REVIEW PAPER

UROLOGICAL ONCOLOGY

Testicular microlithiasis: what urologists should know. A review of the current literature

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Introduction Testicular microlithiasis is a finding incidental to the ultrasound examination of the scrotum. This article presents some new data regarding the etiopathology of testicular microliths. As there is a growing body of literature available, which associates testicular microlithiasis with a testicular germ cell tumor or male infertility, our review focuses on these relations (based on a new meta-analysis and retrospective follow-up programs). The purpose of this review is to summarize the knowledge about testicular microlithiasis and discuss the latest recommendations.

Material and methods A comprehensive literature review was performed using Science Direct and Scopus with MeSH terms and keywords 'testicular microlithiasis', testicular tumor', male infertility'.

Results The clinical consequences of testicular microlithiasis depend on the co-occurrence of specific risk factors. The presence of testicular microlithiasis alone in the absence of risk factors is not an indication for further investigation.

Conclusions A link between testicular microlithiasis and testicular cancer as well as male infertility has been analyzed. Follow-up is only recommended where risk factors of testicular cancer other than testicular microlithiasis are present.

Key Words: testicular cancer ‹› male infertility ‹› testicular microlithiasis

INTRODUCTION

Testicular microlithiasis (TM) is a relatively rare condition detected incidentally during the ultrasound examination of the scrotum. Intratesticular calcifications in cadavers were reported by Oiye et al. in 1928, whereas the first sonographic identification of TM was described by Doherty in 1987 as "innumerable tiny bright echoes diffusely and uniformly scattered throughout in the substance of testes" [1]. The prevalence of TM varied in the past data, depending on the study group. In symptomatic adults, it oscillated between 0.6% and 9.0% [1, 2] and from 2.4% to 5.6% in adults without symptoms [1]. In a group with genetic disorders, the prevalence of TM has been reported much more frequently compared to the general population. The frequency of TM is as high as 17.5% in men with Klinefelter syndrome [3] and 36% in men with Down syndrome [4].

Ultrasound appearance and definition of testicular microlithiasis

The typical ultrasound (US) appearance of TM is characterized by multiple small, same-sized echogenic non-shadowing foci observed throughout the testicles [1] (Figures 1, 2). TM can be either unilateral or bilateral. The number of calcifications counted on any single image may vary considerably, ranging from five to more than sixty [5]. When evaluating the testes, US should be performed, as a minimum, with a 15 MHz high-frequency transducer. The detection of TM has low inter-observer variability by ultrasound ($\kappa = 0.86$) [6]. The microcalcifications are not

visible on MRI [7]. The microliths do not bring about pain or symptoms and are impalpable. The Scrotal Imaging Subcommittee of the European Society of Urogenital Radiology (ESRU) published a consensus report on TM in 2015, proposing 2 definitions of TM [7]: five or more microliths per field of view, or five or more microliths in the whole testis. In TM's ultrasound appearance, particular attention should be paid to clustering. A cluster (a few microliths per field in a cluster) may be more worrying than TM scattered throughout the testis. It may indicate a dysgenic area in the testis, in which carcinoma in situ (CIS) may develop [7].

The microscopic appearance and cause of testicular microlithiasis

Based on the Renshew et al. study, two types of testicular microliths have been described: hematoxylin bodies and lamellated calcifications [8]. Under the optical and electron microscopes, microliths are found to consist of two zones, namely a central calcified zone and multi-layered envelope-stratified collagen fibres, both of which are covered with a thin fibrous capsule of spermatogenic epithelium. Microliths may occupy 30 to 40% of the seminiferous tubules and range in size from 50 to 400 μm. They do not typically affect Leydig cells and the majority of the uninvolved seminiferous tubules often have abnormal spermatogonia and reduced luminal diameters.

A definitive explanation of the cause of TM is not known. Shanmugasundaram et al. reported a number of theories proposed in an attempt to explain the origin of TM. Among them were hypotheses variously attributing TM to a range of causes, including liquefaction of protoplasmic dendrites of a spermatocyte, ectopic oocytes in dysgenetic testes, displaced spermatogonia, undifferentiated or desquamated calcified cells, deposition of glycoprotein around the nidus of cell material sloughed into the tubular lumen and abnormal Sertoli cells [9].

Microliths can be seen in the testis as well as in extratesticular structures such as the lungs and the central nervous system, with genetic factors also thought to play a role in their development. Mutation in the SLC34A2 gene (4p15) has been found to occur in patients with pulmonary alveolar microliths. Patients with this mutation are found to have TM as well [10].

