Testicular microlithiasis and testicular tumor: a review of the literature

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Abstract

Introduction: There are numerous scientific publications on testicular microlithiasis (TML) detected during ultrasound (US) examination. We wished to update the data.

Methods: PubMed was used to identify original articles published between 1998 and May 2017 describing the association between TML and testicular tumor. Studies were only included if TML was diagnosed by US. Studies were then classified into subgroups according to the following criteria: asymptomatic, symptomatic, infertility, cryptorchidism, family or personal history of testicular cancer, and "no given reason for US". A Z-Test was used to identify differences within these subgroups. In addition, we identified prospective cohorts of TML patients. Numbers, duration of follow-up, and occurrence of the "testicular tumor" event were recorded for each of them.

Results: One hundred and seventy-five articles were identified, 40 of which were included. Our review has not showed a clear evidence that cryptorchidism associated with TML is a risk factor for testicular tumor. However, there seems to be a correlation between infertility associated with TML and a higher tumor risk. There were not enough studies to confirm a relationship between family or personal history associated with TML and the tumor risk. There was also a correlation with a higher tumor risk for symptomatic associated with TML and "no given reason for US" plus TML groups. However, these groups are assumed to contain bias and caution must be taken regarding conclusions. Regarding the prospective cohort studies, 16 testicular tumors appeared in the follow-up of patients with TML, 13 patients had risk factors.

Conclusion: In cases of TML incidental finding by US with the presence of risk factors (personal history of testicular cancer, testicular atrophy, infertility, cryptorchidism) a consultation with a specialist should be considered. In the absence of risk factors, the occurrence of testicular cancer in patients with TML is similar to the risk of the general population.

Keywords: Testicular microlithiasis, Testicular tumor, Testicular cancer, Germ cell tumor, Infertility, Ultrasound

Résumé

Introduction: Il existe de nombreux articles sur les microlithiases testiculaires découvertes au cours d’une échographie. Nous voulions mettre à jour les données.

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**Background**

Testicular microlithiasis (TML) corresponds to concretions of hydroxyapatite surrounded by fibrosis located in the seminiferous tubes [1]. They are due to the insufficient capacity of Sertoli cells to phagocyte the degenerate cells present in these tubes. They are commonly discovered by ultrasound (US). They are not visible on Magnetic Resonance Imaging (MRI). In 1987, Doherty et al. [2] described their appearance on US, which is characterized by a hyperechoic focus measuring between 1 and 3 mm in the testicular parenchyma without posterior shadow cone [3] with a number greater than or equal to 5 per testis. The discovery is mostly fortuitous because there is no clinical manifestation. Their historical radiological classification is described by Backus et al. [4]. Three grades are distinguished according to the number of TML described by parenchyma (grade 1: 5 to 10, grade 2: 10 to 20 and grade 3 with more than 20 TML). In recent years, US has substantially improved with the advent of higher resolutions enhancing TML detection. In 2015, the European Society of Urogenital Radiology (ESUR) proposed a summary of guidelines and reported another classification with 3 groups, based on the number of TML per field of vision [5]. These three groups were defined as follows, limited TML: less than 5 per field of view (Fig. 1), classic TML: greater than or equal to 5 per field of view (Fig. 2) and finally diffuse TML, labelled “snowstorm” (Fig. 3). There are many observational studies on TML and testicular cancer risk. The objective was to perform a review of the available literature to date.

**Methods**

**Search strategy**

The literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 4) [6]. PubMed was used to identify original articles describing the association between TML and testicular tumor, published between 1998 and May 2017. The following keywords were used in the search strategy: testicular microlithiasis, testicular tumor, testicular cancer, testicular neoplasm. Additional studies were included by analyzing the references cited in the review articles. Relevant studies were selected based on the title and abstract.

**Inclusion and exclusion criteria**

Studies were included if TML was diagnosed by US. Articles in the English language only were included. Case reports and experimental animal studies were excluded. The following characteristics were collected for each article: year of publication, number of patients included, number of TML carriers, and number of tumor carriers. The studies were classified into subgroups according to the following...
criteria: asymptomatic, symptomatic, infertility, cryptorchidism, family or personal history of testicular cancer, “no given reason for US”. Finally, prospective cohorts of TML patients were also identified. The number of patients, duration of follow-up and finally the occurrence of the “testicular tumor” event were then recorded for each of them.

