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Pathogenesis and Active Prevention of Testicular Germ Cell Neoplasia

J. Slowikowska-Hilczer, A. Guminska, K. Kula

Most testicular neoplasms originate from fetal germ cells (germ cell tumors [GCT]). Intratubular germ cell neoplasia (ITGCN) or testicular carcinoma in situ (CIS) are terms used for the state when these cells are present in the seminiferous epithelium. The highest risk of neoplastic lesions occurs in testes with disturbed organogenesis (in our study, 65 %). Genetic, hormonal, and environmental factors are suspected to lead to disturbed testicular organogenesis (dysgenesis), which creates the milieu favorable for GCT development. An external environment can cause a block or delay in fetal germ and somatic cell differentiation. CIS cells in dysgenetic testes of children reveal a predominantly aneuploid DNA pattern (62.2–97.6 % of germ cells) and they do not express an RBM protein (present in normal germ cells), this indicates that CIS cells are neoplastic from fetal life on. Most of the neoplastic germ cells die, however, some survive and proliferate, leading to a clonal expansion and giving rise to gonadoblastoma, CIS, and GCT. Neoplastic germ cells located inside underdeveloped testicular tubules have an intratesticular environment favorable for their survival – this was confirmed by the finding that the highest incidence of neoplastic lesions occurred in patients with partial (90.9 %) and mixed gonadal dysgenesis (76.9 %). It was hypothesized that the transformation of CIS into overt GCT may be promoted by gonadotropin action. We found that in gonadal dysgenesis, serum concentrations of FSH and LH reveal highly significant, positive correlations with the number of CIS cells, even in childhood. At present, surgical biopsy of the testis is the only reliable method to detect CIS and hence to actively prevent the development of overt GCT. Accordingly, early bilateral gonadectomy is recommended in all types of disturbance of testicular organogenesis because of the high risk of various neoplastic lesions in dysgenetic testes (86 % of adult patients with retained dysgenetic gonads developed GCT, CIS, gonadoblastoma or combinations). In other risk groups, the most frequently recommended method of CIS treatment is radiotherapy, with the exception of unilateral CIS, for which orchiectomy is the treatment of choice. *J Reprodukcijsmed Endokrinol* 2007; 4 (6): 313–21.

Key words: testis, dysgenetic gonads, testicular carcinoma in situ, germ cell tumors

Testicular tumors account for 0.5–1.0 % of all neoplasms in men and for 4–5 % of neoplasms of the male reproductive system. Almost all testicular tumors derive from germ cells, therefore they are called germ cell tumors (GCT) [1, 2]. GCT are divided into seminoma (about 55 % of GCT) and non-seminoma (about 40 % of GCT). Embryonal carcinoma, teratoma, and choriocarcinoma are distinguished among non-seminoma tumors. Spermatocytic seminoma also belong to the GCT, but they are characterized by biological features different from other GCT [3, 4].

The incidence of GCT in European men depends on the country (1.1–11.8/100,000/year) and is highest in Denmark. The incidence of GCT increased rapidly in all countries after World War II, by 2–3.5 % annually in Nordic countries and by about 5 % in Poland and Germany [5–7]. The rising trend was more pronounced for ages below 30.

GCT is most common among young men, with a peak incidence between the age of 20 and 45 years [3]. Non-seminoma are more frequent in younger men (20–30 years of age, 58 % of cases), while seminoma are more often diagnosed in the older men (35–60 years of age, 69 % of cases) [3, 7]. The incidence of GCT in children up to the age of 15 is 0.5–2 % of all malignant tumors in this period of life [8, 9].

Dieckmann and Pichlmeier [10] performed an epidemiological analysis of established and suspected risk factors for GCT. They attributed levels of evidence to each of the putative risk factors in analogy to the methods of evidence-based medicine (EBM) and adapted them to clinical

epidemiology. Level I represents the highest quality of evidence (systematic review, meta-analysis with homogenous results) while level V denotes the lowest level (case reports, small case series, expert opinions). The authors established that the risk factors with a high level of evidence are undescended testes (cryptorchidism) (level I), GCT of contralateral testis (level II a [several cohort studies with widely homogenous results]), and familial testis cancer (level III a [several case control studies with widely homogenous results]). Risk factors with a median level of evidence (levels II–III), i. e. probable but not finally proven factors, are infertility, twinning (dizygotic), and testicular atrophy. Gonadal (testicular) dysgenesis, which leads to disturbances of male genitalia differentiation, was assessed as high risk but, because of rare, heterogenous cases and small case series involved, was given only level IV (case series with calculated or historical controls) in the formal hierarchy of evidence. Extragonadal GCT is also recognized as a high-risk factor for testicular CIS [11, 12], nevertheless, this condition is not placed in the ranking described above. There is some evidence that urogenital abnormalities, hypospadias, inguinal hernia, and low birth weight are also risk factors for GCT [13–15].

