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Sonographic Testicular Microlithiasis as an Indicator of Premalignant Conditions in Normal and Infertile Men

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ABSTRACT: Sonographic detection of multiple, small hyperechogenic lesions in the testis (testicular microlithiasis; TM) can indicate germ cell tumors. However, it has not been well established whether this finding signifies a risk factor for development of testicular neoplasm in all cases or whether it indicates premalignant changes only in those men with additional risk factors for germ cell cancer, such as infertility, a history of testicular maldescent, or the presence of an atrophic testis. In a retrospective analysis of 1701 consecutively performed scrotal sonographies of patients with (n = 1399) and without (n = 219) infertility or with contralateral testicular tumors (n = 83), the prevalence of TM was compared with that in 198 healthy men who volunteered for different clinical trials. TM was equally frequent in all groups (2.3% [32/1399] of infertile patients, 2.3% [5/219] of other patients without infertility, and 1.5% [3/198] of healthy men). Results of testicular biopsies were available for a subgroup of infertile men. Carcinoma in situ (CIS) was present only in cases with TM (2/11). In addition, sonographic follow-up examinations were performed in another 14 men with TM. Testicular tumors had developed in 2 patients, one whom was infertile and one in the control group. None of these patients had a history of testicular maldescent but all testes affected either by CIS or tumors were reduced in volume. We conclude that diagnosis of TM, especially if it is present in an atrophic testis, demands a diagnostic biopsy or at least sonographic follow-up examinations.

Key words: Carcinoma in situ, echogenic foci, infertility, testicular tumor, ultrasonography.

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With extended use of scrotal ultrasound it has become evident that infertile men frequently have abnormalities of testicular texture such as patchy inhomogeneities, hypoechogenic lesions, or hyperechogenic foci (Lenz et al, 1994; Pierik et al, 1999; Behre et al, 2000). Numerous, small hyperechogenic lesions, so-called testicular microlithiasis (TM), are of special clinical interest because the sonographic picture may be associated with the presence of germ cell tumors or carcinoma in situ (CIS; Lenz et al, 1996; Miller et al, 1996; Ganem et al, 1999). The increased prevalence of testicular malignancy in infertile men is well documented. On careful investigation that includes scrotal sonography, a tumor is diagnosed in 1 out of every 200–250 men with any history of infertility (Pierik et al, 1999; Behre et al 2000). However, it remains unclear whether TM is especially prevalent in infertile men and in which cases the finding implies an increased risk for CIS or possible progression to testicular malignancy.

In order to clarify these questions, we compared in a retrospective, cross-sectional study (study 1) the frequency of hyperechogenic foci in 3 series of patients. The first group consisted of infertile men who were examined between 1993 and 1995 (n = 1399). A second group encompassed 219 men who presented with primary or secondary hypogonadism or who were seen for cryopreservation of sperm due to nontesticular malignancies. The third group consisted of 83 men who were examined prior to sperm cryopreservation after removal of a contralateral testicular tumor. Data were compared with those of 198 healthy men who had been recruited for different clinical studies.

To determine the predictive value of echogenic lesions for the presence of CIS or development of malignancies we retrospectively analyzed histology in the subset of infertile men (76/1399) in whom bilateral biopsy had been obtained (study 2). Sonographic findings were correlated with histological results for the presence of CIS cells. In addition, we analyzed tumor development in follow-up sonographies that had been performed in patients with TM in our department.

Materials and Methods

Patients

Cross-Sectional Analysis (Study 1)—Group 1 (198 healthy men) served as the control group. They had been recruited between 1993 and 1999 for different male contraceptive trials (Behre et al, 1995; Büchter et al, 1999; Kamischke et al, 2000) and a study on proven fatherhood (Simoni et al, 1999). Scrotal ultrasound had been performed on each man prior to entry in all studies.

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All men had normal sperm parameters according to World Health Organization (1992) guidelines, and normal values for serum gonadotropins and testosterone. The presence of any serious diseases was excluded through a normal medical history and physical examination, including clinical chemistry and hematology.

All patients who were first seen at our institute between January 1993 and December 1995 were included in the analysis (n = 1701). We routinely perform sonography of scrotal contents as part of an initial examination. Group 2 consisted of 1399 men who were investigated because of an infertile partnership. Group 3 consisted of 219 patients who had presented with different endocrine or nonendocrine diseases, including 46 men with primary hypogonadism; 10 men with hypopituitarism; 83 men in whom cryopreservation of sperm was performed because of nontesticular malignancies; and 80 men with different concerns, primarily gynecomastia, erectile dysfunction, or pubertal delay. Eighty-three men who came to our department for cryopreservation of sperm after unilateral orchidectomy because of testicular cancer were grouped separately (group 4). Data on testicular volume, echogenicity of the testis, and sonographic appearance were obtained from patients' charts.