Statistic analyses
We used a Z-Test to indicate differences in these groups. A $p$ value of 0.05 or less was considered statistically significant. The analysis was performed with Microsoft Excel 2016 (Microsoft, Seattle, WA, USA).

Results
One hundred and seventy-five articles were identified. Of these, 119 were excluded by examining the title and abstract (case reports, written in a language other than English). These articles were then read in their entirety. The studies of Yee et al. [7] and Negri et al. [8] included several risk conditions (infertility and cryptorchidism). The same population was found in two articles [9, 10]. A few articles were excluded for missing data.

Finally, a total of 40 articles were selected for our literature review and 135 articles were excluded (Fig. 4).

Two studies concerned asymptomatic cases, 12 concerned symptomatic cases, 11 concerned infertility, 6 concerned cryptorchidism, 2 concerned family or personal history of testicular cancer and 8 referred to “no given reason for US” (Tables 1, 2, 3, 4, 5, 6).

Asymptomatic cases
Two studies were identified regarding the asymptomatic population [9, 11], the TML prevalence was 2.4% [11] and 5.6% [9]. Only one testicular tumor was identified in the TML-free population, and no cases were observed in the population with TML. The pooled data revealed no difference in tumor prevalence within the two groups (NS).
Fig. 3 Diffuse testicular microlithiasis (TML). With agreement from authors [8]

Fig. 4 Flowchart and design of the study

References identified by PubMed research
n = 161

Articles excluded: n = 123
61 Case reports, 51 missing data, 10 other language than English, 1 same population studied in 2 articles.

Articles included: n = 38

Bibliographic search for additional articles
n = 14

Articles excluded: n = 12
9 Case reports, 3 missing data.

Articles included: n = 40
Symptomatic cases
We included 12 studies regarding the symptomatic population [5, 12–22], the TML prevalence was between 0.8% and 12.8%. The criteria for performing US were testicular pain, testicular edema or increased testicular volume. Seventy four cases of testicular tumors were identified in the TML group. Data analysis has shown that testicular tumor prevalence of symptomatic cases with TML was 11.2% and 1% in symptomatic cases TML-free (p < 0.0001).

Infertility
Eleven studies concerned infertility associated with TML [7, 8, 23–31]. In cases of infertility, the TML prevalence varied between 0.9% and 20.1%. Data analysis showed that testicular tumor prevalence was 22.6% in the infertility with TML group versus 1.7% in the infertility TML-free group (p < 0.0001). De Gouveia et al. [27] described a correlation between TML and intratubular germ cell neoplasia by performing a systematic bilateral testicular biopsy in all patients.

Cryptorchidism
We included 6 studies concerning cryptorchidism [32–37]. Two of these series reported a TML frequency of 100% [32, 33]. Three cases of testicular tumor only were found in the TML population. No testicular tumor was reported in the TML-free population.

Table 1 Asymptomatic cases

| Author          | Year | N = A | Presence of TML | TML Prevalence | No TML | Total |
|-----------------|------|-------|-----------------|----------------|--------|-------|
| Serter et al.   | 2006 | 2179  | 0               | 53             | 2.4%   | 0     | 2926  |
| Peterson et al. | 2001 | 1504  | 0               | 84             | 5.6%   | 1     | 1420  |
| Total           |      | 3683  | 0               | 137            | 4%     | 1     | 4346  |

A Asymptomatic cases, N Number of patients, TML Testicular microlithiasis

Table 2 Symptomatic population

| Author         | Year | N = S | Presence of TML | TML Prevalence | No TML | Total |
|----------------|------|-------|-----------------|----------------|--------|-------|
| Pedersen et al.| 2017 | 1538  | 8               | 197            | 12.8%  | 25    | 1358  |
| Richenberg et al. | 2015 | 2656  | 0               | 51             | 1.9%   | 0     | 2605  |
| Volokhina et al. | 2014 | 2266  | 1               | 87             | 3.8%   | 8     | 2179  |
| Deganello et al.| 2012 | 516   | 1               | 45             | 8.7%   | 0     | 474   |
| Kosan et al.    | 2007 | 197   | 3               | 21             | 10.6%  | 1     | 176   |
| Ahmad et al.    | 2007 | 4259  | 3               | 32             | 0.8%   | 80    | 4227  |
| Pourbagher et al. | 2005 | 5263  | 4               | 40             | 0.8%   | 0     | 5223  |
| Ringdahl et al. | 2004 | 160   | 4               | 12             | 8%     | 2     | 148   |
| Bach et al.     | 2003 | 528   | 12              | 48             | 9%     | 36    | 480   |
| Middleton et al.| 2002 | 1079  | 3               | 40             | 3.7%   | 3     | 884   |
| Derogee et al.  | 2001 | 1535  | 30              | 54             | 1.8%   | 31    | 1472  |
| Skyrme et al.   | 2000 | 2215  | 5               | 34             | 1.4%   | 24    | 2181  |
| Total           |      | 22,212| 74              | 661            | 5.3%   | 210   | 21,407|