Pathogenesis of Testicular Germ Cell Neoplasia

In 1972, Skakkebaek [1] suggested that all types of GCT, except for spermatocytic seminoma, originate from intratubular germ cell neoplasia (ITGCN), also called testicular carcinoma in situ (CIS). In this state, neoplastic germ cells are present among other cells of the seminiferous epithelium inside the seminiferous tubules. In the International Germ Cell Consensus Classification of GCT from 1997, CIS is classified as a tumor in situ (Tis) [16]. In the WHO Histologic Classification of Testicular Tumors, CIS belongs to this group: Germ Cell Tumor – Precursor lesion – Intratubular germ cell neoplasia [17].

CIS cells are considered fetal germ cells (gonocytes), which have undergone the process of neoplastic transfor-

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mation, probably during fetal life and have not differentiated into spermatogonia. They persist during infancy and may give rise to the overt GCT in adulthood [2, 18]. Factors taking part in the initiation, promotion, and progression of GCT are not exactly known. Genetic, hormonal, and environmental influences are considered to be of importance.

Genetic Factors

GCT are 40 times more frequent in Caucasian than African or Asian men [19, 20]. The possibility of the participation of genetic factors is also demonstrated by epidemiological data of the different incidence rates of GCT in different countries. For instance, the incidence of GCT is low in Finland and Estonia but high in Denmark and Norway [5]. In the study of a Danish population, it was found that a specific Y chromosome haplogroup (hg26) is significantly over-represented in men with unexplained reduced sperm counts. It was suggested that the factors encoded by genes on this class of Y chromosome may be particularly susceptible to environmental pollutions that cause testicular disturbances, including neoplastic changes [21].

About 2 % of patients with GCT have a family member with previously diagnosed GCT. The risk of GCT is 10 times higher in brothers and 4 times higher in sons of patients with GCT [22]. In 35 families, relationships between GCT and aberrations of chromosomes 1, 4, 5, 14, and 18 were found [23]. In another study, the relationship with mutations of chromosome 18 was confirmed in 54 families [24]. Moreover, bilateral appearance of GCT and cryptorchidism has been associated with genes located in q27 of chromosome X [25, 26].

The most consistent and specific chromosomal change found in all GCT and CIS cells is the presence of an isochromosome of the short arm of chromosome 12-i(12p) [27]. Tumors which are i(12p)-negative have been sporadically reported, but even in these tumors, rearrangements or over-expression of chromosome 12 has been detected [28].

Normal germ cells can be identified by the presence of the expression of the RBM (RNA-binding motif) protein which is encoded by the genes located in the azoospermia factor-b (AZF-b) region on the human Y chromosome long arm [29]. The RBM protein is expressed in male germ cell nuclei of fetal (from the second trimester of gestation), pubertal, and adult testes. This marker can assess the state of differentiation of male germ cells since RBM is not expressed in GCT or CIS cells of the testes in adult, otherwise normal, men [30]. Our own studies showed for the first time that germ cells, resembling fetal gonocytes, did not express RBM protein in dysgenetic testes of prepubertal children, supporting the concept that they were previously neoplastically transformed and could be recognized as CIS cells [31]. Recently, a novel, Y-chromosome 1.6-Mb deletion, designated "gr/gr", has been described and found to be associated with spermatogenic failure, infertility, and GCT [32, 33]. Although AZF microdeletions are frequently found in patients with idiopathic infertility, in 160 Danish patients with GCT, the Yq region was found to be intact [34]. The conclusion is that the molecular etiology of GCT most likely does not involve the same pathways as male infertility caused by AZF deletions.

