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ORIGINAL ARTICLE

Testicular microlithiasis in pediatric age group: ultrasonography findings and literature review

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PURPOSE
To evaluate the occurrence of testicular microlithiasis in pediatric age group by means of ultrasonography (US) examinations and to review the literature for pediatric testicular microlithiasis cases accompanied by testicular and extratesticular tumors.

MATERIALS AND METHODS
Nine children aged 3-16 years (mean age, 9.2 years) with testicular microlithiasis had been evaluated with US in a period ranging from 6 months to 6 years. In addition to the testicular ultrasonographic evaluation, liver US and abdominopelvic US were performed in all patients.

RESULTS
Typical testicular microlithiasis findings were seen in a total of 17 testicles. In one patient, testis did not exist in either the scrotum or the inguinal canal or the abdomen unilaterally. None of the patients displayed a focal lesion during the evaluation. The abdominal ultrasonographic findings were normal in all patients.

CONCLUSION
Although no tumoral lesion accompanying testicular microlithiasis or occurring in the course of evaluation was detected in this study, larger population and longer control periods are required, considering the co-existence of benign and malign lesions with testicular microlithiasis in the literature.

Key words: • *testicular neoplasms* • *infant* • *child* • *ultrasonography*

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Testicular microlithiasis (TM) is a rare disease and its frequency detected by ultrasonography (US) has been reported between 0.6% and 9% (1, 2). Relatively small number of cases has been reported for the pediatric age group (3-10). The wide usage of high resolution US in the evaluation of scrotal diseases has resulted in a coincidental increase in the number of TM cases. Co-occurrence of many benign and malign (malignant) pathologies with TM such as cryptorchidism, hypogonadism, ischemic damage, pulmonary alveolar microlithiasis, varicoceles, testicular torsion, male pseudohermaphroditism, Klinefelter syndrome, AIDS, carcinoma in situ, neurofibromatosis type 1 and germ celled tumors have been reported. However, there is no common agreement on whether these co-occurrences are related to the cause and effect or totally incidental (6, 11-14). Although the co-occurrence of germ cell tumors and TM has been reported to have a frequency of 40% in adults, the natural history of TM is not known well (15). In addition, the method that is to be used in the evaluation is controversial. The co-existence of TM with testicular tumors and occurrence of malignant process in patients with TM have raised the suspicion that TM could be a premalignant lesion (3, 6, 16-18). However, the number of patients and pediatric age group are limited in the majority of publications in the literature. In this study, we reviewed the US images obtained from nine children with TM, US examination results, and the literature articles concerning pediatric cases and cases having TM, accompanied with testicular/extratesticular tumors.

Materials and methods

A total of 17 testicles in 9 children diagnosed with typical microlith formations (microliths) were examined during a period between February 1998 and September 2004 in two different radiology centers. The ages ranged between 3 and 16 years (mean age, 9.2 years) at the time of diagnosis. US examinations were performed with two different US equipments by using 7.5-10 MHz linear transducers. US indications were bilateral undescended testes (n=1), unilateral undescended testis (n=1), Klinefelter syndrome with bilateral orchiopexia (n=1), trauma (n=1), varicoceles (n=2), scrotal pain (n=2) and insufficient growth or development (n=1). The follow-up of these patients had been carried out for periods ranging between 6 and 62 months at an interval of 3-12 months in accordance with the co-existing pathologies after the diagnosis of TM. When performing the US examination, the number and distribution patterns of the testicular calcifications seen in US were examined, and the echogenicities smaller than 1-3 mm, with no acoustic shadows, that were visible in a single plane were included. In addition, it was also recorded whether they were diffuse or focal, bilateral or unilateral with or without accompanying nodules. US examination was performed in various planes so as to include the inguinal canal.

