Germ Cell Tumors of the Ovary
An Update

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Context.—The field of ovarian germ cell tumors (OGCTs) has remained relatively unchanged in the last 2 decades. However, the introduction of new stem cell pluripotency markers has provided a new understanding into the identification and taxonomy of OGCT types. New data have provided new insights into unusual teratoma-associated autoimmune disorders and the origin of gliomatosis peritonei.

Objective.—To review the impact of new pluripotency markers in the diagnosis of malignant OGCT (MOGCT) and analyze new nomenclature proposals and clinicopathologic entities.

Data Sources.—Ovarian germ cell tumors from routine material and expert consultation files at San Cecilio University Hospital, Granada, Spain, and the relevant literature were reviewed.

Conclusions.—Although a correct diagnosis of MOGCT can often be made with histologic and classic immunohistochemical studies, the new immunohistochemical pluripotency markers give higher diagnostic accuracy. Germ cell tumors represent a caricature of the phases of normal embryonic differentiation from primordial germ and stem cells to extraembryonal and somatic tissue differentiation. Since every stage of differentiation and its related tumor type exhibit characteristic markers, the analysis of their expression facilitates tumor typing, thus complementing the use of classic antibodies. They also allow a more precise evaluation of the degree of immaturity in teratoma. The new term, primitive endodermal tumors, simplifies the understanding of the complex histology of the yolk sac tumor group, as this terminology encompasses its multiple endodermal differentiations. Recently described autoimmune encephalitis due to antibodies against the N-methyl-D-aspartate receptor has become the most frequent autoimmune disorder associated with ovarian teratoma.


The aging of the population in Western countries has resulted in a decrease in the overall number of ovarian germ cell tumors (OGCTs), as they are usually found in younger patients. Nevertheless, they still represent a high percentage of ovarian neoplasms in many countries, most being mature teratomas. As the histologic features and clinical behavior of these benign neoplasms are well known, only rarely do they present diagnostic problems such as identification or degree of maturity of particular tissue components, presence of secondary malignancies, or some unusual clinical manifestations.

On the other hand, malignant ovarian germ cell tumors (MOGCTs) account for only a small fraction of ovarian germ cell neoplasms. Interest in their clinical and histologic features has somewhat diminished in the last 2 decades, with relatively few clinicopathologic series reported.1,2 This low priority may be a consequence of their fortunately good response to platinum-based chemotherapy, regardless of histologic type, which would be reflected in a more relaxed attitude in grossing and sampling standards, histologic analysis, and possibly, less meticulous staging and surgery.

Some MOGCTs share a similar histologic profile with malignant testicular germ cell tumors (MTGCTs) of the adult, which occur far more frequently than their ovarian counterparts. The latter have, however, a different histogenesis, originating in the testis from malignant germ cells,3 as opposed to ovarian germ cell neoplasms, which are mostly parthenogenetically conditioned.4,5 Consequently, MTGCTs exhibit genetic markers, such as a 12p isochromosome and chromosome 12 overrepresentation,6 that are less frequently observed in MOGCTs,7 which often resemble testicular infantile teratomas/yolk sac tumours,8 with the pure ovarian teratomas showing negativity for 12p.9 For this reason, although equating ovarian and testicular germ cell tumors may not be totally correct biologically, their morphology and diagnostic immunohistochemistry are practically similar.

An unknown percentage of malignant germ cell tumors reported in phenotypic women may, in fact, represent MTGCTs (seminomas, embryonal carcinomas, mixed germ cell tumors), as they may have originated from the malignant germ cell component of gonadoblastomas present in dysgenetic gonads of patients with an unrecognized Y
chromosome–containing genotype, often difficult to demonstrate. The GBY locus, a portion of the centromeric region of the short arm of chromosome Y, contains the testis-specific protein 1 gene (TSPY1), which seems to play a critical role in the pathogenesis of gonadoblastoma. Historically, this fact was exemplified in 1930 when Robert Meyer coined the term dysgerminoma as the characteristic tumor of the dysgenetic gonad. Moreover, the recent recognition of neoplasms with a germ cell phenotype, but derived from normal and somatic tissue tumors, has provided yet another origin for rare, usually malignant, teratoid tumors, which may arise from a pluripotent malignant stem cell population of somatic neoplasms.

