Recently Described and Clinically Important Entities in Testis Tumors

A Selective Review of Changes Incorporated Into the 2016 Classification of the World Health Organization

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Context.—In 2016 the World Health Organization published a revised classification of testicular neoplasms based upon advances in understanding their pathogenesis and molecular biology. The rationale for this revision and additional clinically relevant observations were the topics of a talk given to the Houston Society of Clinical Pathologists in April 2017. This paper summarizes that talk.

Objective.—To summarize and explain the most important changes to the classification of testicular neoplasms in the World Health Organization 2016 revision.

Data Sources.—Peer-reviewed published literature and contributions by individuals with expertise in this area that were also reviewed by genitourinary pathologists.

Conclusions.—Most changes occurred in the germ cell tumor classification, including replacement of the terms intratubular germ cell neoplasia unclassified and carcinoma in situ by germ cell neoplasia in situ; subdivision of the tumors into 2 main categories, those derived from germ cell neoplasia in situ and those not derived from germ cell neoplasia in situ; distinction of germ cell neoplasia in situ from germ cells with delayed maturation and pre–germ cell neoplasia in situ; expansion of the trophoblastic tumor category to include epithelioid trophoblastic tumor and cystic trophoblastic tumor; and substitution of spermatoctytic tumor for spermatocytic seminoma and its placement in the non–germ cell neoplasia in situ group. Other revisions included eliminating sclerosing Sertoli cell tumor as a distinct entity; the recognition of intratubular hyalinizing Sertoli cell tumor; and acceptance of the role of undifferentiated gonadal tissue in the pathogenesis of gonadoblastoma.

A group of 28 pathologists with a special interest in testicular and paratesticular pathology and who had contributed to its literature provided drafts for the 4th edition revision of the World Health Organization’s (WHO’s) Tumours of the Urinary System and Male Genital Organs (WHO 2016) in late 2014 and early 2015. Problematic issues were discussed in group email communications, and a select subcommittee of 7 met in Zurich, Switzerland, in March 2015 to finalize the revision during a 3-day interval. The resultant monograph was published in January 2016 and incorporated several substantive changes to the classification of testicular neoplasms, especially the germ cell tumors. This article reviews some of the most important changes, which were largely presented in lecture format at the Houston Society of Clinical Pathologists spring symposium in April 2017.

A landmark in our understanding of testicular germ cell tumors occurred in the 1970s when, in a series of papers, Skakkebaek2–5 convincingly demonstrated the intratubular cellular precursor to the great majority of germ cell tumors of young men. The obligate nature of this precursor became established,6 but its nomenclature was a source of controversy. The initial term, carcinoma in situ, became established in Europe but was objected to in North America on histogenetic grounds. The alternative, intratubular germ cell neoplasia, unclassified type,7 was used on this side of the Atlantic but was objected to in Europe, where it was considered unwieldy and felt to convey an inappropriate sense of uncertainty concerning its clinical significance. In WHO 2016, germ cell neoplasia in situ (GCNIS) replaces both prior terms; it was regarded as an optimal hybrid, conveying the correct precursor nature of the lesion and remaining histogenetically accurate. An essential feature of GCNIS, perhaps previously less emphasized than it should have been, is its requisite location at the base of seminiferous tubules in what has been termed the spermatogonial niche (Figure 1, A). This is one of the essential features that serves

