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UROLOGY - REVIEW

Testicular microlithiasis and testicular cancer: review of the literature

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Abstract
Purpose To perform a systematic literature review to assess whether the occurrence of testicular microlithiasis (TML) in conjunction with other risk factors is associated with testicular cancer.
Methods A systematic literature search was performed of original articles in English published 1998 to 2015. Relevant studies were selected by reading the title and abstract by two of the authors. Studies were included if TML was diagnosed by ultrasonography and a risk condition was reported. Studies were only eligible if the particular risk condition was reported in more than one article.
Results In total, 282 abstracts in were identified. Based on title and abstract the eligibility was assessed and 31 studies were included. Five conditions in relation to TML and testicular cancer emerged: Down syndrome, McCune–Albright syndrome, cryptorchidism, infertility and familial disposition of testicular cancer.
Conclusion Data support the conclusion that TML is not an independent risk factor for testicular cancer but associated with testicular cancer through other conditions. In male infertility, TML appears to be related to an increased risk of testicular cancer possibly as part of a testicular dysgenesis syndrome.

Keywords Testicular dysgenesis syndrome · Testicular microlithiasis · Testicular cancer · Ultrasonography

Introduction

Modern ultrasonography (US) gives more detailed information than previously. As a consequence, testicular microlithiasis (TML) is diagnosed more frequently. The origin of TML is unknown. Typically, TML is diagnosed by scrotal US performed for a variety of indications. Recently, it was demonstrated that both inter- and intraobserver agreement with regard to detecting TML with US is high [1]. TML is characterised by the presence of multiple microintratubular calcifications without any acoustic shadow in the testicle and is often an incidental finding in US examinations of the scrotum. The size of TML typically has a range of 1–3 mm [2].

Several studies deal with prevalence of TML in both asymptomatic and symptomatic men. Peterson et al. [3] reported a prevalence of 5.6 % in 1504 asymptomatic males (18–35 years old) from the US army reserve officer training corps. In another study of a 2179 asymptomatic males form a similar population, the prevalence was found to be 2.4 % [4]. Goede et al. [5] investigated 670 asymptomatic boys in the age range 0–19 years and found a prevalence of 4.2 %. The reported prevalence in healthy populations in other series varies from 0.6 to 9.0 % [6–9]. In symptomatic males, the prevalence in general is higher than in asymptomatic males ranging from 8.7 to 18.1 % [10–12].

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TML has consistently been associated with carcinoma in situ (CIS) and testicular cancer; however, the relation is still controversial. In the literature, several independent conditions have been reported to have very high frequencies of TML. If TML, as suggested by some authors, is the visible sign of a premalignant condition, one would expect that these disease states also would be associated with testicular cancer.

The aim of this paper was through a systematic literature review to evaluate whether TML, alone or in conjunction with other risk factors, is related to occurrence of testicular cancer.

Materials and methods

Search strategy

A literature search of original articles reporting on the relation between TML and specific conditions was performed using MEDLINE/PubMed starting January 2013 until January 2015. The included articles were published in the period from 1998 to 2015. The following keywords were used in the search strategy: testicular microlithiasis, microlithiasis calcification. Review articles were used to identify other relevant studies through the snowball method. All abstracts were read though and only English-language articles were included. Relevant studies were selected by reading the title and the abstract by two of the authors (MRP and PJO).

Inclusion and exclusion criteria

Studies were included if TML was diagnosed by US and a risk condition was reported. Studies were only eligible if the particular risk condition was reported in more than one article. There were no criteria on number of patients enrolled in each study.

Included studies

The search strategy identified 344 abstracts, of which 282 were in English. Of these, a total of 31 studies met the inclusion criteria. Two studies (Yee et al. [13] and Negri et al. [14]) had data on more than one risk condition (cryptorchidism and infertility). Seven studies investigated only children or adolescents and seven both men and boys and 17 studies investigated men only. Tables 1, 2, 3, 4, 5 and 6 present characteristics of the different studies.

Data extraction from the papers

Data were collected on study design, patient characteristics, prevalence of TML, *p* value if available; country, number of patients enrolled and reported cancer cases.

