

Testicular Microlithiasis among Infertile Men: A Reason for Concern?

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Abstract

Testicular microlithiasis is an infrequently diagnosed condition that can be associated with a variety of pathologies of the testis, the best known of which is its association with testicular cancer. This study examines the frequency of testicular microlithiasis from a large group of men attending an infertility clinic where all men undergo genito-urinary ultrasound screening. Of 749 men, a total of 46 men were found to have testicular microlithiasis (6.1%) of which the lesion was bilateral in 39 and unilateral in 7 men. In one man, the testicular microlithiasis was found to be in association with a testicular tumour. The semen profile was categorized normal in 25 men (54%) and sub-fertile in the remaining 21 men, implying an elevated rate in this population. Testicular microlithiasis is therefore commonly seen among infertile male patients and may be a marker for serious pathology and testicular malignancy. Its presence is thus highly relevant to the assessment of infertility in the male and has implications regarding follow-up. We conclude that testicular ultrasound should be an important part of the evaluation of all males attending infertility clinics and the infertility clinicians should be aware of the condition of testicular microlithiasis.

Keywords: Testicular microlithiasis; Male infertility; Testicular cancer; Testicular ultrasound

Introduction

The condition known as testicular microlithiasis was first described 35 years ago [1]. It is completely undetectable on clinical examination and can only be diagnosed by testicular ultrasound. Doherty and colleagues have defined it as the presence of 5 or more specks of calcification in one or more ultrasound planes of the testis [1,2]. It may even be seen in the testes of children [3,4]. The incidence of microlithiasis in a healthy adult population (17-35 years) is reported as 5.6%, but higher at 14.1% in African Americans [5]. The incidence in boys is reported lower at 1.1% and 4.2% [4], higher rates being associated with undescended testes, hydroceles and varicoceles. As fertility clinicians, we have become interested in testicular microlithiasis as we have developed a strengthening view over the 34 year period of managing infertility cases in our centre that the male partner should be examined as closely as the female. Given that most fertility clinicians are gynecologists, this is enhanced by routine

ultrasound scanning of the male genito-urinary anatomy where much pathology are diagnosable, some with major clinical relevance. This has meant the finding of testicular microlithiasis and we are concerned that the feature has been reported to be closely associated with germ cell testicular cancer [6]. This report is an audit focusing on those cases where testicular microlithiasis was identified and examines its association with the relevant fertility features and other genitourinary pathologies in this population presenting to an infertility clinic.

Materials & Methods

Consultations

It has become the policy at PIVET Medical Centre for all men attending the infertility clinic to undergo a testicular ultrasound. This is conducted as part of a genito-urinary tract ultrasound examination (scrotal, prostate and renal), regardless of the semen profile. In all cases both partners were each required to provide their medical history and undergo a clinical examination which, for all males, included examination of their genitalia. These clinical consultations were undertaken by a number of different clinicians, all specialist gynecologists (FRANZCOG), although some have additional specialist qualifications including general surgery (FRCS or FRACS) or certification as a sub-specialist in reproductive endocrinology and infertility (CREI).

Patients

A total of 749 men underwent a testicular ultrasound between January 1st 2006 and May 31st 2008 i.e. a period of 29 months. All these men had come to the clinic as partners in an infertile setting in the context of primary or secondary infertility.

Testicular ultrasound

The ultrasound examinations were performed by a single operator (NP) using a Philips HD15000 Sono CT machine (Philips Electronics NV, Netherlands). Testicular volume was estimated using a 10 MHz linear array transducer. The testes were scanned in both transverse and longitudinal sections. The testicular volumes were calculated as for an ellipse (length x width x depth x 0.52). Each epididymis was also examined ultrasonically in two planes and any relevant structural abnormalities recorded. These examinations were conducted as part of a complete genito-urinary ultrasound examination, but only the testicular component is relevant to this study.

The diagnostic feature for testicular microlithiasis was the finding of 5 or more bright echogenic reflections against the uniformly homogeneous feature of the normal testis creating a "stars by night" or "starry sky" appearance (Figure 1). The examinations are conducted across many planes of the testis for a complete coverage, often more than 5 specks of calcification being detected in one or more planes [1,2]. The diagnosis of varicocele was based on the presence of wide veins (≥ 3 mm) in the testicular cord and which demonstrate retrograde venous flow on Valsalva manoeuvre [7].