The groundbreaking research of Kleinsmith and Pierce in the early 1960s represents a paradigmatic model of progressive neoplastic differentiation from pluripotent stem cells, whereby germ cell tumors constitute a caricature of normal embryogenesis. This is worth noting, since recent stem cell research has provided various pluripotency markers that have been applied to the diagnostic immunopathology of malignant germ cell tumors. Since these markers are sequentially expressed in tumors according to their differentiation stage (in a progressive flow from primordial germ cells to extraembryonal and somatic malignancies), they can be highly diagnostic of a particular tumor type. This is especially applicable to the MOGCTs, for which mixed forms are rare and overlapping among various neoplastic phenotypes is minimal.

In this review, we will especially emphasize the impact of some of the newly reported and readily available pluripotency markers (SALL4, OCT3/4, and SOX2) on the diagnosis of MOGCTs. We have not included other nuclear (AP-2, NANOG, UTF1, TCL1, etc) and cytoplasmic (Lin28 and IMP-3) pluripotency markers, since they broadly identify in data and are not as widely used for diagnostic purposes. We also propose integration of these markers with other specific markers, such as α-fetoprotein (AFP), and with characteristic but nonspecific ones such as cytokeratins, CD30, podoplanin (D2-40), placental alkaline phosphatase (PLAP), c-KIT (CD117), and glypican-3 (GLP3).

We will also review recent nomenclature proposals concerning the yolk sac tumor group and, in benign germ cell tumors, we will only consider new and relevant advances in paraneoplastic manifestations of mature cystic teratoma and on the origin of gliomatosis peritonei.

**DYSGERMINOMA**

The histologic profile of dysgerminoma is stereotypic and identical to that of testicular seminoma and midline germinomas. Large, clear, neoplastic, primitive-type germ cells are consistently associated with a variable cytotoxic T-cell lymphocytic response that helps to identify the tumor, even in cases with complex histology. Adequate fixation is important for a prima facie diagnosis, but often poor fixation destroys highly labile cells owing to a minimal amount of cytoskeletal fibrils. Cells are usually arranged in sheets or islands but they can grow in individual cords. Rarely, microcysts (Figure 1, A) or pseudoglandular spaces distort the usual architecture, creating differential diagnosis problems with the highly malignant small cell carcinoma of hypercalcemic type or even struma ovarii (Figure 1, B). Further complex diagnoses include dysgerminomas with minimal lymphocytic response or exhibiting cells with an epithelioid eosinophilic cytoplasm (Figure 2, A), which, as they occur in the testis, should be differentiated from the rare solid varieties of embryonal carcinoma (EC) and yolk sac (primitive endodermal) tumors (YS[PE]Ts).

Cases showing isolated cells, embedded in an extensive fibrous or chronic inflammatory (granulomatous) matrix (Figure 3, A), can also represent diagnostic pitfalls. Finally, solid clear cell carcinomas can also mimic dysgerminomas.

**Immunophenotype**

Diagnostic immunohistochemistry for dysgerminomas still relies, in many laboratories, on the classic membrane staining of PLAP. In our experience, however, PLAP is relatively unreliable, especially in poorly fixed material; furthermore, it may stain positively in a high percentage of cases of both EC and YS(PE)T, as it also occurs with CD117 (c-KIT). c-KIT mutation has been shown to occur in a third of cases of dysgerminoma, however, its expression does not imply a response to imatinib mesylate. This, nevertheless, would be redundant owing to its already excellent response to cisplatin-based regimens, which remain the gold standard for treatment of these tumors.

Clone D2-40 of podoplanin is a glycoprotein initially identified in renal podocytes that is also a good marker of both the endothelium of lymph vessels and mesothelium. In dysgerminoma it behaves as a relatively specific and stable marker, even in poorly fixed and necrotic material, where it strongly stains the cytoplasm and cell membranes. D2-40 only stains seminoma when antigen retrieval technique is not performed. However, when this is performed in the testis, it can also show a characteristic apical expression in glandlike areas of EC.

