



Testicular Microlithiasis: What Should You Recommend?

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OBJECTIVE. Ultrasound surveillance of patients with testicular microlithiasis (TM) has been recommended because of the reported association between TM and testicular cancer (TC). The purpose of this review is to summarize what is known about TM and discuss recent recommendations.

CONCLUSION. The most recent recommendations do not support the use of routine ultrasound surveillance for patients with TM who are at low risk for TC. A template for possible use in reporting TM is also provided.

The identification of intratesticular calcifications in autopsy specimens was reported by Oiye et al. [1] in 1928 and by Blumenfaat [2] in 1929. In 1961, Azzopardi et al. [3] noted the presence of such calcifications in the dilated seminiferous tubules of patients with choriocarcinoma. Priebe and Garret [4] reported the first imaging manifestation of this entity in 1970, noting bilateral diffuse testicular calcifications on the radiograph of the pelvis of a 4-year-old boy who was undergoing evaluation for thigh tenderness. In 1973, Weinberg et al. [5] also reported radiographic visualization of bilateral testicular microlithiasis (TM) in a boy with an undescended testicle. The first sonographic description of TM is attributed to Doherty et al. [6], who, in 1987, reported observing “innumerable tiny bright echoes diffusely and uniformly scattered throughout in the substance of testes” [7]. Since then, innumerable publications have discussed the association between sonographically detected TM and TC [8–33].

Ultrasound Appearance

On ultrasound, the classic appearance of TM (Fig. 1) involves the observation of multiple small echogenic nonshadowing foci of uniform size throughout the testicles. The maximum number of calcifications counted on any one image may vary considerably, ranging from five to more than 60 calcifications in one report [9]. Classic TM is arbitrarily defined by the presence of five or more

microliths on at least one ultrasound image, whereas limited TM is defined by the presence of fewer than five microliths on all images [10]; however, a large number of varying definitions have been used in the extensive sonographic literature on this topic [21].

What Is It Under the Microscope?

Two types of testicular calcifications have been described: hematoxylin bodies and lamellated calcifications. Microliths may occupy as many as one-third of the seminiferous tubules and may range in size from 50 to 400 μm . They do not typically affect Leydig cells. For an excellent detailed review on this topic, please see the report by Shanmugasundaram et al. [7].

Cause of Testicular Microlithiasis

Shanmugasundaram et al. [7] also reported 10 widely varying proposed theories attempting to explain the origin of TM. One such theory proposed genetic alterations as a cause, because microliths may be seen in extratesticular sites like the CNS and the lungs. For example, TM has been detected in male patients with pulmonary alveolar microliths. To our knowledge, a definitive explanation for the cause of TM is not known at this time.

How Common Is Testicular Microlithiasis?

A wide range of data on the frequency of sonographically detectable TM has been reported. Some of the variation in such data is attrib-

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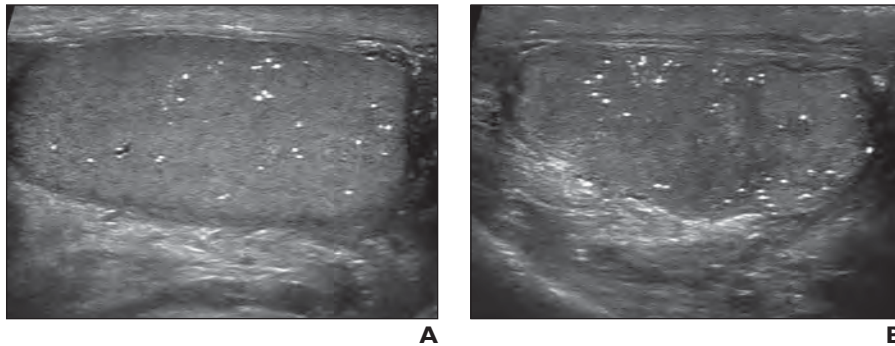


Fig. 1—54-year-old man seen in emergency department for testicular pain of 6 months' duration. **A** and **B**, Ultrasound images show classic testicular microlithiasis in right (**A**) and left (**B**) testicles. More than 5 microliths per image are noted within each testicle. Heterogeneity in upper portion of left testicle (**B**) was chronic (i.e., stable for decades) and was attributed to sequelae of prior infection or segmental infarct.