Testicular Histology and Follow-Up Examinations (Study 2)—To determine the prevalence of CIS-positive testes among men with TM, we analyzed results of testicular histology or follow-up ultrasounds performed in our department. Histological findings were available from 76 out of 1399 infertile patients. Biopsies had been obtained for diagnosis of spermatogenic status or because of abnormal testicular texture. Ultrasound revealed TM in 11 of these patients. All biopsy specimens had been fixed in Bouins solution. Sections had been stained with placental-like alkaline phosphatase for detection of CIS.

Follow-up sonographies had been performed in our department on another 14 men with TM (12 patients and 2 healthy volunteers). Intervals between the first and the follow-up ultrasound ranged from 3 to 5 years.

Ultrasongraphy

Ultrasound of scrotal contents was performed between 1993 and 1994 with a Siemens (Erlangen, Germany) Sonoline SI450, and since the beginning of 1995 with the Siemens Sonoline versa pro (Siemens), using a 7.5-Mhz sector transducer. As described previously (Behre et al, 1989), calculation of testicular volume was computed from longitudinal and transverse testicular sections. Ultrasound was performed by 4 different investigators who were all trained at our center and who used a standardized examination procedure and terminology (Behre et al, 1995). Testicular texture was classified as being homogenous (texture 1), exhibiting moderate or severe inhomogeneities defined as patchy areas of hypoechogenicity without echogenic lesions (texture 2; panel a in the Figure; Harris et al, 2000), demarcated hypodense areas suspicious of tumors (texture 3), testicular cysts (texture 4), and the presence of echogenic lesions. Images with echogenic lesions were classified according to the number of foci detected per transducer field. The sonographic picture of TM is generally defined as the presence of numerous, echodense, nonshadowing foci in the testis. However, the number of echogenic foci needed to make the diagnosis of TM is not well defined. For our study we followed the definition suggested by Backus et al (1994). Fewer than 5 foci per image were regarded as isolated (texture 5) and more than 5 foci were regarded as multiple lesions equivalent to TM (texture 6; see panels b and c in the Figure).

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (Cary, NC) for Windows (version 8.0). All variables were checked for normal distribution by the Kolmogorov-Smirnov one-sample test for goodness of fit. Nonnormal distribution values were given as minimum, median, and maximum. Frequencies were compared by Chi-square analysis. For comparison of continuous figures the Mann-Whitney *U*-test was performed. For both tests, the level of significance was $P < .05$.

Results

Prevalence of Hyperechogenic Foci

Patients and controls were comparable in age (Table 1). In 25 men, less than 5 echogenic lesions were identified (texture 5). In another 54 men multiple foci (texture 6) were detected, which were unilateral in 48 men and bilateral in 6 men. The frequency of echogenic lesions did not differ between healthy volunteers (group 1) and patients with (group 2) and without (group 3) infertility. The only exception were men with contralateral testicular malignancies (group 4) in whom TM (texture 6) was significantly more prevalent, with 16.9% of the tumor-free testis being affected. Because we saw these patients after orchidectomy we cannot comment on the prevalence of echogenic foci in the affected testis. Data are summarized in Table 1.

Men in groups 1 and 2 were further analyzed according to other risk factors for testicular carcinoma, such as the presence of an atrophic testis (volume <12 mL; Behre et al, 2000) or a history of testicular maldescent. TM was not especially prevalent in atrophic or maldescended testes. TM was found in ⅓ of atrophic testes in group 1 and in 11 out of 451 testes in group 2.

A history of cryptorchidism was reported by 3 men in group 1 and by 62 in group 2. TM was present in none of these healthy volunteers, but it was present in 7 of the 62 infertile men with cryptorchidism.

TM was found in connection with the following different diagnoses: hyperprolactinemia (n = 3), idiopathic infertility (n = 18), maldescended testis (n = 9), varicocele (n = 11), genital tract infection (n = 2) or obstruction (n = 1), immunological infertility (n = 2), secondary hypogonadism (n = 1), Klinefelter syndrome (n = 2), extragonadal malignancies (n = 4), and pubertal delay (n = 1) (Table 2).