OCT3/4, also known as POU5F1, is possibly one of the most useful antibodies in the diagnosis of MOGCTs. OCT3/4 is a nuclear transcription factor interacting with other nuclear factors, such as NANOG, SOX2, SALL4, and KLF4, that maintain pluripotency in primordial germ and stem cells. It is expressed very early during embryogenesis and has an essential role in blastocyst differentiation. After gastrulation, its expression is limited to primordial germ cells throughout their migration (Figure 4, A) until their eventual transformation into spermatogonia during the second trimester of gestation; on the other hand, when female germ cells enter meiosis the expression of OCT3/4 is down-regulated. It is constantly expressed in precursor lesions of malignant germ cell tumors, such as the germ cell component of gonadoblastoma and intratubular germ cell neoplasia. OCT3/4 regularly shows positivity in dysgerminoma but can also be expressed in EC and in some immature neural elements of ovarian teratoma. However, considering that EC is exceptionally rare in the ovary, OCT3/4 can be considered as a selective marker of ovarian dysgerminoma.

OCT3/4 is particularly useful in demonstrating the primitive germ cell identity of poorly fixed tissue or microcystic cases, helping to differentiate them from small cell tumors and even struma ovarii (Figure 1, C and D). It also identifies isolated dysgerminoma cells masked by fibrosis or inflammation (Figure 3, B). Furthermore, it is particularly useful in the identification of the primary tumor in distant metastases.

SALL4 is a nuclear factor and a member of the family of SALL genes, which are also involved in totipotency and are expressed at an early stage of embryogenesis. We have been able to identify SALL4 nuclear expression in retroper-
itoneal primitive germ cells during their migration toward the gonadal crests in two 12-week-old embryos (Figure 4, B). SALL4 is strongly expressed by dysgerminomas. However, since it is a pluripotency marker, it can show positivity in EC, YS(PE)T, and primitive areas of immature teratoma; consequently, it represents a good, broad marker for MOGCTs. Nevertheless, its expression has also been shown in myeloid leukemia and in some gastric carcinomas.

Cytokeratin expression does not exclude the diagnosis of dysgerminoma, since positivity ranging from strongly diffuse to focal and dotlike (Figure 2, B) can be seen, in our experience, in up to a third of cases. Thus, it is not advisable to differentiate dysgerminoma from EC by using this antibody alone, as was initially thought. Expression of cytokeratins has unknown significance but it may be related to an eventual differentiation of primitive germ cells from dysgerminoma into somatic-type cells. This assumption is partly supported by the focal positivity of blood group-related antigens in the cytoplasm of dysgerminomas, which may reflect a somatic-type differentiation. Additionally, trophoblastic cell differentiation in dysgerminoma is always cytokeratin positive.

In summary, the diagnostic problems associated with dysgerminoma are frequently related to poor fixation and unusual growth patterns, and in both situations immunohistochemistry enables a correct identification of the proliferating germ cells. These data should be considered together with classic histologic dysgerminoma features such as lymphocytic infiltrates.

YOLK SAC (PRIMITIVE ENDODERMAL) TUMORS

We have recently reviewed the current data on the histopathology and immunophenotype of these neoplasms and proposed the new term *primitive endodermal tumors*. This is a more apt definition of their complex, multifaceted histologic features, which comprise early endodermal differentiation into secondary yolk sac and primitive gut, and their derivatives, such as intestine, liver, and lung. This proposal parallels the widely accepted terminology for primitive neuroectodermal tumors (PNETs), which encompasses the multiple differentiation capacity into diverse neural cell lines present in PNET. Other terms, such as *endodermal sinus tumors*, are arcane, as the structure it purports to represent is nonexistent in human embryogenesis. The YS(PE)T terminology also defines endodermal
Figure 2. Compact architecture of an epithelioid dysgerminoma with minimal lymphocytic infiltration (A) that simulates solid embryonal carcinoma. Cytokeratin (CAM 5.2) staining shows only a dotlike expression (B) (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×200 [B]).

