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

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Abstract

Introduction Testicular microlithiasis (TM), characterized by the presence of intra-tubular 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. Tumorectomy with parenchymal sparing surgery was performed in a teratoma associated with TM.

Conclusion TM is a controversial entity, often associated with several inguinogenital features, which rarely can recover.

Testicular malignancy, although present in TM, has not proven definitively associated to microliths. Proper counseling, yearly ultrasound, and self-examination are long-term recommended

Keywords

- testicular microlithiasis
- microcalcifications
- gonadal dysgenesis
- seminoma
- germ

Introduction

Testicular microlithiasis (TM) is an entity of unknown etiology that results in the development of a variable number of intratubular calcifications in one or both the gonads. Although the first descriptions were published in the late Twenties,[1,2] the entity was better focused only more recently.[3] It can be an isolated phenomenon or observed in association with other urogenital features, such as varicocele, undescended testis, inguinal hernia, hypoplastic testis. TM can also be associated with congenital syndromes, such as Down, Klinefelter, X-fragile, and McCune–Albright.[4–7] The diagnosis of TM is based on the aspect at the ultrasonographic scan (US). Two categories of microlithiasis have been described: Classic testicular microlithiasis (CTM) is defined as having five or more microliths within a single US image, while less than five microliths are named limited testicular microlithiasis (LTM).[8,9]

TM may cause concern to the pediatric and the urologist surgeon because of the possible association with intratubular germ cell malignancy at puberty or in young adulthood.[8,10]

Since 2008, the Italian Society of Pediatric Urology (SIUP) approved a multicenter prospective cohort study on TM in pediatric and adolescent age. The long-term results are presented.

Patients and Methods

From January 2008 to December 2014, 11 units of pediatric urology and pediatric surgery participated in this prospective study, after approval of the institutional ethical committees. The following items were recorded in a specific database: age at diagnosis, presenting symptoms, associated abnormalities, US findings, and classification of TM (CTM/LTM), surgery (when needed), and gonadal biopsy results, if performed. α-Fetoprotein and β-human chorionic gonadotropin were evaluated in selected cases presenting significant testicular hypotrophy or hypertrophy.

All patients were followed up by urological examination in outpatient basis and the testicular US at 12-month intervals. The TM was compared with the initial observation and classified as unchanged, improved, and worsened. Improvement was considered the disappearance or reduction of more than 50% of microliths; worsening was defined as an increase of more than 50% of microliths. All patients older than 14 years of age were taught to practice monthly testicular self-examination according to Brenner et al[11] and Rovito et al[12] recommendations. The results were evaluated utilizing the chi-square pair test and the Fisher exact test when appropriated for statistical analysis, assuming a $p < 0.05$ as significant.

Results

Out of 85 patients identified with TM, 81 patients, aged from 6 months to 17 years at diagnosis (mean age, 10.1 years), were yearly followed up: 54 boys (66.6%) presented bilateral TM ($p < 0.05$) and 27 unilateral TM (12 on the right side and 15 on the left side, p ¼ ns). Four patients were lost at follow-up. A total of 73 patients (90.12%) underwent testicular US for coexisting urological pathologies (see ►Table 1) while 8 patients (9.8%) had an incidental diagnosis. In 12 patients (14.81%), gonadal biopsy was performed during surgery for acute scrotum or correction of varicocele. At histology, intratubular calcifications were found inside the tubuli, associated with little surrounding inflammatory reaction (►Fig. 1). In eight patients, considered at risk (9.87%) for testicular malignancy or dysgenesis, α-fetoprotein and β-human chorionic gonadotropin were dosed and found normal. The median follow-up was 4.7 years (range, 1–7 years). Three patients (3.7%) underwent orchiectomy: a 6 month-old baby with TM and severe testicular hypoplasia, and two 17 year-old boys with bilateral CTM who underwent unilateral orchiectomy for testicular seminoma. In one patient, CTM was observed at the time of testicular mass diagnosis. In the other patient, the testicular mass appeared after 5 years of US follow-up for bilateral TM: Seminoma was diagnosed at the intraoperative histological examination. The contrast-enhanced abdominal CT was negative for spread of disease in both patients with germ cell tumor. At a mean follow-up of 3 years no recurrence of the disease was detected in both the patients and the contralateral CTM remained unchanged (►Fig. 2A–C). A mature teratoma occurred in the upper pole of the left testis in a 9-year old boy with CTM, who previously had right orchiectomy for benign testicular mass. In this case testis-sparing surgery was performed (►Fig. 3).