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to distinguish GCNIS from germ cells with delayed maturation.8–12 In WHO 2016, the concept of germ cells with delayed maturation is introduced and the importance of their distinction from GCNIS is emphasized; this distinction will likely be most needed in the evaluation of biopsies from the cryptorchid testes of children at the time of orchiopexy. There is no question that immature germ cells have been confused with GCNIS for many years, as papers have been published purporting to show "intratubular germ cell neoplasia" in the fetal testis13 and adjacent to testicular germ cell tumors of children.14 A major contributing factor to this confusion is the fact that the commonly used immunohistochemical markers for GCNIS (eg, OCT3/4, placental alkaline phosphatase, CD117) are also markers of immature germ cells, which acquire them approximately midway through the second trimester of gestation. Additionally, immature germ cells show morphologic features of primordial germ cells or gonocytes and, as such, have large nuclei, prominent nucleoli, and pale to lightly eosinophilic cytoplasm (Figure 1, B). Their cytologic features therefore overlap with those of GCNIS. If germ cells do not undergo normal maturation, the combination of continued expression of immature/neoplastic germ cell markers and morphology may lead to misinterpretation as GCNIS, and it is also apparent that delayed maturation of germ cells is an essential early step in a pathway that may lead to germ cell neoplasia.8–12 The following features, however, define maturation-delayed germ cells, with the latter 2 serving to distinguish them from GCNIS: (1) expression of OCT3/4 beyond 6 months of age (Figure 1, C); (2) morphologic features of primordial germ cells/gonocytes (Figure 1, B); (3) central or parabasal position in the seminiferous tubules; and (4) absence of such cells at the tubular basement membrane (ie, in the spermatogonial niche). Although the issue has been clouded by reports of GCNIS in prepubertal children, thanks in part to misinterpretations of maturation-delayed germ cells, careful studies by a number of different investigative groups15–19 have now firmly established that the pediatric germ cell tumors are not related to GCNIS and

Figure 1. A, Germ cell neoplasia in situ consists of seminoma-like cells arranged in a linear fashion at the base of seminiferous tubules (ie, in the spermatogonial niche) that characteristically lack spermatogenesis. Sertoli cells are displaced adluminally. B, Germ cells with delayed maturation resemble gonocytes, with large nuclei and prominent nucleoli. Unlike germ cell neoplasia in situ, they occupy central or parabasal positions. C, An OCT3/4 immunostain of a cryptorchid testis with maturation delay of germ cells demonstrates their occurrence outside of the spermatogonial niche. D, The presence of gonocyte-like cells that occur bothbasally andcentrally is considered characteristic of pre–germ cell neoplasia in situ (hematoxylin-eosin, original magnification ×400 [A, B, and D]; OCT3/4 immunostain, original magnification ×100 [C]).
that GCNIS essentially does not occur in young (prepubertal-aged) children outside of a disorder of sex development, where gonadoblastoma, a distinctive morphologic manifestation of GCNIS, may often serve as the precursor.

Another entity related to GCNIS is also defined in WHO 2016: what has been termed pre-GCNIS. Like maturation delay, pre-GCNIS consists of cells resembling primordial germ cells/gonocytes, but differs from the former by these locating centrally, parabasally, and in the spermatogonial niche (Figure I, D). Unlike GCNIS, which shows uniform coexpression of 2 factors felt to be key to its malignant nature, OCT3/4 and testis-specific Y-encoded protein (TSPY), pre-GCNIS cells show heterogeneous expression for these proteins. An additional feature of pre-GCNIS is the expression of stem cell factor (also known as KIT ligand) in the seminiferous tubules having pre-GCNIS; this is also a feature of GCNIS but is absent in maturation delay.

The importance of making the distinction among maturation delay, pre-GCNIS, and GCNIS is related to the high rate of progression of GCNIS to an invasive germ cell tumor (perhaps approaching 100% if the follow-up period is sufficiently lengthy) but the absence of information regarding the progression of both maturation delay and pre-GCNIS to an invasive tumor.

One of the fundamental changes made in WHO 2016 was the subdivision of the germ cell tumors into 2 pathogenetically distinct groups: those derived from GCNIS and those not derived from GCNIS (Table 1). The concept for this subdivision was initially put forth by Oosterhuis and Looijenga,21 who regarded the GCNIS-derived tumors in the subdivision as type II germ cell tumors and the tumors not derived from GCNIS as type I (the pediatric germ cell tumors) and type III (spermatocytic tumor) germ cell tumors. The GCNIS-derived tumors are much more common and typically occur in postpubertal men from 18 to 45 years of age. The histotypes include seminoma, embryonal carcinoma, yolk sac tumor, trophoblastic tumors, teratoma, mixed germ cell tumor, and regressed germ cell tumor. Most of the histotypes are essentially restricted to this age group, although they may infrequently occur in older men; with the exceptions of yolk sac tumor and teratoma, they do not occur in prepubertal-aged children unless the patient has a disorder of sex development. Because yolk sac tumor and teratoma may either develop from GCNIS or not be derived from GCNIS, the WHO recommended that the GCNIS-derived variants be further designated as postpubertal type because of their marked predominance in this age group. Similarly, the non–GCNIS-related counterparts are designated prepubertal type. The addition of the type suffix relates to the uncommon occurrence of pathogenetically identical neoplasms outside of the postpubertal and prepubertal age ranges.