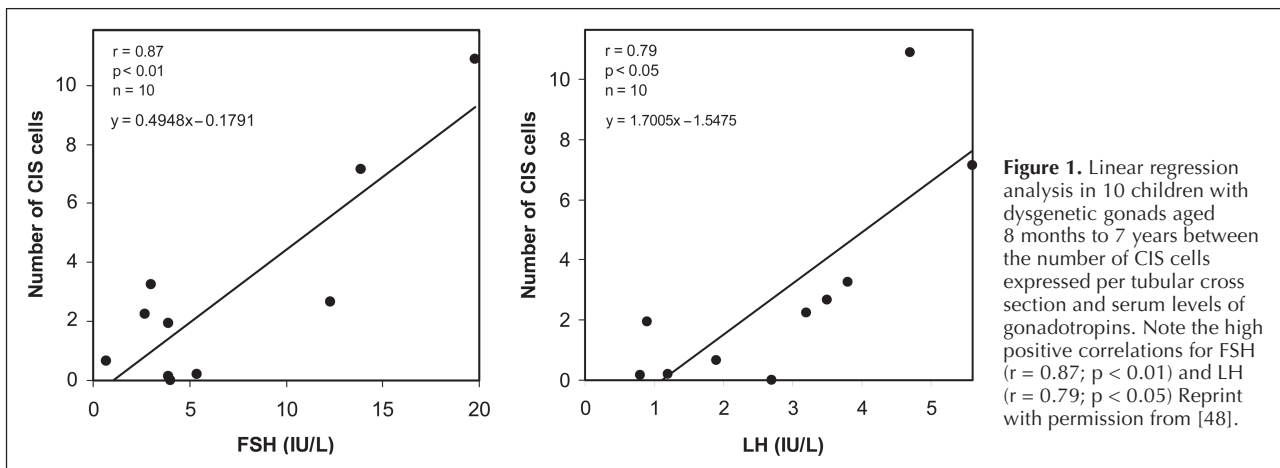
As they are frequently associated with gonadal dysgenesis, different numerical and structural aberrations of sex chromosomes, mostly 45,X/46,XY, have been postulated to play a role in gonadal tumorigenesis [35–37]. In our study based on 46 patients with disturbed gonadal organogenesis (dysgenetic testes and bisexual gonads – ootestis), the incidence of germ cell neoplastic lesions was estimated to be 71.4 % for patients with 46,XY and only 35.3 % for patients with aberrations of sex chromosomes [38]. We therefore concluded that aberrations of sex chromosomes are not prerequisite for the development of GCT in dysgenetic testes or ootestis.

It was suggested that aneuploidisation of primordial germ cells during fetal life may represent the earliest stage in the pathogenesis of GCT [39]. In fact, we found that the DNA pattern of CIS cells in dysgenetic testes of young children (8 months to 3 years old) was predominantly aneuploid (62.2–97.6 % of cells), mainly tri- or tetraploid [40]. It has been previously presented that in adult men with GCT, DNA ploidy of testicular CIS cells located adjacent to invasive GCT is also tri- or tetraploid [41], while it has never been seen in non-malignant germ cells [8, 20, 42]. This implicates that fetal germ cells, which are present in the testes with disturbed organogenesis, are susceptible to replication errors during mitosis, resulting in gain or loss of chromosomes and that these cells should be considered neoplastic.

Hormonal Factors

Steroid sex hormones promote development of the neoplasm both in male and female reproductive systems, e. g. carcinoma of the uterus and prostate. Estrogens are most commonly pointed out as hormones involved in the pathogenesis of GCT. Namely, it has been suggested that sons of mothers being in first pregnancy, suffering from obesity and frequent vomiting in early pregnancy (associated with the excessive secretion of estrogens) may have an increased risk of GCT [43–45]. Administration of diethylstilbestrol (DES), a synthetic potent estrogen, which was widely used in women as post-coital contraception and for the treatment of high-risk pregnancies (against imminent miscarriage) as well as to suppress lactation after pregnancy, was found to be associated with an increased prevalence of male urogenital tract abnormalities, cryptorchidism, GCT, and reduced fertility in sons of mothers exposed [46, 47].