Figure 3. Dysgerminoma with extensive inflammatory response: malignant germ cells are difficult to identify at medium power (A). OCT3/4-positive nuclear staining recognizes characteristic germ cells (B) (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×100 [B]).

Figure 4. Migrating germ cells in the retroperitoneum of a 12-week fetus are positive for pluripotentiality markers OCT3/4 (A) and SALL4 (B) (original magnifications ×200 [A and B]).
tumors developing from somatic neoplasms, such as endometrioid carcinoma and some unusual clear cell, AFP-secreting neoplasms of the stomach, lung, and bladder.

Classic histologic features in these tumors almost always include reticular microcystic areas with hyaline globules and amorphous acellular basement membrane material, which often provide the diagnostic clue in tumors exhibiting complex histologic profiles. Pure patterns, such as the polyvesicular type, hepatic, and intestinal, are extremely rare and often mimic other neoplasms such as hepatoid and endometrioid carcinoma. Rarely, the mature intestinal component of YS(PE)T may give rise to a mucinous carcinoid.

Yolk sac tumors can originate from malignant stem cells present in somatic tumors of the ovary and uterus, usually endometrioid adenocarcinoma and carcinosarcoma. The histology of these unusual YS(PE)Ts is identical to that of tumors of germ cell origin. Their characteristic immunophenotype helps to differentiate them from the somatic tumor from which they arise.

**Immunophenotype**

Presence of α-fetoprotein remains the gold standard for the diagnosis of YS(PE)Ts. This protein is expressed by the primary yolk sac before specialized tissue differentiation occurs and it is a marker of the secondary yolk sac until its involution at the 11th week. It is also expressed in early endodermal derivatives, such as allantois and liver, and focally, in the early intestine. In the normal secondary human yolk sac, AFP is secreted in the cytoplasm and is transferred to intercellular and intracellular vesicles and channels. In YS(PE)Ts, AFP is strongly expressed in the labyrinthine network of microcystic reticular patterns where it has a granular cytoplasmic stain (Figure 6, A) and often, but not always, stains positively in hyaline globules. Its expression is generally patchy and often associated with a dirty background of serum proteins. Both endodermal hepatic and intestinal glandular patterns, displaying characteristic apical and basal vacuolation, often exhibit variable AFP staining. α-fetoprotein staining can become negative in some recurrences occurring after treatment with chemotherapy.

Glypican 3 is a useful marker in liver cell carcinoma and is a complementary antibody in the diagnosis of YS(PE)Ts. Glypican 3 is also secreted by the early secondary yolk sac and liver. Glypican 3 cytoplasmic, and less often membranous, staining is almost, but not exactly, parallel to that of AFP, having the advantage of presenting a clean background. (Figure 6, B). There are AFP-negative tumors that are GLP3 positive. We believe that since AFP is such a specific marker, the coexpression of both markers is a sure diagnostic feature of YS(PE)Ts. However, GLP3 positivity alone does not allow a diagnosis of YS(PE)T unless it is associated with other characteristic YS(PE)T markers. Glypican 3 may also be focally present in EC, teratoid glands, neuroepithelium, and syncytiotrophoblasts.

SALL4 has a consistently strong expression in the nuclei of YS(PE)Ts regardless of their germ cell or somatic origin (Figure 5, B) and of their diverse growth patterns, namely, microcystic, intestinal (Figure 6, C), and even hepatic. Neoplastic stromal cells are also frequently stained, thus indicating their pluripotent character, which would be reflected in several mesenchymal differentiations from YS(PE)T. Furthermore, its expression is evident in the secondary human yolk sac until its final involution.
Endodermal tissue specializations from YS(PE)T express their characteristic markers: hepatic areas are positive for hepatocyte paraffin antigen 1 (HepPar-1) (Figure 6, D) and intestinal areas, for CDX2 (Figures 5, C, and 6, E) and villin (Figure 6, F). Glands differentiating into foregut express thyroid transcription factor 1. Other markers, such as Lin28, CD117, and IMP-3, are also expressed in varying percentages in YS(PE)Ts.