In our series, TM remained unchanged in 77 of the 81 patients (93.82%). Four patients underwent inguinoscrotal surgery (one inguinal hernia repair, one orchidopexy, and two left varicocelectomy) and experienced significant improvement of TM on the operated side with reduction of the microliths > 50% at US (►Fig. 4a, b).

Table 1 Distribution of TM, according to the associate pathology, laterality, classification, and outcome at 4 to 7 years median follow-up

Patients	%	Presenting symptoms and associated diagnosis	MT distribution no. (%)	US classification (CTM/LTM)	Outcome no. (%)
19	2.34	Undescended/retractile testis	Unilateral 8 (42.1%) Bilateral 11	1 Unilateral LTM	1 bilateral improved (5.26%)
14	17.8	Painful testis	Unilateral 8 (57.14%) Bilateral 6	14 CTM	100% Unchanged
18	22.2	Left varicocele	Unilateral 3 (16.6%) Bilateral 15	3 Bilateral LTM	2 Bilateral CTM Improved (11%)
5	6.17	Hydrocele	Unilateral 1 (20.0%) Bilateral 4	1 Unilateral LTM 4 CTM	100% Unchanged
6	8.37	Congenital inguinal hernia	Unilateral 3 (50.0%) Bilateral 3	6 CTM	1 Improved (16%)
6	7.4	Acute scrotum	Unilateral 1 (16.6%) Bilateral 5	1 Unilateral LTM 1 Bilateral LTM	100% Unchanged
2	2.47	Epididymal cyst	Unilateral 0 Bilateral 2	2 CTM	100% Unchanged
7	9.84	Incidental	Unilateral 1 (14.2%) Bilateral 6	7 CTM	100% Unchanged
2	2.47	Testicular malignancy	Bilateral 2	2 CTM	Orchiectomy, TM unchanged
1	1.23	Severe hypoplasia	Unilateral 1	1 CTM	Orchiectomy
1	1	Benign tumor	Unilateral 1	CTM	Organ sparing-surgery

Abbreviations: CTM, classic testicular microlithiasis; LTM, limited testicular microlithiasis; TM, testicular microlithiasis.

Discussion

The first description of TM was in 1928, when Oiye found so called “calculations” on autopsy in 6 testes out of 192 adult cadavers.[1] In the following year, Blumensaat identified the same testicular intratubular bodies during the postmortem examina- tion of 6 out of 51 prepubertal children, hypothesizing that TM was caused as a result of the degeneration of spermatogonia in the tubular lumen.[2] In the early 60s, Bunge and Bradbury hypothesized that these bodies could be considered, resulting from intratubular oocytes, were trapped in dysgenetic testicles or ovotestis, as a result of the persistence of bisexual gonads.[13] In 1970, Priebe and Garret[14] described TM in the X-ray of a healthy 4-year-old boy. In 1982, Ikinger et al[10] first identified the association of microcalcifications with testicular cancer. In 1988, Martin et al[15] reported further ultrasonographic diagnosis of TM with associated testicular neoplasia. In 1987, Doherty defined the typical ultrasonographic appearance of TM, as the presence of countless “brilliant” echoes distributed throughout the testicular structure.[9] Later, he described these hyperechoic lesion as located in the epididymis and testicular parenchyma, whereas the scrotal wall was not interested. These calcifications measured from 1 to 3 mm in diameter and showed no posterior acoustic shadowing, probably due to their small size.[9] Diagnosis of TM is based on the following criteria at US[8,9]: (1) more than five calcifications per image field, (2) calcifications less than 2 mm in diameter, (3) diffuse in nature, (4) no acoustic shadowing, (5) no loss of testicular shape, or volume. TM has been divided into two different entities: CTM, with five or more microliths on any single view, and LTM, presenting less than five microliths. It has been graded as minimal/mild (grade I: 5–10 microliths), moderate (grade II: 10–20 microliths), and severe (grade III: > 20 microliths) depending on the microliths count as seen in any single view.[16]