Table 1 Characteristics of studies evaluating TML in Down syndrome

Author	Year	Country	Mean age (range)	*N* = DS	*N* = TML and DS (prevalence)	*N* = total TC^{DS}/TC^{DS} with TML
Cebeci et al. *N* = 50	2015	Turkey	2.4 (1–22)	25	9 (36.0 %)	0/0
Goede et al. *N* = 79	2012	Netherlands	8.8 (0–18)	79	18 (22.8 %)	0/0
Vachon et al. *N* = 92	2006	USA	10.7 (0–30)	92	27 (29.3 %)	1/1[a]

DS Down syndrome, TC^{DS} testicular cancer in males with Down syndrome, *TML* testicular microlithiasis

[a] Ninety-two patients with Down syndrome, and 200 healthy controls. In the healthy controls, 14 men had TML; no TCs were found in control cases. One Leydig cell tumour was found in a male with Down syndrome with TML after 4-year follow-up

Table 2 Characteristics of studies evaluating TML in McCune–Albright syndrome

Author	Year	Country	Mean age (range)	*N* = MAS	*N* = TML and MAS (prevalence)	*N* = total TC^{MAS}/TC^{MAS} with TML
Boyce et al. *N* = 54	2012	USA	NR (3–59)	54	13 (24.1 %)	1/0[a]
Wasniewska et al. *N* = 40	2004	Italy	13.9 (5–21)	8	5 (62.5 %)	0/0

MAS McCune–Albright syndrome, TC^{MAS} testicular cancer in males with McCune–Albright syndrome, *TML* testicular microlithiasis

NR Not reported

[a] One male with MAS was reported with an embryonal cell tumour, and 5 years later with a seminoma in the contralateral testis. There was no information on TML in this case

Table 3 Characteristics of studies evaluating TML in cryptorchidism

Author	Year	Country	Mean age (range)	$N = C$	$N =$ TML and C (prevalence)	$N =$ total TC^C/TC^C with TML
Cooper et al. $N = 3370$	2014	USA	11 (1–18)	9	9 (100 %)	10/3
Chiang et al. $N = 31$	2012	Singapore	NR (5–15)	12	12 (100 %)	0/0
Dutra et al. $N = 1504$	2011	Brazil	7.5 (1–5)	127	5 (3.9 %)	0/0
Yee et al. $N = 1439$	2011	Korea	19.1 (0–87)	310	7 (2.3 %)	NR
Goede et al. $N = 501$	2010	Netherlands	12.5 (3–29)	501	14 (2.8 %)	0/0
Negri et al. $N = 2172$	2008	Italy	37 (20–62)	232	23 (9.9 %)	NR
Kosan et al. $N = 197$	2007	Turkey	28.3 (NR)	8	2 (25 %)	NR
Konstantinos et al. $N = 391$	2006	Greece	37 (15–76)	36	2 (5.5 %)	0/0
Patel et al. $N = 112$	2005	USA	19.6 (18–29)	112	8 (7.1 %)	0/0

C cryptorchidism, *NR* not reported, TC^C testicular cancer in males with cryptorchidism, *TML* testicular microlithiasis

Statistics

Z-test was used to evaluate differences in proportions between groups.

Results

In analysing the association between TML and possible conditions, five conditions had been studied. Three studies referred to *Down syndrome*, two referred to *McCune–Albright syndrome*, nine referred to *cryptorchidism*, seventeen referred to *infertility*, and two studies dealt with *familial disposure to testicular cancer* (Tables 1, 2, 3, 4, 6). In the following section, we discuss the relationship between TML and malignancy in relation to these conditions (Fig. 1).

Down syndrome

The three studies concerning TML and Down syndrome (DS) were conducted in children (Table 1). The boys with Down syndrome had higher prevalence of TML than the general healthy population. The prevalence of TML was reported between 22.8 and 36.0 %, compared to 0–7 % in healthy controls [15–17]. The overall prevalence of TML in DS was 27.6 %. No case of testicular cancer was recorded among 142 DS men with TML. Only one study found a testicular cancer (Leydig Cell tumour) in an individual with DS and TML (1/54 = 1.9 %), and the cancer was diagnosed during the fourth year of follow-up.

McCune–Albright syndrome

McCune–Albright Syndrome (MAS) is a congenital disease characterised by polyostotic fibrous dysplasia, café-au-lait pigmentation and early puberty. Two studies were included concerning TML and MAS. Both studies included boys and men (Table 2). The prevalence of TML in MAS males was 24.1 % [18] and 62.5 % [19]. Combining both studies, the prevalence was 29.0 %. One testicular cancer (embryonal cell tumour) was reported among 62 cases of MAS [18], with no known risk factors or TML.