The GCNIS-derived tumors share a number of features in addition to the usual presence of GCNIS in the seminiferous tubules of the residual parenchyma. They have common epidemiologic associations that include an increasing incidence during the 20th century, marked tendency to occur in first-world countries that are heavily industrialized and have a Western lifestyle, occurrence in testes with what have been termed dysgenetic changes, uniform occurrence of amplification of a segment of the short arm of chromosome 12 (often but not always in the form of an isochromosome), and, of course, typical development in young men. A unifying link to many of these associations is the notion that testicular germ cell tumors originate in maldeveloped testes with impaired Sertoli cell function. Residents of industrialized countries more often have exposure to endocrine disruptors, including the antiandrogen additives used in the manufacture of certain plastics, phthalates, which can leach into food from plastic containers and become airborne in household dust. Additionally, industrialized countries are linked to a sedentary lifestyle, high calorie intake, and obesity. Maternal obesity results in hyperestrogenism, which has a negative impact on the developing testis. The positive association of testis cancer with hyperemesis gravidarum, an increased frequency of testicular cancer in the firstborn of sibships, and the temporary decline in testis cancer incidence in Norwegian babies born during the deprivations of World War II support an important role of maternal hyperestrogenism in predisposing to testicular cancer. This concept is further reinforced by the very high incidence of germ cell neoplasia in patients with disorders of sex development, many of whom have mutations in genes involved in testicular development. Normal Sertoli cell function is important for the maturation of gonocytes in the early testis,
and delayed maturation, as already discussed, predisposes to germ cell neoplasia but at an unknown frequency.

On the other hand, there are 4 types of germ cell tumors that do not develop from GCNIS—spermatocytic tumor (no longer termed spermatocytic seminoma) and 3 neoplasms that are largely, but not exclusively, restricted to prepubertal children: teratoma, prepubertal type; mixed germ cell tumor, prepubertal type (teratoma and yolk sac tumor); and yolk sac tumor, prepubertal type. These tumors lack the epidemiologic associations seen in the GCNIS-derived germ cell tumors and have no established risk factors apart from occurrence in older men (spermatocytic tumor) or children (the prepubertal-type tumors). Whereas the GCNIS-derived tumors experienced a rapid rise in incidence in North America and northern Europe in the 20th century, the incidence of the prepubertal germ cell tumors remained stable and much lower. Furthermore, again contrasting with the GCNIS-derived tumors, all of the neoplasms in this category lack chromosome 12p amplification.