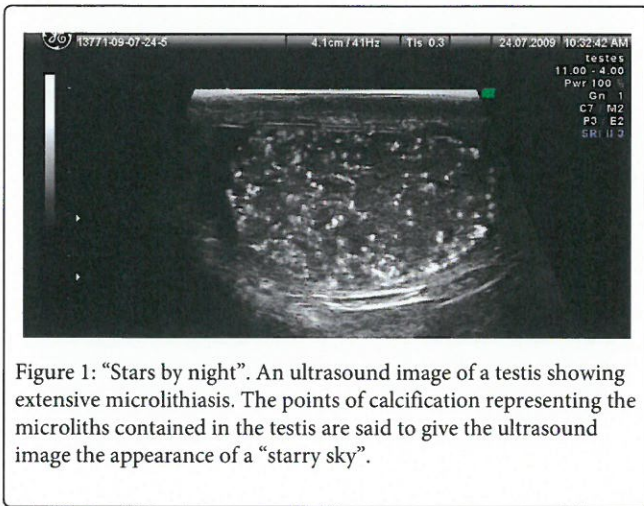


Figure 1: "Stars by night". An ultrasound image of a testis showing extensive microlithiasis. The points of calcification representing the microliths contained in the testis are said to give the ultrasound image the appearance of a "starry sky".

Semen analyses

The semen analyses were performed according to the protocol described by the World Health Organization [8]. However because of the different opinions concerning the judgement of sperm morphology and the manner in which it should be assessed [9] as well as the poor discriminatory powers of a semen analysis in the definition of male infertility, our definition of a normal semen profile was more consistent with advanced WHO criteria [10] but which post-dates the study period.

Results

Patients

The ages of these 749 men ranged from 27-61 years with a median age of 39 years. They were asymptomatic apart from some men with large varicoceles sometimes noting discomfort or swelling.

Prevalence of testicular microlithiasis

Of these men a total of 46 (6.1%) were found, on ultrasound examination, to have the changes known as testicular microlithiasis. The lesion was present bilaterally in 39 men and was unilateral in 8 men demonstrating that testicular microlithiasis occurred more commonly as a bilateral rather than a unilateral pathology. All these men with testicular microlithiasis were entirely asymptomatic.

This is a similar prevalence as our earlier reported series i.e. 66 of 1203 cases (5.5%) and together defines 112 cases from 1952 men examined (5.7%).

Semen analysis

Of the 46 men with testicular microlithiasis, the semen analysis was deemed sub-fertile in 21 but was categorized as normal in the remaining 25 men (54%). Of the 21 men with a sub-fertile semen analysis, 3 were azoospermic due to the presence of a past vasectomy procedure. Perhaps 24 men could then be classified as normal fertility potential (61%). Given that male-factor infertility ranges from 5-10% within any reproductive age community, the finding of 39-46% association with testicular microlithiasis is a relevant associative observation.

Co-existent pathologies with the testicular microlithiasis

In one man, the microlithiasis was associated with the presence of a testicular seminoma (Figure 2) giving a prevalence of seminomata among these men with testicular microlithiasis of 2% (similar to the earlier series being only 1 of the 5 seminomata occurring within the 66 cases of microlithiasis). In this man, the microlithiasis was unilateral but it occurred on the same side as the seminoma.

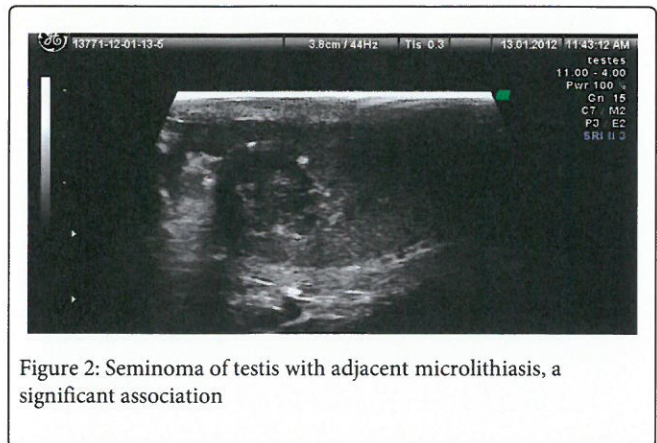


Figure 2: Seminoma of testis with adjacent microlithiasis, a significant association

Two more men had concomitant cystic ectasia of the rete testis, one unilaterally and the other bilaterally (Figure 3).