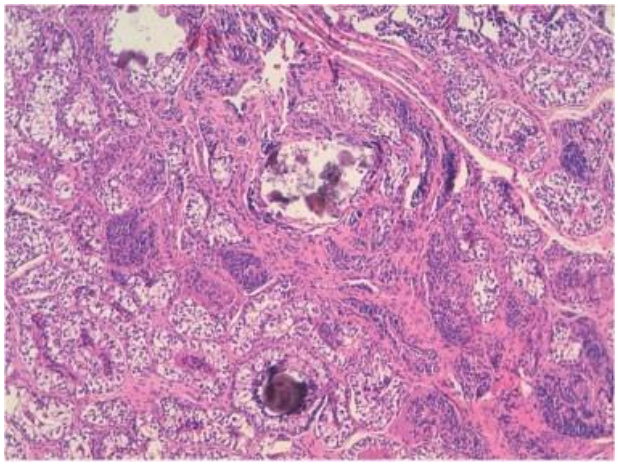

Fig. 1 Acute scrotum caused by testicular appendix torsion in a 11-year old-boy. Right testis biopsy: typical CTM with little inflammatory reaction surrounding small intratubular calcifications (hematoxylin– eosin, ×10). CTM, classic testicular microlithiasis.

However, this classification, which is actually arbitrary, does not imply any relationship between the risk of onset of testicular cancer and the distribution or intensity of microliths.

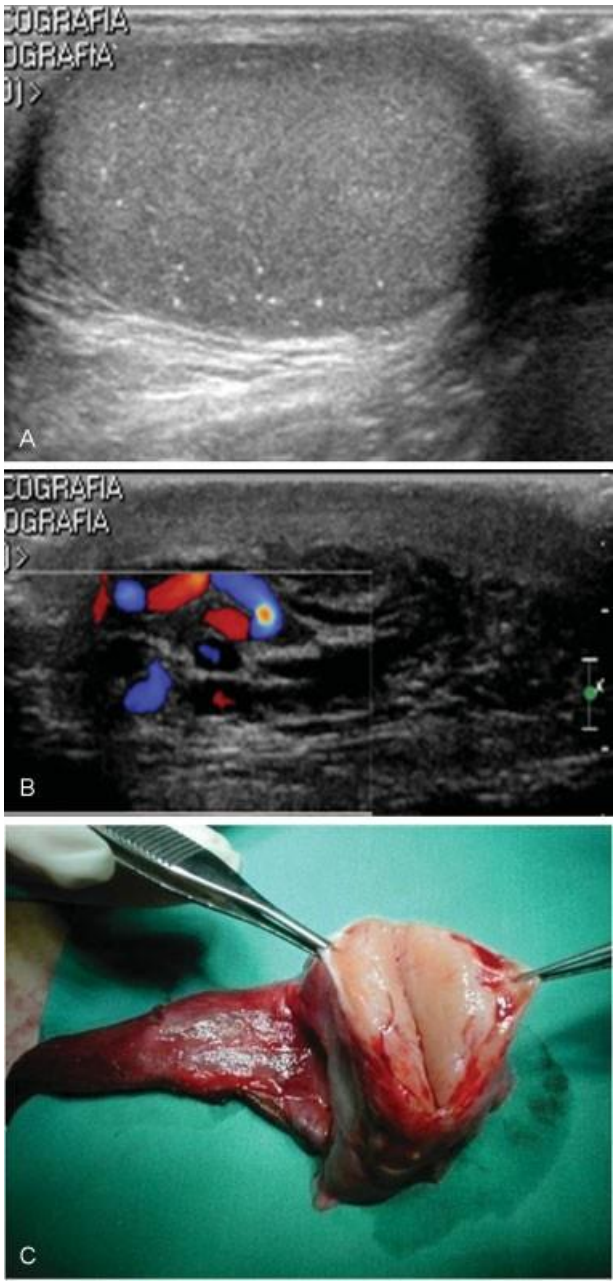

Fig. 2 (A) CTM, 2 years before seminoma onset. (B) Same case: Color Doppler. Hypervascularized testicular mass. (C) Same case: Macroscopic view of the testicular seminoma. CTM, classic testicular microlithiasis.