S Symptomatic population, N Number of patients, TML Testicular microlithiasis
Family or personal history of testicular cancer
One study was found regarding TML associated with family or personal history of testicular tumor, the TML prevalence was 48%. Korde et al. [38] reported that TML was more common in the contralateral testis of men with a personal history of testicular tumor. Coffey et al. [39] was not selected because there was no information on whether patients had TML or not. Bach et al. [19] analyzed the association of TML and contralateral tumor in monorchid patients who underwent contralateral orchidectomy for a testicular tumor. Of the 156 patients examined, 23 had TML (15%). A contralateral testicular tumor was diagnosed in 5 patients with TML (21% versus 2% in the TML-free group).

Table 3 Infertility

| Author                  | Year | N = I | Presence of TML | TML prevalence | No TML |
|-------------------------|------|-------|------------------|----------------|--------|
|                         |      |       | Tumor         | Total         |        |
| La Vignera et al. [23]  | 2012 | 320   | 10             | 60            | 18.8%  |
|                         |      |       |                |               |        |
|                         |      |       |                |               | 5      |
|                         |      |       |                |               | 260    |
| Yee et al. [7]          | 2011 | 60    | 10             | 10            | 16.7%  |
|                         |      |       |                |               | 37     |
|                         |      |       |                |               | 50     |
| Negri et al. [8]        | 2008 | 415   | 12             | 17            | 4.1%   |
|                         |      |       |                |               | 2      |
|                         |      |       |                |               | 2029   |
| Sakamoto et al. [24]    | 2006 | 545   | 0              | 30            | 5.5%   |
|                         |      |       |                |               | 1      |
|                         |      |       |                |               | 515    |
| Qublan et al. [25]      | 2006 | 234   | 0              | 23            | 9.8%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 211    |
| Mazilli et al. [26]     | 2005 | 281   | 0              | 13            | 4.6%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 268    |
| De Gouveia et al. [27]  | 2004 | 263   | 0              | 6 CIS          | 20.1%  |
|                         |      |       |                |               | 1 CIS  |
|                         |      |       |                |               | 210    |
| Von Eckardstein et al. [28] | 2001 | 1399  | 22             | 32            | 2.3%   |
|                         |      |       |                |               | 61     |
|                         |      |       |                |               | 1367   |
| Thomas et al. [29]      | 2000 | 159   | 0              | 10            | 6.3%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 149    |
| Pierik et al. [30]      | 1999 | 1372  | 0              | 12            | 0.9%   |
|                         |      |       |                |               | 7      |
|                         |      |       |                |               | 1360   |
| Aizenstein et al. [31]  | 1998 | 180   | 0              | 5             | 2.8%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 175    |
| Total                   |      | 5228  | 60             | 265           | 8.3%   |
|                         |      |       |                |               | 114    |
|                         |      |       |                |               | 6594   |

Table 4 Cryptorchidism

| Author                  | Year | N = I | Presence of TML | TML prevalence | No TML |
|-------------------------|------|-------|------------------|----------------|--------|
|                         |      |       | Tumor         | Total         |        |
| Cooper et al. [32]      | 2014 | 9     | 3              | 9             | 100%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 0      |
| Chiang et al. [33]      | 2012 | 12    | 0              | 12            | 100%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 19     |
| Dutra et al. [34]       | 2011 | 127   | 0              | 5             | 3.9%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 122    |
| Goede et al. [35]       | 2010 | 501   | 0              | 14            | 2.8%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 487    |
| Konstantinos et al. [36]| 2006 | 36    | 0              | 2             | 5.5%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 34     |
| Patel et al. [37]       | 2005 | 112   | 0              | 8             | 7.1%   |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 104    |
| Total                   |      | 797   | 3              | 50            | 36.5%  |
|                         |      |       |                |               | 0      |
|                         |      |       |                |               | 766    |

C Cryptorchidism, N Number of patients, TML Testicular microlithiasis
We included 8 studies where there was no given reason for US. The prevalence of TML varied between 0.7% to 14.4%. Data analysis showed that the tumor prevalence for "no given reason for US" with TML was 9.4% and 1.3% TML-free (p < 0.0001).