Among the GCNIS-derived tumors, the trophoblastic category has undergone a substantial revision in the current WHO classification, which now adds 2 additional forms under the nonchoriocarcinomatous trophoblastic tumors—epithelioid trophoblastic tumor and cystic trophoblastic tumor—to the previously established entity placental site trophoblastic tumor. Furthermore, monophasic choriocarcinoma is no longer separately categorized, but is recognized as a morphologic variant of choriocarcinoma (Figure 2, A). Although epithelioid trophoblastic tumor and cystic trophoblastic tumor had been recognized for a number of years in metastatic sites following chemotherapy, documentation of their development in the untreated testis recently occurred. Both placental site trophoblastic tumor and epithelioid trophoblastic tumor are highly analogous to their better-known uterine counterparts. Placental site trophoblastic tumor consists of a discohesive proliferation of pleomorphic intermediate trophoblast cells (Figure 2, B) with a tendency to invade vascular walls and having the same immunohistochemical properties as implantation site figures.
trophoblasts—positive for human placental lactogen and negative for p63. In contrast, epithelioid trophoblastic tumor consists of cohesive aggregates of squamoid trophoblastic cells in a fibrin-rich background and frequently contains admixed eosinophilic, apoptotic cells and fibrinoid deposits in vascular walls (Figure 2, C). It shows the immunohistochemical profile of the intermediate trophoblast cells of the chorion laeve: p63 positive and human placental lactogen negative. Cystic trophoblastic tumor consists of variably stratified, often vacuolated, and mostly mononucleated trophoblast cells lining cysts that frequently contain eosinophilic, fibrinous fluid (Figure 2, D). Immunostains for GATA3 and α-inhibin tend to show greater reactivity than those for human chorionic gonadotropin. It is likely that these 3 trophoblastic lesions bear no clinical significance when found in primary germ cell tumors, where they are invariably associated with one or more aggressively behaving histotypes. In the postchemotherapy, metastatic setting it is known that cystic trophoblastic tumor behaves similarly to metastatic teratoma, but there is too little information at the present time to assess the prognostic significance of metastatic epithelioid trophoblastic tumor and placental site trophoblastic tumor.

Spermatocytic tumor is one of the few testicular germ cell tumors not derived from GCNIS. In order to avoid confusion with the much more common classic seminoma, the term for this entity was changed from the previous one, spermatocytic seminoma, in the 2016 WHO revision. It is well known to occur at an older mean age than seminoma (an average in the sixth decade as opposed to about 40 years old), although it certainly may be seen in younger men as well. It originates only in the testis, does not occur together with other forms of germ cell tumor (except in a unique case that developed in a patient who also had a gonadoblastoma with germinoma), lacks the chromosome 12p amplification of the GCNIS-derived tumors, and shows a characteristic amplification of the DMRT1 gene near the telomeric end of chromosome 9p. It often shows a multinodular growth pattern (Figure 3, A), with the cellular tumor nodules lacking the fibrous septa and lymphocytic infiltrate of seminoma. Edema may be a striking feature in many spermatocytic tumors and is responsible for the formation of irregular to follicle-like spaces (Figure 3, B) in

Figure 3. Spermatocytic tumor. A, Low power showing multiple cellular nodules with scant stroma. B, Follicle-like structures with central edema fluid. C, Numerous intermediate-sized cells with prominent nucleoli, sometimes designated anaplastic change. D, Many clusters of apoptotic tumor cells (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B], ×400 [C], and ×200 [D]).
many of them. At high magnification, the characteristic tripartite morphology can be appreciated in virtually every case, although this may be only a focal finding in some that have a predominance of intermediate-sized cells with prominent nucleoli (Figure 3, C) (a finding that has been termed anaplastic, although this is a designation that is not recommended by the WHO because it is not established that such tumors show a different clinical behavior than the tumors with the characteristic appearance). Cellular apoptosis is often prominent in spermatocytic tumors, often occurring in small clusters (Figure 3, D). Many of the immunostains that are often used in the diagnosis of testicular germ cell tumors (OCT3/4, placental alkaline phosphatase, α-fetoprotein, human chorionic gonadotropin, CD30) are negative, but CD117 is positive in about two-thirds of cases (as it is in almost all seminomas) and SALL4 is uniformly positive. Immunohistochemistry for DMRT1 is positive, as are stains for several cancer-testis antigens.