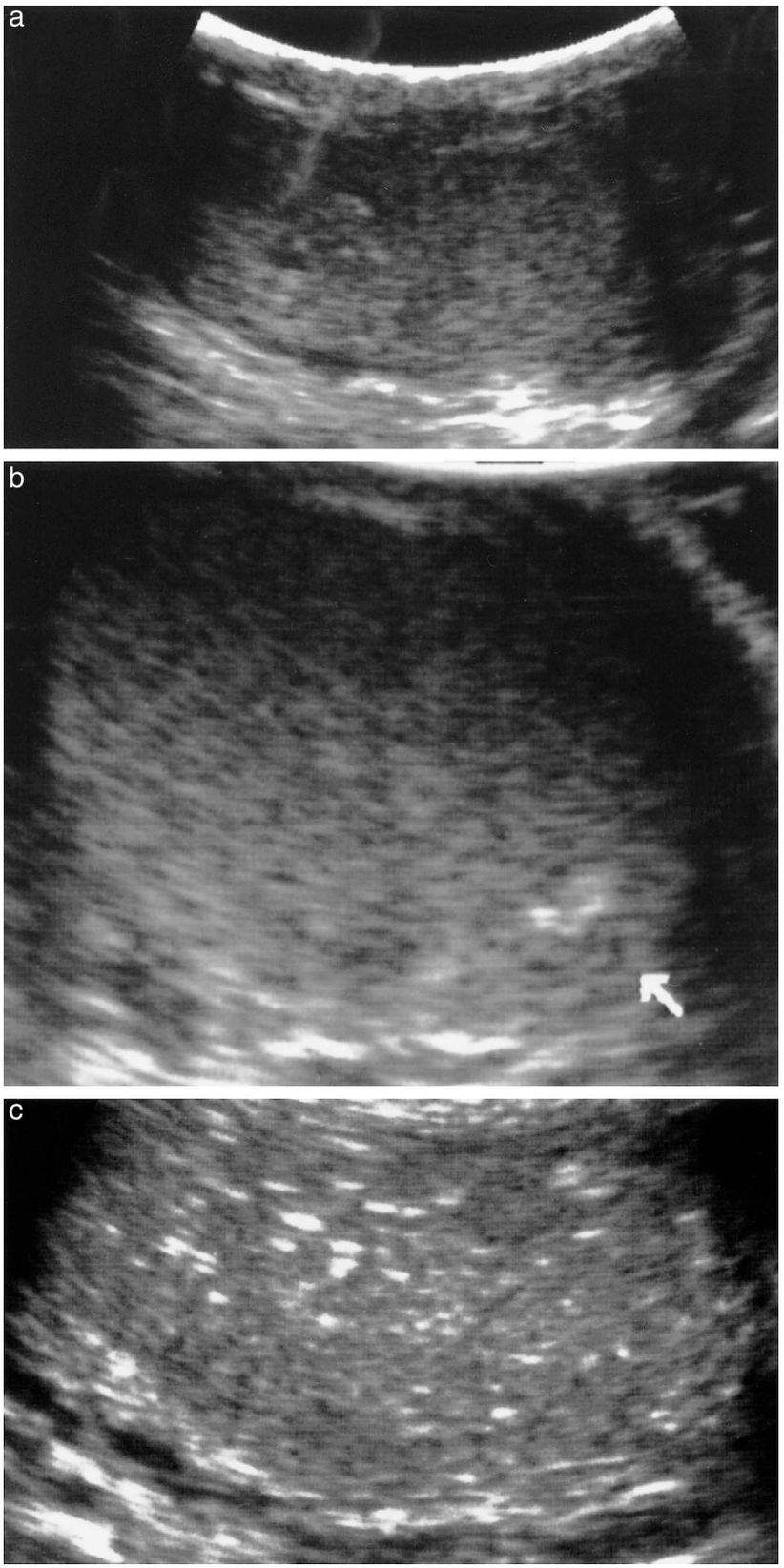
a
b
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Table 1. *Prevalence of echodense areas**

Diagnosis (Group)	n	Age, y	Texture 5 n (%)	Texture 6 (Unilateral) n (%)	Texture 6 (Bilateral) n (%)
Healthy volunteers (1)	198	30.0 ± 4.9	3 (1.5)	2 (1.0)	1 (0.5)
Infertility (2)	1399	33.7 ± 6.1	13 (0.9)	27 (1.9)	5 (0.4)
No infertility (3)	219	30.2 ± 10.7	1 (0.5)	5 (2.3)	0
Testicular tumor contralateral testis (4)	83	30.0 ± 6.1	8 (9.6)†	14 (16.9)†	Not applicable

* Texture 5 is equivalent to the presence of <5 echogenic foci in the testis and texture 6 to >5 foci (TM).
† Significant differences in frequency on Chi square test ($P < .05$).