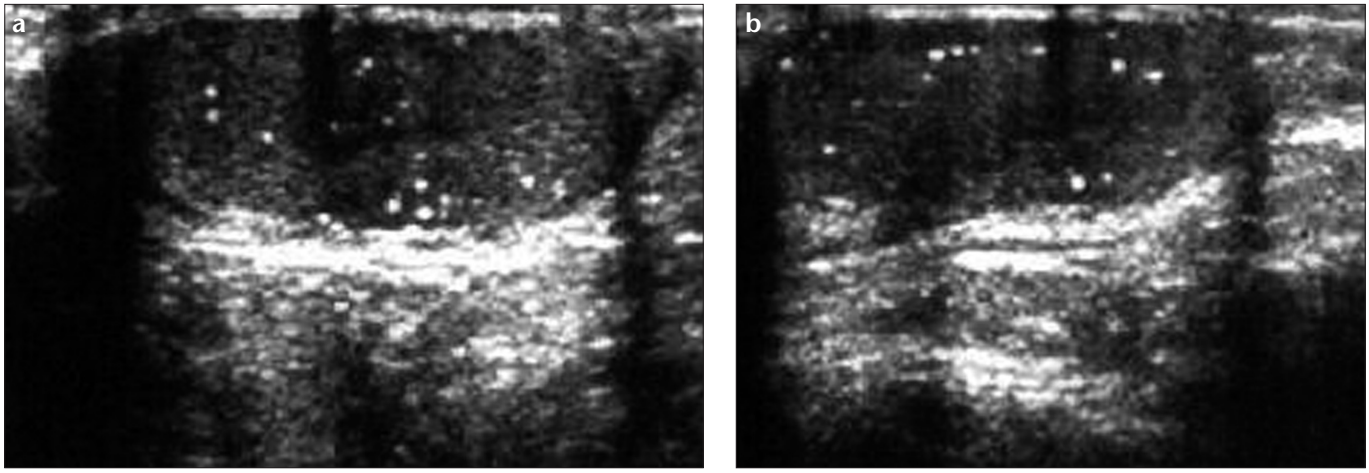

Figure 1. Asymmetric, diffused echogenicities (microliths) without acoustic shadows are observed in the right **(a)** and left **(b)** testicles of a 6-year-old patient who has undergone US due to pain.

In addition to the scrotal US, all patients were examined with abdominopelvic US and chest X-ray during the follow-up period.

Results

TM diagnosis was reached by means of US for all patients. The ages of the patients, TM pattern, follow-up period, follow-up intervals and examination indications are given in Table 1. TM was detected in all of the 17 testes that were evaluated and the image displayed a diffuse distribution pattern in seven children and focal distribution in two (Figures 1-3). In one patient, only the right testicle could be examined. The left testicle of this patient could not be displayed with US either in the scrotum, the ingunial canal or in the abdomen. The testicles of the patient with Klinefelter syndrome who was operated on due to both hypospadias as well as the testicles of the patient with bilateral undescended testes who showed failure to thrive were atrophic. There was rete testis dilatation in a patient diagnosed with TM who was subject to US due to scrotal pain. There were left varicoceles in two patients. The patients were taken in a follow-up programme for periods ranging from 3 to 12 months depending on the accompanying disease. One patient failed to show up at the follow-up examinations except once after being diagnosed. The chest X-ray and abdominopelvic US results were normal in all patients. No patient had a focal lesion and none of them developed a focal lesion during the follow-up.

Discussion

Testicular microlithiasis is a pathology of which actual cause is unknown and that is believed to resulted from the degeneration of the seminiferous epithelium wiped into the tubular lumen. The debris, which has flown into the lumen, accumulates there in the forms of a glycoprotein and calcium layers and evolves into the histologically and pathologically characteristic form. Biopsies have proved that 20-60% percent of seminiferous tubules were involved (7, 19). Some authors suggest that microliths result from Sertoli cell dysfunction in connection with abnormal gonadal embriogenesis (20).

Testicular microlithiasis was first described by Priebe and Garret in a 4-year-old healthy boy (21). It was sonographically identified by Doherty et al. for the first time in 1987 (22). In US examination, testicular microlithiasis is seen as echogenicities smaller than 1-3 mm, with no acoustic shadows. They develop in the testicular parenchyma, however, they may show peripheral or segmentary distribution. Although they are usually bilateral, unilateral TM cases have been reported as well (1, 3, 15, 21, 23). Today, the number of microliths to reach the TM diagnosis is agreed upon to be 5 and above for each sonographic plane (1, 15). However, the cases with a smaller number of microliths are associated with malignancy and therefore classification according to the number of microliths may not be practical (24). Inflammatory scars were identified in some benign pathologies such as hemorrhagic infarction and granuloma as well as the calcifications that were identified in different patterns in testicular

Table 1. Demographics, follow-up intervals, follow-up periods and testicular microlithiasis patterns of our patients