Figure 6. Immunophenotype of yolk sac (endodermal primitive) tumor: α-fetoprotein staining in epithelial cells delineates intracellular vesicles (A). Glypican 3 reveals a similar expression (B). SALL4 stains positively in epithelial and in some mesenchymal cells (C). Cystic spaces are lined by an epithelium positive for hepatocyte paraffin 2 antibody (D). CDX2 stains epithelial cells focally (E). Villin shows a diffuse epithelial expression (F) (original magnifications ×200 [A through F]).
Some metastases of unusual gastric tumors, such as the clear cell adenocarcinoma with hepatoid change, can mimic an ovarian YS(PE)T, particularly when only 1 ovary is involved. They may show an identical immunophenotype expressing all characteristic markers such as AFP, GLP3, HepPar-1, and SALL4. It must be borne in mind, however, that unilateral ovarian involvement of Krukenberg tumors occurs in as many as 37% of cases, although in many instances both ovaries are not removed or rigorously examined microscopically.

**EMBRYONAL CARCINOMA**

Embryonal carcinoma represents a malignant stem cell tumor with a totipotent differentiation capacity, as demonstrated by Kleinsmith and Pierce as early as 1964 in an experimental murine model that provided the first demonstration of the stem cell origin of cancer. Embryonal carcinoma is, however, a characteristic testicular tumor that represents, together with seminoma, the pluripotent component of mixed germ cell tumors. This preference for a testicular location reflects the different histogenesis of testicular and ovarian germ cell tumors, the former originating from primitive germ cells with a malignant character, while the latter mostly have a parthenogenetic origin from postmeiotic or meiotic cells. For these reasons, the presence of EC in the ovary is extremely rare. In 40 years' experience of ovarian germ cell tumor consultations, the senior author of this article has only identified 3 bona fide cases. It is possible that many of the embryonal carcinomas reported in older series were misinterpretations of solid forms of YS(PE)T, or epithelioid dysgerminomas. It is also likely that some reports may have included cases of Y chromosome–containing gonadal dysgenesis. In these cases, the precursor lesion would be a gonadoblastoma. Therefore, any diagnosis of EC in a female patient should prompt a chromosomal study.

Solid and glandular patterns of EC can overlap and mimic both dysgerminoma and YS(PE)T, which occur far more frequently in the ovary. For this reason, the putative immunophenotype of a rare EC should be excluded in the differential diagnoses of MOGCT.

**Immunophenotype**

Most EC immunophenotypic data arise from testicular tumors, but we have identified a similar staining pattern in the few available cases of ovarian EC. All ECs are cytokeratin positive. CD30 membrane expression remains one of the most reliable and accessible markers for EC. Anti-CD30 is an antibody against a surface glycoprotein corresponding to a cytokine receptor, and CD30 is a member of the superfamily of tumor necrosis factor receptors. CD30 is expressed by many other tumors, including anaplastic lymphomas, and by Reed-Sternberg cells. Some reactive inflammatory conditions may also show CD30-positive immunoblasts.

SOX2 is another nuclear transcription factor also involved in totipotency. It is also responsible for neuronal differentiation and useful, together with CD30, in the differentiation of solid areas of EC with dysgerminoma. SOX2 and OCT3/4 coexpression in the papillary areas of EC contrasts with these markers' negativity in Schiller-Duval sinususes of YS(PE)T (Figure 7, A and B). Expression of PLAP, OCT3/4, and SALL4 in EC is shared with dysgerminoma. D2-40 has a particular apical membranous positivity in the glandular and papillary areas of EC.

Glypican3 shows patchy positivity in EC, especially in areas of early endodermal differentiation, such as the organoid areas (primitive yolk sac endodermal cavities) of embryoid bodies in the rare polyembryoma.

**CHORIOCARCINOMA**

Pure nongestational choriocarcinoma is exceptionally rare in the ovary. Similar to dysgerminoma and EC, it represents more a testicular-type tumor, and its presence should prompt an analysis of the patient’s genotype. It should be differentiated from the also rare dysgerminoma with syncytiotrophoblastic giant cells, which accounts for fewer than 10% of dysgerminomas and has a behavior identical to classic dysgerminoma. Choriocarcinoma is positive to a host of antibodies. Trophoblast stains strongly for cytotkeratin, human chorionic gonadotropin, α-inhibin, CD10, and GLP3. Human placental lactogen can identify the intermediate (extravillous) trophoblastic component.