Prospective cohorts of TML
Finally, 16 studies analyzed the occurrence of a "testicular tumor" event in follow-up of patients with TML (Table 7). Out of 1465 patients in total, with a median follow-up of 35.4 months, 16 developed a testicular tumor. Thirteen of the 16 patients had contributing factors. Three patients had a personal history of testicular tumor in the studies by Derogee et al. [21] and Otite et al. [46]. Von Eckardsein et al. [28] reported 2 cases of germ cell tumors involved patients with testicular atrophy. Of the 8 tumor cases reported by Negri et al. [8], 4 patients were infertile and the other 4 had cryptorchidism. Ahmad et al. [16] identified 2 cases of testicular tumor during the follow-up of 29 patients, however no further details were given by the authors. Decastro et al. [10] identified one case of testicular tumor in the follow-up of 63 patients, but no risk factor was reported for this patient.

Discussion
In recent years, TML have been the source of several epidemiological studies. Older studies reported low TML prevalence: 1.4% [22] and 0.68% [47]. Prevalence is higher in more recent studies: 12.8% [12] and 18.8% [23]. The advent of new generation probes with improved resolution explains this increase. However, there is a higher prevalence in specific populations at risk: patients with cryptorchidism, infertility, family or personal history, testicular tumor. This raises the question of an association between TML and the risk of developing a testicular tumor.

A history of cryptorchidism is a risk factor for testicular cancer [32, 48, 49]. Negri et al. [8] reported a correlation between germ cell tumor and cryptorchidism associated with TML (odds ratio 7.5, p = 0.04). In our review, there is no clear evidence showing that TML associated with cryptorchidism is a risk factor for testicular tumor. As only a few studies have shown this association, further research should be carried out to confirm it.

Infertility is a risk factor for testicular cancer [50, 51]. Some studies have assumed a correlation between testicular cancer and infertility associated with TML [38, 52, 53]. Our study seems to confirm a correlation between infertility with TML and a higher tumor risk.

Family or personal history is a risk factor for testicular cancer [54, 55]. In our review, only one study was identified, however no correlation was found between this factor associated with TML and a higher tumor risk. More studies are required to better assess any potential correlation.

In 2016, the literature review by Pedersen et al. [56] showed similar results. TML are not an independent risk factor for testicular cancer. However, when associated

| Author       | Year | N = | Presence of TML | TML prevalence | No TML |
|--------------|------|-----|------------------|----------------|--------|
| Heller et al. [40] | 2014 | 6002 | 53 | 456 | 7.6% | 84 | 5546 |
| Chen et al. [41] | 2010 | 513 | 6 | 74 | 14.4% | 2 | 481 |
| Sanli et al. [42] | 2008 | 4310 | 17 | 78 | 1.8% | 58 | 4232 |
| Miller et al. [43] | 2007 | 3279 | 5 | 67 | 2% | 27 | 3212 |
| Ou et al. [44] | 2007 | 1978 | 9 | 150 | 7.6% | 17 | 1828 |
| Lam et al. [45] | 2007 | 2957 | 8 | 137 | 4.6% | 1 | 137 |
| Otite et al. [46] | 2001 | 3026 | 16 | 54 | 1.8% | 66 | 2972 |
| Cast et al. [47] | 2000 | 4892 | 7 | 33 | 0.7% | 47 | 4786 |
| Total | 26,957 | 121 | 1284 | 5% | 302 | 23,194 |

| Author       | Year | N = | Presence of TML | TML prevalence | No TML |
|--------------|------|-----|------------------|----------------|--------|
| Korde et al. [38] | 2008 | 81 | 23 | 48% | 0 | 25 |

F Family history, N Number of patients, TML Testicular microlithiasis
with infertility, the risk of testicular tumor increases. Other risk factors identified are McCune-Albright Syndrome and Down Syndrome. Family history of testicular cancer is a risk condition for the presence of TML but not for the risk of testicular cancer.

There are confounding factors regarding the symptomatic group. Some inclusion criteria such as testicular pain, testicular edema or increased testicular volume may reflect the presence of a germ cell tumor and consequently influence the results. These confounding factors are also found in studies in which US is performed without any given indication. Patients included in these cases may have risk factors for testicular tumor.