Patient	Age (years)	US indication	Follow-up interval (months)	Follow-up period (months)	Testicular microlithiasis pattern	Number of microliths per US section
1	16	Varicocele	6-12	47	Asymmetric, focal	5-10
2	5	Failure to thrive	6-12	36	Asymmetric, diffuse	10-30
3	6	Pain	6-12	37	Asymmetric, diffuse	20-30
4	3	Unilateral undescended testicle	3-6	9	Symmetric, diffuse	>60
5	15	Bilateral orchiopexia	3-12	62	Asymmetric, focal	5-10
6	14	Varicocele	6	12	Asymmetric, diffuse	10-20
7	8	Pain	6-12	39	Asymmetric, diffuse	5-10
8	11	Trauma	12	12	Asymmetric, diffuse	10-30
9	5	Bilateral undescended testes	6-12	24	Asymmetric, diffuse	20-30

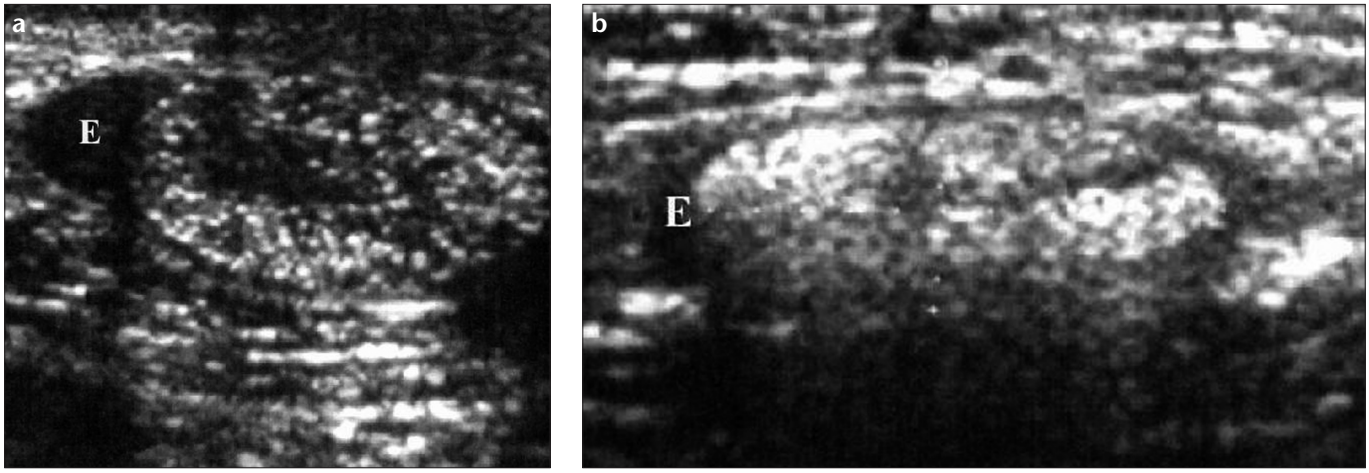

Figure 2. A 3-year-old patient who has undergone US examination due to undescended testicle. **a.** Diffused microliths are visible in the right testicle **(a)** that is localized in the upper scrotum. The left testicle of the same patient **(b)** is atrophic and located in the ingunial canal and the diffused microliths are seen throughout the entire testicle. (E: head of epididymis.)

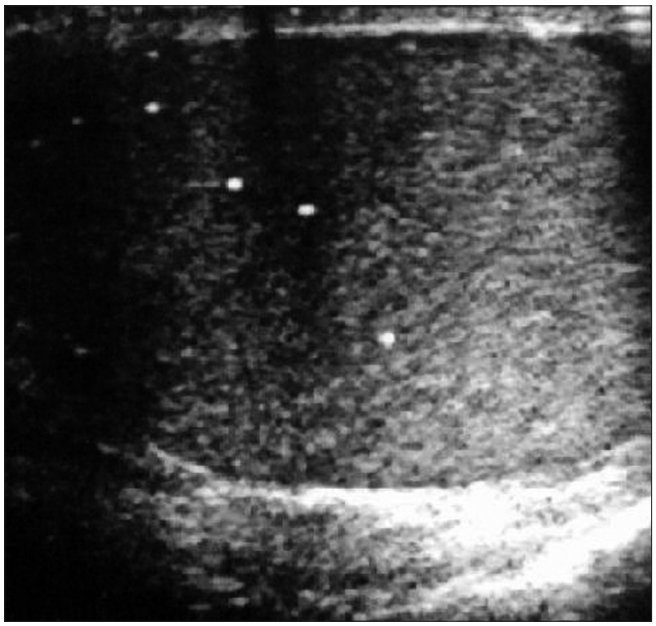

Figure 3. Asymmetric focal microliths are seen on US of a 15-year-old patient who has undergone bilateral undescended testicle surgery.

tumors; however, these do not show the characteristic configuration of the TM defined above (1).

