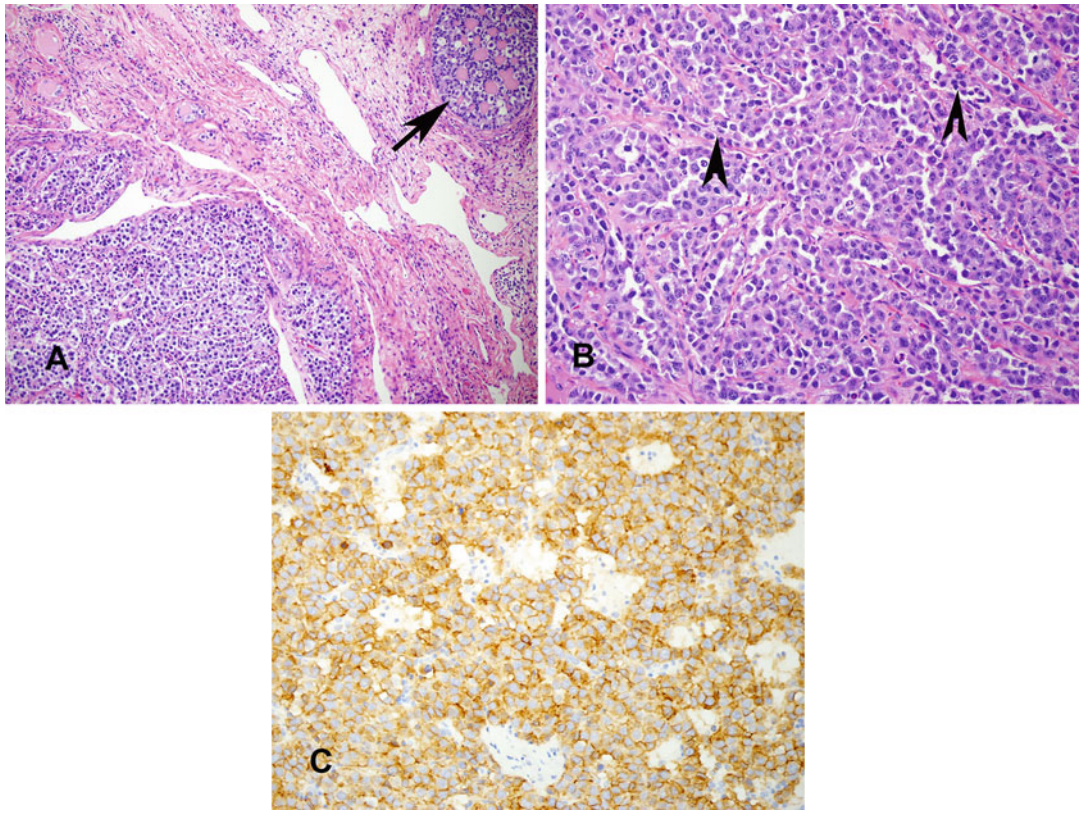

Fig. 9 Dysgerminoma. A germ cell tumor commonly arises in patients with gonadal dysgenesis in a gonadoblastoma (*arrow*) (**a**). The tumor cells grow in sheets of uniform neoplastic cells with centrally placed nuclei and well-defined cell membranes separated by a delicate stroma studied with lymphocytes (*arrow heads*) (**b**). The tumor cells are often positive for CD117 immunohistochemical stain (**c**)

terms have historically been used for these tumors, including endodermal sinus tumors and primitive endodermal tumors. The classic histologic features include reticular microcystic spaces with hyaline globules and amorphous acellular basement membrane like material (Nogales-Fernandez et al. 1977). The cells lining the cystic spaces are clear and flattened that form papillary fibrovascular structures with central blood vessels surrounded by tumor cells and projecting into the space lined by the tumor cells in a characteristic Schiller-Duval bodies (Fig. 10). The stroma is usually myxoid, loose, and hypocellular. Other patterns include polyvesicular type, hepatoid, and intestinal,

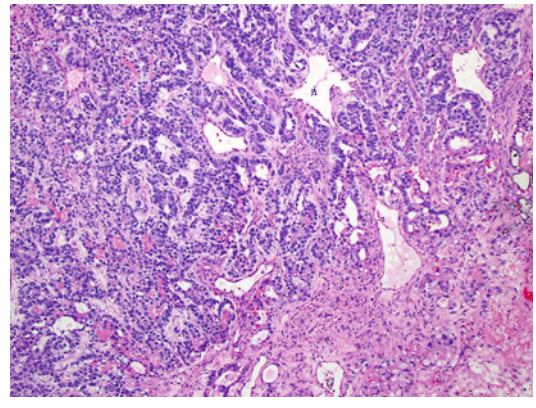

Fig. 10 Yolk sac tumor. The tumor cells grew in microcystic and glandular patterns

Table 2 Selected immunohistochemistry markers used in the diagnosis and/or differentiation of rare ovarian germ cell tumors

	Dysgerminoma	Yolk sac tumor	Choriocarcinoma	Embryonal carcinoma
HCG-Beta	7%	0	100%	23%
OCT 3/4	70%	0	0	100%
Glypican 3	16%	89%	78%	7%
CD117	92%	37%	0	11%
Alpha- fetoprotein	N/A	69%	0	31%
SALL4	53%	99%	50%	99%
PLAP	96%	46%	49%	100%
SOX2	67%	0	0	100%

The percentage represents the reported positive cases. See text for references
N/A not reported

which are rare and may mimic other neoplasms (Cohen et al. 1987; Kao et al. 2012).