Cryptorchidism

Our search resulted in nine studies of cryptorchidism and TML (Table 3). In four series of cryptorchidism reported the frequencies of TML were 100 % [20], 3.9 % [21], 2.8 % [22] and 7.1 % [23]. No testicular malignancy was reported. One series [14] found an association of the previous cryptorchidism and an increased risk of testicular cancer (odds ratio 7.5), but there was no information linking TML to the cancer cases (Table 3). In the study of Cooper et al., nine patients with cryptorchidism and TML were found, and three of these were diagnosed with intratubular germ cell neoplasia [24].

Infertility

We included seventeen studies concerning infertility (Table 4). The prevalence of TML in infertile men varied

Table 4 Characteristics of studies evaluating TML and male infertility

Author	Year	Country	Mean age (range)	N = infertile	N = TML in infertile (prevalence)	N = total TC^I/TC^I with TML
Jiang et al. $N = 22$	2012	China	31.6 (25–40)	22	22 (100 %)	0
La Vignera et al. $N = 1056$	2012	Italy	43.3 (0.3–87)	320	60 (18.8 %)	15/10[a]
Yee et al. $N = 1429$	2011	Korea	19.1 (0–87)	60	10 (16.6 %)	47/10
Zhang et al. $N = 34$	2010	China	31.1 (NR)	34	17 (50 %)	0/0
Negri et al. $N = 2172$	2008	Italy	37 (19.8–61.9)	415	17 (4.1 %)	14/NR
Ou et al. $N = 1978$	2007	Taiwan	32 (1–88)	12	4 (33.3 %)	17/9[a]
Parenti et al. $N = 14$	2007	Italy	NR (19–43)	2	0 (0 %)	11/2
Qublan et al. $N = 384$	2006	Jordan	31 (21–63)	234	23 (9.8 %)	0/0
Sakamoto et al. $N = 969$	2006	Japan	40.9 (20–97)	550	31 (5.6 %)	0/0
Sakamoto et al. $N = 545$	2006	Japan	35.8 (22–56)	545	30 (5–5 %)	1/0
Mazzilli et al. $N = 303$	2005	Italy	NR (29–51)	281	13 (4.6 %)	0/0
Brazao et al. $N = 263$	2004	Netherlands	NR (NR)	263	53 (20 %)	7 CIS/6 CIS[a]
Von Eckardstein et al. $N = 1701$	2001	Germany	NR (NR)	1399	32 (2.3 %)	NR/2 CIS[a]
Thomas et al. $N = 159$	2000	UK	NR (NR)	159	10 (6.3 %)	0/0
Pierik et al. $N = 1372$	1999	Netherlands	NR (20–58)	1372	12 (0.9 %)	7/0
Ganem et al. $N = 22$	1999	USA	29 (8–63)	5	5 (100 %)	8/2[a]
Aizenstein et al. $N = 180$	1998	USA	37 (31–49)	180	5 (2.8 %)	0/0

NR not reported, *CIS* carcinoma in situ, *TC^I* testicular cancer, *TML* testicular microlithiasis

[a] For cancer subtypes please refer to Table 5

Table 5 Cancer subtypes reported in patients with testicular tumours and TML

Cancer subtype	Risk factor				Total (%)
	Down syndrome	McCune–Albright syndrome	Cryptorchidism	Infertility	
Seminoma	–	–	6	24	30 (36)
Mixed germ cell tumour	–	–	6	11	17 (20)
Leydig cell tumour	1	–	–	8	9 (11)
Teratoma	–	–	2	4	6 (7)
Yolk sac tumour	–	–	1	1	2 (3)
Embryonal carcinoma	–	–		1	1 (1)
IGCN/CIS	–	–	3	15	18 (22)
Total	1		18	64	83

IGCN/CIS intratubular germ cell neoplasia/carcinoma in situ

Table 6 Characteristics of studies evaluating TML in males with familial disposition to testicular malignancy

Author	Year	Country	Mean age (range)	N = Cancer cases	N = TML (prevalence)	$N = TC^F/TC^F$ with TML
Korde et al. $N = 81$	2008	UK	39 (NR)	48	23 (48 %)	0/0[a]
Coffey et al. $N = 328$	2007	UK	47 (25–78)	169	62 (36.7 %)	NR[b]

NR not reported, TC^F testicular cancer in males with familial disposition, *TML* testicular microlithiasis

