Follow up of Testicular Microlithiasis

ESUR Scrotal Imaging Group
Jonathan Richenberg
The Issues – our agenda

• The initial scare and the error of confusing association with causation
• Learn to recognize and evaluate TML
• Learn the evidence, 2015 and beyond
• Learn the associated risk factors
• Learn an evidence based pragmatic follow up strategy – in adults
• [Learn what to do with paediatric TML]
Why all the fuss?

• Blame the 1990s
• TML is associated with testicular germ cell cancer
• Actually TML is associated with on retrospective review of GCT cases was noted with unexpected frequency
• Some studies reported co-occurrence over 40%
• Analysis of published studies: quoted prevalence of TML in men with GCT 15% - 45%

Derogee M, Bevers RF, Prins HJ, Jonges TG, Elbers FH, Boon TA (2001) Testicular microlithiasis, a premalignant condition: prevalence, histopathologic findings, and relation to testicular tumor. Urology, 57(6)

A Backwards Glance

• Big problems with the retrospective studies
  • Inconsistent definition
  • Poor or at least inconsistent logging in published studies of other risk factors such as testicular atrophy
  • Over reliance on anecdote = case studies
What’s in a name?

• TML is an ultrasound diagnosis
• Initially a flurry of different definitions and classifications
• Ultimately two possible definitions for TML have been proposed:
  • five or more microliths in the whole testis or
  • five or more microliths per field of view.
• The latter definition captures the idea of clustering
• Clustering may be important (dysgenic ‘unstable’ area in the testis, wherein carcinoma in situ (CIS) can develop
Classification

• The grading system was based on the number of microliths per testis.
• Grade 1: 5-10 microliths
• Grade 2: 11-20 microliths
• Grade 3: 21-30 microliths
• Grade 4: more than 30 microliths
Pathology…and how it looks on high frequency ultrasound

- TML is a condition in which calcium deposits form in the lumina of seminiferous tubules or arise from the tubular basement membrane components.

- The histology shows micro calcium deposits with surrounding fibrosis.

- On US: an echogenic non-shadowing focus less than 3 mm
The evidence base now

• Prevalence in real world asymptomatic men ~2%
• Inverse correlation among ethnic groups in prevalence of TML and incidence of GCT
• Prospective studies and metanalysis of literature <1% rate interval cancer appearance in men with TML as an isolated finding
The 2015 position


Testicular microlithiasis imaging and follow-up: guidelines of the ESUR scrotal imaging subcommittee.

Richenberg J1, Befffield J, Ramchandani P, Rocher L, Freeman S, Tsili AC, Cuthbert F, Studniarek M, Bertolotto M, Turpein AT, Dogra V, Derchi LE.

Abstract

OBJECTIVES: The subcommittee on scrotal imaging, appointed by the board of the European Society of Urogenital Radiology (ESUR), have produced guidelines on imaging and follow-up in testicular microlithiasis (TML).

METHODS: The authors and a superintendent university library, independently, performed a computer-assisted literature search of medical databases: MEDLINE and EMBASE. A further parallel free-text search was made for the genetic conditions Klinefelter's syndrome and McCune-Albright syndrome.

RESULTS: Proposed guidelines are; follow-up is not advised in patients with an isolated TML in the absence of risk factors (see Key Points below); annual ultrasound (US) is advised for patients with risk factors up to the age of 55; if TML is found with a testicular mass, urgent referral to a specialist centre is advised.

CONCLUSION: Consensus opinion of the scrotal subcommittee of the ESUR is that the presence of TML alone in the absence of other risk factors is not an indication for regular scrotal US, further US screening or biopsy. US is recommended in the follow-up of patients at risk, where risk factors other than microlithiasis are present. Risk factors are discussed and the literature and recommended guidelines are presented in this article.

KEY POINTS: • Follow up advised only in patients with TML and additional risk factors. • Annual US advised for patients with risk factors up to age 55. • If TML is found with testicular mass, urgent specialist referral advised. • Risk factors - personal/family history of GCT, maldescent, orchidopexy, testicular atrophy.

