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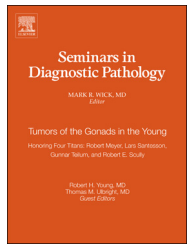

Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development

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ABSTRACT

Some patients with disorders of sex development (DSDs), previously known as intersex disorders, have abnormal gonadal development and an increased risk of germ cell tumors. Because of their relative rarity, however, many pathologists are unfamiliar with the morphological findings in the gonads of DSD patients and their clinical significance. This review concentrates on some of the most common DSDs where gonadal specimens may come to the attention of pathologists. It highlights the findings in gonadal dysgenesis, a DSD with a spectrum of clinical, pathologic, and molecular features but with the shared attributes of having both Y chromosomal material (even if in very limited amounts) in the gonad and also having mutations or deletions in genes necessary for normal gonadal development, mostly in those upstream of the *SOX9* gene. This situation results in testicular tissue lacking normal Sertoli cells, which are now considered an essential element for the normal maturation of the primordial germ cells that migrate to the gonad from the embryonic yolk sac. Germ cells with delayed maturation mimic neoplastic germ cells, but there are both morphological and immunohistochemical differences. If the gonad having germ cells with delayed maturation also harbors the *TSPY* gene on the GBY locus of the Y chromosome, the cells may undergo neoplastic transformation and result in the distinctive gonadoblastoma, whose pathologic features are explored at length herein, including its potential for variant morphologies, such as a "dissecting" pattern. Another important DSD, the androgen insensitivity syndrome (AIS), is discussed at length, including the varied appearances of the testis and its distinctive lesions—hamartomas and Sertoli cell adenomas. The potential for germ cell neoplasia in the partial AIS is also discussed and contrasted with that of the complete AIS. A third major topic is ovotesticular DSD (true hermaphroditism). The clinical features and morphology of this condition are reviewed, including the arrangements of the tissue components in an ovotestis. Several other DSDs with distinctive gonadal findings are also considered, including Klinefelter syndrome, 5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency, and female adrenogenital syndrome.

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Introduction

Patients with disorders of sex development (DSDs), previously known as intersex disorders but changed at the recommendation of an international consensus conference of experts in the field,[1] may develop gonadal lesions and neoplasms that come to the attention of pathologists. These have varied histopathologic features that few have significant experience with and can easily cause problems in interpretation. The patients are often young (in the first 3 decades of life) and, accordingly, merit consideration in this focused review of gonadal tumors and tumor-like lesions in the young. DSDs are also complex clinically and have varied underlying pathogeneses that include karyotypically detectable chromosomal anomalies, mutations involving pathways essential for normal gonadal development, genetic changes that affect the biosynthetic pathways or mechanisms of action of sex hormones, and exposure to exogenous agents. This article does not represent a comprehensive review of this topic. Instead, it concentrates on those conditions having distinct gonadal findings that pathologists may encounter (even if infrequently) and that typically present in patients younger than 20 years. The reader requiring a more thorough exploration of the clinical features, including the nongonadal findings, and the underlying genetic or metabolic mechanisms is referred to other sources.[2–8] It is salutary to reflect that much information in this area is new, in part due to techniques only available in recent years, but also because key morphologic observations concerning many lesions have been made only in the last half century or so, and further refinements in pathologic details continue to evolve.

