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Review Article

Gonadal dysgenesis in disorders of sex development: Diagnosis and surgical management

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Summary
Recent studies on gonadal histology have improved the understanding of germ cell malignancy risk in patients with disorders of sex development (DSD), and evidence-based gonadal management strategies are gradually emerging. Especially in 46,XY DSD and 45,X/46,XY DSD, which are characterized by gonadal dysgenesis, the risk of germ cell malignancy is significantly increased. This paper summarized the progress over the past 10 years in malignancy risk assessment in patients with DSD, and its implications for optimal surgical handling of the involved gonads.

Introduction

It has long been known that gonadal germ cell cancer (GCC) risk in patients with a disorder of sex development (DSD) is linked to the presence of part of the Y-chromosome — the gonadoblastoma locus (GBY) [1,2]. Subsequent research has identified the testis-specific protein on Y (TSPY) as a putative key factor in tumorigenesis [3,4].

There are great dissimilarities in GCC risk within the various DSD subgroups. For instance, the risk in a patient with 46,XY DSD, which is characterized by a congenital aberrant or incomplete gonadal development that is commonly known as gonadal dysgenesis (GD), is significantly higher than in a case of 46,XY DSD with defective androgen action or biosynthesis (e.g. androgen insensitivity syndrome, AIS) [5].

Meticulous histological research in the last decades on gonadal tissue from patients with DSD has improved insight into GCC risk in various diagnostic groups by identifying distinct histological lesions. These pre-invasive malignancies are carcinoma *in situ* (CIS), currently known as germ cell neoplasia *in situ* (GCNIS) [6], and gonadoblastoma (GB), as well as their precursors, including undifferentiated gonadal tissue (UGT). The final piece in this evolution was the introduction of histopathological criteria to discriminate pre-malignant germ cells from benign germ cells with delayed maturation [7–9].

Despite these advances, the actual risk assessment of invasive GCC for patients with DSD is currently still incomplete. Another drawback is the requirement of gonadal material for risk inventory; at present, non-invasive markers for screening are lacking. Conventional serum markers like α-fetoprotein (AFP) and human chorionic gonadotropin (hCG) can only be used for detection of progressed and defined histological types of GCC, and are inappropriate for screening purposes. Non-invasive tools, including (epi)genetic markers associated with increased GCC risk and serum microRNA (miRNA) for early stage malignancy detection, have recently been developed, but have yet to be implemented in clinical practice [8]. These non-invasive tools, although promising, are beyond the scope of this review.

This paper summarizes the aforementioned latest insights into GD, either associated with an already known DSD condition, or as an incidental finding during abdominal or inguinal surgery, and focuses on the implications for surgical treatment.

Gonadal dysgenesis: embryonic aspects

Failure of normal embryonic development in the originally bi-potential gonad may result in a more-or-less aberrant postnatal testis or ovary. Disruption of this genetically controlled, but yet incompletely understood, gonadal differentiation process is believed to underlie the increased risk of GCC in the

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involved gonads. In case of a disruption early in the differentiation pathway, the normal microscopic structure of the gonad, composed of germ cells embedded by supporting cells in a sex-specific way (i.e. Sertoli cells in the testis and granulosa cells in the ovary) may be hard to identify. The resulting group of conditions, which are characterized by a varying degree of abnormally configured or differentiated gonads, is referred to as gonadal dysgenesis (GD). In complete gonadal dysgenesis (CGD), the ordinary tissue arrangement of the gonad is entirely lost, while it is retained to some extent in partial gonadal dysgenesis (PGD). Gonadal dysgenesis may occur unilaterally or bilaterally, when respectively one or both gonads are affected to a greater or lesser extent [10]. In 46,XY CGD, the lack of hormonal function affects the development of internal and external genitalia, resulting in a female phenotype. Individuals with GD have a particular high GCC risk profile, with reported risks varying between 8 and 54%, making early diagnosis particularly relevant [2,10,11]. Obviously, the presence of germ cells is a prerequisite for GCC development: in a streak or Sertoli-cell only testis, where germ cells are lacking, no GCC will arise [5].