The prepubertal-type germ cell tumors, the other major category of testicular tumors not derived from GCNIS, occur mostly but not exclusively in children. For treatment and prognostic purposes, it is especially important to distinguish the prepubertal form of testicular teratoma from the postpubertal form, because the former is benign but not the latter. Because prepubertal-type teratomas may occasionally be discovered in postpubertal males, age alone cannot serve to discriminate between these lesions, but a combination of careful morphologic and, if necessary, molecular assessment will. Features of prepubertal-type teratomas include absence of all the following: cytologic atypia (Figure 4, A); GCNIS (Figure 4, B); dysemogenic testicular parenchymal changes (ie, tubular atrophy, peritubular sclerosis, Sertoli cell–only tubules, microlithiasis) and testicular scars (Figure 4, B). There is also frequent occurrence of organoid tissue arrangements (Figure 4, C); prominently ciliated epithelium (Figure 4, A); nests of squamous epithelium and smooth muscle (Figure 4, C); and the occasional presence of salivary gland/pancreas acinar cell differentiation (Figure 4, D). When the morphologic features are indicative of a prepubertal-type teratoma, confirmation can be obtained by demonstrating lack of...
chromosome 12p amplification using fluorescent in situ hybridization methodology and probes for the chromosome 12 centromere and 12p telomere.57 Prepubertal-type yolk sac tumor is not morphologically distinct from the postpubertal type. It differs from the latter by the absence of GCNIS,15,16 dysgenetic testicular changes, and 12p amplification.43,44 Instead it often shows gains (1q, 12[p13], 20q, 22) or losses (1p, 4, 6q, 16q) of certain whole chromosomes or portions of chromosomes.21,44 Its occurrence in postpubertal males is less well established than that of prepubertal-type teratoma, but there are 2 well-supported cases of prepubertal-type yolk sac tumor with prepubertal-type teratoma (mixed germ cell tumor, prepubertal type) in 23-year-old men.58 The distinction of the prepubertal-type yolk sac tumor from the postpubertal type is important because the former is less apt to metastasize, with about 16% of clinical stage I patients relapsing on surveillance,59,60 whereas the comparable figure for the adult form is about 30%. Furthermore, when it does metastasize it is more likely to follow a hematogenous distribution rather than a lymphatic-based distribution.61

The classification of testicular sex cord–stromal tumors (Table 2) remains largely unchanged in WHO 2016, except for the Sertoli cell tumor category. Because of the identification of CTNNB1 gene mutations and consequent nuclear positivity for β-catenin in both the Sertoli cell tumor, not otherwise specified (Figure 5, A and B), and the sclerosing Sertoli cell tumor62–64 (Figure 5, C and D), these neoplasms are now considered the same entity, with the less common sclerosing form deemed a morphologic variant of Sertoli cell tumor, not otherwise specified. The finding of malignant behavior in a sclerosing type65 provided additional support that there were no intrinsic differences between the 2 and that the lesser frequency of metastasis in the sclerosing variant likely relates to its lower cellularity. Additionally, the intratubular hyalinizing Sertoli cell tumor66 receives formal recognition as a distinct form of neoplasia. This is a multifocal, intratubular neoplasm of Sertoli cells that occurs, as far as is known, exclusively in

Figure 5. A, Sertoli cell tumor, not otherwise specified, showing cords, solid tubules, and small nests of cells, some with single, large cytoplasmic vacuoles. B, Strong nuclear and cytoplasmic staining for β-catenin of the tumor in A. C, This tumor would have previously been designated sclerosing Sertoli cell tumor because of the predominance of stroma over tumor cells. D, Strong nuclear and cytoplasmic staining for β-catenin of the tumor in C (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [C]; original magnifications ×200 [B] and ×400 [D]).
patients with Peutz-Jeghers syndrome. Clusters of expanded tubules are filled with large Sertoli cells with vacuolated, pale cytoplasm and internalized, globoid deposits of basement membrane that project from thickened peritubular basement membrane (Figure 6, A and B). It is generally managed conservatively with follow-up and aromatase inhibitors to diminish the frequent estrogenic manifestation attributable to aromatase synthesis by the neoplastic cells.