It is postulated that impaired androgen synthesis and action observed in several congenital syndromes of male sexual development (dysgenetic testes, cryptorchidism, partial androgen insensitivity, and Klinefelter syndrome) may increase the risk of GCT [3]. In our clinical observations, the reduced basal and hCG-stimulated testosterone secretion was significant in children with gonads bearing germ cell neoplastic lesions [48]. Consequently, in African women (as compared to Caucasian women), relatively high blood levels of androgens in early pregnancy have been reported to be associated with a lower incidence of GCT in their sons [19]. However, GCT occur very rarely in pre-pubertal children and the peak incidence of GCT is observed during or after puberty, when increased secretion of sex hormones takes place. In addition, it has been found that, in contrast to normal germ cells, naturally lacking androgen receptors, immunoreactive androgen receptors are expressed in neoplastic germ cells in as much as 40–45 % of patients [49], suggesting



that androgens may participate in the neoplastic transformation of CIS cells.

During and after puberty, the secretion of gonadotropins increases and they may be further candidates responsible for the promotion of GCT. In fact, one report describes subfertile patients who developed GCT of the testis after treatment with gonadotropins for infertility [50]. Martin et al [51] reported GCT that occurred in a 35-year-old man, in whom GnRH-independent, familial, male-limited precocious puberty was present due to constitutively activating mutation of LH/chorionic gonadotropin receptor. Stronger evidence for the possible involvement of gonadotropins in promoting GCT through increased multiplication of CIS cells was presented by our group [48]. We showed that both FSH and LH serum levels positively and highly significantly correlate with the number of CIS cells evaluated within seminiferous tubules of dysgenetic testes in prepubertal children (Fig. 1). This finding was methodologically verified by the same authors who used the same quantitative analysis of the seminiferous epithelium to demonstrate positive correlations between basal or GnRH-stimulated serum levels of FSH and LH and the number of spermatogonia or spermatocytes in testes of infertile men [52–54]. These data are also consistent with reports that the administration of FSH stimulates the number of gonocytes and spermatogonia in men, non-human primates or rats [55, 56]. It seems, therefore, that both fetal germ cells and CIS cells are targets for endogenous and exogenous gonadotropins which may potentially promote the maintenance of neoplastic germ cells by their increased multiplication. Further studies are warranted to ascertain if FSH and/or LH may promote the neoplastic progression of CIS cells into overt GCT.

Environmental Factors

The environmental and lifestyle changes associated with developing industry and agriculture are considered causative for the increased frequency of reproductive abnormalities [57]. In Poland, the incidence of GCT is about 6 times higher in industrially developed regions in comparison to ecologically pure areas [6]. Exposure to causal factors increases over time, so the age-standardized incidence of GCT is doubled every 15 to 25 years [5].

There are hypotheses that environmental pollution, especially estrogen-like synthetic substances (xenoestrogens), often exerting also anti-androgen action, may influence

fetal testes, causing developmental disturbances and neoplastic lesions [58–60]. These hypotheses are confirmed by the growing number of reports on male reproductive system anomalies in wild-living animals [61–64]. The variability in estrogen receptor (ER) isoforms and their tissue-specific distribution gives xenoestrogens an opportunity to exert different actions in the organisms. Despite their different chemical structure they can bind to ER, mimic to some extent the action of the natural sex hormone, 17 β -estradiol, or act as an anti-androgen.

The fetal period of life between pregnancy weeks 6 and 20 is critical for the development of gonads and the male reproductive system. Xenoestrogens do not bind to either SHBG (sex hormone binding globulin) or to alpha-fetoprotein (AFP), which are present in the fetal circulation and act against (through inactivation) the influence of endogenous estrogens on the male fetus. Thus, the male fetus is not protected against these exogenous estrogen-like chemicals [65].

Exposure to exogenous estrogens may diminish production of fetal FSH via a negative feedback mechanism. Lower fetal FSH serum levels may result in a decreased rate of Sertoli cell proliferation and disturbed synthesis of substances which create an intratesticular milieu and control the activity of germ cells during fetal life. This in turn may result in diminished Müllerian Inhibiting Hormone (AMH) production. AMH is a protein secreted by Sertoli cells which induces the regression of Müllerian ducts (primordium of female internal sex organs) and testicular descent. AMH is suggested to stimulate the transformation of pre-spermatogenic germ cells into spermatogonia [66, 67]. Consequently, deficiency of AMH may lead to the persistence of undifferentiated gonocytes, which may be more prone to neoplastic transformation [68]. Moreover, because of too few or too poorly functioning Sertoli cells primordial germ cells may not receive clear signals to differentiate either into female or into mature male germ cells and therefore they may keep their fetal characteristics as multipotential gonocytes (stem cell potential). Disturbed biosynthesis of Sertoli cell products results in differentiation disorders of the male reproductive system, cryptorchidism, formation of testicular neoplastic changes, and, furthermore, infertility.