Co-existence of many benign and malign pathologies with TM such as cryptorchidism, pulmonary alveolar microlithiasis, male pseudohermaphroditism, Klinefelter syndrome, AIDS, germ cell tumors, Down syndrome, and infertility have been reported (3, 6, 11-14, 22, 23). In one of our cases, contrary to the literature, TM was accompanied by rete testis dilatation, which is a non-neoplastic pathology that occurs following a trauma or infection. Differential diagnosis of focal lesions and TM is important. Being localized to the testicles' mediastinum, its composition of little anechoic tubular groups and the co-existence of the epididymal pathologies are consistent with the diagnosis of TM (25). The most important accompanying pathology in cases with TM is a testicular neoplasia. The occurrence of TM with testicular and extratesticular neoplasia with a frequency of 18-45% as reported in the literature leads one to think this co-existence is not a coincidence. However, there is no proven cause and effect relationship between these conditions. Some authors have attributed the increased risk of testicular neoplasia to the pathologies such as undescended testicle, infertility, chromosomal anomaly, and atrophy (1, 23, 26). Another pathology that accompanies testicular microlithiasis is intratubular germ cell neoplasia (IGCN) which is the germ cell version of carcinoma in situ. In 50% of the cases, the intratubular germ cell neoplasia transforms into germ cell tumor within 5 years following the diagnosis and IGCN is encountered in the biopsies of patients with TM (27, 28). For that reason, TM may be an indicator of IGCH revealing a high risk for germ cell tumors. Since there were no focal lesions that would require biopsy in our cases, the occurrence of IGCN could not be examined. Although the co-occurrence of TM with testicular and extratesticular tumors is known and the relative frequency of tumor in the patients with TM was calculated to be between 19.8% and 21.6% when compared with the patients without TM, the number of pediatric cases is relatively smaller when compared to adult cases (4-10, 17, 18, 20, 30-33) (Table 2). In addition, the co-occurrence of TM with tumors was not reported as frequent in the pediatric age group. The pediatric cases reported in the literature has an age range between 2 to 12 years, and the follow-up period varies between 2 weeks and 7 years depending on the accompanying pathologies. In the course of an average follow-up period of 6 years, Leenen et al. have detected a germ cell tumor, which was metastatic at the time of the diagnosis in one patient and Sertoli cell tumor in 2 patients out of a group of 16 children within an age range of 6-18 years. In this study, there was no interval tumor development within the follow-up pe-

riod of 6 years (30). Furness et al. have not observed any tumors during the follow-up of 26 patients (aged between 6 months and 21 years) with TM for a period ranging between 1 month and 7 years (6). Dell'Acqua et al. followed up 6 patients aged between 3 and 12 for a period between 2 weeks and 12 months. There was no tumor development during this period (5).

In the co-occurrence of testicular microlithiasis with testicular tumor, the probability of tumor development is the most important factor that determines the follow-up and treatment methods for the patients (17, 18, 23, 34-44) (Table 3). When we look at the patients who developed tumor within a certain period, we see that the patients were aged between 11 and 47 at the time of tumor diagnosis and the tumor interval ranges between 6 months and 7 years following the TM diagnosis. Only two children has interval tumor out of these patients. Mc Eniff et al. have detected the development of testicular yolk sac tumor during the fourth year of the routine US follow-up of a 17-year-old patient (17). Biege et al. have detected microlith one year after the diagnosis and gonadoblastoma development 6 years after the diagnosis in a 4.5-year-old patient who had male pseudohermaphroditism and bilateral undescended testes (18).

Another interesting group of pathologies that co-occurs with testicular microlithiasis is the presence of extratesticular tumors without testicular primary tumor, which is a rare situation (13, 32, 45-49) (Table 4). These cases presented with complaints related with mediastinal, supraclavicular and abdominal masses and were all accompanied by TM. Although it can be thought that TM might mask the primary masses and that chemotherapy treatment aiming to cure the primary mass might avoid the detection of the testicular tumor in some patients, no testicular tumor was encountered in the biopsies that were performed in such cases (49). Although the clinical significance of the co-occurrence of testicular microlithiasis with extratesticular tumors is not clear, the thorax and abdomen should also be radiologically examined and/or the tumor indicators such as AFP and HCG should be followed up during the routine controls in order to detect a new extratesticular tumor.