Gonadal dysgenesis and gonadoblastoma

Gonadal dysgenesis represents improper development of the gonad with frequent loss of the normal compartmental organization as well as abnormalities in the sex cord and germ cell components. A shared finding in patients with gonadal dysgenesis is a mutation in at least one of the many genes involved in the normal development of the gonad. These include the *WT1* gene, resulting in the formation of a dysgenetic testis in 46,XY individuals who, depending on the particular mutation, develop the Denys–Drash, Frasier, or Wilms tumor, aniridia, genitourinary anomalies, and retardation (WAGR) syndromes.[9–11] Similarly, mutations in *SRY*, *SOX9*, *DHH*, *ARX*, *NR5A1* (*SF1*), and *TSPYL1* have resulted in dysgenetic testes in 46,XY patients.[3] Female or ambiguous external genitalia are common to all of these conditions. Gonadal dysgenesis that retains more than a rudimentary resemblance to an ovary, in contrast to testicular dysgenesis, is rare.[12] Ovarian maldevelopment occurs most commonly in 45,XO patients with Turner syndrome, who develop "streak" gonads consisting of gonadal stroma with greatly reduced or absent germ cells and sex cord cells. Similar streak gonads have also been found in 46,XX phenotypic females in the second decade with leukodystrophy.[13] Autosomal trisomies may also result in streak morphology manifest in infancy.[14] Patients with 46,XX DSDs who have mutations in *SRY*, *RSPO1*, and *WNT4* may develop an ovotestis, a condition sometimes referred to as "true hermaphroditism," and, although abnormal, such gonads are not classified as part of gonadal dysgenesis.

Mixed gonadal dysgenesis usually develops in patients with either a 46,XY or 46,XY/45,XO mosaic karyotype. As originally defined,[15,16] it is referred to the presence of an abnormal "dysgenetic" testis on one side, with the opposite side having no gonad or a streak/rudimentary gonad. It has become clear, however, that patients with bilateral dysgenetic testes and many Y chromosome-positive patients with bilateral streak gonads (definitionally, "pure" or "complete" gonadal dysgenesis) have features identical to those with mixed gonadal dysgenesis. Most patients have ambiguous external genitalia, which cause them to come to medical attention in the neonatal period, and most (70%) are reared as females.[17] Patients with 46,XY/45,XO mosaicism may have stigmata of Turner syndrome.[18] Amenorrhea may be a presenting feature in teenagers.

The dysgenetic testis may be intraabdominal, in the inguinal canal, or scrotal. It is smaller than normal and, because of abnormal thinning of the tunica albuginea, its external aspect may be brown or pink rather than the normal white appearance (Fig. 1).[18] Occasionally it may show pink–yellow spots on its surface due to penetration by underlying seminiferous cords.[19] It may be attached to the epididymis by only a thin fragment of connective tissue. About 40% have an associated fallopian tube. On microscopic examination,[4,5,18,19] the testis has a thin tunica albuginea with a stroma that may resemble that of the ovarian cortex. Immediately subjacent, solid seminiferous tubules (or seminiferous cords) form an anastomosing network in a widened, edematous interstitium and penetrate the inner aspect of the tunica albuginea. More deeply, the tubules have a normal, closely packed, and non-

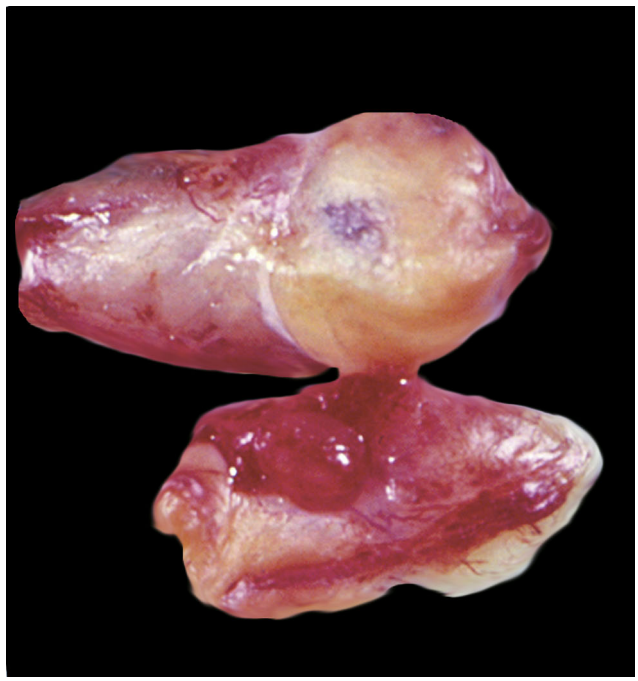

Fig. 1 – A 0.8-cm, bivalved dysgenetic testis showing a pink-tan external surface (lower) and tan cut surface.