Androgens are factors stimulating the secretion of AMH by Sertoli cells. The excess of estrogens leads to the inhibition of androgen production by the testes. Estrogens may inhibit steroidogenic enzymes and receptors for LH

in Leydig cells. Nielsen et al [69] found that ERA may be involved in the development of Leydig and peritubular cells. Enhanced estrogenic signaling can suppress the biosynthesis of insulin-like 3 hormone (Insl3) by Leydig cells, which is necessary for the development of the gubernaculum, and by attenuating the production of androgens necessary for the regression of the cranial suspensory ligament [70, 71]. Defects of Insl3 action cause cryptorchidism in male mice, while over-expression in female mice causes ovarian descent.

The Significance of Disturbed Organogenesis of the Testis

Patients with gonadal dysgenesis are at the high risk of GCT, therefore, it is expected that abnormalities in the organogenesis of gonadal blastema may participate in the initiation/progression of GCT. In our study among 70 patients from different high-risk groups of GCT, the incidence of CIS cells was highest in children with dysgenetic gonads (43.5 %) [72]. In our other study on patients with disturbed gonadal organogenesis, the incidence of neoplastic changes in dysgenetic gonads was 65 % [38]. Nevertheless, fetal germ cells in gonadal dysgenesis and androgen insensitivity syndrome may exhibit a developmental delay [73, 74]. The morphology of non-malignant infantile germ cells is somewhat similar to that of malignant cells, so it may be difficult to distinguish them. Immunohistochemical markers normally expressed in embryonic germ cells and in use to demonstrate CIS in adult testes show prolonged expression in dysgenetic gonads [73, 75]. Therefore, Cools et al [74] claimed that most of the data on the incidence of CIS cells in dysgenetic gonads of children are overestimated because of a mistake in the recognition of the real neoplastic germ cells. However, germ cells recognized in our studies as CIS cells, apart from the positive immunohistochemical reaction for PLAP, also revealed characteristics typical for neoplastic changes. This includes that CIS cells were morphologically heterogeneous, had nuclei of irregular shape, containing irregular coarse clumps of chromatin, and were located near the tubular membrane (Fig. 2). Moreover, in a group of children with aberrant organogenesis 42–97 % of CIS cells revealed aneuploid DNA content, most frequently tri- and tetraploidy, typical for

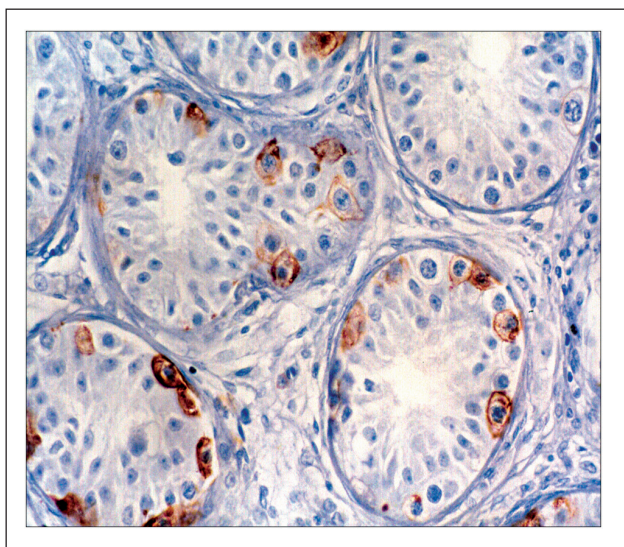


Figure 2. Result of immunostaining for the presence of placenta-like alkaline phosphatase (PLAP) in the testis of a 3-years-old child with partial gonadal dysgenesis. Note the presence of PLAP-positive (yellow-brownish staining of cytoplasm) CIS cells near the tubular membrane (magnification 400×).