Testicular Texture and Histology

Testicular biopsies had been obtained in 76 men with infertility. The mean age of men was 33.4 ± 6.4 years. Clinical diagnosis included hyperprolactinemia (n = 1), idiopathic infertility (n = 22), maldescended testis (n = 24), varicocele (n = 18), infection (n = 4), and genital tract obstruction (n = 7). Sonographic texture was bilaterally homogeneous in 41 cases. Testicular texture 2 was classified in 22 men, texture 5 in 2 cases, and texture 6 (TM) in 11 cases. A total number of 149 testes underwent biopsy, 12 of which exhibited TM in a normal-sized testis and 5 in an atrophic testis. CIS cells were detected in 2 specimens, both from atrophic testes with TM detected by sonography. Idiopathic infertility had been diagnosed in one case and genital tract infection in the second. Sperm concentrations were 0.3 million/mL and 16.2 million/mL, respectively.

Follow Up

Results of follow-up examinations performed in our department 3 to 5 years after the initial examination were available from 14 men with TM (12 patients and 2 healthy volunteers). Testicular tumors had developed in 2 men. In both cases histology revealed seminomas. Case 1 was a volunteer from group 1 who had been enrolled in the placebo group of a 1993 clinical study. The tumor developed in the right testis (volume, 10 mL), which previously had been found to exhibit TM. The homogenous texture of the contralateral testis (27 mL) remained unchanged. The second patient had bilateral, echodense foci and a longstanding history of infertility. Biopsy had been performed on this patient elsewhere in 1994 without detection of CIS cells. In 1999 a tumor was diagnosed after follow-up sonography in our department. Both testes affected were reduced in size (2 and 4 mL).

Taken together, either CIS or testicular tumors occurred in 4 out of 25 (16%) men exhibiting TM. If TM was present in an atrophic testis, malignant changes were even more frequent, with 4 out of 10 (40%) men affected. However, biopsies or follow-up examinations were performed only in 15 out of 25 (60%) men with TM in a normal-sized testis and in 10 out of 15 (66.6%) men with TM and testicular atrophy.

Discussion

Scrotal sonography significantly contributes to early diagnosis of testicular tumors in men who are infertile (Behre et al, 2000). It has also been suggested that detection rates of premalignant changes (ie, CIS) can be increased if indication for biopsy is based on the presence of inhomogeneities in testicular texture (Giwercman et al, 1993a). A number of case reports suggest that the presence of numerous hyperechogenic foci strongly indicates either intratubular germ cell neoplasia (Kessaris and Mellinger, 1994) or an increased risk for later occurrence of testicular cancer (Table 3). However, because of the heterogeneity in the populations studied and confusing terminology in use, it is difficult to interpret the results (Renshaw et al, 1998). In most sonographic studies multiple echogenic lesions are called TM. Morphologically, TM is characterized by degeneration of the seminiferous epithelium with deposition of laminated rings of glycoprotein and calcium (Nistal et al, 1979) or by calcified, hematoxylin-positive bodies (Renshaw et al, 1998). Microliths are frequently found in CIS-positive biopsies (Kang et al, 1994) and may also be associated with intratubular neoplasia (Table 3). Despite this association TM is considered to be a symptom of impaired testicular development rather than a premalignant condition on its own (Rajpert-De Meyts and Skakkebaek, 1999). In the few studies in which biopsies were obtained from testes exhibiting hyperechogenic foci (Kragel et al, 1991; Backus et al, 1994;

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Longitudinal sonograms of testes showing inhomogeneities without echodense foci equivalent to texture 3 **(a)**; with a single, echodense lesion (marked by an arrow) equivalent to texture 5 **(b)**; and one with multiple, echodense foci equivalent to texture 6 or TM **(c)**.