[a] Forty-eight affected males and 33 unaffected male blood relatives from 31 multiple-case testicular germ cell tumour families. TML was found in 8 of 33 unaffected males and in 23 of 48 affected males

[b] A total of 169 cancer cases found (76 seminoma, 92 non-seminoma and one of unknown origin) and four developed a second tumour (two seminoma and two CIS), but no information if any had TML. No cancers found in the 58 relatives, and 1 cancer was diagnosed in the 101 control cases, but no information if TML or not

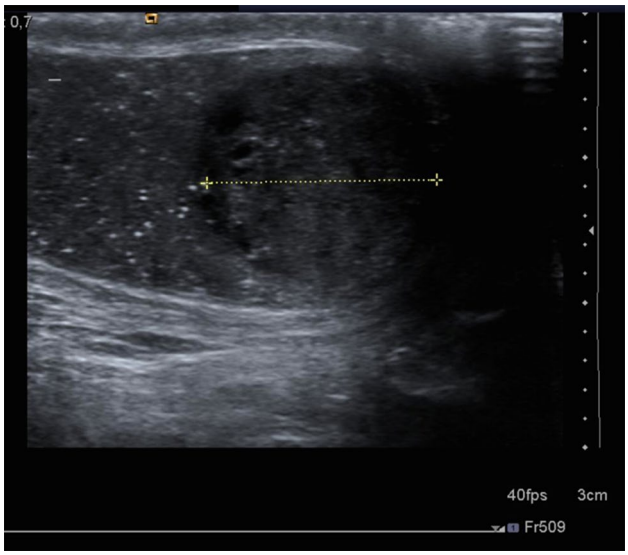

Fig. 1 An ultrasonography of a 16-year-old male with testicular cancer and multiple TML diagnosed in 2014 in our Department of Radiology. The longitudinal size of the tumour was 1.6 cm

between 0.9 and 18.8 %, compared to 2.3–9.8 % in studies who also included fertile men [14, 25–29]. By pooling the data, the overall prevalence of TML was 6.0 and 4.8 % in infertile and fertile men, respectively ($p < 0.05$). The relation between testicular cancer and TML was inconsistently reported. In the following analysis, only studies reporting both cancer cases and TML are considered. In total, 44 cancers were reported in 5092 infertile males (0.90 %) compared to 52 cancers in 2889 fertile men (1.8 %) ($p < 0.01$) [13, 14, 25–35]. Analysing the relation between TML and testicular cancer (including CIS) in infertile men, the pooled data revealed that the cancer prevalence of infertility plus TML was 10.9 and 1.6 % in case of infertility without TML ($p < 0.001$). Correspondingly, the cancer prevalence of fertility plus TML was 6.1 % compared to 2.6 % in fertile men without TML (NS). Comparing cancer prevalence between infertility plus TML and fertility plus TML, there was only a weak trend towards a higher cancer rate among the infertile TML men. Cancer subtypes in infertile men with TML are presented in Table 5.

Familial disposition to testicular cancer

Two studies concerning TML and family history of testicular cancer were identified (Table 6). Both studies were conducted prospectively in adults with TML prevalence between 48.0 to 36.7 %. Korde et al. [36] found that TML was more frequent in the contralateral testis of men with a history of testicular germ cell tumours and that TML was more prevalent among family members than previously described in the general population. Eighty-one men (48 with testicular cancer and their 33 unaffected relatives) from 31 families were investigated; 14 had brothers with testicular cancer; 6 had fathers with testicular cancer; 3 cousins with testicular cancer; and 8 had more than two affected family members with testicular cancer. The prevalence of TML was significantly higher among cases than among unaffected men (48 vs. 24 %; $p = 0.04$). No cancer was found in the group of relatives with TML (8 of 33 relatives).

Coffey et al. [37] analysed ultrasound data of 328 men (169 testicular cancer cases; 58 relatives to the cases; 101 controls). A greater concordance for TML in relatives of testicular cancer cases than would be expected was demonstrated. No testicular cancer case was found in the group of relatives, whereas one testicular cancer was found in the control group and three in the remaining testis of the case group (Table 5). Overall TML was present with a higher frequency in cases with prior testicular cancer (36.7 %) compared to controls (17.8 %).

