LITERATURE REVIEW

Testicular microlithiasis: Systematic review and Clinical guidelines

Micro-lithiases Testiculaires: revue systématique de la littérature et arbre décisionnel

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Summary
Introduction. — There are no clear recommendations on how patients with testicular microlithiasis should be followed up. The aim of our systematic review is to give clinical guidelines based on the evidence in the literature.

Methods. — A web search was conducted during February 2018 based on Pubmed data, Embase and Cochrane database. The eligibility of articles was defined using the PICO/S method, in concordance with the PRISMA recommendations.

Results. — Fifty three articles were selected for our final synthesis. Our review highlighted an association between testicular microlithiasis and the already known risk factors of testicular germ cell tumor. The presence of testicular microlithiasis in patients with such risk factors

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Introduction

Testicular microlithiasis is an ultrasonographic incidental finding of multiple, 1 to 3 mm-sized, non-shadowing hypoechoic foci within the parenchyma of the testicles [1]. Recently, the European Society of Urogenital Radiology proposed a classification of testicular microlithiasis based on their number per field of vision: limited (<5/field of view), classic (≥ 5/field of view) and diffuse [2]. Of note, testicular microlithiasis are commonly found bilaterally. Histologically, they are defined as testicular microcalcifications [3]. They consist of a core of hydroxyapatite surrounded by concentric layers of collagen fibers and glycogen. This deposit is found in the lumen of the seminiferous tubules.

Testicular microlithiasis were first identified on imaging in 1970 when two American researchers described them on a radiograph of the pelvis in a 4-year-old child [4]. Three years later, Weinberg et al. were the first to histologically characterize these microlithiasis as intra-tubular deposits in a normally appearing testicular parenchyma on histology [4]. Three years later, Schantz and Milsten reported a case of male infertility associated with testicular microcalcifications. Their first association with testicular cancer dates back to 1982 when Ikinger et al. examined 92 pieces of orchiectomy using radiographic techniques [5]. The incidence of these microcalcifications was significantly higher in tumor specimens compared to normal peers (74% vs. 16%, P < 0.05). The first description of testicular microcalcifications on ultrasound was in the late eighties where scrotal ultrasound - albeit of poor quality at that time- was increasingly used [1]. These intra-tubular deposits were described as "snowstorm" or "starry sky appearance". In 1988, Martin et al. described for the first time an association between testicular microcalcifications on ultrasound and a testicular tumor in an orchietomy specimen [6]. Few years later, the incidence of testicular microcalcifications increased significantly due to the improvement of the image quality of the ultrasound machines (more efficacious transducers of 12-15 MHz) and the awareness of medical professionals to describe and report these findings. In the late 90s, an increase in the prevalence of testicular microcalcifications in the subfertile population was also noted [7]. Thirty years later, despite technological progress and multitude of epidemiological studies, their clinical significance and their association with testicular germ cell tumors (TGCTs) remain controversial [8]. The purpose of our systematic review is to synthesize knowledge about testicular microcalcifications, to highlight their clinical significance and to propose a decision tree for daily medical practice.
Material and methods

Research Strategy

A web search was conducted during February 2018 based on Pubmed data, Embase and Cochrane database. The use of filters made it possible to limit the search to clinical trials written in either English or French. The keywords used (MesH language) were: "Testicular Microlithiasis" or "Testicular microcalcifications".

Selection of articles (PICOS/PRISMA method)

The eligibility of articles was defined using the PICOS method, in concordance with the PRISMA recommendations: Participants (P), Interventions (I), Comparators (C), Outcomes (O) and Study Design (S) [9]. An article was considered relevant for this review of the literature if it evaluated: a male population with testicular microlithiasis (P); observed with a good follow-up (I); compared the association with testicular cancer or infertility (C); in terms of incidence or prevalence (O). Only original and research articles have been included in this review (S). Two of the authors (AS, JMA) reviewed all the abstracts and selected the relevant articles. These were fully read by a third author (FA) before proceeding to final eligibility.

Extraction of data

Data extraction was performed by two authors (AS, JMA). The data collected were arranged by type of study, country of origin, time interval and the date of publication. The quality of studies, the number of patients, the presence of a comparison arm, the incidence or the prevalence of testicular cancer and infertility were also reported.