The pathogenesis of these "bodies" in the testicular parenchyma has been a matter of debate for years, and is still unclear. Halley referred that microliths were not intraluminal deposits, but rather products of acute lesions of the basement membrane of the seminiferous tubules.[17] Huber et al noticed from serial sections and reconstructions of tubules that the "bodies" were always within a dilated portion of a seminiferous tubule.[18] Finally, in 1970 Priebe and Garret,[14] reported the first case of a healthy child, 4-years old with TM. The boy underwent biopsy, which clarified the histopathological lesions.

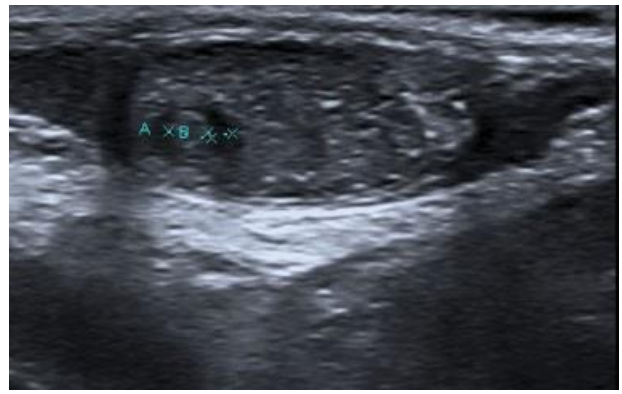

Fig. 3 Polar mature testicular teratoma with CTM in a 9-year-old boy.

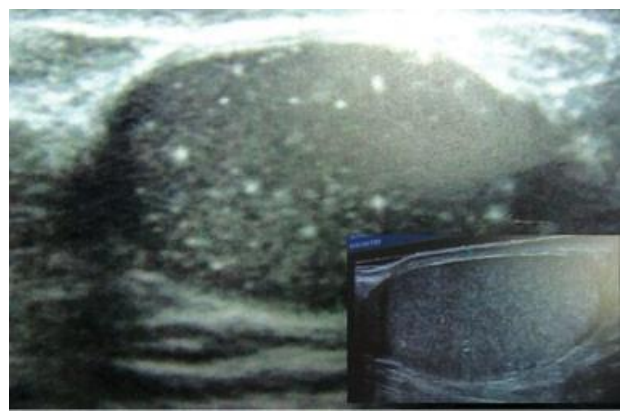

Fig. 4 (A) Left varicocele associated to CTM. (B) (small window): Reduction of microliths number 6 months after varicocelectomy. CTM, classic testicular microlithiasis.

The use of electron microscopy has provided new data on the etiology, the structure, and development of microliths, suggesting that these are located at the points of rupture of the basal membrane in the seminiferous tubules as a result of obstruction and/or degeneration.[18] Other studies have shown that the microliths, located within the seminiferous tubules are constituted by a core of hydroxyapatite, surrounded by several concentric layers of connective tissue fibers: the outer layer consists of cytoplasmic residues with vesicles, mito- chondria, and degenerated collagen fibers; the intermediate layer is composed of bundles of collagen fibers and the inner
layer presents multiple lamellae.[19,20]

The natural history of this condition has not been clearly defined yet and the recommended follow-up is still controversial among pediatric surgeons/urologists. Kocaoğlu et al[21]
in a follow-up of 0.5 to 6 years out of nine boys with TM (mean age: 9.2 years, range: 3–16 years) did not observe any testicular tumor. However, they concluded that a larger population and a longer period of monitoring were needed before any definitive conclusion. Furness et al[22] conducted a multicenter study involving seven centers of pediatric surgery/urology to assess the incidence of TM occasionally discovered. Data were collected on 26 patients with a mean age of 12.3 years (range: 0.5–21 years). The mean follow-up of