Comment in
Re: Testicular Microlithiasis Imaging and Follow-up: Guidelines of the ESUR Scrotal Imaging Subcommittee. [J Urol. 2015]
PubMed 2016-September 2018:40 ‘hits’
Testicular microlithiasis in patients with testicular cancer in the United Kingdom and in Denmark.


Abstract

INTRODUCTION: Testicular cancer is the most common type of cancer in young Caucasian men. It has been suggested that testicular microlithiasis (TML) is a premalignant condition. This study's objective was to investigate TML histology prevalence in testicular cancer patients in two European populations.

METHODS: We analysed archived histopathology orchietomy specimens from 152 patients diagnosed with testicular cancer at Fredericia Hospital in Denmark from 2004 to 2014, and 105 patients diagnosed at St Thomas' Hospital in London from 2011 to 2015.

RESULTS: The Danish patients' median age was 37 years (range: 16-74 years) and the English patients' 36 years (range: 18-78 years). In the Danish patients, 29 (18.1%) had TML, and in the English patients, 43 (40.6%) had TML (p < 0.001). Haematoxylin bodies were slightly more common in the English patients. Laminated calcification was more often seen in seminomas than in non-seminomas. CONCLUSIONS: The English testicular cancer patients had a statistically significantly higher TML prevalence than the Danish patients. This observation questions the hypothesized biological association between TML and testicular cancer.


Testicular Microlithiasis: What Should You Recommend?

Winter TC^1, Kim E^2, Lowrance WT^3, Middleton WD^4

Abstract

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 role of follow-up of the asymptomatic patient with TM remains under investigation.
Risk Factors

• Previous germ cell tumour
• History of maldescent
• History of orchidopexy
• Atrophy <12 ml volume
• History of germ cell tumour in 1st degree relative
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comments</th>
<th>Yes &gt;=5 ML per FoV</th>
<th>Yes Diffuse</th>
<th>No TML i.e. no FoV contains 5 or more microliths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maldescent</td>
<td>Ask patient for relevant history</td>
<td>Annual US</td>
<td>Annual US</td>
<td>Discharge</td>
</tr>
<tr>
<td>Orchidopexy</td>
<td>Ask patient for relevant history</td>
<td>Annual US</td>
<td>Annual US</td>
<td>Discharge</td>
</tr>
<tr>
<td>Previous GCT</td>
<td>Likely to have orchidectomy so this should be easy to ascertain. If there is any doubt, ask the patient</td>
<td>Annual US</td>
<td>Annual US</td>
<td>Discharge</td>
</tr>
<tr>
<td>Genetic disease</td>
<td>Ask patient for relevant history</td>
<td>Repeat US at 6 and 12 months, D/C if no nodule &gt;3mm</td>
<td>Refer</td>
<td>Discharge</td>
</tr>
<tr>
<td>Family history of GCT</td>
<td>Ask patient for relevant history</td>
<td>Encourage self-examination and offer open access</td>
<td>Encourage self-examination and offer open access</td>
<td>Discharge</td>
</tr>
<tr>
<td>Atrophic testis</td>
<td>Should be noted during the ultrasound examination</td>
<td>Annual US</td>
<td>Annual US</td>
<td>Discharge</td>
</tr>
</tbody>
</table>
Recommended management

As an isolated finding at scrotal US, in the absence of any risk factors

The patient may be discharged with advice about performing monthly scrotal self-examination and a patient information leaflet.

When TML is discovered in the setting of another risk factor, when there is no focal lesion within either testis

• a. Annual follow-up with US up to age 55 years.
• b. Monthly self-examination
• c. If self-examination reveals a new mass within the scrotum, there should be direct access to fast track US, without the need for repeat clinical referral

If TML is discovered together with a focal testicular mass/ marked hypoechoic area

Immediate referral should be made to a specialist urology centre

If there are too many microliths to adequately assess the testicular parenchyma, or if TML appears clearly asymmetric with alterations of echotexture