Gonadoblastoma is now the only recognized entity in the mixed germ cell–sex cord stromal tumor category. The previously recognized unclassified type was eliminated based on insufficient evidence that it is different from sex cord–stromal tumors with entrapped, nonneoplastic germ cells. One could also make an argument that gonadoblastoma is not a true mixed germ cell–sex cord stromal tumor because the sex cord component is almost certainly nonneoplastic and that it is, instead, a distinctive form of GCNIS with a characteristic morphology that occurs almost exclusively in the malformed testes of patients with disorders of sex development. Gonadoblastoma is now recognized to be frequently accompanied by a spindle cell stroma containing small nests, cords, and individual germ cells closely associated with sex cord cells (Figure 7, A). This tissue, which has been referred to as either undifferentiated gonadal tissue or dissecting gonadoblastoma of Scully, should be considered equivalent to gonadoblastoma from the clinical perspective because its germ cells have the same immunohistochemical properties as those in classical gonadoblastoma nests (Figure 7, B). Furthermore, there is documentation of its progression to a germinoma in a case where it was not initially recognized. Recent work has verified the heterogeneity of the germ cells in gonadoblastoma. Careful light microscopic examination reveals not only germ cells identical to those of GCNIS but also germ cells resembling normal spermatogonia. Furthermore, some germ cells in gonadoblastoma nests are positive for OCT3/4 whereas others are negative. This heterogeneity is also reflected in ploidy values of the germ cell population, with values ranging from diploid to aneuploid. The sex cord cells strongly express FOXL2, but, in contrast to granulosa cells, often show weak expression for SOX9, findings that argue they are incompletely differentiated. An expansile pattern of gonadoblastoma has also been described that is characterized by large interconnecting islands rather than the classic separate, round nests (Figure 7, C). At low magnification this form of gonadoblastoma closely mimics germinoma (seminoma/dysgerminoma) until the consistent sex cord component and basement membrane deposits are appreciated upon closer inspection (Figure 7, D).

| Table 2. World Health Organization 2016 Classification of Sex Cord–Stromal Tumors of the Testis* |
|---------------------------------------------------------------|
| **Sex cord–stromal tumors**                                    |
| Pure tumors                                                   |
| Leydig cell tumor                                             |
| Malignant Leydig cell tumor                                    |
| Sertoli cell tumor                                            |
| Malignant Sertoli cell tumor                                   |
| Large cell calcifying Sertoli cell tumor                      |
| Intratubular large cell hyalinizing Sertoli cell neoplasia     |
| Granulosa cell tumor                                          |
| Adult granulosa cell tumor                                    |
| Juvenile granulosa cell tumor                                  |
| Tumors in the fibroma-thecoma group                           |
| Mixed and unclassified sex cord–stromal tumors                |
| Mixed sex cord–stromal tumor                                  |
| Unclassified sex cord–stromal tumor                           |

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Figure 6. Intratubular large cell hyalinizing Sertoli cell tumor. A, Vaguely lobular clusters of enlarged seminiferous tubules are scattered in the parenchyma. B, Expanded tubules contain large Sertoli cells with abundant, pale cytoplasm, lack germ cells, and are surrounded by thickened basement membrane that projects into the lumina, producing globoid eosinophilic deposits (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B]).
In summary, a number of important changes were made to the classification of testicular tumors in the 2016 revision of the WHO monograph dealing with the male genital system. Arguably, the single most important revision involved the subdivision of the germ cell tumors into 2 categories depending on whether or not a tumor derived from GCNIS. Additionally, the term GCNIS replaced both intratubular germ cell neoplasia, unclassified and carcinoma in situ. The distinction of delayed maturation of germ cells from GCNIS was newly emphasized, and the concept of pre-GCNIS was introduced. The trophoblastic tumor category was expanded by the addition of epithelioid trophoblastic tumor and cystic trophoblastic tumor. The sclerosing Sertoli cell tumor was eliminated as a separate entity apart from Sertoli cell tumor, not otherwise specified. Simultaneously, intratubular large cell hyalinizing Sertoli cell tumor was added to this group. Finally, the only recognized entity in the mixed germ cell–sex cord-stromal category was gonadoblastoma, but the morphologic spectrum of gonadoblastoma was expanded to include both undifferentiated gonadal tissue (dissecting gonadoblastoma of Scully) and a confluent pattern of growth.