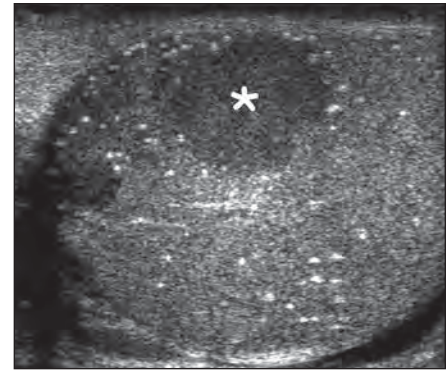


Fig. 2—Classic testicular microlithiasis and accompanying lobulated seminoma (*asterisk*). With very few exceptions, solid masses in testicle should be presumed to be malignant until proven otherwise.

utable to the differing definitions of TM [21] and the different populations studied, with estimates of the frequency of TM in adults ranging from 0.6% to 9% in adults with symptoms [20, 28] and from 2.4% to 5.6% in adults without symptoms [20]. In the pediatric population, Goede et al. [20] noted that the prevalence of classic TM was 2.4% in male patients without symptoms who were 0–19 years of age, with an increase in prevalence noted with increasing patient age. In one of the larger investigations performed to date, which was less prone to selection bias than other studies and which is often quoted in the literature, Peterson et al. [27] reported that, among 1504 asymptomatic healthy men (mean age, 22.4 years), the frequency of TM was 5.6%; it is important to note, however, that this study defined TM as the presence of five or more foci in one testicle, not in a single image.

Association of Testicular Microlithiasis With Entities Other Than Cancer

At least 20 conditions have been reported in association with TM [7, 17, 21]. Other than the association with TC, which is relevant to the discussion in the present study, the more frequently reported associations include infertility, testicular atrophy, cryptorchid testicle, pulmonary alveolar microlithiasis, hypogonadism, Klinefelter syndrome, Down syndrome, fragile X syndrome, testicular or appendiceal torsion, postorchiopey testis, male hermaphroditism, neurofibromatosis, AIDS, and other conditions. The truly interesting question is whether these documented associations are coincidental or causal.

Other Risk Factors for Testicular Cancer

Some of the reported risk factors for testicular cancer are listed in Table 1. The more commonly mentioned risk factors are listed near the top of Table 1, whereas more controversial or less commonly mentioned risk factors are shown near the bottom of Table 1.

Early Ultrasound Studies Describing the Association of Testicular Microlithiasis With Testicular Cancer

An extensive literature documents the association of TM with TC, providing much discussion of the topic [7–10, 15, 17, 21, 27–29]. For example, to our knowledge, one of the first studies that explored this association was published in 1994 by Backus et al. [9], who evaluated 42 patients and reported that primary testicular neoplasm occurred in association with TM in 40% of the patients. In 2001, a study of 48 patients with TM documented a 27% association with testicular cancer [8]. Another study published in 2001 reported findings for 63 patients with TM, documenting an association between TM and TC in 46% of those patients [17]. In 2000, Cast et al. [15] calculated a 21.6-fold relative risk of concurrent tumor in patients with TM. Multiple case reports with titles like, “Testicular carcinoma in a patient with previously demonstrated testicular microlithiasis” [32] heightened the interest in this association. Apparently isolated TM has also been reported in association with abdominal and thoracic germ cell tumors (GCTs) [10, 15, 34, 35].

On the basis of these and similar investigations, an association of TC with TM was

strongly suggested. For example, in 2001, Derogee et al. [17] stated that “TM should be regarded as a premalignant condition,” and in 1994, Backus et al. [9] indicated that “TM cannot continue to be regarded as a benign, incidental finding.”

The recommendations that emerged from many of these studies included very strongly worded implications regarding costly follow-up examinations, including biopsy, CT, analysis of serum tumor markers, and ultrasound and physical examinations, with morbidity potentially associated with the use of such follow-up methods. Among such recommendations are those from Furness et al. [18], who, in 1998, proposed the use of “yearly testicular ultrasound, physical examination, and judicious tumor marker determinations.” Peterson et al. [27] and Sheynkin and Goldstein [30] describe recommendations for routine analysis for testicular tumor markers, including α -fetoprotein, lactate dehydrogenase, and human chorionic gonadotropin, in addition to annual scrotal ultrasound and physical examinations. In 1996, Miller et al. [24] suggested the use of CT of the chest and abdomen, followed by periodic scrotal ultrasound examination, whereas Parra et al. [25] said, “We propose that in the presence of microlithiasis, testicular biopsy should be performed routinely.” Derogee et al. [17] suggested that “Urologists should consider testis biopsy in patients with TM.” In 2000, Cast et al. [15] stated, “Surveillance of patients with testicular microlithiasis for tumor appears mandatory. We recommend annual sonographic follow-up and patient education about self-examination.” One year lat-