Figure 3: Cystic ectasia of the rete testis with associated minor degree of microlithiasis; an incidental association

However, in both these men the microlithiasis was bilateral. Two more men had a testicular cyst present and one further patient had undergone a right orchidectomy for testicular maldescent. One further man was found to have calcification of the tunica albuginea, the cause of which was unknown. Including subclinical cases, varicoceles were detected in 389 men (52% of the total scanned population). Ipsilateral testicular volumetric reduction of ≥ 5 mls was noted in 59 cases (15%) constituting a potentially relevant diagnostic group. A total of 19 men with testicular microlithiasis were diagnosed with concomitant varicoceles (41%) of which 3 were bilateral and the remaining 16 were unilateral left-sided (Figure 4). Regardless, there appears no increased association of microlithiasis with varicoceles.

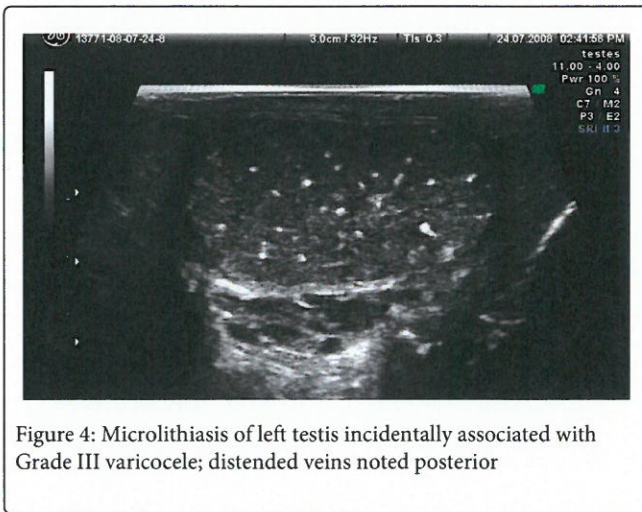


Figure 4: Microlithiasis of left testis incidentally associated with Grade III varicocele; distended veins noted posterior

Histology on discrete testicular biopsies

When initially detected, we were concerned to exclude pathologies, particularly carcinoma-in-situ. Five men had bilateral testicular biopsies performed but no abnormal histological findings were revealed. A case of unusual echogenicity in an African male was shown to be due to filariasis; but the echogenicity pattern is very different from the cases of microlithiasis (Figure 5).

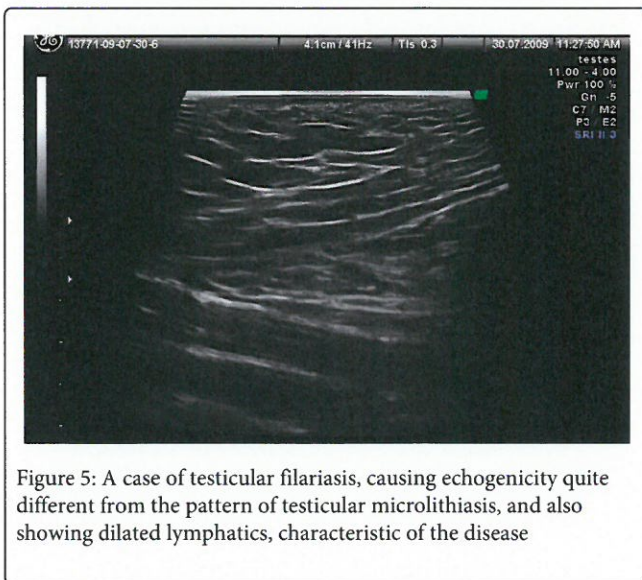


Figure 5: A case of testicular filariasis, causing echogenicity quite different from the pattern of testicular microlithiasis, and also showing dilated lymphatics, characteristic of the disease

We no longer undertake testicular biopsies in the absence of significant additional ultrasound findings such as hypo-echoic regions in the testis or concomitantly when undertaking testicular sperm recovery in azoospermic men.

Discussion

Testicular microliths appear to be formed from small clumps of germinal cells that have arisen from an unstable spermatogenic epithelium and which have been shed into the lumen of the seminiferous tubules. Around these clumps of cells, layers of collagen are formed [11] upon which calcium salts are deposited. As these

microliths are themselves very small, it is very rare to find an example of a microlith in a testicular biopsy particularly as a histological section is only some 1-3 microns thick. However in some papers in the medical literature, histological sections of microliths can be seen [12].

Although these clumps of cells with their coating of collagen and calcium are usually less than 1 mm in diameter, they are still probably too large to leave the seminiferous tubule and are thus mostly only ever seen in the testis. However testicular microliths have been reported in the rete testis and even in the epididymis [13]. It is thus possible that a microlith could occasionally be seen in the ejaculate but in this situation it is very likely to go unrecognized.