References

1. Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. Lyon, France: International Agency for Research on Cancer; 2016.
2. Skakkebaek NE. Abnormal morphology of germ cells in two infertile men. Acta Pathol Microbiol Scand A. 1972;80(3):374–378.
3. Skakkebaek NE. Possible carcinoma-in-situ of the undescended testis. Lancet. 1972;2(7776):516–517.
4. Skakkebaek NE. Atypical germ cells in the adjacent “normal” tissue of testicular tumours. Acta Pathol Microbiol Scand A. 1975;83(1):127–130.
5. Skakkebaek NE. Carcinoma in situ of the testis: frequency and relationship to invasive germ cell tumours in infertile men. Histopathology. 1978;2(3):157–170.
6. Skakkebaek NE, Berthelsen JG, Visfeldt J. Clinical aspects of testicular carcinoma-in-situ. Int J Androl. 1981;4(suppl):153–162.
7. Scully RE. Intratubular germ cell neoplasia (carcinoma in situ): what it is and what should be done about it. World Urol Update Ser. 1982;lesson 17.
8. Chemes HE, Venara M, Del Rey G, et al. Is a CIS phenotype apparent in children with disorders of sex development? milder testicular dysgenesis is associated with a higher risk of malignancy. Andrology. 2013;3(1):59–69.
9. Rapert-De Meyts E, Jorgensen N, Brondum-Nielsen K, Muller J, Skakkebaek NE. Developmental arrest of germ cells in the pathogenesis of germ cell neoplasia. APMIS. 1998;106(1):198–204.

Figure 7. A, Undifferentiated gonadal tissue/dissecting gonadoblastoma of Scully showing small nests and cords of variable-appearing germ cells with associated sex cord cells set in a spindle cell stroma. B, Some of the germ cell nuclei shown in A are highlighted by an OCT3/4 immunostain; the sex cord cells are negative. C, An expansile form of dissecting gonadoblastoma of Scully mimicking the low-power appearance of germinoma. D, At higher magnification of the tumor in C, numerous sex cord cells are appreciable (hematoxylin-eosin, original magnifications ×400 [A], ×40 [C], and ×200 [D]).
10. Stoop H, Honecker F, van de Geijn GJ, et al. Stem cell factor as a novel diagnostic marker for early malignant germ cells. J Pathol. 2008;216(1):43–54.

11. Cools M, van Aerdle K, Kersemakers AM, et al. Morphological and immunohistochemical differences between gonadal maturation delay and early germ cell neoplasia in patients with undervirilization syndromes. J Clin Endocrinol Metab. 2005;90(9):5295–5303.

12. Oosterhuis JW, Stoop H, Dohle G, et al. A pathologist’s view on the testis biopsy. Int J Androl. 2011;34(4):pt.2:e14–e19.

13. Jacobsen GK, Henriques UV. A fetal testis with intratubular germ cell neoplasia (ITGCN). Mod Pathol. 1992;5(5):547–549.

14. Aleman DE, Tape T, Hugenholtz G. Intratubular germ cell neoplasia (ITGCN) with p53 and PCNA expression and adjacent mature teratoma in an infant: an immunohistochimical and morphological study with a review of the literature. Am J Surg Pathol. 1994;18(9):947–952.

15. Gaudin S, Heidinger C. Cellules germinales atypiques et tumeur germinale mixte chez l’enfant. Ann Pathol. 1981;1(4):251–257.

16. Manivel JC, Simonot S, Wold LE, Dehpner LP. Absence of intratubular germ cell neoplasia in testicular yolk sac tumors in children: a histochimical and immunohistochemical study. Arch Pathol Lab Med. 1988;112(6):641–645.

17. Jorgensen N, Muller J, Giewercman A, Vosfeldt J, Moller H, Skakkebaek NE. DNA content and expression of tumour markers in germ cells adjacent to germ cell tumours in childhood: probably a different origin for infantile and adolescent germ cell tumours. J Pathol. 1995;176(3):269–278.

18. Hawkins E, Heiselt SA, Giller R, Cushing B. The prepubertal testis (prepubertal and postnatal): its relationship to intratubular germ cell neoplasia: a combined Pediatric Oncology Group and Children’s Cancer Study Group. Pediatr Surg. 2005;31(3):210–222.