GCT [40]. So, we still believe that, from a clinical point of view, it is more dangerous for the further fate of a child not to recognize real neoplastic changes among fetal germ cells than to overestimate them, considering all as CIS.

Besides CIS, germ cell neoplastic lesions include sex cord-derived tumors. These are gonadoblastoma and are a rarely recognized, unclassified type of mixed germ cell-sex cord stromal tumor (MGCSCST), previously described only in testes of normally differentiated adult men [76] or recognized as undifferentiated gonadal tissue in underdeveloped testes [77]. Both are composed of a mixture of gonocytes/CIS cells and somatic cells, resembling immature Sertoli or granulosa cells. Recently, Cools et al [77] proposed a complex model of testicular neoplastic pathogenesis in dysgenetic gonads. In gonadal dysgenesis, inaccurate expression of SRY (genes of the sex region of the Y chromosome) or other male-determining genes inhibits sex cord formation or their further differentiation. The unfavorable intragonadal environment can cause a block or delay in the normal fetal germ and Sertoli/granulosa cell differentiation and disturbance in their function. The initiation of the malignant transformation is most probably caused by the disturbance in the microenvironment of fetal germ cells. Most of the germ cells die, however, some, possibly due to the prolonged expression of OCT3/4 (a protein essential for the survival of pluripotent primordial germ cells) and to up-regulation of TSPY (testis-specific protein Y encoded, normally related to the mitotic division of spermatogonia), survive and proliferate, leading to a clonal expansion and final organization into gonadoblastoma nests. Over time, gonadoblastoma may undergo atrophy and/or calcification, but another possible way of their transformation is to give rise to GCT.

CIS cells located inside underdeveloped seminiferous tubules in dysgenetic testes may have the environment favorable for their survival. However, in this context we have found that, unexpectedly, in gonadal dysgenesis less disturbed testicular organogenesis predisposes more for germ cell neoplastic lesions than more profound testicular aberrations [38]. Namely, while the incidence of neoplastic lesions in patients with partial gonadal dysgenesis (bilateral testes with incomplete organogenesis) was 90.9 %, it appeared less frequently in cases with mixed type (streak of connective tissue on one side and the testis-like stroma on the other, 76.9 %) and only in 23.1 % in cases with pure gonadal dysgenesis (bilateral streak gonads). The incidence of CIS was even less frequent (16.7 %) in the testicular compartment of bisexual gonads (ovotestis), this suggests that the testicular microenvironment favors survival of germ cell neoplasia, while this is not the case in more pronounced testicular developmental damage. In turn, the ovarian compartment may have a preventive influence on germ cell neoplasia [38].

The natural history of neoplastic lesions in gonadal dysgenesis is not completely elucidated because of the paucity of the older patients. Patients with dysgenetic gonads, who carry a Y chromosome, are usually submitted to bilateral gonadectomy in childhood to prevent the development of GCT. However, we had the opportunity to investigate 7 patients with dysgenetic testes, aged 17–25, carrying the 46,XY or 45,X/46,XY karyotype, having gonads preserved because of apparently “female phenotype” or intact testosterone secretion [78, 79]. Overall,

germ cell neoplasia (GCT, CIS, and gonadoblastoma) appeared in 6 cases (86%). Merely one 25-year-old patient with Sertoli-cells-only was devoid of neoplasia.

Skakkebaek et al [80] proposed the existence of a new clinical syndrome – a testicular dysgenesis syndrome (TDS), which comprises the wide range of developmental retardations of the testes, including disturbed organogenesis and cryptorchidism. The authors also proposed that male infertility (oligo- and azoospermia) and cases with testicular GCT resulted from TDS, as well. The justification is that in all of these disturbances the immature seminiferous tubules with undifferentiated Sertoli cells, Sertoli-cell-only tubules, intratubular microliths and tubules containing CIS were detected. The structural lesions of the testes may suggest that functional lesions of Sertoli and Leydig cells also exist, causing reproductive system anomalies in the fetal period of life and spermatogenic failure in adulthood.