26.7 months (range: 1 month–7 years) did not demonstrate any testicular cancer. Coley[23] reported the case of a 8-year-old boy presenting with left scrotal pain and bilateral TM, who showed no signs of TM at 4-year US follow-up. A recent research from Finland still emphasizes that outcome data for pediatric TM should be interpreted with caution due to the poor quality evidence available.[24] There is a common agree- ment that long-term longitudinal evaluation may be particularly indicated in the patients with additional testicular dysgenetic features presenting TM.[24,25]

The usefulness of testicular biopsies is very controversial. Guidelines from Europe advocate to consider a testicular biopsy in younger patients and in those who are at an increased risk for germ cell tumor, whereas self-examination is recommended for older patients.[11,12,26] According to the recent literature, self-examination and US are considered necessary, limiting testicular biopsy to the cases of TM associated with suspected testicular malignancy.[27–29] In the present series, gonadal biopsy was performed in 12 patients (14.8%), with no significant new information.

Although longitudinal studies are limited, imaging reports of TM would suggest that TM is relatively stable, changing little over time. Frush et al reported the interval development of TM over 15 months in a patient with a contralateral germ cell tumor.[30] In a follow-up of 31 patients with CTM, Bennett et al reported 1 case of progression over 3.2 years and 1 case of development of TM in a previously normal testis over 4.25 years of follow-up.[31] Dell'Acqua et al reported one case of TM in a 6-year-old boy arising in a previously undescended testis with prior heterogeneous echogenicity over 1 year.[32] Our series, however, is in line with recent sporadic case reports in the literature, showing the possible improvement of TM over time. Coley[23] reported a case of disappearance of TM in a 12-year-old boy, while Leenen et al[33] reported the reduction of the size of TM foci in a 6-year-old boy with a history of a Sertoli cell tumor. We observed improvement of TM in four cases (6.8%), all after inguinogenital surgery on the affected side. The pathophysiology of this phenomenon is not yet understood, but it seems limited to the pediatric age and so far has not been described in adults. Whether surgery is responsible of improvement or disappearance of TM remains to be confirmed.

The analysis of the results of our multicenter survey shows that a change in TM can occur in some cases over a period of follow-up ranging from a few months to a few years. Surgery may increase the microliths regression, if the gonadal trophism is improved.

The possibility of healing shows that the TM could be a developmental disorder and confirms the hypothesis that this disorder can be considered as an expression of testicular parenchyma suffering: it could improve if the underlying pathology resolves. A long-term follow-up must be offered to the patients considering not only the prevention of testicular malignancy but also the evolution of TM. No therapy has been ever referred for this condition: surgery, where indicated, could improve trophism of the gonad and stimulate improve- ment or disappearance of the TM in very unusual cases. A recent meta-analysis on a total of 14 studies involving 35,578 patients showed that TM was associated with an increased incidence of testicular cancer. The study concludes that oncological risk is increased in TM, but more researches are still necessary to better understand this association.[34]

Conclusion

As points of strength, our prospective observational study presents the largest multicenter series in literature, with a yearly check of the enrolled patients and a properly long follow-up (mean: 4.7 years). As limitations, the follow-up of our series is not yet adequate to give information on fertility at the postpubertal age. TM was found not so uncommon in pediatric and adolescent age. Etiopathogenesis is still contro- versial. TM was demonstrated not rarely associated with several inguinogenital features (90.1% in our experience), but it may be fully asymptomatic with occasional diagnosis (10% of our series). So, the real prevalence of TM in the normal pediatric and adolescent population is not clear.[3,21]

The results of our survey confirm that TM can be found in association with testicular germ cell malignancy (2.47% of our series). The higher incidence of testis cancer in our series, when compared with other authors[22] may be explained by the longer follow-up and it justifies the opportunity of a proper long-term surveillance of these patients.

According to the suggestion from the SIUP guidelines, the follow-up of TM in children and adolescent should be based on a proper counseling, reassuring parents, and suggesting annual follow-up. Education to practice self-examination from pubertal age associated with regular clinical and US examination is recommended. Only in cases presenting testicular dysplasia or suspected malignancy, markers dosage and/or surgical exploration with gonadal biopsy could be deemed necessary.

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