19. Kao CS, Badve SS, Ulbright TM. The utility of immunostaining for NUT, DMRT1 and TERT as candidate chromosome 9 gene. Cancer. 2009;113(3):529–535.

20. Hu R, Ulbright TM, Young RH. Spermatocytic seminoma: a report of 85 cases emphasizing its morphologic spectrum including some aspects not widely known. Am J Surg Pathol. 2013;37(6):827–835.

21. Liang DC, Chen SH, et al. The stage I yolk sac tumor of testis in young males: a report from the Northern Region Young Person’s Malignant Disease Registry, United Kingdom. Oncol Res. 2007;25(1):32–37.

22. Perlman EJ, Cushing B, Hawkins E, Griffin CA. Cytogenetic analysis of childhood endodermal sinus tumors: a Pediatric Oncology Study Group. Pediatr Pathol. 1994;14(4):605–708.

23. Bhatia M, Ulbright TM, Young RH. Primary cystic trophoblastic tumor in a male patient with mixed germ-cell tumor of the testis. Am J Surg Pathol. 2009;33(12):1902–1905.

24. Gondim DD, Ulbright TM, Cheng L, Young RH. Cytologic and molecular analysis of childhood endodermal sinus tumors by comparative genomic hybridization. J Pediatr Hematol Oncol. 2010;32(2):100–105.

25. Idrees MT, Kao CS, Epstein JJ, Ulbright TM. Nonchonoricarcinomatous trophoblastic tumors of the testis: the widening spectrum of trophoblastic neoplasia. Am J Surg Pathol. 2015;39(11):1466–1478.

26. Skakkebaek NE, Holm M, Hoei-Hansen C, Jorgensen N, Rajpert-De Meyts E. Insensitivity syndrome: factors influencing gonadal histology including germ cell neoplasia (ITGCN). Int J Androl. 1992;15(3):177–186.

27. Ulbright TM, Young RH, eds. Tumors of the Testis and Adjacent Structures. Silver Spring, MD: American Registry of Pathology; 2013. 2013:6(11):2350–2356.
68. Scully RE. Gonadoblastoma; a gonadal tumor related to the dysgerminoma (seminoma) and capable of sex-hormone production. *Cancer*. 1953;6(3):455–463.

69. Ulbright TM, Srigley JR, Reuter VE, Wojno K, Roth LM, Young RH. Sex cord-stromal tumors of the testis with entrapped germ cells: a lesion mimicking unclassified mixed germ cell sex cord-stromal tumors. *Am J Surg Pathol*. 2000;24(4):535–542.

70. Cools M, Stoop H, Kersemaekers AM, et al. Gonadoblastoma arising in undifferentiated gonadal tissue within dysgenetic gonads. *J Clin Endocrinol Metab*. 2006;91(6):2404–2413.

71. Kao CS, Idrees MT, Young RH, Ulbright TM. “Dissecting gonadoblastoma” of Scully: a morphologic variant that often mimics germinoma. *Am J Surg Pathol*. 2016;40(10):1417–1423.

72. Ulbright TM, Young RH. Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development. *Semin Diagn Pathol*. 2014;31(5):427–440.

73. Jorgensen N, Muller J, Jaubert F, Clausen OP, Skakkebaek NE. Heterogeneity of gonadoblastoma germ cells: similarities with immature germ cells, spermatogonia and testicular carcinoma in situ cells. *Histopathology*. 1997;30(2):177–186.

74. Kao CS, Ulbright TM, Idrees MT. Gonadoblastoma: an immunohistochemical study and comparison to Sertoli cell nodule with intratubular germ cell neoplasia, with pathogenetic implications. *Histopathology*. 2014;65(6):861–867.

75. Buell-Gutbrod R, Ivanovic M, Montag A, Lengyel E, Fadare O, Gwin K. FOXL2 and SOX9 distinguish the lineage of the sex cord-stromal cells in gonadoblastomas. *Pediatr Dev Pathol*. 2011;14(5):391–395.