Recently, it has been found that exposure in utero of male rats to di(n-butyl) phthalate (DBP) causes changes in testes similar to TDS in humans, i. e. areas of malformed seminiferous cords/tubules with intratubular Leydig cells, multinucleated gonocytes, immature Sertoli cells, and abnormal aggregation of Leydig cells [81–83]. Phthalates are a class of additives used in some plastic products made from polyvinyl chloride (PVC) to make the material soft and flexible. They exert estrogenic and anti-androgenic effects in rodents and humans [84]. The mechanism of phthalate action has not yet been completely elucidated. They interfere mainly with Leydig cell function and act predominantly as anti-androgens. This indicates that disturbances of testicular organogenesis may be caused by environmental factors.

Diagnosis of CIS

Testicular CIS is not accompanied by any specific clinical symptoms. In some cases, the testis volume is decreased and the consistency is more tight because of degeneration of seminiferous tubules and hypertrophy of the interstitial connective tissue. In 70 % of cases, severe oligozoospermia is found [85, 86]. Serum GCT markers (AFP, bhCG) are not elevated if CIS is not accompanied by the invasive neoplastic process [87, 88].

In recent years, attempts have been made to develop non-invasive techniques for the detection of CIS. Only ultrasonography of testes is of value as a screening method but cannot be used as a single procedure in the diagnosis of CIS. Irregular echo patterns, often with calcifications, suggest the possibility of testicular neoplastic lesions and may help in the selection of patients for testicular biopsy [88–90]. At present, surgical biopsy of the testis is the only reliable method to detect CIS. Indication for testicular biopsy is the increased probability of neoplastic changes in the testis. Considering that CIS is the pre-invasive germ cell neoplastic lesion, the risk groups for CIS are the same as for overt GCT. Nevertheless, it is still difficult to reach a consensus about whether or not it is necessary to perform a biopsy of both testes [91]. However, the European Association of Urology recommends in the 2006 “Guidelines on Testicular Cancer” to offer biopsy of contralateral testes to all patients, especially high-risk patients with a testicular volume < 12 ml and aged < 30 years [92]. Contralateral biopsy should be

performed preferably at the time of orchiectomy. A routinely performed bilateral testicular biopsy is not recommended in patients with extragonadal GCT because they will receive platin-based chemotherapy, which will eliminate a substantial percentage of testicular CIS. Nevertheless, if a biopsy is planned in patients with a higher risk for testicular CIS (atrophy of the testis and young age) following extragonadal GCT, this should be preferably performed prior to chemotherapy, if not prior then no more than 6 months afterwards [91].

Proper fixation of testicular specimen in Bouin’s, Stieve’s or Cleland’s fluids (but not in formalin) is of great importance for the microscopic evaluation of different types of germ cells and changes in the tubular membrane and interstitial tissue. Morphological criteria for recognizing CIS cells include the appearance of a nucleus that is irregular in shape, with a diameter of > 7.5 mm, with irregular, coarse clumps of chromatin. Cytoplasm is light and abundant [35]. CIS cells are located near the tubular membrane as a single cell line, closely associated with Sertoli cells. Usually, no other types of germ cells are present. The tubular diameter is diminished (< 150 mm) and the tubular membrane is thickened (> 15 mm). The neighboring tubules can be normal with full spermatogenesis (Fig. 3).

Antigens specific for CIS cells, identified with the use of immunohistochemical methods, are identical with those in normal fetal germ cells. These include: placenta-like alkaline phosphatase (PLAP) [93], M2A, 43-9F, TRA-1-60 [94, 95], c-kit receptor [96], stem cell factor (SCF) [97], Gb3 [98], neuron-specific enolase (NSE) [99], AP-2 [100], OCT-3/4 [101, 102], and others which can facilitate the diagnosis.

Treatment of Testicular CIS

After diagnosis of CIS, management depends on the age and location of the neoplastic lesion. In adults, when CIS is diagnosed in one testis and there is no evidence for