Evaluation of the quality of studies and level of proof

Randomized clinical trials were evaluated by their adherence to the CONSORT 2010 checklist [10]. Non-randomized trials (case-control studies or case series) were evaluated using the Newcastle-Ottawa scale. This scale gives a score with stars according to the quality of the selection (4 stars), the comparability between selected population and the control group (2 stars), and the finding of results in relation to the exposure (3 stars). The maximum score being 9 stars, a study with a score ≥ 7 was considered of good quality. The level of evidence provided by each study was reported following the recommendations of the Oxford Center for Evidence-Based Medicine.

Results

Three hundred thirty two articles were identified. Of these, 263 were excluded by examining the title or the abstract (articles not written in French or English, case reports, review articles, meta-analyses, editorial, and letters to the editor). Nineteen articles were then excluded when the full article was read (missing data, overlapping population). A total of 53 articles were selected for our final synthesis (Fig. 1).

Prevalence of testicular microlithiasis in asymptomatic cases (general population) vs. symptomatic cases

Two studies were identified regarding the asymptomatic population. In the first, Petersen et al. examined ultrasonographically 1504 healthy volunteers aged between 18 to 35 years old from the annual Army Reserve Officer Training Corps [11]. They found a 5.6% prevalence of testicular microlithiasis. At a 5 year follow-up interval, only one patient with testicular microlithiasis developed testicular tumor 64 months after the initial screening study [12]. In the second, healthy male volunteers were recruited from the training camp at Manisa, Turkey [13]. The testicular microlithiasis prevalence was 2.4%. No cases of testicular tumor were observed in the two groups after a short follow-up of 12 months. Of note, testicular microlithiasis was defined, in these two studies, as more than 5 high intensity signals on ultrasound. This definition could underestimate the true prevalence of testicular microlithiasis in the general population.

Fifteen studies were identified regarding symptomatic population. In symptomatic patients, the testicular microlithiasis prevalence varied between 0.6% and 18.1% [14–28]. This wide range is certainly related to the retrospective nature of the majority of studies, the definition of microlithiasis and the quality of the ultrasound probe. Scrotal ultrasound was performed for testicular pain, testicular edema, testicular atrophy, previous orchidopexy or increased testicular volume. In nine studies, scrotal ultrasounds were retrospectively reviewed but reasons for testicular ultrasound were not mentioned [29–33]. Ötite et al. followed-up their patients for a median of 36 months and demonstrated an increased relative risk of testicular tumors in the presence of testicular microlithiasis (RR 13.2, 95% CI:8.3–21.5). A recent pooled analysis of all these data showed an increased prevalence of testicular tumor in symptomatic patients with testicular microlithiasis compared to symptomatic patients without testicular microlithiasis (11.2% vs. 1%, P<0.0001), respectively [34].

Prevalence of testicular microlithiasis in subfertile population

Fourteen studies reported on testicular microlithiasis and subfertility [7,35–47]. The testicular microlithiasis prevalence varied between 0.9% and 20.1%. In the study with the highest prevalence, the authors examined the association between testicular microlithiasis on ultrasound and CIS on testicular biopsy in a group of 263 men referred for subfertility. No CIS or TGCT was identified in men with unilateral testicular microlithiasis. In contrast, 20% of men with bilateral testicular microlithiasis were diagnosed with CIS. Therefore, the authors concluded that bilateral testicular microlithiasis is indicative for CIS in subfertile men.
Prevalence of testicular microlithiasis in undescended testes

Eight studies regarding cryptorchidism and testicular microlithiasis were included in the final synthesis [48–55]. In a large study of 500 patients with undescended testes, Goede et al. found a testicular microlithiasis prevalence of 2.8% and Nicolas et al. reported a testicular microlithiasis prevalence of 9.52% in patients operated several years ago for cryptorchidism [49]. Higher prevalence were also reported by several researchers [50,51]. Renshaw examined a large series of orchiectomy specimen and found microcalcifications in two out of four undescended testes [56].

