Testicular microlithiasis: Clinical significance and review of the literature

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Abstract

Testicular microlithiasis (TM) is an uncommon and asymptomatic benign entity, typically detected incidentally on scrotum sonography. Typical sonography findings include the emergence of tiny, highly reflective foci within the testis, which are not accompanied by acoustic shadowing. Five (5) or more foci with the above features, present in at least one US image, is the most commonly used criterion for the diagnosis of classic TM. TM has been associated with diverse pathologies, including testicular carcinomas, intratubular germ cell neoplasia, infertility, cryptorchidism, atrophy and testicular dysgenesis. To date, there is no documented evidence that TM is a predisposing factor for testicular neoplasia. Therefore, no surveillance is warranted for men found to have TM alone in the ultrasound examination. However, for men with predisposing or risk factors for a testicular germ cell neoplasm, such as a previously diagnosed testicular carcinoma, a family history of the disease, cryptorchidism, infertility, testicular atrophy and gonadal dysgenesis, surveillance is mandatory.

Introduction

Testicular microlithiasis (TM) is an uncommon, asymptomatic condition, in which small calcifications are observed inside the testicular parenchyma¹⁶. This is usually an incidental finding in the sonography of the scrotum¹⁶. The incidence of testicular microlithiasis in the general population is not accurately known. The reported rates of testicular microlithiasis range from 2.4% to 5.6% in asymptomatic adults, and from 0.6 to 9% in symptomatic men¹⁴,⁷,¹⁸. In childhood, the reported incidence of the condition in the asymptomatic population is 4.2%, and 2% in boys with clinical symptomatology ⁴,⁷,¹⁸-²².

Pathogenesis - histological findings

The pathogenesis of testicular microlithiasis appears to be related to the disruption of the basement membrane of the seminiferous tubules and the deposition of glycoprotein rings in their lumen, which is then calcified. In electron microscopy, the size of the microcalcifications does not exceed 1 mm; these consist of a central calcified ring, surrounded by concentric layers of collagen fibres ¹,²,⁴,⁸-¹⁰. According to another theory, the microcalcifications are located within the testicular stroma, already since the earliest stages of embryogenesis of the gonads.

The aetiology of testicular microlithiasis remains...
unclear. Although metabolic and inflammatory causes have been proposed, as have as differences in the incidence of microlithiasis depending on ethnicity and geographical area, it appears that the condition is more related to a dysfunction of the Sertoli cells, which are responsible for phagocytosis and the elimination of cellular debris from the seminiferous tubules.

**Sonography findings**

The sonography findings of testicular microlithiasis were initially reported in 1987 by Doherty et al. and were detailed in 1994 by Janzen and Backus, who first described the sonographic criteria of classic TM. These consist in the emergence of multiple tiny highly reflective foci, which are usually located in both testes, with diameters ranging from 1 to 3 mm (Figure 1). Due to their very small size, these foci are not accompanied by acoustic shadowing. The criterion that has been used for the diagnosis of classic TM comprises the emergence of five (5) or more foci with the above features, present in at least one US image. The term limited microlithiasis (limited TM) covers the detection of at least one stone in the testicular parenchyma, but their total number is no more than five. In literature, terms such as starry sky or snow-storm pattern have been used to describe the sonographic findings of TM. The number and distribution of the stones varies considerably. The typical pattern is that of a diffuse, bilateral, symmetrical testicular insult, but the localisation of microlithiasis may be distal, segmental, unilateral or asymmetric. The extent of testicular insult has been classified in grades. We should mention the classification of classic TM as grade I: 5 - 10 stones (Figure 2), II: 11 - 20 stones, III: 21 - 30 and IV: more than 30 stones per US image (Figure 1). However, it should be stressed that the sonographic findings are not always associated with the pathological findings.

**The relationship of TM with other benign entities**

Although TM is an asymptomatic and often incidental finding in ultrasound testing, it has been reported to co-exist with a multitude of benign conditions, including torsion of the testis or parts thereof, testicular infarction, varicoceles, testicular atrophy, epididymal cysts, epidermoid cysts (Figure 1), Klinefelter syndrome and hypogonadism.