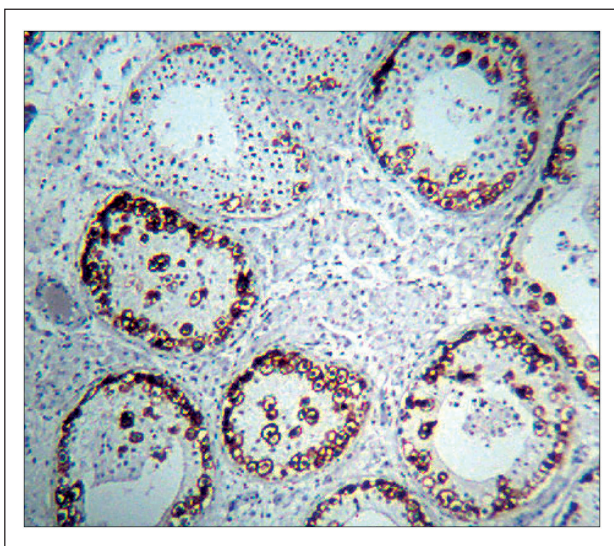


Figure 3. Intratubular germ cell neoplasia in the testis of an adult man with an invasive germ cell tumor in the opposite testis. Note seminal tubules containing CIS cells with the positive immunostaining for placental-like alkaline phosphatase (PLAP) and the neighboring seminal tubule with several CIS cells and numerous normal spermatogenic cells (magnification 200×).

neoplasia in the contralateral testis (negative biopsy), unilateral orchiectomy is the treatment of choice. Orchiectomy is preferred over irradiation because of the potential damage of the contralateral, not affected testis by scattered radiation. In patients with one testis or when CIS is diagnosed bilaterally radiotherapy is recommended. The dose of 20 Gy in 10 fractions is sufficient to destroy CIS cells which are very sensitive to irradiation [103, 104]. To preserve testosterone production by Leydig cells, radiation doses < 20 Gy were investigated [105], however, sporadic failures may occur [106], so the dose of 20 Gy is still recommended [91]. To confirm treatment effectiveness another biopsy after 1–2 years is indicated [107]. As a positive effect, the Sertoli-cell-only syndrome is diagnosed. The hormonal action of Leydig cells after radiotherapy is usually diminished, but in most cases it improves and is sufficient to maintain androgenic activity [105]. Another method of CIS treatment is chemotherapy with cisplatin [107, 108]. Due to many side effects and unpredictable final effects it is not recommended.

Unfortunately, currently there is no agreement concerning the therapy of pre-pubertal individuals with CIS. Bilateral early gonadectomy is usually recommended in cases with male pseudohermaphroditism (gonadal dysgenesis, androgen insensitivity) as a prevention therapy for GCT. Recently, Cools et al [77] suggested that gonadal biopsy should be performed first. The presence of underdeveloped gonadal tissue or testicular tissue with germ cells positive for embryonal/CIS markers on the basal lamina contains a high risk for GCT and should imperatively lead to gonadectomy. According to the authors, testicular tissue displaying only maturation delay of germ cells can be left in place and be adequately followed-up. A streak gonad is not functional, so preserving it is not rational.

In cryptorchidism without other malformations of the urogenital system, it is advisable to perform testicular biopsy shortly after puberty, especially if a testis is small and with an irregular echo pattern. Testicular biopsy has a high sensitivity to detect CIS, but cases with negative results and development of GCT some years thereafter have been described [109, 110]. Therefore, a negative biopsy result does not absolve a doctor from responsibility for the longitudinal follow up of a patient with undescended testes. Ultrasonography of the testes is recommended every year [90, 111]. It may seem too frequent, but if a testicular ultrasonographic picture is inhomogenous, azoospermia in semen is present and a patient is below 30 years of age it may be a useful tool to find early neoplastic lesions. The patient should be also aware of the neoplastic risk and perform the regular self-control of the testes by palpation.

Conclusions

There is already strong evidence that GCT originate from fetal germ cells. Genetic, hormonal, and environmental factors are suspected to lead to disturbed testicular organogenesis which creates a milieu favorable for the development of GCT. Thus, different degrees of testicular dysgenesis determine the high risk of GCT. Patients with this risk should be under particular medical control. Early diagnosis of testicular neoplastic lesions enable active prevention of the invasive neoplastic process and complications connected with the disease or its treatment. In

this review, we support the statement that preventive resection of dysgenetic gonads should be performed in pre-pubertal children because in this disease the risk of GCT in adulthood is extremely high. When a dysgenetic gonad is preserved, its hormonal function is usually not appropriate and testosterone substitution is mandatory.

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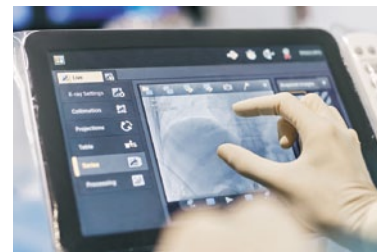
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