Health status, lifestyle characteristics and ethnicity of men with testicular microlithiasis

In general, there were limited differences in health and lifestyle among men with TM and those who did not suffer from the disease. New data suggests some

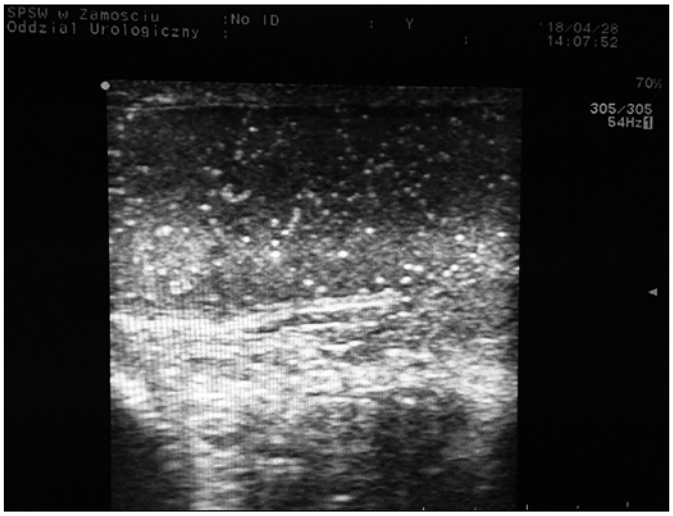

Figure 1. *Ultrasonographic image of testicular microlithiasis (34-year-old man seen in emergency department for testicular pain).*

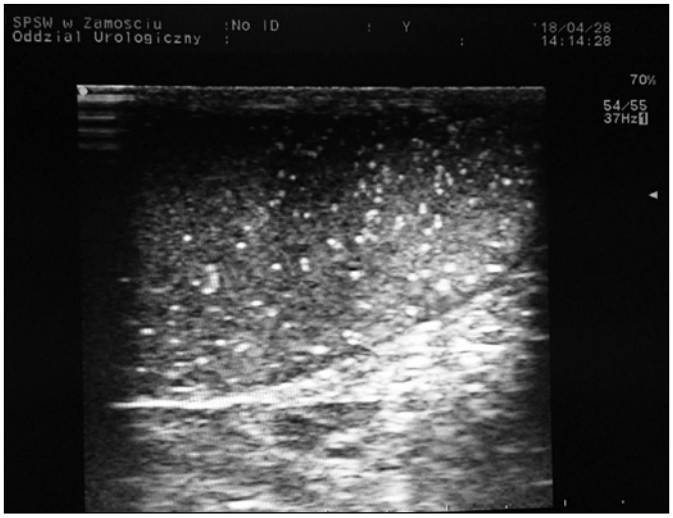

Figure 2. *Ultrasonographic image of testicular microlithiasis (28-year-old infertile man).*

differences. Men with TM reported significantly less physical exercise than men without microliths (38.6% vs. 48.2%, p = 0.011) [11]. The authors also suggest some discrepancies in food intake. Men with TM consumed more crisps and popcorn than men without TM (35.6% vs. 22.0%, p <0.001) [11]. Crisps and popcorn contain acrylamide, which is known for its potential health hazards, but according to the American Cancer Society, it is not clear whether acrylamide consumption increases the risk of developing cancer [12]. Mothers smoking during pregnancy have been associated with testicular cancer in the male offspring [13]. Pederson et al. found a negligibly more widespread tendency for men affected with TM to have

been exposed to maternal smoking than men without it [11]. Another potential analysed factor of TM is men's height (known risk factor of testicular cancer). Pederson et al. reported no differences in height between men with and without TM [11]. There exists an interesting piece of research concerning TM and its relation to ethnicity and socioeconomic status. Based on the Pederson et al. study, black men had increased prevalence of TM (odds ratio [OR] = 2.17, 95% confidence interval [CI] = 1.17–2.75) compared with white men. Whereas men from the most deprived socioeconomic groups had higher prevalence of TM (OR = 1.17, 95% CI = 0.71–1.93) than men in the most affluent groups.

Association of testicular microlithiasis with testicular cancer

In recent years, numerous studies have reported a relationship between TM and the risk of testicular cancer but provided ambiguous results. Currently, the most reliable data is reported by Wang et al. The meta-analyses were based on data from 12 cohort studies and 2 case-control studies (involving 35578 participants). The authors found that compared with non-TM individuals or the general population, TM men might have more than a 12-fold higher incidence of testicular cancer (RR = 12.70, 95% CI = 8.18–19.71, p <0.001) [14]. On the other hand, data published as part of a follow-up program showed controversial results. DeCastro et al. published a 5-year follow-up study of 63 asymptomatic men with TM, of whom only one participant (1.6%) developed testicular cancer after 64 months of observation [15].

Patel et al. investigated a follow-up program in a single centre for a period of 14 years with 442 men with TM among more than 20,000 participants. In the follow-up period only 2 men (0.5%) developed testicular cancer [16]. Afterwards, Pederson et al. concluded – based on the two-year follow-up program – that none of the investigated men had developed testicular cancer within the minimum time frame of 50 months [17].