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TABLE I: Risk Factors for Testicular Cancer (TC)

Risk Factor	Increased Risk	Comment	Reference(s)
Previous TC	12- to 18-fold	2% of men with TC in one testicle will have TC develop in the other testicle 3–4% of men with TC in one testicle will have TC develop in the other testicle	[28], [29] [31] [13] [14]
History of cryptorchidism or testicular maldescent			[13], [14], [29]
	3- to 4-fold		[31]
	3- to 17-fold		[12]
Family history			[13, 14]
	8- to 9-fold	Brother	[31, 36]
	4- to 5-fold	Father	[31, 36]
	37-fold; 67.5-fold	Dizygotic twin brothers; monozygotic twin brothers	[36]
Infertility			[28]
Subfertility			[12]
	59% higher		[31]
Intratubular germ cell neoplasia or carcinoma in situ			[14, 28]
	50% risk of TC in contralateral testicle within 5 years		[12]
Presence of an atrophic testis			[12, 28, 29]
Younger age		84% of patients with TC were 15–49 years old, peak occurrence of TC was in patients 30–34 years old More than half of cases occurred in patients 20–45 years old Approximately one-half of cases occurred in patients 20–34 years old	[31] [13] [14]
HIV/AIDS			[13, 14]
	35–79% higher		[31]
Gonadal dysgenesis			[12, 28, 31]
White race			[13, 31]
	4 times greater in white patients than in black patients		[12]
	4–5 times greater in white patients than in black patients		[14]
Hypospadias	88–141% higher		[31]
Inguinal hernia	37–63% higher		[31]
Trisomy 21			[31]
Height			[14]
	11–13% higher per 5-cm increment in height		[31]
Exogenous estrogen administration			[28]
Polyorchidism			[31]
Muscle-building supplements	Up to 65% higher		[41]
Testicular dysgenesis syndrome	May not confer an increased risk of TC		[36]

er, Bennett et al. [10] also recommended annual follow-up with ultrasound examination. Ganem [19] indicated that “most authors recommend intervals of six to twelve months for ultrasound imaging.”

Evolving Thinking

It is well known in science that correlation does not prove causation. Most of the publications that discussed an association between TM and TC were retrospective case series or case reports only. In their large study emphasizing an association between TM and GCTs, Backus et al. [9] were careful to acknowledge a selection bias in their study and indicated that “longitudinal follow-up of patients with TM is necessary to further define the true frequency of tumor in patients with TM” [9]. Having risk factors for testicular cancer (e.g., previous cancer, cryptorchidism, and other risk factors) increases the likelihood that these patients will undergo a testicular ultrasound examination, whereas low-risk individuals are much less likely to undergo sonography, thus potentially skewing the results. To quote Bach et al. [8] in what is, to our knowledge, one of the earliest reports (published in 2001) to cast doubt on the association, “testicular microlithiasis does not appear to add independent diagnostic information for testicular cancer.”

To our knowledge, one of the first widely read studies that questioned the association of TM with TC was published in 2001 by Bennett et al. [10]. They noted that zero of 72 patients with TM who underwent repeat ultrasound examinations (mean follow-up duration, 45 months) developed a testicular tumor, and zero of 19 patients with TM who underwent a clinical follow-up examination only (mean follow-up duration, 48 months) developed testicular cancer. At the time, they recommended that patients undergo annual ultrasound follow-up examinations, but they estimated that 266 sonograms would have to be obtained annually before the first tumor would be detected. They also postulated that, given the high cure rate for all GCTs of the testis, it is doubtful that ultrasound screening would have much effect on survival, saying that “the risk of developing a testicular tumor for patients with isolated TM at original presentation is so low it is doubtful that regular US follow-up will substantially affect patient outcome.”