Table 2. *Testicular texture in relation to clinical diagnosis in 1701 consecutive patients**

Diagnosis	Total Number	Texture 1 n (%)	Texture 2 n (%)	Texture 3 n (%)	Texture 4 n (%)	Texture 5 n (%)	Texture 6 n (%)
Hypogonadotropic hypogonadism†	12	12 (100)	0	0	0	0	0
Hyperprolactinemia†	31	23 (74.2)	5 (16.1)	0	0	1 (3.2)	2 (6.5)
Idiopathic infertility†	511	455 (89.0)	38 (7.4)	0	0	7 (1.4)	11 (2.2)
Cryptorchidism†	113	62 (54.9)	41 (36.3)	0	1 (0.9)	2 (1.8)	7 (6.2)
Varicocele†	435	378 (86.9)	44 (10.1)	0	2 (0.5)	2 (0.5)	9 (2.1)
Genital tract infection†	69	54 (78.3)	13 (18.8)	0	0	0	2 (2.8)
Obstruction†	44	36 (81.8)	7 (15.9)	0	0	1 (2.3)	0
Immunological infertility†	164	156 (95.1)	5 (3.1)	0	1 (0.6)	1 (0.6)	1 (0.6)
Other diagnosis†	20	16 (80.0)	4 (20.0)	0	0	0	0
Contralateral testicular tumor	83	41 (49.4)	19 (22.0)	1 (1.2)	0	8 (9.6)	14 (16.9)
Nontesticular malignancies	83	67 (80.7)	12 (14.5)	0	1 (1.2)	1 (1.2)	2 (2.4)
Klinefelter syndrome	26	17 (65.4)	7 (26.9)	0	0	0	2 (7.8)
Primary hypogonadism	20	16 (80.0)	4 (20.0)	0	0	0	0
Pituitary insufficiency	10	9 (90.0)	0	0	0	0	1 (10.0)
Congenital adrenal hyperplasia	2	0	0	2 (100)	0	0	0
Other diagnosis (gynecomastia, erectile dysfunction, pubertal delay)	80	66 (82.5)	14 (17.5)	0	0	0	0

* Textures are classified as follows: 1, homogenous; 2, inhomogeneities (patchy areas of hypoechogenicity) without echogenic lesions; 3, demarcated hypodense areas suspicious of tumors; 4, testicular cysts; 5, less than five echogenic points per image; 6, testicular microlithiasis.
† Patients who were examined because of infertility.

Lenz et al, 1996) histology showed microliths in only a small subset of specimens. However, several case reports show either a correlation of the sonographic picture with the presence of CIS tubules (Table 3) or subsequent development of cancer. In men with testicular tumors CIS is verified 22.2% of the time in the contralateral testis if echogenic foci are seen in sonography (Lenz et al, 1996). It has been suggested that TM is also more frequent in men with any kind of infertility (Kessaris and Mellinger, 1994; Pierik et al, 1999). Unfortunately, none of these studies included a direct control group but rather, they referred to data from unselected urological patients (Hobarth et al, 1993; Ganem et al, 1999). Our results do not support an increased frequency of echogenic lesions among an unselected population of infertile men. When patients are strongly selected in favor of those having

Table 3. *Summary of cases with multiple echodense areas reported in the literature with either progression to tumors or histologically confirmed intraepithelial germ cell neoplasia*

Age, y (first ultra sound)	Reason for Investigation	Sperm Count (Spermatogenesis)	Affected Testis	Testis Volume (Not Affected/ Affected)	Interval to Detection of Tumor	Histology (Testis)	Reference
32	Infertility, left side cryptorchidism until the age of 11	19.4 million mL	Right	Normal/ smaller	10 months	Embryonal carcinoma (right)	Salisz et al, 1990
17	Discrepancy in testicular volume	Not reported (impaired)	Left and right	Normal	4 years	Yolk sac tumor (right)	McEniff et al, 1995
21	Testicular pain, hematospermia		Left	Not reported	3 years	Mixed germ cell tumor (left)	Winter et al, 1996
25	Testicular enlargement	Not reported	Left and right	Not determined/ normal	16 months	Mixed germ cell tumor (left)	Frush et al, 1996
29	Seminoma, right testis	Not reported	Left	Not reported/ atrophic	11 years	Seminoma	Gooding, 1997
47	Testicular pain	Not reported	Left and right	Right atrophic, left normal	6 months	Seminoma, right	Golash et al, 2000
25	Testicular atrophy	Not reported	Left	20 mL/12 mL		CIS* (left)	Giwercman et al, 1993a
31	Testicular tumor (left)	Not reported	Right	Not reported		CIS (right)	Parra et al, 1996

* CIS indicates carcinoma in situ.