**TERATOMAS**

Most ovarian teratomas show differentiation of either mature or, less frequently, immature tissues derived from the 3 germ layers. Stem cell scientists usually restrict the term teratoma to tumors differentiating tissues from the 3 germ layers. In gynecologic pathology, however, this strict differentiation is not possible, since monodermal ovarian teratomas with 1-sided tissue differentiation (monophyletic teratomas), such as struma ovari, often occur. Furthermore, the presence of ovarian tumors containing an uncommon tissue unrelated to normal embryogenesis (eg, ependymoma and nephroblastoma) does not always imply a germ cell origin, as they may originate from totipotent stem cells from the same tumor (so-called neometaplasia).

Human reprogrammed/induced pluripotent stem cells transplanted subcutaneously or by intratesticular injection into immunodeficient mice can grow, in a short period of time, tumors that are histologically identical to ovarian immature teratomas with characteristic neuroepithelial tubules (Figure 8, A) and AFP-positive embryonal endodermal areas resembling either Schiller-Duval sinuses or gut elements of glandular YS(PE)Ts (Figure 8, B).

Immature teratoma is the most frequent MOGCT and the histologic assessment of its degree of immaturity is a highly reliable prognostic factor and therapeutic indicator. Grading is performed by a subjective, semiquantitative analysis of the relative number and atypicality of the foci of immature neural tissues (neuroepithelial tubules and neural blastema) present in the tumor. This is accomplished either by a 2-tier system (low grade and high grade) or by assigning 4 grades ranging from fully mature (0) to highly immature (3). Rarely, immature and atypical neural components may overgrow the original teratoma, displaying various patterns of PNETs. This overgrowth is often difficult to separate from a high-grade (grade 3) immature teratoma. The differentiation usually lies in the mainly monomorphic appearances of the PNET overgrowth.

Mature cystic teratomas may show minute, isolated neuroepithelial/ependymal foci lacking any prognostic significance. Their presence, however, may be worrisome and should not be reported as grade 1 immature teratoma but as prognostically irrelevant microscopic foci of immature tissue in mature cystic teratoma.
Gliomatosis peritonei (GP) is a fascinating condition whereby immature and, less often, mature teratomas become associated with a myriad of peritoneal nodular or miliary implants composed of mature glia. Despite its clinical stage III, its behavior is benign, since mature glial cells are not aggressive and remain stable for long periods of time. However, on rare occasions, GP can induce a florid vascular proliferation that may result in peritoneal hemorrhage and shock\(^8\) (Figure 9, A) and can even develop a secondary malignant glial tumor.\(^8\)

In the last decade, attention has been paid to the histogenesis of this rare phenomenon. Genetic studies of microdissected peritoneal implants that analyzed multiple microsatellite markers\(^8\) revealed a heterozygosity pattern identical to that of normal tissue and different from ovarian teratoma, which showed homozygosity of the same loci. These findings proposed a different genetic identity for ovarian tumor and GP, the latter originating from peritoneal pluripotent cells stimulated by growth factors present in the primary tumor that would induce differentiation into glial cells. Although the genetic evidence is incontrovertible,\(^8\) the traditional origin for GP as a peritoneal seeding via capsular rupture from the ovarian teratoma is also supported by the following facts: (1) GP nodules often show multiple tissue differentiation (skin, gut, cartilage); (2) neural tissue itself is polydifferentiated with several neurogenic lines including microglia (Figure 9, B); (3) immature neuroepithelial tubules coexist in some cases with mature glia, indicating maturation from embryonal precursors; (4) shed hair and keratin scales from teratoma (Figure 9, C) are often found associated with GP; and (5) lymph node involvement by mature glia may occur in the absence of GP.\(^8\) These facts would support an origin from ovarian teratoma in most cases, although it may be possible that some cases of GP with a monomorphic cell population have a metaplastic identity.