Perhaps the most widely quoted study that cast doubt on the strength of the association between TM and TC was the seminal investi-

gation by Peterson et al. [27], which was published in 2001. In this previously mentioned study of 1504 male cadets (mean age, 22.4 years) who attended the annual Reserve Officers’ Training Corps training at Fort Lewis in Washington, TM was detected in 5.6% of the cadets. A few points from their study weighed against the existence of a causal relationship between TM and TC. First, the frequency of TC was 1000-fold lower than the frequency of TM. Second, a higher frequency of TM was noted among black men than among men of other races, although the frequency of TC among black men is generally more than fivefold lower than that noted among men of other races. Third, a negative geographic correlation was reported; TM was most commonly noted among recruits from the southeastern part of the United States, the area of the country that has the lowest prevalence of TC. Fourth, TM was found to be bilateral in two-thirds of patients, whereas TC would be expected to have a local field effect. Peterson et al. [27] therefore concluded that:

Current recommendations to perform aggressive screening in patients with testicular microlithiasis appear to be based largely on anecdotal associations. ... The economic burden of evaluating and following men with testicular microlithiasis ... is estimated to be greater than \$18 billion. Furthermore, testicular cancer can be diagnosed easily with minimal cost by testicular self-examination or clinical examination with a current cure rate approaching 100%.

Other researchers soon began to echo a similar sentiment, with Rashid et al. [28] commenting that “there appears to be no definitive association with TM and cancer.”

Seven years after publication of their initial report, two of the authors of the study by Peterson joined another investigator in publishing a 5-year follow-up study of 84 patients who were found to have TM in an initial investigation [16]. Of the 63 patients who underwent follow-up examinations, one patient had a mixed GCT approximately 5 years after diagnosis; therefore, on the basis of findings for this solitary subject in the cohort, the odds ratio (OR) for developing TC was 317 compared with the general population. Despite this increased OR, the authors of this study, DeCastro et al. [16], noted that 98.4% of men did not develop TC within 5 years, and they concluded that, “an intensive screening program

for men with testicular microlithiasis is not cost-effective and would do little to improve outcomes associated with testicular cancer.” They performed several cost-effectiveness calculations and noted that surveillance for TM would cost \$7.8 billion per year, compared with the total amount spent annually to treat urologic disease, which is \$11 billion. The cost to diagnose TC in one patient after an incidental finding of TM would be \$1.7 million. DeCastro and colleagues then presented data and argued that it is very unlikely that an extensive (and costly) screening program would decrease the burden of treatment or improve the cure rate and that it would not decrease the morbidity and mortality rates associated with TC.

TC can be detected early and easily by testicular self-examination. In their study, DeCastro et al. [16] stated that effort and resources should be directed toward patient education (self-examination with immediate physician follow-up required for detection of a palpable mass), noting that only two-thirds of their cohort with incidental TM were actually performing routine self-examination (despite having received extensive counseling to do so). The authors noted that many patients with newly diagnosed TC tell their physicians that no one ever informed them that they should be performing routine testicular self-examination.

In 2012, Richenberg and Brejt [29] published a study that evaluated eight studies in the literature combined with findings for patients at their own institution, for analysis of a total of 389 pooled patients with TM. Four of the 389 patients had TC develop during follow-up, and three of these four patients had additional risk factors for TC, including atrophy ($n = 1$) and previous history of GCTs ($n = 2$); therefore, only one of 386 patients at low risk for TC had TC develop during follow-up (median follow-up, 33 months). On the basis of these data, the authors argued that the likelihood of a low-risk patient developing TC is, at most, 1:100, and they concluded that there is no causal link between TM and TC.

Richenberg and Brejt [29] hypothesized that TM and GCT most likely occur secondary to a common defect (tubular degeneration), which hence explains why TC is associated with TM. In other words, TM is a marker for tubular degeneration but is not a predisposing risk factor for tubular degeneration. The authors mentioned an overwhelming body of evidence indicating that TM denotes premalignant change only in those men

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with additional risk factors for TC. Similar to Peterson et al. [27], DeCastro et al. [16], and Rashid et al. [28], they also raised the question of whether detection of a nonpalpable mass during an annual screening ultrasound examination confers any survival advantage, compared with the benefits of regular testicular self-examination, and they note that “the evidence base supporting [ultrasound surveillance] is questionable.”

In 2015, Patel et al. [26] reported an analysis of 442 patients with TM who were successfully monitored (mean follow-up duration, 28 months). Only two of the 442 patients developed TC, and both had independent risk factors for TC (including testicular atrophy and a history of contralateral orchiectomy for GCT).

Shanmugasundaram et al. [7] presaged these sentiments in 2007, by saying that “the benefit of strict follow-up in patients incidentally diagnosed to have TM has not been documented.”