Prevalence of testicular microlithiasis in patients with familial or personal history of testicular cancer

Only three studies dealing with the association between testicular microlithiasis and familial or personal history of testicular cancer were included in the final synthesis. A Danish study compared clinical and histological data from the records of 79 men regarding the contralateral testicle in a population of men diagnosed with testicular germ cell cancer [57]. The testicular ultrasound pattern showed microlithiasis in 14% of cases. The frequency of microlithiasis seen on ultrasound was significantly higher among patients with CIS compared to those with a normal echo pattern. A slightly higher percentage was reported in a similar study [23]. The presence of a contralateral testicular tumor was significantly higher in patients with testicular microlithiasis compared to patients without testicular microlithiasis, respectively (21% vs. 2%) [23]. Korde et al. reported the ultrasound findings in men with familial testicular germ cell tumors and their unaffected relatives. Testicular microlithiasis were more frequent in the contralateral testicles of men with a history of TGCT (affected men) than in unaffected men (48% vs. 24%, $P=0.04$) [58]. In this study, testicular microlithiasis were more prevalent among family members than described previously in the general population, and were more common among familial testicular germ cell tumors cases vs. unaffected blood relatives. Similarly, higher prevalence of testicular microlithiasis were demonstrated in patients with testicular germ cell tumor (36.7% vs. 17.8%, $P=0.0001$) and their relatives (34.5% vs. 17.8%, $P<0.02$) compared to the general population [59].

Discussion

The superficial position of testes within the scrotum makes them ideally suited to ultrasound evaluation, which permits imaging with high frequency linear array transducers, producing images of high resolution. Advances in ultrasound technology in recent years have further increased...
ultrasound image quality and resulted in increased detection of testicular microlithiasis. These testicular microlithiasis consist histologically of concretions of calcifications surrounded by concentric layers of collagen fibers found in the lumen of the seminiferous tubules. The physiopathologic mechanism proposed initially by Vegni-talluri in the 80s was revisited in 2002 [60,61]. It is believed to be a failure of phagocytosis by Sertoli cells of the spermatogenic or epithelial cells of the seminiferous tubules. The result is the accumulation of debris and initiation of an immune reaction. This increases the permeability of the basal membrane and leads to the above mentioned deposits in the lumen and the interstitium. The clinical significance of these microlithiasis and their association with testicular germ cell tumors remains to be elucidated. Testicular microlithiasis may be detected in different clinical scenarios which may require an individualized approach for follow-up.
It is well known that intra-tubular germ cell neoplasia (ITGCN) is the precursor lesion for invasive testicular germ cell tumors of adolescents and young adults with evidence suggesting a 70% risk to develop an invasive tumor in the affected testis by 7 years [62]. In addition, ITGCN is commonly found in the parenchyma adjacent to the tumor on orchiectomy specimens (90% of cases) [63]. Two studies compared ultrasonographic findings of testicular microlithiasis and pathological correlates on systematic biopsies. They demonstrated an increased risk of ITGCN in patients with microlithiasis [39,57]. Tan et al. confirmed these findings in a meta-analysis performed in 2010 [64]. Epidemiological studies have demonstrated an increased prevalence of testicular microlithiasis in patients with risk factor to harbor/develop testicular tumors: cryptorchidism, testicular atrophy, subfertility, family or personal history of testicular cancer, testicular dysgenesis syndrome, CIS and symptomatic. Testicular microlithiasis per se is not an independent risk factor for testicular cancer according to these studies [8,65—67]. However, the association of testicular microlithiasis with cryptorchidism, testicular atrophy, subfertility, family or personal history of testicular cancer, testicular dysgenesis syndrome increases significantly the risk to harbor a CIS or to develop a testicular germ cell tumor [65]. The prevalence of CIS in an undescended testis is 2 to 4% [68]. The presence of testicular microlithiasis in an undescended testis increases the risk to harbor a CIS up to 39% (7-39%) [69]. The risk to harbor a CIS is significantly higher in the subfertile population with testicular microlithiasis compared to their peers without testicular microlithiasis (20% vs. 1.1%), the risk in the general population being less than 1% [8]. Similarly, the presence of microlithiasis in the contralateral testis in a patient with a past medical history of testicular cancer increases the risk of harboring a CIS from 5% up to 78% (22%-78%) [39]. Additionally, testicular microlithiasis appear to cluster in certain families [58]. These findings suggest both a familial predisposition to testicular microlithiasis and an association between testicular microlithiasis and familial testicular germ cell tumors. Thus the presence of testicular microlithiasis in a first degree relative could be considered as a predisposition to testicular cancer. Symptomatic patients with testicular microlithiasis could have a higher risk to develop testicular germ cell tumors. However, patients included in these reports had an increased testicular volume, testicular edema and pain that may reflect the presence of a germ cell tumor and consequently influence the results.