**Immunophenotype**

The use of new pluripotency markers can enhance the identification of tissue components as well as their degree of immaturity, contributing to a better grading of immature teratoma. It is necessary to identify the immature character...
Figure 9. Mature peritoneal glial implants can show a marked vascular proliferation leading to hemoperitoneum (A). Glial implants are rarely monomorphic, harboring multiple cell lines. Here, microglia-like cells are stained by CD68 (B). Hairs (left arrow) shed into the peritoneum from primary ovarian teratoma can be found next to glial nodules (arrow, right lower corner) (C) (hematoxylin-eosin, original magnifications ×25 [A and C]; original magnification ×100 [B]).

Figure 10. Immature ovarian teratoma showing neuroepithelial tubules with a strong SOX2 expression (A). Tubules express SALL4, which is also positive in other immature stromal and epithelial elements (B). Glypican 3 also shows a patchy expression in neuroepithelium (C) (original magnifications ×100 [A through C]).
of some areas when hematoxylin-eosin images are not conclusive. This may occur in cases of mature teratoma containing both glandular structures and ependymal spaces that may resemble the standard diagnostic immature neuroepithelial tubules useful for grading. Markers such as SOX2 and SALL4 (Figure 10, A and B) are strongly expressed by immature neuroepithelium but are weaker or absent in well-differentiated neural areas. However, implanted GP astrocytes may still express SOX2, indicating that they are not terminally differentiated. Glypican 3 may also show a patchy neuroepithelial staining (Figure 10, C). In our experience, SOX2 behaves as the more specific antibody for immature neural areas, being particularly useful in PNET overgrowths of teratoma. Identification of neural areas can be complemented by more characteristic neural makers such as glial fibrillary acidic protein, nestin, and others. OCT3/4 has been reported to be focally positive in neural components.36

Benign and malignant ovarian mucinous tumors associated with mature cystic teratomas may show massive mucin secretion, goblet cells, carcinoid-like patterns, pseudomyxoma ovarii and peritonei, and signet ring cells characteristic of a gastrointestinal phenotype, with markers such as CDX2, HepPar-1 and villin, as well as a cytokeratin 7–negative/cytokeratin 20–positive profile.86 All these features would point toward a teratoid origin for this mucinous component, which should be differentiated from a metastasis from a gastrointestinal primary tumor. Demonstration of teratoma foci may be difficult in rare cases when they are small and escape sampling or become overgrown by the mucinous neoplasm.36

A recent interesting clinical breakthrough on ovarian teratomas has been their identification as a causative factor of severe neurologic disease. Since 2005 Dalmau et al77,87 and Vitaliani et al88 have reported more than 100 cases of autoimmune encephalitis due to antibodies against the N-methyl-d-aspartate receptor (anti-NMDAR), a condition that frequently involves temporal lobes and hippocampus. Its recognition is important, as removal of the ovarian tumor associated with concomitant teratomas. This association has now become the most frequent autoimmune disorder associated with ovarian teratoma.90

**CONCLUSIONS**

Even if careful histologic and classic immunohistochemical studies allow a relatively correct diagnosis of MOGCTs, the use of new immunohistochemical pluripotency stem cell markers results in a higher diagnostic accuracy. This is accomplished by the specific expression of these markers as they are switched on or off according to the stage of differentiation, thus permitting a better identification of the tumor, which in germ cell tumors is determined by a progressive flow from primordial germ cells to extraembryonal and somatic malignancies. This is especially applicable to ovarian MOGCTs for which mixed forms of malignant germ cell tumors are rare and overlapping among various neoplastic phenotypes is minimal. The new antibodies also permit a more precise evaluation of immature, diagnostic areas in teratoma. The Table shows the comparative expression of diagnostic immunohistochemical markers analyzed in this review. Recently described autoimmune encephalitis due to antibodies against the N-methyl-d-aspartate receptor has become the most frequent autoimmune disorder associated with ovarian teratoma. New data have provided new insights into the origin of gliomatosis peritonei.

**References**


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