Gonadal dysgenesis: macroscopic aspects

The microscopic cellular misalignment in GD can also affect the overall appearance of a dysgenetic gonad, including an aberrant size, color, shape or consistency, or abnormal Wolffian and/or Müllerian derivatives. Although GD will usually be associated with an overt DSD, macroscopic atypical gonadal features can be the starting point of a clinical diagnosis of DSD. An example of a DSD that usually remains unnoticed prior to surgery is persistent Müllerian duct syndrome (PMDS), when testes with an attached uterus and fallopian tubes are found accidentally during orchidopexy or hernia repair in a phenotypical boy. Another typical illustration of an unsuspected DSD is the detection of a testis during inguinal hernia repair in a girl with 46,XY DSD with a defect in androgen action (i.e. complete androgen insensitivity syndrome, CAIS).

However, in situations as outlined above, it is important to notice that the macroscopic aspect of the gonad alone is insufficient to predict the histological constitution. A clear example is the so-called streak-like gonad. This descriptive clinical term of a flat, scar-like gonad should not be confused with the histological diagnosis of a streak, which is a dysgenetic gonad entirely composed of fibrous tissue and devoid of germ and supporting cells [9]. In case of a clinically suspected streak, based on the macroscopic aspect of the gonad, histological confirmation, preferentially supported by immunohistochemistry, is mandatory before a final diagnosis can be established. This is illustrated in Fig. 1, where the histology of apparently identical gonads in two boys with 45,X/46,XY DSD, both with an ambiguous genital phenotype, proved to be considerably distinct, as is the corresponding GCC-risk. To overcome this confusing terminology, the use of different names is proposed and the following words are reserved: 'streak' and 'streak gonad' for the histological diagnosis, and the term 'streak-like gonad' for the clinical finding of a scar-like gonad. Provided that the histological criteria are met, a streak-like gonad may be termed a streak gonad [9].

It should be emphasized that pathology staff with expertise and special interest in the field of gonadal development are pivotal for accurate and reliable assessment of gonadal specimens from DSD patients. It is, however, equally important to provide the pathologist with representative gonadal tissue, as well as relevant clinical information. In cases of macroscopic homogeneous gonads that are suspect for GD, one standard representative biopsy yielding a small sample of approximately 3 × 3 × 2 mm will

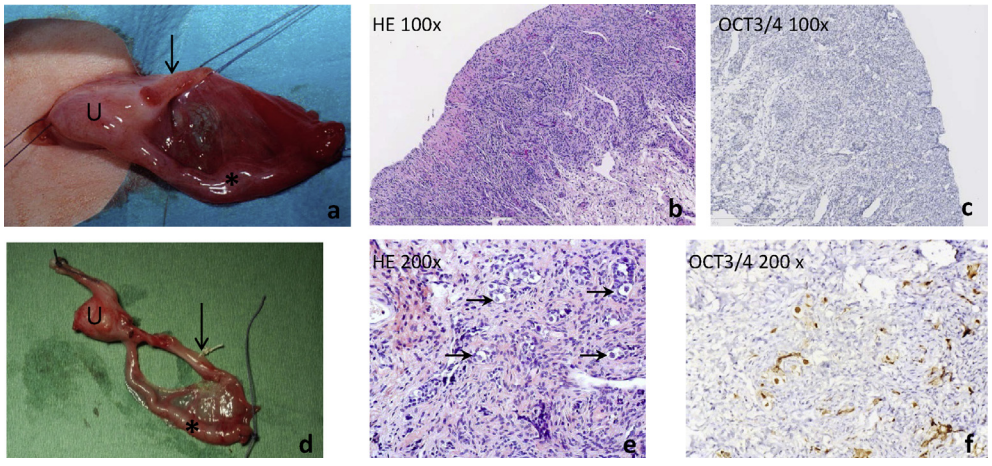

Figure 1 Streak-like gonad in 2 patients with 45,X/46,XY DSD with ambiguous genitalia. **Upper panel a**: left gonad (arrow), hemi-uterus (U) and fallopian tube (*). **b and c**: streak gonad. **b**: histology shows fibrous tissue without germ cells. **c**: Immunohistochemistry for OCT3/4 and TSPY (not shown) shows negative staining results, confirming the absence of germ cells. **Lower panel d**: right gonad (arrow), hemi-uterus (U) and fallopian tube (*). **e and f**: dysgenetic gonad with GCC-precursor lesions: UGT and a small GB lesion (not shown). **e**: histology shows a mixed pattern of sex cords and fibrous tissue, with both clustered and isolated germ cells (arrows). **f**: many germ cells express OCT3/4 (shown in brown). (For interpretation of the references to colour in his legend, the reader is referred to the web version of this article.)