Table 4. *Comparison of sperm concentration, gonadotropins, and testicular volume in healthy volunteers (group 1) and infertile men (group 2) exhibiting different frequencies of echodense areas in the testis**

Testicular Texture	Sperm Concentration (Million/mL)	LH (IU/L)	FSH (IU/L)	Volume of Affected Testis (mL)	Volume of Unaffected Testis (mL)
Texture 5	0—35.1—214	2.3—3.0—5.6	1.3—4—13.4	12—20.5—41.9	14—22.2—39
Texture 6 (unilateral)	0—9.6—222	0.1—4.5—16.3	0.1—7.5—36.3	1.2—13—33†	3.2—14—30†
Texture 6 (bilateral)	0.1—23.6—114	0.1—2.6—8.3	3.4—5—31.1	6.8—15.5—24†	

* Due to non-normal distribution, values are given as minimum—median—maximum. LH indicates luteinizing hormone; FSH, follicle-stimulating hormone.

† Significant differences ($P < .05$) analyzed by ANOVA between patterns of texture.

severe oligozoospermia and moderately reduced testicular volume, considerably higher proportions of TM are reported (Lenz et al, 1994), indicating that TM is especially prevalent in those men having spermatogenic defects. However, our histological and follow-up data suggest that a reduction in sperm concentration is less indicative for premalignant changes than the presence of an atrophic testis.

In follow-up examinations a tumor was detected in 1 patient who 10 years before had had a biopsy that was negative for CIS tubules. However, it should be noted that there are a few false negative results, with 0.3% of cases in which, upon careful reexamination, intraepithelial neoplasia can be detected in a testis that was initially rated as CIS-negative (Dieckman et al, 1999).

In our study, interestingly, detection of CIS as well as development of tumors always occurred in atrophic testes. Testicular atrophy is an established risk factor for the presence of intratubular germ cell neoplasias. However, when atrophy is applied as an indication for contralateral biopsy in patients with tumor, detection rates of CIS are slightly lower (Harland et al, 1993) than when sonography is performed (Lenz et al, 1996). In accordance with our results, in 5 of 6 the cases from the literature, development of tumors occurred in testes that had been affected by both findings (ie, reduced size and TM [Table 4]).

Apart from maldescent and testicular atrophy, infertility itself is considered to be a risk factor for testicular cancer (Testicular Cancer Study Group, 1994). Previously, it had been postulated that echogenic foci are especially frequent in men with oligozoospermia (Aizenstein et al, 1998). The rate of multiple echogenic lesions we observed in men with normal sperm parameters was comparable to the prevalence of 2.8% reported by Aizenstein (1998) for men with fewer than 3.5 million sperm/mL. Whereas in men with unilateral testicular cancer a reduced sperm count is highly indicative of the presence of contralateral CIS (Giwercman et al, 1993b), our data show that sperm parameters do not provide additional information to indicate whether a diagnostic biopsy or follow-up examination should be performed if echogenic foci are present. Not a single case of CIS was detected in a prospective series of bilateral biopsies in 207 men with reduced sperm count (Giwercman et al, 1997), but unfortunately, sonographic results were not reported.

In conclusion, several of our findings confirm the indicative value of echogenic foci in the testis for the presence of a premalignant condition. However, the study has some limitations in that the overall number of cases observed is low and biopsies or follow-up examinations were available in only a small, selected subset of men. If the number and the interval of follow-up examinations had both been larger, detection rates for tumors might have changed considerably. Sonography was performed by several investigators, which resulted in interobserver variability. For determination of testicular volume interobserver variability is around 15% (Carlsen et al, 2000). To our knowledge, so far no attempts have been made to control for differences in rating of testicular texture. However, we believe that our data allow valid clinical conclusions because they probably reflect the current practice of routine sonography involving different examiners.

The incidence of testicular cancer in young men (Oliver et al, 1990) has been increasing in recent decades. Prognosis improves if the disease is detected early (Horwich et al, 1998). Clinical indicators of an increased risk for testicular malignancies, such as a history of testicular maldescent, or a positive family history or the presence of male infertility, are absent in about 40% of men who present with germ cell cancer. Because CIS cells have an extraordinarily high potential to progress to cancer, early detection is important for prevention. Considering the low overall prevalence of CIS at 0.4% to 0.8% in the male population (Giwercman et al, 1991), only noninvasive and easy-to-perform screening procedures are attractive diagnostic tools for establishing prevention programs. Based on our results and those of others, sonography provides an excellent means for identifying men who are at an increased risk for tumor development in the absence of other known risk factors. In conclusion, men with TM as evident with ultrasonography may benefit from either diagnostic biopsy (Rajpert-De Meyts and Skakkebaek, 1999) or precautionary follow-up examinations.

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