Current Recommendations

Presented in this section is a compendium of recommendations based on more recent thinking.

To begin with, in 2004, Rashid et al. [28] suggested:

[There] appears to be no definitive association with TM and cancer. Therefore, follow-up at this time should be dictated based on risk factors for developing testis cancer more than on the presence of TM.

Later, in 2007, Shanmugasundaram et al. [7], made the following recommendation:

For patients with TM, who are asymptomatic and are not at high risk of development of CIS [Carcinoma in Situ] and invasive tumor, regular self-examination and prompt reporting to the physician in case of appearance of any new lesions should suffice. In the present scenario, TM detected during routine ultrasound evaluation for various scrotal conditions other than those with high risk does not warrant biopsy. The anxiety and economic burden that are imposed on patients with TM when prolonged follow-up is advised should be considered against the backdrop of a malignancy with excellent outcome.

In 2008, after stating “We continue to recommend testicular self-examination in men

at risk,” DeCastro et al. [16] summarized their thoughts as follows:

We believe that an intensive screening program for men with TM is not cost-effective and would do little to improve outcomes associated with TC. We continue to recommend testicular self-examination in all men, particularly those at risk for TC.

Goede et al. [20], in 2009, said the following:

We advise testicular self-examination every 3 months in asymptomatic boys with CTM beginning at age 15 years, since testicular malignancies can occur from this age onward.

Richenberg and Brejt [29] made the following observation in 2012:

In the absence of additional risk factors surveillance is not advocated. ... In the presence of additional risk factors (previous testicular cancer, a history of maldescent or testicular atrophy) patients are likely to be under surveillance; nonetheless monthly self-examination should be encouraged, and open access to ultrasound and formal annual surveillance should be offered. ... The aim of the annual surveillance [is not] the detection of subclinical masses but maintaining patient’s engagement with the process as indefinite self-examination without intermittent contact with medical care is likely to fail.

Recommendations in two studies published in 2015 are also of note. Patel et al. [26] advised that “US surveillance is not required when TM is the only abnormality in the absence of any clinical risk factors for the development of GCT.” The recommendation of Richenberg et al. [36] was as follows:

The presence of [testicular microlithiasis] alone in the absence of other risk factors is not an indication for regular scrotal [ultrasound], further [ultrasound] screening or biopsy. [Ultrasound] is recommended in the follow-up of patients at risk, where risk factors other than microlithiasis are present.

Despite all of these recommendations regarding self-examination, it should be not-

ed, however, that neither the prestigious U.S. Preventive Services Task Force [37] nor the equally well known Cochrane Collaboration [38] has identified any studies that have successfully determined the effectiveness of self-examination or clinical examination of the testicles in reducing the mortality rate associated with TC [39]. Furthermore, major organizations (e.g., the U.S. Preventive Services Task Force, the American Urology Association, the European Association of Urology, the National Comprehensive Cancer Network, and the main radiology organizations) do not recommend any type of formal imaging screening program for TC in the absence of risk factors.

Summary and Our Recommendations When Testicular Microlithiasis Is Noted

The management of TM detected on ultrasound can be divided into four categories. First, TM in the presence of a mass is irrelevant (Fig. 2). The mass trumps all. “Most masses in the testicle are assumed to represent testicular cancer until proven otherwise” [40]. Second, the patient can be reassured that if the patient is at low risk for TC, the risk of TC developing in the setting of isolated TM, although not precisely known, is extremely small (with the worst estimate of risk being 1 in 100 cases). Third, and of most importance, the patient should be educated about the need for regular monthly testicular self-examination. Finally, the risk of TC should be stratified on the basis of other factors (Table 1), and follow-up ultrasound examination should be reserved for high-risk patients. In addition, it should be noted that the value of annual ultrasound examination is not so much the ultrasound study itself but rather the involvement of the patient in a formalized follow-up program to maintain his contact with the medical system.

A Possible Dictation Template to Follow

Our own recommendation for a possible dictation template is as follows: Testicular microlithiasis is present without intratesticular mass or other worrisome findings. In the absence of any other risk factors for testicular cancer (e.g., personal history of testicular cancer, a father or brother with testicular cancer, history of cryptorchidism or maldescent, testicular atrophy, or other risk factors), no further imaging or biochemical follow-up is necessary; all that is recommended is routine monthly testicular self-examination. However, if the patient has risk

factors for testicular cancer, referral to a urologist for evaluation and determination of an optimal follow-up strategy is recommended.

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