8.2 Serum Markers and Immunophenotype

YSTs produce AFP which is considered the gold standard for the diagnosis and follow-up of YSTs. YSTs are positive for AFP, Glypican 3 (Kandil and Cooper 2009), SALL4, HepPar-1 in hepatoid areas, CDX2 and villin in intestinal areas, TTF 1, and CD117 by IHC (Liu et al. 2010; Table 2).

9 Embryonal Carcinoma

EC is an extremely rare malignant ovarian germ cell tumor. Due to its rarity, any diagnosis of EC in a female patient should prompt a chromosomal study. Differential diagnosis includes dysgerminoma and YST (Kao et al. 2012; Prat et al. 2014).

9.1 Clinical Features

ECs are aggressive but chemosensitive tumors that occur in children and young adults with an average age of 15 years. Precocious pseudopuberty and isochromosome 12p may be associated with EC (Gershenson 2012).

9.2 Gross and Histopathology

ECs are usually large tumors with an average diameter of 15 cm. The tumors are solid with soft, fleshy cut surfaces with cyst formation, hemorrhage, and necrosis. Histologically, the tumor grows in solid sheets with glandular differentiation. The cells are polygonal with vesicular nuclei, coarse chromatin, and prominent nucleoli. Mitotic figures are numerous. Areas of necrosis and hemorrhage are extensive. Syncytiotrophoblasts are common (Fig. 11; Pallesen and Hamilton-Dutoit 1988).

9.3 Serum Markers and Immunophenotype

EC may produce β-hCG and AFP with the former being more common. ECs are positive for cytokeratin, CD30 (Pallesen and Hamilton-Dutoit 1988), SOX2, PLAP, OCT3/4, and SALL4 (Liu et al. 2010; Table 2).

10 Choriocarcinoma

Pure nongestational CC is exceptionally rare in the ovaries. These tumors occur mostly in children and young adults (Prat et al. 2014). Grossly, these tumors are large with solid and cystic components, extensive hemorrhage, and necrosis. The tumors show mononuclear trophoblasts and sheets of multinucleated syncytiotrophoblasts arranged in plexiform pattern. Areas

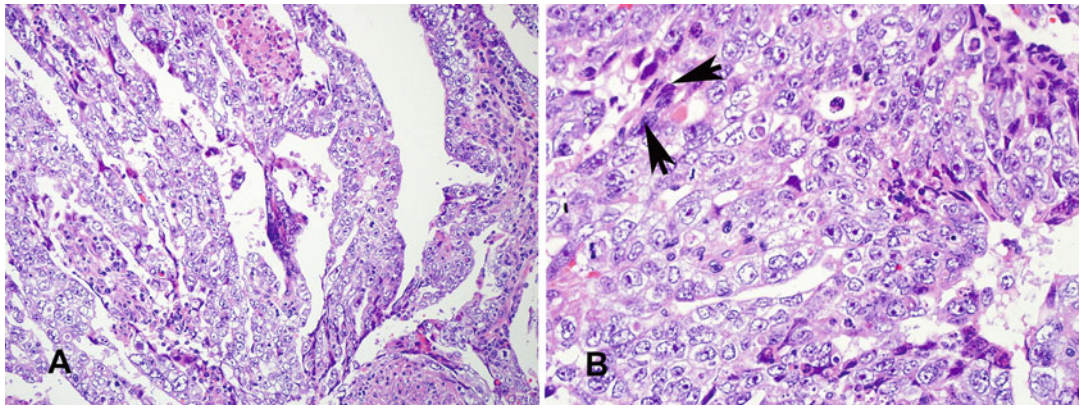

Fig. 11 Embryonal carcinoma. Tumor cells are polygonal and grow in solid sheets (**a**). The cells have vesicular nuclei, coarse chromatin, prominent nucleoli, and frequent mitotic figures (**b**). Notice areas of necrosis and hemorrhage. Syncytiotrophoblasts are common (*arrows*)

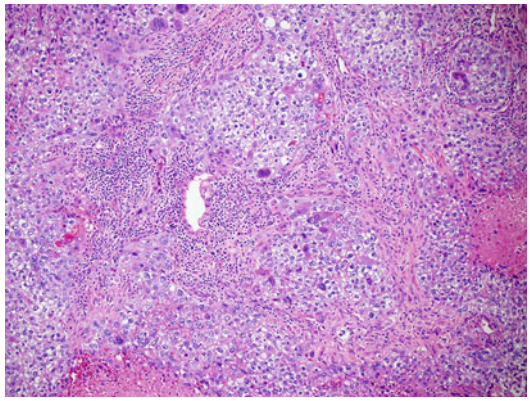

Fig. 12 Choriocarcinoma. The tumor composed of mononuclear trophoblasts and sheets of syncytiotrophoblasts arranged with areas of hemorrhage and necrosis

of hemorrhage and/or necrosis may be so extensive as to obscure the malignant cells (Fig. 12). β-hCG is a well-known serum marker that is frequently elevated in patients with choriocarcinoma, CC is positive for cytokeratin, β-hCG, α-inhibin (McCluggage 2001), SALL4, CD10, and glypican-3 (Liu et al. 2010; Table 2).

11 Conclusion

Ovarian germ cell tumors develop from primordial totipotential germ and stem cells that can differentiate into extraembryonal and somatic tissues. The most common OGCT is mature cystic teratoma. Dysgerminoma is the most common immature malignant OGCT followed by YST. Clinical information, morphology, and immunohistochemical profile are crucial to assign an ovarian mass to the right category of ovarian tumors.

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