Discussion

Males with Down syndrome and McCune–Albright syndrome appear to have the highest frequencies of TML,

ranging from 23 to 63 %. The present analysis revealed that in these conditions there seemed to be no relation between TML and development of testicular cancer. This observation questions TML as an independent risk factor for testicular malignancy. Males with Down syndrome had higher risk of testicular cancer [38, 39], and possibly decreased spermatogenesis [40], but from the present analysis TML does not seem to be related to higher risk of malignancy. Individuals with MAS are often affected by hormonal disorders such as early puberty, which also is the case among males with Down syndrome. This association between TML and chromosomal abnormalities may indicate TML as part of a degenerative process of the testis.

Cryptorchidism is associated with increased risk of testicular cancer [41–44]. As seen from the present analysis, there is, however, no clear evidence whether TML and cryptorchidism or TML and testicular cancer are interlinked. However, as TML-related cancer risk in cryptorchidism was inconsistently reported, further studies are warranted.

Infertility is a risk factor for testicular cancer [45–47]. Numerous studies have suggested the association between testicular malignancy, TML and infertility [7, 36, 37, 48]. The prevalence of TML in infertile men is generally higher than in fertile men [6–9, 13, 30]. Our analysis showed that TML was associated with an approximated sevenfold higher cancer risk compared to infertile men without TML (10.9 vs. 1.6 %), confirming that TML, infertility and testicular cancer seem to be interlinked. Thus, TML may be an indicator of a "testicular dysgenesis syndrome", consisting of infertility, cryptorchidism, CIS and testicular cancer [49].

Families with both TML and testicular malignancy have been reported [36, 37], as well as TML in siblings [50]. In the two included studies, 28 relatives with TML were found, but no cancer cases reported. The relative risk of developing testicular cancer if ones brother is diagnosed with testicular germ cell tumour is 8–10 times higher [51, 52]. A higher TML frequency among family members may be due to both genetics and shared exposures. Prevalence of TML in male blood relatives has been reported as high as 48 % [37]. The high prevalence may be an indicator of a genetic factor rather than exposure due to the high prevalence in TML families. Also, TML cluster in certain families has been suggested to be linked to development of testicular germ cell tumours [36, 37]. The present analysis questions this, since no testicular cancers were reported among TML blood relatives. Further studies are needed to clarify whether a family relation with regard to TML increases risk of testicular cancer.

Our review highlights that TML cannot be viewed isolated, as current clinical practice has tended to do. Decisions on clinical management should be based on associated risk factors, a point of view that has been supported by recent papers [53, 54]

With regard to cancer subtypes, data in the literature are sparse, and as evident from our analysis, cancer subtypes were inconsistently reported (Table 5). Recently, it was suggested that there might be a positive association between TML and seminoma, and a negative association between TML and embryonal cell carcinoma. This was confirmed in our review, in which seminoma accounted for 36 % of cancer cases reported with TML compared to 1 % for embryonal carcinoma (Table 5). There appears to be no association between TML, age and tumour size [55].

Holm et al. [56] compared clinical and histological data regarding the contralateral testicle in a population of men diagnosed with testicular germ cell cancer to find features associated with an increased risk of bilateral neoplasia. Ultrasound examination of the contralateral testicle was performed in 64 cases. They found that the frequency of TML seen on ultrasound was significantly higher among patients with CIS compared to those with a normal echo pattern. They concluded that the finding of contralateral TML on ultrasound in a patient with testicular germ cell cancer increases the risk of harbouring CIS in that testicle (odds ratio 28.6; CI 4.8–170.4). On the other hand, a normal ultrasound pattern does not exclude the risk of CIS and as evident from the present analysis, whether sonographic TML found in other subgroups of patients or in men from the general population also implies an increased risk of testicular CIS remains questionable. In the present review CIS/Intratubular Germ Cell Neoplasia accounted for 22 % of reported tumours with TML.

The main limitation of the present analysis is that the included studies had different objectives, which may have resulted in selection bias and misrepresentation of the relation between TML and testicular cancer. Furthermore, results in adults and boys may not be comparable.

Data in the literature seem to support the conclusion that TML is not an independent risk factor for testicular cancer. In male infertility, TML appears to be related to an increased risk possibly as part of a testicular dysgenesis syndrome. Many of the findings may simply be due to surveillance bias as some groups are further examined.

Further longitudinal clinical studies are required to evaluate the true relationship between TML and testicular cancer. Evaluation of other imaging modalities, for instance MRI, may help in defining subgroups of TML patients at special risk of malignant development.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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