A strong correlation has been reported between testicular microlithiasis and infertility. According to literature, its frequency in the subfertile population ranges from 0.8 - 20% in adults and 6 - 46% in adults and up to 12.5% in children. The risk of developing a malignant testicular neoplasm was stated to be 2 to 20 times higher than in the healthy population.

**The relationship of TM with testicular neoplasms - the view of the past**

For several years, it was perceived that testicular microlithiasis was a primary manifestation of a disorder of the testicular parenchyma and that this disorder resulted in an increased incidence of malignant testicular germ cell neoplasms (GCNs). The reported frequency of coexistence of testicular neoplasms in subjects with microlithiasis is 30 - 35%, or 6 - 46% in adults and up to 12.5% in children (Figure 3). The risk of developing a malignant testicular neoplasm was stated to be 2 to 20 times higher than in the healthy population.
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scrotal symptomatology, the reported frequency of microlithiasis was 4.1%, with a mean age of 35.4 years at diagnosis. In the same report, 46% of subjects with microlithiasis also suffered from a primary testicular carcinoma.33

Factors that are considered of increased risk for developing malignant testicular germ cell neoplasms, such as subfertility and cryptorchidism, are closely correlated with microlithiasis.7, 14, 27 - 29, 32. This condition has also been associated with testicular intratubular germ cell neoplasia (ITGCN), which is considered a pre-malignant condition.4, 7, 32 - 34, 37, 38. Nearly all malignant testicular germ cell neoplasms are believed to originate from a common cell, the carcinoma in situ (CIS) cell, except for the uncommon spermatocytic seminomas found in adults and neonatal testicular neoplasms (yolk sac tumours and mature teratomas).37 The development of invasive testicular GCNs is expected to be observed in 50% of people with ITGCN over 5 years, if left untreated, and in 70% of cases after 7 years.37 It is estimated that all patients with ITGCN will eventually develop invasive testicular neoplasms, although some extremely rare cases of burned out CIS have been described.37

There are studies reporting an increased incidence of ITGCN in subfertile men with sonographic findings of microlithiasis.7 It has also been reported that individuals with microlithiasis and atrophic testes are more likely to develop ITGCN.7 In a study of 263 subfertile men, 53 (20%) had microlithiasis findings.5, 39. Six of 30 patients in the same report, with bilateral localisation of microlithiasis, were diagnosed with ITGCN, leading to the conclusion of a significantly higher incidence of ITGCN in the subfertile population with bilateral microlithiasis compared to those with a unilateral localisation.39

After monitoring subfertile men for 24 months, Negri et al. report a 24.3% chance of development of GCNs in men with microlithiasis.32 In contrast, Kosan et al. report that none of the 194 subfertile men in their study, which included 18 men with microlithiasis findings, developed testicular GCNs after being monitored over 19.5 months.32 Husmann et al. report that ultrasound testing in a 2-year follow-up after preceding orchidopexy in men with cryptorchidism showed microlithiasis in the resected testes in 10% of cases.29 The monitoring of 19 individuals in the same study for 8 years showed the delayed development of testicular malignancies in 2 cases. This report concluded that the risk of malignancy in men with cryptorchidism is 2 - 3 times greater in the presence of microlithiasis,
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Testicular microlithiasis (TM) has also been associated with the development of malignant neoplasms in the contralateral testis in patients with a history of orchiectomy due to GCNs. Bach et al. reported the development of contralateral malignant testicular neoplasms in 22% of men with microlithiasis, compared to 2% of patients without microlithiasis. In patients with a history of surgery for testicular GCNs, an increased incidence of ITGCN in the contralateral testis is also reported, when microliths coexist in this, which, if not treated will lead to development of a delayed neoplasm (the relative risk is about 28.6%). Other studies report the existence of microlithiasis in the contralateral testis in 20% of people with primary germ cell neoplasms (Figure 4). The risk of coexistence of ITGCN in the same patient group is 8.9 times higher for men with microlithiasis, compared to patients with a similar history of malignancy, but without microlithiasis.

The reported incidence of testicular microlithiasis is also higher in the relatives of patients with GCNs, leading to the conclusion that it is a familial predisposing factor for the development of testicular neoplasms. Epidemiological studies have shown that the likelihood of development of malignancies is 8 - 10 times greater for the brothers and 4 times greater for the fathers and male children of men with testicular germ cell neoplasms.