In 2015, Sharmeen et al. investigated the relationship between TM and the histologic subtypes of germ cell tumor to determine whether microliths correlate with tumor stage at diagnosis. The authors suggest that TM may be associated positively with seminomas (p = 0.03) and negatively with embryonal cell carcinomas (p = 0.007). What is more, they reported a link between a higher TM count and a lower initial stage at diagnosis, which suggests that TM may be associated with less aggressive tumors (p = 0.02). No association was found between TM and age, tumor size and the presence of lymphovascular / rete testis invasion (p >0.12, respectively) [18]. The foregoing studies had not found elevated tumor markers in those with incidental TM, hence monitoring serum tumor markers in follow-up is not appropriate [14].

Association of testicular microlithiasis with male infertility

TM association with male infertility is still debated. Previous studies showed incidence of TM ranging from to 20% in a subfertile population [19, 20]. Evidence showed that TM was a testicular dysgenesis syndrome, which was postulated to underpin abnormalities related to male reproductive disorders [21]. Reduction in sperm count and sperm motility in a man with microliths is attributable to TM-related obstruction of seminiferous tubules present in 30 to 60% of patients with TM [22]. The obstruction of seminiferous tubules may cause secondary inflammation, increased intraseminiferous pressure and change the blood supply of testicles. Inflammation and calcification in the seminiferous tubules area bring about deterioration in sperm quality and cause subinfertility [22]. Thomas et al. reported a relationship between the degree of calcification and poor sperm function. The study showed a statistical difference between the number of investigations in those patients with minimal degrees of calcification and those with marked TM [(analysed parameters: sperm migration test, namely sperm migration and sperm motility (p <0.005)] [19]. Xu et al. investigated the association between TM and semen parameters in Chinese adult men with infertility intention. TM is associated with worse semen parameters in adult men with infertility. The authors showed significant changes between TM group versus non-TM group in semen volume (p <0.001), sperm concentration (p<0.001) and total motility (p <0.001) [22]. TM was reported to be more prevalent in patients with spermatogenic defects such as severe oligospermia and reduced testicular volume [22].

Subfertility is reported to be a risk factor for a testicular tumor. Bilateral testicular microlithiasis is indicative of CIS (carcinoma in situ) in subfertile men. De Gouveia Brazao et al. reported that 20% of patients with bilateral testicular microlithiasis were diagnosed with CIS. Therefore, the prevalence of CIS in subfertile men with bilateral testicular microlithiasis is significantly higher than in patients without testicular microlithiasis (0.5%) and with unilateral testicular microlithiasis (0%) (p <0.0001) [23]. Thus, men with CIS are at particular risk for invasive testicular germ cell tumor (TGCT). An assessment of testicular microlithiasis is a valuable tool for the

early diagnosis of this disease. Approximately 50% of CIS progresses to germ cell tumor within 5 years [24]. Nearly 20% of patients with a previous testicular germ cell tumor have TM in their contralateral testes. Those patients have an increased risk ratio of 8.9 for concurrent CIS compared with patients who do not have TM [25].

Currently recommended follow-up based on ESUR and EAU Guidelines

Based on European data on the incidence of testicular cancer by age in the male population, follow-up for patients with TM is recommended up to the age of 55 years [25]. Management depends on the existing risk factors which are described by ESUR scrotal imaging subcommittee and EAU (Table 1). The presence of TM alone (without any coexistence risk factors) is not an indication for a regular scrotal ultrasound, it does not require biopsy or further ultrasound screening [26, 27]. When TM is detected in conjunction with any risk factors (regardless of whether it is unilateral or bilateral) and provided that there is no focal mass within either testis, annual follow-up with ultrasound and monthly self-examination should be advised [7]. Recommendation for testicular biopsy in TM is still a hotly debated topic. Patients with small or atrophic testes with microliths are at increased risk of CIS [30]. At orchidectomy in patients with germ cell tumor, if there is TM in the contralateral testis, or if the contralateral testis is atrophic, biopsy of contralateral testis may be recommended in order to look for CIS [7].

Table 1. *Risk factors that need follow-up of patients with TM*

Previous GCT
History of maldescent
History of orchidopexy
Atrophy <12 ml volume (the normal mean testicular volume is estimated at 18 ml) [28]
History of GCT in 1st degree relative (standardised incidence ratios for familial risk are 3.8-fold when a father and 7.6-fold when a brother have testicular cancer) [29]

TM – testicular microlithiasis; GCT – germ cell tumor

CONCLUSIONS

Testicular microlithiasis is a finding incidental to the ultrasound examination of the scrotum. A link between TM and testicular cancer as well as male infertility has been reported. The clinical consequences of TM depend on the co-occurrence of specific risk factors. The presence of TM alone in the absence of risk factors is not an indication for further investigation. Follow-up is only recommended where risk factors of testicular cancer other than TM are present.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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