The incidence of testicular microlithiasis in the general population is unclear. Its prevalence in studies among non-infertile men has been reported to be as low as 0.68% from 4892 testicular ultrasound examinations in healthy men [6] and similarly 1.1% from a study of 711 cases, a similar size study to our series [14] but our cases numbered 5-fold. In a large series of healthy army recruits in Turkey the prevalence of testicular microlithiasis was 2.4% [15]. However others report a moderately high rate at 5.6% [16] or even as high as 9% [17]. The rate of 6.1% from our study implies an association with infertility, but may represent the high end of a normal range when compared with two of the afore-mentioned studies. The detection of 54% normal semen profiles (and, if the vasectomy cases are included, possibly 61% males with normal fertility potential) implies no clear association with male-factor infertility. However, the contribution of the male to an infertility setting remains unclear, and may be much higher than defined from semen profiles.

Testicular microlithiasis has also been reported in association with a number of other conditions in particular with both carcinoma-in-situ and testicular germ cell cancer and many publications would confirm this relationship [2,18-21]. Testicular microlithiasis has also been reported in relation to the condition known as testicular dysgenesis [22] indicating another indirect relationship with testicular germ cell cancer. However as carcinoma-in-situ is itself a progenitor of testicular germ cell cancer, this relationship is not surprising.

Testicular microlithiasis also appears to be present with increased prevalence among men with Down's syndrome [23]. One unique apparent relationship of testicular microlithiasis is seen in children with the McCune-Albright syndrome. This syndrome consists of polyostotic fibrous dysplasia, precocious puberty and café-au-lait spots on the skin [24,25]. In boys this combination may also be associated with macro-orchidism. Indeed testicular microlithiasis may be viewed as a marker for the McCune-Albright syndrome as it is present in some 62% of all cases of this syndrome [26].

In this communication, the testicular microlithiasis was associated with cystic ectasia of the rete testis [27] in one patient and thus this is likely to be a random association. In only one of the 46 men with testicular microlithiasis in this series was a germ cell cancer also present, and the degree of microlithiasis in that case was rather minor. As few of the patients with unassociated microlithiasis went on to have a testicular biopsy, the prevalence of carcinoma-in-situ in this series is not known.

The important question to ask of this study is whether or not testicular microlithiasis relates to infertility in the male as often suggested. In the series of 749 men described in this study, the number of men with a semen analysis that was deemed to be infertile was very similar as that where the semen analysis appeared to be fertile. In fact the association was actually fewer with primary subfertility at 46%,

even lower at 39% if the three vasectomy cases are categorized as secondary subfertility. However these rates are at least 4-5 folds higher than unselected males of comparable age and means there is a strong association with infertility.

The clinical relevance of ultrasonic varicocele detection has yet to be determined, and only a small proportion (e.g. 15% may be clinically relevant, e.g. where comparative testicular volumetric reduction of ≥ 5 ml occurs. Regardless, there appears no increased association of microlithiasis with varicoceles.

One interpretation that can be put on these results is that testicular microlithiasis may not be a serious pathology in itself but is a marker for testicular disease [28]. It may simply be an important indicator of a malignant potential within the testes [29] or be a benign lesion with malignant potential [30]. However, it certainly appears to be closely associated with some form of testicular pathology [31] even though the nature of the testicular pathology may not be easily demonstrable in every patient at the time of detection of the microlithiasis. However the association of testicular microlithiasis with either a malignant potential or even with an actual testicular cancer must be borne in mind. The last question to be asked is whether all infertile patients should undergo a testicular ultrasound examination as the prevalence of testicular microlithiasis appears relatively high at around 6% i.e. 1:16 men, higher in syndromic cases. The numbers presented in this study not only suggest that a routine testicular ultrasound would be diagnostically important but that clinical follow up and perhaps even treatment has also been suggested because of the observed association with testicular germ cell tumour and intratubular germ cell neoplasia of unclassified type [32]

However, in the light of one 5-year follow-up study revealing no progression to tumour [33], perhaps the risk may be considered low. Current advice is that men with testicular microlithiasis should be encouraged to self-examine the testes on a routine basis and present for further scanning if a lump is suspected. Some cases in the category of testicular dysgenesis syndrome should be considered at higher risk and may warrant additional ultrasound surveillance, perhaps under regular Urologist review. It is clearly very important that infertility clinicians become familiar with this condition. Even if they do not embrace routine genitourinary scanning, they will find cases of testicular microlithiasis on selective scanning and will need some reference data to consider the implications. This report is presented to provide some stimulus to fertility Consultants to consider closer evaluation of their male patients and be prepared to consider management of specific pathologies such as testicular microlithiasis. Hopefully this report provides an appropriate perspective.

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