The association of testicular microlithiasis with malignancy is further supported by literature reports of some isolated cases of patients with sonographic diagnosis of microlithiasis, whose monitoring showed delayed development of testicular germ cell neoplasms. The mean time for neoplasm development in these patients was 48 months from initial diagnosis of microlithiasis, and the findings concerned extended microlithiasis in some cases and the presence of few microliths in others.

Finally, in rare cases, testicular microlithiasis has been associated with extragonadal germ cell tumours, localised in the mediastinum and/or abdomen, usually in adults. A similar correlation has been reported in childhood, coupled with Klinefelter syndrome.

Based on the above data, testicular microlithiasis was considered a pre-malignant condition and the surveillance of these men had been proposed, aiming to the early diagnosis of testicular neoplasms. The protocols proposed in literature displayed significant differences, ranging from simple monitoring, accompanied by self-examination or not, to the measurement of tumour markers in blood serum, to recommendations for testicular biopsy in combination with regular visits to the urological clinic and sonography. Another monitoring protocol recommended an annual scrotal sonography in men with microlithiasis aged 20-50 years. Some authors have proposed control with axial tomography of the chest and abdomen at diagnosis of microlithiasis, followed by periodic sonographies at intervals of 6-12 months. In 2006, studying the protocols for monitoring men with TM in England, Ravichandran et al. reported significant variations, concluding that most urologists are not entirely convinced as to the usefulness of screening. However, a significant proportion continues to monitor these men for a long time, which is also different: some continue monitoring for life, others until the age of 55 years and some stop if the sonographic findings remain stable after 5 years. The screening protocols included sonographies combined with clinical examinations, usually every year or every six months or at greater intervals. However, it should be emphasised that the above monitoring protocols will create a huge economic burden on the National Health System in the future. It is also known that an interval of 3-6 months intervenes from the moment a man feels a testicular mass on palpation to the time he seeks medical assistance; this delay does not have a significant impact on prognosis and on the treatment of testicular neoplasm. Given the satisfactory response to treatment of the majority (90%) of malignant testicular neoplasms.
neoplasms, it is doubtful whether the earlier diagnosis of the neoplasm by sonography in fact contributes to a better final outcome, compared to diagnosis by clinical examination.48.

The relationship of TM with testicular neoplasms - the current view

According to the latest literature, there seems to be no documented proof that TM is a predisposing factor or cause of the development of testicular neoplasms. The prevailing view now is that microlithiasis is rather a manifestation of a disorder of the testicular parenchyma, and not a poorly defined condition that predisposes both for the development of malignancies and for coexistence with benign conditions.1,4,5,12,14,15,30. A review of recent literature shows that TM is not associated with an increased risk of developing GCNs in asymptomatic men. Recent studies report smaller percentages of coexistence of malignant testicular neoplasms and microlithiasis and the non - delayed development of malignancies after the long - term monitoring of these men1,4,5,12,14,15,30,32.

A study of 2,656 men who came for sonography testing by Richenberg et al. reported 51 (1.92%) cases with TM, of which none developed neoplasms following monitoring for a mean of 33.3 months.25 Following a review of the literature, the same author team reports the development of malignancies in 4 out of 389 men. Excluding three incidents with predisposing factors for developing testicular neoplasia, only one case of 389 developed a malignancy during the follow - up, leading to a probability of about 1 in 100 for the delayed development of testicular GCNs in otherwise healthy people with microlithiasis.25.

The presence of malignant testicular GCNs has rarely been reported in healthy, asymptomatic men.32 Serter et al. report that microlithiasis rates are 2.4% in asymptomatic men without presence of malignant neoplasms.32 A study of 1,504 asymptomatic men aged 18 - 35 years who visited a military hospital reported the presence of microlithiasis in 84 men (5.6%) and in one case the presence of a testicular GCN, without coexistence of microlithiasis however11. The same study reports a greater frequency of microlithiasis in black men (14.1%) compared to white (4%), which raises questions about the relationship of microlithiasis with neoplasias, as the incidence of testicular malignancies is significantly lower in the black race (0.9/100,000) than the white race (5/100,000).11