Referral is made to a specialist centre
<table>
<thead>
<tr>
<th>US finding</th>
<th>&lt;5 ML per FoV</th>
<th>&gt;5 ML per FoV</th>
<th>Diffuse*</th>
<th>&lt;5 ML per FoV but ≥5 total[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal tests, no risk factor</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Annual US</td>
<td>Discharge with open access</td>
</tr>
<tr>
<td>Normal tests but prior GCT*, maldescend, orchidopexy or atrophic testis</td>
<td>GCT under oncology surveillance</td>
<td>F/U annual US</td>
<td>GCT under oncology surveillance</td>
<td>Maldescend, orchidopexy, atrophy: D/C with advice</td>
</tr>
<tr>
<td>Genetic disease (Klinefelter)</td>
<td>F/U ultrasound at 6 &amp; 12 months looking for nodule &gt;3 mm, D/C if none detected</td>
<td>F/U at 6 &amp; 12 months looking for nodule &gt;3 mm, D/C home if none detected</td>
<td>Refer to specialist D/C</td>
<td>Refer to specialist</td>
</tr>
<tr>
<td>Focal lesion</td>
<td>Refer to specialist centre (for urology ± oncology input)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolcalfication</td>
<td>As for focal lesion above</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RF risk factors which include previous malignancy, maldescend, small testis, orchidopexy, TML testicular microlithiasis, 5 or more microlcalfications per field of view, FoV field of view, D/C discharge from follow-up with advice about self-examination, F/U follow-up, MRI/scrotal MRI with gadolinium sequences, CEUS contrast enhanced (microbubble) ultrasound, US scrotal ultrasound, GCT germ cell tumour, ML microliths

*Often associated with atrophy and infertility
[b] Very unlikely in reality to have >10 ml in total, as would then be ≥5 in a FoV
[c] Men with prior history of GCT will be under surgical/oncological review
Practical points

• Lead time bias in a highly curable condition
• Rationalization of limited services
• Decrease patient anxiety when minimal risk
• Maintain patient involvement when the risk is higher
• Be confident, this is evidence based
Is the paediatric population different?

Impression: recommendation, appropriately, is IMMATURE – linkage through other risk factors

Long-Term Follow-Up of Testicular Microlithiasis in Children and Adolescents: Multicenter Prospective Cohort Study of the Italian Society of Pediatric Urology.

Marie A¹, Pintozi L¹, Creti G², Chiesa FL³, Renzo DD³, Gasparella M⁴, Maggio GD⁴, Bagnara V⁵, Merini E⁶, Tadini B⁷, Caiderulo E⁸, Sangiorgio L⁹, Battaglino G¹⁰, Nappo SG¹¹, Caione C¹¹.

Author information

Abstract

Introduction  Testicular microlithiasis (TM), characterized by the presence of intratubular calcifications in a single or both the gonads, is an uncommon entity with unknown etiology and outcome in pediatric and adolescent age. In this study, the results of a multicenter long-term survey are presented. Materials and Methods  From 11 units of pediatric urology/surgery, patients with TM were identified and yearly, followed up in a 7-year period, adopting a specific database. The recorded items were: age at diagnosis, presenting symptoms/associated abnormalities, ultrasonographic finding, surgery and histology at biopsy, if performed. Results  Out of 85 patients, 81 were evaluated yearly (4 patients lost to follow-up). TM was bilateral in 66.6% of the patients. Associate genital abnormalities were present in 90%, more frequently undescended/retractile testis (23.4%) and varicocele (22.2%). TM remained unchanged at 4.7 years follow-up in 77 patients (93.8%) and was reduced in 4 patients after 1 to 5 years of inguinoscrotal surgery. Orchiectomy was performed in three patients (3.7%), one for severe testicular hypoplasia and two for seminoma (2.5%), respectively, concurrent and metachronous to diagnosis of TM. Tumor excision with parenchymal sparing surgery was performed in a teratoma associated with TM. Conclusion  TM is a controversial entity, often associated with several inguino-genital features, which rarely can recover. Testicular malignancy, although present in TM, has not proven definitively associated to microoliths. Proper counseling, yearly ultrasound, and self-examination are long-term recommended.
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