There is no agreement on the follow-up procedure in the literature. Since the cure rate is quite high regardless of the phase that the tumor is in, some suggest

Table 2. Pediatric testicular microlithiasis cases reported in the literature

Patient[a]	Sources (reference number)	Number of patients
1	Leenen[b] (30)	16
2	Dell'Acqua (5)	6
3	Furness (6)	26
4	Vegni-Talluri (4)	4
5	Nistal (7)	2
6	Moran (10)	1
7	Jaramillo (31)	1
8	Weinberg (9)	1
9	Kwan (8)	1
10	McEniff[c] (17)	1
11	Howard[d] (32)	1
12	Bieger[c] (18)	1
13	Drut (33)	1
14	Drut (20)	11

[a] The patients were aged between 2 and 21 years and the follow-up periods ranged between 2 weeks and 7 years.
[b] There was metastatic germ cell tumor in one patient and Sertoli cell tumor in two patients at the time of the diagnosis.
[c] Yolk sac tumor (17) and gonadoblastoma (18) developed during the follow-up.
[d] Co-existence of mediastinal germ cell tumor with testicular microlithiasis.

Table 3. Testicular microlithiasis patients who developed tumor during follow-up

Patient[a]	Reference number	Tumor interval	Tumor	Accompanying pathology (indications)
1	McEniff[b] (17)	4 years	Yolk sac tumor	Size difference between testes
2	Winter (34)	3 years	Mixed germ-cell tumor	Pain, hemospermia
3	Gooding (35)	11years	Seminoma	Received seminoma therapy for the other testis
4	Golash (36)	6 months	Seminoma	Atrophic right testis, scrotal pain
5	Salisz and Goldman (38)	10 months	Embryonal cell carcinoma	Infertility, right-sided TM, undescended testis
6	Bieger[b] (18)	6 years	Gonadoblastoma	Pseudohermaphroditism, bilateral undescended testes
7	Frush (23)	17 months	Mixed germ-cell tumor	Incidental finding, paraaortic LAP
8	Ortiz (39)	13 months	Mature teratoma and IGHN	Chromosomopathy, orchitis
9	Lawrentschuk (40)	12 months	Seminoma	Hydrocele
10	Bach (37)	4 years	Yolk sac tumor	Size difference
11	Derogee (41)	35 months	Mixed germ-cell tumor	History of embryonal-cell carcinoma on the left
13	Cornford (42)	12 months	Seminoma	Retractile testis
14	Otite (43)	2 years	Left-sided atrophic testis	
		4 years	Right-sided mixed germ-cell tumor	
15	vonEckardstein (44)	3 years	Seminoma	Volunteer
		5 years	Seminoma	Infertility

[a] Patients' aged ranged between 11-47 years.
[b] Pediatric patients
TM: testicular microlithiasis, IGHN: intratubular germ-cell neoplasia, LAP: lymphadenopathy

Table 4. Co-existence of testicular microlithiasis with extratesticular tumors

Patient	Source (reference number)	Age (year)	Histopathology and location of tumor
1	Sato (45)	19	Mediastinal seminoma
2	Quane (46)	22	Mediastinal germ cell tumor
3	Matsumoto (47)	43	Supraclavicular seminoma
4	Nishiyama (48)	19	Mediastinal choriocarcinoma
5	Howard (32)	15	Mediastinal immature teratoma
6	Aizenstein (13)	18	Mediastinal germ cell tumor (mature teratoma, malign mesenchymal origin)
7	Emberton (49)	39	Paraaortic nodular seminoma

that the US follow-up has not a significant influence on the survival rate of the patient in all germ cell tumors and the US follow-up is necessary between the ages 15 and 34 during which particularly the germ cell tumors peak due to the low risk of tumor development (6, 14, 15, 24, 28, 29, 50). In addition, some authors suggest to check on the the tumor indicators, which makes the process more expensive, to support US follow-up. However, the co-occurrence of TM with tumors is somehow known. A fairly large population should be examined prior to declaring the TM as a benign or premalignant lesion since it is reported to be seen in patients with interval tumors. Since the number of existing cases and the follow-up period are insufficient, much longer periods of follow-up are needed in order to shed light to the epidemiological studies and to determine the natural history of the disease. Although the results that were obtained in our study are similar to those of the previous studies, we believe that our patients will be evaluated with the other cases, thus will contribute to the determination of the natural history of TM.

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