After 1987, literature reports 15 cases of men with testicular microlithiasis and delayed development of malignant neoplasms after a mean period of 35.7 months.5, 17 The majority of these cases however are retrospective reports or isolated incidents and the correlation of microlithiasis with testicular cancer is not well documented or concerns high - risk individuals.5, 17

According to the above data, not all persons with TM will develop malignant neoplasms. Nonetheless, microlithiasis is a worrying finding in men with predisposing factors for testicular neoplasms. In this population, the existence of microlithiasis is associated with an 8.5 - fold and 10.5 - fold higher risk, respectively, for the diagnosis of concurrent malignant testicular germ cell neoplasms and ITGCN compared to the general population.14, 32 The delayed appearance of testicular malignancies has also been reported in these cases.14, 32

The high - risk group includes men with a history of testicular GCNs (the relative risk is 25 times higher than in the healthy population), a history of cryptorchidism (relative risk: 4.8), family history of testicular malignancies (relative risk: 3 - 10), subfertility, testicular atrophy and gonadal dysgenesis.12, 15, 16, 42, 47.

Patients with Down’s syndrome are also at high risk.30 The reported incidence of microlithiasis in these cases is significantly higher than in the rest of the population. Other population groups that belong to the high - risk category are patients with extragonadal germ cell tumours, as well as children with syndromes associated with a mutation of the WT1 gene, McCune - Albright syndrome and Klinefelter syndrome.22, 27

Conclusions

The above show that people with TM without predisposing factors for the development of malignant neoplasms not require monitoring, but only self - examination of the testes. Monitoring, mainly by regular clinical examinations and sonography, is only necessary for men with microlithiasis and predisposing factors for developing testicular germ cell neoplasms. In these individuals, the emergence or suspicious findings at sonography or at the clinical examination should lead to a testicular biopsy or orchiectomy. The above are included in the recent guidelines of the European Association of Urology.49, 50
Η μικρολιθίαση του όρχεως αποτελεί μια σπάνια, ασυμπτωματική οντότητα, κατά κανόνα τυχαίο εύρημα κατά τον υπερηχοτομογραφικό έλεγχο του οσχέου. Τα τυπικά υπερηχοτομογραφικά ευρήματα περιλαμβάνουν την ανάδειξη πολύ μικρού μεγέθους, έντονα υπερηχοικών εστιών εντός του όρχεως, οι οποίες δεν συνοδεύονται από ακουστική σκιά. Σαν κριτήριο για την διάγνωση της «κλασσικής μικρολιθίασης» θεωρείται η ανάδειξη πέντε (5) ή περισσότερων εστιών, με τους ανωτέρω χαρακτήρες σε ένα τουλάχιστον οπτικό πεδίο κατά τον υπερηχογραφικό έλεγχο. Η μικρολιθίαση του όρχεως έχει συσχετισθεί με ένα μεγάλο αριθμό παθολογικών καταστάσεων, μεταξύ αυτών το καρκίνωμα του όρχεως, η ενδοσωληναριακή νεοπλασία από γεννητικά κύτταρα, η υπογονιμότητα, η κρυψορχία, η ατροφία και η δυσγενεσία του όρχεως. Μέχρι σήμερα, δεν υπάρχει τεκμηριωμένη απόδειξη ότι η μικρολιθίαση του όρχεως αποτελεί προδιαθεσικό παράγοντα για την ανάπτυξη καρκινώματος του όρχεως. Για αυτό το λόγο δεν συστήνεται παρακολούθηση των ανδρών με μοναδικό εύρημα την μικρολιθίαση κατά τον υπερηχογραφικό έλεγχο. Αντίθετα, σε άνδρες με προδιαθεσικούς η παράγοντες για καρκίνωμα του όρχεως από γεννητικά κύτταρα, όπως παλαιό ιστορικό κακοήθειας του όρχεως, οικογενειακό ιστορικό της νόσου, κρυψορχία, υπογονιμότητα, ατροφία ή δυσγενεσία των γονάδων η παρακολούθηση είναι αναγκαία.

**Λέξεις ευρετηριασμού**

Μικρολιθίαση όρχεως, κακοήθες νεόπλασμα όρχεως από γεννητικά κύτταρα, υπερηχοτομογραφικός έλεγχος

**References**

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