In a 2015 meta-analysis, Wang et al. [57] concluded that TML have a significant association with testicular cancer. All patients with TML should therefore benefit from close US monitoring. The studies with the most significant forest plot results, Middleton et al. [20], Derogee et al. [21] and Cooper et al. [32], included infertile patients in their samples. The inclusion of studies without distinction of the study population is a confounding factor potentially invalidating the conclusion. Prospective cohort studies have shown that the occurrence of the testicular tumor event in patients with TML occurred more frequently in patients with testicular cancer risk factors (personal history, infertility, atrophy and cryptorchidism). Patel et al. [58] confirmed the same results in a large retrospective study with a follow-up of 14 years. Among the 442 patients studied, only 2 patients developed a testicular tumor, and both had an independent risk factor of testicular cancer. Furthermore, Pedersen et al. [56] showed that patients often forget to attend their US follow-up. A long term prospective study is difficult to organize.

In 2010, in another meta-analysis, Tan et al. [59] investigated the potential association between TML and intratubular germ cell neoplasia (ITGCN). The study reports a high risk of concomitant discovery of ITGCN and TML when a biopsy is performed on a contralateral testicle of a patient with a history of testicular cancer. ITGCN is where dysplastic cells proliferate inside the seminiferous tubules without crossing the basal membrane. In 2015, Richenberg et al. [5] showed that clustering of TML could cause an unstable area inside the testicle where ITGCN can grow. In patients with a history of orchiectomy for testicular tumors, when TML are present in the contralateral testis, ITGCN is present in 20% of cases. Fifty percent of ITGCN evolve into malignancy within 5 years [60]. A testicular biopsy is then recommended. When an ITGCN is found, therapeutic options can be either external radiotherapy or straight follow up with delayed treatment when a testicular tumor appears. Given the lack of benefit to overall survival, morbidity treatment must be considered, including hypogonadism.

The studies included had different objectives, which may have resulted in selection bias and therefore modify the relationship between TML and testicular cancer. This is the main limitation of the present paper.

We have not studied the histological types of tumor, which may constitute a second bias. Other longitudinal clinical studies should be carried out to determine the association between TML and testicular tumors.

Table 7 Follow-up of patients with TML

| Author             | Year | Number | Median follow-up | Tumor event |
|--------------------|------|--------|------------------|-------------|
| Richenberg et al. [5] | 2015 | 51     | 33               | 0           |
| Cooper et al. [32]  | 2014 | 83     | 50               | 0           |
| Bennet et al. [3]   | 2011 | 72     | 45               | 0           |
| Negri et al. [8]    | 2008 | 835    | 24               | 8           |
| DeCastro et al. [10]| 2008 | 63     | 64               | 1           |
| Ou et al. [44]      | 2007 | 48     | 29               | 0           |
| Lam et al. [45]     | 2007 | 30     | 19               | 0           |
| Kosan et al. [15]   | 2007 | 21     | 19               | 0           |
| Ahmad et al. [16]   | 2007 | 29     | 40               | 2           |
| Serter et al. [11]  | 2006 | 53     | 12               | 0           |
| Sakamoto et al. [24]| 2006 | 32     | 11               | 0           |
| Pourbagher et al. [17]| 2005 | 36     | 34               | 0           |
| Von Eckardstein et al. [28]| 2001 | 14 | 48               | 2           |
| Ottie et al. [46]   | 2001 | 38     | 36               | 2           |
| Derogee et al. [21] | 2001 | 31     | 62               | 1           |
| Skryme et al. [22]  | 2000 | 29     | 41               | 0           |

N = Number of patients, TML Testicular microlithiasis, Median follow-up in months; Tumor event: occurrence of the “testicular tumor” event.
Conclusion
In cases of TML incidental finding by US with the presence of risk factors (personal history of testicular cancer, testicular atrophy, infertility, cryptorchidism) a consultation with a specialist should be considered. In the absence of risk factors, the occurrence of testicular cancer in patients with TML is similar to the risk of the general population.

Abbreviations
CIS: Carcinoma In Situ; ITGCN: Intratubular Germ Cell Neoplasia; MRI: Magnetic Resonance Imaging; TML: Testicular microlithiasis; US: Ultrasound

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Authors' contributions
LL and FL analysed and interpreted the literature and wrote the manuscript. BM and FL analysed the literature. PE and JH critically revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Competing interests
The authors declare that they have no competing interests.

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