The most plausible theory linking all these features is summarized in Fig. 2. Fetal gonad is composed of Sertoli cells, Leydig cells and fetal germ cells. Intrauterine growth disorders, genetic defects and polymorphism as well as lifestyle factors and environmental exposure will disrupt fetal gonad leading to testicular dysgenesis. Disturbed Sertoli cell function can lead to impaired germ cell differentiation and phagocytosis. Impaired germ cell differentiation results in an alteration of spermatogenesis and the development of ITGCN and testicular tumors. Impaired phagocytosis leads to the development of testicular microlithiasis. Decreased Leydig cell function will alter the production of INSL3 and causes cryptorchidism. It will result also in an androgen deficiency causing hypospadias, short ano-genital distance and impaired spermatogenesis. Based on the severity of the insult, testicular dysgenesis syndrome is classified as mild (impaired spermatogenesis), moderate (impaired

![Figure 4](https://example.com/figure4.png)

**Figure 4.** A decision tree for patients having testicular cancer and contralateral testicular microlithiasis.
spermatogenesis and cryptorchidism), and severe (impaired spermatogenesis, hypospadias and cryptorchidism). The risk to develop a testicular cancer increases with the number of features and the presence of testicular microlithiasis [61,70,71].

Management of patients with testicular microlithiasis varies significantly among practitioners. According to EAU guidelines, patients with testicular microlithiasis and no testicular germ cell tumor risk factor should be encouraged to perform self-examination [72]. Compliance is a crucial point. Testicular biopsy, follow-up scrotal ultrasound and routine use of biochemical markers are not justified. Biochemical markers were negative in all patients with testicular microlithiasis in the study of Peterson et al. [11]. In symptomatic patients with testicular microlithiasis and a suspicious lesion, surgical exploration with testicular biopsy or orchietomy should be considered [72]. In contrast, there is no consensus on how to manage patients with testicular microlithiasis and risk factors to develop testicular germ cell tumor. At present, testicular biopsy remains the gold standard to detect ITGCN and novel immuno-cytological markers in the semen cannot be recommended due to their high false negative rates [73]. Some authors advocate observation with testicular self-examination to early detect testicular tumor while others preconize testicular biopsy to rule out ITGCN [8,65,73–75]. The latter approach allows treating early these patients with radiotherapy therefore avoiding orchietomy and the risk of subsequent chemotherapy. However, such an approach could alter definitively spermatogenesis. Of note, this approach has no impact on overall survival. An individualized approach based on the age of the patient, the presence of concurrent features of testicular dysgenesis syndrome, the fertility of the couple, the desire of paternity and the ultrasound pattern (bilateral and clustered vs. unilateral and limited) is recommended (Fig. 3). When biopsy is indicated for fertility purposes in patients with testicular microlithiasis, a search for ITGCN should be systematically performed. Biopsy is also encouraged in young patients with testicular microlithiasis and several features of the testicular dysgenesis syndrome. Observation versus testicular biopsy is also debatable in patients previously treated by orchietomy for a testicular cancer and harboring microlithiasis in the contralateral testis (Fig. 4). The risk in such a patient to have an ITGCN is 20%. Observation is preferred when fertility is an issue in order to allow fathering. In addition, the risk to develop metachronous tumor is reduced when chemotherapy is administered in the adjuvant setting or in metastatic cases [76]. The advantage of immediate biopsy is to detect ITGCN, a condition highly curable with radiotherapy alone (98% success rate) [77]. Therefore, orchietomy and the need to testosterone replacement therapy can be avoided in these patients.

Conclusion
Incidental finding of testicular microlithiasis in the absence of risk factor (familial or personal history of testicular cancer, testicular atrophy, infertility, hypospadias, and cryptorchidism) should trigger no additional interest. If the patient is at risk to develop TGCT, two options (testicular self-examination with an advice to seek early medical attention if necessary vs. immediate testicular biopsy to rule out ITGCN/to treat accordingly) are debatable. Several variables such as the age of the patient, the desire of paternity, the association of several risk factors, the presence of a testicular dysgenesis syndrome and if the patient received previous chemotherapy after a contralateral orchietomy could help in the decision making.

Disclosure of interest
The authors declare that they have no competing interest.

References


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